

*Part A: Palladium-Catalyzed C–H Bond
Functionalization*

*Part B: Studies Toward the Synthesis of
Ginkgolide C using Gold(I) Catalysis*

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Table of Contents

1	1
1.1	<i>Introduction</i> 1
1.2	<i>Overview of the Mechanistic Work on the Concerted-Metallation-Deprotonation Pathway</i> 3
1.2.1	Examples of deprotonation by metal/base complexes 4
1.2.2	Early evidence of the concerted metallation-deprotonation pathway 5
1.2.3	Directed metallation of arenes 8
1.2.4	Directed catalytic functionalization of arenes 11
1.2.5	Intermolecular C–H bond metallation 15
1.2.6	Catalytic Functionalization of Electron Deficient Arenes 17
1.2.7	Concluding remarks 21
2	22
2.1	<i>Additives used to enhance the reactivity of metal-catalyzed C–H functionalization</i> 22
2.1.1	Discovery of the pivalic acid as a rate enhancing additive 23
2.1.2	Use of different additives in other systems 25
2.2	<i>Development of mild and efficient intramolecular direct arylation reactions using the palladium-carboxylic acid co-catalysis system</i> 26
2.2.1	Optimization of the reaction conditions 27
2.2.2	Substrate scope of the reaction 31
2.3	<i>Concluding remarks</i> 33
3	34
3.1	<i>Introduction to the mechanistic studies on the C–H bond functionalization of electron rich arenes</i> 34
3.1.1	Interpretation of the results of kinetic isotope effect experiments 37
3.2	<i>Experimental evidence in favor of the CMD mechanism</i> 40
3.2.1	Non S_EAr -type of reactivity of 3-fluorobenzothiophene 41
3.2.2	Re-examination of the reactivity of indolizine toward direct arylation and Friedel-Crafts acylation reactions 43
3.3	<i>Computational analysis of the concerted metallation-deprotonation pathway</i> 52

3.3.1	Evaluation of the free energy of activation of the C–H bond functionalization of (hetero)arenes <i>via</i> the CMD pathway.	52
3.3.2	Activation–Strain analysis of the CMD transition states	55
3.3.3	Concluding remarks	58
3.4	<i>Establishment of broadly applicable reaction conditions for the palladium-catalyzed direct arylation of heteroaromatic compounds</i>	59
3.4.1	The effect of pivalic acid on the kinetic profile in the palladium-catalyzed direct arylation of heteroarenes with aryl bromide	60
3.4.2	Scope and limitations of the direct arylation of heteroarenes under general conditions	62
3.4.3	Concluding remarks	69
3.5	<i>Predictable and Site-Selective Functionalization of Poly-(Hetero)Arene Compounds by Palladium Catalysis</i>	71
3.5.1	Conditions-based site-selectivity	73
3.5.2	Predicted selectivity with the DFT calculated CMD pathway	78
3.5.3	Concluding remarks	84
3.6	<i>General Conclusion</i>	85
4		86
4.1	<i>General Introduction</i>	86
4.2	<i>Palladium-Catalyzed Functionalization of Benzyl Chlorides</i>	87
4.2.1	Optimization of the reaction conditions	92
4.2.2	Scope of the palladium-catalyzed benzylation of heteroarenes	97
4.2.3	<i>Post facto</i> improvement of the benzylation conditions	100
4.2.4	Concluding remarks	104
4.3	<i>Development of a Domino 1,2-Migratory Insertion–Intermolecular Direct Arylation Process Catalyzed by Palladium</i>	104
4.3.1	Reaction development	108
4.3.2	Concluding remarks	116
4.4	<i>General Conclusion</i>	116
5		117
5.1	<i>General Introduction</i>	117
5.1.1	Phosphino-amide ligands	118

5.1.2	Phosphino-quinolinone ligands	124
5.2	<i>Platinum-Catalyzed Benzene H/D Exchange with Deuterated Solvent</i>	128
5.2.1	Metal-acetate promoted C–H bond cleavage of simple arenes and heteroarenes	129
5.2.2	Ligands preparation and testing	135
5.2.3	Concluding remarks	139
5.3	<i>Conclusion</i>	140
6		141
6.1	<i>Introduction</i>	141
6.1.1	Mechanistic work precedents	143
6.2	<i>Results and Discussion</i>	145
6.2.1	Detailed DFT analysis of the process leading to CMD (π -complexes)	149
6.2.2	Metallation-Deprotonation: Concerted or Not?	151
6.2.3	Thiophenes	154
6.3	<i>Efforts toward the establishment of predictable arene C–H bond functionalization guidelines</i>	160
6.3.1	Arene distortion energy	160
6.3.2	Metal-arene interaction energy	162
6.4	<i>Conclusion</i>	163
7		165
7.1	<i>Introduction</i>	165
7.1.1	Corey's retrosynthesis and strategy for the synthesis of ($\pm$)-ginkgolide B	167
7.1.2	Crimmins' synthesis of ($\pm$)-Ginkgolide B	170
7.2	<i>Current approach to the synthesis of Ginkgolide C</i>	173
7.3	<i>Gold(I)-catalyzed cyclization reactions</i>	176
7.3.1	Gold(I) catalyzed Rautenstrauch reaction	177
7.3.2	Gold(I) catalyzed 5- <i>exo-dig</i> cyclization	180
7.4	<i>Efforts toward the preparation of the spirobicyclic core of Ginkgolide C</i>	183
7.4.1	Preparation of enone 11	183
7.4.2	Model studies for the 5- <i>exo-dig</i> cyclization	188
7.5	<i>Conclusion</i>	193
8		195

8.1	<i>Organization and General Considerations</i>	195
8.2	<i>Chapter 2: Utilization of Additives in the Development of Mild and Efficient Reactions</i>	
	<i>Conditions for the Intramolecular Direct Arylation of Simple Arenes</i>	196
8.3	<i>Chapter 3: Analysis of the CMD mechanism in Palladium-catalyzed direct arylation</i>	
	<i>across a broad range of aromatic substrates and examples of its application</i>	201
8.3.1	Section 3.4: Establishment of broadly applicable reaction conditions for the palladium-catalyzed direct arylation of heteroaromatic compounds	215
8.3.2	Section 3.5: Predictable and Site-Selective Functionalization of Poly-(Hetero)Arene Compounds by Palladium Catalysis	224
8.4	<i>Chapter 4: Palladium-Catalyzed sp^3-sp^2 C–C bond Formation by C–H Functionalization</i>	
	<i>Reactions</i>	244
8.4.1	Section 4.2.3: <i>Post facto</i> improvement of the reaction conditions	256
8.4.2	Section 4.3: Tandem 1,2-migratory insertion–Direct arylation	258
8.5	<i>Chapter 5: Development of ligands to promote the CMD pathway in C–H bond functionalization reactions.</i>	260
8.6	<i>Chapter 6: Analysis of the Palladium-Catalyzed (Aromatic)C–H Bond Metallation-Deprotonation Mechanism Spanning the Entire Spectrum of Arenes</i>	270
8.7	<i>Part B, Chapter 7: Studies Toward the Synthesis of Ginkgolide C Spirobicyclic Core by Au(I)-Catalyzed Cyclizations</i>	281

List of Schemes

Scheme 1.1 General representation of traditional cross-coupling reactions.	2
Scheme 1.2 Metal/Base promoted C–H bond functionalization.	4
Scheme 1.3 Examples of internal deprotonation reactions.	5
Scheme 1.4 Representation of the mechanism proposed in 1955 for the acetolysis of diphenylmercury(II).	6
Scheme 1.5 Benzenium ion and Olah’s description of the arene mercurium ion intermediate complexes.	7
Scheme 1.6 Mechanism of cyclometallation of DMBA-H with palladium.	9
Scheme 1.7 Selectivity observed with a trifluorinatediphenyl and a simple phenyl group.	13
Scheme 1.8 Reaction pathway for the functionalization of phenyl imines.	14
Scheme 1.9 Geometry changes in the palladium(II)-formate promoted C–H bond functionalization.	15
Scheme 1.10 [RuTp(OH)] and [Ir(acac) ₂ (OMe)] promoted metallation of benzene.	16
Scheme 1.11 Selectivity observed with electronically biased pyridines <i>N</i> -oxides.	17
Scheme 1.12 Selective arylation of picoline <i>N</i> -oxide achieved by the choice of base.	18
Scheme 2.1 Palladium-catalyzed direct arylation of benzene with pivalic acid as co-catalyst.	24
Scheme 2.2 Plausible pathway for benzene arylation.	25
Scheme 3.1 Indole-C2 arylation mechanism proposed by Sames. ^{2b}	36
Scheme 3.2 Examples of different k_H/k_D values obtained from intermolecular and intramolecular KIE experiments.	37
Scheme 3.3 Synthesis of 3-fluorobenzothiophene.	41
Scheme 3.4 Competition reactions between electronically biased benzothiophenes.	42
Scheme 3.5 Incorporation on deuterium at the C1 and C3 positions of indolizine.	43
Scheme 3.6 Measurement of the <i>in-situ</i> KIE under the original reaction conditions.	44
Scheme 3.7 Observation of a C3 phenyl side-product under the original conditions.	44
Scheme 3.8 <i>In-situ</i> kinetic isotope effect of C2-ester indolizines.	47
Scheme 3.9 Preparation of the ethyl indolizine-2-carboxylate.	49
Scheme 3.10 Aluminum trichloride promoted acetylation of ethyl indolizine-2-carboxylate.	50
Scheme 3.11 Aluminum trichloride promoted <i>p</i> -nitrobenzoylation of ethyl indolizine-2-carboxylate.	51
Scheme 3.12 Regioselective palladium-catalyzed arylation of 4-chloropyrazoles, by Mateos, Mendiola <i>et al.</i> ³⁸	70
Scheme 3.13 Site-selective azaindole arylation at the azole and azine rings <i>via N</i> -oxide activation.	74

Scheme 3.14 Preparation of the model substrates 9 to 13 .	75
Scheme 3.15 Preparation of the model substrates 23 , 26 and 29 .	82
Scheme 4.1 General catalytic cycle for a direct arylation reaction catalyzed by palladium.	87
Scheme 4.2 Representative examples of the heteroarenes alkylation limitations.	88
Scheme 4.3 Precedents of direct arylation of sp ³ C–Halide.	91
Scheme 4.4 Direct benzylation of thiazole under the preliminary reaction conditions.	92
Scheme 4.5 Control experiment, product inhibition.	97
Scheme 4.6 Selected precedents of domino 1,2-migratory insertion–intramolecular direct arylation.	105
Scheme 4.7 Sequential 1,2-migratory insertion–intramolecular direct arylation–hydrogenation reaction.	106
Scheme 4.8 Examples of fully intramolecular version of the targeted domino 1,2-migratory insertion–direct arylation reaction.	107
Scheme 4.9 Proposed 1,2-migratory insertion/C–H functionalization catalytic cycle.	108
Scheme 4.10 Preparation of bromoarene 33 .	108
Scheme 4.11 Reaction progression over nearly 8 hours (470 minutes).	113
Scheme 5.1 Suggested mechanism of C–H bond cleavage with phosphino-amide ligands.	118
Scheme 5.2 Preparation of ligands 1–8 .	120
Scheme 5.3 Suggested formation of palladacycle phosphino-benzamide ligands 2 and 5 .	123
Scheme 5.4 Activation-Strain analysis of the CMD TS.	125
Scheme 5.5 Synthesis of C8-diphenylphosphino quinolidin-2-one 12 .	126
Scheme 5.6 Proposed individual steps leading to the C–H bond cleavage of the CMD pathway.	128
Scheme 5.7 Deuterium incorporation into benzene- <i>h</i> ₆ catalyzed by WG-1a .	130
Scheme 5.8 Preparation of complex 14 .	135
Scheme 6.1 Overview of the parameters that governs the C–H bond cleavage via a concerted metallation-deprotonation mechanism.	143
Scheme 6.2 Activation–strain analysis for the CMD transition state. Benzene is shown as a representative substrate.	146
Scheme 6.3 Possible CMD pathways for C–H functionalization with various arenes (C ₆ F ₅ H: purple, C ₆ H ₆ : green, C ₄ H ₄ S: black).	150
Scheme 7.1 Corey’s retrosynthetic approach to ginkgolide B.	168
Scheme 7.2 Key sequence in Corey’s synthesis of (±)-ginkgolide B.	169
Scheme 7.3 Completion of Corey’s synthesis of (±)-ginkgolide B.	170
Scheme 7.4 Crimmins’ retrosynthetic approach to (±)-ginkgolide B.	171
Scheme 7.5 Crimmins’ synthesis of (±)-ginkgolide B.	172
Scheme 7.6 Our retrosynthetic analysis of ginkgolide C.	175
Scheme 7.7 Retrosynthetic analysis of ginkgolide C, preparation of intermediate 11 .	176

Scheme 7.8 Rautenstrauch cycloisomerization and cyclopropanation reactions of propargylic esters.	177
Scheme 7.9 Toste Au(I)-catalyzed cyclopentenone synthesis.	178
Scheme 7.10 Mechanism for the Au(I)-catalyzed cyclopentenone synthesis proposed by Toste <i>et al.</i> ¹¹	179
Scheme 7.11 Mechanism of the Au(I)-catalyzed cyclopentenone synthesis evaluated by DFT proposed by de Lera <i>et al.</i>	180
Scheme 7.12 Group precedents on the gold(I)-catalyzed formation of carbon-bridged and fused bicyclic systems.	181
Scheme 7.13 Key sequence of steps of the synthesis of (+)-fawcettimine by Toste <i>et al.</i> ¹⁷	182
Scheme 7.14 Gold(I)-catalyzed 5- <i>exo-dig</i> cyclization step in the synthesis of platencin by Nicolaou <i>et al.</i>	182
Scheme 7.15 Keto-alkynes gold(I)-catalyzed 5- <i>exo-dig</i> and 6- <i>exo-dig</i> cyclizations.	183
Scheme 7.16 Initial attempts to prepare enone 13 .	184
Scheme 7.17 Preparation of 13 by an aldol/dehydration sequence.	184
Scheme 7.18 Optimization of the base for the domino adol/dehydration sequence.	185
Scheme 7.19 Optimization of the stoichiometry, reaction temperature and solvent for the domino aldol/dehydration sequence.	186
Scheme 7.20 Preparation of the Rautenstrauch precursor 21 .	186
Scheme 7.21 Initial attempts to perform the Rautenschtrauch reaction.	188
Scheme 7.22 Model studies on the development of the conjugate addition and the enolate C-alkylation sequence.	189
Scheme 7.23 Proposed sequence to prepare the spiro[4.4]bicyclic core of ginkgolide C with a model system.	190
Scheme 7.24 Hydrosilylation of enone 27 .	191
Scheme 7.25 5- <i>Endo-dig</i> cyclization approach to the spiro[4.4]bicyclic core.	192
Scheme 7.26 Proposed Barton-McCombie approach to the spiro[4.4]nonane core.	193

List of Figures

Figure 1.1 Computed reaction profile of DMBA-H with Pd(OAc) ₂ (values in kcal*mol ⁻¹).	10
Figure 1.2 Selectivity observed with electronically biased substrates.	12
Figure 1.3 Mechanisms evaluated for the intramolecular direct arylation.....	13
Figure 1.4 Comparison between acetate 6M TS and 4M TS with acetate or hydroxide ligand.	17
Figure 1.5 Possible Mechanisms for the C–H bond functionalization evaluated.	19
Figure 1.6 Relative reactivity of the polyfluorinated arenes observed by competitions reactions.....	20
Figure 2.1 Other additives used to promote C–H bond cleavage.....	26
Figure 2.2 Ligand evaluation in intramolecular direct arylation reactions.	28
Figure 2.3 Evaluation of the effect of pivalate on the rate of the direct arylation reaction. (Data collected by Marc Lafrance) ¹⁴	31
Figure 3.1 Hammett plot derived for the palladium-catalyzed C2 arylation of C6-substituted <i>N</i> -methylindoles. ^{2b}	35
Figure 3.2 Comparison of the side-by-side and <i>in-situ</i> KIE experiments.	39
Figure 3.3 HOMO and LUMO electron densities of indolizine.....	48
Figure 3.4 X-ray structure of ethyl 3-acetylindolizine-2-carboxylate.	49
Figure 3.5 Comparison of the NMR spectra of C3 acetylated (top spectrum) and C1 acetylated (bottom spectrum) indolizines.	50
Figure 3.6 X-Ray structure of ethyl 3-(<i>p</i> -nitrobenzoyl)indolizine-2-carboxylate.	51
Figure 3.7 Calculated free energy of activation ($\Delta\Delta G^\ddagger$) for the CMD pathway. The red bonds correspond to the experimental site of arylation. (Values in kcal/mol).....	53
Figure 3.8 Representation of CMD pathway for benzene with activation-strain analysis.	55
Figure 3.9 a Distortion/Interaction analysis for the lowest CMD transition states ($\Delta E^\ddagger$).	57
Figure 3.10 Effect of pivalic acid on the kinetic profile in the Pd-catalyzed direct arylation of heteroarenes. ^{a,b}	61
Figure 3.11 Representative examples of unsuccessful coupling products (The results were estimated by GC-MS or by thin layer chromatography).	69
Figure 3.12 Examples of drugs and drug candidates containing multiple functionalizable	71
Figure 3.13 Relative reactivity of various heteroarenes toward direct arylation. ^{a,b}	80
Figure 4.1 Biologically active compounds containing the diarylmethane motif.....	90
Figure 4.2 Reactions monitored over 6 hours (360 minutes).....	96
Figure 5.1 Initial phosphino-amide ligands tested in direct arylation reactions.....	119

Figure 5.2 Deuterium incorporation (mmol) into benzene- <i>h</i> ₆ catalyzed by WG-1a in <i>d</i> ₄ -AcOD at 120 °C over 2 hours. (Reproduction from Bischof <i>et al.</i>) ¹⁵	130
Figure 5.3 B3LYP/LACV3P+**//LACVP** enthalpy surface for benzene H/D exchange catalyzed by WG-1a in <i>d</i> ₄ -acetic acid (ΔH at 298 K, kcal/mol).....	131
Figure 5.4 Deuterium incorporation (mmol) into benzene- <i>H</i> ₆ catalyzed by WG-1b in <i>d</i> -trifluoroacetic acid at 120 °C over 2 hours. (Reproduction from Bischof <i>et al.</i>) ¹⁵	132
Figure 5.5 B3LYP/LACV3P+**//LACVP** enthalpy surface for benzene H/D exchange catalyzed by WG-1b in trifluoroacetic- <i>d</i> ₁ acid (ΔH at 298 K, kcal/mol).....	132
Figure 5.6 Energy changes by the metal-formate promoted C–H bond cleavage. Energies of the relevant intermediate and transition states for palladium and platinum (shown in parentheses) complexes are given in kcal·mol ⁻¹ (relative to reactants).	133
Figure 5.7 Turnover numbers for H/D exchange between benzene and TFA- <i>d</i> ₁ catalyzed by Pt complexes MS-1 to MS-8	134
Figure 5.8 Structure of the platinum complexes evaluated for reactivity.	135
Figure 5.9 Initial results of the distribution of benzene's isotopologues with catalysts MS-6 , 14 and 15 after approximately 12 hours.....	136
Figure 5.10 Distribution of benzene isotopologues with catalysts MS-6 , 14 , 15 after 90 and 180 minutes.....	137
Figure 5.11 Turnover numbers of catalysts MS-6 , 14 and 15 over 180 minutes.	138
Figure 5.12 Possible mechanisms for complex 14	139
Figure 6.1 Free energy of activation (ΔG _{298K} , kcal mol ⁻¹) for C–H bond functionalization <i>via</i> the CMD pathway with the [Pd(C ₆ H ₅)(PMe ₃)(OAc)] catalyst. Red bonds correspond to the experimentally observed sites of arylation except for arene 4	148
Figure 6.2 Correlation between metal–C(arene), (base ligand)O–H and C–H(arene) bond orders for CMD TS structures for arenes 1–22h with the Pd(C ₆ H ₅)(PMe ₃)(OAc) catalyst (red triangles for Class I arenes, blue squares for Class II arenes and black filled circles for Class III arenes) and with the [Ir(C ₅ H ₅)(PMe ₃)(CO ₃)] catalyst (benzene is the substrate), ³⁴ and for the intramolecular CMD for the [Rh(C ₅ H ₅)(X)(OAc)] and [Ru(C ₆ H ₆)(X)(OAc)] complexes ^{34,35} (open circles).	154
Figure 6.3 Experimentally observed relative reactivity of C2 substituted thiophenes (except 22c , 22f , 22g and 22h). Values in red correspond to the Gibbs free energy of activation (ΔG _{298K} , kcal mol ⁻¹) for the CMD pathway with the [Pd(C ₆ H ₅)(PMe ₃)(OAc)] catalyst. R ₁ = <i>i</i> -Pr was modeled as Me. R ₂ = <i>n</i> -Pr was modeled as Me. See Supporting Information for full experimental and computational details.....	156
Figure 6.4 Activation–strain parameters (kcal mol ⁻¹) for the Pd(II)-catalyzed CMD transition states as a function of σ _p values for C2 substituted thiophenes 22a–h	158

Figure 6.5 Comparison of DFT-calculated CMD activation barriers and barriers estimated from Equations 1–3 for C2 substituted thiophenes.	159
Figure 6.6 Arene distortion energies (black circles) and the C–H bond distortion energies (red circles) for the CMD TS structures with the Pd(C ₆ H ₅)(PMe ₃)(OAc) catalyst as a function of the C–H bond elongation for different arene substrates.	161
Figure 6.7 Arene distortion energies for the CMD TS structures with the [Pd(C ₆ H ₅)(PMe ₃)(OAc)] catalyst as a function of the C-H bond deprotonation energies for substrates 1–22h (Class I arenes are red triangles, Class II arenes are blue squares and Class III arenes are black circles). Linear correlation (red line) for Class I arenes is shown.	162
Figure 7.1 Ginkgolide Family.....	166
Figure 8.1 Label compounds for the competition experiments.	232
Figure 8.2 Results of the competition experiments between C2 substituted thiophenes.	279

List of Tables

Table 1.1 Activation and thermodynamic parameters for the mercuration of benzene and toluene (values in kcal*mol ⁻¹). ¹⁵	8
Table 1.2 Kinetic isotope effects for the mercuration of benzene and toluene. ¹⁵	8
Table 1.3 Predicted product distribution with the different mechanisms (values in kcal*mol ⁻¹).	14
Table 2.1 Effect of the carboxylic acid additives on the intramolecular direct arylation reactions.	29
Table 2.2 Influence of the base on the intramolecular direct arylation reactions.	30
Table 2.3 Substrate scope of the intramolecular direct arylation reaction.....	32
Table 3.1 Relative rate for the acylation and direct arylation of C2 substituted indolizines.	36
Table 3.2 Re-optimization of the direct arylation reaction conditions for the indolizine.	45
Table 3.3 Scope of the direct arylation of heteroarenes. ^a	64
Table 3.4 Effect of (pseudo)halide on the direct arylation of heteroarenes.	68
Table 3.5 Site-selective direct arylation based on mild (hetero)arene specific conditions.	76
Table 3.6 Direct Arylation of Aromatic Heterocycles. ^a	83
Table 4.1 Optimization of the ligand for the direct benzylation reaction.	93
Table 4.2 Effect of the benzylic leaving group on the reactivity.	94
Table 4.3 Effect of the source of palladium and additive on the reactivity.	95
Table 4.4 Direct benzylation of sulfur-containing heterocycles. ^{a,b}	98
Table 4.5 Additional examples of heteroarene benzylation. ^{a,b}	100
Table 4.6 Optimization of the benzylation reaction with benzyl chloride.....	102
Table 4.7 Benzylation of <i>bis</i> -heteroarenes. ^a	103

Table 4.8 Preliminary optimization of the reaction conditions.	110
Table 4.9 Preliminary scope of the domino reaction.	111
Table 4.10 Re-optimization of the reaction conditions.	112
Table 4.11 Scope of the formation of dihydobenzofurans by the 1,2-migratory insertion- intermolecular direct arylation sequence. ^a	114
Table 4.12 Scope of the formation of indolines and oxindoles by the 1,2-migratory insertion- intermolecular direct arylation sequence. ^a	115
Table 5.1 Evaluation of the reactivity of ligands 1–8 toward the direct arylation of pyridine- <i>N</i> -oxide.	121
Table 5.2 Evaluation of the reactivity of ligands 1–8 toward the direct arylation of benzene.....	121
Table 5.3 Evaluation of the reactivity of ligands 1–8 toward the intramolecular direct arylation.	122
Table 5.4 Optimization of the reaction conditions with ligand 4	124
Table 5.5 Evaluation of the reactivity of 12 in the direct arylation of thiazole.	127
Table 6.1 Gibbs free energies and electronic energies of the pre-CMD intermediates for the lowest- energy CMD pathway with the ArH substrates and the [Pd(C ₆ H ₅)(PMe ₃)(OAc)] catalyst, the catalyst and substrate preparation energies, the difference between the preparation energies for CMD transition state structures and pre-CMD intermediate structures, and the metal-arene interaction energies (kcal mol ⁻¹).	151
Table 6.2 Distortion/interaction analysis (kcal mol ⁻¹) for C2 substituted thiophenes 22a–h for CMD TS structures with the [Pd(C ₆ H ₅)(PMe ₃)(OAc)] catalyst.	157
Table 6.3 Activation barriers (kcal mol ⁻¹) for C2 substituted thiophenes 22a–h calculated using the linear correlations with σ_p parameters (Figure 4).	159
Table 8.1 Data of the evaluation of the effect of pivalic acid on the rate of arylation of indolizine (Figure 3.10)	215
Table 8.2 Data of the evaluation of pivalic acid on the rate of direct benzylation of thiazole. (Figure 4.2).....	245
Table 8.3 Gibbs free energies and electronic energies of the CMD transition states for the ArH substrates with the Pd(C ₆ H ₅)(PMe ₃)(OAc) catalyst, the catalyst and substrate preparation energies and the catalyst-substrate interaction energies (kcal mol ⁻¹). (Data collected by Serge Gorelsky).....	270
Table 8.4 The C-H bond orders for free (hetero)arenes with the “reactive” C–H bonds (bold C–H bonds in Figure 1) at their bond lengths in the lowest-energy CMD TS structures. (Data collected by Serge Gorelsky)	279

List of Abbreviations

Ac	acetyl
aq.	aqueous
Ar	aryl
Atm	atmosphere
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
Bz	Benzoyl
Cy	cyclohexyl
CsPiv	cesium pivalate
dba	dibenzylideneacetone
DCM	dichloromethane
DIPEA	di- <i>iso</i> -propylethylamine
DMA	<i>N,N</i> -dimethylacetamide
DMAP	4-(dimethylamino)pyridine
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethyl sulfoxide
Dppf	1,1'-Bis(diphenylphosphine)ferrocene
ee	enantiomeric excess
equiv.	equivlents
Et	ethyl
Et ₂ O	diethyl ether
EtOAc	ethyl acetate
GC-MS	gas chromatography-mass spectrometry
HMPA	hexmethylphosphoramide
HRMS	high resolution mass spectrometry
ⁱ Mes	1,3-dimesitylimidazol-2-ylidene
ⁱ Pr	<i>iso</i> -propyl
ⁱ PrOAc	<i>iso</i> -propylacetate
IR	infrared

KIE	kinetic isotope effect
KOPiv	potassium pivalate
L	ligand
M	generic metal
Me	methyl
Mp	melting point
Ms	mesyl
NMR	nuclear magnetic resonance
NMP	<i>N</i> -methylpyrrolidinone
Ph	Phenyl
Piv	pivalate
py	pyridine
R	generic alkyl group
rt	room temperature
T°	temperature
TBAF	tetrabutylammonium fluoride
^t Bu	<i>tert</i> -butyl
TBS	<i>tert</i> -butyldimethylsilyl
Tf	triflate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
Ts	tosyl
X	generic halide

Abstract

The field of metal-catalyzed C–H bond functionalizations is an incredibly vibrant and spans beyond the formations of biaryl motifs. The introduction chapter will cover the mechanistic aspects of the C–H bond functionalization with metal-carboxylate complexes. The mechanistic facets of this reaction will be the main conducting line between the different sections and chapters of the first part of this thesis. In the second chapter, will be described additives that can readily promoted C–H bond arylation of poorly reactive substrates. More specifically, we will revisit the intramolecular direct arylation reaction we will demonstrate the effect of pivalic acid as a co-catalyst by developing milder reaction conditions. In the third chapter we be described experimental and computational studies which suggested that the a single pathway might be involved in the palladium-catalyzed C–H bond functionalization of a wide range of (hetero)arene. Following this we will describe a general set of conditions for the direct arylation of wide range of heteroarenes. Also, we will present two different strategies to selectively and predictably arylate substrates containing multiple functionalizable C–H bonds. In the fourth chapter will be presented our efforts toward the development of new C–H bond functionalization methods in which we could apply our knowledge on the C–H bond cleavage and apply it to the formation of new scaffolds. The development of two new palladium-catalyzed methods were also described. In the fifth chapter, our effort toward the development of ligands to specifically promoted C–H bond cleavage will be presented. In the sixth chapter will be presented the latest results on the study of the mechanism of the C–H bond cleavage combining experimental and computational studies. In part B of this thesis will be presented our strategy toward the total synthesis of ginkgolide C that included two gold(I)-catalyzed reactions as key steps in the preparation of the spiro[4.4]nonane core of this natural product. The first studies on the feasibility of the key steps of the synthesis will be described.

Remerciements

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Chapter

1

Introduction and Overview of the Mechanistic Work on the Concerted Metallation-Deprotonation Pathway

1.1 Introduction

The field of synthetic chemistry has evolved dramatically over the past decades, current synthetic methods offer a vast array of reagents and strategies for the preparation of almost any natural and unnatural products. In the recent years, research on metal-catalyzed transformations has been at the forefront of methodology development. For instance, in the pharmaceutical industry a survey comparing the reactions employed between 1985–1996 and 1997–2002 revealed an important increase of the proportion of metal-catalyzed transformations employed.¹ Palladium-catalyzed reactions have become prevalent in the recent years especially for the formation of C–C and C–N bonds.^{1,2}

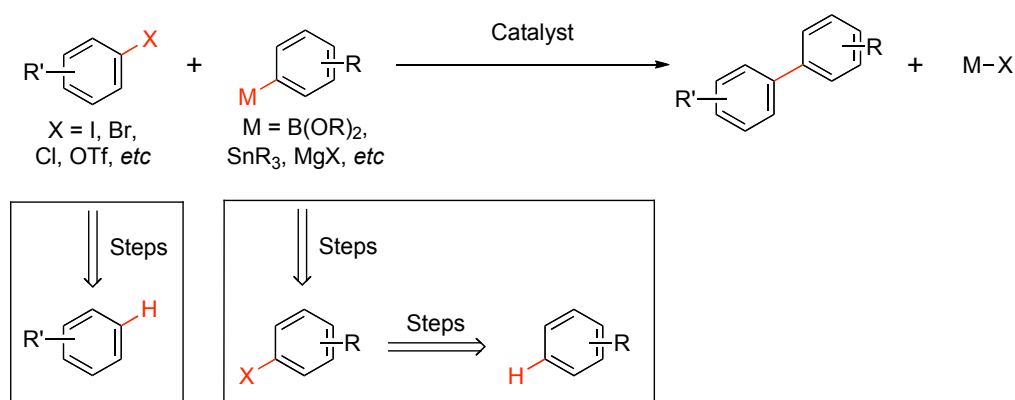
Within the palladium-catalyzed C–C bond formation reactions, the preparation of biaryl motifs through cross-coupling constitutes an important portion of the reaction employed. In the traditional cross-coupling reactions, one of the partners is a pre-

1 Dugger, R. W.; Ragan, J. A.; Brown Ripin, D. H. *Org. Proc. Res. Dev.* **2005**, 9, 253.

2 Carey, J. S.; Laffran, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, 4, 2337.

activated organometallic species and the other coupling partner is an aryl halide or pseudo-halide (Scheme 1.1). While these reactions are highly reliable and commonly employed, it is important to recognize that the activating functional groups of both coupling partners have to be installed prior to the coupling reaction. This can involve several steps, diminish the overall efficiency of the synthesis plan and ultimately lead to formation of extra waste in addition to the one generated in the coupling reaction itself by the activating groups.

Scheme 1.1 General representation of traditional cross-coupling reactions.



The direct functionalization of C–H bond became in the recent years an increasingly practical alternative to traditional cross-coupling reactions. This approach consists of replacing one or both pre-activating group(s) by a simple C–H bond. This limits the number of pre-activation steps, increases the overall efficiency of the C–C bond formation process and avoids the formation of potentially hazardous organometallic wastes. After the publication of seminal articles on the intramolecular direct arylation of aryl derivatives by Echavarren³ and the intermolecular direct arylation of azoles by Miura,⁴ the number of reports on direct arylation increased exponentially in the subsequent years.⁵ Unsurprisingly, the metal-catalyzed C–H bond functionalizations is

3 González, J. J.; García, N.; Gómez-Lor, B.; Echavarren, A. M. *J. Org. Chem.* **1997**, 62, 1286.

4 Pivsa-Art, S.; Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, 71, 467.

5 Selected reviews on direct arylation: a) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, 34, 633. b) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, 102, 1731. c) Daugulis, O.; Zaitsev, V. G.; Shabashov, D.; Pham, Q.-N.; Lazareva, A. *Synlett* **2006**, 3382. d) Alberico, D.; Scott, M. E.; Lautens,

incredibly vibrant field and it spans way beyond the formations of biaryl motifs field.^{6,7} The introduction chapter will cover the mechanistic aspects of the C–H bond functionalization. As it will develop throughout the following chapters, the mechanistic facets will be the main conducting line between the different sections and chapters of the first part of this thesis.

1.2 Overview of the Mechanistic Work on the Concerted-Metallation-Deprotonation Pathway

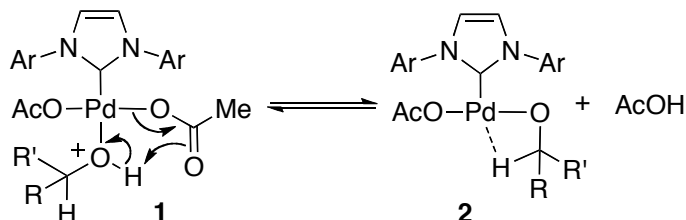
The direct functionalization of C–H bonds with transition-metal complexes has emerged in the past years as an economical and efficient alternative to the use of traditional activating-groups for the functionalization of (hetero)arenes.^{5,6,7} Many mechanisms have been studied or proposed for the cleavage of C–H bonds such as oxidative addition and sigma-bond metathesis,⁸ however this section will be focusing on

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- M. *Chem. Rev.* **2007**, *107*, 174. e) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. f) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200. g) Campeau, L.-C.; Stuart, D. R.; Fagnou, K. *Aldrichim. Acta* **2007**, *40*, 35. h) Campeau, L.-C.; Fagnou, K. *Chem. Soc. Rev.* **2007**, *36*, 1058. i) Li, B.-J.; Yang, S.-D.; Shi, Z.-J. *Synlett* **2008**, 949. j) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, 3013. k) McGlacken, G. P.; Bateman, L. M. *Chem. Soc. Rev.* **2009**, *38*, 2447. l) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. m) Kulkarni, A. A.; Daugulis, O. *Synthesis* **2009**, *24*, 4087. n) Bellina, F.; Rossi, R. *Tetrahedron* **2009**, *65*, 10269. o) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792. p) Roger, J.; Gottumukkala, A. L.; Doucet, H. *ChemCatChem* **2010**, *2*, 20.
- 6 Selected reviews on C–H bond functionalization from 2009–2011: a) Hartwig, J. F. *Chem. Soc. Rev.* **2011**, *40*, 1992. b) Gutekunst, W. R.; Baran, P. S. *Chem. Soc. Rev.* **2011**, *40*, 1976. c) McMurray, L.; O'Hara, F.; Gaunt, M. J. *Chem. Soc. Rev.* **2011**, *40*, 1885. d) Mkhaliid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890. e) Willis, M. C. *Chem. Rev.* **2010**, *110*, 725. f) Ackermann, L.; Potukuchi, H. K. *Org., Biomol. Chem.* **2010**, *8*, 4503. g) Daugulis, O. *Top. Curr. Chem* **2010**, *292*, 57. h) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Commun.* **2010**, *46*, 677. i) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. j) Fagnou, K. *Top. Curr. Chem.* **2010**, *292*, 35. k) Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem.; Eur. J.* **2010**, *16*, 2654. l) Lei, A.; Liu, W.; Liu, C.; Chen, M. *Dalton Trans.* **2010**, *39*, 10352. m) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. n) Dudnik, A. S.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2010**, *49*, 2096. o) Giri, R.; Shi, B.-F.; Engle, K. M.; Mangel, N.; Yu, J.-Q. *Chem. Soc. Rev.* **2009**, *38*, 3242. p) Thansandote, P.; Lautens, M. *Chem.; Eur. J.* **2009**, *15*, 5874. q) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074.
- 7 a) *Handbook of C–H Transformation*, ed. by G. Dyker, Wiley-Interscience, New York, **2005**. b) *Topics in Current Chemistry: C–H Activation*, ed. by J.-Q. Yu, Z. Shi, Springer, Berlin, **2010**, Vol. 292.
- 8 For other reviews on the mechanistic studies of transition-metal catalyzed C–H bond functionalization, see: a) Lin, Z. Y. *Coord. Chem. Rev.* **2007**, *251*, 2280. b) Boutadla, Y.; Davies, D. L.; Macgregor, S. A.;

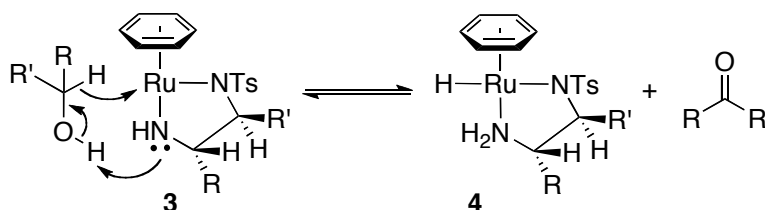
some authors have used other names such as internal electrophilic substitution (IES)¹² and ambiphilic metal-ligand activation (AMLA).^{8b,13}

Scheme 1.3 Examples of internal deprotonation reactions.

(a) Sigman Pd-cat. oxidation of alcohols



(b) Noyori Hydrogen transfer reaction



1.2.2 Early evidence of the concerted metallation-deprotonation pathway

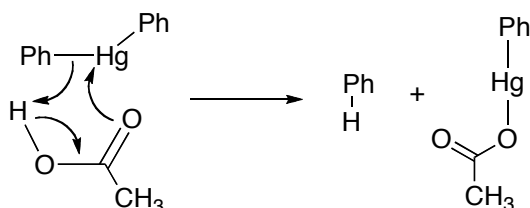
To the best of our knowledge, the earliest proposal of a CMD transition state was made by Winstein and Traylor in 1955 for the acetolysis of diphenylmercury in acetic acid (Scheme 1.4).¹⁴

12 Oxgaard, J.; Tenn III, W. J.; Nielsen, R. J.; Periana, R. A.; Goddard III, W. A. *Organometallics* **2007**, 26, 1565.

13 Boutadla, Y.; Davies, D. L.; Macgregor, S. A.; Poblador-Bahamonde, A. I. *Dalton Trans.* **2009**, 5887.

14 Winstein, S.; Traylor, T. G. *J. Am. Chem. Soc.* **1955**, 77, 3747.

Scheme 1.4 Representation of the mechanism proposed in 1955 for the acetolysis of diphenylmercury(II).



Interestingly, before Roberts and coworkers published an elegant mechanistic study on the subject,¹⁵ there were no in-depth kinetic studies performed on the mechanism of the mercuration of simple arenes (eq. 1). Earlier mechanistic proposals suggested an electrophilic aromatic substitution (S_EAr) mechanism based on the electrophilic character of mercury.¹⁶ The rate law derived from these kinetic analyses of the mercuration of benzene (eq. 2) showed that the arene and the electrophilic mercuric salt combined rapidly and reversibly to form an intermediate, followed by an irreversible proton transfer yielding the final product (eq. 1). Based on large observed primary kinetic isotope effects (ca. 6.0-7.0), the proton transfer step was determined to be rate limiting.¹⁷



$$k_{\text{obs}} = \frac{k_2 K_1 [\text{ArH}]}{1 + K_1 [\text{ArH}]} \quad (2)$$

The structure of the intermediate was initially presumed to be a σ complex, however in 1976, Olah and coworkers studied the nature of this intermediate by NMR spectroscopy.¹⁸ In this study, they compared the ^1H and ^{13}C chemical shifts and the $J_{\text{C-H}}$ of benzenium ions with the Hg(II) -arene intermediate (Scheme 1.5). The $J_{\text{C-H}}$ and the ^1H shifts of these intermediates indicated that all the carbons remained sp^2 hybridized and the chemical environment of the hydrogens were not too affected. The changes in the ^{13}C

15 Fung, C. W.; Khorramdel-Vahed, M.; Ranson, R. J.; Roberts, R. M. G. *J. C. S. Perkin II* **1980**, 267.

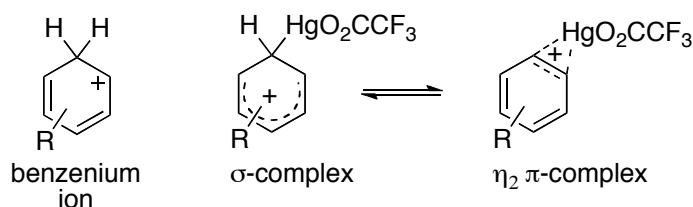
16 H.; Naylor, M. A. *J. Am. Chem. Soc.* **1947**, 69, 1004. b) Klapproth, W. L.; Westheimer, F. H. *J. Am. Chem. Soc.* **1950**, 72, 4461. c) Brown, H. C.; McGary Jr., C. L. *J. Am. Chem. Soc.* **1955**, 77, 2300. d) Brown, H. C.; McGary Jr., C. L. *J. Am. Chem. Soc.* **1955**, 77, 2306. e) Brown, H. C.; McGary Jr., C. L. *J. Am. Chem. Soc.* **1955**, 77, 2310. f) Brown, H. C.; Nelson, K. L. *J. Am. Chem. Soc.* **1955**, 75, 6292.

17 Kresge, A. J.; Brennan, J. F. *J. Org. Chem.* **1967**, 32, 752.

18 Olah, G. A.; Yu, S. H.; Parker, D. G. *J. Org. Chem.* **1976**, 41, 1983.

chemical shift of only certain carbons in the Hg(II)-arene intermediate suggested that the Hg(II) was interacting with the arene at a single carbon. Olah's conclusions were that the intermediate species formed was a weakly bonded complex, which he proposed to be rapidly exchanging between σ -complex and $\eta_2 \pi$ -complex.

Scheme 1.5 Benzenium ion and Olah's description of the arene mercurium ion intermediate complexes.



Roberts and coworkers were able to examine individually the two steps of the process by isolating the equilibrium constant (K_1) and the rate constant (k_2) values from the observed rates (k_{obs}). To do so, they rewrote the rate equation (eq. 2) as a linear regression equation (eq. 3).¹⁵

$$\frac{1}{k_{\text{obs}}} = \frac{1}{k_2} \cdot \frac{1}{K_1[\text{ArH}]} + \frac{1}{k_2} \quad (3)$$

Without going into the all detailed of Roberts *et al.* studies, Table 1.1 and Table 1.2 summarize the outcome of their analyses.¹⁵ They showed that the intermediate was indeed a π -complex rather than a σ -complex, based on the experimental free energy of formation. In the second step of the reaction (k_2 , eq. 1), the discrete KIEs of the reaction indicated that the C–H bond was cleaved at that step. The negative $\Delta S^\ddagger$ for the second step corresponded to a very organized transition state while the reaction exhibited no rate enhancement upon the addition of base, suggesting that an intramolecular proton transfer was occurring. This data was consistent with a simultaneous C–H bond cleavage and a C–Hg bond formation mechanism proposed by Winstein and Traylor in 1955, Roberts, although, could not completely rule out the $S_E\text{Ar}$ mechanism.

Table 1.1 Activation and thermodynamic parameters for the mercuration of benzene and toluene (values in kcal* mol^{-1}).¹⁵

Arene (ArH)	$\Delta H^\ddagger_{\text{obs}}$	$\Delta H^\ddagger(k_2)$	$\Delta H^\ddagger(K_1)$	$\Delta S^\ddagger_{\text{obs}}$	$\Delta S^\ddagger(k_2)$	$\Delta S^\ddagger(K_1)$
Benzene	13.5 $\pm$ 0.9	15.2 $\pm$ 0.9	-1.7	-20.3 $\pm$ 3.0	-19.1 $\pm$ 2.9	-1.2
Toluene	8.4 $\pm$ 0.9	10.5 $\pm$ 0.9	-2.1	-31.8 $\pm$ 1.9	-28.0 $\pm$ 1.4	-3.8

Table 1.2 Kinetic isotope effects for the mercuration of benzene and toluene.¹⁵

Arene (ArH)	$(k_{\text{H}}/k_{\text{D}})_{\text{obs}}$	$(k_{\text{H}}/k_{\text{D}})(k_2)$	$(K_{\text{H}}/K_{\text{D}})(K_1)$
Benzene	5.6	3.7	1.5
Toluene	7.0	7.5	0.93

1.2.3 Directed metallation of arenes

In the seminal publication on palladium-catalyzed formation of biphenyl in 1968, Davidson and Triggs recognized the strong resemblance that existed between the palladation and mercuration of benzene.¹⁹ The first types of palladation reactions that were studied in detail were cyclometallation reactions, mainly using nitrogen-based ligands to direct the reaction.²⁰ The initial mechanistic studies were performed soon after their discovery in the 1960's.²¹ These studies established that the choice of palladium source was crucial for reactivity. It was found that palladium(II) acetate was generally the best source of palladium, since the acetato ligand is believed to play multiple roles in cyclometallation reactions.²² It facilitates the solvolysis of the reaction intermediates due to its larger effective volume compared to chloride. It also enhances the electrophilicity of the palladium(II) center due to the reversible ability of acetate to act as a bidentate or monodentate ligand, and potentially act as an intramolecular base for deprotonation.^{22c}

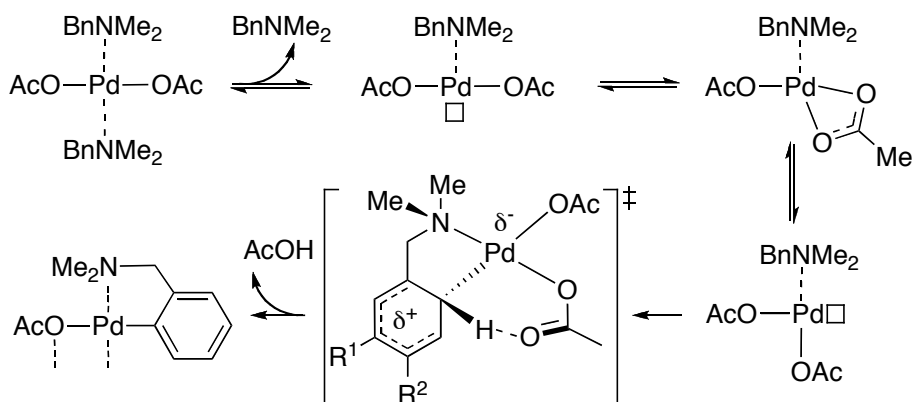
19 Davidson, J. M.; Triggs, C. *J. Chem. Soc. A* **1968**, 1324.

20 For recent reviews on catalytic directed C–H bonds functionalization, see ref 5l and 6m.

21 a) Kleiman, J.; Dubeck, M. *J. Am. Chem. Soc.* **1963**, 85, 1544. b) Cope, A. C.; Siekman, R. W. *J. Am. Chem. Soc.* **1965**, 87, 3272. c) Cope, A. C.; Friedrich, E. C. *J. Am. Chem. Soc.* **1968**, 90, 909.

22 For reviews, see: a) Bruce, M. I. *Angew. Chem. Int. Ed. Engl.* **1977**, 16, 73. b) Ryabov, A. D. *Chem. Rev.* **1990**, 90, 403. c) Vicente, J.; Saura-Llamas, I. *Inorg. Chem.* **2007**, 28, 39.

Scheme 1.6 Mechanism of cyclometallation of DMBA-H with palladium.



One of the first detailed mechanistic studies on the reactivity of palladium towards C–H bonds was made by Ryabov and coworkers on the *ortho*-palladation of *N,N*-dimethylbenzylamine (DMBA-H).²³ An analysis of the reaction kinetics and the observation of certain reaction intermediates by NMR allowed for the establishment of the reaction profile (Scheme 1.6). The negative slope of the Hammett plot ($\rho = -1.6$) indicated that the palladium(II) had an electrophilic character. The kinetic isotope effect (k_H/k_D) of 2.2 and the negative calculated entropy of activation ($\Delta S^\ddagger = -60 \text{ cal}^\circ\text{K}^{-1}\cdot\text{mol}^{-1}$) of $\text{Pd}(\text{OAc})_2[\text{DMBA-H}]$ were suggestive of a highly ordered and compact transition state in which the leaving proton is abstracted intramolecularly by acetate ligand (Scheme 1.6).

Arguably, the way Ryabov depicted the transition state in Scheme 1.6 can be interpreted as the deprotonation of a Wheland intermediate although there is no mention in the paper of the formation of such an intermediate. Nonetheless, in a later mechanistic study on the cyclopalladation of primary benzylamines, Ryabov stated that “*the transition state of the [orthopalladation of *N,N*-dimethylbenzylamine] process involved concerted formation of the palladium-carbon and cleavage of the C–H bond with a nucleophilic assistance by the coordinated acetate.*”²⁴ While this statement does not elude to the formation of a charged intermediate, Ryabov’s proposed transition state likely took into account the development of a small positive character at the transition state, as suggested

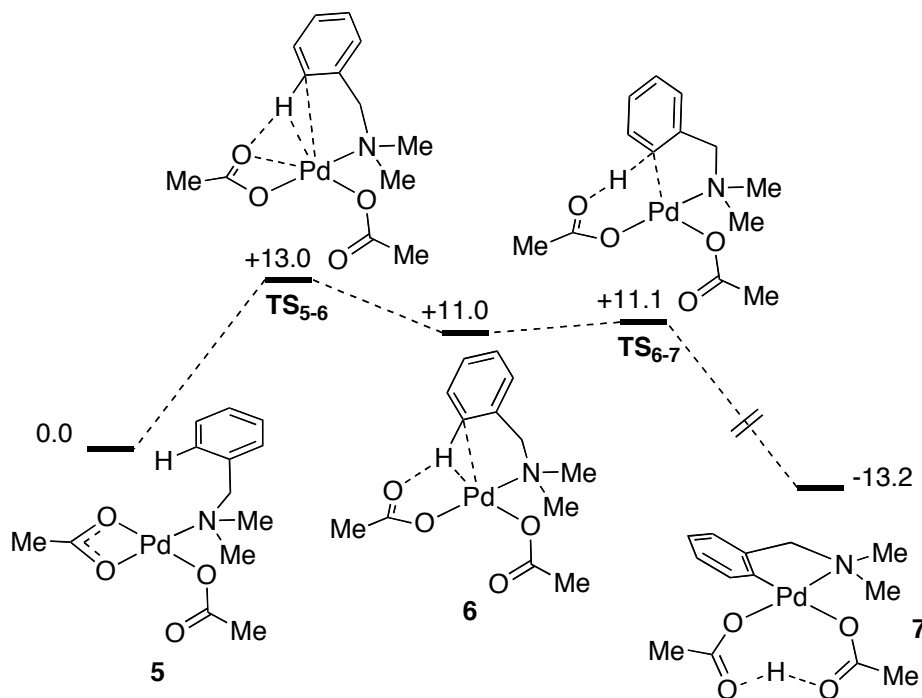
23 Ryabov, A. D.; Sakodinskaya, I. K.; Yatsimirsky, A. K. *J. Chem. Soc., Dalton Trans.* **1985**, 2629.

24 Kurzev, S. A.; Kazankov, G. M.; Ryabov, A. D. *Inorg. Chim. Acta* **2002**, 340, 192.

by the negative slope of the reaction's Hammett plot. It is important to note that the majority of subsequent publications referred this work as the seminal demonstration of a S_EAr palladation mechanism, but in our opinion careful analysis of the work proves otherwise.

More recently, a computational study on the mechanism of a *N,N*-dimethylbenzylamine system was reported by Davies, Donald and Macgregor.²⁵ The results showed that the most accessible route proceeds *via* an agostic C–H interaction (**6**, Figure 1.1) followed by an acetate-assisted deprotonation *via* a six-membered cyclic transition state. The agostic interaction polarizes the C–H bond which results in an enhancement of the acidity of the *ortho* proton and it can then be readily deprotonated by the acetate base.²⁶

Figure 1.1 Computed reaction profile of DMBA-H with $Pd(OAc)_2$ (values in $kcal \cdot mol^{-1}$).



25 Davies, D. L.; Donald, S. M. A.; Macgregor, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 13754.

26 Vigalok, A.; Uzan, O.; Shimon, L. J. W.; Ben-David, Y.; Martin, J. M. L.; Milstein, D. *J. Am. Chem. Soc.* **1998**, *120*, 12539.

Hydrogen bonding between the acetate oxygen and arene's proton orients the base for the C–H bond cleaving step and also increases the electron density of the C–H bond which in turn further favors the agostic interaction.²⁷ The combination of these effects leads to a nearly barrier-less proton transfer ($\Delta E = +0.1 \text{ kcal}\cdot\text{mol}^{-1}$) to yield the thermodynamically favorable palladacycle **7** (Figure 1.1). The calculated atomic charges for the species **5** to **7** showed very little if any evidence for the contribution of a Wheland intermediate. Also, the calculated KIE ($k_H/k_D=1.2$) obtained with this mechanism does not contradict the experimental value found by Ryabov ($k_H/k_D= 2.2$).²³ In addition to palladium-acetate promoted cyclometallation, Davies showed that other transition-metals, such as $[\text{RuCl}_2(p\text{-cymene})]_2$, $[\text{RhCl}_2\text{Cp}^*]_2$ and $[\text{IrCl}_2\text{Cp}^*]_2$, in combination with an acetate base reacted to form cyclometallated products by the same mechanism when reacted with *N,N*-dimethylbenzylamine.^{13,28}

The mechanistic work of Roberts on the mercuration of benzene and Ryabov's work on the cyclometallation of benzylamine constitute the early examples of the CMD mechanism using a stoichiometric amount of metal. In the following sections, the focus of the discussion will be directed toward catalytic transformations.

1.2.4 Directed catalytic functionalization of arenes

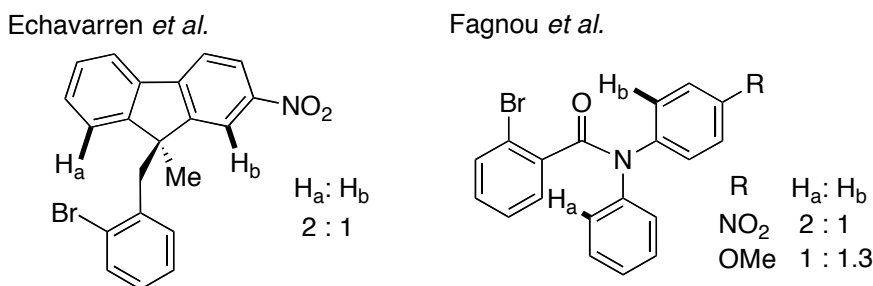
In recent years, the metal-catalyzed functionalization of unactivated arenes has become an increasingly viable alternative to classical cross-coupling reactions.^{5,6,7} Electron-rich heteroarenes were the first systems to be studied in the context of catalytic transformations (*vide infra*). The first experimental mechanistic study on the catalytic direct functionalization of simple arenes were mainly carried out by the group of

27 Vicente, J.; Saura-Llamas, I.; Palin, M. G. *Organometallics* **1997**, *16*, 826.

28 a) Davies, D. L.; Al-Duaij, O.; Fawcett, J.; Giardiello, M.; Hilton, S. T.; Russell, D. R. *Dalton Trans.* **2003**, 4132. b) Davies, D. L.; Donald, S. M. A.; Al-Duaij, O.; Macgregor, S. A.; Pölleth, M. *J. Am. Chem. Soc.* **2006**, *128*, 4210. c) Davies, D. L.; Donald, S. M. A.; Al-Duaij, O.; Fawcett, J.; Little, C.; Macgregor, S. A. *Organometallics* **2006**, *25*, 5976.

Echavarren^{3,29} and our group³⁰ in the studies on the intramolecular formation of biaryl bonds.

Figure 1.2 Selectivity observed with electronically biased substrates.

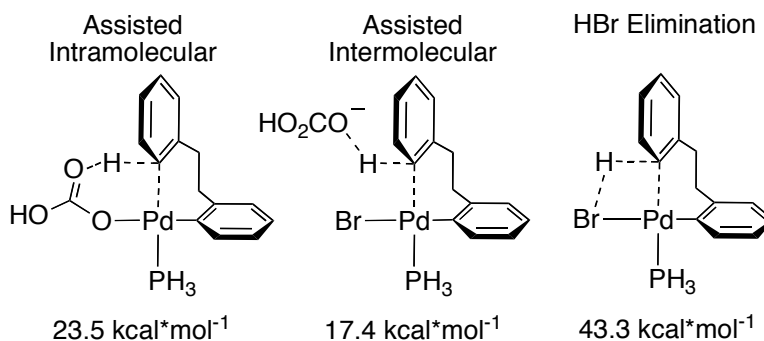


During the optimization of the intramolecular direct arylation conditions, it was observed that the reaction was highly dependent on the nature of the base. Typically, carboxylate bases showed good reactivity whereas amines and hydroxide bases led mainly to dehalogenation.^{3,29,30} The groups of Echavarren and Fagnou showed that intramolecular C–H bond functionalization is not significantly influenced by the electronic nature of the arene, which is uncharacteristic of an S_EAr pathway (Figure 1.2). Large kinetic isotope effects (3.5 to 6.7) were obtained from intramolecular competitions indicated that the C–H bond cleavage step is kinetically significant, which is in support of the CMD mechanism.^{29,30a,30d}

29 García-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 1066.

30 a) Campeau, L.-C.; Parisien, M.; Leblanc, M.; Fagnou, K. *J. Am. Chem. Soc.* **2004**, *126*, 9186. b) Lafrance, M.; Blaqui re, N.; Fagnou, K. *Chem. Commun.* **2004**, 2874. c) Parisien, M.; Valette, D.; Fagnou, K. *J. Org. Chem.* **2005**, *70*, 7578. d) Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581.

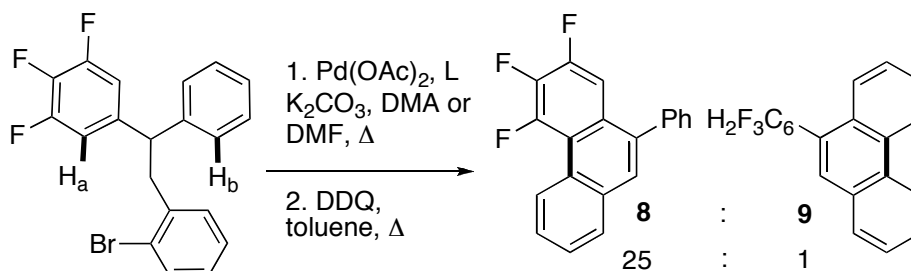
Figure 1.3 Mechanisms evaluated for the intramolecular direct arylation.



Maseras, Echavarren and coworkers evaluated by DFT three possible proton abstraction mechanisms, two of which are intra- and intermolecularly carbonate-assisted and the other being an unassisted HBr elimination (Figure 1.3).³¹ Computationally, the intermolecular assisted pathway was favored over the intramolecular base assistance by 6.1 kcal*mol⁻¹, while the HBr elimination pathway was far less accessible.

The calculated ratio of product distribution (**8:9**) for both the intra- and intermolecular processes were in favor of the trifluorinated arene which is in agreement with the observed experimental results (Scheme 1.7). The computed product distribution with the intermolecular pathway more closely reflected what was observed experimentally, suggesting that this was the most likely pathway of the two (Table 1.3).³¹

Scheme 1.7 Selectivity observed with a trifluorinated diphenyl and a simple phenyl group.



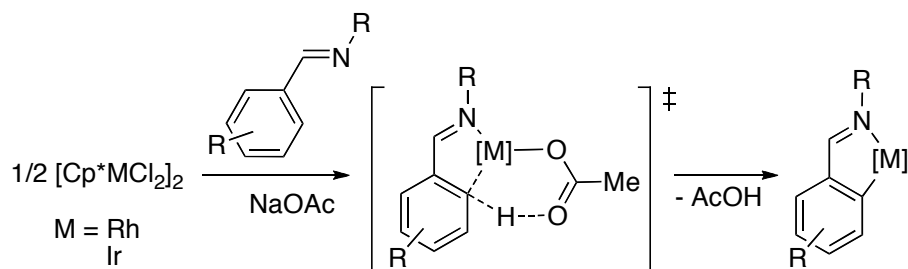
31 García-Cuadrado, D.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2007**, *129*, 6880.

Table 1.3 Predicted product distribution with the different mechanisms (values in kcal*mol⁻¹).

	$\Delta E_a(H_a)$	$\Delta E_a(H_b)$	$\Delta\Delta E_a(H_a)$	Theoretical ratio 8:9
Assisted Intramolecular	23.5	13.2	10.3	$7 \times 10^5:1$
Assisted Intermolecular	17.4	14.4	3.0	40:1
HBr Elimination	43.3	34.5	8.8	–

To further support the proposed intermolecular carbonate assisted mechanism, Maseras, Echavarren and coworkers used bidentate ligands, such as dppe, dppe, dppf and Xantphos, in the development of a new set of conditions for the palladium-catalyzed intramolecular direct arylation of aryl bromides.³² Since it is unlikely that a carbonate could displace a bidentate phosphine ligand on the palladium, the intermolecular carbonated-assisted pathway is more likely to occur.³³

Scheme 1.8 Reaction pathway for the functionalization of phenyl imines.



Jones and coworkers studied the mechanism of functionalization of phenyl imines with [Cp*RhCl₂]₂ or [Cp*IrCl₂]₂ with NaOAc (Scheme 1.8).³⁴ The conclusion of these studies were in agreement with those of Ryabov (*vide supra*), the proton was most likely abstracted by the acetate present on the metal while a metal-carbon bond was formed.

32 Pascual, S.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *Tetrahedron* **2008**, 64, 6021.

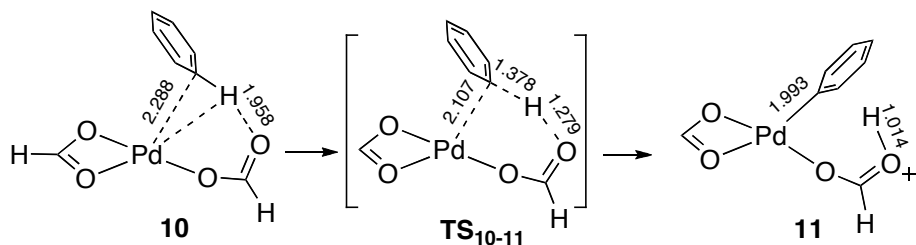
33 An analogue pathway was also proposed in a similar coordinately-saturated Pd complex, see: Young, K. J. H.; Meier, S. K.; Gonzales, J. M. J.; Oxgaard, J.; Goddard III, W. A.; Periana, R. A. *Organometallics* **2006**, 25, 4734.

34 Li, L.; Brennessel, W. W.; Jones, W. D. *Organometallics* **2009**, 28, 3492.

1.2.5 Intermolecular C–H bond metallation

In 2000, Sakaki and coworkers reported the DFT investigation of the intermolecular C–H bond metallation of benzene by $\text{Pd}(\kappa_2\text{-O}_2\text{CH})_2$ to form a σ -phenylpalladium(II) formate complex and brought clarification to the overall process and its transition state (Scheme 1.9).³⁵ From previous mechanistic studies, it is known that palladium(II) acetate, when reacting with simple arenes, exhibits an electrophilic character as shown by the negative slope of the Hammett plot ($\rho^+(\sigma^+) = -1.4$ to -0.4).³⁶ This metallation reaction also exhibited large primary kinetic isotope effects ($k_{\text{H}}/k_{\text{D}} = 4.5\text{--}5.1$).³⁶ Kinetics studies on the oxidative homo-coupling of benzene catalyzed by $\text{PdCl}_2\text{-NaOAc}$ in acetic acid revealed that the reaction rate was independent of acetate base, although the presence of carboxylate was essential to the reactivity of the system.³⁷ This suggests that the proton was abstracted by the acetate on the palladium and not by an external base.

Scheme 1.9 Geometry changes in the palladium(II)-formate promoted C–H bond functionalization.



In Sakaki's computational studies, the energetic profile for the palladium(II)-formate promoted C–H bond metallation was consistent with experimental precedent.³⁶ Starting from the dissociated metal complex and benzene, the initial steps of the process led to the formation of a thermodynamically favorable $\kappa_1 \pi$ -complex (**10**). The C–H bond that interacts with the metal has an out-of-plane angle of 12° , which based on precedent

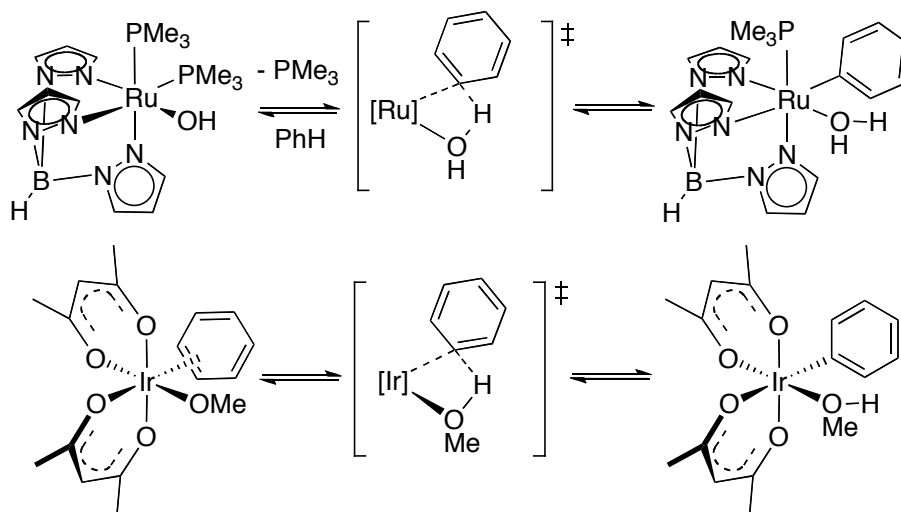
35 Biswas, B.; Sugimoto, M.; Sakaki, S. *Organometallics* **2000**, *19*, 3895.

36 Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879.

37 Yokota, T.; Sakaguchi, S.; Ishii, Y. *Adv. Synth. Catal.* **2002**, *344*, 849.

was proven to be a $\kappa_1 \pi$ -complex instead of the commonly proposed σ -complex.²⁶ From this intermediate, the proton can be abstracted from the arene by the distal oxygen on the formate in a six-membered cyclic transition state (**TS**₁₀₋₁₁, Scheme 1.9). Sakaki and coworkers also investigated the metallation of benzene using platinum(II) formate and obtained results which indicated that the platinum-benzene π -complex was even more stable than its palladium analogue. Consequently, the subsequent deprotonation step became less accessible, which is reflected by the greater reactivity of palladium over platinum.³⁵

Scheme 1.10 [RuTp(OH)] and [Ir(acac)₂(OMe)] promoted metallation of benzene.



The metallation of benzene has also been reported by the groups of Gunnoe³⁸ and Periana³⁹ using [Ru-OH] and [Ir-OMe] complexes respectively (Scheme 1.10). Both experimental and theoretical mechanistic studies on these systems have shown that the metal bonds to the carbon as the proton is abstracted by the basic ligand on the metal.^{12,40} Since no carboxylate bases were used in these systems, four-membered rings metallation-

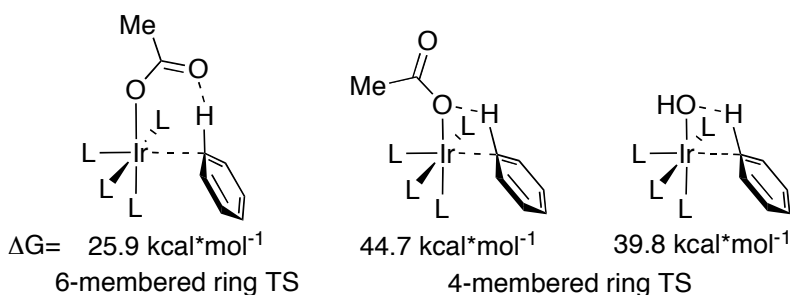
38 Feng, Y.; Lail, M.; Barakat, K. A.; Cundari, T. R.; Gunnoe, T. B.; Peterson, J. L. *J. Am. Chem. Soc.* **2005**, 127, 14174.

39 Tenn III, W. J.; Young, K. J. H.; Bhalla, G.; Oxgaard, J.; Goddard III, W. A.; Periana, R. A. *J. Am. Chem. Soc.* **2005**, 127, 14172.

40 a) Feng, Y.; Lail, M.; Foley, N. A.; Gunnoe, T. B.; Barakat, K. A.; Cundari, T. R.; Peterson, J. L. *J. Am. Chem. Soc.* **2006**, 128, 7982. b) Tenn III, W. J.; Young, K. J. H.; Oxgaard, J.; Nielsen, R. J.; Goddard III, W. A.; Periana, R. A. *Organometallics* **2006**, 25, 5173.

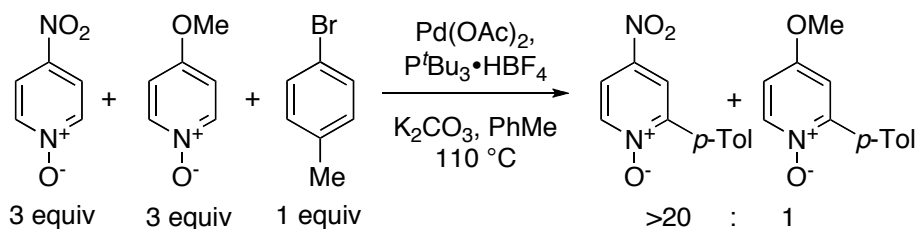
deprotonation transition states were proposed instead of the six-membered ring. When compared computationally, the six-membered ring transition state using iridium proved to be more easily accessible than the four-membered ring transition state with either a hydroxide ligand or the acetate (Figure 1.4).⁴¹ Recently, Larrosa and coworkers showed that gold(I) combined with base could metallate arene rings, with primarily results suggesting a CMD mechanism.⁴²

Figure 1.4 Comparison between acetate 6M TS and 4M TS with acetate or hydroxide ligand.



1.2.6 Catalytic Functionalization of Electron Deficient Arenes

Scheme 1.11 Selectivity observed with electronically biased pyridines *N*-oxides.



In 2005, our group developed a palladium-catalyzed regioselective direct arylation of pyridine, diazine and azole *N*-oxides with aryl-halides.⁴³ Experimentally, competition

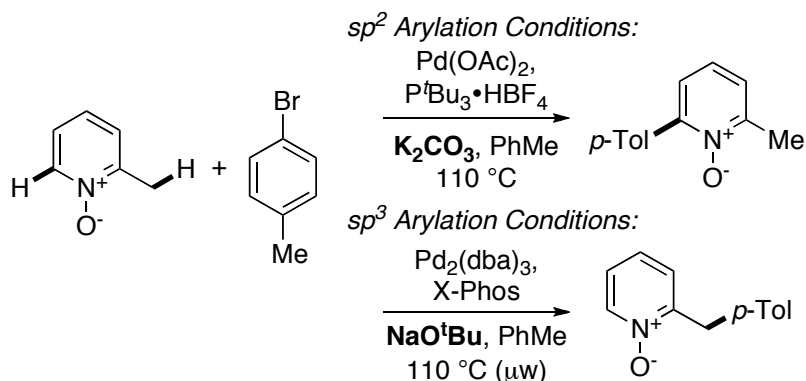
41 Ess, D. H.; Bischof, S. M.; Oxgaard, J.; Periana, R. A.; Goddard III, W. A. *Organometallics* **2008**, 27, 6440.

42 Lu, P.; Boorman, T. C.; Slawin, A. M. Z.; Larrosa, I. *J. Am. Chem. Soc.* **2010**, 132, 5580.

43 a) Campeau, L.-C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, 127, 18021. b) Leclerc, J.-P.; Fagnou, K. *Angew. Chem. Int. Ed.* **2006**, 45, 7781. c) Campeau, L.-C.; Bertrand-Laperle, M.; Leclerc,

reactions showed that the electron deficient 4-nitropyridine *N*-oxide reacts more readily than the more electron rich 4-methoxypyridine *N*-oxide (>20:1) which is unusual considering that for direct arylation processes the palladium(II) complex is considered as electrophilic in nature (Scheme 1.11). A large primary KIE of 4.7 is observed with pyridine *N*-oxide.^{43a} These results can not be explained by an S_EAr mechanism. A mechanism involving heterolytic cleavage of the proton can be discarded based on studies on site-selective arylation of 2-methyl azine *N*-oxides. The sp₂/sp₃ selectivity was found to be tunable with the choice of base: with K₂CO₃ the arylation occurs at the C₆ position of azine *N*-oxide (Scheme 1.12), however using a stronger base (NaO^tBu) the arylation occurs exclusively at the most acidic benzylic position.⁴⁴

Scheme 1.12 Selective arylation of picoline *N*-oxide achieved by the choice of base.



A rigorous mechanistic investigation of the palladium-catalyzed direct arylation of pyridine *N*-oxides was reported.⁴⁵ Many mechanistic scenarios were investigated including: Heck-type, C–H oxidative insertion, S_EAr, and both the inner- and outer-sphere CMD (Figure 1.5). Computationally, both the Heck-type and the C–H oxidative insertion transition states were found highly energetic ($\Delta G^\ddagger > 50$ kcal·mol⁻¹). The

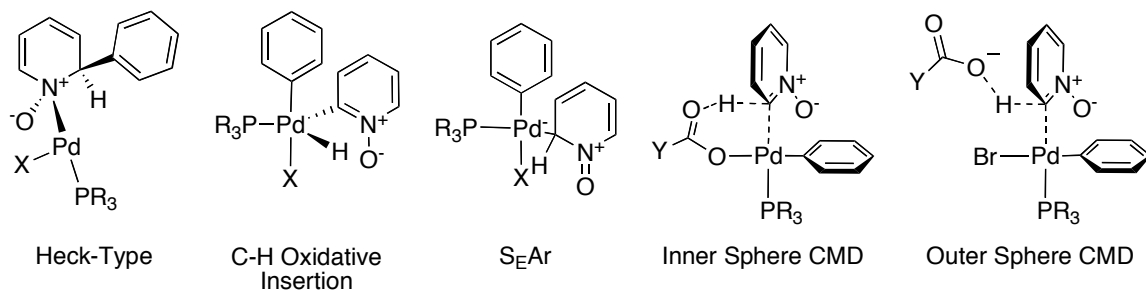
J.-P.; Villemure, E.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3276. d) Campeau, L.-C.; Stuart, D. R.; Leclerc, J.-P.; Bertrand-Laperle, M.; Villemure, E.; Sun, H.-Y.; Lasserre, S.; Guimond, N.; Lecavallier, M.; Fagnou, K. *J. Am. Chem. Soc.* **2009**, *131*, 3291.

44 a) Campeau, L.-C.; Schipper, D. J.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3266. b) Schipper, D. J.; Campeau, L.-C.; Fagnou, K. *Tetrahedron* **2009**, *65*, 3155.

45 Sun, H.-Y.; Gorelsky, S. I.; Stuart, D. R.; Campeau, L.-C. C.; Fagnou, K. *J. Org. Chem.* **2010**, *75*, 8180.

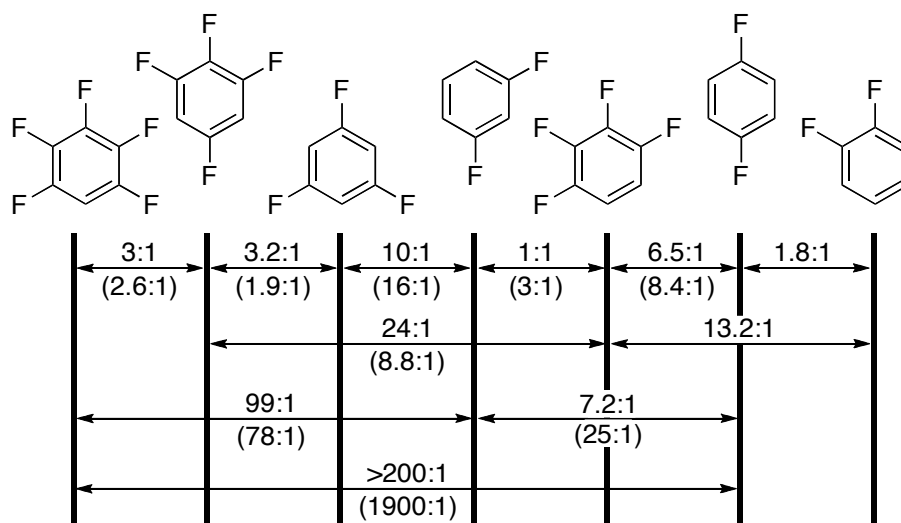
Hammett plot of C4 substituted pyridine *N*-oxide gave a positive slope ($\rho = +1.53$), which is suggestive of the development of a slightly negative charge at the transition state, therefore incompatible with the formation of a Wheland intermediate in the S_EAr pathway.

Figure 1.5 Possible Mechanisms for the C–H bond functionalization evaluated.



The dependence of the reactivity with the presence of soluble carboxylate/acetate base was also assessed in both catalytic and stoichiometric variations of the transformation and it was proved to play critical role in this transformation. Computationally, the barriers of activation for the C–H bond palladation of pyridine *N*-oxide through the inner-sphere CMD using both acetate and carbonate bases matched the observed C2 arylation obtained experimentally, in opposition to the outer-sphere CMD that predicted the C4 arylation.

Figure 1.6 Relative reactivity of the polyfluorinated arenes observed by competitions reactions



(The ratios between brackets were estimated by DFT calculation, $\Delta\Delta G^\ddagger$)

Our group has also extended the intermolecular direct arylation of electron deficient arenes to polyfluorinated arenes.⁴⁶ Experimentally, it was observed that the most electron deficient polyfluorinated arene reacted preferentially over less electron deficient polyfluorinated arenes (Figure 1.6). A KIE of 3.0 was observed, which is similar to the one observed with azine *N*-oxides. Furthermore, the trend of reactivity with polyfluorinated benzene paralleled the computed barrier of activation with the CMD mechanism.^{46a} Fagnou and coworkers recently reported that chlorinated electron-rich heteroarenes benefit from similar activation effects on C–H bond reactivity as fluorinated arenes.⁴⁷

46 a) Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 8754. b) Lafrance, M.; Shore, D. G.; Fagnou, K. *Org. Lett.* **2006**, *8*, 5097. c) René, O.; Fagnou, K. *Org. Lett.* **2010**, *12*, 2116.

47 Liégault, B.; Petrov, I.; Gorelsky, S. I.; Fagnou, K. *J. Org. Chem.* **2010**, *75*, 1047.

1.2.7 Concluding remarks

Herein we have presented a selection of mechanistic studies which have led to a better understanding of the metal/base catalyzed functionalization of arene C–H bonds with a emphasis on the catalytic transformation. Both the early work by Roberts and Ryabov had proposed a concerted metallation-deprotonation pathway instead of the S_EAr pathway. Later computational and experimental studies on similar systems have come to the nearly identical conclusions. The pivotal role of the base on the metal, particularly carboxylate type bases, was highlighted throughout these studies. In the following chapters will be presented studies that further stress the role of the carboxylate type bases and additives in the C–H bond functionalization reactions.

Chapter

2

Utilization of Additives in the Development of Mild and Efficient Reactions Conditions for the Intramolecular Direct Arylation of Simple Arenes

2.1 Additives used to enhance the reactivity of metal-catalyzed C–H functionalization

While there have been many reports on the direct arylation of electron deficient arenes, such as pyridine *N*-oxides¹ and polyfluorinated arenes,² and of electron-rich

-
- 1 a) Campeau, L.-C.; Bertrand-Laperle, M.; Leclerc, J.-P.; Villemure, E.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3276. b) Campeau, L.-C.; Stuart, D. R.; Leclerc, J.-P.; Bertrand-Laperle, M.; Villemure, E.; Sun, H.-Y.; Lasserre, S.; Guimond, N.; Lecavalier, M.; Fagnou, K. *J. Am. Chem. Soc.* **2009**, *131*, 3291.
- 2 a) Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 8754. b) Lafrance, M.; Shore, D. G.; Fagnou, K. *Org. Lett.* **2006**, *8*, 5097. c) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 1128. d) Nakao, Y.; Kashiwara, N.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2008**, *130*, 16170. e) Wei, Y.; Kan, J.; Wang, M. Su, W.; Hong, M. *Org. Lett.* **2009**, *11*, 3346. f) Johnson, S. A.; Huff, C. W. Mustafa, F.; Saliba, M. *J. Am. Chem. Soc.* **2008**, *130*, 17278. g) Xie, K.; Yang, Z.; Zhou, X.; Li, X.; Wang, S.; Tan, Z.; An, X.; Guo, C.-C. *Org. Lett.* **2010**, *12*, 1564. h) René, O.; Fagnou, K. *Org. Lett.* **2010**, *12*, 2116.

heteroarenes,³ until 2006 little progress had been made on the intermolecular arylation of simple arenes such as benzene. As described in chapter 1, the reactivity the electron-deficient arenes was in part governed by the acidity of the proton abstracted in the process. The reactivity of the electron-rich heteroarenes was thought to rely on their nucleophilicity.⁴ Since benzene does not benefit from either enhanced C–H bond acidity nor great π -nucleophilicity, the direct functionalization of such a simple arene under the palladium-carboxylate template represented a significant challenge.

2.1.1 Discovery of the pivalic acid as a rate enhancing additive

Our group was attracted by the difficulty of functionalizing simple arenes since addressing this limitation would lead to the development of better catalysts for performing C–H functionalizations of more complex substrates and possibly under milder conditions. The initial hypothesis to develop a better catalyst was to increase the solubility of the base. After much optimization, it was found that pivalic acid could be used as a co-catalyst along with the Buchwald phosphino biaryl ligand DavePhos, to efficiently achieve the direct arylation of benzene and other simple arenes (Scheme 2.1).⁵ Without this additive, little conversion of starting material to product was obtained. It is also important to mention that prior to these findings, Larock⁶ and Sames⁷ had used stoichiometric amounts of pivalate salts in palladium and rhodium catalyzed systems, although, in the direct arylation of benzene, the use of stoichiometric amounts of pivalate base led to poor yield of product.

3 Selected reviews on the C–H bond functionalization of heteroarenes, see: a) Ackermann L.; Vicente, R.; Kapdi, A. R. *Angew. Chem. Int. Ed.* **2009**, *48*, 9792. b) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173.

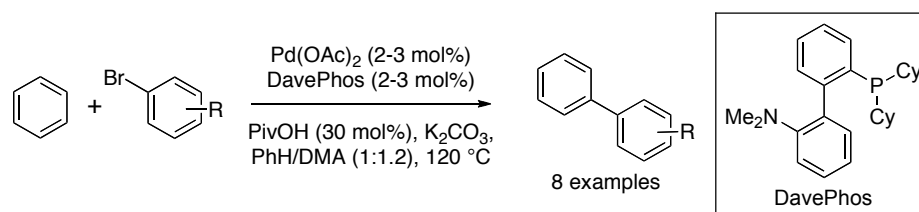
4 The various mechanistic proposals for the C–H bond functionalization of such systems will be discussed in detail in Chapter 3.

5 Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496.

6 a) Huang, Q.; Fazio, A.; Dai, G.; Campo, M. A.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 7460. b) Zhao, J.; Yue, D.; Campo, M. A.; Larock, R. C. *J. Am. Chem. Soc.* **2007**, *126*, 5288.

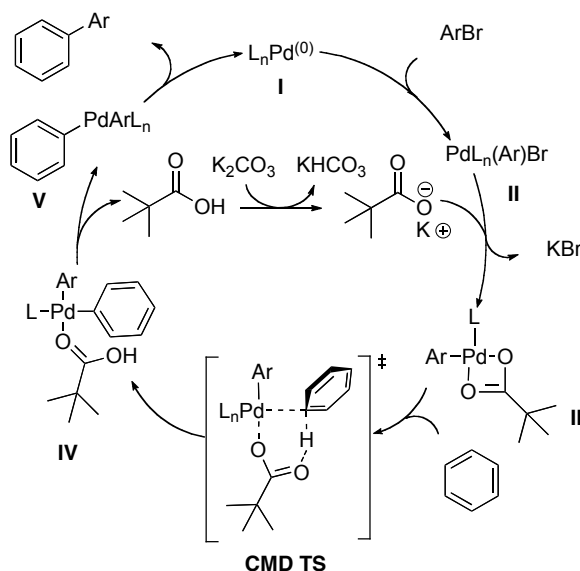
7 Wang, X.; Lane, B. S.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 4996.

Scheme 2.1 Palladium-catalyzed direct arylation of benzene with pivalic acid as co-catalyst.



Scheme 2.2 illustrates the proposed catalytic cycle of benzene direct arylation. Following the oxidative insertion of the aryl bromide into the palladium(0) complex (**I**), the pivalate anion is believed to substitute the bromide on the palladium to form the ArPd(κ_2 -O₂C'Bu) complex (**II**→**III**). From that point the benzene could be added to the palladium(II) complex through the concerted metallation-deprotonation (CMD) pathway, yielding an intermediate bearing the weakly coordinated pivalic acid (**IV**). Upon its dissociation from the metal centre, the acid may be deprotonated by the carbonate base, thus reforming the initial pivalate anion. Intermediate **V** then reductively eliminates the biaryl product and completes the catalytic turnover. Computationally, the influence of the pivalate anion on the benzene C–H bond cleaving transition-state results in a decrease of 1.3 kcal*mol⁻¹ compared to the bicarbonate anion (24.9 vs 26.2 kcal*mol⁻¹). This is not sufficient to justify the difference in reactivity observed experimentally, although the increased solubility of the base could justify the enhancement of the reactivity in the pivalate system.

Scheme 2.2 Plausible pathway for benzene arylation.



2.1.2 Use of different additives in other systems

Aside from pivalic acid, other additives have been used in C–H functionalization reactions. For instance, Ackermann and coworkers have used heteroatom-substituted secondary phosphine oxides (HASPO) as pre-ligands in ruthenium-catalyzed⁸ and palladium-catalyzed⁹ direct arylations of simple arenes. Presumably, the phosphine oxide acts as an intramolecular base (Figure 2.1a).¹⁰ Ackermann also uses 2,4,6-trimethylbenzoic acid and 1-adamantylcarboxylic acid as co-catalyst in ruthenium- and palladium-catalyzed C–H bond functionalization reactions (Figure 2.1).^{11,12} Furthermore, Larrosa and coworkers employed *o*-nitrobenzoic acid as an additive in the palladium-

8 a) Ackermann, L. *Org. Lett.* **2005**, 7, 3123. b) Ackermann, L.; Mulzer, M. *Org. Lett.* **2008**, 10, 5043.

9 a) Ackermann, L.; Barfüßer, S. *Synlett* **2009**, 808. b) Ackermann, L.; Barfüßer, S.; Kornhaass, C.; Kapdi, A. R. *Org. Lett.* **2011**, 13, 3082.

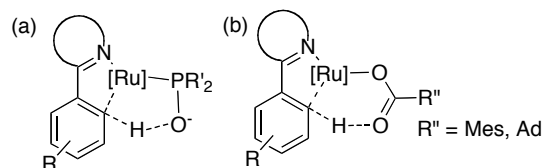
10 Ackermann, L.; Vicente, R.; Althammer, A. *Org. Lett.* **2008**, 10, 2299.

11 For ruthenium-catalyzed reactions, see: a) Ackermann, L.; Novák, P.; Vicente, R.; Hofmann, N. *Angew. Chem. Int. Ed.* **2009**, 48, 6045. b) Ackermann, L.; Novák, P. *Org. Lett.* **2009**, 11, 4966. See also refs 9a and 10.

12 For a palladium-catalyzed reaction, see: Ackermann, L.; Vicente, R. *Org. Lett.* **2009**, 11, 4922.

catalyzed C2 arylation of indoles.¹³ In some cases, the choice of the additive and its effect on the reactivity is dependant on the system.

Figure 2.1 Other additives used to promote C–H bond cleavage.



2.2 Development of mild and efficient intramolecular direct arylation reactions using the palladium-carboxylic acid co-catalysis system¹⁴

The use of pivalic acid as an additive (to be further discussed in following chapters) allowed for the development of milder conditions and improved regioselectivity for many intramolecular direct arylation reactions,^{14,15,16} as well as in the functionalization of electron-deficient arenes,^{1,17,18} and electron-rich heteroarenes.^{17a,19,20,21,22,23} In the following

13 Lebrasseur, N.; Larrosa, I. *J. Am. Chem. Soc.* **2008**, *130*, 2926.

14 Lafrance, M.; Lapointe, D.; Fagnou, K. *Tetrahedron* **2008**, *64*, 6015.

15 García-Cuadrado, D.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2007**, *129*, 6880.

16 Pascual, S.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *Tetrahedron* **2008**, *64*, 6021.

17 a) Huestis, M. P.; Fagnou, K. *Org. Lett.* **2009**, *11*, 1357. b) Schipper, D. J.; El-Salfiti, M.; Whipp, C. J.; Fagnou, K. *Tetrahedron* **2009**, *65*, 4977.

18 Caron, L.; Campeau, L.-C.; Fagnou, K. *Org. Lett.* **2008**, *10*, 4533.

19 Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 10848.

20 Liégault, B.; Petrov, I.; Gorelsky, S. I.; Fagnou, K. *J. Org. Chem.* **2010**, *75*, 1047.

21 a) Liégault, B.; Lapointe, D.; Caron, L.; Vlassova, A.; Fagnou, K. *J. Org. Chem.* **2009**, *74*, 1826. And references herein b) Lapointe, D.; Fagnou, K. *Org. Lett.* **2009**, *11*, 4160. c) René, O.; Lapointe, D.; Fagnou, K. *Org. Lett.* **2009**, *11*, 4560.

22 a) Ackermann, L.; Vicente, R.; Born, R. *Adv. Synth. Catal.* **2008**, *350*, 741. b) Ackermann, L.; Althammer, A.; Fenner, S. *Angew. Chem. Int. Ed.* **2009**, *48*, 201.

23 Zhao, D.; Wang, W.; Lian, S.; Yang, F.; Lan, J.; You, J. *Chem.-Eur. J.* **2009**, *15*, 1337.

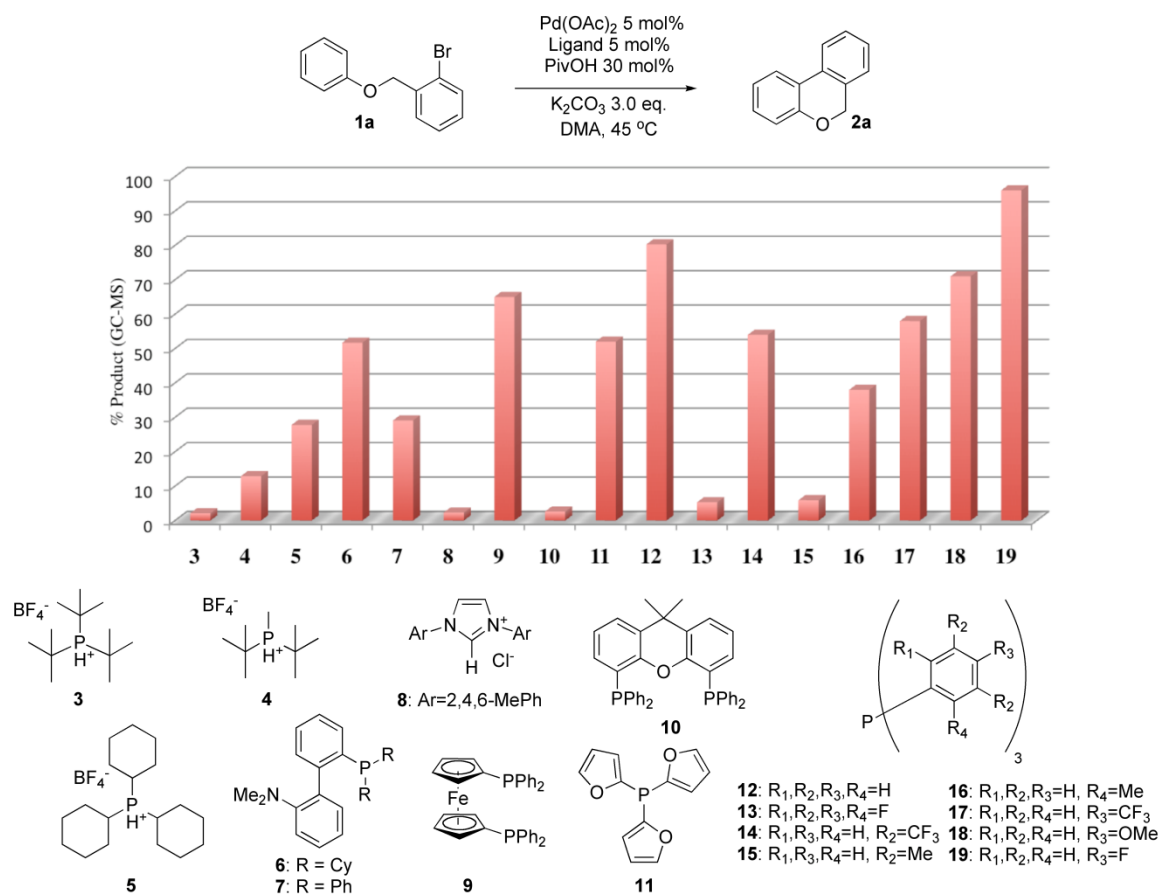
sections of this chapter, our findings on the effect of pivalic acid on intramolecular direct arylation processes will be discussed.^{14,24}

2.2.1 Optimization of the reaction conditions

Fine-tuning of reaction conditions for the transformation of **1** to **2a** mainly focused on the choice of the appropriate ligand. Previous attempts at reaction optimization allowed for the lowering of reaction temperature from 120 °C to 45 °C using 30 mol% of pivalic acid.^{24a} The initial survey of ligands included a wide variation on the range of steric and electronic properties (ligands **3-12**, Figure 2.2). Under these conditions, the ligand used in the initial reports of intramolecular direct arylation^{24a} (**7**) performed relatively poorly. On the other hand, triphenylphosphine (**12**) gave good yield of product, which prompted us to evaluate more triarylphosphines (**13-19**). From the second round of ligand optimization, we found that the tri(*p*-fluorophenyl)phosphine **19** gave the best result.

24 a) Campeau, L.-C.; Parisien, M.; Leblanc, M.; Fagnou, K. *J. Am. Chem. Soc.* **2004**, *126*, 9186. b) Lafrance, M.; Blaqui re, N.; Fagnou, K. *Chem. Commun.* **2004**, 2874. c) Parisien, M.; Valette, D.; Fagnou, K. *J. Org. Chem.* **2005**, *70*, 7578. d) Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581.

Figure 2.2 Ligand evaluation in intramolecular direct arylation reactions.



Continuing the optimization process using palladium acetate and tri(*p*-fluorophenyl)phosphine, the choice of the carboxylic acid additives was evaluated (Table 2.1). In the absence of additives (entry 1) we only observed 31% conversion to product. It was found that with the addition of 30 mol% of carboxylic acid, and increase in yield was observed as the steric bulk of the acid was augmented, (entries 2-5), pivalic acid (entry 5) giving the best result. In contrast, adamantylcarboxylic acid gave poorer yield (entry 6). Furthermore, the addition of more acidic additives, such as trifluoroacetic acid (entry 7), did not improve the outcome of reaction.

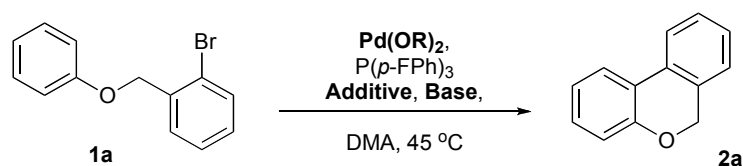
Table 2.1 Effect of the carboxylic acid additives on the intramolecular direct arylation reactions.

Entry	Additive	Conv. (%) ^a	Entry	Additive	Conv. (%) ^a
1	none	31	5		100
2		32			
3		36	6		56
4		63	7		28

^a Determined by GC-MS

The choice of the base also had a marked effect on the reaction outcome (Table 2.2). In the absence of acid additives, potassium carbonate provided a slightly higher yield than sodium carbonate and cesium carbonate gave very low conversion (entries 1-3). The use of the a catalytic amount of pivalic acid in combination with the stoichiometric amount of potassium carbonate (which generates potassium pivalate *in-situ*) proved to be superior to simply employing potassium pivalate as the sole stoichiometric base as illustrated by entries 4 and 5. The enhanced reactivity associated with the use of 30 mol% of pivalic acid can partially be retained by using palladium pivalate without any additives (entry 6 *vs* entries 2 and 5). Furthermore, the reactivity of Pd(OPiv)₂ and Pd(OAc)₂ are indistinguishable after 12 hours of reaction time. Both resulted in complete conversion of starting material to product (entries 5 and 7). The conditions reported in entry 7 were selected as the optimal conditions.

Table 2.2 Influence of the base on the intramolecular direct arylation reactions.



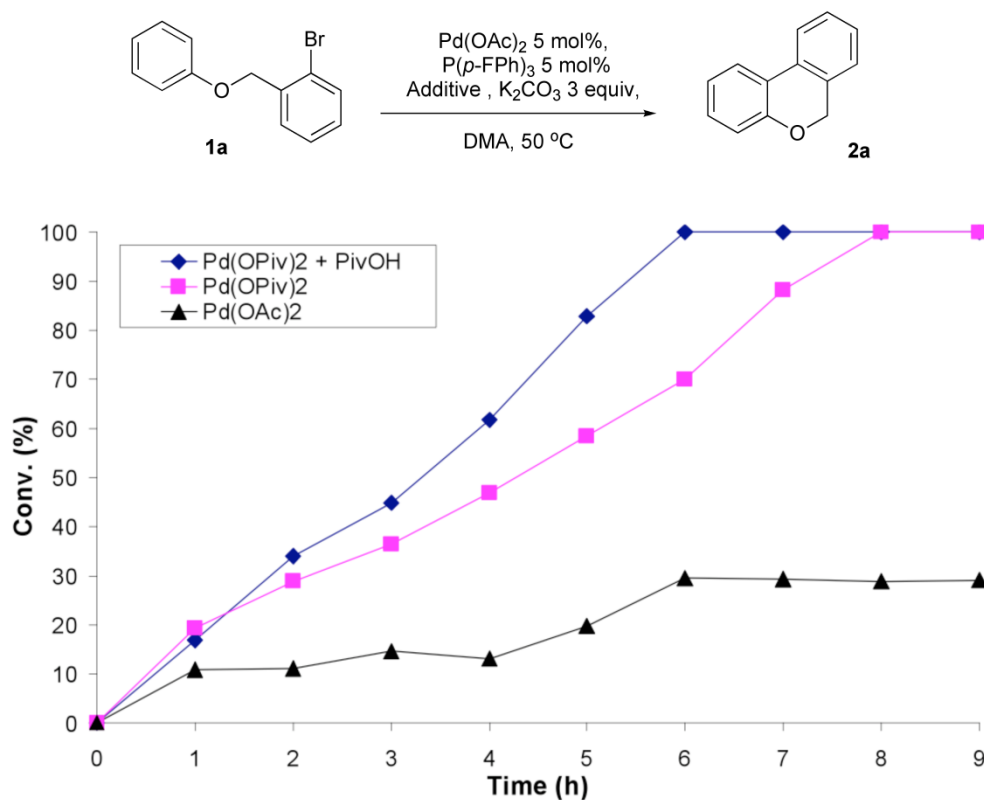
Entry	Pd Source	Additive	Base	Conv. (%) ^a
1	Pd(OAc) ₂	None	Na ₂ CO ₃	22
2	Pd(OAc) ₂	None	K ₂ CO ₃	32
3	Pd(OAc) ₂	None	Cs ₂ CO ₃	5
4	Pd(OAc) ₂	None	KOPiv	22
5	Pd(OAc) ₂	PivOH	K ₂ CO ₃	100
6	Pd(OPiv) ₂	None	K ₂ CO ₃	71
7	Pd(OPiv) ₂	PivOH	K ₂ CO ₃	100

a. Determined by GC-MS.

2.2.1.1 Rate enhancement of the reaction with the use of pivalic acid additives

The rate enhancement of the intramolecular direct arylation caused by the addition of 30 % mol of pivalic acid and/or the use of Pd(OPiv)₂ is illustrated in Figure 2.3. From this figure, we can see that when Pd(OAc)₂ is employed without any additives (black triangles), the reaction progresses slowly for approximately six hours before stopping at ~30 % conversion. On the other hand, when Pd(OPiv)₂ was employed (pink squares), we observe that the reaction progresses steadily until its completion after eight hours. Finally, the addition of 30 mol% of pivalic acid further increases the rate of the cyclization (blue diamonds), the reaction completing in six hours.

Figure 2.3 Evaluation of the effect of pivalate on the rate of the direct arylation reaction. (Data collected by Marc Lafrance)¹⁴

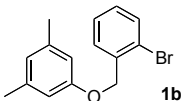
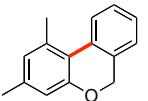
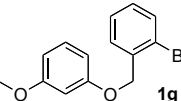
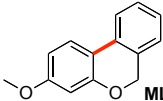
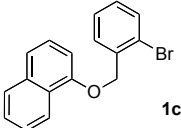
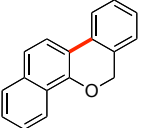
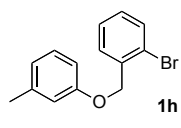
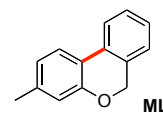
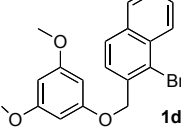
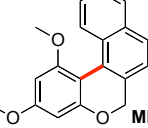
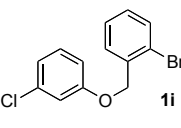
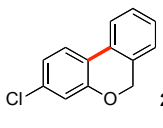
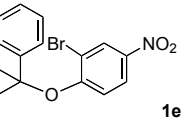
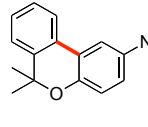
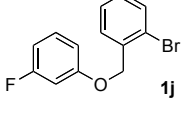
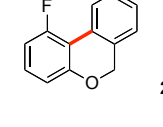
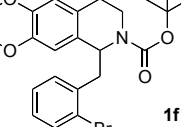
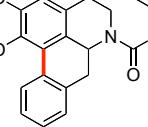
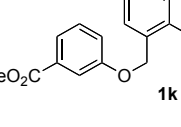
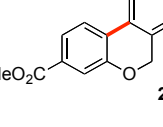


2.2.2 Substrate scope of the reaction

As illustrated in Table 2.3, a broad range of substrates was compatible with the optimized reaction conditions. A range of substitution patterns was found to be well-suited, including electron-donating (entries 2, 3 and 6) and withdrawing groups (entries 4, 9 and 10). The reaction at sterically congested positions can also occur in high yield (entries 1, 3 and 5). Highly functionalized substrates, like the aporphine precursor **1f** (entry 5), can also be employed. Increased regioselectivity in favor of the most sterically accessible positions were generally obtained for *meta*-substituted arenes (entries 5-10) when compared to the results obtained under the previous conditions.^{24d} The *meta*-fluoro substituted arene (entry 9) constituted the exception to the general trend of improved regioselectivity. A possible explanation to this outcome could be that at 45 °C, the steric

bulk of the fluorine overcomes its *ortho* activating property² thus yielding a ~1:1 mixture of regioisomers in comparison to the 4.3:1 mixture obtained at 130 °C.^{24d}

Table 2.3 Substrate scope of the intramolecular direct arylation reaction.

Entry	Substrate	Product	Yield (%) ^b	Entry	Substrate	Product	Ratio ^c	Yield (%) ^b
1			96 ^d	6			>30:1 (10:1) ^f	99
2			97	7			>30:1 (15:1) ^f	98
3			95	8			15:1 (3.2:1) ^f	96
4			94	9			1.2:1 (4.3:1) ^f	93
5			70 ^e	10			>30:1 (>30:1) ^f	92

^a Conditions: substrate, Pd(OPiv)₂ (5mol %), P(*p*-FPh)₃ (5mol %), PivOH (30mol%) and K₂CO₃ (3.0 equiv.) are dissolved in DMA (0.25M) and heated to 50 °C for 12 hours. ^b Isolated yield. ^c Ratio of regioisomers formed at the unequivalent *ortho* positions. ^d Reaction performed at 60 °C. ^e Reaction performed at 70 °C. ^f Ratio of products obtained under previous conditions.^{24d} Compounds associated with the initials "ML-" were obtained by Marc Lafrance.¹⁴

2.3 Concluding remarks

In this chapter, additives which readily promoted C–H bond arylation of substrates which were otherwise not very reactive were discussed. More specifically, the effect of pivalic acid as a co-catalyst on the reactivity of benzene was examined. To further demonstrate the importance of pivalic acid as a co-catalyst on the efficiency of catalyst turnover, we revisited the intramolecular direct arylation reaction previously developed in our group with the objective of developing milder reaction conditions. With the use of a more compatible ligand in combination with 30 mol% of PivOH, the reaction temperature could be dropped from ≥ 120 °C to only 45 °C. The particular mildness of these conditions enabled improved regioselectivity for non-symmetrical substrates and could potentially enable the coupling of substrates prone to decomposition.

Chapter

3

Analysis of the CMD mechanism in Palladium-catalyzed direct arylation across a broad range of aromatic substrates and examples of its application

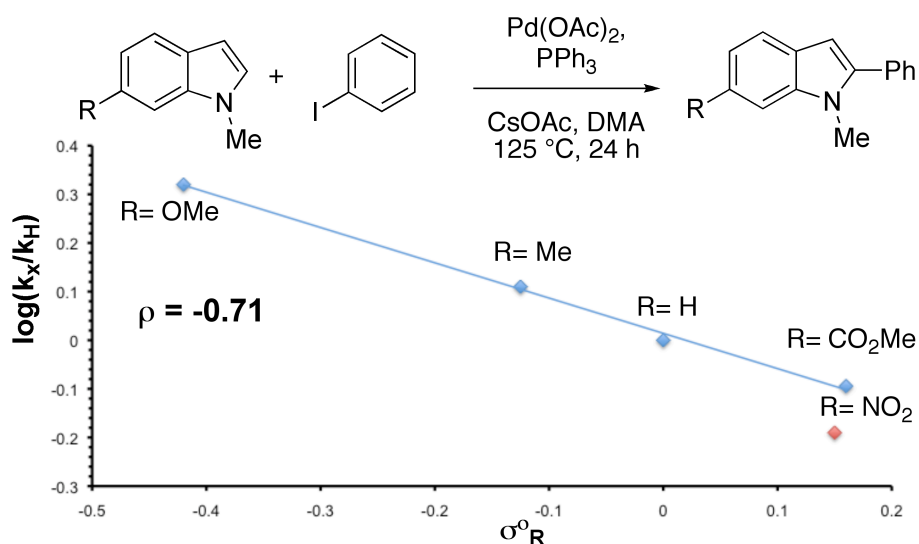
3.1 Introduction to the mechanistic studies on the C–H bond functionalization of electron rich arenes

Over the years, several pathways have been proposed for C–H bond functionalization with the S_EAr and CMD mechanisms being proposed the most often. The most commonly proposed mechanisms for C–H bond cleavage of electron-rich heteroarenes often precede through a Heck-like mechanism¹ or S_EAr mechanism,

¹ Selected examples for which a Heck-type mechanism as been proposed, see: a) McClure, M. S.; Glover, B.; McSorley, E.; Millar, A.; Osterhout, M. H.; Roschinger, F. *Org. Lett.* **2001**, 3, 1677. b) Glover, B.; Harvey, K. A.; Liu, B.; Sharp, M. J.; Tymoschenko, M. F. *Org. Lett.* **2003**, 5, 301. c) Li, W.; Nelson, D. P.; Jensen, M. S.; Hoerrner, R. S.; Javadi, G. J.; Cai, D.; Larsen, R. D. *Org. Lett.* **2003**, 5, 4835. d)

although the latter has gained more attention.² For instance, an S_EAr mechanism has been proposed to explain the regioselectivity observed in the direct arylation of electron-rich arenes, such as azoles, indolizines and indoles, since the same the regioselectivity has been observed in Friedel-Crafts reactions.² Sames and coworkers reported a ρ value of -0.71 derived from a Hammett plot for the C2 arylation of C6 substituted indoles (Figure 3.1).^{2b} Although the small negative slope of the Hammett plot is usually attributed to the development of a partial positive charge (δ^+) the transition state, Sames proposed that the slope was indicative of the formation of a Wheland-type intermediate (Scheme 3.1). However, the slope of Hammett plot (ρ) values for electrophilic aromatic substitution are usually in the range of ~ -6 to -13 .³ From our point of view, a slope of only -0.7 does not constitute strong enough evidence to support the development of a positive charge on the indole, nonetheless it conveys the electrophilic character of the catalyst.

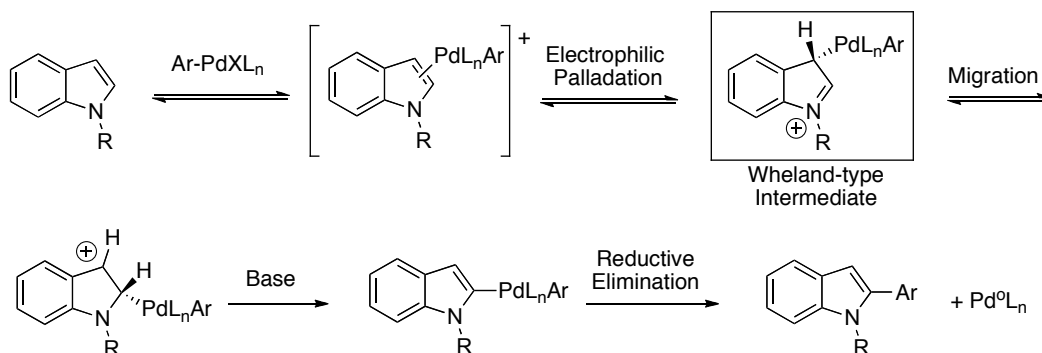
Figure 3.1 Hammett plot derived for the palladium-catalyzed C2 arylation of C6-substituted *N*-methylindoles.^{2b}



Wang, J.-X.; McCubbin, J. A.; Jin, M.; Laufer, R. S.; Mao, Y.; Crew, A. P.; Mulvihill, M. J.; Snieckus, V. *Org. Lett.* **2008**, *10*, 2923.

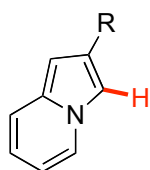
- 2 a) Pivsa-Art, S.; Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, B. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 467.
 b) Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050. c) Park, C.-H.; Ryabova, V.; Seregin, I. V.; Sromek, A. W.; Gevorgyan, V. *Org. Lett.* **2004**, *6*, 1159.
- 3 Rys, P.; Skrabal, P.; Zollinger, H. *Angew Chem. Int. Ed. Engl.* **1972**, *11*, 874.

Scheme 3.1 Indole-C2 arylation mechanism proposed by Sames.^{2b}



In the mechanistic studies of the direct arylation of substituted indolizines, Gevorgyan and coworkers observed that the relative rate of C2 substituted indolizine arylation parallels the relative rate for Friedel-Crafts acylation (Table 3.1). In combination with the lack of a kinetic isotope effect (KIE), according to Gevorgyan, these results were consistent with an S_EAr mechanism.^{2c}

Table 3.1 Relative rate for the acylation and direct arylation of C2 substituted indolizines.



R	Relative rate of reaction	
	Friedel-Crafts Acylation	Direct Arylation
H	1.0	1.0
Me	0.67	0.97
CO ₂ Et	0.33	0.66

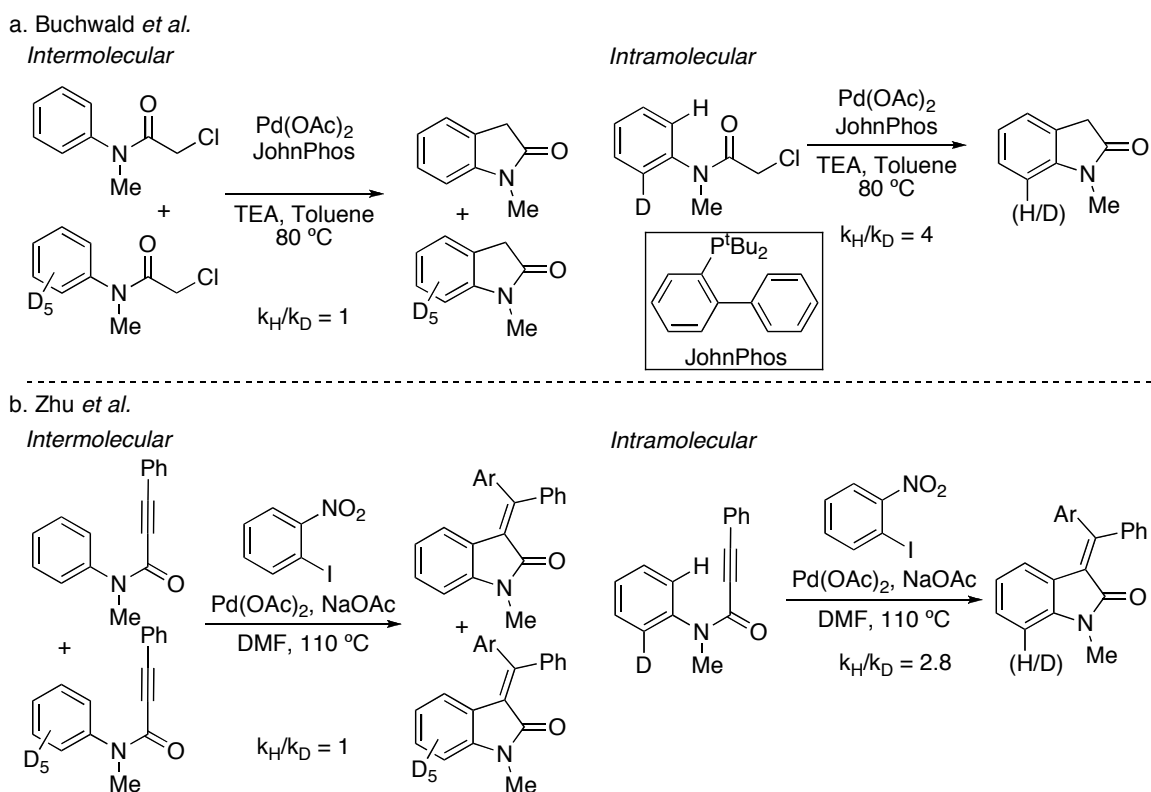
In light of the breadth of knowledge on the direct palladation (or metallation) of C–H bonds, which was also available at the time these studies were conducted,⁴ these mechanistic insights were shown to not be conclusive enough to support the formation of palladium-arenium σ -complexes. Nonetheless, similar to Sames case, these mechanistic studies highlighted that the nucleophilic character of those electron-rich heteroarenes toward electrophilic palladium catalysts is an important factor contributing to the transformation.

4 See Chapter 1 for a detailed discussion on this transformation.

3.1.1 Interpretation of the results of kinetic isotope effect experiments

Kinetic isotope effect (KIE) experiments have frequently been invoked to support or dismiss proposed mechanisms. Although, these experiments bring insightful information about the mechanism of the reaction of interest, careful attention must be addressed to the interpretation of the results. The study of KIE is a rich and complex domain of physical-organic chemistry,⁵ in this section we will simply discuss some of the different ways to obtain KIE values and how those values should be interpreted.

Scheme 3.2 Examples of different k_H/k_D values obtained from intermolecular and intramolecular KIE experiments.



5 For a review on KIE in studies of the mechanism of organometallic reactions, see: Gomez-Gallego, M.; Sierra, M. A. *Chem. Rev.* **2011**, ASAP DOI 10.1021/cr100436k

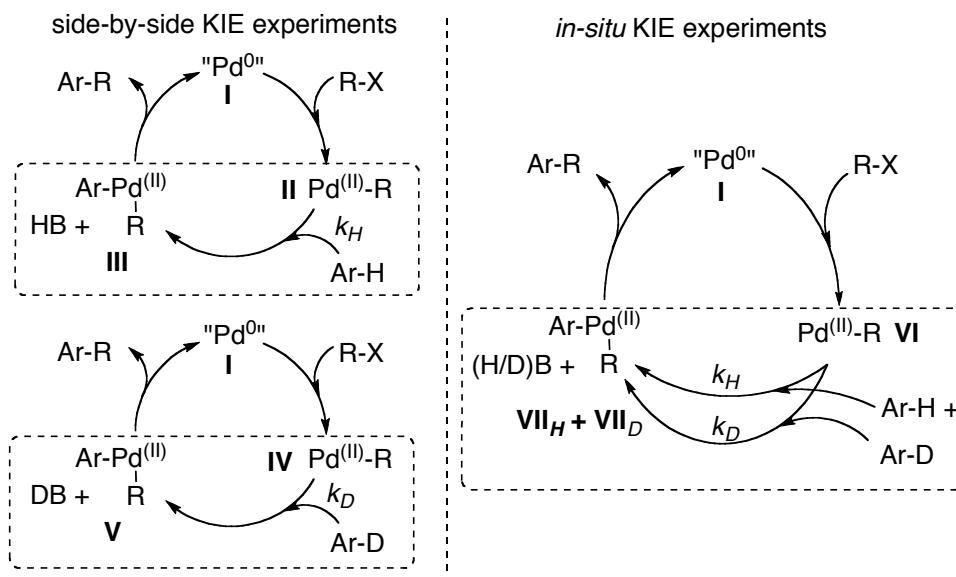
Scheme 3.2 presents two examples of the use different KIE experiment within the same mechanistic study from the groups of Buchwald⁶ and Zhu.⁷ In Buchwald study, no KIE ($k_H/k_D = 1$) was observed in the intermolecular reaction of *N*-methyl chloroacetanilide and its d_5 analogue (Scheme 3.2a). However, an intramolecular KIE of 4 was obtained in the cyclization of the *ortho*- d_1 -substrate. On the basis of these findings, they proposed that the cleavage of the C–H bond was not the rate-determining step in the catalytic cycle. Based on the intermolecular KIE experiment, they suggested that the slow step of the catalytic cycle was the oxidative insertion of the palladium(0) into the C–Cl bond. The intramolecular KIE, on the other hand, suggested that the cleavage of the C–H bond was slow relative to the palladation process. However, with these results in hand the authors did not propose a particular mechanism for C–H bond palladation.

The source of the different values of KIE observed with the two sets of experiment in Buchwald's example can be illustrated in Figure 3.2: the intermolecular experiment can be compared to the side-by-side KIE experiment and the intramolecular experiment to the *in-situ* KIE experiment.^{ref} The reason why Buchwald's intermolecular KIE experiment is compared to the two separated catalytic cycles is because the “R–X” substrate is attached to the arene (Ar–H(or D)), therefore once the Pd catalyst (I) reacts with the R–X (to form II and IV), it is committed to react with either h_5 -arene or the d_5 -arene (to form III and IV). The KIE values obtained from the comparison of side-by-side experiments give information about the rate of C–H bond cleavage relative to the complete catalytic cycle. In the case of when there is no kinetic isotope effect, these experiments do not confer any information about the C–H bond cleavage mechanism. By contrast, in the case of the intramolecular KIE experiment, once the Pd insert into C–Cl bond (to form VI), it still as the option to react with either C–H or C–D bonds (to form VII_H or VII_D). The *in-situ* KIE experiments do not give information about the turn-over limiting step of a catalytic cycle, since a reaction can choose from two pathways (k_H or k_D) in the same reaction pot regardless of the rate of the other steps in the catalytic cycle.

Hennessy, E. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, 125, 12084.
 Pinto, A.; Neuville, L.; Retailleau, P.; Zhu, J. *Org. Lett.* **2006**, 8, 4927.

Since in a catalytic cycle, an intermediate will always choose between the k_H or the k_D pathways, a KIE >1 is more likely to arise under pseudo first order conditions.

Figure 3.2 Comparison of the side-by-side and *in-situ* KIE experiments.



Nonetheless, a drawback of observing intermolecular KIE in a cyclization reaction, as the first example in Scheme 3.2a, implies that even if a value >1 was obtained this value would necessarily be smaller than the actual KIE value. Because, at the beginning of the catalytic cycle, the palladium inserts into C–Cl bond with no discrimination in respect to the presence or absence of deuterium on the linked arene. Once the palladium has inserted into a substrate, it is committed to react with this substrate. After each catalyst turnover, the catalyst will have equal odds to react with the standard substrate or its deuterated analogue. As a result, after multiple catalyst turnovers the observed KIE will converge toward 1.

In the mechanistic studies of Zhu *et al.* (Scheme 3.2b),⁷ a similar case to the Buchwald example was studied, however in this example the reaction is a bimolecular process, a putative KIE would not be converging to 1 under pseudo first order conditions. Nevertheless, the intermolecular KIE experiment equaled 1, suggesting that the cleavage

of the C–H bond was not rate determining in the catalytic cycle. However, the intramolecular KIE value of 2.8 observed in the cyclization of the *ortho*-*d*₇-acetanilide, suggesting that the C–H bond cleavage was incompatible with a S_EAr mechanism, since typical S_EAr KIE equals 1.

In the context of Gevorgyan's mechanistic studies discussed earlier (or any other mechanistic work), the interpretation of KIE data should be done in consideration of the method use to get those data, unfortunately there is no mention in either the article or supplementary information. In our opinion, the absence of a KIE and a loose correlation with a different reaction do not provide enough support to dismiss or support any mechanistic proposals. A more detailed analysis of the indolizine as well as other heteroarenes systems will be discussed in the following sections.

3.2 Experimental evidence in favor of the CMD mechanism⁸

In the previous chapter were discussed about a series of reactions for which a S_EAr mechanism were initially proposed and then more in-depth mechanistic analysis lead to propose the concerted metallation-deprotonation mechanism. This was especially the case for studies on the mercuration of benzene^{9,10} and the cyclopalladation of *N,N*-dimethylbenzylamine.^{11,12} The following section will discuss our work which lead us to believe that the CMD pathway could be a very general mechanism involved in the C–H functionalization of a wide range of (hetero)arenes.

8 Part of the following results were published in this article: Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 10848.

9 Fung, C. W.; Khorramdel-Vahed, M.; Ranson, R. J.; Roberts, R. M. *G. J. C. S. Perkin II* **1980**, 267.

10 Olah, G. A.; Yu, S. H.; Parker, D. G. *J. Org. Chem.* **1976**, *41*, 1983.

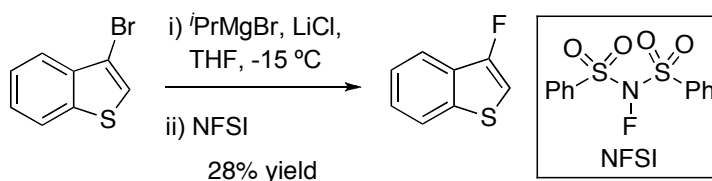
11 Ryabov, A. D.; Sakodinskaya, I. K.; Yatsimirsky, A. K. *J. Chem. Soc., Dalton Trans.* **1985**, 2629.

12 Davies, D. L.; Donald, S. M. A.; Macgregor, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 13754.

3.2.1 Non S_EAr-type of reactivity of 3-fluorobenzothiophene

Based on the knowledge we have on the activating effect of fluorine in the direct arylation of simple arenes,¹³ we were interested in evaluating the effect of fluorine on the reactivity of an electron-rich system. For this, we have chosen to prepare 3-fluorobenzothiophene from 3-bromobenzothiophene (Scheme 3.3).¹⁴

Scheme 3.3 Synthesis of 3-fluorobenzothiophene.



Initially, to evaluate the relative nucleophilicity of the fluorinated benzothiophene compared to its parent analogue, we submitted a 1:1 mixture of benzothiophene and 3-fluorobenzothiophene to standard Friedel-Crafts acylation conditions¹⁵ and looked at the product distribution (Scheme 3.4, path a). The outcome of the competition reaction resulted in the preferential acylation of the benzothiophene over the fluorinated analogue in a 6.7:1 ratio and the ratio of product distribution between the C3 and C2 position of benzothiophene was 4.4:1, respectively. On the other hand, when the same 1:1 mixture of benzothiophenes were subjected to standard direct arylation conditions (Scheme 3.4, path b),¹⁶ the outcome of the reaction were in striking contrast with the Friedel-Crafts acylation results. Indeed, according to NMR spectrum of the crude mixture, the 3-fluorobenzothiophene reacted exclusively over the more nucleophilic benzothiophene

13 a) García-Cuadrado, D.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2007**, *129*, 6880. b) Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 8754. c) Lafrance, M.; Shore, D. G.; Fagnou, K. *Org. Lett.* **2006**, *8*, 5097. See also Chapter 1.

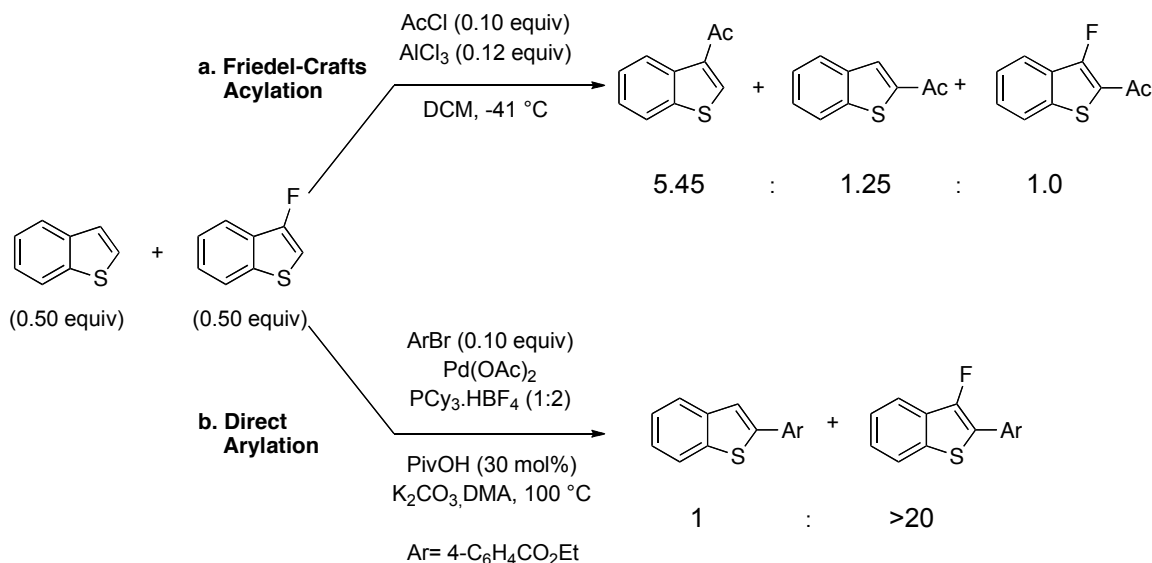
14 Krasovskiy, A.; Knochel, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 3333.

15 Okuyama, T.; Tani, Y.; Miyake, K.; Yokoyama, Y. *J. Org. Chem.* **2007**, *72*, 1634.

16 The development of these standard direct arylation reaction conditions will be discuss in sections 3.2.2.1.1 and 3.4 of this chapter.

(>20: 1), this result was undeniably in contradiction with the generally accepted S_EAr reactivity of electron rich heteroarenes in direct arylation reactions.

Scheme 3.4 Competition reactions between electronically biased benzothiophenes.



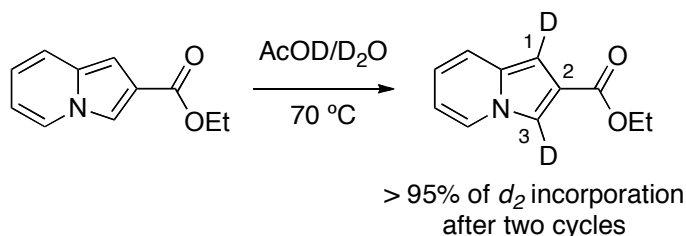
The surprising outcome of these competition reactions prompted us to explore if the non- S_EAr reactivity of benzothiophene toward the palladium-catalyzed direct arylation reaction might be general towards all electron-rich heteroarenes. Owing to the body of work done on the mechanism of this reaction on indolizines, we choose to conduct a re-examination into the reactivity of this heteroarene.

3.2.2 Re-examination of the reactivity of indolizine toward direct arylation and Friedel-Crafts acylation reactions

3.2.2.1 Determination of the *in-situ* kinetic isotope effect

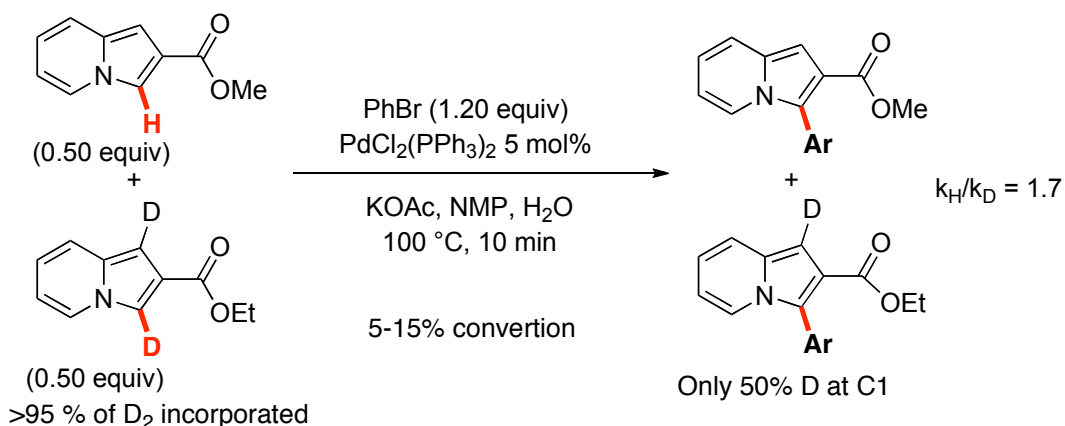
In section 3.1.1 was discussed the interpretation of KIE data in light of the type of experiments conducted to measure those values. In the hope of gaining more information on the C–H bond cleavage step in the direct arylation of indolizines, we first performed a hydrogen-deuterium exchange reaction to form the ethyl d_2 -indolizine-2-carboxylate by stirring the non-deuterium enriched indolizine in a mixture of D_2O and d_1 -acetic acid at 70 °C (Scheme 3.5).

Scheme 3.5 Incorporation on deuterium at the C1 and C3 positions of indolizine.



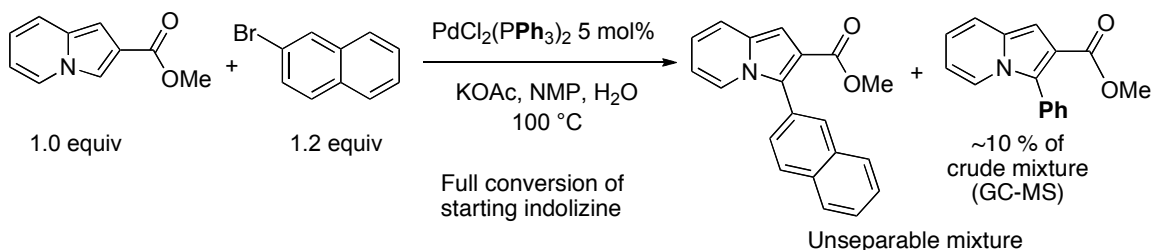
With this deuterated substrate in hand, we next conducted an *in-situ* KIE experiment by submitting equal amounts of the Et- d_2 -indolizine-2-carboxylate and Me-indolizine-2-carboxylate with 1.2 equivalents of bromobenzene under the conditions develop by Gevorgyan (Scheme 3.6).^{2c} After ten minutes, the reaction was stopped and following the work-up, analysis of the crude mixture revealed a KIE of 1.7. However, during the examination of the NMR of the final product, we noted that 50% of the deuterium at C1 was lost. This observation made us doubt the validity of our KIE result, since this could indicate that a rapid deuterium-hydrogen exchange with water could occur in the reaction mixture.

Scheme 3.6 Measurement of the *in-situ* KIE under the original reaction conditions.



Furthermore, in our original investigations leading to the measurement of the KIE, we always observed the formation of significant amounts (~10 mol%) of C3 phenyl indolizine by GC-MS (e.g. in Scheme 3.7). After many attempts to eliminate the formation of this side product, we eventually reasoned that these phenyl groups came from the transfer of a phenyl group of the triphenylphosphine.¹⁷

Scheme 3.7 Observation of a C3 phenyl side-product under the original conditions.



Due to the complications we encountered with this reaction under the originally developed conditions, we were forced to re-optimize conditions for the direct arylation of indolizines in order to conduct our studies.

17 Studies suggest that the phenyl transfer occurs from the R₂PhP(O) derivative, for recent studies, see: (a) Derrah, E. J.; Ladeira, S.; Bouhadir, G.; Miqueu, C.; Bourissou, D. *Chem. Commun.* **2011**, 47, 8611. For reviews on transition metal promoted C–P bond cleavage, see: (b) Garrou, P. E. *Chem. Rev.* **1985**, 85, 171. (c) Goodman, J.; Macgregor, S. A. *Coord. Chem. Rev.* **2010**, 254, 1295.

3.2.2.1.1 Re-optimization of direct arylation reaction conditions for C2-substituted indolizine

The re-optimization of the reaction conditions was not an exhaustive process; first we decided to change the triarylphosphine ligand present in the reaction for a trialkylphosphine in order to avoid the transfer of a group of the ligand to the palladium. We tested di-*tert*-butylmethylphosphonium and tricyclohexylphosphonium tetrafluoroborate salts.¹⁸ Under these similar conditions, we observed that the tricyclohexylphosphine gave 86% yield of the desired product while the di-*tert*-butylmethylphosphine did not react (Table 3.2, entries 1 and 2). Surprised by the striking resemblance of these conditions and the reaction conditions developed for the direct arylation of benzene,¹⁹ we then decided to add 30 mol% of pivalic acid, replace the solvent mixture by DMA and the base by potassium carbonate (Table 3.2, entry 3). Under those “CMD-like” conditions, we were astonished to obtain 95% yield. Satisfied with these conditions, we decided to evaluate once again the KIE value of indolizine.

Table 3.2 Re-optimization of the direct arylation reaction conditions for the indolizine.

1.0 equiv 1.2 equiv Pre-Catalyst
Base, Solvent
100 °C 2-Napht

Entry	Pre-Catalyst	Base, Solvent	Yield (%)
1	Pd(OAc) ₂ 5 mol%, P ^t Bu ₂ Me*HBF ₄ 10 mol%	KOAc, NMP/H ₂ O	No rxn
2	Pd(OAc) ₂ 5 mol%, PCy ₃ *HBF ₄ 10 mol%	KOAc, NMP/H ₂ O	86
3	Pd(OAc) ₂ 5 mol%, PCy ₃ *HBF ₄ 10 mol%, PivOH 30 mol%	K ₂ CO ₃ , DMA (0.3 M)	95

18 Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, 3, 4295.

19 Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, 128, 16496. See also Chapter 2.

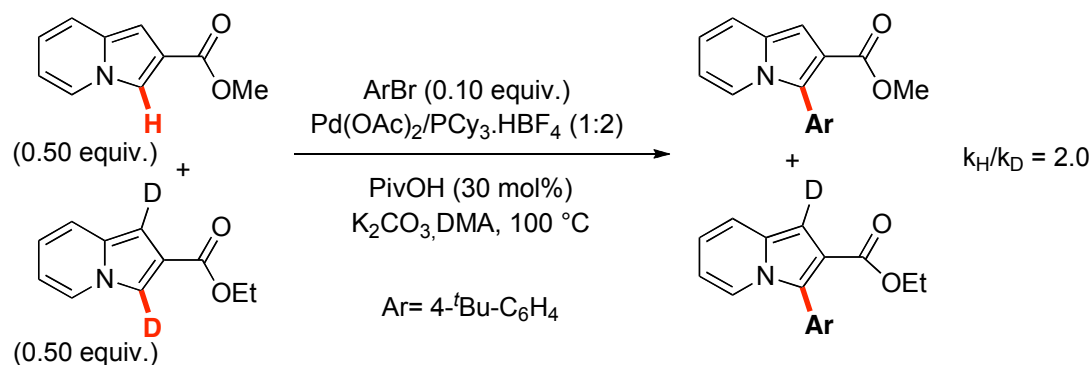
3.2.2.1.2 *In-situ* kinetic isotope effect under the re-optimized direct arylation conditions

With the re-optimized conditions in hand, we next looked at conducting the *in-situ* KIE once again. Prior to perform the competition reaction, we sought to evaluate the kinetic profile of the reaction. We generally observed an induction period of ~10–20 minutes during which no product was formed, then once initiated, 70% of the product was formed in the following 10 minutes.²⁰ For the KIE experiment we were planning, we needed to be able stop the reaction after ~10–20% conversion, this fairly unpredictable initiation induction period and very fast reaction was not suitable for our purpose, therefore minor adjustments were needed. These fine-tunings of the reaction were made by simply reducing the amount of the arylbromide from 120 mol% to 10 mol% in respect to the total amount of indolizines (Scheme 3.8). In that way, it avoids the need to closely monitor the reaction profile in order to stop it at low conversions. As a result, under these re-optimized and finely tuned conditions, the one-pot competition experiment with indolizines led to a KIE of 2.0. Although, this KIE value was small compared to other KIE's obtained for the direct arylation in different systems,²¹ it was nonetheless in opposition to the absence of KIE observed by Gevorgyan. Both this new KIE value and the CMD-like reaction conditions seem to refute the S_EAr mechanism originally proposed for the direct arylation of indolizine. The following section will present other data that supports this hypothesis.

²⁰ A more detail analysis of the reaction kinetic profile will be discuss in section 3.4.1.

²¹ For the direct arylation of benzene, a KIE of 5.5 was obtained (ref 19), pyridine-*N*-oxide had a KIE of 4.7 (ref 26a), pentafluorobenzene had a KIE of 3 (ref 28c) and the intramolecular direct arylation reaction had KIEs varying between 3.5 and 6.7, see: a) Campeau, L.-C.; Parisien, M.; Leblanc, M.; Fagnou, K. *J. Am. Chem. Soc.* **2004**, *126*, 9186. b) Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581. c) García-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 1066.

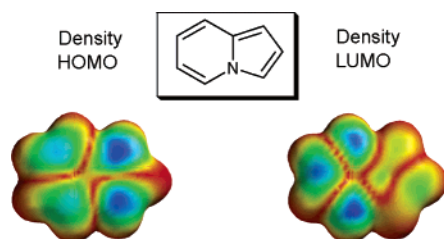
Scheme 3.8 *In-situ* kinetic isotope effect of C2-ester indolizines.



3.2.2.2 Determination of the regioselectivity of Friedel-Crafts reactions on C2-substituted indolizine

We then decided to focus our investigation on the Friedel-Crafts acylation of indolizines. In Gevorgyan's mechanistic studies of the direct arylation of indolizine, the authors evaluated by DFT the electronic densities of the HOMO and LUMO of indolizine (Figure 3.3). From the electron density of the HOMO, we clearly see that the C1 and C3 carbons bear the highest electron density, thus making them the most nucleophilic positions on the molecule. However, simply from a qualitative observation of the HOMO density, one should expect to obtain a mixture of regioisomers from a Friedel-Crafts type reaction and/or by fine-tuning the reaction conditions, one should be able to obtain selectivity for either the C1 or C3 regioisomers. Intrigued by this question, we decided to look into this issue in greater detail.

Figure 3.3 HOMO and LUMO electron densities of indolizine.



(reproduction of Gevorgyan *et al.*)^{2c}

The first indication that the regioselectivity of the acylation could be tuned by a set of conditions came from the preparation of the C2-ethyl-ester indolizine. The allylic alcohol was obtained from the simple Baylis-Hillman reaction in generally excellent yield (Scheme 3.9). Then the pyrrole ring of the indolizine was formed by heating the allylic alcohol to 120 °C in neat acetic anhydride.²² The desired indolizine can generally be obtained in moderate yield, however from the crude mixture we could also isolate an acetylated product. Aside from the presence of the nitrogen, the core structure of the indolizine was symmetrical and very difficult to confirm by NMR, consequently the structure of the C3-acetylated product was confirmed by X-ray crystallography (Figure 3.4).

Scheme 3.9 Preparation of the ethyl indolizine-2-carboxylate.

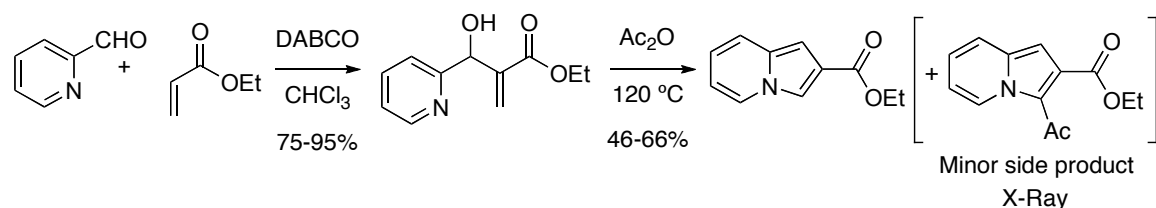
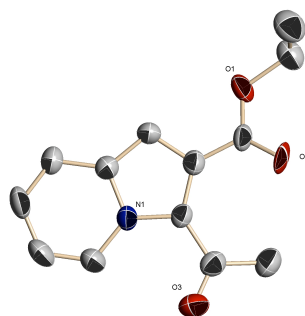


Figure 3.4 X-ray structure of ethyl 3-acetylindolizine-2-carboxylate.



We then repeated the Friedel-Crafts acetylation procedure employed by Gevorgyan *et al.* to determine the relative reactivity of C2 substituted indolizines (Scheme 3.10).²³ The product, obtained as a single regioisomer, matched the NMR data reported by Gevorgyan (Figure 3.5, bottom spectrum). However, the spectrum did not match the NMR spectrum of the acetylated product obtained with acetic anhydride (Figure 3.5, top spectrum). Since the regioselectivity of the C3 acetylated indolizine was confirmed by X-ray crystallography, the regioselectivity of the product reported in Gevorgyan's mechanistic study was not accurate (Table 3.1). As a consequence, the comparison between the relative rate of acetylation and the direct arylation used to support the $\text{S}_{\text{E}}\text{Ar}$ mechanism was not a suitable comparison due to the different reaction regioselectivity.

²³ Sawada, K.; Okada, S.; Kuroda, A.; Watanabe, S.; Sawada, Y.; Tanaka, H. *Chem. Pharm. Bull.* **2001**, *49*, 799.

Scheme 3.10 Aluminum trichloride promoted acetylation of ethyl indolizine-2-carboxylate.

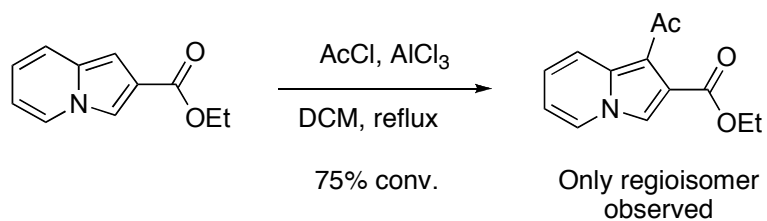
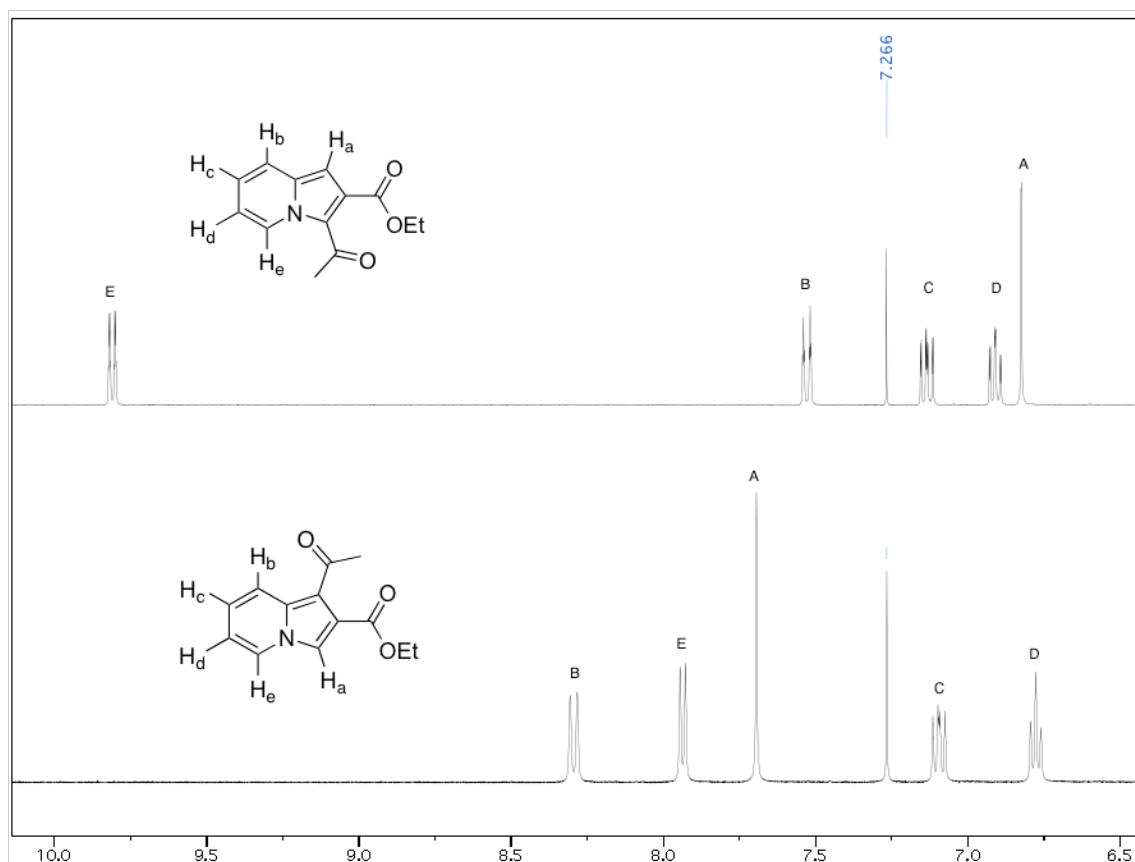


Figure 3.5 Comparison of the NMR spectra of C3 acetylated (top spectrum) and C1 acetylated (bottom spectrum) indolizines.



The regioselectivity of the aluminium trichloride promoted acetylation was also evaluated with various electrophiles. As expected, the regioselectivity of the reaction was dependable on the nature of the electrophile, for instance when *p*-nitrobenzoylchloride was treated under the same condition, we obtained a 3.1:1 mixture of regioisomers in

favor of the C3 position (Scheme 3.11). The structure of the major regioisomer was also confirmed by X-ray analysis (Figure 3.6).

Despite the numerous examples reported in the literature, the direct comparison of Friedel-Crafts acylations to palladium-catalyzed direct arylation represents an oversimplification of the reaction and can certainly lead to incorrect conclusions. In our perspective, these few examples demonstrate that although resemblances were observed between Friedel-Crafts reactions and palladium-catalyzed direct arylations, these two reactions remain very distinct processes and careful studies should be conducted in order to support mechanistic proposals.

Scheme 3.11 Aluminum trichloride promoted *p*-nitrobenzoylation of ethyl indolizine-2-carboxylate.

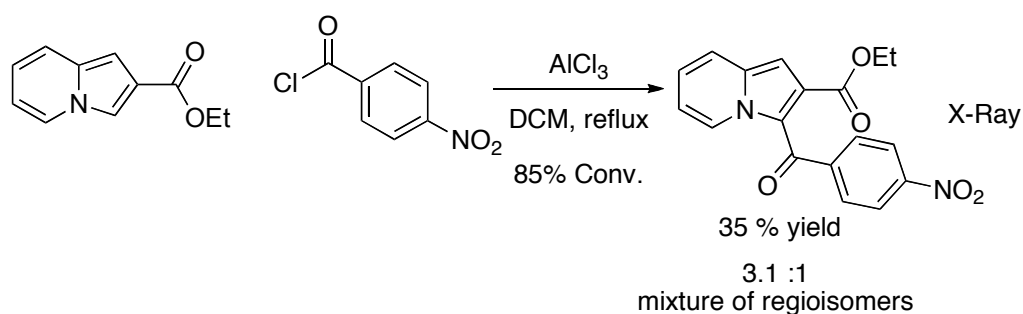
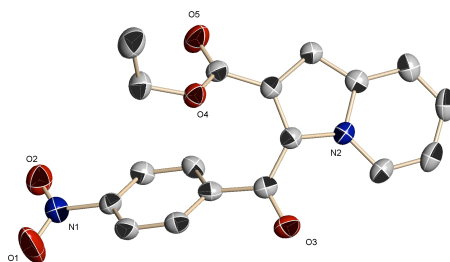


Figure 3.6 X-Ray structure of ethyl 3-(*p*-nitrobenzoyl)indolizine-2-carboxylate.



3.3 Computational analysis of the concerted metallation-deprotonation pathway

The mechanism for reaction of various (hetero)arenes was evaluated by DFT with the B3LYP²⁴ exchange-correlation functional.²⁵ Herein we demonstrate that the CMD pathway not only predicts the reactivity and regioselectivity observed with some simple and electron-deficient arenes but also does so for a diverse set of heteroarenes spanning the majority of the spectrum of known C–H functionalization coupling partners.

3.3.1 Evaluation of the free energy of activation of the C–H bond functionalization of (hetero)arenes *via* the CMD pathway.

Palladium-acetate catalyzed C–H bond functionalization of azine- and azole-*N*-oxides has been proposed to follow the concerted metallation-deprotonation (CMD) pathway.²⁶ Computationally, the barrier of activation for each position of the pyridine-*N*-oxide and thiazole-*N*-oxide were evaluated *via* the CMD transition state. The DFT-predicted site of reaction as well as the order of reactivity matched the experimental site of arylation and relative reactivity²⁷ in the cases shown in Figure 3.7a. As discussed in chapter 1, both benzene and poly-fluorinated benzene are believed to react through a CMD transition state,^{19,28} and the free energy of activation evaluated by DFT also predicted the difference in their relative reactivity (Figure 3.7b).

24 a) Becke, A. D. *J. Chem. Phys.* **1993**, 98, 5648. b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev.* **1988**, B37, 785.

25 Serge Gorelsky conducted the computational mechanistic investigation.

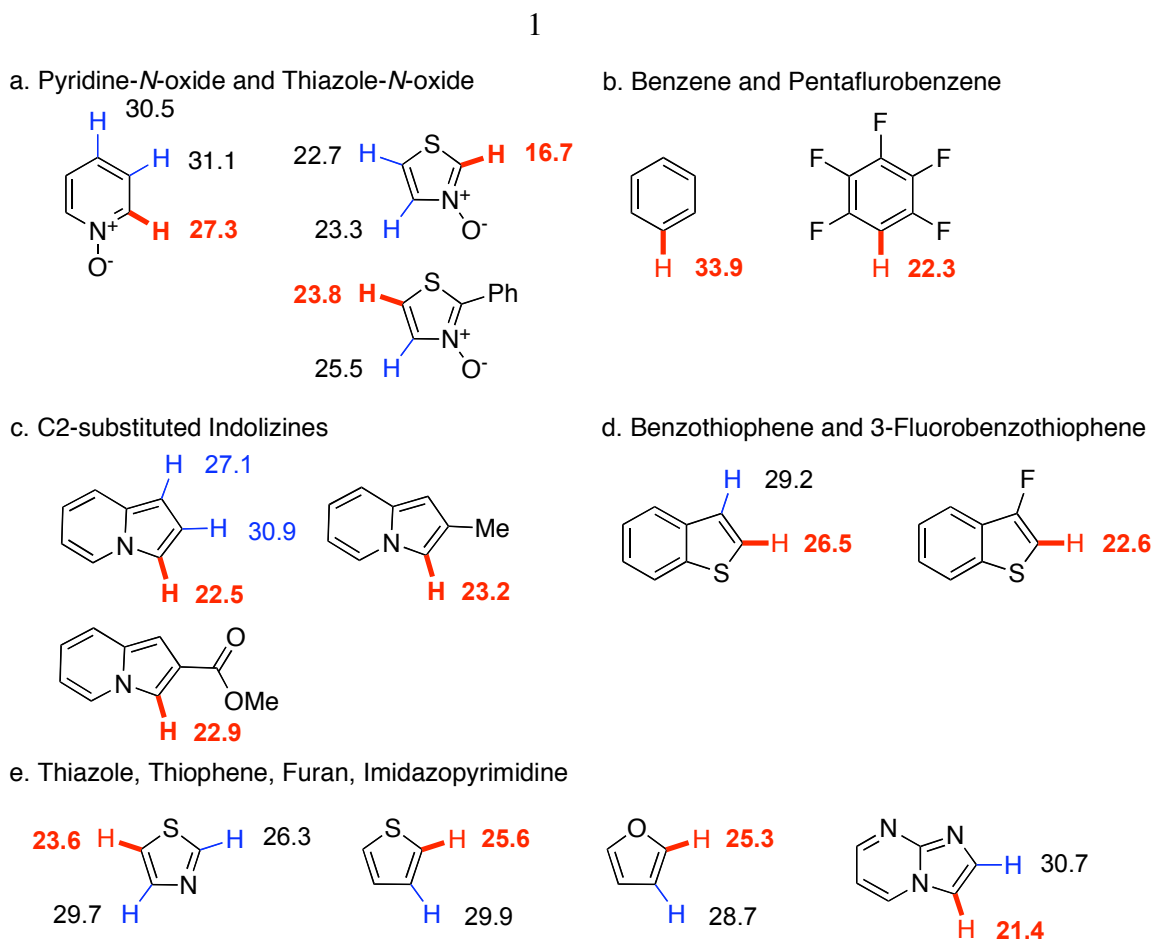
26 a) Campeau, L.-C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, 127, 18021. b) Leclerc, J.-P.; Fagnou, K. *Angew. Chem. Int. Ed.* **2006**, 45, 7781. c) Campeau, L.-C.; Bertrand-Laperle, M.; Leclerc, J.-P.; Villemure, E.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, 130, 3276. d) Campeau, L.-C.; Stuart, D. R.; Leclerc, J.-P.; Bertrand-Laperle, M.; Villemure, E.; Sun, H.-Y.; Lasserre, S.; Guimond, N.; Lecavallier, M.; Fagnou, K. *J. Am. Chem. Soc.* **2009**, 131, 3291. e) Sun, H.-Y.; Gorelsky, S. I.; Stuart, D. R.; Campeau, L.-C. C.; Fagnou, K. *J. Org. Chem.* **2010**, 75, 8180. See also chapter 1.

27 See Section 3.5.2.

28 a) René, O.; Fagnou, K. *Org. Lett.* **2010**, 12, 2116. b) Lafrance, M.; Shore, D.; Fagnou, K. *Org. Lett.* **2006**, 8, 5097. c) Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, 128, 8754.

The mechanism of the C–H bond cleavage by the palladium-acetate complex was also evaluated over a range of π -nucleophilic heteroarenes (Figure 3.7 c-e), palladium-arenium complexes were not located for any of the (hetero)arenes investigated. In each case, a relevant transition state for the CMD pathway was located. This pathway corresponded to the lowest energy pathway and matched the regioselectivity observed for each heteroarenes, regardless of their electronic properties.²⁹ Furthermore, the calculated relative reactivity of C2-substituted indolizines under the CMD pathway correlated well with the minimal impact of these substituents on experimental outcomes (Figure 3.7c).^{2c,30}

Figure 3.7 Calculated free energy of activation ($\Delta\Delta G^\ddagger$) for the CMD pathway. The red bonds correspond to the experimental site of arylation. (Values in kcal/mol)



29 Other pathways that were investigated include C–H oxidative insertion, outer sphere CMD, and Heck-like carbometallation, they resulted with a higher barrier of activation.

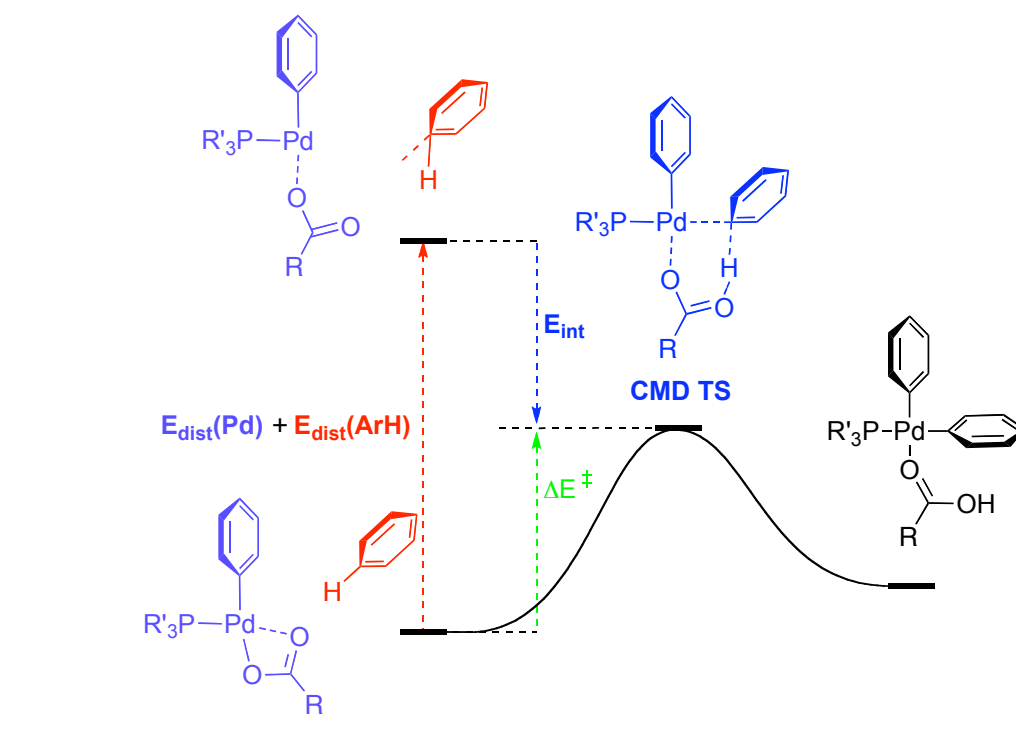
30 See also Table 3.1.

In section 3.2.1, the non-S_EAr reactivity of benzothiophene and its C3-fluorinated analogue in direct arylation reaction was discussed (Scheme 3.4). the increased reactivity of the 3-fluorobenzothiophene was confirmed by the DFT evaluated barrier of activation compared to the standard benzothiophene (Figure 3.7d). Thiazole, thiophene, furan and imidazopyrimidine were also evaluated computationally and the predicted site of reaction matched the experimental site of arylation (Figure 3.7e).

3.3.2 Activation–Strain analysis of the CMD transition states

To gain a better understanding of some of the factors that come into play in establishing the CMD barrier of activation from the ground state of the various substrates and the catalyst, an activation strain analysis was employed.^{31,32} In such analysis the activation barrier ($\Delta E^\ddagger$, green) is divided into two components. On one hand there is the energetic cost associated with the distortion of both the catalyst ($\Delta E_{\text{dist}}(\text{Pd})$, purple) and the substrates ($\Delta E_{\text{dist}}(\text{ArH})$, red) to reach their transition state geometries without interacting together, on the other hand there is energetic gain (ΔE_{int} , blue) arising from the interaction of the substrates with the catalyst at the transition state (Figure 3.8).

Figure 3.8 Representation of CMD pathway for benzene with activation-strain analysis.



31 This model is related to the deformation/interaction method developed by Morokuma: Morokuma, K. *J. Chem. Phys.* **1971**, 55, 1236.

32 Recent application of the model in organometallic chemistry: a) Schoenebeck, F.; Houk, K. N. *J. Am. Chem. Soc.* **2010**, 132, 2496. b) van Zeist, W.-J.; Visser, R.; Bickelhaupt, F. M. *Chem.–Eur. J.* **2009**, 15, 6112. c) Legault, C. Y.; Garcia, Y.; Merlic, C. A.; Houk, K. N. *J. Am. Chem. Soc.* **2007**, 129, 12664. d) de Jong, G. T.; Bickelhaupt, F. M. *ChemPhysChem* **2007**, 8, 1170. e) de Jong, G. T.; Bickelhaupt, F. M. *J. Chem. Theory Comput.* **2007**, 3, 514.

In Figure 3.9 are presented the results of the activation-strain analyses conducted on the (hetero)arenes presented in Figure 3.7. In order to facilitate the understanding of these results, the data is presented in columns, from left to right: green columns represent the energy of activation ($\Delta E^\ddagger$), red columns represent the energetic cost associated with the distortion of the (hetero)arene ($\Delta E_{\text{dist}}(\text{ArH})$) and purple columns are for the distortion energy of the catalyst ($\Delta E_{\text{dist}}(\text{Pd})$). Finally, the blue columns represents the absolute values of the energetic gain obtained from the interaction of the both the catalyst and (hetero)arene (ΔE_{int}).

From the analysis of the data (Figure 3.9 a-c), we can see that the energy cost for the distortion of the catalyst (purple) is nearly independent of the nature of the (hetero)arene. In comparison with benzene, we can see that electron-deficient arenes benefit from lower arene distortion energy cost, in the case of the thiazole-*N*-oxides those substrates benefit also from greater interaction energies which contributed to lower their activation barrier compared to benzene (Figure 3.9a).

Figure 3.9 a Distortion/Interaction analysis for the lowest CMD transition states ($\Delta E^\ddagger$).

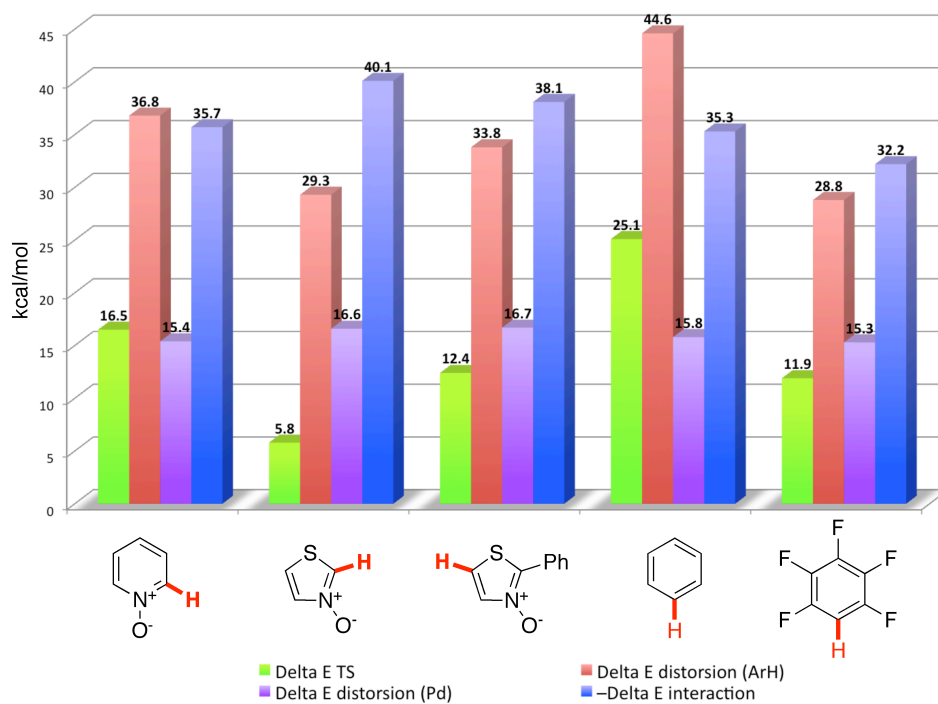


Figure 3.9 b

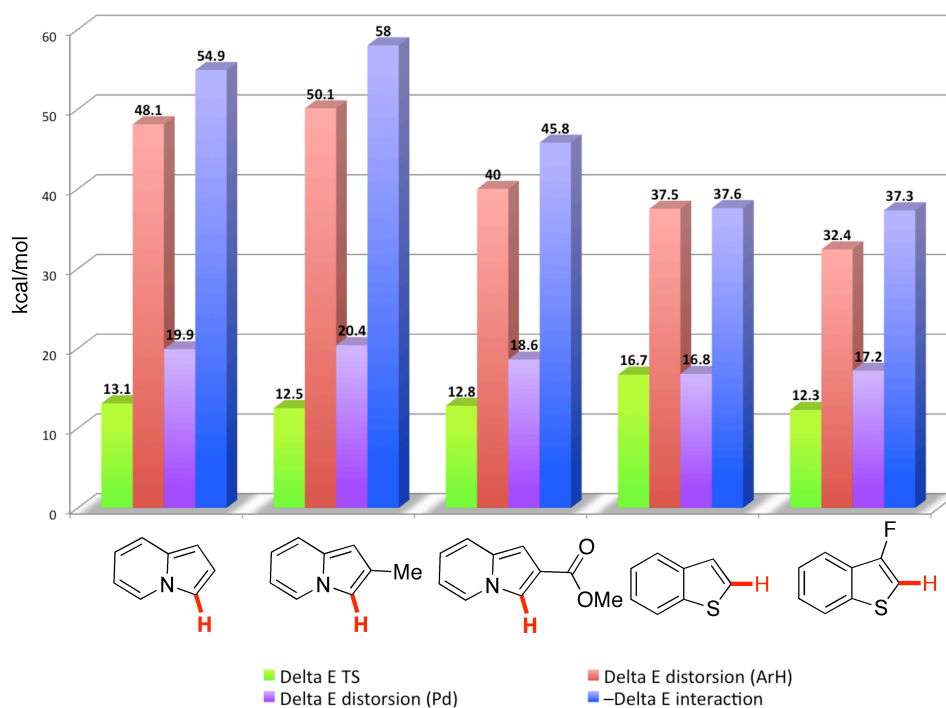
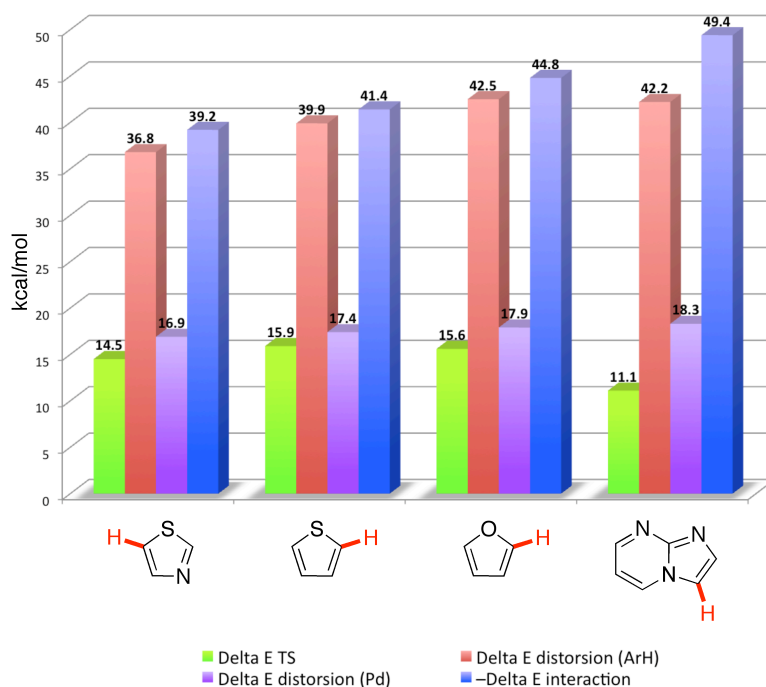


Figure 3.9 c



The general trend observed with π -electron-rich heteroarenes is that they benefit from large energies of interaction (ΔE_{int}). This gain is also offset by large $\Delta E_{\text{dist}}(\text{ArH})$ (Figure 3.9 b,c). The substituted indolizines are subjected to similar distortion and interaction energies and the sum of these factors results in very similar barriers of activation. As for benzothiophene and 3-fluorobenzothiophene, the difference in their $\Delta E^\ddagger$ arises from the difference in their $\Delta E_{\text{dist}}(\text{ArH})$ due to the presence of the electron withdrawing fluorine atom (Figure 3.9b). A similar phenomenon can be observed in the comparison of the benzene and the pentafluorobenzene.

3.3.3 Concluding remarks

This section presented experimental and theoretical data that suggest that the CMD pathway might be involved in a very large number of palladium-catalyzed C–H bond functionalization reactions. The DFT evaluated barriers of activations for the (hetero)arenes of Figure 3.7 perfectly matched the regioselectivity observed

experimentally. The activation-strain analyses resumed in Figure 3.9 casted light on the factors contributing to the CMD transition state, in a latter chapter of this document will be presented our latest efforts to gain a better understanding of those factors. In the following sections of this chapter the advancement made in the C–H functionalization field will be presented. These advancements were made based on the knowledge gained in this section.

3.4 Establishment of broadly applicable reaction conditions for the palladium-catalyzed direct arylation of heteroaromatic compounds

Heteroatom-containing biaryls are undoubtedly common motifs in biologically active compounds, in organic materials and polymers. The traditional method of preparation of this motif over the years has been dominated by transition-metal catalyzed cross-coupling reactions, where an organometallic species is coupled to an aryl halide partner.³³ For over a decade now, alternatives have emerged for which at least one the coupling partners (typically the organometallic component) have been replaced by the corresponding simple arene.³⁴ Since the pioneering work nearly 30 years ago, many research groups, ours included, have been involved in the development of biaryl formation methods containing heteroatoms.^{34o}

33 a) *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 2004. b) Hassan, J.; Sévignon, M.; Gozzi, C. Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359.

34 For reviews on direct arylation, see: a) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633. b) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731. c) Daugulis, O.; Zaitsev, V. G.; Shabashov, D.; Pham, Q.-N.; Lazareva, A. *Synlett* **2006**, 3382. d) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. e) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. f) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200. g) Campeau, L.-C.; Stuart, D. R.; Fagnou, K. *Aldrichim. Acta* **2007**, *40*, 35. h) Campeau, L.-C.; Fagnou, K. *Chem. Soc. Rev.* **2007**, *36*, 1058. i) Li, B.-J.; Yang, S.-D.; Shi, Z.-J. *Synlett* **2008**, 949. j) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, 3013. k) McGlacken, G. P.; Bateman, L. M. *Chem. Soc. Rev.* **2009**, *38*, 2447. l) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. m) Kulkarni, A. A.; Daugulis, O. *Synthesis* **2009**, *24*, 4087. n) Bellina, F.; Rossi, R. *Tetrahedron* **2009**, *65*, 10269. o) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792. p) Roger, J.; Gottumukkala, A. L.; Doucet, H. *ChemCatChem* **2010**, *2*, 20.

Although the important growth of methodologies to couple heteroarenes with aryl halides, several challenges remain relatively unsolved, including the establishment of conditions of general applicability that can enable the successful cross-coupling of the broadest range of heterocyclic compounds possible and the frequent need to use one of the coupling partners in excess. The primary issue associated to these challenges was the diversity of mechanistic pathways related to the C–H bond functionalization which preclude a more rational approach to reaction development. In sections 3.2 and 3.3 were presented experimental and computational evidence that suggested that the involvement of the CMD mechanism might be largely implicated in the coupling of π -rich heteroarenes. These studies prompted us to explore the use of the CMD-type reactions conditions presented in section 3.2.2.1.1 (with a focus on the use of pivalic acid as a co-catalyst) in the establishment of broadly useful direct arylation reaction conditions. In the following section, the outcomes of these studies that lead to the development of generally useful direct arylation reaction conditions between a wide range of coupling partners in a 1:1 substrate stoichiometry will be described.³⁵

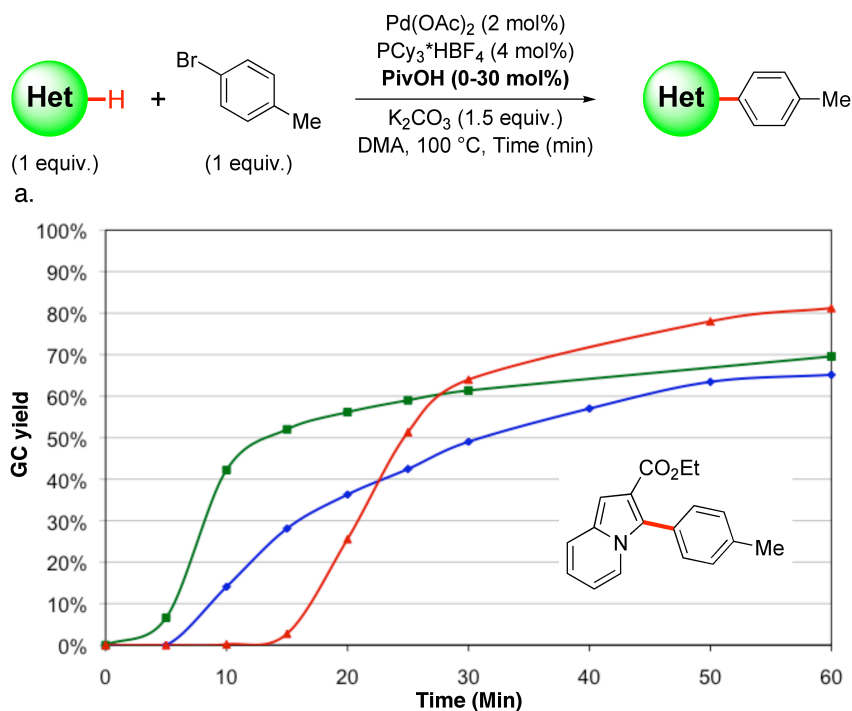
3.4.1 The effect of pivalic acid on the kinetic profile in the palladium-catalyzed direct arylation of heteroarenes with aryl bromide

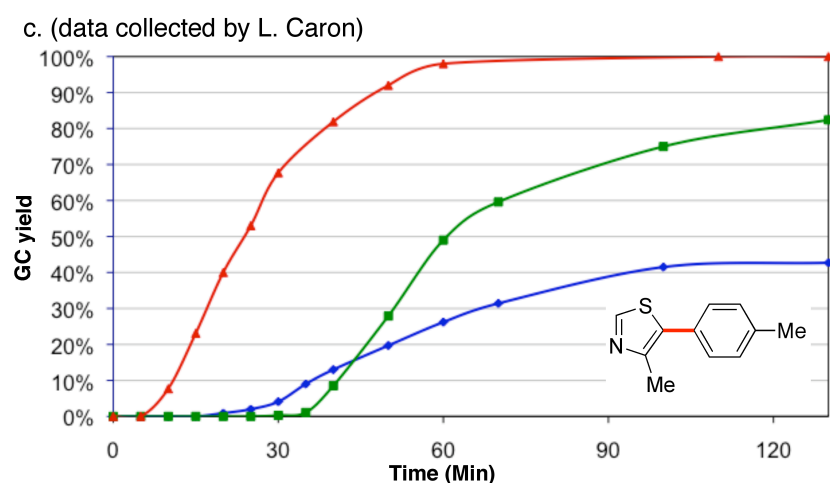
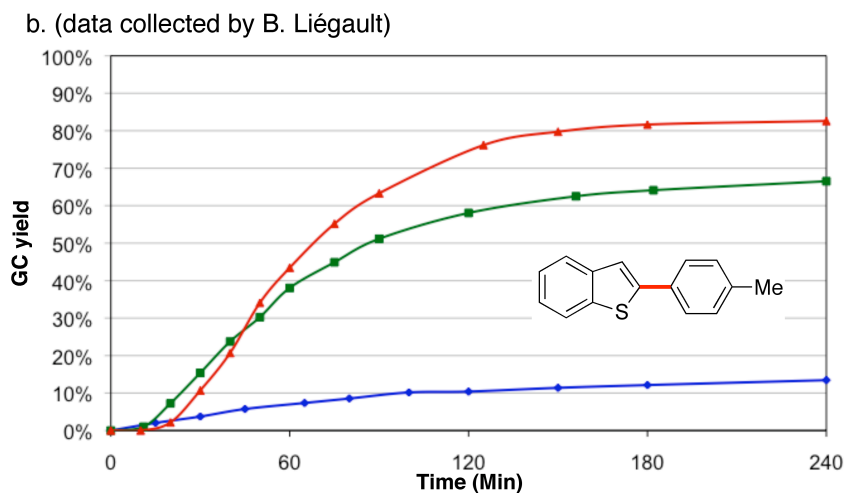
Three heteroarenes were selected to evaluate the impact of added pivalic acid (*in situ* transformed into potassium pivalate): indolizine, benzothiophene and 4-methylthiazole (Figure 3.10). Under the conditions initially developed to limit the erosion of the deuterium labeling (see section 3.2.2.1), we decided to study the effect of pivalic acid additives on the kinetic profile of the direct arylation reaction of these heteroarenes. In the absence of pivalic acid (blue curves in Figure 3.10), low conversion were generally observed during the time scale of the experiment, with the exception of indolizine which exhibited good reactivity. For example, benzothiophene yielded only ~12% of product after 4 hours of reaction, the indolizine yielded ~65% after only one hour. On the other

³⁵ This work was done in collaboration with Benoît Liégault, Laurence Caron and Anna Vlassova. Part of following results were published in the following article: Liégault, B.; Lapointe, D.; Caron, L.; Vlassova, A.; Fagnou, K. *J. Org. Chem.* **2009**, *74*, 1826.

hand, addition of 10 mol% of pivalic acid (green curves in Figure 3.10) significantly increased the rate and yield of the reaction for each arene evaluated. The rates and yields of the transformation were found to be optimal when 30 mol% of the pivalic acid (red curves in Figure 3.10) is added as co-catalyst in the reaction mixtures. Up to 50 mol% of pivalic acid were found to not further enhance the efficacy of the transformation. These trends demonstrated that the use of a substoichiometric quantity of pivalic acid in conjunction with a stoichiometric amount of insoluble carbonate base should be used to establish direct arylation reaction conditions of general applicability.

Figure 3.10 Effect of pivalic acid on the kinetic profile in the Pd-catalyzed direct arylation of heteroarenes.^{a,b}





- a) GC yields of product overtime (min) using tetradecane as internal standard.
 b) Blue lines: No pivalic acid, Green lines: 10 mol% of pivalic acid, Red lines: 30 mol% of pivalic acid.

3.4.2 Scope and limitations of the direct arylation of heteroarenes under general conditions

To evaluate the potential breadth of these reaction conditions, a broad range of heteroarenes and aryl halides, mainly aryl bromides, were tested under the same set of conditions in a 1:1 heteroarene/haloarene stoichiometry (Table 3.3). Standard reaction conditions for these processes were adopted to involve the use of the heterocycle (1 equiv.), an aryl bromide (1 equiv.), $\text{Pd}(\text{OAc})_2$ (2 mol%), $\text{PCy}_3 \cdot \text{HBF}_4$ (4 mol%), PivOH (30 mol%), and K_2CO_3 (1.5 equiv.) in DMA (0.3 M) at 100 °C.

The logic behind the establishment of reaction conditions using equimolar amounts of both coupling partners arose from our concern related to the practicality of this methodology in medicinal chemistry/industrial settings. Indeed if one (or both) of the coupling partners were available in limited quantity, ideal reaction conditions should not require an excess amount of this coupling partner. Therefore, the choice of not using an excess of either coupling partners might not give the maximum yield for any particular reactions, but it should give a better overview of the efficiency of the transformation. Furthermore, the use of equimolar coupling partners and low catalyst loading (2 mol% as opposed to 5 mol% which is more commonly employed when evaluating the scope of these transformations) differentiates many of these examples from previous reports.

C2 substituted indolizines are substrates for this transformation, as first described by Gevorgyan. For example electron neutral or withdrawing functional groups on the aryl bromide are well tolerated and gave C3 arylated products in good yields (entries 1–5 and 9–11). Furthermore, the C1 position of indolizine can be functionalized under the same conditions when the C3 position is blocked (entries 6–8). A reaction between indolizine and 5-acetyl-2-bromothiophene also furnished the heterocyclic biaryl product in good yield (entry 11). The yield of these reactions can easily be optimized by simply by using slight excess of either the aryl bromide or the heteroarene (entries 2 vs 3 and 6–8).

Substituted 1,2,3-triazoles can also be functionalized at the C5 positions with both electron-rich and -poor aryl bromides in moderate to good yields (entries 12–16). Imidazopyrimidines are also excellent substrate for direct arylation, they tolerate both electron-rich and -poor aryl bromides (entries 17–22) and the sterically congested 1-bromo-2-nitrobenzene (entries 19–20).

Table 3.3 Scope of the direct arylation of heteroarenes.^a

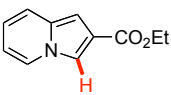
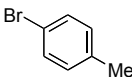
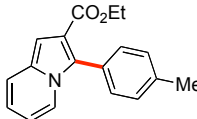
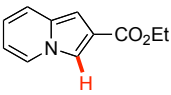
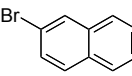
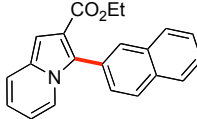
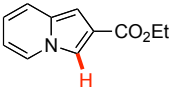
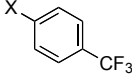
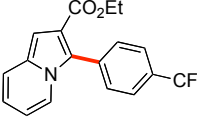
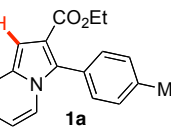
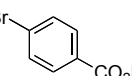
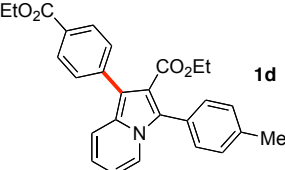
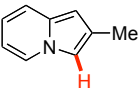
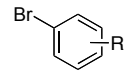
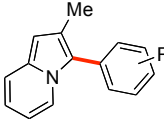
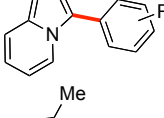
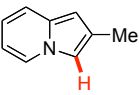
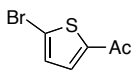
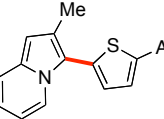
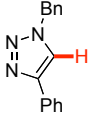
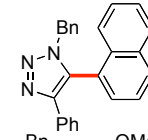
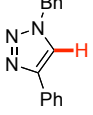
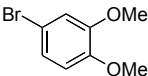
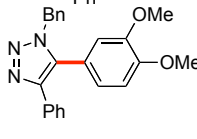
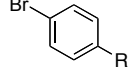
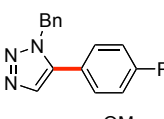
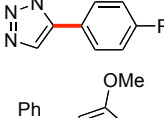
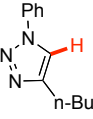
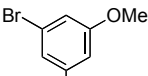
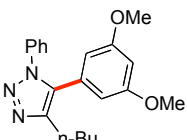
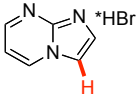
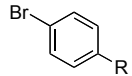
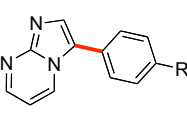
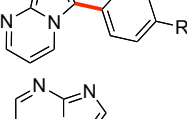
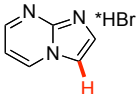
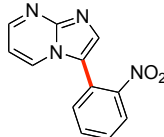
Entry	Heterocycle	Aryl-halide	Product	Time (h)	Yield (%)
1			 1a	4	89
2 3 ^h			 1b	4 4	86 99
4 5		 X = Br X = Cl	 1c	4 16	82 59
6 7 ^e 8 ^c	 1a		 1d	24 24 24	54 63 82
9 10		 R = 4-NO ₂ R = 2-CO ₂ Et	 2a  2b	4 24	85 56
11			 2c	16	81
12			 3a	16	26
13			 3b	16	62
14 15		 R = OMe R = CO ₂ Et	 4a  4b	6 6	60 60
16			 5	24	87
17 ^g 18 ^g		 R = F R = NMe ₂	 6a  6b	4 4	77 80
19 ^g 20 ^g		 X = Br X = Cl	 6c	4 16	86 46

Table 3.3 continued

Entry	Heterocycle	Aryl-halide	Product	Time (h)	Yield (%)
21				4	76
22				4	82
23				4	91
24				4	65
25				4	72
26				4	60
27				4	69
28				4	63
29				4	58
30				24	63
31				4	82
32				14	22
33 ^{a,9}				16	86
34				16	80
35				16	72
36				16	74
37				16	38
38				22	68
39				16	58
40				16	40
41				16	53
42				16	54
43				16	40
44				24	87
45 ^d				24	87
46				24	87
47				16	29
48				16	61

Table 3.3 continued

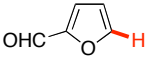
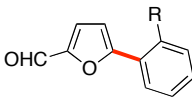
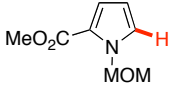
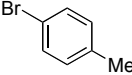
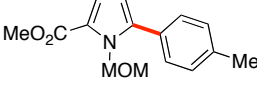
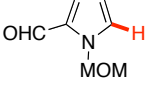
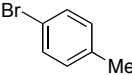
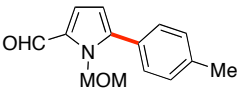
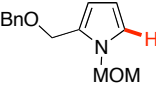
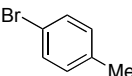
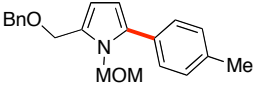
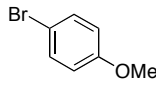
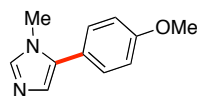
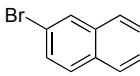
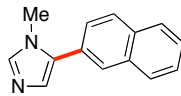
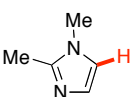
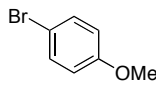
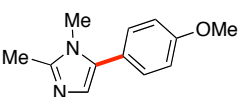
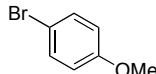
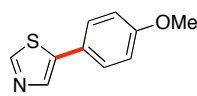
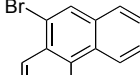
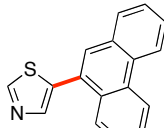
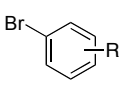
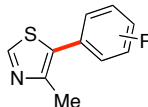
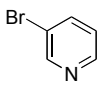
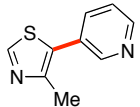
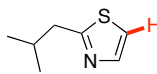
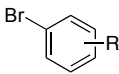
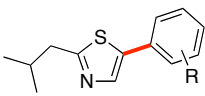
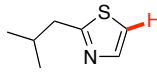
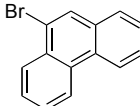
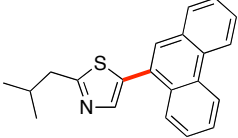
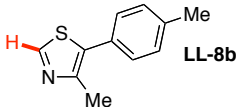
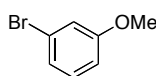
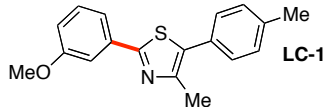
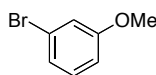
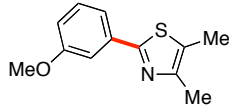
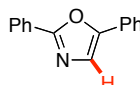
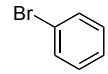
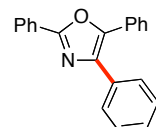
Entry	Heterocycle	Aryl-halide	Product	Time (h)	Yield (%)
49 ^c 50 ^c		 R = F R = Ph	 BL-14a BL-14b	16 16	44 70
51 52 ^b			 LC-1	13 14	57 69
53 ^b			 LC-2	14	52
54 ^b			 LC-3	14	65
55			 LC-4a	25	34
56			 LC-4b	27	40
57			 LC-5	23	32
58 ^b			 LC-6	19	62
59			 LC-7	18	60
60 61 62 63		 R = 4-Cl R = 4-Me R = 4-OMe R = 3-OMe	 LC-8a LC-8b LC-8c LC-8d	4 1.5 2.5 1.5	66 78 65 74
64			 LC-8e	25	56
65 66		 R = H R = 4-Me	 LC-9a 8	3.5 4	89 77
67			 LC-9b	3.5	88

Table 3.3 continued

Entry	Heterocycle	Aryl-halide	Product	Time (h)	Yield (%)
68	 LL-8b		 LC-10	74	54
69			 LC-11	42	42
70 ^b			 LC-12	14	83

^a Conditions (unless otherwise specified): heterocycle (1 equiv.), aryl halide (1 equiv.), Pd(OAc)₂ (2 mol %), PCy₃*HBF₄ (4 mol %), PivOH (30 mol %), K₂CO₃ (1.5 equiv), DMA (0.3 M), 100 °C. ^b Heterocycle (1.5 equiv.). ^c Heterocycle (2 equiv.). ^d Aryl bromide (1.5 equiv.), K₂CO₃ (2 equiv.). ^e Aryl bromide (2 equiv.), K₂CO₃ (2.5 equiv.). ^f Pd(OAc)₂ (4 mol %), PCy₃*HBF₄ (8 mol %). ^g K₂CO₃ (2.5 equiv.). ^h Aryl bromide (1.2 equiv.). Compounds followed by the initials **BL-** were prepared by Benoît Liégault and Anna Vlassova, and those associated with the initials **LC-** were prepared by Laurence Caron.

Under the standard conditions, benzothiophene was reacted with a wide range of aryl bromides, providing the C2 arylated products generally in good yields (entries 23–32). C2 substituted thiophenes, including 2,2'-bithiophene, are good substrates for the direct arylation at C5 positions. Electron withdrawing and donating groups on either the thiophene or the aryl bromide are tolerated under the standard condition developed herein (entries 34–46). As opposed to benzothiophene, benzofuran was found to be a more problematic substrate under these conditions (entry 47). Furans reacted at the C2 position, although that slight excess of the heteroarene (2 equiv.) were needed to improve the yield of the reaction, nonetheless this compares favorably to the larger excess (2–10 equiv.) used in the previous reports.

Direct arylation of pyrrole substrates, which has previously been achieved with a small excess of the zinc chloride or as the SEM-protected pyrrole with a slight excess of aryl halide, can be accomplished under the standard conditions to give C5 arylated products in moderate to good yields and with good regioselectivity (entries 51–54). Similarly, other heterocycles, such as imidazoles, thiazoles and oxazole reacted efficiently with electron-rich and -deficient aryl bromides to give C5 arylated products (entries 55–67, 70). For C4 and C5 substituted thiazoles, the C2 arylation was also

possible although the products were obtained in moderate yield and required longer reaction time (42 to 72 hours, entries 68–69).

Table 3.4 Effect of (pseudo)halide on the direct arylation of heteroarenes.

$\text{HetAr-H} + \text{X-C}_6\text{H}_4\text{-Me} \xrightarrow[\text{DMA, 100 } ^\circ\text{C, Time}]{\text{Pd(OAc)}_2 \text{ (2 mol\%)}, \text{PCy}_3\cdot\text{HBF}_4 \text{ (4 mol\%)}, \text{PivOH (30 mol\%)}, \text{K}_2\text{CO}_3 \text{ (1.5 equiv.)}}$
 $\text{HetAr-C}_6\text{H}_4\text{-Me}$

(1 equiv.) (1 equiv.)

Entry	Heterocycle	Aryl-halide	Time (h)	Yield (%)
1		I	24	46
2 ^a		I	24	33
3		Br	4	77
4		Cl	24	0
5		OTf	24	34
6		I	8	18
7 ^a		I	8	32
8		Br	4	91
9		Cl	24	9
10		OTf	16	19

^a 0.5 equiv. of Ag₂CO₃ was added.

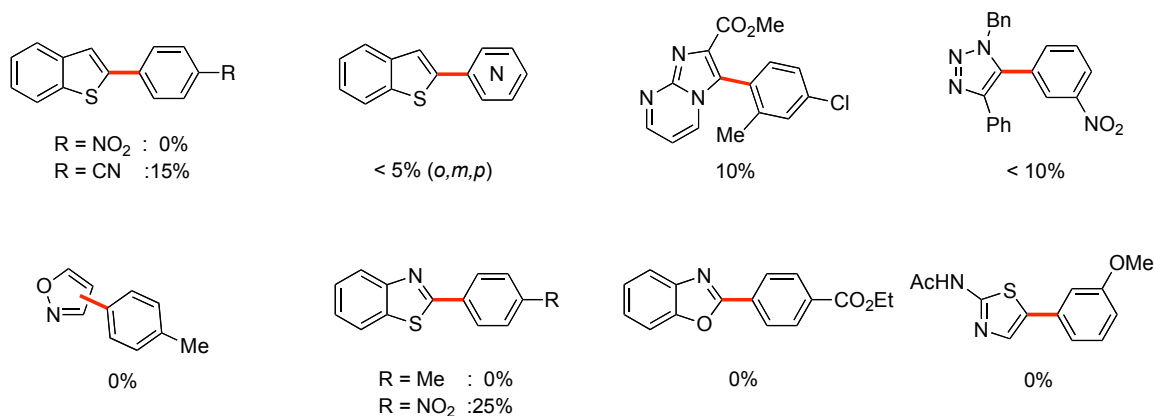
In Table 3.3 we included two examples in which an aryl chloride was used instead of an aryl bromide (entries 5 and 20). In both cases, the reaction time was longer (16 hours instead of 4 hours) and resulted in lower yield. To evaluate if the effect of the halide might be more general, we probed the reactivity of typical aryl (pseudo)halide with two different heteroarenes (Table 3.4). The use of 4-iodotoluene with both the thiazole and benzothiophene gave 46% and 18% yield, respectively (entries 1 and 6). We have previously observed that iodides had a catalyst poisoning effect in direct arylation reactions.³⁶ However, the addition of silver salts to the reaction mixture, which are believed to abstract the iodide from the palladium catalyst, did not restore the reactivity to the system (entries 2 and 7). Despite the use of an electron rich phosphine ligand, which is known to facilitate the oxidative-insertion of the palladium(0) specie into the aryl–chloride bond in other direct arylation processes,³⁷ the use 4-chlorotoluene also gave

36 Campeau, L. C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581–590.

37 For a review of palladium-catalyzed cross-coupling reactions of aryl chloride, see: Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176.

an inferior yield or even no product (entries 4 and 9). Due to importance of aryl triflates as a privileged motif in medicinal chemistry, we were slightly disappointed to find out that they did not give good yields under the standard reaction conditions (entries 5 and 10). Nonetheless, we believed that aryl triflates could be more broadly used in direct arylation reactions if some optimizations were realized for that purpose.

Figure 3.11 Representative examples of unsuccessful coupling products (The results were estimated by GC-MS or by thin layer chromatography).



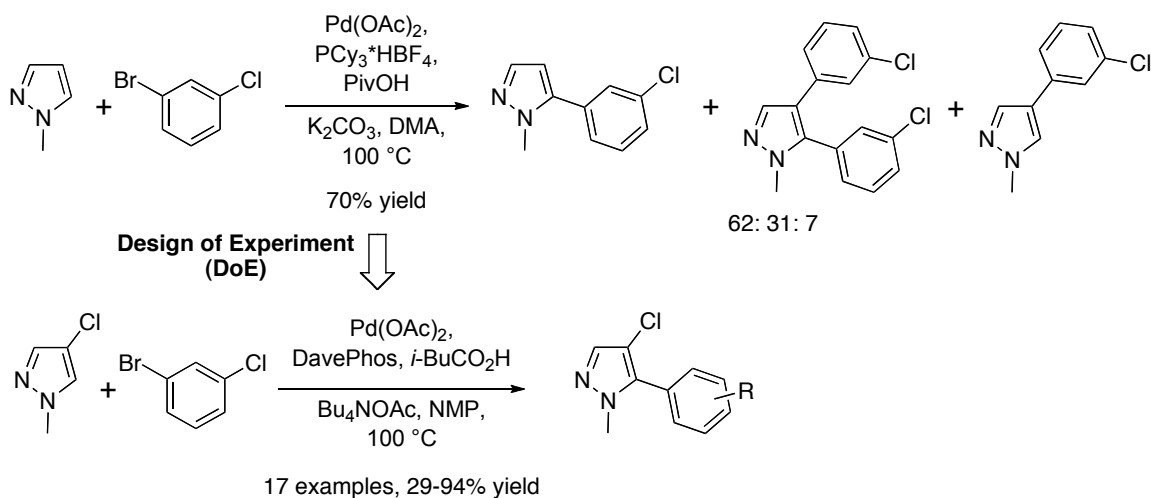
While the conditions were found to be generally applicable to a wide range of heteroarenes and aryl bromides, we observed low yields or poor reactivity on several occasions (Figure 3.11). For instance, many times we were unable to couple two heteroarenes together although it was possible depending on the combination of heteroarene and heteroaryl bromide (Table 3.3 entries 11, 32 and 64). Not surprisingly, some sterically demanding aryl bromides gave poor reactivity. Unprotected monoprotected 2-aminothiazole as well as some heterocycles, such as isoxazoles, were found to be incompatible with the standard reactions conditions.

3.4.3 Concluding remarks

In summary, we have established practical reaction conditions readily applicable to a broad range of coupling partners without any significant optimization. These conditions

highlight the use of substoichiometric amount pivalic acid to enhance the reaction rates. These conditions should provide a starting point to those wishing to functionalize novel heteroarenes C–H bonds. An excellent example this purpose was reported by Mateos, Mendiola *et al.* (Scheme 3.12).³⁸ Starting from *N*-methylpyrrole and 1-bromo-3-chlorobenzene using the standard reactions conditions, they first obtained a mixture of products. Using “Design of Experiment” techniques coupled with statistical methodology, they were able to find a set of conditions to arylate at C5 position *N*-methyl-4-chloropyrrole with aryl bromides.

Scheme 3.12 Regioselective palladium-catalyzed arylation of 4-chloropyrroles, by Mateos, Mendiola *et al.*³⁸



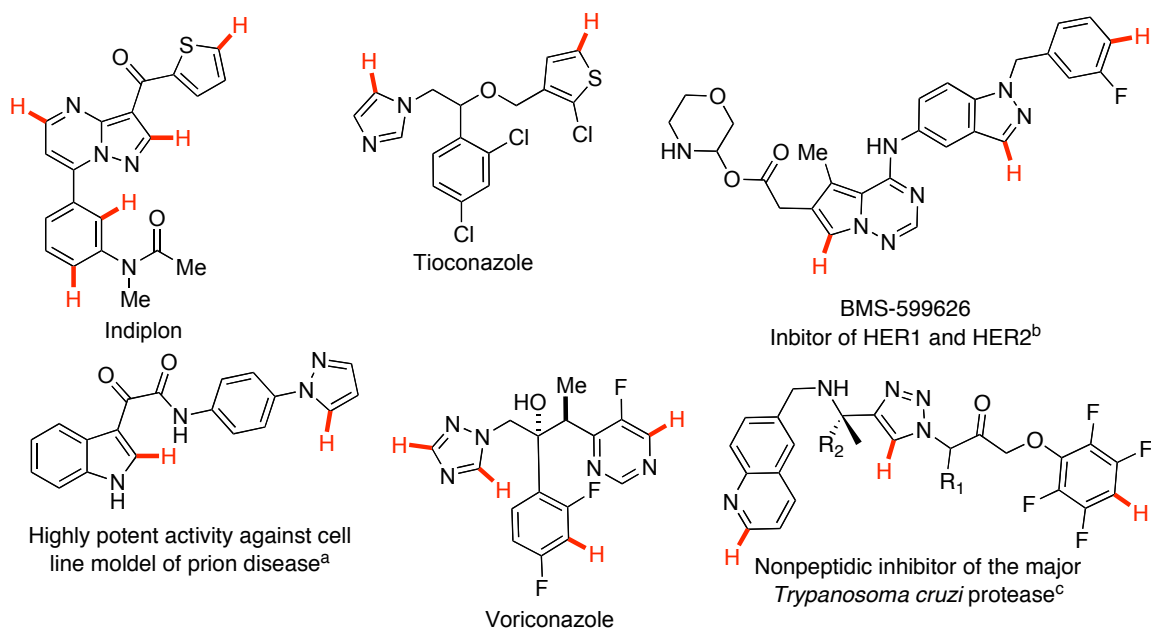
38 Mateos, C.; Mendiola, J.; Carpintero, M.; Mínguez, J. M. *Org. Lett.* **2010**, *12*, 4924.

3.5 Predictable and Site-Selective Functionalization of Poly-(Hetero)Arene Compounds by Palladium Catalysis

Despite the enormous interest in the recent literature for C–H bond functionalization reactions, to date there have been very few reports, if any, on the direct reaction of complex substrates containing multiple (hetero)arenes functionalizable at multiple C–H bonds. With the prevalence of multiple arenes, aromatic heterocycles as well as biaryl linkages in medicinally relevant molecules (Figure 3.12), efficient methods to directly functionalize complex poly-(hetero)arenes through transition metal catalysis would be of great value.

Figure 3.12 Examples of drugs and drug candidates containing multiple functionalizable

C–H bonds.³⁹



39 (a)Thompson, M. J.; Borsenberger, V.; Louth, J. C.; Judd, K. E.; Chen, B. *J. Med. Chem.* **2009**, 52, 7503. (b) Gavai, A. V.; Fink, B. E.; Fairfax, D. J.; Martin, G. S.; Rossiter, L. M.; Holst, C. L.; Kim, S.-H.; Leavitt, K. J.; Mastalerz, H.; Han, W.-C.; Norris, D.; Goyal, B.; Swaminathan, S.; Patel, B.; Mathur, A.; Vyas, D. M.; Tokarski, J. S.; Yu, C.; Oppenheimer, S.; Zhang, H.; Marathe, P.; Fagnoli, J.; Lee, F. Y.; Wong, T. W.; Vite, G. D. *J. Med. Chem.* **2009**, 52, 6527. (c) Brak, K.; Kerr, I. D.; Barrett, K. T.; Fuchi, N.; Debnath, M.; Ang, K.; Engel, J. C.; McKerrow, J. H.; Doyle, P. S.; Brinen, L. S.; Ellman, J. A. *J. Med. Chem.* **2010**, 53, 1763. (d) Lumeras, W.; Caturla, F.; Vidal, L.; Esteve, C.; Balagué, C.; Orellana, A.; Domínguez, M.; Roca, R.; Huerta, J. M.; Godessart, N.; Vidal, B. *J. Med. Chem.* **2009**, 52, 5531.

A large number of arenes have been functionalized by direct arylation and alkylation methods, including a wide variety of electron-rich, electron-deficient and simple (hetero)arenes.³⁴ The substrate scopes for the arylation of electron-deficient and simple (hetero)arenes are often limited to either a specific heteroarene or a set of chemically similar (hetero)arenes. As described in section 3.4, for electron-rich heteroarenes however, two general direct arylation methods capable of accommodating a large range of arenes have been developed.^{35,40,41} The conditions reported by Daugulis *et al.* employed a palladium acetate/adamantylphosphine pre-catalyst to couple aryl chlorides with a variety of electron-rich heteroarenes.⁴⁰ The method that our group has developed was based on the advances made on the functionalization of simple arenes employing pivalate additives to increase the reactivity of the system.^{35,41} Due to the lack of general approaches to functionalize complex substrates containing multiple (hetero)arenes and multiple C–H bonds, we sought to address this issue.

The underlying challenges of functionalizing complex substrates containing multiple reactive C–H bonds are (1) to achieve site-selectivity in the transformation by choosing the appropriate conditions, and (2) to predict the outcome of the transformation when general/non-specific conditions are applied. Being able to select and/or predict the outcome of such reactions would greatly improve the applicability of C–H bond functionalization methods in the late stage of the synthesis of biologically active analogues. As part of our program dedicated to site-selective functionalization of aromatic C–H bonds, we were interested in addressing this challenge.

Herein are presented a systematic evaluation of reaction conditions and heteroarene reactivity to obtain selective and predictable functionalization at various positions on substrates containing multiple functionalizable C–H bonds. We show that electron-deficient (hetero)arenes can be selectively arylated in the presence of electron rich arenes by applying mild (hetero)arene specific conditions. In contrast, electron rich arenes can

40 Chiong, H. A.; Daugulis, O. *Org. Lett.* **2007**, 9, 1449.

41 Liégault, B.; Petrov, I.; Gorelsky, S. I.; Fagnou, K. *J. Org. Chem.* **2010**, 75, 1047.

also be selectively arylated in the presence of electron-deficient (hetero)arenes by applying different mild (hetero)arene specific conditions. In parallel, we established the first reactivity chart for a range of heteroarenes based on their relative reactivity toward C–H functionalization. This reactivity chart was in good agreement with the predicted reactivity obtained from the concerted metallation-deprotonation (CMD) barriers of activation calculated by DFT.^{8,42} From this, we demonstrated that by using general/non-specific conditions, we could predict the outcome of the C–H bond functionalization with substrates containing two reactive C–H bonds on two different electron-rich heteroarenes.⁴³

3.5.1 Conditions-based site-selectivity

Our attention was first directed toward the use of mild reaction conditions selective for specific classes of (hetero)arenes. In a previous report,⁴⁴ 6- and 7-azaindoles were selectively functionalized at either the azine or the azole rings by utilizing two specific sets of mild conditions – one which was developed to functionalize azine-*N*-oxides⁴⁵ and another set that was developed by Larrosa *et al.*⁴⁶ to arylate at the C2 position of indoles (Scheme 3.13).

⁴² See section 3.3.

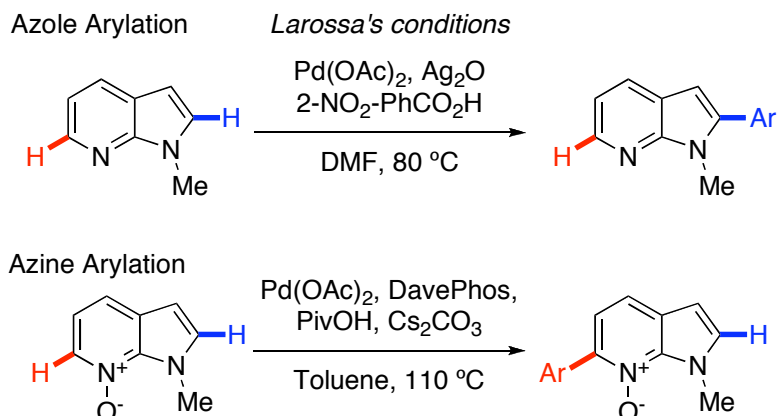
⁴³ This work was done in collaboration with Thomas Markiewicz, Christopher Whipp and Amy Toderian. Part of following results were published in this article: Lapointe, D.; Markiewicz, T.; Whipp, C. J.; Toderian, A.; Fagnou, K. *J. Org. Chem.* **2011**, *76*, 749.

⁴⁴ Huestis, M. P.; Fagnou, K. *Org. Lett.* **2009**, *11*, 1357.

⁴⁵ a) Campeau, L.-C.; Stuart, D. R.; Leclerc, J.-P.; Bertrand-Laperle, M.; Villemure, E.; Sun, H.-Y.; Laserte, S.; Guimond, N.; Lecavallier, M.; Fagnou, K. *J. Am. Chem. Soc.* **2009**, *131*, 3291. b) Schipper, D. J.; El-Salfiti, M.; Whipp, C. J.; Fagnou, K. *Tetrahedron* **2009**, *65*, 4977. c) Schipper, D. J.; Campeau, L.-C.; Fagnou, K. *Tetrahedron* **2009**, *65*, 3155. d) Campeau, L.-C.; Schipper, D. J.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3266. e) Campeau, L.-C.; Bertrand-Laperle, M.; Leclerc, J.-P.; Villemure, E.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3276. f) Leclerc, J.-P.; Fagnou, K. *Angew. Chem. Int. Ed.* **2006**, *45*, 7781. g) Campeau, L.-C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *127*, 18020.

⁴⁶ Lebrasseur, N.; Larrosa, I. *J. Am. Chem. Soc.* **2008**, *130*, 2926.

Scheme 3.13 Site-selective azaindole arylation at the azole and azine rings *via* *N*-oxide activation.



We envisioned extending the scope of conditions-based selectivity to include perfluorinated arenes.²⁸ We also opted to employ additional site-selective conditions such as Gaunt's Cu-catalyzed method for the C3 arylation of indoles⁴⁷ and the conditions developed for the palladium-catalyzed C2 arylation of pyridine *N*-oxides using aryl triflates.^{45b}

Preliminary test reactions showed that the targeted conditions were specific for their respective class of substrates.⁴⁸ Although, of the two electron-poor arenes we investigated (*i.e.* the pentafluorobenzene and the pyridine *N*-oxide), the polyfluorinated arene reacted preferentially over the pyridine *N*-oxide regardless of the conditions. Consequently, substrates **9** to **13** (Table 3.5) were prepared using known direct arylation methods in order to test the site-selectivity of the various sets of conditions with actual substrates containing two different (hetero)arenes. While the first two of the three syntheses could have possibly cause problems of homo-coupling of the 5-bromoindole under the second generation conditions for the direct arylation reaction^{28b} and the original pyridine-*N*-oxide conditions,^{45g} no such products were observed. The model substrate **11** could be prepared from the reduction of the *N*-oxide moiety of **10** using two sets of conditions, both giving good yields. Substrate **12** was prepared using the original direct

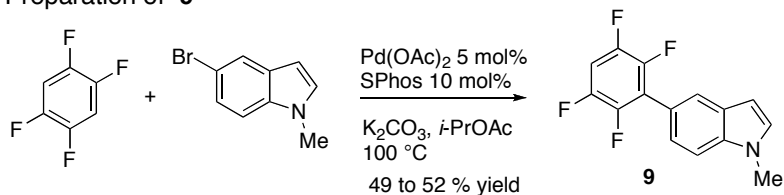
47 Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 8172.

48 For a detailed description of the preliminary studies conducted on this project, see Christopher J. Whipp thesis entitled: "Part 1: The Direct Arylation of Azine N-Oxides with Aryl Triflates, Part 2: The Site-Selective Direct Arylation of Substituted Indoles" University of Ottawa, 2010, Chapter 4.

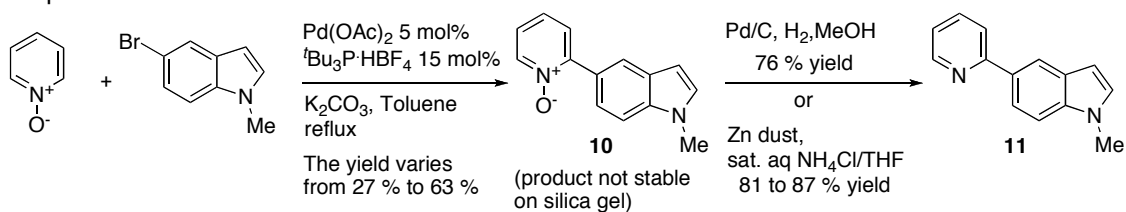
arylation conditions of pentafluorobenzene with an excess of the 1,2,4,5-tetrafluorobenzene.^{28c} The subsequent oxidation of **12** to prepare **13** was performed under the rhenium-catalyzed conditions with hydrogen peroxide as the stoichiometric oxidant.

Scheme 3.14 Preparation of the model substrates **9** to **13**.

Preparation of **9**



Preparation of **10** and **11**



Preparation of **12** and **13**

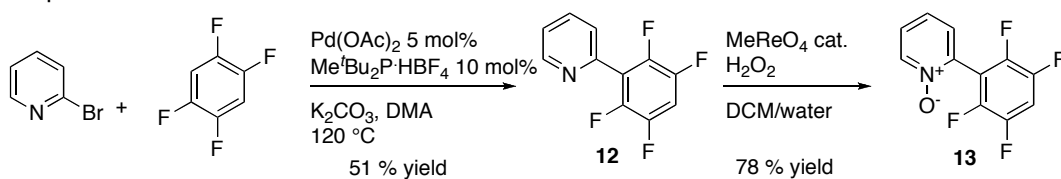


Table 3.5 Site-selective direct arylation based on mild (hetero)arene specific conditions.

Entry	Substrate	Ar-X	Conditions ^a	Product	Yield (%)
1			A		65
2	9		B		64
3	9		C		54
4	9		D		58
5			A		53
6	Y = N ⁺ -O ⁻ (10) N (11)		A	Y = N ⁺ -O ⁻ (15) N (16)	no rxn ^b
7	10		B		55
8	11		B		no rxn ^b
9	10		E		24
10	10		F		(CW) 51
11			C		no rxn ^b
12	Y = N ⁺ -O ⁻ (13) N (12)		C		N (21)

a) **Conditions A**⁴⁶ (Larrosa's protocol): indole (1.0 equiv.), aryl iodide (2.0 equiv.), Pd(OAc)₂ (5 mol%), 2-nitrobenzoic acid (1.5 equiv.), Ag₂O (0.75 equiv.) in DMF (0.5 M) at 45 °C; **Conditions B**⁴⁷ (Gaunt's protocol): indole (1.0 equiv.), diaryliodonium triflate (1.3 equiv.), Cu(OTf)₂ (10 mol%), 2,6-di-*t*-butylpyridine (1.0 equiv.) in DCM (0.1 M) at 50 °C; **Conditions C**^{28b} perfluorinated arene (1 equiv.), aryl bromide (1.0 equiv.), Pd(OAc)₂ (5 mol%), SPhos (10 mol%), PivOH (30 mol%), K₂CO₃ (2 equiv.) in *iso*-propyl acetate (1.0 M) at 80 °C; **Conditions D**^{28a} perfluorinated arene (1 equiv.), aryl iodide (1.1 equiv.), Pd(OAc)₂ (5 mol%), MePhos (10 mol%), Ag₂CO₃ (0.50 equiv.), K₂CO₃ (2 equiv.) in ethyl acetate:water (2.5:1, 0.35 M) at ambient temperature; **Conditions E**^{45a,g} pyridine *N*-oxide (1.0 equiv.), aryl bromide (1.5

equiv.), Pd(OAc)₂ (5 mol%), P^tBu₃·HBF₄ (15 mol%), K₂CO₃ (2 equiv.) in toluene (0.30 M) at reflux; **Conditions F**:^{45b} pyridine *N*-oxide (1.0 equiv.), aryl triflate (2.0 equiv.), Pd(OAc)₂ (5 mol%), P^tBu₂Me·HBF₄ (10 mol%), PivOH (30 mol%), K₂CO₃ (2 equiv.) in toluene (0.50 M) at reflux; b) No reaction observed. The entries associated with the initials **CW** are reactions performed by Christopher Whipp.

Gratifyingly we were able to selectively arylate each of the molecules at the desired position in the presence of other potentially reactive site(s). Starting with substrate **9**, bearing an electron-rich indole ring and an electron-deficient perfluorinated arene ring, we achieved the selective arylation at the C2 position of the indole ring to yield product **CW-1** in 65% yield (entry 1, Table 3.5) using Larrosa's protocol⁴⁶ (Conditions A). Starting from the same substrate (**9**), the C3 position of the indole ring was arylated to give **CW-2** in 64% yield (entry 2, Table 3.5) using Gaunt's Cu-catalyzed protocol⁴⁷ (Conditions B). Using two different sets of conditions developed in our group (Conditions C^{28b} and D^{28a}), we were able to selectively arylate the fluorinated arene **9** using both an aryl bromide and an aryl iodide affording **14** in acceptable yields of 54% and 58% respectively (entries 3 and 4, Table 3.5). Similarly, compound **10** could be selectively functionalized at the C2 position of the indole to give the arylated product **15** in 53% (entry 5, Table 3.5) and the C3 arylated indole **17** in 55% (entry 7, Table 3.5). Unfortunately, we were not able to functionalize both C2 and C3 position of the indole when we used substrate **11**, containing an un-activated azine in place of the activated azine-*N*-oxide (entries 6 and 8, Table 3.5).⁴⁹ We believe that the pyridine moiety in **11** coordinated the metals and potentially formed a stable metallacycle with the adjacent ring, which would prevent any further reaction. Also, the C2 position of the pyridine *N*-oxide **10** could also be functionalized selectively to afford **19** in 24% yield using an aryl bromide (Conditions E),^{45a,g} however the yield could be increased to 51% yield when using an aryl triflate instead (Conditions F)^{45b} (entries 9 and 10, Table 3.5, respectively). Substrate **13**, which contains both a poly-fluorinated phenyl groups and a pyridine-*N*-oxide, was found to be incompatible with conditions C. However substrate **12**, which contains a non-activated pyridine, reacted with the perfluorinated ring affording product **21** in 85% yield (entries 11 and 12, Table 3.5).

49 Contrary to the report on azaindoles (see ref. 44), in which the functionalization of the azole ring gave better yields when the unactivated azine ring was used compared to the yields obtained when the azine ring was activated as the *N*-oxide.

For all the examples presented using the condition-based site-selectivity approach, we only isolated the targeted regioisomer each time and generally the remaining mass balance was recovered starting material and/or decomposition products. Even though we cannot rule-out the formation of undesired regioisomers in small amounts, the examples shown in Table 3.5 demonstrate the applicability of this approach. It would also be beneficial to further expand the breadth of the known reaction conditions that are (hetero)arene selective.

3.5.2 Predicted selectivity with the DFT calculated CMD pathway

The second main challenge with the selective functionalization of polyaromatic compound is to be able to predict the outcome of a reaction when two (or more) different C–H bonds can react under the same reaction conditions. In sections 3.2 and 3.3 were discussed the combined experimental and computational study in which was demonstrated that for a wide range of electron-poor, -neutral and -rich (hetero)arenes that can undergo direct arylation reactions catalyzed by a Pd^{II}–carboxylate complex, the most accessible pathway for the C–H bond cleavage was the concerted metallation-deprotonation (CMD) pathway.⁵⁰ We have seen that computationally, the CMD pathway was able to accurately predict the regioselectivity observed experimentally for the palladium-catalyzed direct arylation of each (hetero)arene evaluated. In addition to accurately predicting the site-selectivity on individual arenes, the calculated barriers of activation for the CMD mechanism should also reflect the relative reactivity of the various studied arenes. As a result, one could utilize these values to determine the site-selectivity of a reaction where two or more heteroarenes are present on a single substrate.

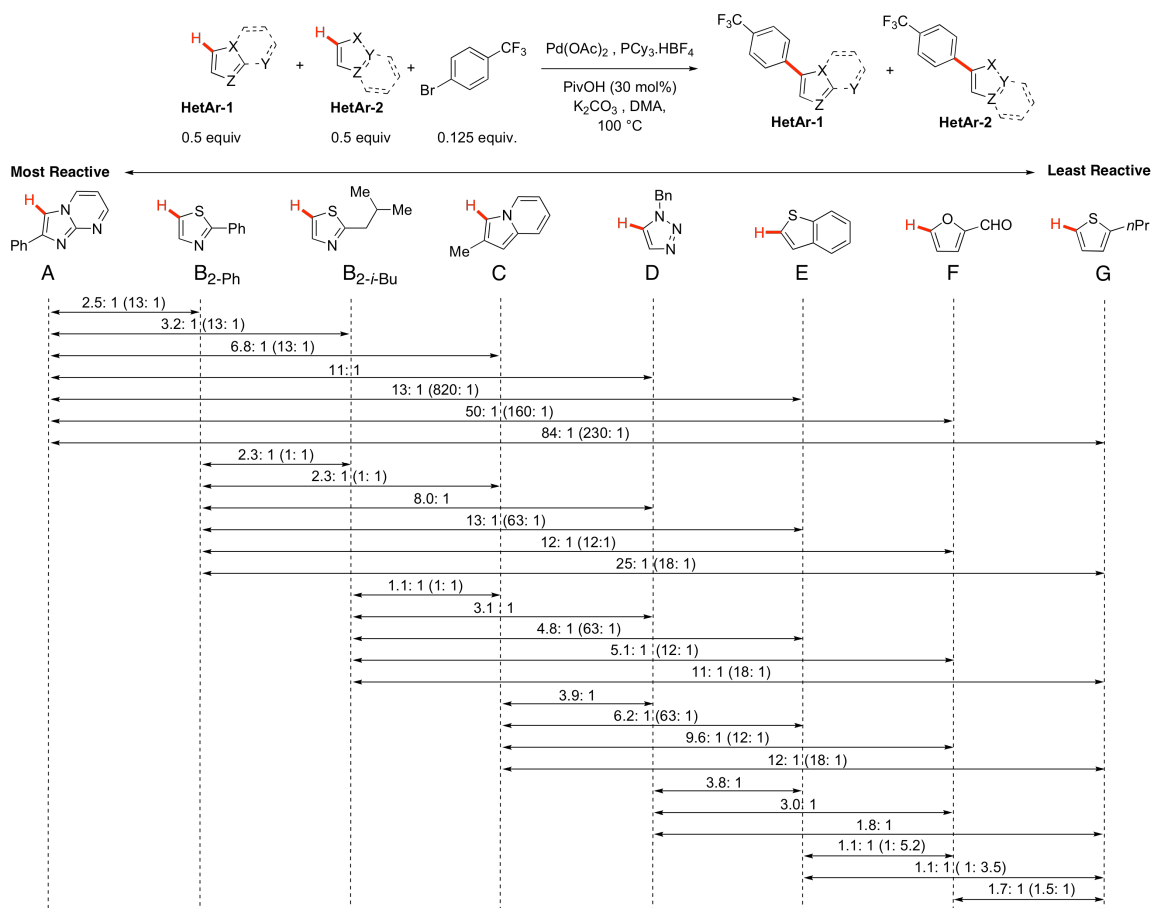
To evaluate experimentally the accuracy of the site-selectivity prediction obtained from the calculated CMD barrier of activation,⁴² a series of competition experiments were

⁵⁰ For reviews on the mechanistic work done on the CMD mechanism, see Chapter 1 or: a) Lapointe, D.; Fagnou, K. *Chem. Lett.* **2010**, 39, 1118. b) Boutadla, Y.; Davies, D. L.; Macgregor, S. A.; Poblador-Bahamonde, A. I. *Dalton Trans.* **2009**, 5820. c) Ackermann, L. *Chem. Rev.* **2011**, 111, 1315.

performed using a range of electron-rich heteroarenes to determine their relative reactivity. The competition experiments consisted of measuring the product distribution using ^{19}F NMR spectroscopy⁵¹ in the reaction of *p*-CF₃-bromobenzene (0.125 equiv.) with two heteroarenes (0.5 equiv. each), using palladium acetate (5 mol%) and tricyclohexylphosphonium tetrafluoroborate (10 mol%) as the pre-catalyst, pivalic acid (30 mol%) as a rate enhancing additive and potassium carbonate (1.5 equiv.) as the base in *N,N*-dimethylacetamide (0.3 M) at 100 °C. These conditions have already been proven to be applicable for the direct arylation of a wide variety of electron-rich heteroarenes and have shown to be reliable.^{41a} The results of these competitions are summarized in Figure 3.13 and in parentheses are found the theoretical product distributions. The theoretical values were obtained using the difference in free energy of activation ($\Delta\Delta G^\ddagger$) at 373 K for each substrate. Also, it is important to mention that we have limited our study mostly to heterocycles that were previously examined computationally and restricted our attention to their single most reactive C–H bond of each heterocycle instead of examining the reactivity of each potentially reactive position.

51 For examples of studies utilizing *para*-trifluoromethylphenyl groups and ^{19}F NMR spectroscopy, see: a) Geyer, A. M.; Wiedner, E. S.; Gary, J. B.; Gdula, R. L.; Kuhlmann, N. C.; Johnson, M. J. A.; Dunietz, B. D.; Kampf, J. W. *J. Am. Chem. Soc.* **2008**, *130*, 8984. For other recent examples of mechanistic studies utilizing ^{19}F NMR spectroscopy, see: b) Viciu, M. S.; Gupta, L.; Collum, D. B. *J. Am. Chem. Soc.* **2010**, *132*, 6361. c) De Vries, T. S.; Goswami, A.; Liou, L. R.; Gruver, J. M.; Jayne, E.; Collum, D. B. *J. Am. Chem. Soc.* **2009**, *131*, 13142. d) Gupta, L.; Hoepker, A. C.; Singh, K. J.; Collum, D. B. *J. Org. Chem.* **2009**, *74*, 2231.

Figure 3.13 Relative reactivity of various heteroarenes toward direct arylation.^{a,b}



a) The competitions reactions of were performed by Thomas Markiewicz with the exception of the competitions involving the furan F; b) Conditions: Heteroarene 1 (0.50 equiv.), Heteroarene 2 (0.50 equiv.), 4-bromotrifluorotoluene (0.125 equiv.), Pd(OAc)₂ (5 mol%), PCy₃·HBF₄ (10 mol%), PivOH (30 mol%), K₂CO₃ (1.5 equiv.) in DMA (0.3 M) at 100 °C; c) Experimental product ratios (¹⁹F NMR) and between parentheses are the theoretical product ratios obtained from DFT calculated barriers of activation of the CMD pathway (Figure 3.7).⁸

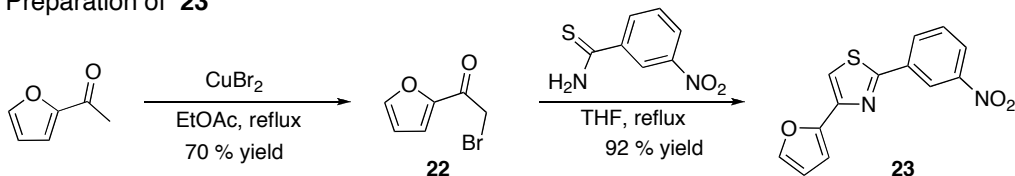
The aim of this reactivity chart (Figure 3.13) is to obtain a comprehensive estimate of the reactivity for a range of heteroarenes regardless of the effects of the substituents in order to apply it to the functionalization of complex substrates. With substrates for which the CMD barrier of activation has been calculated by DFT (Figure 3.7), we can see that the computationally predicted site-selectivity accurately matches the selectivity observed experimentally. Moreover, considering the sum of the various approximations made in the DFT calculations (such as ligand and solvent approximations and the lack of

substituents on the heteroarenes) and the inherent experimental variability of these competition reactions (e.g. the choice of reactions conditions, high volatility or low solubility of some heteroarenes and the precision of the product peak integration), a good overall agreement between the experimental and theoretical results was observed. Imidazopyrimidine (A) and thiazoles (B) were the most reactive substrates, which is in agreement with the DFT predicted reactivity. The presence of C2 substituents on thiazole (B) had a significant effect on the reactivity. Indeed, 2-phenylthiazole reacted 2.5 times faster than the 2-*iso*-butylthiazole (B_{2-Ph} vs. B_{2-i-Bu}), although the difference in the reactivity of the two analogues remains relatively small so that the general order of reactivity of the heteroarenes is not affected. Similarly, the effect of substituents at the C2 position of indolizine (C) has been reported previously by Gevorgyan *et al.* in the context of mechanistic studies, the authors found small reactivity changes when the 2-methyl is abstracted or replaced by an ester functionality.⁵² Furthermore, the relative reactivity of *N*-benzyl-1,2,3-triazole (D) has not been evaluated computationally, but was found experimentally to be situated in between the indolizine (C) and the benzothiophene (E). Finally, benzothiophene (E), furan (F) and thiophene (G) were the least reactive substrates that were evaluated, conformably with the DFT predictions.⁵²

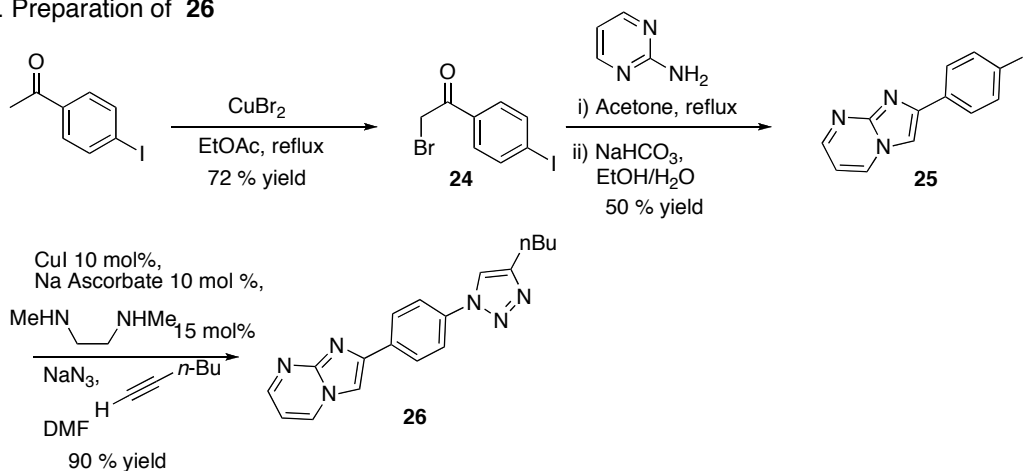
52 As one of our reviewers pointed-out, a close examination of the various product ratios reveals that the ratios are not always cumulative when the reactivity of the heteroarenes are compared together. Certainly, it is a very interesting observation and it would be worth to examine in detail, however at the moment we cannot propose an explanation.

Scheme 3.15 Preparation of the model substrates **23**, **26** and **29**.

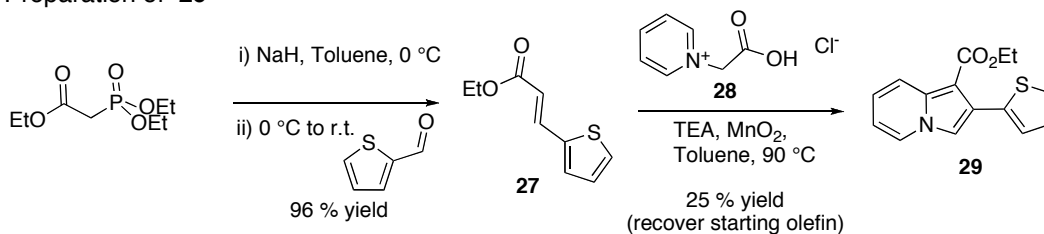
a. Preparation of **23**



b. Preparation of **26**



c. Preparation of **29**

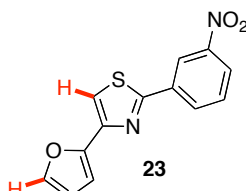
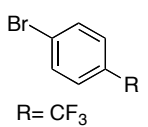
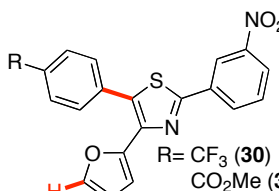
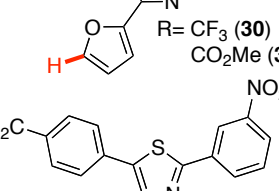
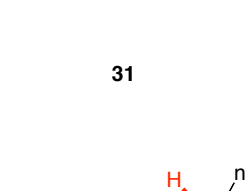
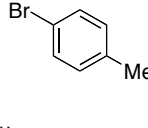
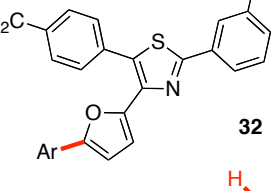
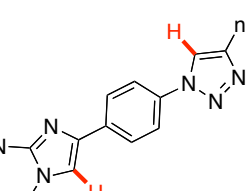
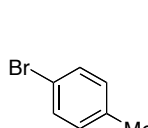
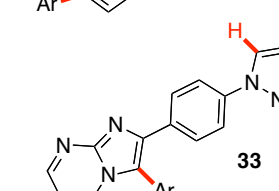
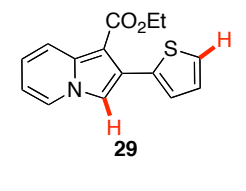
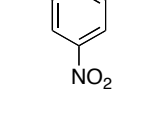
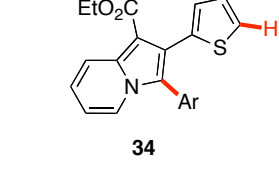


With the results of these competitions in hand, our efforts were directed towards using them as a reactivity guideline in the functionalization of model substrates bearing two potentially reactive heteroarenes. We first prepared substrate **23** (Scheme 3.15a) to test the difference in reactivity between the C5 C–H bond of 2-arylthiazole and the C5 C–H bond of C2 substituted furan. Starting for 2-acetylfuran, the methyl group was brominated using copper(II) bromide in ethyl acetate at reflux. The thiazole ring was then formed by the condensation of thioamide onto **22** in THF at reflux.⁵³ Product **23** was obtained in an overall yield to 65%. Afterward, a substrate containing both an imidazopyrimidine ring and a *N*-aryl-1,2,3-triazole (**26**) was prepared (Scheme 3.15b).

⁵³ Turner, G. L.; Morris, J. A.; Greaney, M. F. *Angew. Chem., Int. Ed.* **2007**, *46*, 7996.

Following the same bromination procedure, 4'-iodoacetophenone was brominated. This was followed by the addition of 2-aminopyrimidine and dehydration to form the imidazopyrimidine **25**.⁵⁴ The triazole ring was formed by “Click” chemistry⁵⁵ to give **26** in an overall yield of 32%. Lastly, the combination of an indolizine arene and a thiophene was also evaluated (**29** Scheme 3.15c). Following a literature procedure, intermediate **27** was prepared by a Horner-Wadsworth-Emmons reaction between the phosphonate anion and 2-thiophenecarboxaldehyde.⁵⁶ The indolizine ring of **29** was formed in low yield by a 1,3-dipolar cycloaddition with **28** in the presence of an oxidant, however unreacted starting material **27** could be recovered by flash chromatography and recycled.⁵⁷

Table 3.6 Direct Arylation of Aromatic Heterocycles.^a

Entry	Substrate	Coupling Partner	Product	Yield (%)
1	 23	 R = CF ₃ CO ₂ Me	 30	80
2			 31	69
3 ^b	 31	 Me	 32	76
4	 26	 Me	 33	65
5	 29	 NO ₂	 34	75

⁵⁴ Rivall, Y.; Grassy, G.; Taudou, A.; Ecalle, R. *J. Med. Chem.* **1991**, 26, 13.

⁵⁵ Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, 41, 2596.

⁵⁶ Bonini, C.; Chiummiento, L.; De Bonis, M.; Funicello, M.; Lupattelli, P.; Pandolfo, R. *Tetrahedron: Asymmetry* **2006**, 17, 2919.

⁵⁷ Zhang, L.; Liang, F.; Sun, L.; Hu, Y.; Hu, H. *Synthesis* **2000**, 12, 1733.

a) Conditions: *bis*-heteroarene (1.1 equiv.), aryl bromide (1.0 equiv.), Pd(OAc)₂ (5 mol%), PCy₃·HBF₄ (10 mol%), PivOH (30 mol%), K₂CO₃ (1.5 equiv.), DMA (0.3 M), 100 °C; b) *bis*-heteroarene (1.0 equiv.), aryl bromide (1.2 equiv.).

With the model substrates in hand, starting with the substrate **23**, we choose to use a slight excess (1.1 equiv.) of *bis*-heteroarene in the reaction, in order to limit the formation of double arylation product that we observed in our initial attempts (~10 mol%) using equimolar amounts of both coupling partners.⁵⁸ Although this was not the ideal reagent to use in excess, the formation of double arylation product was very undesirable since it resulted in the consumption of both the desired final product and the starting aryl bromide partner. Moreover, the unreacted starting material could, in principle, be recovered at the end of the reaction. Using the conditions of the general method of direct arylation developed by our group⁴¹ with 1.1 equivalents of **23**, we were able to isolate the mono-arylated product **30** in 80% yield (entry 1, Table 3.6), the double arylation was still observed in approximately 5 mol%. Substrate **23** could also be sequentially and selectively functionalized with two different aryl bromides, the thiazole moiety was first selectively functionalized with methyl *para*-benzoate affording **31** in 69% yield, followed by a second arylation at the furan ring with a *para*-tolyl bromide yielding the highly conjugated product **32** in 76% yield (entries 2 and 3, Table 3.6). Similarly, with the substrate containing both an imidazopyrimidine ring and a *N*-aryl-1,2,3-triazole (**26**), the imidazopyrimidine ring could be selectively functionalized in an acceptable yield (65%, entry 4, Table 3.6). As expected, substrate **29**, which combined an indolizine arene and a thiophene, was selectively functionalized in 75% yield on the indolizine arene (entry 5, Table 3.6).

3.5.3 Concluding remarks

In this section we showed that the site-selective direct arylation of substrates containing two different classes of arenes was possible using mild methods developed for specific types of arenes. Also, the results of competition reactions among electron-rich

⁵⁸ See section 3.4.2 for a discussion on the use of equimolar amounts of coupling partners.

heteroarenes allowed for the first experimental classification of these heteroarenes based on their reactivities toward C–H bond functionalization. The presented order of reactivity of those heteroarenes was in good agreement with the order predicted by the DFT-calculated concerted metallation-deprotonation (CMD) pathway promoted by palladium/carboxylate complexes. Importantly, the ability to achieve predictable and selective C–H bond functionalization (without organometallic pre-activation) of more challenging substrates was achieved, which will serve to be an invaluable tool given the demand of the preparation of these types of molecules.

3.6 General Conclusion

In this chapter was described the experimental and the computational studies which suggested that the CMD pathway might be involved in the palladium-catalyzed C–H bond functionalization of a wide range of (hetero)arene spanning the entire spectrum of electronic properties, from the electron deficient to π -rich heteroarenes. From these findings, we developed a general set of conditions for the direct arylation of wide range of heteroarenes inspired by the knowledge we had on the reactivity “CMD-type” substrates, especially regarding the role of pivalic acid as a rate-enhancing co-catalyst. Lastly, we have developed two different strategies to selectively and predictably arylate substrates containing multiple functionalizable C–H bonds. The primary aim of these projects was to develop broadly applicable, simple and reliable methods for the functionalization of aromatic C–H bonds.

Chapter

4

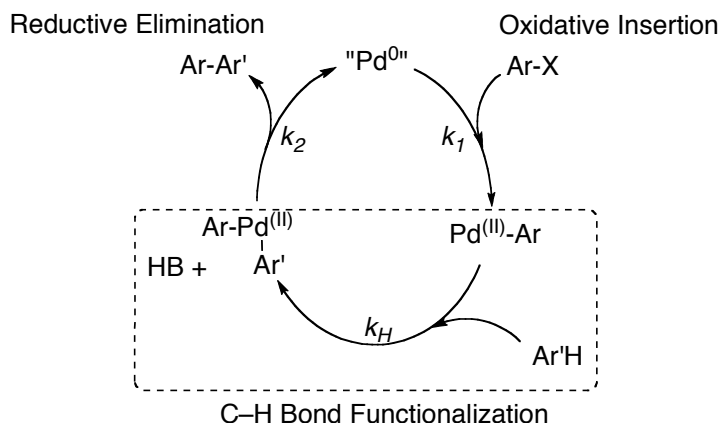
Palladium-Catalyzed $\text{sp}^3\text{-sp}^2$ C–C bond Formation by C–H Functionalization Reactions

4.1 *General Introduction*

In the previous chapters methods to functionalize C–H bonds by palladium-catalysis were described, with a focus on the mechanism for the C–H bond cleavage step. However, the methods presented were limited to the formation of biaryls. Nonetheless, the development of methods leading to the formation of biaryl motifs is an ideal system to study the mechanism of the C–H bond cleavage step since both the oxidative insertion into an aryl halide and reductive elimination are well known steps in the catalytic cycle (Scheme 4.1). Following our work on the development of a general method for the direct arylation of electron-rich heteroarenes, we next sought to develop new methods of C–H bond functionalization in which we could apply our knowledge of C–H bond cleavage to the formation of new scaffolds. In the following chapter will be presented two new palladium-catalyzed methods. The first one is the preparation of diarylmethane motifs in a complementary fashion to Friedel-Crafts approaches. For the second part, the level of

complexity of the transformation was increased by including a 1,2-migratory insertion step prior to C–H bond functionalization step in a domino sequence.

Scheme 4.1 General catalytic cycle for a direct arylation reaction catalyzed by palladium.



4.2 Palladium-Catalyzed Functionalization of Benzyl Chlorides

While Friedel-Crafts reactions are front line methods in the formation of new arene-alkane C–C bonds,¹ application of these methods to many heterocyclic aromatic compounds can be problematic, particularly when electron-withdrawing groups are in resonance or functional groups that are sensitive to strong Lewis/Brønsted acids are present. The reactivity of sulfur-containing heteroarenes are also more problematic since they are less nucleophilic than their corresponding oxa- and aza-homologues.² In those cases, arene deprotonation with strong bases (such as BuLi) followed by electrophilic trapping is the most common alternative,³ although it can occasionally give rise to a

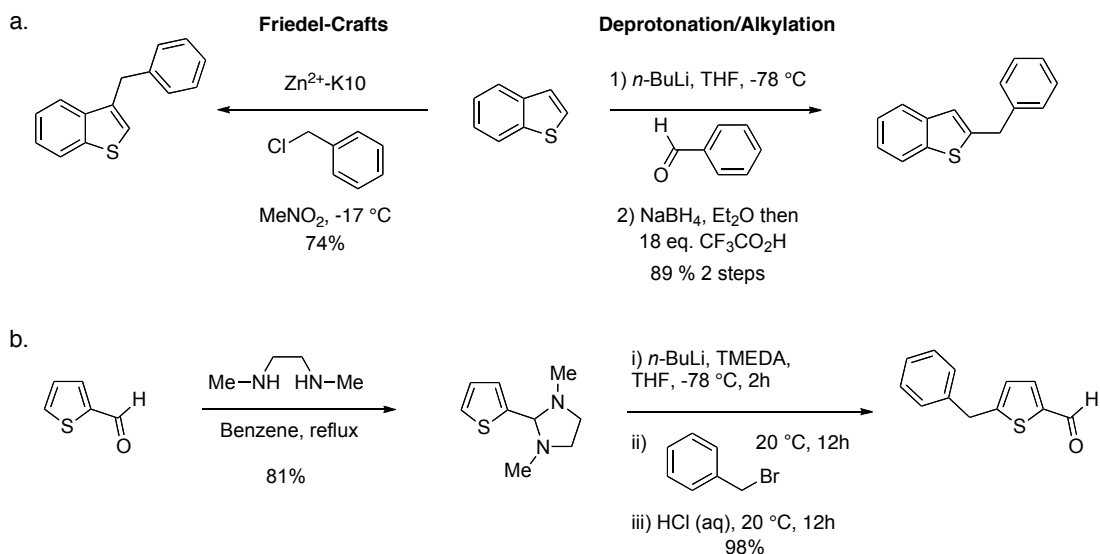
¹ a) Olah, G. A. *Friedel-Crafts and Related Reactions*; Wiley-Interscience: New York, 1964; Vol. II, Part 1. b) Roberts, R. M.; Khalaf, A. A. *Friedel-Crafts Alkylation Chemistry. A Century of Discovery*; Marcel Dekker: New York, 1984. c) Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **2004**, 43, 550. d) Dugger, R.W.; Ragan, J. A.; Ripin, B. *Org. Process Res. Dev.* **2005**, 9, 253. e) Carey, J. S.; Laffran, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, 4, 2337.

² a) Mayr, H.; Patz, M. *Angew. Chem., Int. Ed.* **1994**, 33, 938. b) Gotta, M. F.; Mayr, H. *J. Org. Chem.* **1998**, 63, 9769. c) Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, 36, 9769.

³ a) Knight, D. W.; Nott, A. P. *J. Chem. Perkin Trans. I* **1983**, 791. b) Chinchilla, R.; Nájera, C.; Yus, M. *Chem. Rev.* **2004**, 104, 2667. c) Slocum, D. W.; Shelton, P.; Moran, K.M. *Synthesis* **2005**, 3477.

different regioisomer (Scheme 4.2a).⁴ While valuable, this approach necessitates the protection of all electrophilic and acidic functional groups. It also adds non-productive chemical steps, generates waste and additional costs to a somewhat simple transformation (Scheme 4.2b).⁵

Scheme 4.2 Representative examples of the heteroarenes alkylation limitations.



Recently, metal-catalyzed cross-couplings of benzyl halides with aryl organometallics have emerged as alternatives to the use of strong acids or bases.⁶ Our interest in the use of simple arenes as replacements of stoichiometric organometallic

⁴ a) Shrestha, S.; Hwang, S. Y.; Lee, K.-H.; Cho, H. *Bull. Korean. Chem. Soc.* **2005**, 26, 1138. b) Clark, P. D.; Mesher S. I., *Phosphorus, Sulfur, and Silicon and the Related Elements*, **1995**, 105, 157.

⁵ a) Carpenter, A. J.; Chadwick, D. J. *Tetrahedron* **1985**, 41, 3803. b) Ung, A. T.; Pyne, S. G.; Skelton, B. W.; White, A. H. *Tetrahedron* **1996**, 52, 14069. c) Zhu, Y.; Zhu, Y.-Z.; Song, H.-S.; Zheng, J.-Y.; Liu, Z.-B; Tian, J.-G. *Tetrahedron Lett.* **2007**, 48, 5687. d) Smith, T. E.; Kuo, W.-H.; Balskus, E. P.; Bock, V. D.; Roizen, J. L.; Theberge, A. B.; Carroll, K. A.; Kurihara, T.; Wessler, J. D. *J. Org. Chem.* **2007**, 73, 142. e) Garfinkle, J.; Ezzili, C.; Rayl, T. J.; Hochstatter, D. G.; Hwang, I.; Boger, D. L. *J. Med. Chem.* **2008**, 51, 4392.

⁶ For reviews, see: a) Liégault, B.; Renaud, J.-L.; Bruneau, C. *Chem. Soc. Rev.* **2008**, 37, 290. b) Kuwano, R. *Synthesis* **2009**, 7, 1049. Recent publications: c) Srimani, D.; Sarkar, A. *Tetrahedron Lett.* **2008**, 49, 6304. d) Fairlamb, I. J. S.; Sehnal, P.; Taylor, R. J. K. *Synthesis* **2008**, 508.

reagents⁷ in cross-coupling reactions led us to question whether similar reactivity may also be possible with aliphatic electrophiles. In contrast to the rapid growth in transition metal-catalyzed direct arylation with aryl halide electrophiles,⁷ the use of aliphatic electrophiles is rare despite the non-negligible importance of this motif in the pharmaceutical industry (Figure 4.1). Recently, Yu described palladium(II)-catalyzed benzoic acid alkylation reactions⁸ and Ackermann has reported a directed arene alkylation employing a ruthenium catalyst where the catalytic cycle likely involves arene metallation prior to interaction with the aryl halide.⁹ Palladium(0)-catalyzed arene alkylations employing norbornene have also been described by Catellani¹⁰ and Lautens,¹¹ enabling the preparation of a wide range of alkyl-substituted aromatic compounds.¹²

⁷ For reviews, see: a) Daugulis, O.; Zaitsev, V. G.; Shabashov, D.; Pham, Q.-N.; Lazareva, A. *Synlett* **2006**, 3382. b) Campeau, L.-C.; Fagnou, K. *Chem. Commun.* **2006**, 1253. c) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. d) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. e) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200. f) Campeau, L.-C.; Stuart, D. R.; Fagnou, K. *Aldrichimica Acta*, **2007**, *40*, 35. g) Li, B.-J.; Yang, S.-D.; Shi, Z.-J. *Synlett* **2008**, 949. Selected recent publications, see: h) Liégault, B.; Lapointe, D.; Caron, L.; Vlassova, A.; Fagnou, K. *J. Org. Chem.* **2009**, *74*, 1826. i) Campeau, L.-C.; Stuart, D. R.; Leclerc, J.-P.; Bertrand-Laperle, M.; Villemure, E.; Sun, H.-Y.; Lasserre, S.; Guimond, N.; Lecavallier, M.; Fagnou, K. *J. Am. Chem. Soc.*, **2009**, *131*, 3291. j) Huestis, M. P.; Fagnou, K. *Org. Lett.* **2009**, *11*, 1357.

⁸ Zhang, Y.-H.; Shi, B.-F.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2009**, *48*, 6097.

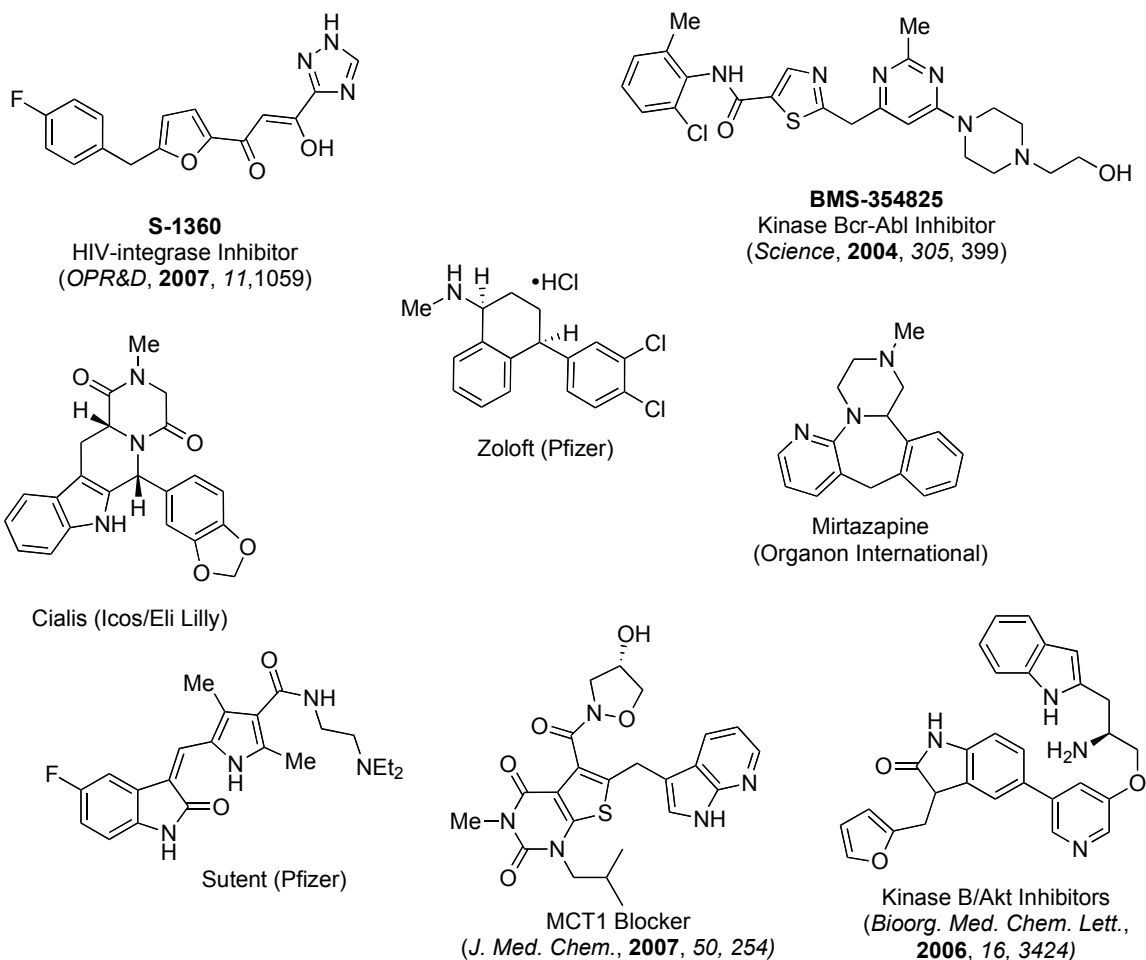
⁹ Ackermann, L.; Novak, P.; Vicente, R.; Hofmann, N. *Angew. Chem. Int. Ed.* **2009**, *48*, 6045.

¹⁰ a) Catellani, M.; Frignani, F.; Rangoni, A. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 119. b) Catellani, M.; Cugini, F. *Tetrahedron* **1999**, *55*, 6595. c) Catellani, M.; Motti, E.; Minari, M. *Chem. Commun.* **2000**, 157.

¹¹ a) Rudolph, A.; Rackelmann, N.; Turcotte-Savard, M.-O.; Lautens, M. *J. Org. Chem.* **2009**, *74*, 289. b) Martins, A.; Lautens, M. *Org. Lett.* **2008**, *10*, 5095.

¹² For reviews, see: a) Frisch, A. C.; Beller, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 674. b) Catellani, M.; Motti, E.; Della Ca', N. *Acc. Chem. Res.* **2008**, *41*, 1512.

Figure 4.1 Biologically active compounds containing the diarylmethane motif.



With a standard Pd(0)/Pd(II) catalytic cycle, important first steps have been made in establishing the intramolecular reactivity of aliphatic halides. For example, Song and Wong reported in 1994 a tandem reaction of two benzylic bromide on a furan bearing a C3 boronic ester (Scheme 4.3a).¹³ Buchwald described the cyclization of α -chloroacetanilides in the formation of oxindoles (Scheme 4.3b).¹⁴ Chang *et al.* reported a cyclization of benzylic halides with a pendant pyrrole to close a six-membered ring (Scheme 4.3c).¹⁵ During the preparation of our manuscript, Hoarau *et al.* reported the first intermolecular palladium-catalyzed C2 alkylation of ethyl oxazole-4-carboxylate

¹³ Song, Z. Z.; Wong, H. N. C. *J. Org. Chem.* **1994**, 59, 33.

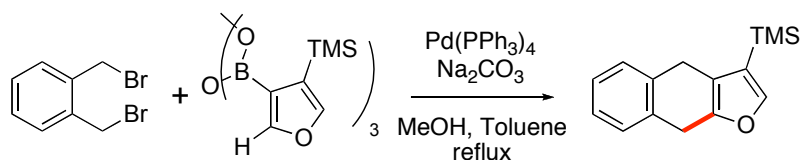
¹⁴ Hennessy, E. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, 125, 12084.

¹⁵ Hwang, S. J.; Cho, S. H.; Chang, S. *J. Am. Chem. Soc.* **2008**, 130, 16158.

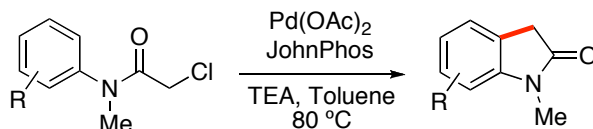
(Scheme 4.3d).¹⁶ In addition to the C2 benzylation of the oxazole, Hoarau also described the olefination and alkylation under the same set of conditions. From a mechanistic perspective, it is interesting to point out that the functionalized C–H bond of the oxazole corresponded to the most acidic proton and not necessarily the position one could have proposed with the CMD pathway. Oxazoles were not part of the arenes evaluated by DFT, however if compared to the analogous thiazoles, the C5 position should be favored. In addition, the C4 ester might also play an important role on the reactivity of the C–H bonds toward the palladium catalyst.

Scheme 4.3 Precedents of direct arylation of sp^3 C–Halide.

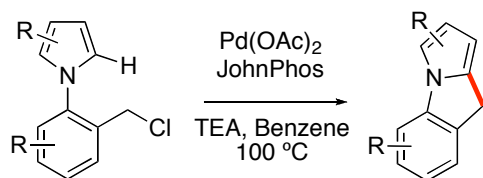
a. Song and Wong (1994)



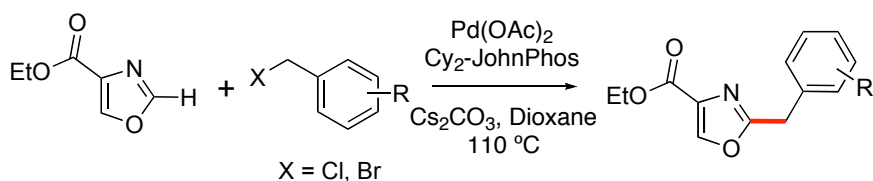
b. Buchwald *et al.* (2003)



c. Chang *et al.* (2008)



d. Hoarau *et al.* (2009)

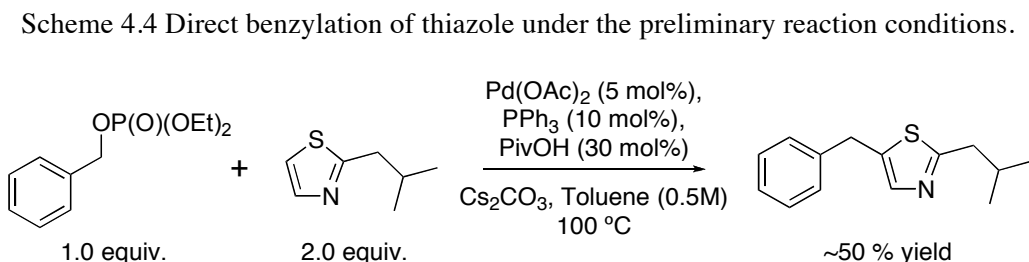


¹⁶ Verrier, C.; Hoarau, C.; Marsais, F. *Org. Biomol. Chem.* **2009**, *7*, 647.

In the following sections, our efforts toward the establishment of a broadly applicable direct benzylation method with a wide array of heteroarenes will be described. A special focus will be address to sulfur-containing heteroarenes and those bearing functional groups that are not compatible with strong Lewis acids and/or strong bases. Furthermore, the generality of the Csp^2-Csp^3 bonds formation methods provides evidence of the wealth of the reactivity with palladium catalysis to functionalized unactivated C–H bonds beyond the formation of biaryls.

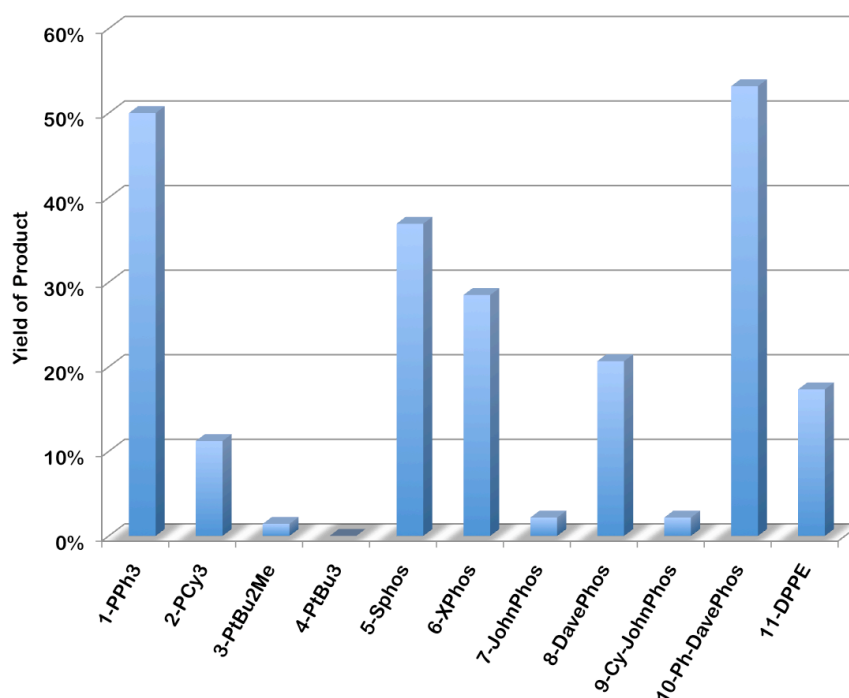
4.2.1 Optimization of the reaction conditions

One of the principal difficulties associated with the development of a single set of reaction conditions that can be applied to a wide range of (hetero)arenes is to choose the right set of representative (hetero)arenes during the optimization. Ideally, representative substrates should be selected to embody diverse characteristics and be optimized in parallel. Unfortunately, this step remains highly subjective and hazardous. The early development of the direct benzylation conditions was done with various arenes ranging from pentafluorobenzene to benzothiophene and the highly nucleophilic indolizine. In the present section, in order to have a comprehensive description of the development of the reaction conditions, we will not go through the enumeration of the various combinations of benzyl-(pseudo)halides, solvents, concentrations and bases that were tested. Nonetheless, the preliminary results designated the reactions conditions depicted in Scheme 4.4 with 2-*iso*-butylthiazole in combination with a benzylic phosphonate to be promising. Certainly the yield still needed to be improved, consequently, further optimization was undertaken to improve the efficiency of the transformation.



The first parameter to be examined was the choice of ligand. Ligand screening showed that the reaction was rather sensitive to the choice of substituent on the phosphine (Table 4.1). Indeed, poor GC yields were obtained with alkylphosphines (entries 2-4), although Buchwald-type ligands gave some promising results (entries 5-10). Even in that series, with the ligands in which the phosphine had alkyl groups on it (entries 5-9), poor yields were obtained compared to triphenylphosphine. Ph-DavePhos, on the other hand, gave a slightly better yield than the initial triphenylphosphine (entry 10, 53% vs ~50%, respectively). As a result, we decided to further optimize the conditions with that ligand.

Table 4.1 Optimization of the ligand for the direct benzylation reaction.



GC yields, C₁₄H₃₀ was used as an internal standard and the product was calibrated accordingly.

From the preliminary investigation on the reaction, we knew that the choice of the benzylic leaving group was also crucial for the reactivity of this system (Table 4.2). While reactions with benzylic bromide, trifluoroacetate, acetate, pivalate and carbonate electrophiles provided modest yields ($\leq 10\%$) or none of the product (entries 3-7), the use

of benzyl chloride proved to give the product in better yield in comparison to the phosphonate (entries 1 and 2). The use of leaving group derived from alcohol could certainly be more advantageous than the use of chloride. However, from a convenience perspective, the availability and slightly increased yields, we decided to pursue our studies with benzyl chloride derivatives.

Table 4.2 Effect of the benzylic leaving group on the reactivity.

entry	Benzyl-X, X =	% GC yield ^a
1	OP(O)OEt ₂	53 (55 ^b)
2	Cl (2a)	58 (62 ^b)
3	Br	6
4	O ₂ CCF ₃	11
5	OAc	0
6	OPiv	0
7	O ₂ COMe	0

(a) C₁₄H₃₀ as internal standard. (b) Isolated yield.

In the development of the reaction, side reactions were found to consume the starting benzyl-chloride. The side products were found to come from the substitution of the chloride with a pivalate anion (**3**) and the homocoupling of the electrophile to form dibenzyl (**4**). Both side products consumed the limiting reagent, especially the dibenzyl, but prior to changing the stoichiometry of the reaction and using an excess of the benzyl chloride, we opted to further optimize the reaction and try to limit the side reactions. To start, without using pivalic acid as an additive, we looked at common sources of palladium (Table 4.3, entries 1–4). Both, palladium acetate and palladium pivalate gave similar yield (56% and 61%) and gave similar amounts of dibenzyl and benzyl acetate and pivalate.¹⁷ On the other hand, the two others source of palladium gave poor yields of product **1** and palladium chloride (entry 3) formed a significant amount of dibenzyl byproduct. Continuing with both Pd(OAc)₂ and Pd(OPiv)₂, we noted that the amount of catalyst could be reduced to 2 mol% (Table 4.3, entries 5–6), surprisingly, the yield

¹⁷ The amount of benzyl acetate formed was not calibrated on the GC, as a result we do not report yields.

increased by 13% by using 2 mol% of Pd(OPiv)₂. Pursuing with Pd(OPiv)₂, we then looked at the effect of additives on the yield of **1** and the formation of benzyl pivalate (Table 4.3, entries 7–9). We found that up to 20 mol% of pivalic acid had little apparent effects on the yield of the reaction and the amount of **3** formed. In agreement with previous studies, we found that the additive had a rate-enhancing effect on the reaction and for some substrates this effect might be beneficial (Figure 4.2).^{7h,18} In a control experiment, we verified that the reaction was indeed catalyzed by palladium (Table 4.3, entry 10). Lastly, to further increase the yield, we decided to use an excess of benzyl chloride (1.5 equiv.) and to slightly increase the reaction temperature to 110 °C (Table 4.3, entry 11). We were somewhat disappointed to obtained only a minor increased in yield to 81%.

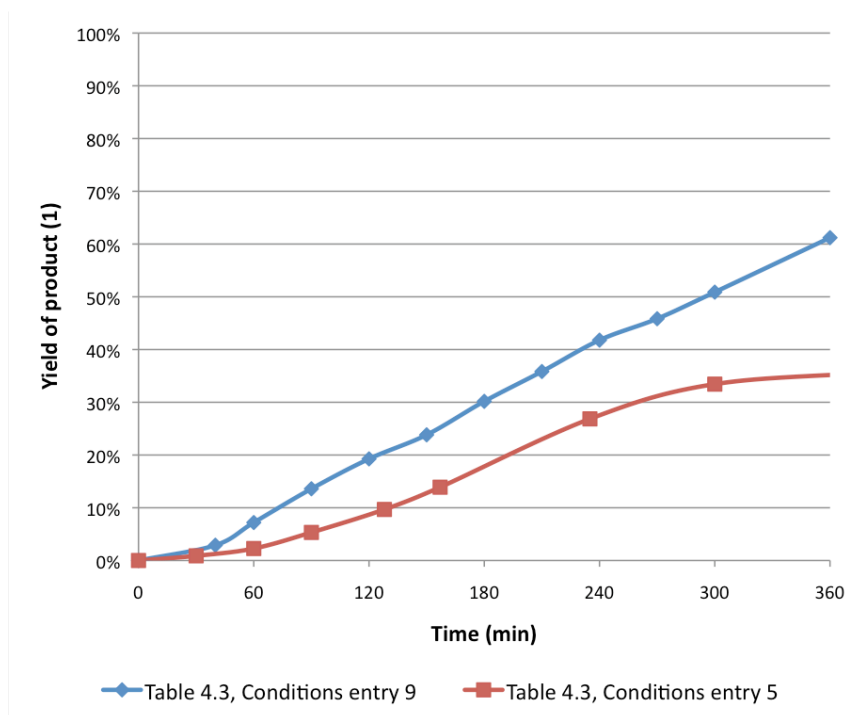
Table 4.3 Effect of the source of palladium and additive on the reactivity.

entry	"Pd"	Additive	Products:	GC yield (%) ^a		
				3	4	1
1	Pd(OAc) ₂	5 mol%	–	N/A	6	56
2	Pd(OPiv) ₂	5 mol%	–	2	4	61
3	PdCl ₂ MeCN	5 mol%	–	N/A	14	34
4	Pd(OTFA) ₂	5 mol%	–	N/A	6	49
5	Pd(OAc) ₂	2 mol%	–	N/A	4	55 (55 ^d)
6	Pd(OPiv) ₂	2 mol%	–	0	3	74 (74 ^d)
7	Pd(OPiv) ₂	2 mol%	PivOH 5 mol%	2	3	73
8	Pd(OPiv) ₂	2 mol%	PivOH 10 mol%	2	3	74
9	Pd(OPiv) ₂	2 mol%	PivOH 20 mol%	2	4	75 (72 ^d)
10 ^b	–	PivOH 5 mol%		6	0	0
11 ^c	Pd(OPiv) ₂	2 mol%	PivOH 20 mol%	11	4	81 (79 ^d)

N/A: Not Applicable (a) C₁₄H₃₀ as internal standard. (b) 4 mol% of ligand were used. (c) Same conditions aside from: Thiazole (1.0 equiv.), Benzyl Chloride (1.5 equiv.), 110 °C. (d) Isolated yield.

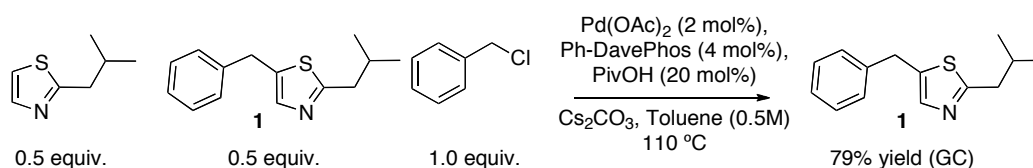
¹⁸ See also Chapter 2.

Figure 4.2 Reactions monitored over 6 hours (360 minutes).



Intrigued by this last result, we wanted to verify if this result was the cause of the degradation of the catalyst overtime or if something else was interrupting the reaction. To find an answer to this question, we setup an experiment reproducing the reaction at 50% conversion. We then let the reaction run overnight and to look at the GC yield of the reaction (Scheme 4.5). From the control experiment, we obtained the same yield as in a regular reaction. To us, this result suggested that the catalyst degradation was not the source of the problem, but instead, it seemed that what we were observing was the result of product inhibitions. A close examination of the exact nature of the inhibition phenomenon would have certainly necessitated further investigations. However we judged more appropriate to focus our efforts toward the elaboration of the scope of this transformation.

Scheme 4.5 Control experiment, product inhibition.



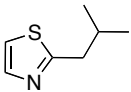
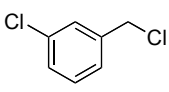
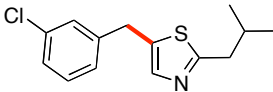
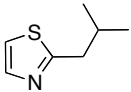
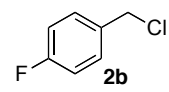
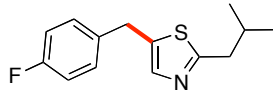
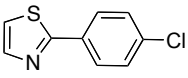
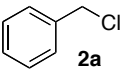
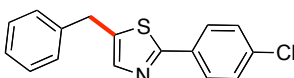
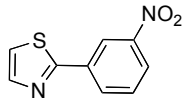
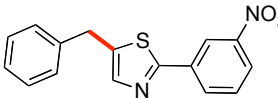
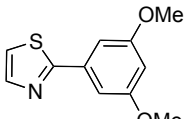
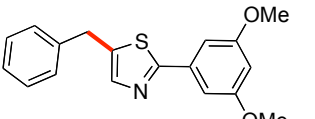
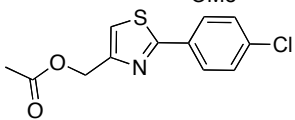
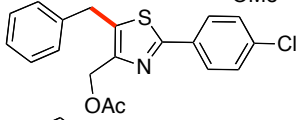
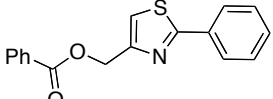
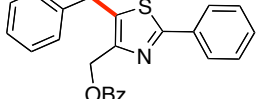
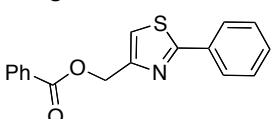
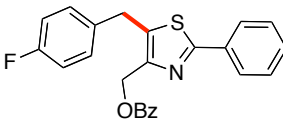
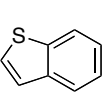
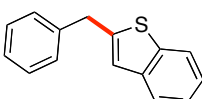
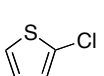
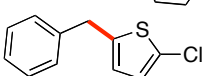
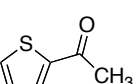
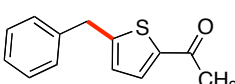
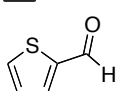
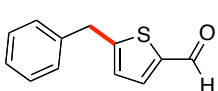
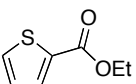
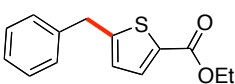
4.2.2 Scope of the palladium-catalyzed benzylation of heteroarenes

Using the optimized set of conditions and using 1.5 equivalent of the electrophile, we initially tested the scope of the reaction with a range of sulfur containing heterocycles (Table 4.4). We also chose, for some examples, to compare the outcome of the reactions for which we used the heteroarenes in excess (entries 2, 4, 13, 16, 18 and 21). In nearly each case, poorer yields were obtained in comparison to the optimized conditions. Thiazole substrates, which are usually problematic under $\text{S}_{\text{E}}\text{Ar}$ benzylation conditions or necessitate deprotonation with strong bases followed by electrophilic trapping,¹⁹ were ideal substrates for palladium-catalyzed benzylation. A variety of aliphatic and aromatic substituents were tolerated including chloride, ester and nitro functionalities (Table 4.4, entries 1 to 10). Benzothiophene also underwent clean C2 benzylation, which is complementary to standard $\text{S}_{\text{E}}\text{Ar}$ -type benzylation outcomes that produce the C3 isomer preferentially (Scheme 4.2a and Table 4.4, entries 11–13).^{4b} Similarly, electron-deficient thiophenes containing electrophilic functionalities, which represent limitations for the Friedel-Crafts approach,²⁰ underwent regioselective palladium-catalyzed benzylation adjacent to the sulfur atom (Table 4.4, entries 14–22).

¹⁹ For examples, see: a) Hamana, H.; Sugawara, T. *Chem. Lett.* **1982**, 333. b) Evans, D. A.; Cee, V. J.; Smith, T. E.; Santiago, K. J. *Org. Lett.* **1999**, *1*, 87. c) Deng, S.; Taunton, J. *Org. Lett.* **2005**, *7*, 291. d) Teng, P.-F.; Tsang, C.-S.; Yeung, H.-L.; Wong, W.-L.; Kwong, H.-L.; Williams, I. D. *J. Organomet. Chem.* **2006**, *691*, 2237.

²⁰ Friedel-Crafts additions of electrophiles to thiophenes bearing EWG are exceedingly rare. For examples involving thiophene deprotonation using a strong base, see Scheme 4.2b: a) Slocum, D. W.; Gierer, P. L. *Chem. Comm.* **1971**, 305. b) Shilai, M.; Kondo, Y.; Sakamoto, T. *J. Chem. Soc., Perkin Trans. I* **2001**, 442. See also ref 5a.

Table 4.4 Direct benzylation of sulfur-containing heterocycles.^{a,b}

entry	arene	benzyl chloride	product	yield (%)
1 2 ^d				5 73 50
3 4 ^d				6 72 67
5				7 84
6		2a		8 75
7		2a		9 78
8		2a		10 78
9		2a		11 80
10		2b		12 89
11 12 ^c 13 ^d		2a		13 65 69 52
14 15 ^c 16 ^d		2a		14 47 66 54
17 ^c 18 ^d		2a		15 70 59
19 20 ^c 21 ^d		2a		16 52 57 45
22		2a		17 67

(a) Conditions: Benzyl chloride (0.75 mmol), heteroarene (0.50 mmol), Pd(OPiv)₂ (0.01 mmol), 2-Ph₂P-2'-(Me₂N)biphenyl (0.02 mmol), PivOH (0.10 mmol), Cs₂CO₃ (0.75 mmol), toluene (1.0 mL), 110 °C, 16 to 20 hours. (b) Isolated yield. (c) Benzyl chloride (1.00 mmol), heteroarene (0.50 mmol), Pd(OPiv)₂ (0.025 mmol), 2-Ph₂P-2'-(Me₂N)biphenyl (0.05 mmol), PivOH (0.10 mmol), Cs₂CO₃ (0.75 mmol), toluene (1.0 mL), 110 °C, 16 to 20 hours. (d) Benzyl chloride (0.50 mmol), heteroarene (0.75 mmol), Pd(OPiv)₂ (0.01 mmol), 2-Ph₂P-2'-(Me₂N)biphenyl (0.02 mmol), PivOH (0.10 mmol), Cs₂CO₃ (0.75 mmol), toluene (1.0 mL), 110 °C, 16 to 20 hours.

The utility of the palladium-catalyzed arene benzylation may be further illustrated by the successful formation of **15** and **16** (Table 4.4, entries 17 and 19). In addition to low nucleophilicity that is problematic for S_EAr-like reactivity, 2-acetylthiophene would be incompatible with the strong alkyl lithium bases required for arene deprotonation required for the formation of **15**, due to the presence of more acidic protons on the acetyl moiety. This example highlights the inherent preference of the palladium catalyst to induce *sp*² C–H bond cleavage under the conditions described herein compared to similar reactions on the same substrate that result in ketone α -arylation when performed in the presence of a stronger base.^{21,22} Similarly, the formation of **16** would be equally problematic under traditional techniques due to the presence of the resonance electron-withdrawing and electrophilic aldehyde group that would necessitate the use of additional protection/deprotection steps (Scheme 4.2).

In addition to the sulfur-containing heteroarenes, a variety of nitrogen and oxygen containing heterocycles were compatible with the palladium-catalyzed benzylation conditions, as illustrated in Table 4.5. The additional set of compatible heteroarenes included indolizines (entries 1–3), imidazopyrimidine (entry 4), 1,2,3-triazole (entries 5 and 6), oxazole (entry 7) and electron-deficient furans (entries 8–10). Another important feature of palladium-catalyzed reactions with benzyl chloride in general is that under these conditions, palladium selectively reacts at the benzylic C–Cl bond rather than the aryl–Cl bond (Table 4.4, entries 1, 5, 8, 14 and Table 4.5, entry 2). In this way, substrates bearing useful functional groups may be employed that can subsequently be applied in other metal-catalyzed functionalization processes.²³

²¹ This tendency was also observed with picoline-*N*-oxide substrates. See: a) Campeau, L.-C.; Schipper, D. J.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3266. b) Schipper, D. J.; Campeau, L.-C.; Fagnou, K. *Tetrahedron* **2009**, *65*, 3155.

²² For ketone α -arylation, see: Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 12382.

²³ Little, A. F.; Fu, G. C. *Angew. Chem. Int. Ed.* **2002**, *41*, 4176.

Table 4.5 Additional examples of heteroarene benzylation.^{a,b}

entry	arene	benzyl chloride	product	yield (%)
1				18 92
2				19 87
3				20 65
4		2a		21 97
5		2a		22 62
6				79 ^c
7		2a		23 61
8		2a		24 72
9		2a		25 67 ^c
10				26 53 ^c

(a) Conditions: Benzyl chloride (0.75 mmol), heteroarene (0.50 mmol), Pd(OPiv)₂ (0.01 mmol), 2-Ph₂P-2'-(Me₂N)biphenyl (0.02 mmol), PivOH (0.10 mmol), Cs₂CO₃ (0.75 mmol), toluene (1.0 mL), 110 °C, 16 to 20 hours. (b) Isolated yield. (c) Benzyl chloride (1.00 mmol), heteroarene (0.50 mmol), Pd(OPiv)₂ (0.025 mmol), 2-Ph₂P-2'-(Me₂N)biphenyl (0.05 mmol), PivOH (0.10 mmol), Cs₂CO₃ (0.75 mmol), toluene (1.0 mL), 110 °C, 16 to 20 hours.

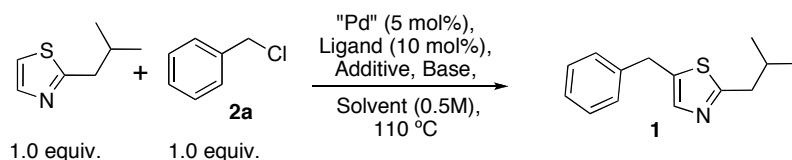
4.2.3 *Post facto* improvement of the benzylation conditions

The development of the reaction and the initial optimizations were made in the perspective of limiting the degradation and side reactions of the benzyl-(pseudo)halide.

As a result, the choice of some reagents was made in that perspective and did not necessarily improve the yield of product. However, since in the end, we resorted using an excess of the benzyl chloride relative to the heteroarene, in this section, we will see that the choice of some reagents might not be entirely justifiable.

During the preparation of the our report on the direct benzylation of heteroarenes, for consistency, we have decided to remake a new optimization table using benzyl chloride instead of the benzyl phosphonate originally used in Table 4.1 (Table 4.6). Starting with conditions very similar to the general conditions of direct arylation,^{7h} DMA gave a very poor yield and we observed an increased in yields when the solvent was changed to toluene (entries 1 and 2). When the base was changed from potassium carbonate to cesium carbonate, identical yields were obtained (entries 2 and 3). Originally, cesium carbonate was chosen in part to limit the hydrolysis of the benzyl chloride, however it is much more expensive than potassium carbonate. The optimization of the ligand revealed that triarylphosphine ligands gave better yields than the phosphines bearing alkyl groups (entries 3–7). Once again, triphenylphosphine and Ph-DavePhos gave identical yields (entrie 6 and 7), still Ph-DavePhos was chosen over PPh_3 owing to a small yield increase in the previous optimization (Table 4.1). However, PPh_3 represents a much more economical alternative to Ph-DavePhos. Changing the palladium source from $\text{Pd}(\text{OAc})_2$ to $\text{Pd}(\text{OPiv})_2$ increased the yield due to the presence of pivalate (entries 7 and 8). The addition of 20 mol% of pivalic acid (entry 9) did not increase the yield of product although its beneficial effect on the rate of the reaction was verified (Figure 4.2). Nonetheless, $\text{Pd}(\text{OPiv})_2$ was a rather exotic source of palladium and we saw that the use of $\text{Pd}(\text{OAc})_2$ in conjuncture with PivOH gave identical results (entry 10). Finally, as expected the use of a greater excess benzyl chloride gave another boost in yield (entries 11–13). In summary, in place of the conditions that we have used to scope the reaction (entry 12), we could replace the expensive and exotic reagents by cheaper and readily available reagents and get similar results.

Table 4.6 Optimization of the benzylation reaction with benzyl chloride.



Entry	"Pd"	Ligand	Additive	Base	Solvent	GC yield (%) ^a
1	Pd(OAc) ₂	PCy ₃ *HBF ₄	–	K ₂ CO ₃	DMA	1
2	Pd(OAc) ₂	PCy ₃ *HBF ₄	–	K ₂ CO ₃	Toluene	22
3	Pd(OAc) ₂	PCy ₃ *HBF ₄	–	Cs ₂ CO ₃	Toluene	20
4	Pd(OAc) ₂	P ^t Bu ₂ Me*HBF ₄	–	Cs ₂ CO ₃	Toluene	2
5	Pd(OAc) ₂	JohnPhos	–	Cs ₂ CO ₃	Toluene	8
6	Pd(OAc) ₂	PPh ₃	–	Cs ₂ CO ₃	Toluene	58
7	Pd(OAc) ₂	LCPhos	–	Cs ₂ CO ₃	Toluene	57
8	Pd(OPiv) ₂	LCPhos	–	Cs ₂ CO ₃	Toluene	70
9	Pd(OPiv) ₂	LCPhos	PivOH 20 mol%	Cs ₂ CO ₃	Toluene	69
10	Pd(OAc) ₂	LCPhos	PivOH 20 mol%	Cs ₂ CO ₃	Toluene	70
11 ^b	Pd(OPiv) ₂	LCPhos	PivOH 20 mol%	Cs ₂ CO ₃	Toluene	85
12 ^{b,c}	Pd(OPiv) ₂	LCPhos	PivOH 20 mol%	Cs ₂ CO ₃	Toluene	85
13 ^d	Pd(OPiv) ₂	LCPhos	PivOH 20 mol%	Cs ₂ CO ₃	Toluene	85

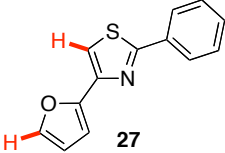
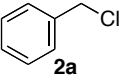
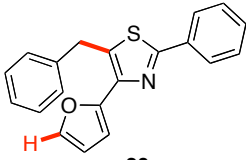
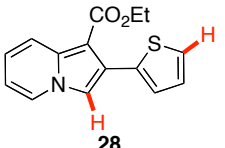
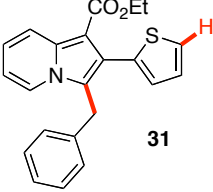
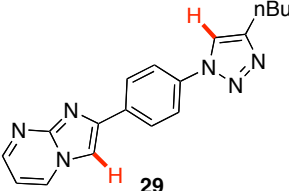
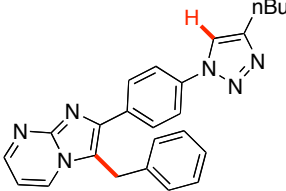
(a) C₁₄H₃₀ as internal standard. (b) **2a** (1.5 equiv.). (c) 2 mol% of Pd(OPiv)₂, 4 mol% of X. (d) **2a** (2.0 equiv.).

Although the improved benzylation reaction conditions were identified after the fact, at that point, we did not had the time to re-evaluate the scope of the reaction. Instead, these conditions were tested in a later project.

Effectively, the reactivity guidelines we established and discussed in the previous chapter can also be used for other types of C–H bond functionalization reactions than the direct arylation.²⁴ The relative reactivity of the heteroarenes was based on the C–H bond cleaving step and should not be affected significantly by the nature of the coupling partner. To illustrate this point and to test the new conditions, we applied these guidelines for the benzylation of *bis*-heteroarene **27–29** (Table 4.7).

²⁴ See Chapter 3, Section 3.5.2.

Table 4.7 Benzylation of *bis*-heteroarenes.^a

Entry	Substrate	Coupling Partner	Product	Yield (%)
1 ^b 2				69 84
3				55
4				55

(a) Conditions: *Bis*-heteroarene (1.1 equiv.), benzyl chloride (1.0 equiv.), Pd(OAc)₂ (5 mol%), PPh₃ (10 mol%), PivOH (20 mol%), K₂CO₃ (1.5 equiv.) in toluene (0.5 M) at 110 °C; (b) *bis*-heteroarene (1.1 equiv.), benzyl chloride (1.0 equiv.), Pd(OPiv)₂ (2 mol%), 2-Ph₂P-2'-(Me₂N)biphenyl (4 mol%), PivOH (20 mol%), Cs₂CO₃ (1.5 equiv.) in toluene (0.5 M) at 110 °C.

Starting with **27**, we were able to selectively benzylate the C5 position of the thiazole arene in 69 % yield using a slightly modified variation of the original conditions we had developed (Table 4.7, entry 1). For this reaction, the *bis*-heteroarene was used in slight excess (1.1 equiv.) compared to the benzyl chloride in order to minimize formation of the double benzylation products. Alternatively, the direct benzylation of substrates **27**–**29** could also be achieved in acceptable yields (Table 4.7, entries 2–4) using Pd(OAc)₂/PPh₃ as pre-catalyst and potassium carbonate. Under those conditions, **30** was obtained in a better yield than with the original conditions (Table 4.7, entry 2). From these examples, we cannot judge if the generality of the new conditions was improved. Nonetheless, the preliminary results are promising.

4.2.4 Concluding remarks

In this section, the development of a palladium-catalyzed heterocycle benzylation method was described. We have established a broadly applicable intermolecular cross-coupling reaction between simple heteroarenes (without organometallic pre-activation) and aliphatic electrophiles. This reaction should find application in the preparation of a wide range of diarylmethane compounds. Notably, the ability to achieve useful reactivity with some of the most problematic cases of traditional techniques should be invaluable when the preparation of these types of molecule is required.

4.3 Development of a Domino 1,2-Migratory Insertion–Intermolecular Direct Arylation Process Catalyzed by Palladium²⁵

In this section, the development of a novel domino process for the preparation of complex motif in a single step will be described. As previously mentioned in the introduction of this chapter, we sought to increase the level of complexity of the C–H bond functionalization processes that are involved. Looking for precedent in the literature, we were able to find several examples in which C–H functionalization steps were involved in multistep processes, more specifically in domino processes.²⁶ Without being an exhaustive enumeration of all cases, here are few representative examples.

A simple example of domino cyclizations was reported by Teitze *et al.* with substrate **FT-1** (Scheme 4.6a) containing an alkyne and a bromonaphthyl moiety.²⁷ The sequence is initiated by the oxidative insertion of the palladium(0) into the bromonaphthyl followed by the 1,2-migratory insertion into the adjacent alkyne to form

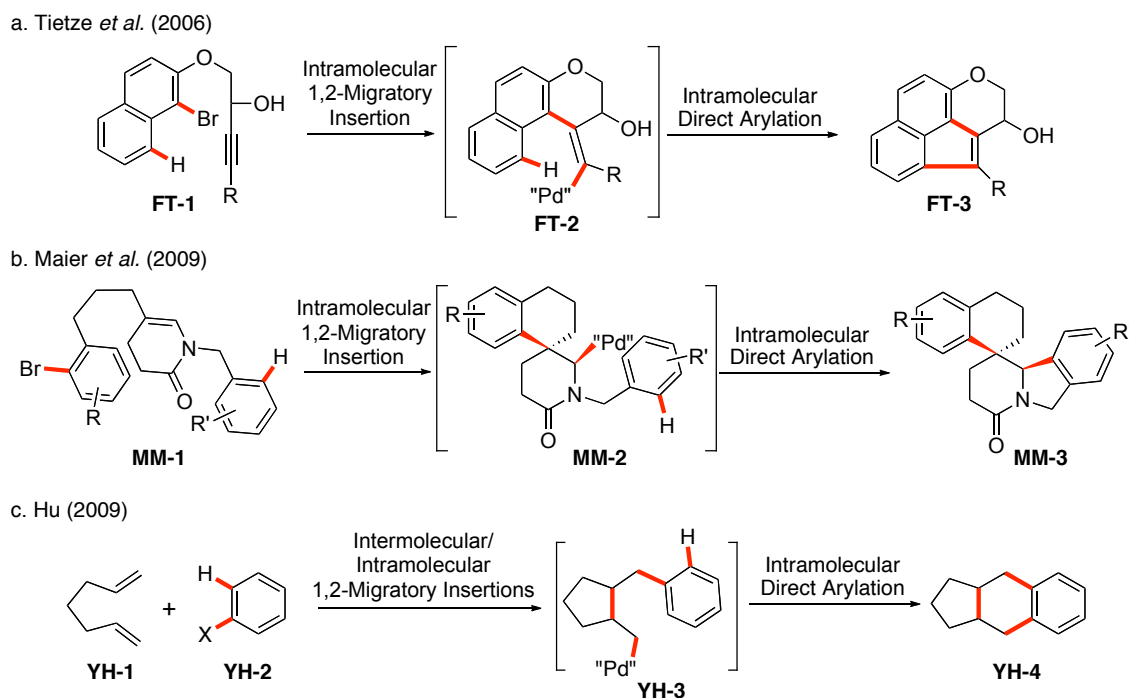
²⁵ Parts of the following section were published in the following article: René, O.; Lapointe, D.; Fagnou, K. *Org. Lett.* **2009**, *11*, 4560.

²⁶ For reviews on domino palladium-catalyzed reactions, see: a) Patil, N. T.; Yamamoto, Y. *Top. Organomet. Chem.* **2006**, *19*, 91. b) Balme, G.; Bossharth, E.; Monteiro, N. *Eur. J. Org. Chem.* **2003**, *21*, 4101. c) De Meijere, A.; Von Zezschwitz, P.; Bräse, S. *Acc. Chem. Res.* **2005**, *38*, 412. d) Patil, N. T.; Yamamoto, Y. *Synlett* **2007**, *13*, 1994.

²⁷ Tietze, L. F.; Lotz, F. *Eur. J. Org. Chem.* **2006**, *24*, 4676.

the a tricyclic intermediate (**FT-2**). The Pd catalyst on the olefin is then in close proximity to the C–H bond on the naphthyl moiety to achieve the intramolecular C–H functionlization. A more complex example was reported by Maier *et al.*²⁸ They developed a method to form spiropentacyclic compounds (**MM-3**) from enamides **MM-1** featuring a 2-bromophenyl substituent which can undergo a *syn*-1,2-migratory insertion into the enamide's double bond (**MM-2**) followed by an intramolecular direct arylation to yield complex substrates. Hu *et al.* developed a double intermolecular–intramolecular 1,2-migratory insertions sequence of **YH-1** and **YH-2** completed by an intramolecular direct arylation to form **YH-4**.²⁹

Scheme 4.6 Selected precedents of domino 1,2-migratory insertion–intramolecular direct arylation.

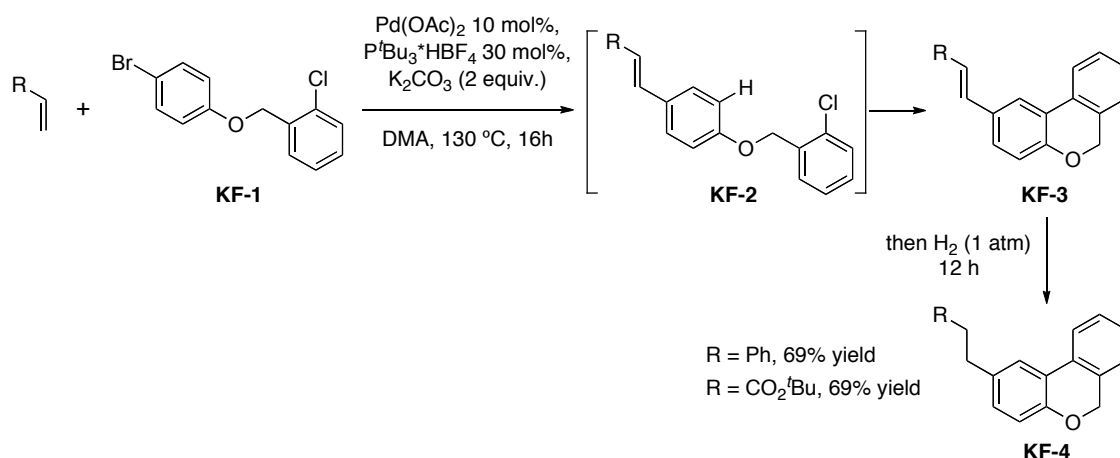


²⁸ Satyanarayana, G.; Maichle-Mössner, C.; Maier, M., E. *Chem. Commun.* **2009**, 1571.

²⁹ Hu, Y.; Yu, C.; Ren, D.; Hu, Q.; Zhang, L.; Cheng, D. *Angew. Chem., Int. Ed.* **2009**, 48, 5448.

A tandem process involving a Heck coupling followed by the intramolecular direct arylation reaction was as well developed in our group (Scheme 4.7).³⁰ Although, this sequence of reactions cannot be identified as a domino sequence since, in principle, either step could occur independently of the one another and does not necessitate the completion of the first reaction to continue. The process was designed in such way that the Heck coupling would occur first with the aryl-bromide (**KF-1**). Once completed, the slower oxidative insertion into an aryl chloride (**KF-2**) allowed the intramolecular direct arylation to occur (**KF-3**). Finally, when both reactions were complete, the argon atmosphere can be replaced with a hydrogen atmosphere and after 12 hours, the reduced product **KF-4** can be isolated.

Scheme 4.7 Sequential 1,2-migratory insertion–intramolecular direct arylation–hydrogenation reaction.



More relevant examples of the transformation we were targeting were reported by Grigg *et al.* and later by Ruck *et al.* (Scheme 4.8).^{31,32} In the transformation reported by Grigg *et al.* (Scheme 4.8a),³¹ the Pd(0) inserted into the aryl-iodide bond of **RG-1**. It was then followed by a carbopalladation of the olefin in a 5-*exo-trig* fashion. Due to lack of

³⁰ Leclerc, J.-P.; André, M.; Fagnou, K. *J. Org. Chem.* **2006**, *128*, 581.

³¹ Brown, D.; Grigg, R.; Sridharan, V.; Tambyrajah, V. *Tetrahedron Lett.* **1995**, *36*, 8137.

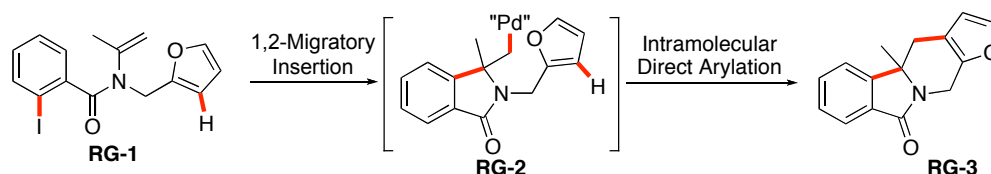
³² Ruck, R., T.; Huffman, M. A.; Kim, M. M.; Shevlin, M.; Kandur, W., V.; Davies, I. W. *Angew. Chem., Int. Ed.* **2008**, *47*, 4711.

β -hydrogen in **RG-2**, *beta*-hydride elimination could not occur. The intermediate was then set to undergo the direct arylation at the C3 position of the adjacent furan ring.

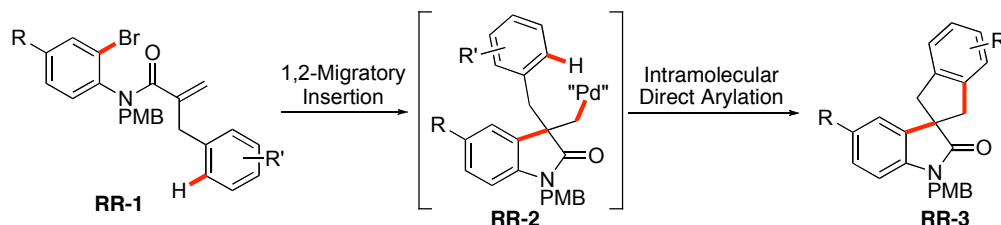
More recently, scientists from Merck led by Ruck reported a similar transformation to generate a spiro-fused indane-oxindoles (Scheme 4.8b).³² Interestingly, they attempted to develop an enantioselective variant of their reaction similar to the work of Overman and others on the enantioselective Heck couplings.³³ Unfortunately, after a considerable ligand screening, their efforts failed to yield any enantioselectivity. According to the authors, these negative results could be explained with a fast and reversible olefin insertion and a subsequent slow C–H cleavage (Scheme 4.9). In this way, facial selectivity may exist for the initial insertion to generate intermediate **RR-2**, but, in a Curtin-Hammett situation, there is a minimal preference for C–H functionalization to occurs from either of the two diastereoisomers of **RR-2**. In the perspective of our targeted domino intramolecular 1,2-migratory insertion–intermolecular direct arylation, a rapid and reversible carbopalladation of the olefin could cause some issues of chemoselectivity on the aryl-bromide/olefin substrates.

Scheme 4.8 Examples of fully intramolecular version of the targeted domino 1,2-migratory insertion–direct arylation reaction.

a. Grigg *et al.* (1995)

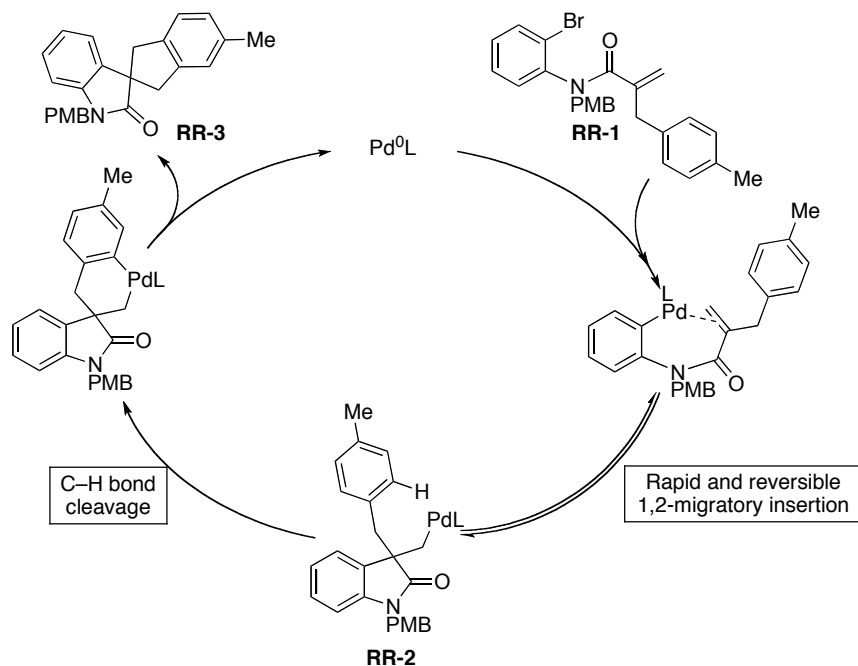


b. Ruck *et al.* (2008)



³³ a) Guiry, P. J.; Kiely, D. *Curr. Org. Chem.* **2004**, 8, 781. b) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, 103, 2945.

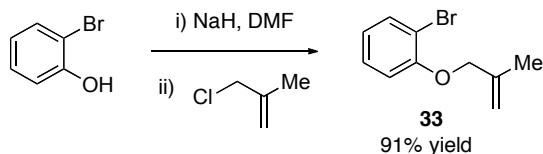
Scheme 4.9 Proposed 1,2-migratory insertion/C–H functionalization catalytic cycle.



4.3.1 Reaction development

The development of our palladium-catalyzed domino 1,2-migratory insertion–intermolecular direct arylation sequence started with the preparation of the model substrate **33**. **33** could be readily prepared in a single step by the alkylation of 3-chloro-2-methylpropene with 2-bromophenolate (Scheme 4.10).

Scheme 4.10 Preparation of bromoarene **33**.



With **33** in hand and benzothiophene, we then tried to perform the domino sequence to form product **34** using the general set of conditions we developed for the

direct arylation of heteroarenes (Table 4.8, entry 1).^{7h} To our delight, the desired product was isolated in 35% yield. We increased the amount of benzothiophene hoping to increase the yield of our initial hit. To our dismay, two equivalents of the heteroarene did not have any beneficial effect on the yield of the transformation (entry 2). Nonetheless, we decided to use two equivalents of benzothiophene for the rest of our preliminary optimization study, since we believed that it would not cause any complication to the reaction. From this initial set of conditions, we looked at the effect of the ligands on the reaction. In the absence of phosphine-based ligand, the reaction yielded a similar result as with the PCy₃ ligand (entry 3). P^tBu₂Me and PPh₃ both gave poor results and the yields were not recorded (entries 4 and 5). We observed a significant boost in yield when Buchwald-type ligands were employed (entries 6–11). From the series of ligands tried, DavePhos came out as the best choice by giving **34** in 70% yield (entry 8). A carbene based ligand gave **34** in poor yield (entry 12). *R*-BINAP was also tried in order to verify if enantioselectivity could be obtained under those set of conditions, although it gave a decent yield of product (49 %), no enantiomeric excess was observed on the HPLC (entry 13). Next, we examined the effect of the base on the reactivity. We sought to look at the effects of both the anion and the metal on the yield. A slight decrease in yield was observed when we employed cesium carbonate (entry 14). Both acetate and pivalate anions gave modest results (entries 15 and 16). On the other hand, when potassium phosphate was used, a significant increase in yield was obtained (85% yield, entry 17). Without surprise, when an alkoxide or an amine base were used, no product was formed (entries 18 and 19). With the partially optimized conditions of entry 17, we decided to use them with a few substrates in order to get an idea of the generality of the transformation.

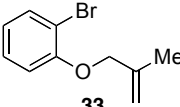
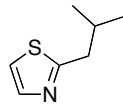
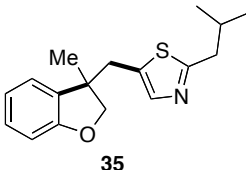
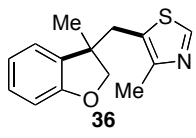
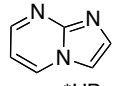
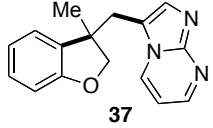
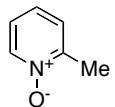
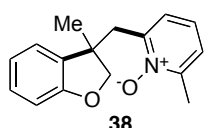
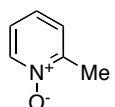
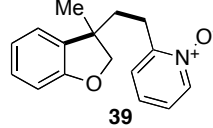
Table 4.8 Preliminary optimization of the reaction conditions.

Entry	Ligand	Base	Yield (%) ^a
1 ^b	PCy ₃ *HBF ₄	K ₂ CO ₃	35
2	PCy ₃ *HBF ₄	K ₂ CO ₃	36
3	—	K ₂ CO ₃	(31)
4	P ^{<i>i</i>} Bu ₂ Me*HBF ₄	K ₂ CO ₃	Low Conv. ^d
5	PPh ₃	K ₂ CO ₃	Low Conv. ^d
6	SPhos	K ₂ CO ₃	56
7	XPhos	K ₂ CO ₃	(54)
8	DavePhos	K ₂ CO ₃	70
9	Ph ₂ -DavePhos	K ₂ CO ₃	(61)
10	JohnPhos	K ₂ CO ₃	(57)
11	Cy ₂ -JohnPhos	K ₂ CO ₃	63
12 ^c	IMes*HCl	K ₂ CO ₃	(9)
13	R-BINAP	K ₂ CO ₃	49
14	DavePhos	Cs ₂ CO ₃	54
15	DavePhos	KOAc	(22)
16	DavePhos	KOPiv	(36)
17	DavePhos	K ₃ PO ₄	85
18	DavePhos	NaO ^{<i>t</i>} Bu	no product
19	DavePhos	DBU	no product

a) Isolated yields. Values between parentheses were estimated by and calibrated with an internal standard (Dibenzofuran). b) Benzothiophene (1.2 equiv.). c) No enantiomeric excess was obtained. d) Low conversion of starting material **33**.

In Table 4.9 is presented the initial scope of the reaction under the conditions developed in Table 4.8. Unfortunately, the breath of the transformation seemed pretty limited in terms of the compatible heteroarenes. Other than 2-*iso*-butylthiazole (entry 1) poor yields or no reactivity were obtained with other heteroarenes (entries 2–4). We have also tested 2-picoline-*N*-oxide, but under the developed conditions no product was obtained (entry 4). Nonetheless, it was shown that the aliphatic C–H position of picoline-*N*-oxides is functionalizable if a strong base, such as sodium *tert*-butoxide, is employed.²¹ Once again, no product was obtained in DMA (entry 5) and only a trace of product was observed by GC-MS when the reaction was performed in toluene (entry 6).

Table 4.9 Preliminary scope of the domino reaction.

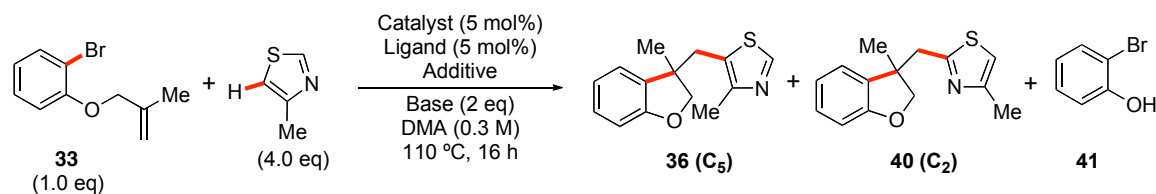
Entry	Substrate	Heteroarenes	Product	Yield (%)
1				80
2	33			14
3	33	 *HBr		0
4	33			0
5 ^b 6 ^{b,c}	33			0 Trace

a) Conditions: heteroarene (2.0 equiv.), bromo arene (1.0 equiv.), Pd(OAc)₂ (5 mol%), Dave-Phos (5 mol%), PivOH (30 mol%), K₃PO₄ (2.0 equiv.) in DMA (0.3 M) at 100 °C;
 b) NaO^tBu instead of K₂CO₃; c) in toluene (0.3M).

4.3.1.1 Re-optimization of the domino 1,2-migratory insertion–intermolecular direct arylation sequence

With these preliminary results in hand, it was obvious that we needed to re-optimize the reaction conditions in order to increase the scope of the reaction. Moreover this optimization should be done using a different heteroarene in place of the benzothiophene. Due to time constraint, the project was then passed on to Olivier René, a new graduate student in the lab at that time. The following section will summarize the work done by Olivier René to increase the efficiency of the domino 1,2-migratory insertion–intermolecular direct arylation sequence and the scope of the reaction.

Table 4.10 Re-optimization of the reaction conditions.

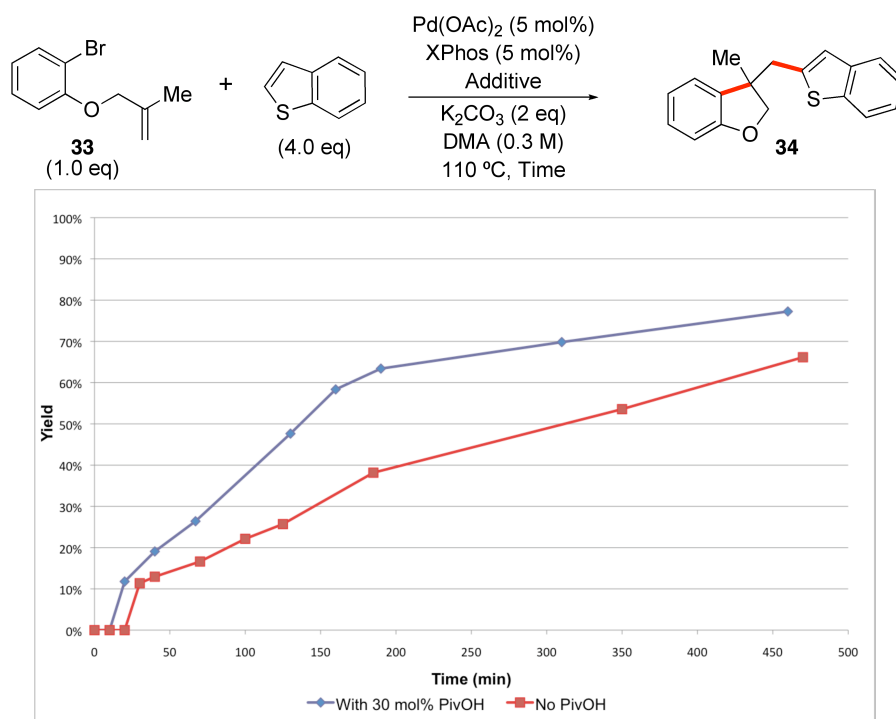


Entry	"Pd"	Ligand	Additive	Base	GC yield (%) ^a		
					36	40	41
1	Pd(OAc) ₂	DavePhos	PivOH 30 mol%	K ₃ PO ₄	14	1	12
2	Pd(OAc) ₂	DavePhos	PivOH 30 mol%	K ₂ CO ₃	15	5	17
3	Pd(OAc) ₂	DavePhos	PivOH 30 mol%	Cs ₂ CO ₃	14	3	16
4	Pd(OAc) ₂	P ^t Bu ₃ ⁺ HBF ₄	PivOH 30 mol%	K ₂ CO ₃	40 (35) ^b	(33) ^b	12
5	Pd(OAc) ₂	XPhos	PivOH 30 mol%	K ₂ CO ₃	57 (58) ^b	5	24
6	Pd(OAc) ₂	XPhos	–	K ₂ CO ₃	58	6	21
7	PdCl ₂	XPhos	PivOH 30 mol%	K ₂ CO ₃	32	4	24
8	Pd(OPiv) ₂	XPhos	PivOH 30 mol%	K ₂ CO ₃	57 (62) ^b	8	36
9	Pd(OPiv) ₂	XPhos	–	K ₂ CO ₃	57	4	18

a) C₁₄H₃₀ as internal standard; b) Isolated yield.

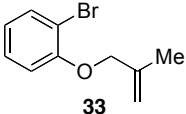
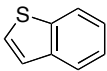
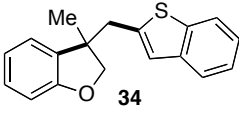
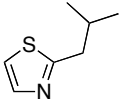
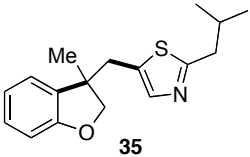
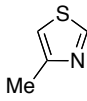
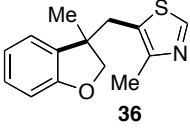
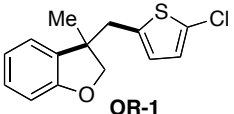
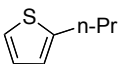
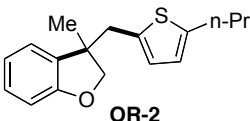
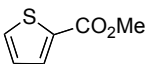
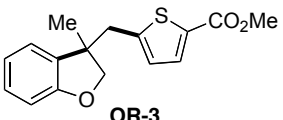
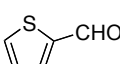
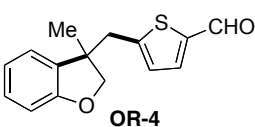
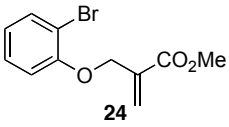
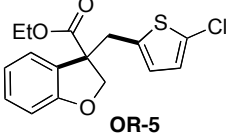
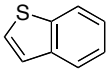
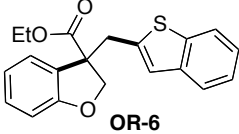
Starting with 4-methylthiazole, the reaction proceeded poorly under the initial optimized conditions (Table 4.10, entry 1). Three reaction products were identified and quantified by GC-MS. These products were found to be the C5- and C2-functionalized isomers of the thiazole and the 2-bromophenol derived from the de-allylation of the starting aryl bromide. The formation of the 2-bromophenol product resulted from the oxidative insertion of the palladium(0) catalyst to form a π -allyl rather than the oxidative insertion into the C–Br bond. From this starting point, the amount of heteroarene was increased to four equivalents and the temperature increased to 110 °C. The base and the ligand were the first reagent to be re-optimized (entries 2–5). For this particular substrate, potassium carbonate and XPhos were identified as optimal reagents. Next, the source of palladium and the influence of the additive were examined. PdCl₂ was found to be a less efficient source of palladium. Both Pd(OAc)₂ and Pd(OPiv)₂ in the presence or absence of pivalic acid as additive gave comparable results. Nonetheless, the pivalate had a beneficial effect on the rate of the transformation (Scheme 4.11). Conditions of entry 5 were elected as the optimal combination and employed to explore the scope of the reaction.

Scheme 4.11 Reaction progression over nearly 8 hours (470 minutes).



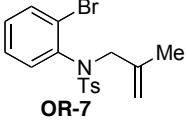
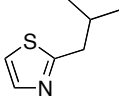
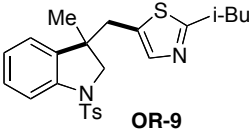
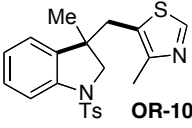
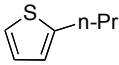
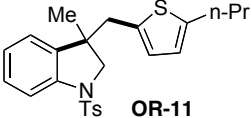
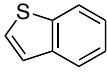
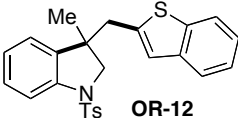
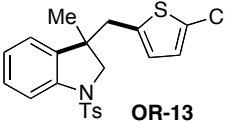
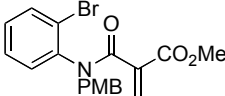
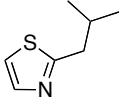
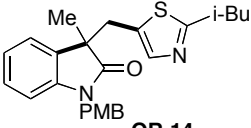
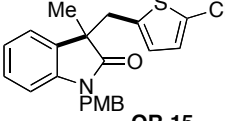
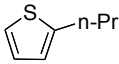
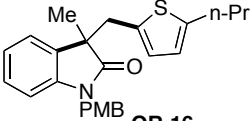
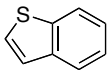
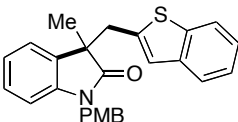
Illustrative examples of the scope are shown in Table 4.11 and Table 4.12. Under the re-optimized conditions, a variety of sulfur containing heteroarenes were compatible in yields up to 99%. 3,3-Disubstituted dihydrofurans were formed in generally good yields. Noticeably, the examples with the benzothiophene and the 2-*iso*-butylthiazole gave lower yields compared to the initially developed conditions (Table 4.11, entries 1 and 2). Nonetheless, the latter conditions allowed the use of 4-methylthiazole as opposed to the former ones (Table 4.11, entry 3). The domino sequence could also be employed for the preparation of different motifs, including a variation of the substitution of the dihydrobenzofuran ring (Table 4.11, entries 8 and 9), as well as the formation of indolines and oxindoles (Table 4.12).

Table 4.11 Scope of the formation of dihyd benzofurans by the 1,2-migratory insertion–intermolecular direct arylation sequence.^a

Entry	Substrate	Heteroarenes	Product	Yield (%)
1				76
2	33			72
3	33			58
4	33			92
5	33			76
6	33			47
7	33			41
8				55
9	24			61

a) Conditions: heteroarene (4.0 equiv.), bromo arene (1.0 equiv.), Pd(OAc)₂ (5 mol%), XPhos (5 mol%), PivOH (30 mol%), K₂CO₃ (2.0 equiv.) in DMA (0.3 M) at 110 °C.

Table 4.12 Scope of the formation of indolines and oxindoles by the 1,2-migratory insertion–intermolecular direct arylation sequence.^a

Entry	Substrate	Heteroarenes	Product	Yield (%)
1	 OR-7		 OR-9	75
2	OR-7		 OR-10	64
3	OR-7		 OR-11	67
4	OR-7		 OR-12	84
5	OR-7		 OR-13	99
6	 OR-8		 OR-14	67
7	OR-8		 OR-15	82
8	OR-8		 OR-16	47
9	OR-8		 OR-17	67

a) Conditions: heteroarene (4.0 equiv.), bromo arene (1.0 equiv.), Pd(OAc)₂ (5 mol%), XPhos (5 mol%), PivOH (30 mol%), K₂CO₃ (2.0 equiv.) in DMA (0.3 M) at 110 °C.

4.3.2 Concluding remarks

In conclusion, we have developed a palladium-catalyzed domino 1,2-migratory insertion–intermolecular direct arylation sequence. This transformation allowed the formation of various motifs, including dihydrobenzofurans, indolines and oxindoles. The reaction was general for sulfur-containing heteroarenes and good to excellent yields were generally obtained.

4.4 General Conclusion

In this chapter was presented our efforts toward the development of new C–H bond functionalization methods in which we could apply our knowledge on the C–H bond cleavage and apply it to the formation of new scaffolds. The development of two new palladium-catalyzed methods were also described. First was the preparation of diarylmethane motifs in a complementary fashion to Friedel-Crafts approaches. The scope of the reaction demonstrated the generality and utility of the transformation when the preparation of such motif is called for. Secondly, we increased the level of complexity of the transformation by including a 1,2-migratory insertion step prior to C–H bond functionalization step in a domino sequence. The method was shown to be quite general including a variety of sulfur-containing heteroarenes.

Chapter

5

Development of ligands to promote the CMD pathway in C–H bond functionalization reactions

5.1 *General Introduction*

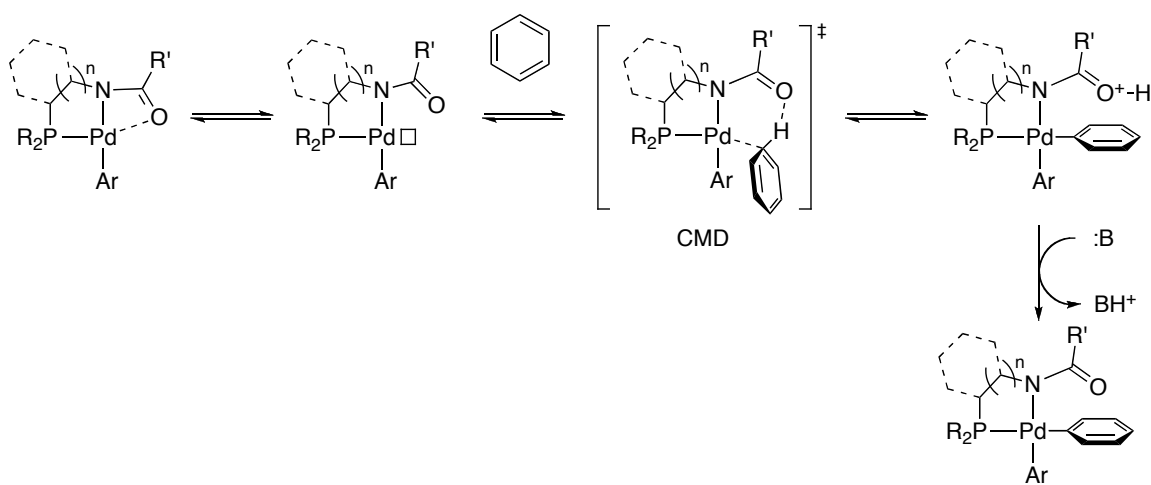
Since the first reports of direct arylation reactions, many mechanistic studies revealed the importance of the base during the C–H bond cleavage step, it did not play the role of an innocent bystander. Mechanistic studies suggested that the base also played the role of an anionic ligand and was directly involved in the C–H bond cleavage event.¹ Capitalizing on these observations, we developed palladium-catalyzed C–H functionalization reactions in which pivalic acid was used as a co-catalyst as described in previous chapters. These findings guided us to design of C–H functionalization specific ligands with the intention of improving the reaction conditions and consequently extending the scope of compatible substrates for C–H bond functionalization. For instance, hypothesized that linking the phosphine donor to the anionic base needed for the

1 See Chapter 1 for discussion on the subject.

C–H bond cleavage could facilitate the process. This would ensure that the base is associated with the palladium and could help the proton transfer.

The first type of ligands we investigated were based on a phosphino-amide core. Hypothetically, the amide moiety would mimic the role of the acetate ligand in the CMD process in addition to having an increased basicity compared to acetate (Scheme 5.1). The process of forming a benzene complex *via* C–H bond cleavage is, in principal, a reversible process made irreversible by the deprotonation of the *bis*-arene palladium complex by the stoichiometric base used in the reaction.²

Scheme 5.1 Suggested mechanism of C–H bond cleavage with phosphino-amide ligands.



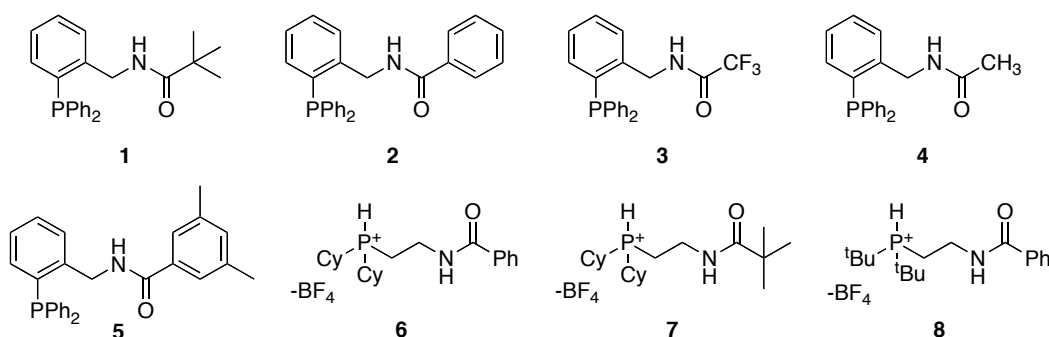
5.1.1 Phosphino-amide ligands

In Figure 5.1 are depicted the initial set of ligands tested for reactivity. Ligands **1–5** were prepared by the addition of a primary amine to acyl chlorides, generally in good yields (Scheme 5.2a). The synthesis of ligands **6–8** was slightly more difficult due to the air sensitivity of the tri-alkyl phosphines (Scheme 5.2b and c). To avoid the phosphine oxidation, dicyclohexylphosphine and di-*tert*-butylphosphine were protected as

2 The reversibility of the CMD process and the importance of the stoichiometric base was demonstrated in catalytic settings, see: Rousseaux, S.; Gorelsky, S. I.; Chung, B. K. W.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 10692.

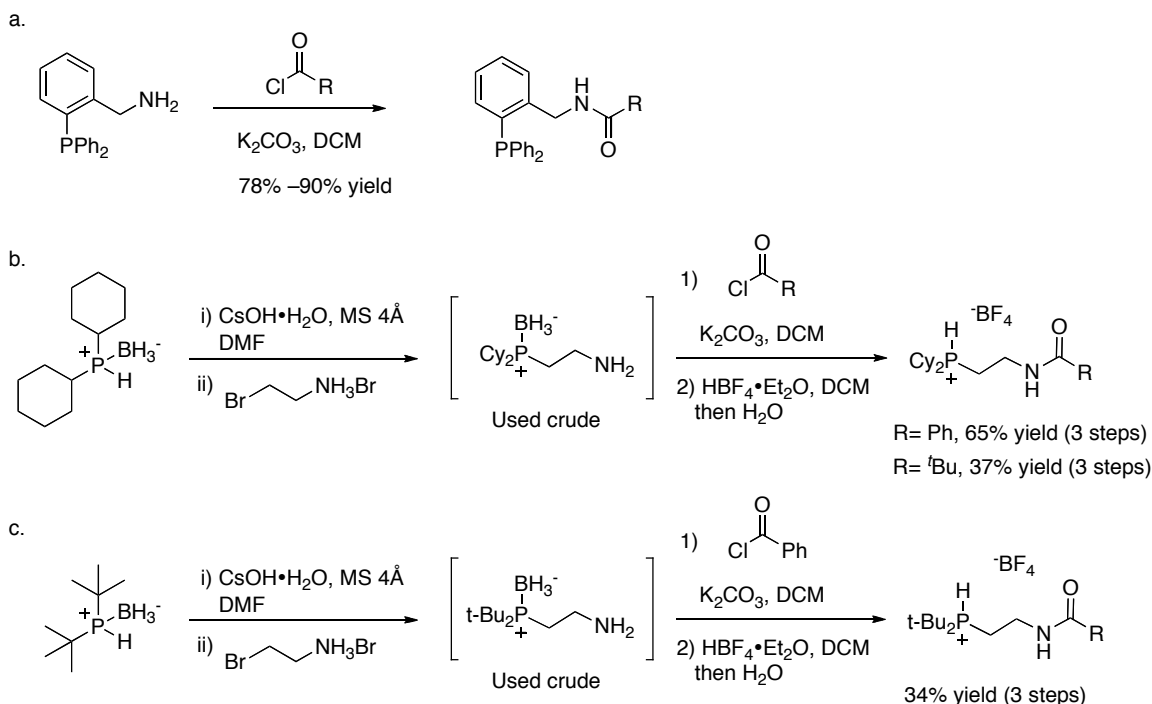
phosphine-borane.³ The protected phosphine could be alkylated with 2-bromoethylamine*HBr, the crude product was then used to form the amide.⁴ The final sequence of borane deprotection and protonation presented some challenges. Typically, phosphine-borane decomplexation is achieved by nucleophilic amines, such as DABCO (1,4-diazabicyclo[2.2.2]octane). Unfortunately in our case, the phosphine-borane complexes were too robust to react.³ The literature on the decomplexation of phosphine-borane employed nucleophilic amines with the exception of a single report that employed tetrafluoroboric acid as the deprotection reagent.⁵ After minor modifications to the initial report, we developed a one-pot procedure in which the air sensitive tri-alkylphosphines were deprotected and reprotected with the tetrafluoroboric acid.^{6,7} The ligands **6–8** were obtained in yields ranging from 34% to 65% over three steps.

Figure 5.1 Initial phosphino-amide ligands tested in direct arylation reactions.



- 3 Procedure from: He, Y.; Hinklin, R. J.; Chang, J.; Kiessling, L. L. *Org. Lett.* **2004**, 6, 4479.
- 4 Honaker, M. T.; Sandefur, B. J.; Hargett, J. L.; McDaniel, A. L.; Salvatore, R. N. *Tetrahedron Letters* **2004**, 44, 8373.
- 5 (a) McKinstry, L.; Livinghouse, T. *Tetrahedron Lett.* **1994**, 35, 9319. (b) McKinstry, L.; Livinghouse, T. *Tetrahedron* **1995**, 51, 7655. (c) McKinstry, L.; Overberg, J. J.; Soubra-Ghaoui, C.; Walsh, D. S.; Robins, K. A.; Toto, T. T.; Toto, J. L. *J. Org. Chem.* **2000**, 65, 2261.
- 6 Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, 3, 4295.
- 7 This sequence of reactions has been independently developed by Denmark *et al.*: Denmark, S. E.; Werner, N. S. *Org. Lett.* **2011**, 13, 4596.

Scheme 5.2 Preparation of ligands **1–8**.



The reactivity of ligands **1–8** was then tested in direct arylation reactions. Each ligand was compared to the original optimal ligand and triphenylphosphine. Pyridine-*N*-oxide (Table 5.1)⁸ and benzene (Table 5.2)⁹ were briefly examined with the ligands available. However, we chose to investigate in greater detail the reactivity of ligands **1–8** in the context of intramolecular direct-arylation (Table 5.3 and Table 5.4) due to the simplicity of the system.¹⁰

Unfortunately, the ligands tested for the direct arylation of pyridine-*N*-oxide reacted poorly in comparison to the tri-*tert*-butylphosphine employed in the original report (Table 5.1).^{8a} Even poorer results were obtained for the direct arylation of benzene in the absence of pivalic acid. No reaction product could be observed by GC-MS (Table 5.2).

8 a) Campeau, L.-C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *127*, 18021. b) Campeau, L.-C.; Stuart, D. R.; Leclerc, J.-P.; Bertrand-Laperle, M.; Villemure, E.; Sun, H.-Y.; Lasserre, S.; Guimond, N.; Lecavallier, M.; Fagnou, K. *J. Am. Chem. Soc.* **2009**, *131*, 3291.

9 Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496.

10 a) Campeau, L.-C.; Parisien, M.; Leblanc, M.; Fagnou, K. *J. Am. Chem. Soc.* **2004**, *126*, 9186. b) Lafrance, M.; Lapointe, D.; Fagnou, K. *Tetrahedron* **2008**, *64*, 6015.

Some product could be observed when 10 mol% of di-*iso*-propylamine was employed to facilitate the formation of Pd(0) from the precatalyst (Table 5.2, entries 8-10).

Table 5.1 Evaluation of the reactivity of ligands **1–8** toward the direct arylation of pyridine-*N*-oxide.

Entry	Ligand	Yield (%) ^a	Entry	Ligand	Yield (%) ^a
1	^t Bu ₃ P ⁺ HBF ₄ ⁻	63	6	4	13
2	PPh ₃	23	7	5	N/A
3	1	0	8	6	40
4	2	33	9	7	N/A
5	3	14	10	8	N/A

a) Determined by NMR. N/A Not Available

Table 5.2 Evaluation of the reactivity of ligands **1–8** toward the direct arylation of benzene.

Entry	Ligand	Yield (%) ^a	Entry	Ligand	Yield (%) ^a
1 ^b	DavePhos	99	6	4	0
2	PPh ₃	0	7	5	0
3	1	0	8	6	0 (5) ^c
4	2	0	9	7	0 (4) ^c
5	3	0	10	8	0 ^c

a) Determined by GC-MS. b) 30 mol% PivOH. c) 10 mol% Di-*iso*-propylamine.

As mentioned, a more extensive evaluation of the ligands was performed on the intramolecular direct arylation reaction. We initially identified the ligand that provided the best reactivity (Table 5.3). To do so, we performed reactions at 95 °C with each

ligand in addition to Ph-DavePhos and triphenylphosphine as control experiments. In order to have more relevant comparisons between Ph-DavePhos, PPh_3 and our ligands, we chose to focus our attention on tri-arylphosphine ligands, so we did not pursue the studies with ligands **6–8**, although ligands **6** and **7** gave excellent results (entries 29-31). Successive rounds of reactions at lower temperatures allowed the identification of ligand **4** as being the most reactive ligand of the series (Table 5.3, entry 24). Interesting observations were made by comparing ligands **2** and **5**, which differ only by methyl groups in *meta* positions of the benzamide. Indeed, the 3,5-dimethylbenzamide analogue (**5**) was found by far more reactive than the simple benzamide **2**. Hypothetically, this could be reasoned by the formation of a stable palladacycle with ligand **2** which would stop the catalytic cycle, however such cyclization would not be possible with **5** due to the steric hindrance of the methyl groups (Table 5.3).

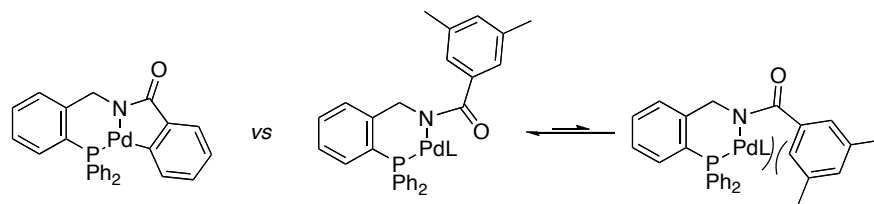
Table 5.3 Evaluation of the reactivity of ligands **1–8** toward the intramolecular direct arylation.

Ph-DavePhos

Entry	Ligand	Temperature (°C)	Conv. (%) ^a	Entry	Ligand	Temperature (°C)	Conv. (%) ^a
1	Ph-DavePhos	95	100	17	3	95	100
2	"	85	100	18	"	85	69
3	"	75	99	19	"	75	N/A
4	"	65	88	20	"	65	N/A
5	PPh_3	95	100	21	4	95	100
6	"	85	100	22	"	85	99
7	"	75	99	23	"	75	100
8	"	65	100	24	"	65	31
9	1	95	96	25	5	95	100
10	"	85	80	26	"	85	99
11	"	75	N/A	27	"	75	49
12	"	65	N/A	28	"	65	N/A
13	2	95	37	29	6	95	99
14	"	85	47	30	7	95	97
15	"	75	24	31	8	95	32
16	"	65	N/A				

a) Determined by GC-MS. N/A Not Available

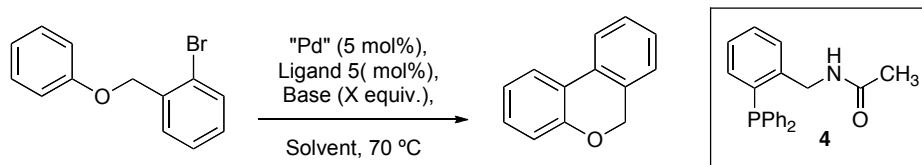
Scheme 5.3 Suggested formation of palladacycle phosphino-benzamide ligands **2** and **5**.



After the identification of **4** as a promising ligand, we decided to optimize the reaction conditions to try to improve the reactivity of **4** over Ph-DavePhos and more particularly triphenylphosphine (Table 5.3, entries 4 and 8 respectively). Our optimization of the reaction started with the evaluation of bases (Table 5.4, entries 1–9). A variety of carbonate counter ions were tested, as well as alkoxide, phosphate and amine bases. From the lot, potassium phosphate gave the best result (entry 6). Next, the amount of base was evaluated, ranging from 1 to 5 equivalent (entries 10–13), 1.5 equivalent of base resulted as the optimal amount yielding the product in 52% (entry 12). Various solvents were also investigated (entries 14–17) and DMA proved to be the solvent of choice for the reaction.

With optimized reaction conditions in hand (entry 12), we performed a series of control experiments to verify if any improvements to the reactivity was achieved in comparison to the conditions with triphenylphosphine (entries 18–22). Unfortunately, when **4** was replaced by PPh_3 , an important jump in yield was obtained (92%, entry 18). Ligand **4** still performed better than a reaction without a phosphine ligand (entry 19). However, when $\text{Pd}(\text{OPiv})_2$ was employed instead of the $\text{Pd}(\text{OAc})_2$, the presence of only 10 mol% of pivalate was enough to overrun the effect of ligand **4** (entries 20–22). These data suggested that our initial approach and our efforts toward the development of CMD specific ligand were unfruitful.

Table 5.4 Optimization of the reaction conditions with ligand **4**.



Entry	"Pd"	Ligand	Base (equiv.)	Solvent	Yield (%) ^a
1	Pd(OAc) ₂	4	K ₂ CO ₃ (3.0)	DMA	35
2	"	"	Na ₂ CO ₃ (3.0)	DMA	28
3	"	"	Cs ₂ CO ₃ (3.0)	DMA	7
4	"	"	KO ^t Bu (3.0)	DMA	3
5	"	"	NaO ^t Bu (3.0)	DMA	3
6	"	"	K ₃ PO ₄ (3.0)	DMA	47
7	"	"	TEA (3.0)	DMA	10
8	"	"	DABCO (3.0)	DMA	2
9	"	"	KOAc (3.0)	DMA	26
10	"	"	K ₃ PO ₄ (1.0)	DMA	26
11	"	"	K ₃ PO ₄ (1.1)	DMA	49
12	"	"	K ₃ PO ₄ (1.5)	DMA	52
13	"	"	K ₃ PO ₄ (5.0)	DMA	24
14	"	"	K ₃ PO ₄ (1.5)	MeCN	0
15	"	"	K ₃ PO ₄ (1.5)	Dioxane	7
16	"	"	K ₃ PO ₄ (1.5)	Toluene	2
17	"	"	K ₃ PO ₄ (1.5)	Isopropanol	2
18	"	PPh ₃	K ₃ PO ₄ (1.5)	DMA	92
19	"	none	K ₃ PO ₄ (1.5)	DMA	7
20	Pd(OPiv) ₂	4	K ₃ PO ₄ (1.5)	DMA	89
21	Pd(OPiv) ₂	PPh ₃	K ₃ PO ₄ (1.5)	DMA	98
22	Pd(OPiv) ₂	none	K ₃ PO ₄ (1.5)	DMA	92

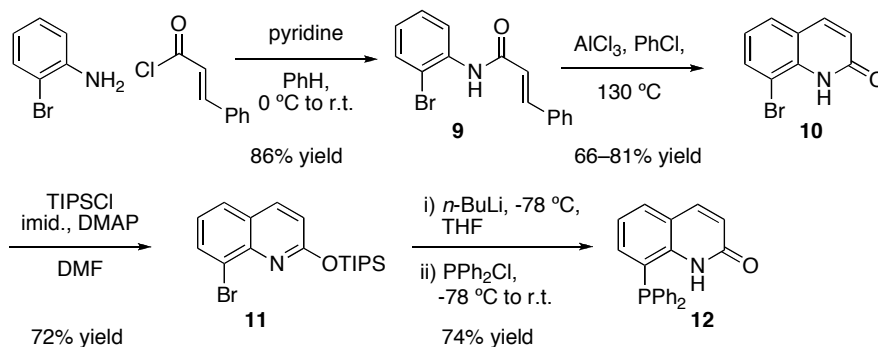
a) Determined by GC-MS

5.1.2 Phosphino-quinolinone ligands

The second strategy we envisaged was inspired by the studies we discussed in chapter 3. More specifically, chapter 3 introduced the notion of the energy cost associated with distortion of the catalyst and the (hetero)arene from their ground state conformations into their respective transition state geometries (Scheme 5.4, $E_{\text{dist}}(\text{Pd})$ and $E_{\text{dist}}(\text{ArH})$) and

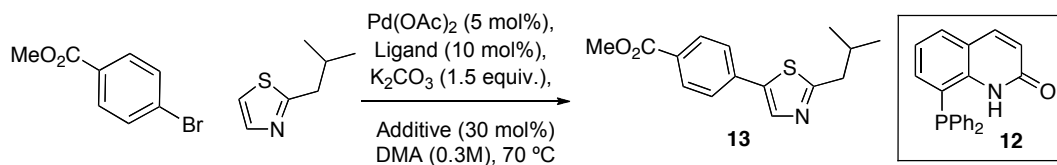
protecting groups were tried prior to the TIPS, such as TBDMS and PMB, however due to the high stability of the of the *N*-H-quinolinone, the other protecting groups would fall off during an aqueous work-up or upon contact with silica gel chromatography. The TIPS protecting group provided enough stability so the compound could be purified on silica gel. With intermediate **11** in hand, treatment with *n*-butyl lithium followed by diphenylphosphine chloride yielded **12** in 28 to 37% overall yield after a pH 6-7 aqueous workup.

Scheme 5.5 Synthesis of C8-diphenylphosphino quinolidin-2-one **12**.



While the reactivity of **12** was not thoroughly tested, Table 5.5 summarizes the preliminary results obtained for the direct arylation of 2-*iso*-butylthiazole with an aryl bromide. The GC yields of **13** are not reported since the calibration of **13** with respect to the internal standard ($\text{C}_{14}\text{H}_{30}$) was not made. Nonetheless the ratio between **13** and tetradecane was indicative of the relative reactivity among the various entries of the table. The analysis of the result revealed that **12** implemented a better reactivity to the catalyst than tricyclohexylphosphine at 70 °C when no pivalic acid was present (Table 5.5, entries 3 and 6). However, once again, **12** and triphenylphosphine shared similar reactivity when no additives were added (entries 5 and 6). The addition of 30 mol% of pivalic acid seems crucial to the reaction at this temperature (entry 4). This last result indicated, once again, that our ligand **12** was not facilitating the direct arylation of thiazole as we were hoping to achieve.

Table 5.5 Evaluation of the reactivity of **12** in the direct arylation of thiazole.



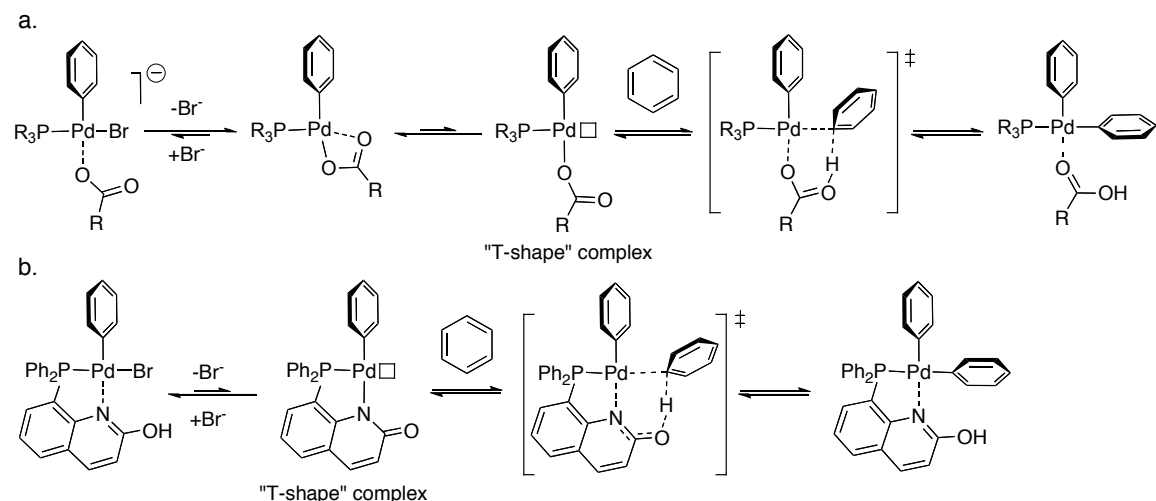
Entry	Ligand	Additive	Ratio 13 /C ₁₄ H ₃₀ ^a
1 ^b	PCy ₃ •HBF ₄	PivOH	9.2 ^c
2	PCy ₃ •HBF ₄	PivOH	2.8
3	PCy ₃ •HBF ₄	–	0.8
4	PPh ₃	PivOH	6.5
5	PPh ₃	–	2.0
6	12	–	2.3

a) GC-MS ratio, C₁₄H₃₀ as internal standard. b) 100 °C.
c) 73% isolated yield.

Following the failure of these ligands in promoting efficient transformations, it became apparent that other steps in the catalytic cycle might have been overlooked and could be responsible for the lack of reactivity. After taking into consideration each step of a complete catalytic cycle for the direct arylation of benzene, we hypothesized that part of the problem of the quinolinone ligand might arise from the steps leading to C–H bond cleavage. In the standard system, after the oxidative insertion of Pd(0) into the aryl bromide, it was proposed that the acetate coordinated to the metal by substituting a labile ligand, a molecule of solvent for instance (Scheme 5.6a). The potential for bidentate binding of the acetate could promote the decomplexation of the bromide by forming a κ_2 -acetate-palladium complex. The reversal κ_1 binding mode of acetate would then favor the approach of an arene and lead to the formation of the C–H bond cleavage.¹² On the other hand, the quinolinone ligand cannot actively promote the dissociation of the Pd–Br bond to form the “T shape” Pd complex (Scheme 5.6b). The unfavorable equilibrium toward the unsaturated palladium species prior to the arene complexation could not promote the facile C–H bond cleavage as we intended and results in catalyst decomposition.

¹² This type of palladium- κ_2 -acetate intermediate was proven to be a viable intermediate in the C–H bond arylation in similar systems, see: a) Sun, H.-Y.; Gorelsky, S. I.; Stuart, D. R.; Campeau, L.-C.; Fagnou, K. *J. Org. Chem.* **2010**, 75, 8180. b) Tan, Y.; Hartwig, J. F. *J. Am. Chem. Soc.* **2011**, 133, 3308.

Scheme 5.6 Proposed individual steps leading to the C–H bond cleavage of the CMD pathway.



The difficulty in forming the T-shape Pd complex might keep us from verifying our concept of facilitated C–H bond cleavage by the reduction of the energy of distortion of the catalyst. In the following section, our efforts to verify the validity of our concept by specifically studying the C–H bond cleavage step in H/D exchange reactions will be presented.

5.2 Platinum-Catalyzed Benzene H/D Exchange with Deuterated Solvent

Hydrogen/deuterium exchange has been studied as model reactions in order to understand the mechanism of C–H bond activation catalyzed by iridium and platinum complexes in methane and benzene oxidation reactions.¹³ Many Pt(II) complexes containing diverse bi- and tridentate nitrogen donor ligands participate in this model reaction. In the perspective of verifying the validity of our approach to ligand design, the study H/D exchange reactions have the advantage of focusing on the C–H cleavage steps without having to consider the other steps of direct arylation catalytic cycle.

13 For a review of C–H activation by Pt(II), see: Lersch, M.; Tilset, M. *Chem. Rev.* **2005**, *105*, 2471, and references therein.

The H/D exchange experiments consist of mixing benzene in the presence of an excess of deuterated acid (~25 equivalents), such as trifluoroacetic acid and acetic acid, in the presence of a catalyst (0.5-2 mol% relative to benzene). Generally, the mixtures are heated to temperatures varying from 100 °C to 180 °C for a couple of hours, at which point a sample of the reaction is analyzed by GC-MS. The distribution of benzene isotopologues ($C_6H_{6-n}D_n$, $n=0$ to 6) is recorded, submitted to a deconvolution process¹⁴ and treated to extract catalyst turn over numbers (TON) and turn over frequencies (TOF).

To provide a clearer understanding of our results, the following section will summarize the conclusions of selected studies on benzene H/D exchange with iridium and platinum complexes. Lastly, we will cover our initial, yet very promising, results of the studies we have conducted with variations of the quinolinone ligand (**12**) previously described.

5.2.1 Metal-acetate promoted C–H bond cleavage of simple arenes and heteroarenes

Goddard and Periana have reported experimental and computational studies on the mechanism of the $[(\text{acac-O,O})_2\text{Ir}(\text{OAc})]_2$ (**WAG-1a**) catalyzed deuterium incorporation from acetic acid- d_4 or trifluoroacetic acid- d_7 to benzene (Scheme 5.7).¹⁵ Along with a meticulous description of the reaction mechanism, their studies revealed a change in the rate-determining step in the process depending on the choice of solvent. In acetic acid- d_4 , deuterium incorporation into the arene leads to the apparition of all benzene isotopologues (Figure 5.2) at related rates, suggesting that once the benzene coordinates to the iridium, multiple H/D exchanges occur before the benzene dissociates from the metal-center.

14 Excel-based worksheet prepared by Periana *et al.*: Young, K. J. H.; Meier, S. K.; Gonzales, J. M.; Oxgaard, J.; Goddard, W. A.; Periana, R. A. *Organometallics* **2006**, 25, 4734.

15 Bischof, S. M.; Ess, D. H.; Meier, S. K.; Oxgaard, J.; Nielsen, R. J.; Bhalla, G.; Goddard III, W. A.; Periana, R. A. *Organometallics* **2010**, 29, 742.

Scheme 5.7 Deuterium incorporation into benzene- h_6 catalyzed by **WG-1a**.

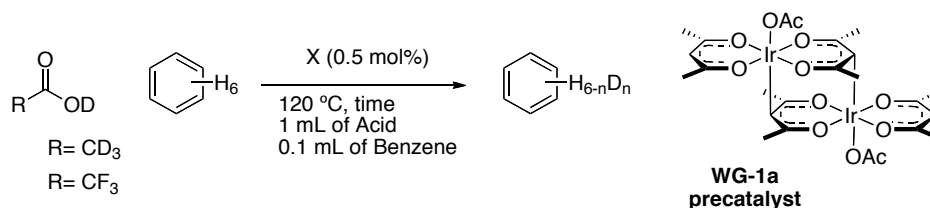
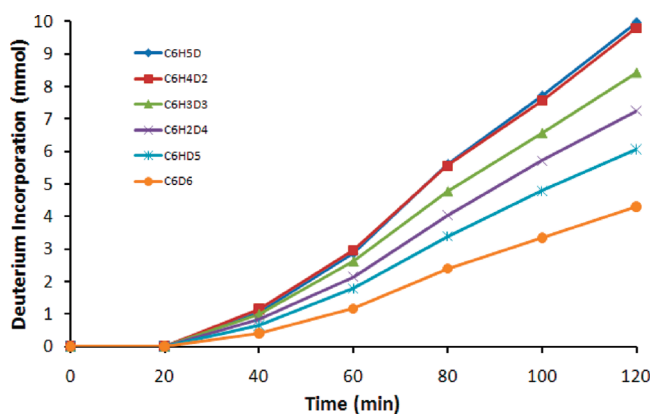
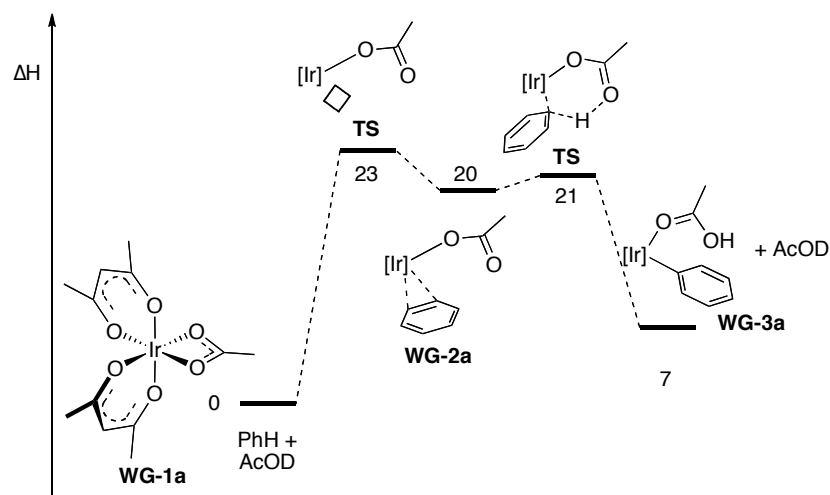


Figure 5.2 Deuterium incorporation (mmol) into benzene- h_6 catalyzed by **WG-1a** in d_4 -AcOD at $120\text{ }^\circ\text{C}$ over 2 hours. (Reproduction from Bischof *et al.*)¹⁵



This observation was corroborated by the DFT evaluation of the mechanism of C–H bond cleavage. As illustrated in Figure 5.3, the rate-determining step of the multi-step reversible process is the dissociation of κ_2 -acetate and coordination of benzene to the catalyst in the forward sense (**WG-1a**→**3a**) and the dissociation of benzene in the reverse process (**WG-3a**→**1a**). This proposed mechanism for reversible C–H bond cleavage matched their experimental observation of the isotopologues distribution, since from the π -intermediate (**WG-2a**) the lowest energy pathway was the C–H bond cleavage rather than benzene dissociation.

Figure 5.3 B3LYP/LACV3P^{++**}//LACVP^{**} enthalpy surface for benzene H/D exchange catalyzed by **WG-1a** in *d*₄-acetic acid (ΔH at 298 K, kcal/mol).



On the other hand, in trifluoroacetic acid-*d*₁, H/D exchange occurred at a faster rate than in acetic acid and, in this case, a single isotopologue of benzene was initially formed (Figure 5.4). This suggested that once the C–H bond of benzene was cleaved by the iridium-trifluoroacetate complex, the process would then immediately return to the dissociated complex and benzene. Computationally, the energy diagram of this system was also in agreement with the experimental observations (Figure 5.5). The overall barrier of activation was lower than the one for the acetic acid system, which supports the increase in the observed rate of H/D exchange. From intermediate **WG-2b**, the relative energy barriers for the C–H bond cleavage and benzene dissociation explain why a single isotopologue of benzene was formed.

Figure 5.4 Deuterium incorporation (mmol) into benzene- H_6 catalyzed by **WG-1b** in d -trifluoroacetic acid at 120 °C over 2 hours. (Reproduction from Bischof *et al.*)¹⁵

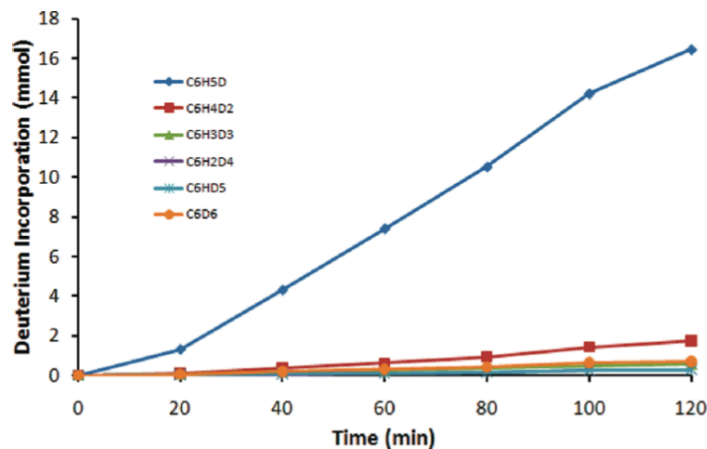
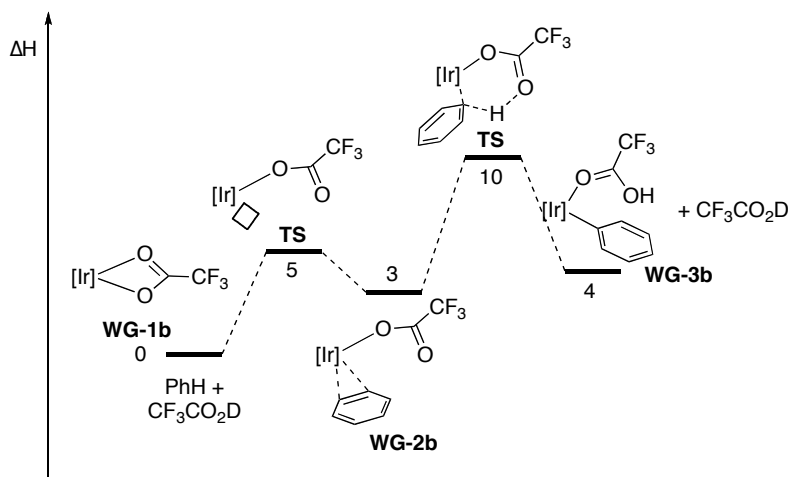


Figure 5.5 B3LYP/LACV3P++**//LACVP** enthalpy surface for benzene H/D exchange catalyzed by **WG-1b** in trifluoroacetic- d_1 acid (ΔH at 298 K, kcal/mol).

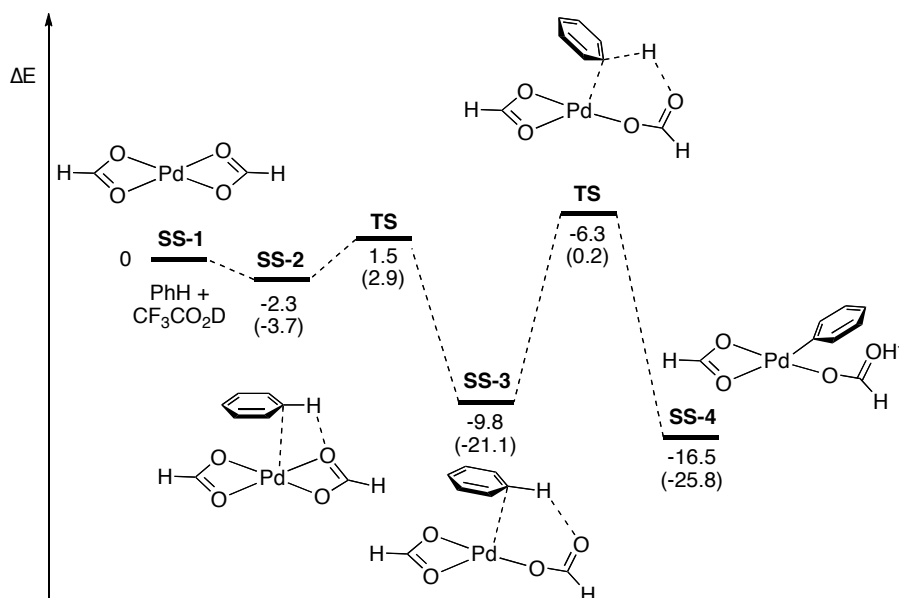


In 2000, Sakaki reported the DFT investigation of benzene C–H bond metallation by $M(\kappa_2\text{-O}_2\text{CH})_2$ (**SS-1(M)**) ($M = \text{Pd}$ or Pt) to form σ -phenylpalladium(II) formate complex.¹⁶ Figure 5.6 describes the computed energetic profile for the palladium(II)-formate promoted C–H bond metallation. The reaction profile with platinum(II) is very similar.¹⁶ The reaction of benzene with $\text{Pd}(\kappa_2\text{-O}_2\text{CH})_2$ proceeds first by the formation of a

16 Biswas, B.; Sugimoto, M.; Sakaki, S. *Organometallics* **2000**, *19*, 3895.

weak van der Waals complex **SS-2(Pd)**. A favored metal-C–H bond agostic intermediate (**SS-3(Pd)**) is formed *via* the dissociation of a κ_2 -formate ligand to a κ_1 coordinated ligand, allowing the arene to bind to the metal. The thermodynamic profile of the reaction indicates that the favorable formation of intermediate **SS-3(Pd)** is more significant with the platinum analogue (values between parentheses) compared with the palladium reaction. More relevant to this section of the chapter, the energetic profile for the reaction with platinum suggested that the dissociation of benzene from the metal center is less favorable than the C–H bond cleavage. This could suggest that in a H/D exchange reaction, the incorporation of deuterium in benzene could follow a trend similar than the one described in Figure 5.2.

Figure 5.6 Energy changes by the metal-formate promoted C–H bond cleavage. Energies of the relevant intermediate and transition states for palladium and platinum (shown in parentheses) complexes are given in kcal* mol^{-1} (relative to reactants).

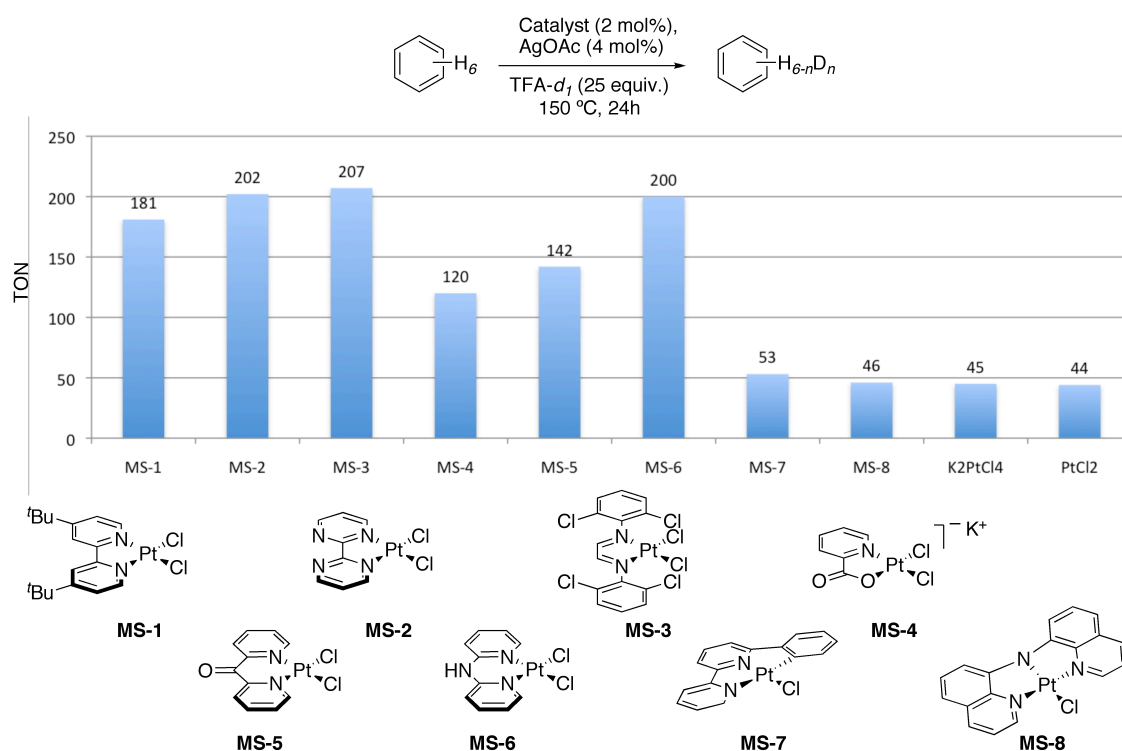


The studies that directly inspired ours were reported by Sanford *et al.*,¹⁷ In which various platinum(II) complexes with nitrogen donor ligands were prepared, compared

17 Hickman, A. J.; Villalobos, J. M.; Sanford, M. S. *Organometallics*, **2009**, 28, 5316.

and studied in H/D exchange experiments.¹⁸ Figure 5.7 resumes the scope of ligands that were tested and their reactivities presented in terms of TON. Silver salts were also added to the reaction mixtures in order to abstract the chlorine atoms from the metal centers. From the list of ligands tested, we can see that platinum species with bidentate ligands stood out as efficient H/D exchange catalysts, over tridentate ligands or the simple platinum salts. Inspired by Sanford *et al.* studies and the ligands that promoted C–H bond cleavages, especially the ligand **MS-6**, we decided to develop new ligands that would incorporate a basic moiety to promote the CMD pathway, in the form of the pyridin-2-one, and to compare them with other catalysts such as **MS-6** depicted in Figure 5.7.

Figure 5.7 Turnover numbers for H/D exchange between benzene and TFA-*d*₁ catalyzed by Pt complexes **MS-1** to **MS-8**.

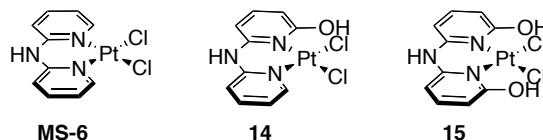


18 There are other reports of Pt catalyzed H/D exchanges, however the reactivity of Pt complexes were not systematically compared, see: a) Ziatdinov, V. R.; Oxgaard, J.; Mironov, O. A.; Young, K. J. H.; Goddard, W. A.; Periana, R. A. *J. Am. Chem. Soc.* **2006**, 128, 7404. b) Young, K. J. H.; Meier, S. K.; Gonzales, J. M.; Oxgaard, J.; Goddard, W. A.; Periana, R. A. *Organometallics* **2006**, 25, 4734. c) Gerdes, G.; Chen, P. *Organometallics* **2004**, 23, 3031. d) Kloek, S. M.; Goldberg, K. I. *J. Am. Chem. Soc.* **2007**, 129, 3460.

5.2.2 Ligands preparation and testing

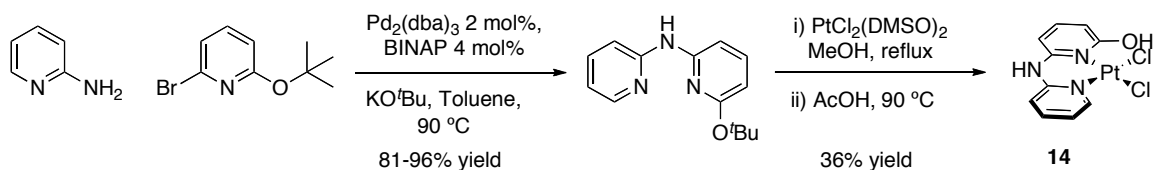
Inspired by Sanford's catalysts, pyridinone variations of ligand **MS-6** were prepared to verify our ligand design approach (Figure 5.8).

Figure 5.8 Structure of the platinum complexes evaluated for reactivity.



Complexes **14** and **15** were prepared following the sequence reported by Sanford *et al.* (Scheme 5.8). The *bis*-(2-pyridine)amine was formed by a Buchwald-Hartwig amination reaction in high yield. The platinum complexes were generated by simply refluxing the mixture of the *bis*-pyridine and $\text{PtCl}_2(\text{DMSO})_2$ in methanol, which also lead to cleavage of the *tert*-butyl group. Subsequent purification by heating of **14** in acetic acid provided pure product with no incorporation of acetate ligand.

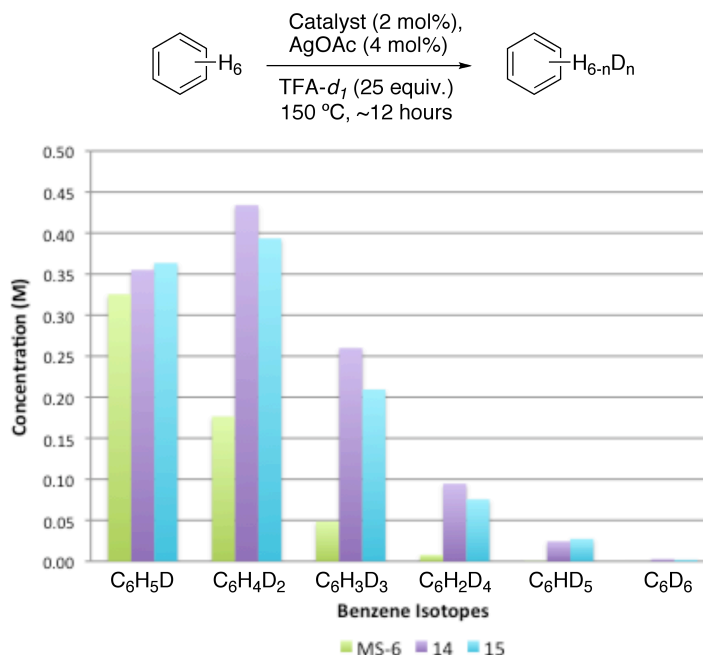
Scheme 5.8 Preparation of complex **14**.



Complexes **14** and **15** were examined as catalysts for H/D exchange between benzene and trifluoroacetic- d_1 acid at 150 °C. For comparison purposes, complexes **14** and **15** were compared to **MS-6**. The standard initial conditions employed 50 μL of benzene (0.563 mmol) in 0.5 mL of TFA- d_1 with 2 mol% of platinum complex and 4 mol% of silver(I) acetate. Although no background reaction check was performed and a precise reaction time not recorded, the deconvolution of the raw data revealed that ligands **14** and **15** had significantly increased H/D exchange TON compared to the parent

MS-6 complex (Figure 5.9). It should be noted that the distribution of the benzene isotopologues is indicative of multiple H/D exchange events prior to the arene decomplexation, as envisioned by Sakaki's DFT calculations (Figure 5.6).

Figure 5.9 Initial results of the distribution of benzene's isotopologues with catalysts **MS-6**, **14** and **15** after approximately 12 hours.

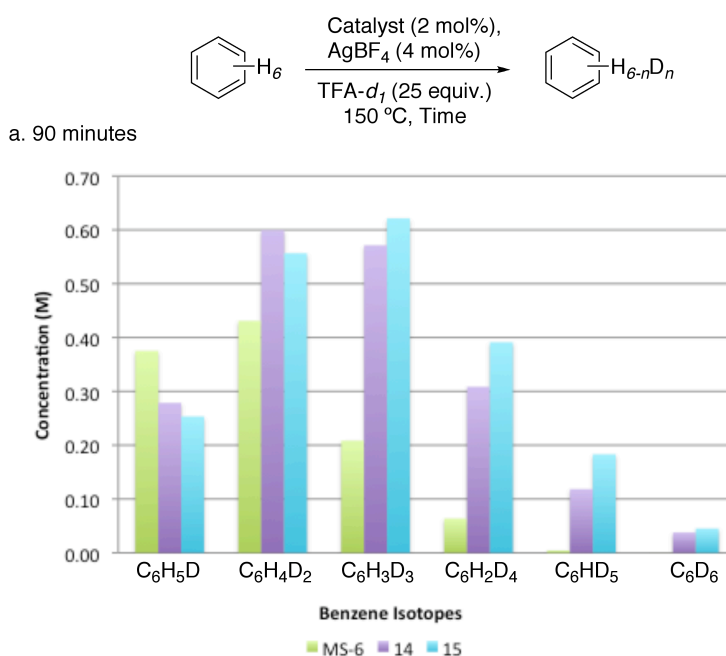


After modifying the reaction conditions, once again were performed the reactions and relevant TONs were recorded for our catalysts. From the original reaction conditions, the silver(I) acetate additive by silver(I) tetrafluoroborate was replaced to avoid the binding of acetate to platinum, which could potentially promote the C–H bond cleavage. The BF₄[−] anion would serve as a non-coordinating counter ion to the cationic metal complex. Furthermore, Sanford *et al.* demonstrated that the addition of AgBF₄ actually increased the TON of the catalyst compared to AgOAc.¹⁷

With these modified conditions, the H/D exchange reactions were performed and the distribution of benzene isotopologues after 90 and 180 minutes was recorded (Figure 5.10). Taking into consideration the background for each reaction, after 90 minutes we

found out that catalysts **14** and **15** underwent approximately twice the catalyst turnover compared to **MS-6**. At 180 minutes, the second round of sampling revealed that all three complexes suffered from reduced reactivity. Catalyst **15** had actually decomposed, while **MS-6** was the least affected of the three Pt complexes (Figure 5.11). At this point, it is not clear whether the loss of reactivity was due to self-decomposition or air-induced degradation of the catalysts.

Figure 5.10 Distribution of benzene isotopologues with catalysts **MS-6**, **14**, **15** after 90 and 180 minutes.



b. 180 minutes

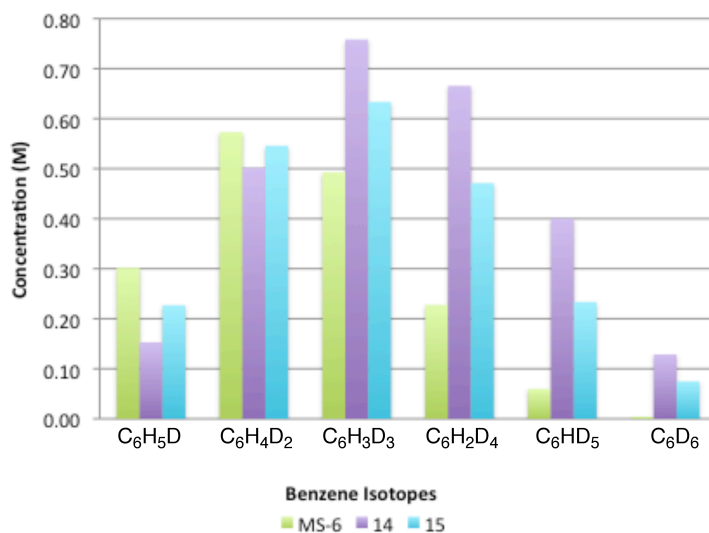
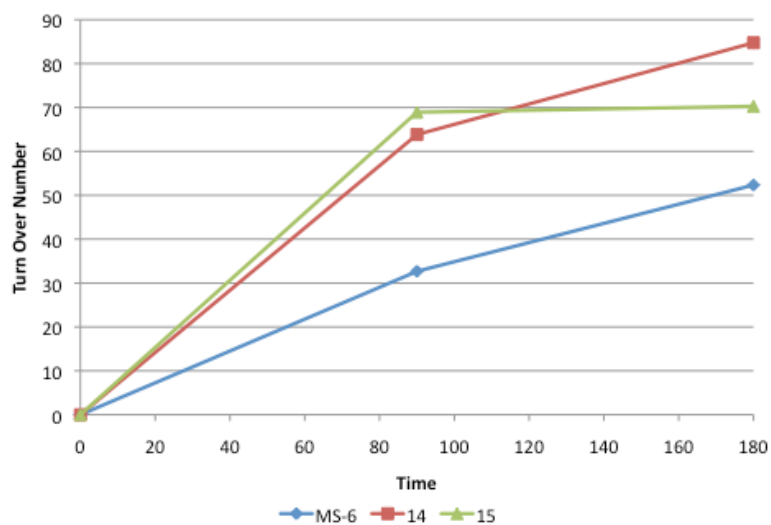


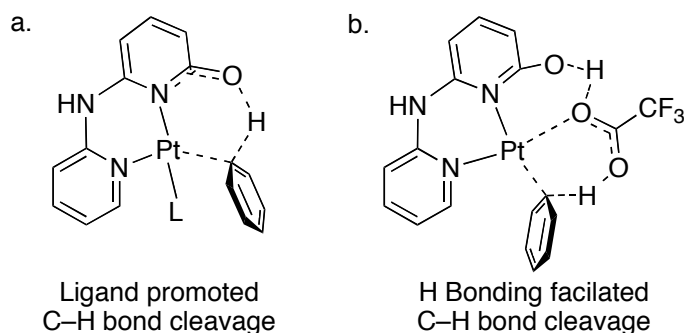
Figure 5.11 Turnover numbers of catalysts **MS-6**, **14** and **15** over 180 minutes.



When the reaction was performed in acetic acid- d_4 , little TON was recorded for all three catalysts after 90 minutes (3 to 5 TON). In methanol- d_4 , the catalysts did not promote isotope incorporation into benzene; only a small background reaction was detected.

The enhanced reactivity of catalyst **14** and **15** compared to **MS-6** over 90 minutes is certainly a promising starting point to support our targeted ligand promoted C–H bond cleavage (Figure 5.12a). However, in order to properly support our mechanistic proposal, more experiments are required to assess in detail the effect of the pyridinone on the reactivity and to evaluate of other plausible mechanistic pathways. For instance, the pyridinone ligand may also accelerate the isotope exchange between the solvent and benzene through hydrogen bonding (Figure 5.12b). This interaction could further stabilized the coordination of TFA to the platinum and facilitate the benzene proton transfer.

Figure 5.12 Possible mechanisms for complex **14**.



5.2.3 Concluding remarks

The objective of studying the incorporation of deuterium into benzene was to verify the concept of ligand promoted C–H bond cleavage in a simplified setting. Initial trials indicated that the designed ligands induced greater turn over numbers than the control ligand (MS-6). Unfortunately, these results do not affirm that complexes **14** and **15** react in the intended way and more studies are required in order to support an exact mechanism.

5.3 Conclusion

In this chapter, our effort toward the development of ligands to specifically promoted C–H bond cleavage were presented. In the first portion, phosphine ligands containing amido groups were developed to mimic the role of the acetate anion in traditional direct arylation reactions. Next, a rigidified version of these ligands, based on a quinolidinone was prepared. This ligand class was developed following the activation-strain analysis of the CMD pathway, to reduce the “distortion” energy of the catalyst to reach the transition state. Unfortunately, these approaches gave poor results. To gain additional insight on our hypothesis, a simpler model reaction was studied in the hope of verifying our ligand design approach. The initials results of theses studies are encouraging, although more data needs to be collected in order to be able to conclude on the most plausible mode of action of those ligands.

Chapter

6

Analysis of the Palladium-Catalyzed (Aromatic)C–H Bond Metallation- Deprotonation Mechanism Spanning the Entire Spectrum of Arenes¹

6.1 Introduction

Transition-metal catalyzed functionalization of (hetero)arene C–H bonds has emerged over the past few years as a rapidly growing and increasingly reliable alternative to traditional cross-coupling reactions. The functionalization of a C–H bond generally depends on the growing array of compatible directing groups to access adjacent C–H bonds or relies on the intrinsic C–H bond reactivity towards catalysts.² In order to employ

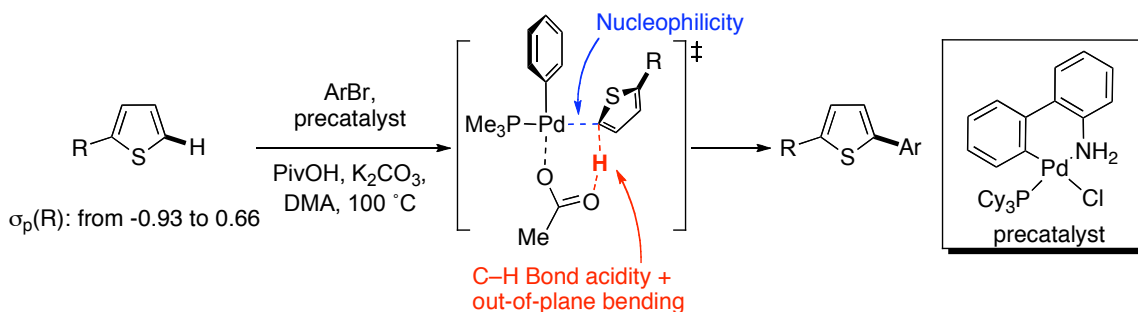
¹ The results presented in this chapter are the result of a collaborative work with Dr. Serge Gorelski and were submitted for publications in November 2011.

² a) Daugulis, O.; Zaitsev, V. G.; Shabashov, D.; Pham, Q.-N.; Lazareva, A. *Synlett* **2006**, 3382. b) Campeau, L.-C.; Fagnou, K. *Chem. Commun.* **2006**, 1253. c) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (d) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. e) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200. f) Campeau, L.-C.; Stuart, D. R.; Fagnou, K. *Aldrichimica Acta* **2007**, *40*, 35. g) Li, B.-J.; Yang, S.-D.; Shi, Z.-J. *Synlett* **2008**, 949. h) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, 3013. i) McGlacken, G. P.; Bateman, L. M. *Chem. Soc. Rev.* **2009**, *38*, 2447. j) Chen,

this transformation over a broad range of substrates and as part of increasingly more complex settings, it will require a more comprehensive understanding of the governing parameters influencing the reactivity and selectivity of the C–H bond cleavage step, especially for the approaches that do not use directing groups. In line with this objective, functionalities on aromatic rings such as fluorine,^{3,4} chlorine,⁵ trifluoromethyl, nitro,^{6,7} nitrile⁷ and some ethers,^{7,8} were found over the years to impart an activating influence on C–H bonds toward functionalization reactions. Also, it was demonstrated that remote substituents of indoles, at the C6 position, were moderately affected the reactivity of the C–H bonds of indoles.⁹ Beyond searching for other activating groups, efforts aimed at the acquisition of a more comprehensive knowledge of the reaction were made by categorizing the reactivity of arenes in terms of relative and absolute rates.¹⁰ More importantly, we are interested in developing reactivity guidelines in order to predict the regioselectivity of C–H bond functionalization with various arenes by extracting as much information as possible from previously investigated (hetero)aromatics.

-
- X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. k) Kulkarni, A. A.; Daugulis, O. *Synthesis* **2009**, *24*, 4087. l) Bellina, F.; Rossi, R. *Tetrahedron* **2009**, *65*, 10269. m) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792. n) Roger, J.; Gottumukkala, A. L.; Doucet, H. *ChemCatChem* **2010**, *2*, 20. o) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147.
- 3 García-Cuadrado, D.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2007**, *129*, 6880.
 - 4 Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 15185.
 - 5 Liégault, B.; Petrov, I.; Gorelsky, S. I.; Fagnou, K. *J. Org. Chem.* **2010**, *75*, 1047.
 - 6 Caron, L.; Campeau, L.-C.; Fagnou, K. *Org. Lett.* **2008**, *10*, 4533.
 - 7 Campeau, L.-C.; Stuart, D. R.; Leclerc, J.-P.; Bertrand-Laperle, M.; Villemure, É.; Sun, H.-Y.; Lasserre, S.; Guimond, N.; Lecavallier, M.; Fagnou, K. *J. Am. Chem. Soc.* **2009**, *131*, 3291.
 - 8 Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581.
 - 9 Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050.
 - 10 Sun, H.-Y.; Gorelsky, S. I.; Stuart, D. R.; Campeau, L.-C.; Fagnou, K. *J. Org. Chem.* **2010**, *75*, 8180.

Scheme 6.1 Overview of the parameters that governs the C–H bond cleavage via a concerted metallation-deprotonation mechanism.



Herein, we present a detailed evaluation of the parameters that govern the barrier of activation for the C–H bond cleavage via a concerted metallation-deprotonation (CMD) mechanism (Scheme 6.1) with palladium-carboxylate complexes for a diverse set of (hetero)arenes covering a wide spectrum of aromatic C–H coupling partners. This work was made in collaboration with the computational expert Serge Gorelski. We identify and analyze various parameters that are common to all the (hetero)arene C–H bond palladium-catalyzed reactions. We assess both experimentally and computationally the effect of substituents at a remote position on the reactivity of C–H bond of thiophenes. From this detailed analysis, we also set the basis of the guidelines that could eventually lead to a simple method which can be used to estimate the barriers of activation for a wide range of (hetero)arenes as well as to accurately predict the regioselectivity for all C–H functionalization reactions.

6.1.1 Mechanistic work precedents

Several previous investigations have focused on the understanding of the C–H bond cleavage mechanism on a wide range of systems and from these studies, several different pathways have been proposed. The two mechanisms that have received the most attention are the electrophilic aromatic substitution (S_EAr) and the CMD pathways.^{11,12} Recently,

11 For consistency with our previous reports, we have chosen to employ the CMD acronym to describe the metal-carboxylate catalyzed C–H bond cleavage mechanism. Although some authors use different term to describe very similar transformations, such as internal electrophilic substitution (IES) and ambiphilic

Studer and Itami proposed a stepwise 1,2-migratory insertion mechanism to support the reversal in the regioselectivity caused by arylboronic acids in their report on the C4 arylation of thiophene and thiazole.¹³ With respect to the CMD process, the earliest C–H bond cleavage mechanistic studies by metal-carboxylate complexes began in the early 1980s¹⁴ and the earliest computational work with palladium was reported in 2000,¹⁵ however these studies were limited to benzene metallation.

Recent mechanistic studies on the palladium-catalyzed direct arylation were conducted on various systems, including benzene,^{16,17} tethered diarenes^{3,8,18} as well as electron deficient arenes, such as polyfluorobenzenes⁴ and azine-*N*-oxides.¹⁰ The results of these studies supported the simultaneous metallation-deprotonation mechanism with the participation of an inner- or outer-sphere base as previously proposed.¹² However, until recently it was generally accepted that electron-rich heteroarenes reacted through a S_EAr mechanism due to their enhanced nucleophilicity. In 2008, we demonstrated that the C–H bond cleavage for a wide range of (hetero)arenes, including electron-rich (hetero)arenes, by the Pd(II)-acetate complex proceed by a CMD pathway.¹⁹ The CMD activation barriers predicted accurately the regioselectivity observed experimentally for the palladium-catalyzed direct arylation of each (hetero)arene evaluated. For the oxidative cross-coupling of indole with benzene,²⁰ both C–H bond cleavages were explained by the same mechanism.²¹ Tan and Hartwig recently demonstrated that the C–

metal-ligand activation (AMLA), see: a) Oxgaard, J.; Tenn III, W. J.; Nielsen, R. J.; Periana, R. A.; Goddard III, W. A. *Organometallics* **2007**, 26, 1565. b) Boutadla, Y.; Davies, D. L.; Macgregor, S. A.; Poblador-Bahamonde, A. I. *Dalton Trans.* **2009**, 5887.

12 For recent reviews on metal-carboxylate promoted concerted metallation/C–H bond cleavage, see: (a) Boutadla, Y.; Davies, D. L.; Macgregor, S. A.; Poblador-Bahamonde, A. I. *Dalton Trans.* **2009**, 5820. (b) Lapointe, D.; Fagnou, K. *Chem. Lett.* **2010**, 39, 1118. (Chapter 1) (c) Ackermann, L. *Chem. Rev.* **2011**, 111, 1315.

13 Tani, S.; Ueda, K.; Yamaguchi, J.; Studer, A.; Itami, K. *Angew. Chem., Int. Ed.* **2011**, 50, 2387.

14 Fung, C. W.; Khorramdel-Vahed, M.; Ranson, R. J.; Roberts, R. M. G. *J. C. S. Perkin II* **1980**, 267.

15 Biswas, B.; Sugimoto, M.; Sakaki, S. *Organometallics* **2000**, 19, 3895.

16 Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, 128, 16496.

17 Tan, Y.; Hartwig, J. F. *J. Am. Chem. Soc.* **2011**, 133, 3308.

18 González, J. J.; García, N.; Gómez-Lor, B.; Echavarren, A. M. *J. Org. Chem.* **1997**, 62, 1286.

19 Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, 130, 10848.

20 a) Stuart, D. R.; Fagnou, K. *Science* **2007**, 316, 1172. b) Stuart, D. R.; Villemure, E.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, 129, 12072. c) Potavathri, S.; Pereira, K. C.; Gorelsky, S. I.; Pike, A.; LeBris, A. P.; DeBoef, B. *J. Am. Chem. Soc.* **2010**, 132, 14676.

21 Meir, R.; Kozuch, S.; Uhe, A.; Shaik, S. *Chem. Eur. J.* **2011**, 17, 7623.

H bond cleavage of benzene by the Pd^{II} catalyst with a DMA ligand has a lower CMD activation barrier than the C–H bond cleavage with the phosphine analog.¹⁷ This finding points to future opportunities in the development of better Pd^{II} catalysts for C–H bond functionalization. Nonetheless, the phosphine ligand is used in a majority of the direct coupling reactions reported in the literature. It was experimentally demonstrated that the calculated barriers of activation for the CMD mechanism are also in agreement with the relative reactivity of the various (hetero)arenes.²² As a result, one can utilize the values of CMD activation barriers to determine the site-selectivity of direct coupling reactions where two or more heteroarenes are present within a single substrate.

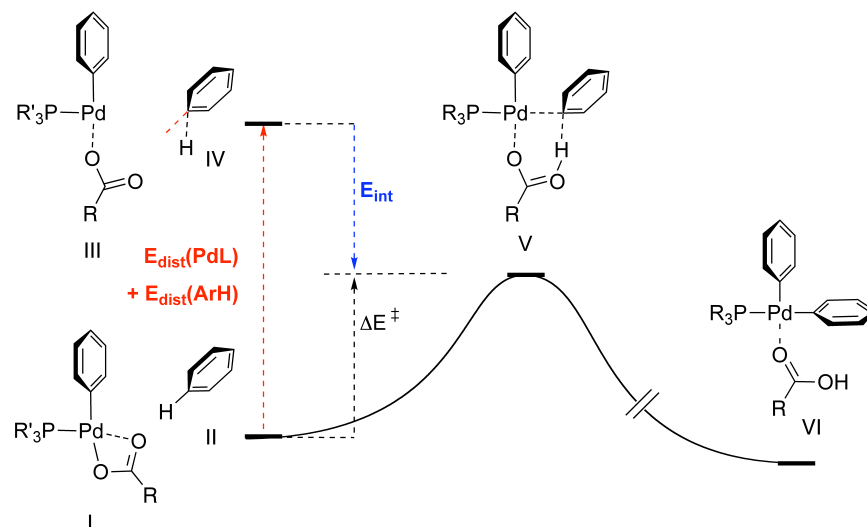
6.2 Results and Discussion

To gain a better understanding of how the CMD mechanism might be applicable to a disparate range of (hetero)arene, an activation–strain analysis was performed for every C–H bond of selected aromatics.²³ This analysis allows to quantify different contributions to the CMD barrier **V** (Scheme 6.2). On one hand there is the energetic cost (distortion energy, ΔE_{dist}) associated with the distortion of the palladium complex and the arene from their ground states structures (**I** and **II**) to their geometries (**III** and **IV**) in the TS structure **V**. On the other hand, there is the energy gain (interaction energy, ΔE_{int}) resulting from the electronic interaction of fragments **III** and **IV** to form the TS structure **V**.

22 Lapointe, D.; Markiewicz, T.; Whipp, C. J.; Toderian, A.; Fagnou, K. *J. Org. Chem.* **2011**, 76, 749.

23 van Zeist, W.-J.; Bickelhaupt, F. M. *Org. Biomol. Chem.* **2010**, 8, 3118.

Scheme 6.2 Activation-strain analysis for the CMD transition state. Benzene is shown as a representative substrate.



To evaluate the parameters governing the palladium-catalyzed C–H bond cleavage, (hetero)arenes **1–22h** were selected to represent a range of (hetero)arenes spanning the entire spectrum of C–H coupling partners (Figure 6.1). The mechanism of the C–H bond metallation by a palladium-acetate complex of each arene was evaluated by density functional theory (DFT) with the B3LYP²⁴ exchange-correlation functional. Even though some of the arenes chosen were part of our original computational study,¹⁹ eight additional substrates (**2**, **3**, **4**, **6**, **9**, **10**, **18**, **19**) were included in order to increase the scope of the study. For each substrate, a lowest-energy transition state corresponding to the CMD pathway was located. Pd(II)-catalyzed C–H bond functionalization of arene **4** is the only example on this list that has not been reported experimentally²⁵ and yet it has been demonstrated that chlorine substituent has similar C–H bond activating properties to fluorine substituent.⁵ While solvent corrections were not employed, the relative barriers of activation on each of the (hetero)arenes employed (**1–22h**) matched the experimental regioselectivity for all cases except anisole (**6**).²⁶ The CMD activation barriers for C–H

24 a) Becke, A. D. *J. Chem. Phys.* **1993**, 98, 5648. b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev.* **1988**, B37, 785.

25 Do, H.-Q.; Kashif Khan, R. M.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, 130, 15185.

26 Several reports on the C–H functionalization reported various *o:m:p* ratios of product under various conditions, see ref 16 and: a) Brasche, G.; García-Fortanet, J.; Buchwald, S. L. *Org. Lett.* **2008**, 10,

bond cleavage of anisole were found to be dependent on the inclusion of solvent effects. For example, the CMD activation barriers for anisole in acetonitrile are 40.9: 42.2: 40.6 kcal mol⁻¹ for *o*:*m*:*p* C–H bonds respectively, while the corresponding barriers in the gas phase are 32.7: 35.1: 34.4 kcal mol⁻¹.

The activation–strain analysis for CMD TS structures for each C–H bonds of arenes **1–22h** revealed several factors that are influencing the regioselectivity for palladium-acetate catalyzed functionalization reactions. These factors allowed for the classification of the arenes into three categories (Scheme 6.2).²⁷ We have categorized as Class I arenes, those for which the regioselectivity of C–H bond functionalization is controlled by the difference in the (hetero)arene distortion energies (ΔE_{dist}).²⁸ In Class II are included the (hetero)arenes for which interaction energies (ΔE_{int}) are the determining factor that define the most reactive C–H bond. The (hetero)arenes in which both the distortion and interaction energies influence the choice of the C–H bond with the lowest barrier of activation are part of Class III compounds. This classification of the (hetero)arenes allows better understanding of their properties based on common characteristics in the following sections of this chapter.

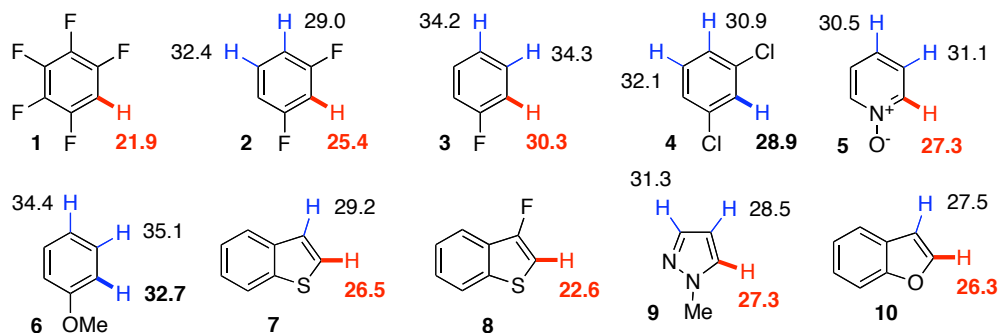
2207. b) Yeung, C. S.; Zhao, X.; Borduas, N.; Dong, V. M. *Chem. Sci.* **2010**, *1*, 331. c) Wang, X.; Leow, D.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 13864.

²⁷ See supporting information for the detailed analyses.

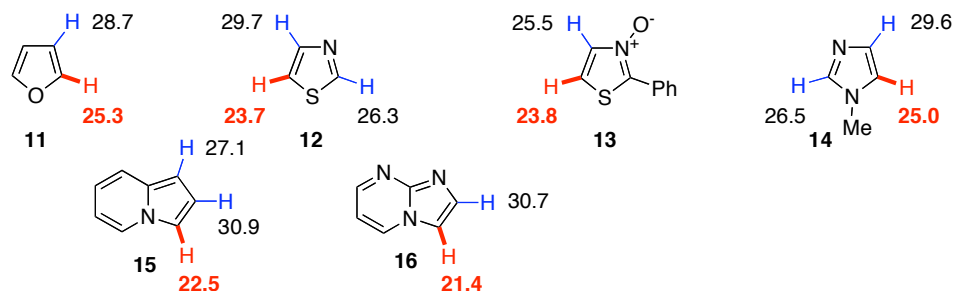
²⁸ Arene **1** was compared to benzene (**17**).

Figure 6.1 Free energy of activation (ΔG_{298K} , kcal mol⁻¹) for C–H bond functionalization *via* the CMD pathway with the [Pd(C₆H₅)(PMe₃)(OAc)] catalyst. Red bonds correspond to the experimentally observed sites of arylation²⁹ except for arene **4**.³⁰

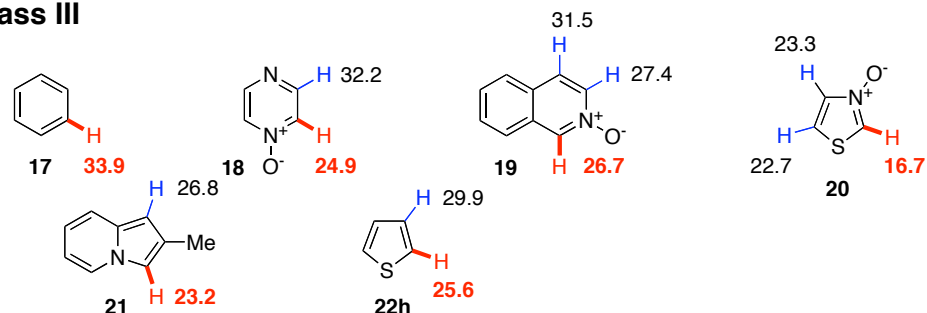
Class I



Class II



Class III



²⁹ For substrates **1–3**, see ref 4; **5**, see: a) Campeau, L.-C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *127*, 18020; **7**, **10–12**, **14–16**, **21** and **22**, see: b) Liégault, B.; Lapointe, D.; Caron, L.; Vlassova, A.; Fagnou, K. *J. Org. Chem.* **2009**, *74*, 1826 and references herein; **9**, see: c) Goikhman, R.; Jacques, T. L.; Sames, D. *J. Am. Chem. Soc.* **2009**, *131*, 3042; **13**, **19** and **20**, see ref 7; **17**, see ref 16; **18**, see: d) Leclerc, J.-P.; Fagnou, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 7781.

³⁰ For a report of copper-catalyzed C2 arylation of **4**, see: Do, H.-Q.; Khan, R. M. K.; Daugulis O. *J. Am. Chem. Soc.* **2008**, *130*, 15185.

6.2.1 Detailed DFT analysis of the process leading to CMD (π -complexes)

Previous mechanistic work on C–H bond functionalization of simple arenes demonstrated the formation of κ_1 , η_1 or η_2 π -complexes between the arene with the metal-carboxylate complex prior to the cleavage of the C–H bond.^{12,15,19,31} Computationally such intermediates are obtained with electron-rich heteroarenes such as thiophene (Scheme 6.3, black pathway). Benzene has also previously been shown to form a π -complex intermediate (Scheme 6.3, green pathway).^{15,31} The analysis of the interaction/distortion components (Table 1) for π -complex intermediates reveals that the major energy expense for the formation of the π -complex results from the distortion of the metal complex ($\Delta E_{\text{dist}}^{\text{I}}(\text{PdL})$) as well as the entropic loss. The geometries of arenes are not significantly perturbed in the structures of the π -complexes as can be seen from very low values for the arene distortion energies ($\Delta E_{\text{dist}}^{\text{I}}(\text{ArH}) \leq 1.4 \text{ kcal mol}^{-1}$). The stabilizing factor favoring the formation of these intermediates is the electronic interaction between the Pd(II) atom with an open coordination site and the π -electrons of the arenes. From the pre-CMD intermediate, the TS can easily be accessed with diminished energetic cost ($\Delta E_{\text{dist}}^{\text{II}}(\text{PdL})$ and $\Delta E_{\text{dist}}^{\text{II}}(\text{ArH})$ in Table 1).

31 a) Ess, D. H.; Bischof, S. M.; Oxgaard, J.; Periana, R. A.; Goddard III, W. A. *Organometallics* **2008**, 27, 6440. b) Bischof, S. M.; Ess, D. H.; Meier, S. K.; Oxgaard, J.; Nielsen, R. J.; Bhalla, G.; Goddard III, W. A.; Periana, R. A. *Organometallics* **2010**, 29, 742.

Scheme 6.3 Possible CMD pathways for C–H functionalization with various arenes ($\text{C}_6\text{F}_5\text{H}$: purple, C_6H_6 : green, $\text{C}_4\text{H}_4\text{S}$: black).

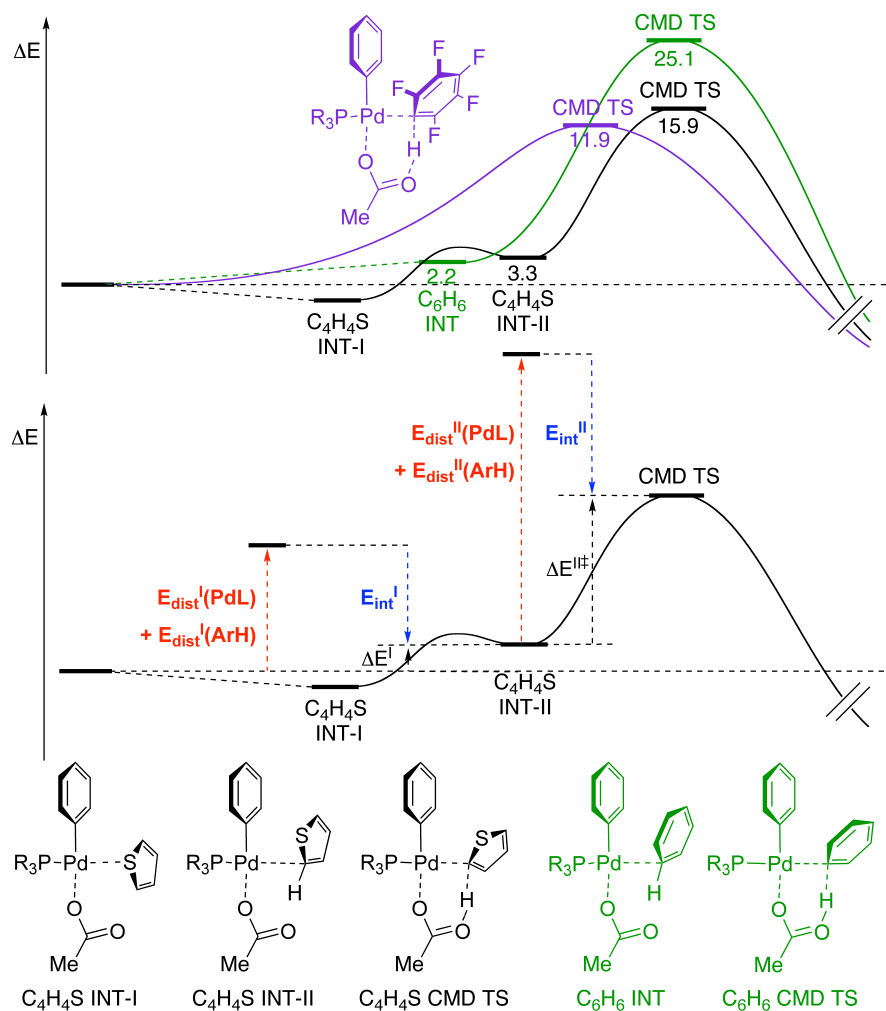


Table 6.1 Gibbs free energies and electronic energies of the pre-CMD intermediates for the lowest-energy CMD pathway with the ArH substrates and the [Pd(C₆H₅)(PMe₃)(OAc)] catalyst, the catalyst and substrate preparation energies, the difference between the preparation energies for CMD transition state structures and pre-CMD intermediate structures, and the metal-arene interaction energies (kcal mol⁻¹).

Arene	ΔG_{298K}	ΔE^I	E_{dist}^I (PdL)	E_{dist}^I (ArH)	E_{int}^I	E_{dist}^{II} (PdL) ^a	E_{dist}^{II} (ArH) ^a	E_{int}^{IIa}
17	14.0	2.2	9.4	0.4	-7.6	7.0	44.2	-28.3
22h	14.8	3.3	12.9	1.0	- 10.7	4.4	38.9	-30.7
22c^b	14.1	2.3	13.4	1.4	- 12.5	4.2	38.2	-30.9
11	11.7	-1.0	12.3	0.8	- 14.2	5.5	41.7	-30.6

a) see Scheme 6.3 for notations and SI for E_{dist} values for CMD TS structures; b) 2-fluorothiophene, see Figure 6.3.

However, not every arene can form a π -complex intermediate. When undergoing the Pd^{II}-catalyzed C–H bond cleavage pentafluorobenzene (**1**), an electron-deficient arene, does not go through the formation of the π -complex intermediate. The analysis of the reaction pathway reveals that, when the arene approaches the empty coordination site on the palladium complex, an interaction with the carbon of the arene C–H bond and the interaction of the C–H bond proton with the base ligand lead into the CMD process (Scheme 6.3, purple pathway). For this substrate, no potential energy minimum corresponding to the π -complex intermediate is present in the reaction pathway before the C–H bond cleavage transition state.

6.2.2 Metallation-Deprotonation: Concerted or Not?

Throughout the mechanistic studies performed in regards to C–H bond cleavage of various (hetero)arenes by metal-carboxylate complexes, quite often these studies were proposing either the stepwise S_EAr mechanism or a single-step concerted process. Recently, Sames *et al.* proposed an intermediary process for the C5 functionalization of

N-SEM-imidazoles, the electrophilic metallation-deprotonation (EMD) mechanism.³² This proposal goes along with the idea of a possible continuum for the mechanisms of the C–H bond cleavage by metal-carboxylate complexes. At one end of this continuum lies a “pure” step-wise S_EAr pathway, on the other end would reside a fully concerted process. The mechanism of C–H bond functionalization of each (hetero)arene with different transition-metal catalysts would fall in between those limiting scenarios. To verify this proposition, we have prepared a More O’Ferrall–Jencks diagram,³³ in which both the O–H and M–C bond formations and the C–H bond breaking at the CMD transition state for (hetero)arenes **1–22h** (Figure 6.2) are characterized by computed Mayer bond orders for the corresponding bonds.

Quite remarkably, all the TS of the (hetero)arenes investigated fit into a fairly narrow region in both 2-dimensional representations of the 3-dimensional More O’Ferrall–Jencks diagram, thus refuting the idea of continuum mechanisms for the systems investigated. The diagrams of Figure 6.2 also give some relevant information regarding the CMD process. At the transition state with the Pd^{II}–acetate catalyst, the bond orders of the forming O–H bonds are narrowly situated in the 0.52–0.59 range. The Pd–C and C–H bond orders are more dependent on the nature of the arene, particularly the Pd–C(arene) bond orders spreads from 0.36 to 0.62, which is still narrow. The distribution of the C–H bond orders in the TS structures are also narrow (from 0.32 to 0.41), but taking into consideration the diversity of the nature of the C–H bonds and the important proximity to the Pd–C bond formation process, they all are similar TS. In general, Class I (hetero)arenes exhibited weaker Pd–C bonding interactions in the CMD TS structures than Class II arenes. This could be attributed to poor nucleophilicity of Class I arenes relative to Class II’s. Yet, these observations remain small trends and should probably not be taken in too much mechanistic interpretation.

To compare the dependence of the concerted metallation-deprotonation process in respect to the nature of the metal catalyst, the transition states of arene C–H bond

32 Joo, J. M.; Tourré, B. B.; Sames, D. *J. Org. Chem.* **2010**, 75, 4911.

33 a) More O’Ferrall, R. A. *J. Chem. Soc. B* **1970**, 274. b) Jencks, W. P. *Chem. Rev.* **1972**, 72, 705.

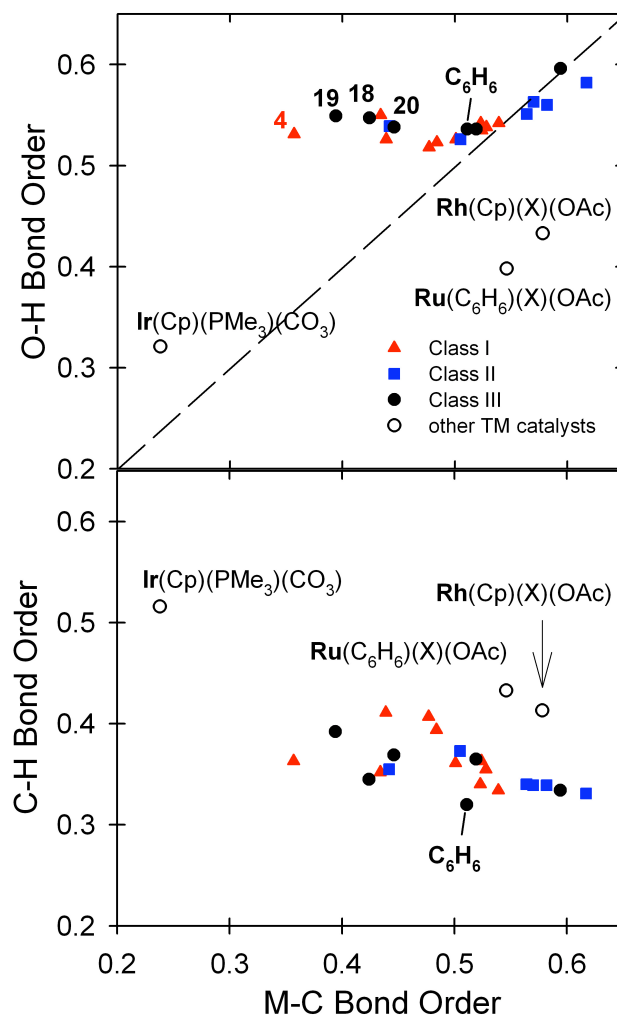
cleavage were calculated for iridium(III)³⁴, rhodium(III)³⁵ and ruthenium(II).³⁶ The CMD TS structure with the Ir^{III}-carbonate catalyst has a high synchronicity for the formation of the O–H and Ir–C bonds although the TS occurs very early in the progression of the metal-benzene interaction. Rhodium(III) and ruthenium(II) are known to be fairly electrophilic and this is reflected by the increased metal–carbon bonding interaction over the O–H bond at the CMD TS structures with the Rh^{III}- and Ru^{II}-acetate catalysts. Overall, the metallation-deprotonation process presents a high level of synchronicity in the formation of the metal–carbon and O–H bonds (dashed line in Figure 6.2), which is in contrast to the formation of a σ -complex (Wheland intermediate) in a S_EAr process. The Wheland intermediate, a signature of a true S_EAr process, would exhibit a fully formed M–C bond without C–H bond cleavage and with no or very little O–H interaction.

34 The reaction with the [Ir(C₅H₅)(PMe₃)(CO₃)] complex was evaluated based on the published results for a similar Ir^{III} complex with dimethylbenzylamine, see: Davies, D. L.; Donald, S. M. A.; Al-Duaij, O.; Macgregor, S. A.; Pölleth, M. *J. Am. Chem. Soc.* **2006**, *128*, 4210.

35 Guimond, N.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2011**, *133*, 6449.

36 Ferrer Flegeau, E.; Bruneau, C.; Dixneuf, P. H.; Jutand, A. *J. Am. Chem. Soc.* **2011**, *133*, 10161.

Figure 6.2 Correlation between metal–C(arene), (base ligand)O–H and C–H(arene) bond orders for CMD TS structures for arenes **1–22h** with the $\text{Pd}(\text{C}_6\text{H}_5)(\text{PMe}_3)(\text{OAc})$ catalyst (red triangles for Class I arenes, blue squares for Class II arenes and black filled circles for Class III arenes) and with the $[\text{Ir}(\text{C}_5\text{H}_5)(\text{PMe}_3)(\text{CO}_3)]$ catalyst (benzene is the substrate),³⁴ and for the intramolecular CMD for the $[\text{Rh}(\text{C}_5\text{H}_5)(\text{X})(\text{OAc})]$ and $[\text{Ru}(\text{C}_6\text{H}_6)(\text{X})(\text{OAc})]$ complexes^{34,35} (open circles).

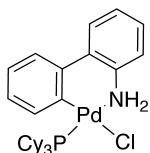


6.2.3 Thiophenes

Previous mechanistic work on the mechanism of direct arylation have highlighted the effect of remote substituent on the reactivity of C–H bonds. To gain a better understanding into the effect of substituents, we chose to focus our attention on the C5 functionalization of C2 substituted thiophenes and attempted to verify the substituent

effects experimentally. These thiophenes reacted in good yields under standard direct arylation reaction conditions without optimizations,^{29b} although we employed a variation of a precatalyst developed by Buchwald *et al.*, [2'-Pd(PCy₃)Cl-2-aminobiphenyl] (**23**), which facilitates the formation of the active catalyst in solution.³⁷ A series of competition experiments provided the data required to compare the experimental reactivity of these thiophenes with the calculated barriers of activation (Figure 6.3). Considering the limitations of the DFT calculations and the inherent experimental variability of the competition reactions, the experimental and theoretical results are in good agreement. Unfortunately, not all the thiophenes in Figure 6.3 could be tested due to either reactivity or availability issues. For instance, the competition reactions with 2-methoxythiophene (**22f**) could not be taken into consideration in the reactivity chart, since **22f** was incompatible with the reactions conditions when tested individually (less than 10% yield). The unsubstituted thiophene (**22h**) could not be employed in the competition reactions since, although it reacted very well under the standard conditions, the arylation product was significantly more reactive than the parent thiophene so it formed a substantial quantity of double arylation product.³⁸

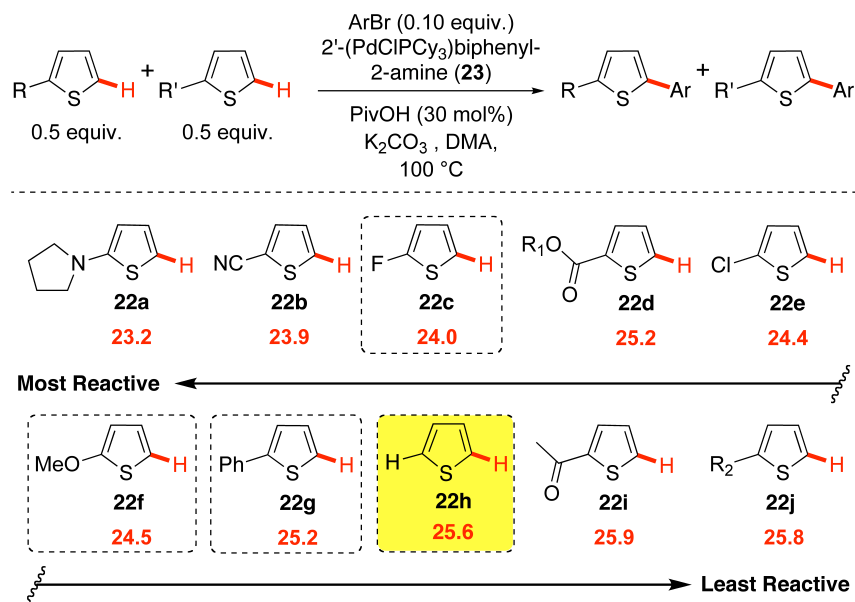
The observed reactivity of substituted thiophenes (Figure 6.3) is not in agreement with S_EAr reactivity. Thiophenes with electron withdrawing groups at the C2 position such as nitrile (**22b**) and ester (**22e**) were found (experimentally and computationally) to be the most reactive substrates along with thiophene containing the strongly electron donating *N*-pyrrolidine substituent (**22a**). Thiophene with a weak electron-donating group such as a propyl chain (**22j**) was found experimentally to be the least reactive substrate along with the thiophene possessing the acetyl substituent (**22i**).



37 Cy₃P **23** was prepared following a procedure reported by Buchwald *et al.*: Kinzel, T.; Zhang, Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 14073.

38 A reaction of direct arylation performed with 1.0 equiv of 5-bromo-*m*-xylene and 1.1 equiv. of thiophene, yielded full conversion of aryl bromide and 1: 2.8 mixtures of mono and double arylation products, respectively. The same reaction with 5.0 equiv of thiophene yielded a 1.2:1 mixture of the same products.

Figure 6.3 Experimentally observed relative reactivity of C2 substituted thiophenes (except **22c**, **22f**, **22g** and **22h**). Values in red correspond to the Gibbs free energy of activation (ΔG_{298K} , kcal mol⁻¹) for the CMD pathway with the [Pd(C₆H₅)(PMe₃)(OAc)] catalyst. R₁= *i*-Pr was modeled as Me. R₂= *n*-Pr was modeled as Me. See Supporting Information for full experimental and computational details.



The activation–strain analysis of the CMD TS structures for thiophenes casts light on the influence of the substituents on both the distortion energy of the arene and the interaction energy in comparison to the unsubstituted thiophene (Table 6.2). Highly π -nucleophilic thiophenes, such as **22a** and **22f**, benefit from more negative E_{int} although this effect is partially counterbalanced by an increase in the arene distortion energy, $E_{\text{dist}}(\text{ArH})$. Electron-withdrawing groups, such as acetyl (**22i**), ester (**22e**), fluorine (**22c**) and nitrile (**22b**), reduce the energetic penalties for the arene distortions, but also reduce the magnitude of the interaction energy between the substrate and the catalyst.

Table 6.2 Distortion/interaction analysis (kcal mol⁻¹) for C2 substituted thiophenes **22a–h** for CMD TS structures with the [Pd(C6H5)(PMe3)(OAc)] catalyst.

Entry	Thiophene	C2 substituent	$\Delta G^\ddagger_{298K}$	$\Delta E^\ddagger$	$E_{\text{dist}}(\text{PdL})^a$	$E_{\text{dist}}(\text{ArH})$	E_{int}
1	22a	-NC ₄ H ₈	23.2	12.3	20.0	47.6	-55.3
2	22b	-CN	23.9	14.1	16.4	34.8	-37.1
3	22c	-F	24.0	13.8	17.6	39.6	-43.4
4	22d	-Cl	24.4	14.3	17.4	37.9	-41.0
5	22f	-OMe	24.5	14.0	18.5	42.4	-46.9
6	22e	-CO ₂ R ₁ ^b	25.2	15.6	17.8	37.3	-39.5
7	22g	-Ph	25.2	15.3	17.4	39.3	-41.4
8	22h	-H	25.6	15.9	17.3	39.9	-41.4
9	22j	-R ₂ ^c	25.8	15.6	17.8	40.7	-42.9
10	22i	-Ac	25.9	16.0	16.4	36.5	-37.0

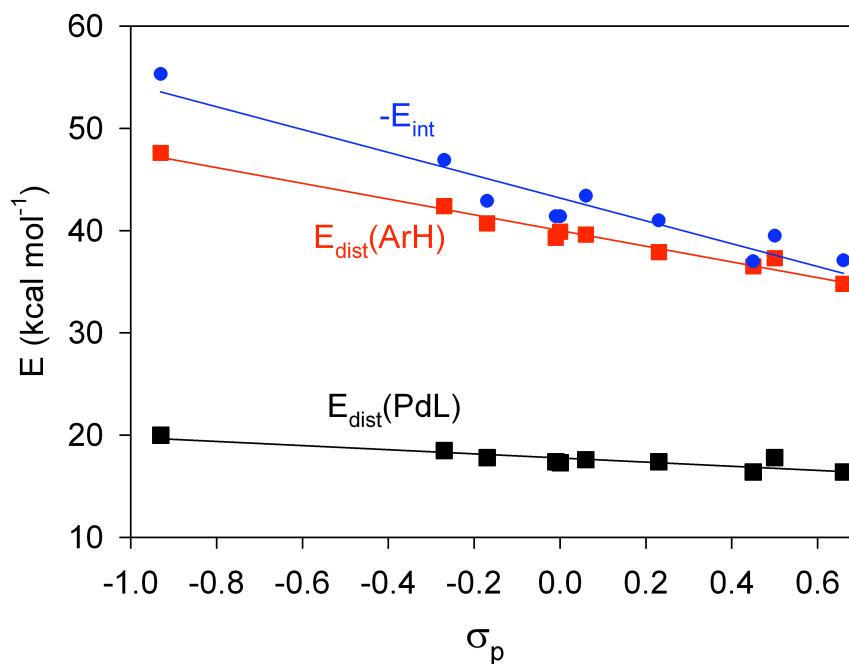
a) Distortion energy for the Pd catalyst. b) R₁= *i*-Pr was modeled as Me.

c) R₂= *n*-Pr was modeled as Me.

A closer examination of the distortion/interaction parameters revealed a correlation with the nature of the C2 substituent. Indeed, the expression of $-E_{\text{int}}$ as a function of Hammett σ_p constants³⁹ for the substituent highlights the relationship between the π -nucleophilicity of the arenes and their interaction with the palladium (Figure 6.4, blue circles). As mentioned before, the beneficial effects of electron donating groups on the E_{int} values are partially offset by the increased $E_{\text{dist}}(\text{ArH})$ penalties (Figure 6.4, red squares). Figure 4 puts in contrast these two factors. The third factor is $E_{\text{dist}}(\text{PdL})$ (Figure 6.4, black squares). The small dependence of $E_{\text{dist}}(\text{PdL})$ on the arene nucleophilicity can be rationalized by the fact that arenes with stronger nucleophilicity and, thus, higher E_{int} are expected to cause greater structural distortion of the metal catalyst to accommodate the incoming substrate.

39 Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165.

Figure 6.4 Activation–strain parameters (kcal mol⁻¹) for the Pd(II)-catalyzed CMD transition states as a function of σ_p values for C2 substituted thiophenes **22a–h**.



Using the linear regression for the activation–strain factors in Figure 6.4 we get:

$$E_{dist}(ArH) = 40.0(2) - 7.7(4) \sigma_p \quad (1)$$

$$E_{dist}(PdL) = 17.8(2) - 2.0(4) \sigma_p \quad (2)$$

$$E_{int} = -43.2(5) + 11(1) \sigma_p \quad (3)$$

Although Hammett plots have previously been employed in the C–H bond cleavage mechanistic studies with various systems, including simple arenes,⁴⁰ indoles⁹ and pyridine-*N*-oxides,¹⁰ to the best of our knowledge this is the first time that σ_p constants are directly linked to the $E_{dist}(ArH)$ and E_{int} factors. Unfortunately, the accuracy of the σ_p model derived from equations 1–3 does not allow precise evaluation of CMD activation barriers for the thiophenes **22a–h** (Table 6.3 and Figure 6.5) due to accumulation of uncertainties of parameters.

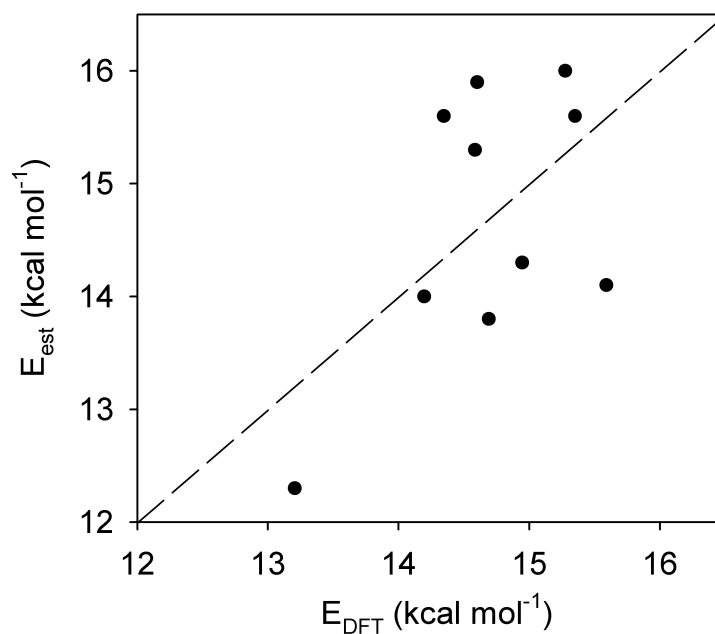
40 a) Ryabov, A. D.; Sakodinskaya, I. K.; Yatsimirsky, A. K. *J. Chem. Soc., Dalton Trans.* **1985**, 2629. b) Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997**, 97, 2879.

Table 6.3 Activation barriers (kcal mol⁻¹) for C2 substituted thiophenes **22a–h** calculated using the linear correlations with σ_p parameters (Figure 4).

Entry	Arene	-R group	σ_p	$\Delta E^\ddagger$	$ \Delta E^\ddagger(\text{calc}) - \Delta E^\ddagger(\text{DFT}) $
1	22a	-NC ₄ H ₈	-0.93	13.2	0.9
2	22b	-CN	0.66	15.6	1.5
3	22c	-F	0.06	14.7	0.9
4	22d	-Cl	0.23	14.9	0.6
5	22f	-OMe	-0.27	14.2	0.2
6	22e	-CO ₂ R ^a	0.50	15.4	0.3
7	22g	-Ph	-0.01	14.6	0.7
8	22h	-H	0.00	14.6	1.6
9	22j	-R ^b	-0.17	14.3	1.2
10	22i	-Ac	0.45	15.3	0.7

a) Experimentally R= *i*-Pr, in modeling R= Me. b) Experimentally R= *n*-Pr, in modeling R= Me.

Figure 6.5 Comparison of DFT-calculated CMD activation barriers and barriers estimated from Equations 1–3 for C2 substituted thiophenes.



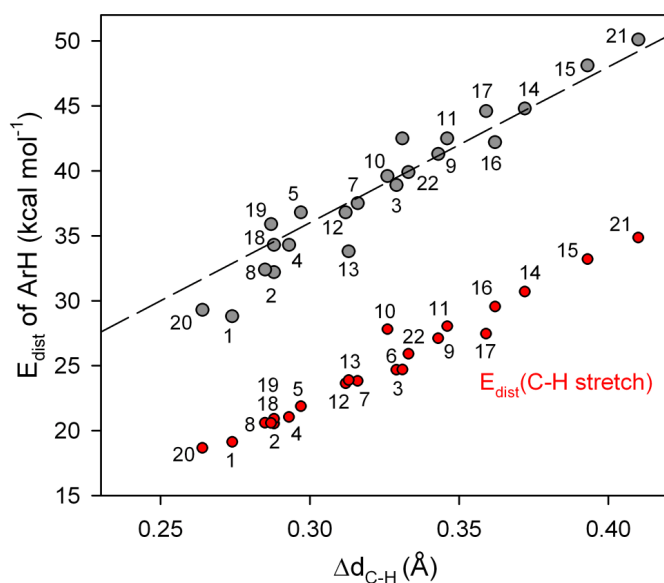
6.3 Efforts toward the establishment of predictable arene C–H bond functionalization guidelines

As mentioned in the introduction, we are interested in deriving general trends from a wide array of (hetero)arenes with a final objective of developing reactivity guidelines for predicting the regioselectivity of C–H bond functionalization of various (hetero)arenes.

6.3.1 Arene distortion energy

The energy cost associated with the distortion of the arenes into their CMD transition state geometry can be separated into two components: 1) the C–H bond elongation and 2) the out-of-plane bending of the C–H bond of the arene. Evaluation of the C–H bond elongation and out-of-plane bending of the C–H bond as contributions to $E_{\text{dist}}(\text{ArH})$ for each arene demonstrated that the out-of-plane bending contribution to the arene distortion energy is, in fact, fairly constant ($13.2 \pm 2.2 \text{ kcal mol}^{-1}$, Figure 6.6).

Figure 6.6 Arene distortion energies (black circles) and the C–H bond distortion energies (red circles) for the CMD TS structures with the $\text{Pd}(\text{C}_6\text{H}_5)(\text{PMe}_3)(\text{OAc})$ catalyst as a function of the C–H bond elongation for different arene substrates.



As shown in Figure 6.2, the C–H bond orders in the CMD TS structures with the Pd(II) catalyst revealed that for all the arenes the C–H bond orders are in a narrow range (0.32–0.41, the mean value is 0.36). This information would simplify the evaluation of arene distortion energies, if one could take the energy cost to elongate a C–H bond to a distance that corresponds to the bond order of ~ 0.36 in free arene and add this value to the out-of-plane bending “constant”, 13.2 kcal mol⁻¹. Unfortunately, this procedure cannot be applied due to the fact that the hydrogen atom of the C–H bond in the TS structure also interacts with the base ligand (acetate). In the absence of the interaction with the base ligand, the C–H bond order would be considerably higher than ~ 0.36 for the same bond elongation and would exhibit significant variation in bond orders (see Table 8.X in Supplementary information

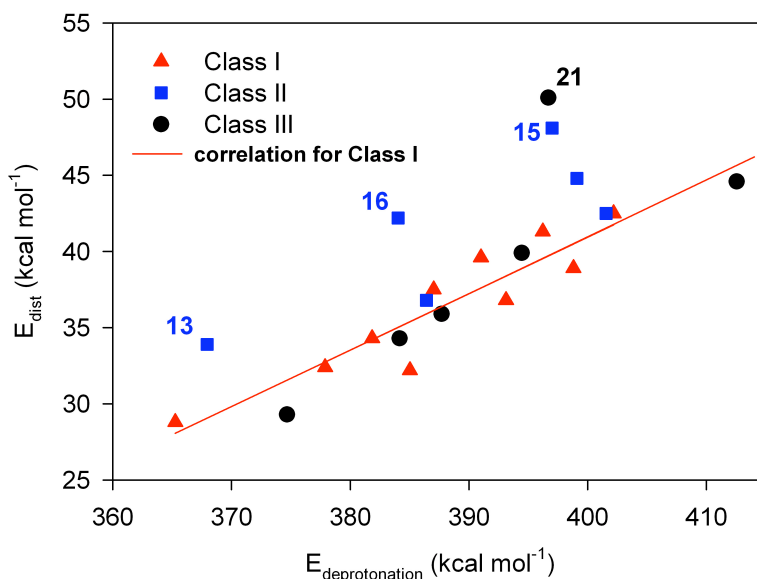
Nonetheless, the estimation of arene distortion energies can be made using the deprotonation energies of the corresponding C–H bonds of free arenes (Figure 6.7). The deprotonation energies could be easily calculated by removing the proton from the arene and optimizing the structure of the resulting anion. For Class I substrates, the linear

regression analysis of the correlation between $E_{\text{dist}}(\text{ArH})$ and $E_{\text{deprotonation}}$ leads to an approximate expression:

$$E_{\text{dist}}(\text{ArH}) = 0.37(5) E_{\text{deprotonation}} - 107(21) \quad (4)$$

Figure 6.7 also indicates that the correlation established for Class I arenes works fairly well for all Class III arenes except one (indolizine **21**) and for three Class II arenes out of six (indolizine **15**, imidazopyrimidine **16** and thiazole-*N*-oxide **13** show significantly higher distortion energies than those expected from equation 4).

Figure 6.7 Arene distortion energies for the CMD TS structures with the $[\text{Pd}(\text{C}_6\text{H}_5)(\text{PMe}_3)(\text{OAc})]$ catalyst as a function of the C-H bond deprotonation energies for substrates **1–22h** (Class I arenes are red triangles, Class II arenes are blue squares and Class III arenes are black circles). Linear correlation (red line) for Class I arenes is shown.



6.3.2 Metal-arene interaction energy

The evaluation of the electronic interaction (E_{int}) when the metal catalyst and the arene in their CMD transition state geometry are brought together remains elusive. We have shown that the E_{int} is linked to the nucleophilicity of C2 substituted thiophenes (*vide*

supra). The principal difficulty resides in the fact that there is little data available to assess the nucleophilicity of different carbon sites in (hetero)arenes structures. The solution may be found in the development of a quantitative method that easily allows the evaluation of carbon site nucleophilicities.

6.4 Conclusion

Activation–strain analysis of the C–H bond cleavage of a wide range of (hetero)aromatics through the concerted metallation-deprotonation pathway has been performed in an attempt to quantify the contributions to the CMD reactivity. Based on this analysis, all (hetero)arene substrates can be divided into three classes. For Class I arenes, the regioselectivity of C–H bond functionalization is controlled by the difference in the arene distortion energies. Class II includes the (hetero)arenes for which interaction energies with the metal catalyst are the determining factor in reactivity. Class III arenes are the (hetero)arenes in which both the distortion and interaction energies influence the C–H bond functionalization. This classification of the (hetero)arenes allows for an easier understanding of their reactivity.

The analysis of the CMD reaction pathway reveals that for some electron-rich and simple heteroarenes π -complexes are formed prior to the C–H bond cleavage step. In such intermediates, the arene fragments undergo only small distortion, refuting the idea of the formation of a Wheland intermediate which would possess strong Pd–(hetero)arene interaction.

The analysis of the bond interactions in the TS structures using a More O’Ferrall–Jencks diagram allows for the assessment of how concerted metallation-deprotonation depends on the nature of the (hetero)arene and the metal catalyst.

The effects of remote C2 substituents on the reactivity of thiophenes were evaluated. The computed trends in the reactivity were corroborated by the experimental

competition studies using six thiophenes. The nucleophilicity of the thiophenes evaluated by the Hammett's σ_p values appears to correlate with the activation-strain parameters including not just the catalyst-substrate interaction energy but also with the distortion energies of the substrate and of the catalyst.

Initial stepping stones were placed on the development of predictive guidelines for the activation of C–H bond functionalization catalyzed by Pd-acetate. It has been shown that there is a correlation between the deprotonation energy of the (hetero)arenes and the distortion energy of arene in the CMD process. The C–H bond out-of-plane bending energetic penalty was found to have a fairly constant value. The principal remaining challenge to the development of the guidelines remains to quantify the relationship between the nucleophilicity of (hetero)arenes and the energy of the interaction of the catalyst and (hetero)arene. Nevertheless, we believe that the findings in this work will be of practical use for future reaction development. We have presented where our conception of the CMD pathway stands and we hope that this manuscript will inspire new ideas and discoveries in the field of C–H bond functionalization.

Part B:

Chapter

7

Studies Toward the Synthesis of Ginkgolide C Spirobicyclic Core by Au(I)-Catalyzed Cyclizations

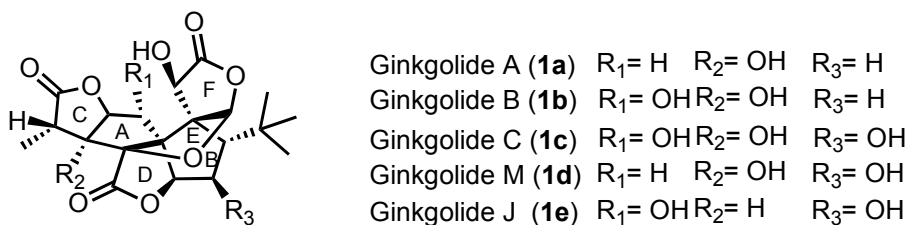
7.1 Introduction

For centuries, extracts of the tree *Ginkgo biloba* have been utilized in Chinese and Indian folk medicines to treat a variety of diseases such as coughs, asthma, and circulatory disorders. The isolation of four terpenes from the bark of this tree in 1932 by Furukuwa marked an important advance in the quest for the identification of the active constituents of *Ginkgo biloba*.¹ In 1967, Nakanishi and his group reported their studies in

¹ Braquet, P. *Drugs of the Future* **1987**, *12*, 643.

which they elucidated the structures of ginkgolides A, B, C and M (Figure 7.1, **1a–d**)² and in 1987, ginkgolide J was isolated and characterized.³ The ginkgolides possess a unique compact diterpene framework bearing six five-membered rings, up to twelve stereogenic centers, eleven oxygen atoms, four contiguous quaternary carbon centers and an unusual *tert*-butyl group. Also, it was found that ginkgolides are very potent platelet-activating-factor (PAF) antagonists.¹ Despite their medicinally important properties, studies toward the synthesis of the ginkgolides and related analogs are rather limited. From a chemical point of view, the ginkgolides constitute daunting synthetic challenges owing their remarkable structural complexity. To date, only the groups of Corey and Crimmins have independently reported the synthesis of ginkgolides A⁴ (**1a**) and B (**1b**).^{5,6} These syntheses are considered as being some of the greatest achievements in total synthesis.⁷ However, to the best of our knowledge, there is no reported total synthesis of the most complicated member of the ginkgolide family, namely ginkgolide C.

Figure 7.1 Ginkgolide Family.



2 Nakanishi, K. *Pure Appl. Chem.* **1967**, *14*, 89.

3 Weinges, K.; Hepp, M.; Jaggy, H. *Liebigs Ann. Chem.* **1987**, 521.

4 Corey, E. J.; Ghosh, A. K. *Tetrahedron Lett.* **1988**, *29*, 3205.

5 a) Corey, E. J.; Kang, M.-C.; Desai, M. C.; Ghosh, A. K.; Houpi, I. N. *J. Am. Chem. Soc.* **1988**, *110*, 649. b) Corey, E. J.; Gavai, A. V. *Tetrahedron Lett.* **1988**, *29*, 3201.

6 a) Crimmins M. T.; Pace, J. M.; Nantermet, P. G.; Kim-Meade, A. S.; Thomas, J. B.; Watterson, S. H.; Wagman, A. S. *J. Am. Chem. Soc.* **1999**, *121*, 10249. b) Crimmins M. T.; Pace, J. M.; Nantermet, P. G.; Kim-Meade, A. S.; Thomas, J. B.; Watterson, S. H.; Wagman, A. S. *J. Am. Chem. Soc.* **2000**, *122*, 8453.

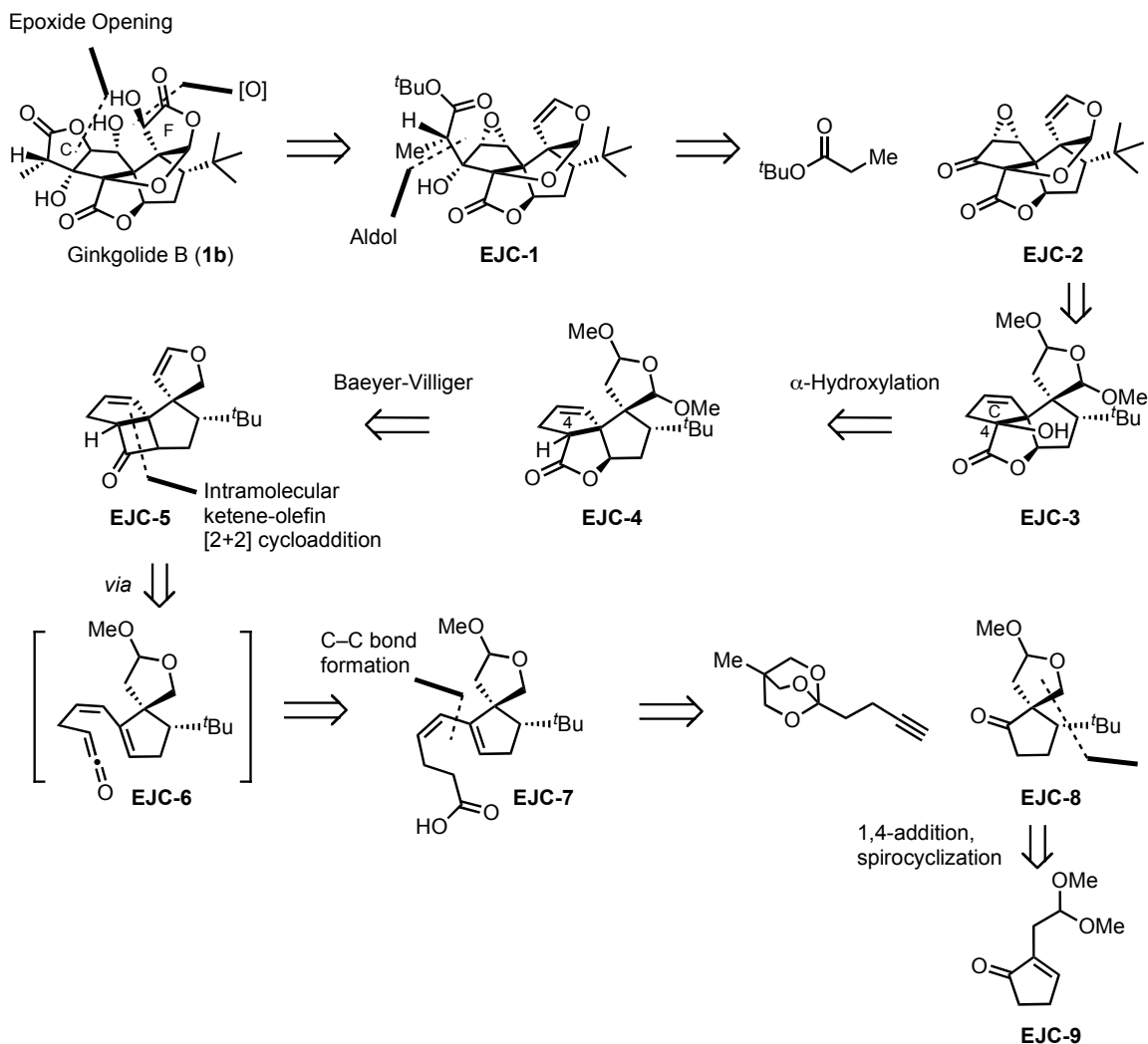
7 Nicolaou, K. C.; Sorensen, E. J., *Classics in Total Synthesis*; Wiley VCH: New York, 1996.

7.1.1 Corey's retrosynthesis and strategy for the synthesis of (±)-ginkgolide B

Starting with Corey's retrosynthesis analysis of ginkgolide B (Scheme 7.1),^{5a} the reactivity of ring F needed to be concealed as a dihydrofuran moiety during the elaboration of the rest of the molecule. The construction of ring C by the ring opening of an epoxide of **EJC-1** was conceived as the first important retrosynthetic maneuver. The construction of the chain that will constitute ring C is joined in a straightforward sequence that includes an aldol reaction, the epoxidation of the enone obtained from the allylic oxidation of ring A. The tetrahydrofuran ring was envisioned to arise from an intramolecular substitution reaction of **EJC-3**.

Before continuing the description of the retrosynthetic analysis of ginkgolide B, it would be interesting to briefly elaborate on the diastereoselectivity and facial selectivity of the aldol condensation onto **EJC-2**. Indeed, the presence of the γ -butyrolactone and the epoxide on the α face of **EJC-2** should *a priori* favor the addition to the β face of the compound. The steric encumbrance between the **EJC-2** and the *Z* propionate enolate should lead to the formation of the desired diastereoisomer as the major product.

Scheme 7.1 Corey's retrosynthetic approach to ginkgolide B.

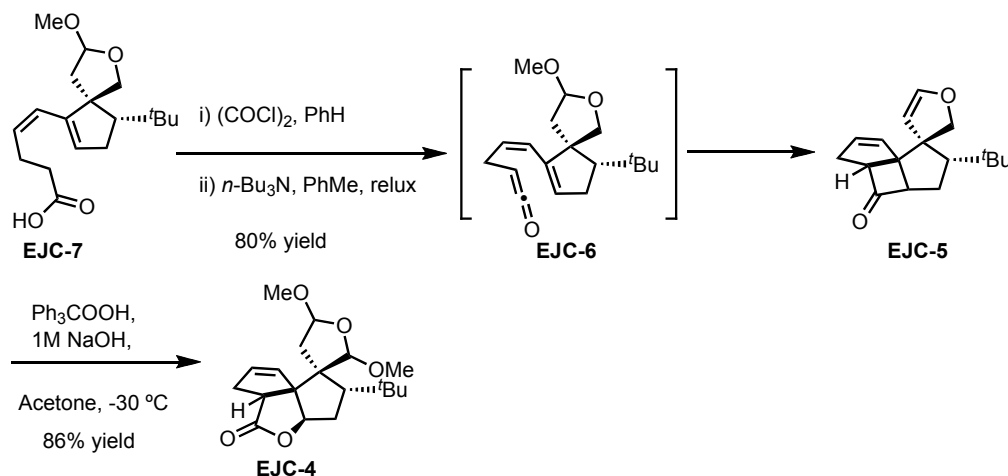


The oxygen on C4 would be obtained from the oxidation α to the lactone **EJC-4**. At this point, the key sequence of Corey's synthesis of ginkgolide B has been reached. The central element of Corey's synthesis is the formation of ring D obtained from the Baeyer-Villiger ring extension of the cyclobutanone ring of **EJC-5**. The rigid cyclobutanone ring is the key intermediate of the synthesis since it is derived from an intramolecular ketene-olefin [2+2] cycloaddition. The stereoselectivity of the reaction of intermediate **EJC-6** would be set by the steric encumbrance of the *tert*-butyl group on the α side of the molecule and force the ketene to approach the olefin from the β face. One can imagine that ketene **EJC-6** would be obtained from the deprotonation of the acyl

chloride derived from the acid **EJC-7**. The appendix carbon-chain on **EJC-7** was installed using a Sonogashira cross-coupling reaction. Finally, the spiro[4.4]nonane core **EJC-8** was prepared *via* 1,4-conjugate addition and cyclization sequence on the starting material **EJC-9**.

Without going into the details of Corey's work, we must revisit some key features of the synthesis of ginkgolide B. Starting right away with the key step of the synthesis, acid **EJC-7** was converted to the corresponding acyl chloride with 5 equivalents of oxalyl chloride, followed by the addition to a tri-*n*-butylamine solution in toluene at reflux furnished stereospecifically the tetracyclic ketone **ECJ-5** in good yield (Scheme 7.2). The reaction conditions also resulted in the elimination of the anomeric methoxy cyclic acetal. The reaction of the ketone **ECJ-5** with a solution of triphenylmethyl hydroperoxide and aqueous 1N NaOH at -30 °C produced a single Baeyer-Villiger product (**ECJ-4**) in excellent yield as well. It is noteworthy that the use of less bulky oxidants, such as basic hydrogen peroxide, led to the formation of a 1:1 mixture of γ -lactones regioisomers.

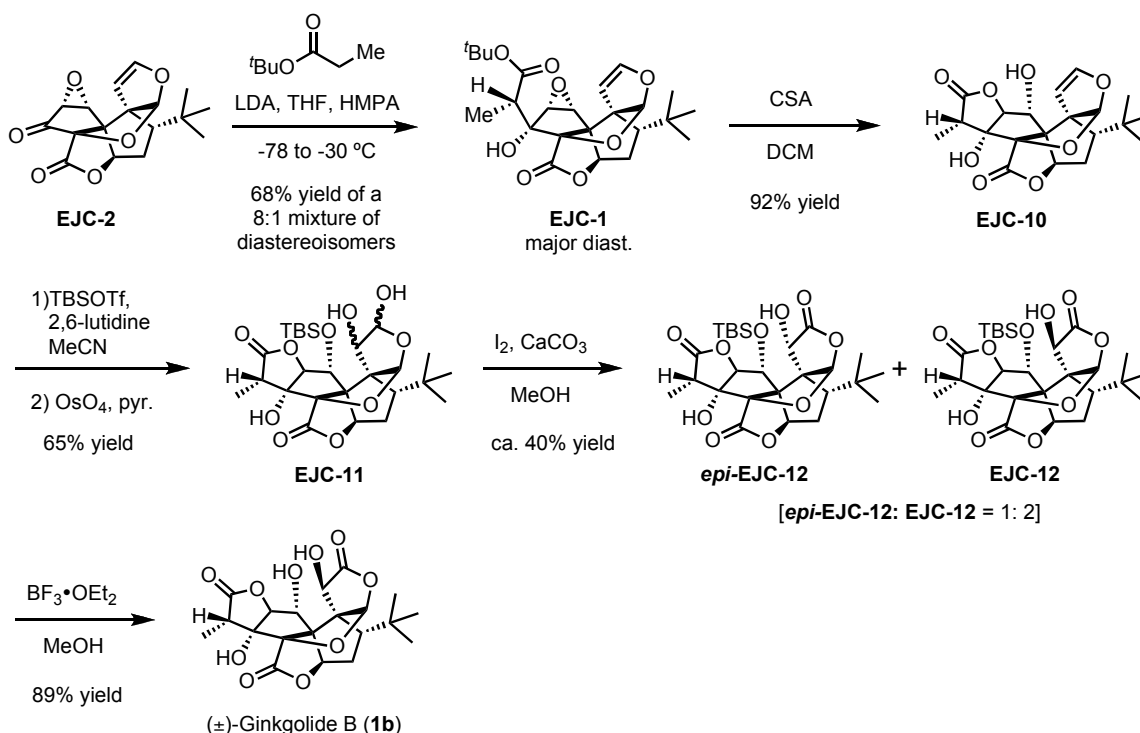
Scheme 7.2 Key sequence in Corey's synthesis of ($\pm$)-ginkgolide B.



Scheme 7.3 presents the steps that led to the completion of the first synthesis of ginkgolide B by Corey. The following aldol reaction on the intermediate **EJC-2** produced, as expected, the desired diastereoisomer **ECJ-1** as the major product in a 8:1

mixture of epimers. The formation of γ -lactone was efficiently promoted by a solution of camphor sulfuric acid (CSA) in dichloromethane yielding **EJC-10** in 92%. The final oxidation sequence to reveal the α -hydroxy lactone from the dihydrofuran resulted in a 2:1 stereoisomeric mixture of *epi*-**EJC-12** and **EJC-12** in 40% yield. The final deprotection of the silane group completed the first total synthesis of ($\pm$)-ginkgolide B.

Scheme 7.3 Completion of Corey's synthesis of ($\pm$)-ginkgolide B.

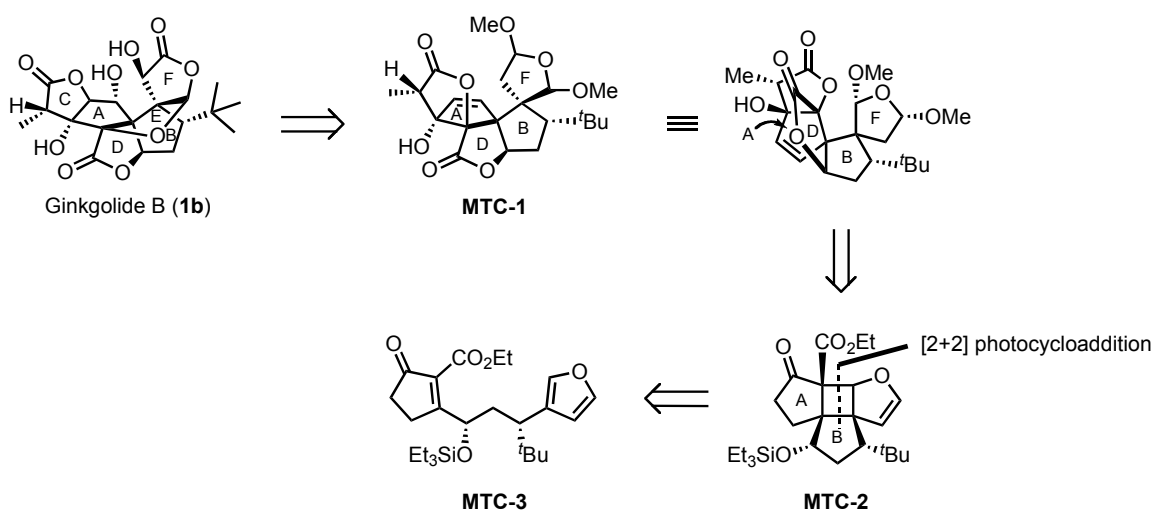


7.1.2 Crimmins' synthesis of ($\pm$)-Ginkgolide B

The second total synthesis of ginkgolide B was reported by the group of Crimmins in 1999 and featured [2+2] photocycloaddition methodology.⁶ Crimmins' description of the challenge that represented the synthesis of **1b** was: “*the diabolical disposition of functionality dictates that introduction of functional groups be judiciously orchestrated.*” Consequently, Crimmins planned to complete synthesis by the late stage formation of rings C and functionalization of ring F, similarly to Corey's approach. Crimmins'

strategy featured the disconnection of ring E as the first key retrosynthetic step (**MTC-1**) (Scheme 7.4). Using a different representation of **MTC-1**, the next key intermediate is the tetracyclic structure **MTC-2**, which features a central cyclobutane ring. The relationship between **MTC-2** and **MTC-1** will be discussed later. To complete the retrosynthetic analysis, the **MTC-2** intermediate can be derived from [2+2] photocycloaddition of **MTC-3**.⁸

Scheme 7.4 Crimmins' retrosynthetic approach to (±)-ginkgolide B.



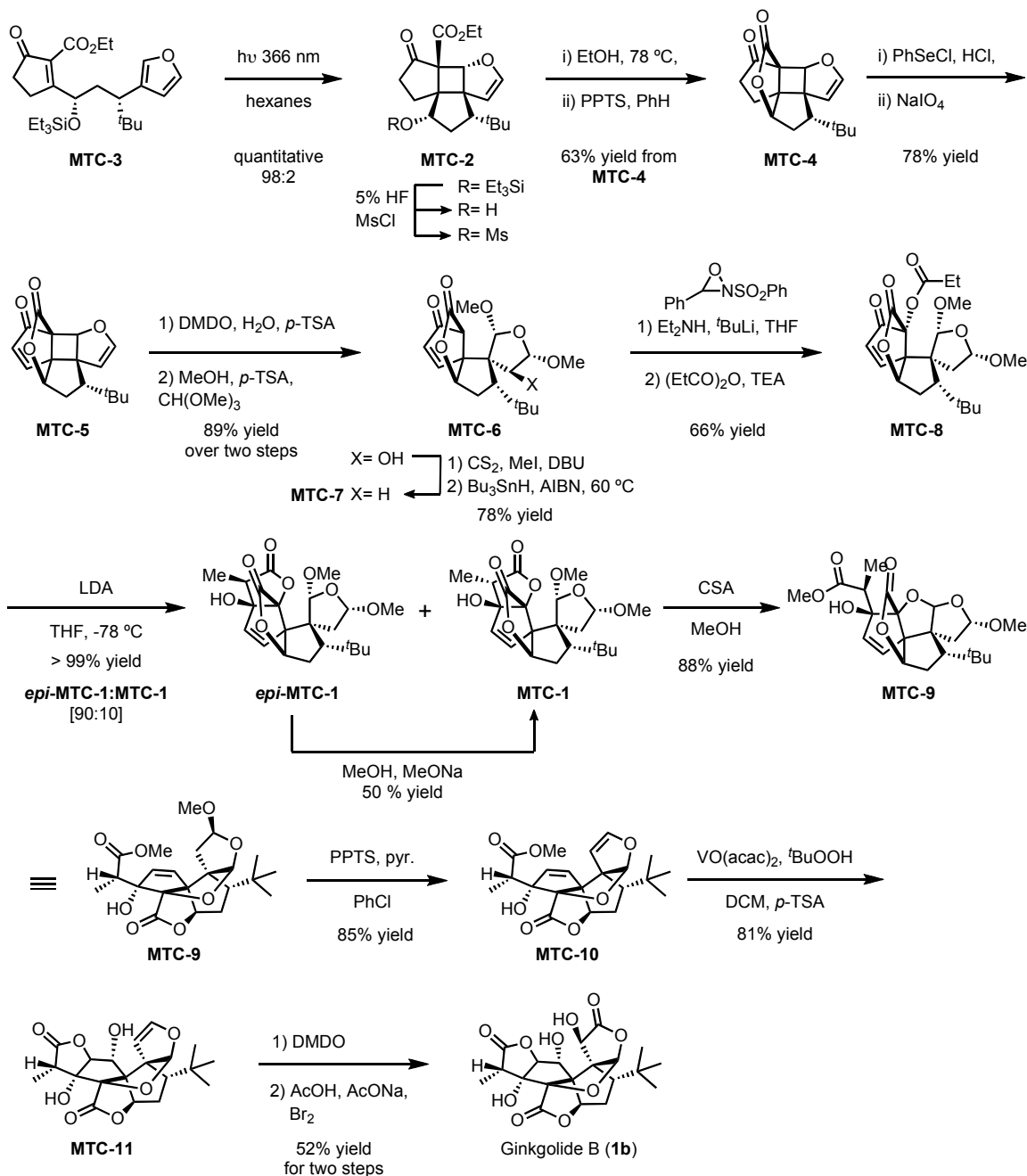
Once again, without going into the details of Crimmins work, we will cover some of the key steps of his synthesis in Scheme 7.5. Starting **MTC-3**, as mentioned the key feature of the synthesis was the photo-induced cycloaddition methodology developed in his laboratory.⁹ Since the FMO (frontier molecular orbital) theory forbids the thermal cycloaddition of the **MTC-3**, light was necessary to allow the reaction to occur and full conversion of starting material to cyclophotoadduct **MCT-2** was obtained. Further steps allowed the formation of the γ -lactone (ring D) as well as the enone present in **MTC-5**. The subsequent oxidative ring-opening of the cyclobutane formed **MTC-6**, which also oxidized the dihydrofuran moiety. Since this undesired oxidation of the dihydrofuran resulted in problems in the latter stage of the synthesis, a Barton–McCombie

8 Crimmins, M. T.; Reinhold, T. L. *Org. React.* **1993**, *44*, 297.

9 Crimmins, M. T.; Thomas, J. B. *Tetrahedron Lett.* **1989**, *30*, 5997.

deoxygenation was necessary (**MTC-7**). The intermediate **MTC-7** was then treated with Davis' oxaziridine and propionic anhydride yielding product **MTC-8**.

Scheme 7.5 Crimmins' synthesis of (±)-ginkgolide B.



From the intermediate **MTC-8**, the intramolecular variation of Corey's aldol reaction was performed to form the first C–C bond that will lead to ring C, but the wrong

diastereoisomers was formed predominately (*epi*-**MTC-1**: **MTC-1** = 9:1). The simple treatment of *epi*-**MTC-1** with sodium methoxide allowed the epimerization to the desired product. The subsequent treatment of **MTC-1** with camphor sulfonic acid in methanol resulted in the methanolysis of the lactone and closure of the ring E in excellent yield. At this point, only the closure of the C ring and the refunctionalization of the F ring remained to be accomplished. To this end, **MTC-8** was treated with acid to eliminate methanol giving the dihydrofuran in **MTC-9**. The alcohol-directed epoxidation of the C1–C2 olefin was achieved using Sharpless conditions¹⁰ and further treatment with acid secured γ -lactone ring. Lastly, the oxidation of the dihydrofuran was made with DMDO and the facial selectivity of the epoxidation was rationalized by the steric shielding of the *tert*-butyl group on the α face. The opening of the epoxide with sodium acetate in acetic acid and further oxidation with Br₂ resulted in the exclusive formation of ($\pm$)-ginkgolide B in 52% yield after purification for the last two steps.

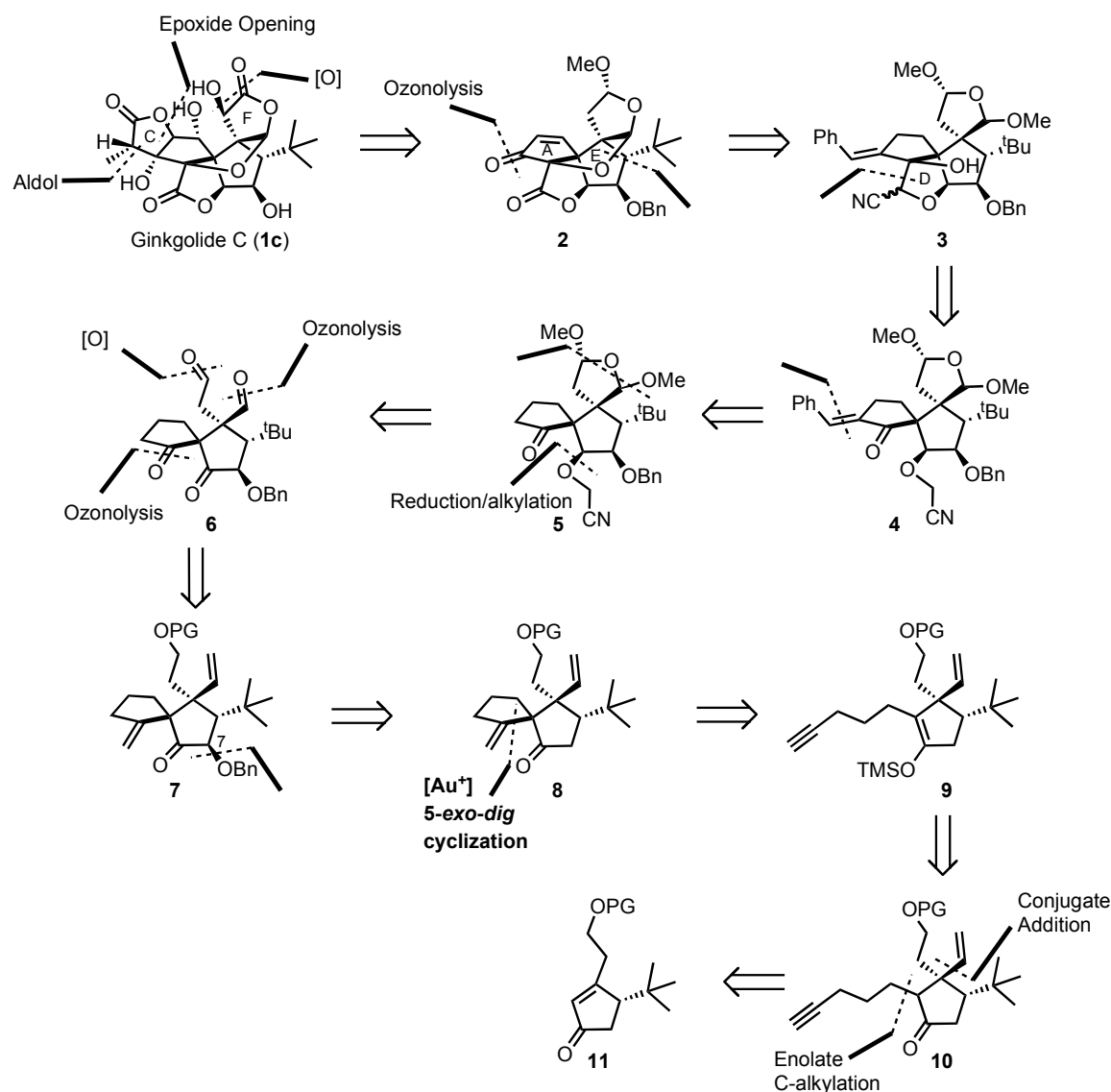
7.2 Current approach to the synthesis of Ginkgolide C

In this section, we will cover in detail our retrosynthetic analysis of ginkgolide C. Likewise the strategy employed by Corey and later by Crimmins, we envisioned as the first key retrosynthetic operations to be the late stage functionalization of the ring F and the construction of ring C. The next key disconnections would be the elaboration of the enone on ring A by ozonolysis of an *exo*-cyclic alkene and oxidation from **3**. With the five remaining cycles, we envisaged a sequence of cyclizations to form rings E and D in potentially a domino fashion. Indeed, starting with intermediate **4**, we envisaged a nucleophilic addition of the cyanohydrin moiety onto the proximal electrophilic ketone, forming ring D, the resulting alcohol could then be cyclized onto the proximal acetal and form ring E. In both Corey's and Crimmins syntheses, the formation of ring E was performed under acidic conditions, thus suggesting that both cyclizations could not be performed simply under basic conditions. Potentially, a one-pot–two step sequence could be envisaged. To construct the tricyclic intermediate **4**, a series of functional group

10 Sharpless, K. B.; Verhoeven, T. R. *Aldrichim. Acta* **1979**, 12, 63.

manipulations could be traced back to the spiro[4.4]nonane core of ginkgolide (**7**). The key intermediate **7** contained all the key stereochemical informations needed to complete the synthesis. Intermediate **7** also contained the oxygen at the C7 position that was not present in ginkgolide B. The installation of the C7 oxygen could be achieved by the oxidation α to the ketone and the stereoselectivity should be governed by the *tert*-butyl group on the back face of the ring (**8**). This bring us to a key feature of our retrosynthetic analysis, we planed to construct the spiro[4.4]nonane core by a gold(I)-catalyzed 5-*exo-dig* cyclization from the silylenol ether–terminal alkyne substrate **9**. The stereoselectivity should also be dictated by the steric bulk of the *tert*-butyl group, in a comparable manner to the [2+2] cycloaddition in Corey’s synthesis.^{5a} The substituted cyclopentene **9** should be accessible by the stereoselective 1,4-conjugate addition on enone **11** with a vinyl nucleophile and followed by trapping the enolate with the alkyne side-chain.

Scheme 7.6 Our retrosynthetic analysis of ginkgolide C.

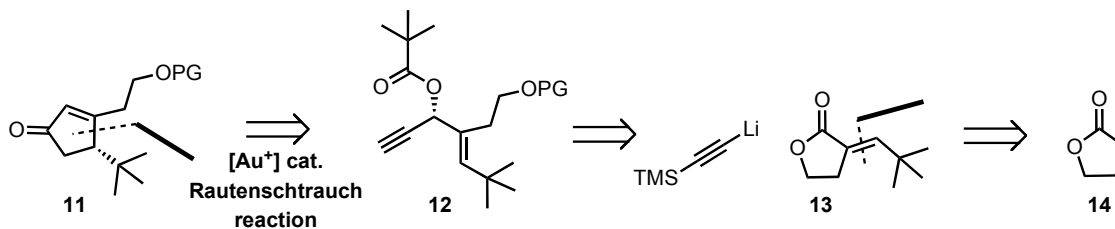


The steric shielding induced by the *tert*-butyl group of **11** is the key element of stereocontrol in our strategy for the synthesis of ginkgolide C. Consequently, if this stereocenter was controlled, the natural enantiomer of ginkgolide C could be synthesized. Indeed, **11** can be generated from **12** via a Rautenschtrauch reaction catalyzed by gold(I) (Scheme 7.7).¹¹ The enantioenriched preparation of the propargylic ester **12** should be feasible by the enantioselective reduction of the corresponding ketone.

11 Shi, X.; Gorin, D. J.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 5802.

Also, in the report on the gold-catalyzed Rautenschtrauch reaction, Toste *et al.* demonstrated that the cyclization occurred with a high level of retention of the stereochemical information, *vide infra*.¹¹ Finally, the preparation of **12** was to be traced back to γ -butyrolactone (**14**).

Scheme 7.7 Retrosynthetic analysis of ginkgolide C, preparation of intermediate **11**.



The retrosynthetic strategy presented in this section represents a highly stimulating challenge. For the short-term, the main objective would be to verify the feasibility of both gold-catalyzed key steps and the elaboration of a robust route to the preparation of the core of ginkgolide C. In the following sections, we will go over the literature precedents that support the viability of both gold-catalyzed cyclization reactions and then will be presented our efforts toward the development of a practical route to the spiro[4.4]nonane core of the natural product.

7.3 Gold(I)-catalyzed cyclization reactions

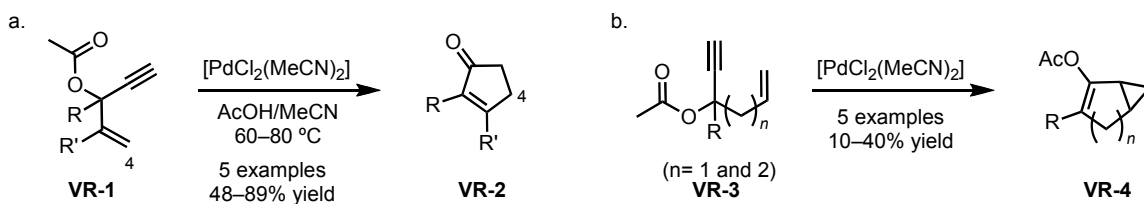
In the recent years, the development of gold catalysis methodology has witnessed an intense diversification. These advances were primarily due to the ability of gold(I) and gold(III) salts to act as soft Lewis acids and to preferentially interact with alkynes and allenes. These interactions enable a variety of transformations that lead to the formations of new carbon-carbon or carbon-heteroatom bonds. Following the initial focus on methodology development, a number of applications of gold-catalysis appeared in the

field of natural products synthesis.¹² The transfer of stereochemical information from the starting material to product, highly efficient rearrangements and cyclizations are some of the features that brought gold catalysis at the forefront of academic research. In the following section, we will focus on the two specific gold-catalyzed transformations that were mentioned in our retrosynthetic strategy.

7.3.1 Gold(I) catalyzed Rautenstrauch reaction

In 1984, Rautenstrauch reported the two types of cycloisomerizations of propargylic esters catalyzed by palladium(II) to form 2-cyclopentenones as well as [3.1.0] and [4.1.0] bicyclic systems (Scheme 7.8).¹³ Of the two transformations reported in this seminal publication, the cyclopropanation (Scheme 7.8b) has been studied more extensively.¹⁴ The reaction of interest for our project is the formation of the 2-cyclopentenones, which was originally described by Rautenstrauch as a formal Pd-catalyzed Nazarov cyclization (Scheme 7.8a).¹³

Scheme 7.8 Rautenstrauch cycloisomerization and cyclopropanation reactions of propargylic esters.



Despite the importance of cyclopentenones as building blocks in organic synthesis, Rautenstrauch's rearrangement was limited to the preparation of achiral product without substitution at the C4 position. Based on Rautenstrauch's work, the group of Toste latter

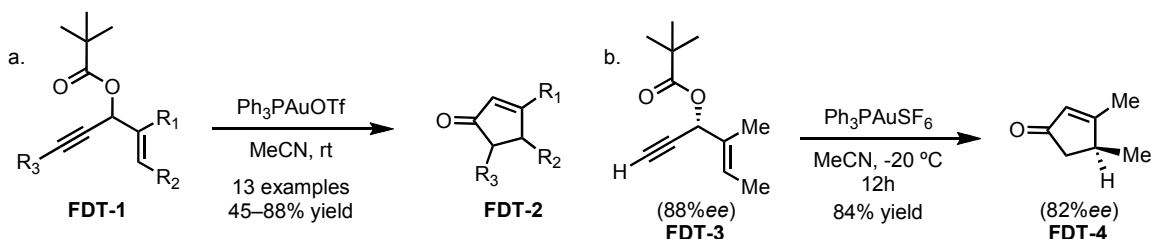
12 Selected recent examples: a) Zeldin, R. M.; Toste, F. D. *Chem. Sci.* **2011**, 2, 1706. b) Gonzalez, A. Z.; Benitez, D.; Tkatchouk, E.; Goddard III, W. A.; Toste, F. D. *J. Am. Chem. Soc.* **2011**, 133, 5500. c) Sethofer, S. G.; Staben, S. T.; Hung, O. Y.; Toste, F. D. *Org. Lett.* **2008**, 10, 4315. For a review, see: d) Hashmi, A. S. K.; Rudolph, M. *Chem. Soc. Rev.* **2008**, 37, 1766, and reference herein.

13 Rautenstrauch, V. *J. Org. Chem.* **1984**, 49, 950.

14 Marco-Contelles, J.; Soriano, E. *Chem. Eur. J.* **2007**, 13, 1350.

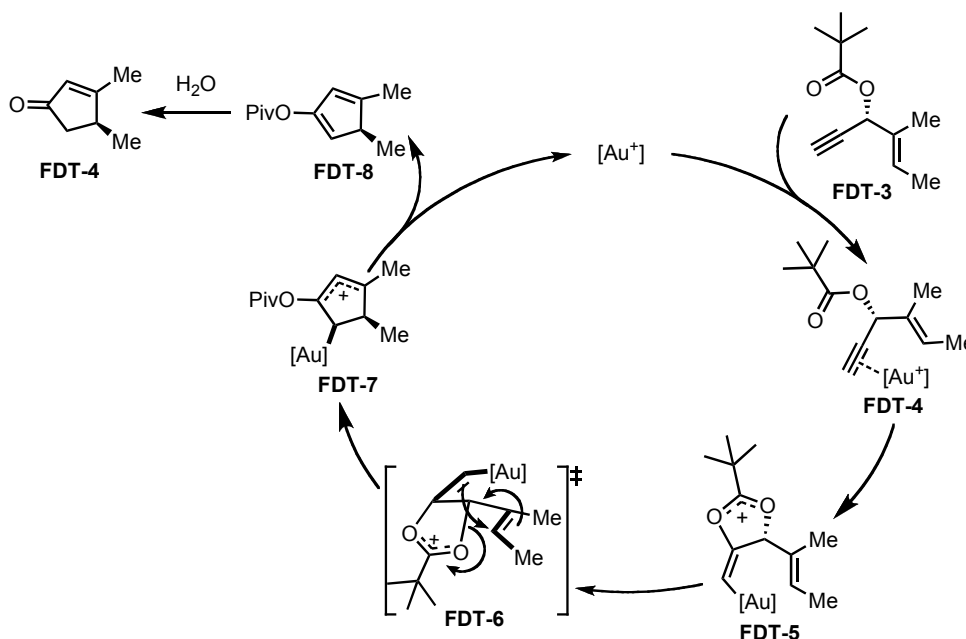
developed a stereoselective methodology using cationic Au(I) catalyst (Scheme 7.9).¹¹ The generality of reactions using $[\text{Ph}_3\text{PAu}]^+$ catalyst was demonstrated with 13 examples and the most relevant example to system is using the enantioenriched **FDT-1** (Scheme 7.9b). After making minor adjustments to the reaction conditions, such as changing the gold catalyst counterion and reduction of the reaction temperature, they were able to perform the Rautenstrauch reaction in good yield and the chiral information was transferred with 94% efficiency.

Scheme 7.9 Toste Au(I)-catalyzed cyclopentenone synthesis.



A mechanistic hypothesis that accounted for the stereochemical course of the reaction is shown in Scheme 7.10. The 1,2-addition of the ester onto the alkyne of **FDT-3** was induced by the complexation of the cationic Au(I) catalyst (**FDT-4**), which formed a cationic vinyl-gold intermediate (**FDT-5**). The stereoselectivity of the Au(I)-catalyzed cyclization could be accounted to the intramolecular cyclization that proceeded through the transition state **FDT-6**. The cyclization produced the cationic intermediate **FDT-7**, which was prone to deauration to regenerate the catalyst and cyclopentadiene **FDT-8**. Finally, the cyclopentadiene was hydrolysed to cyclopentenone **FDT-4**.

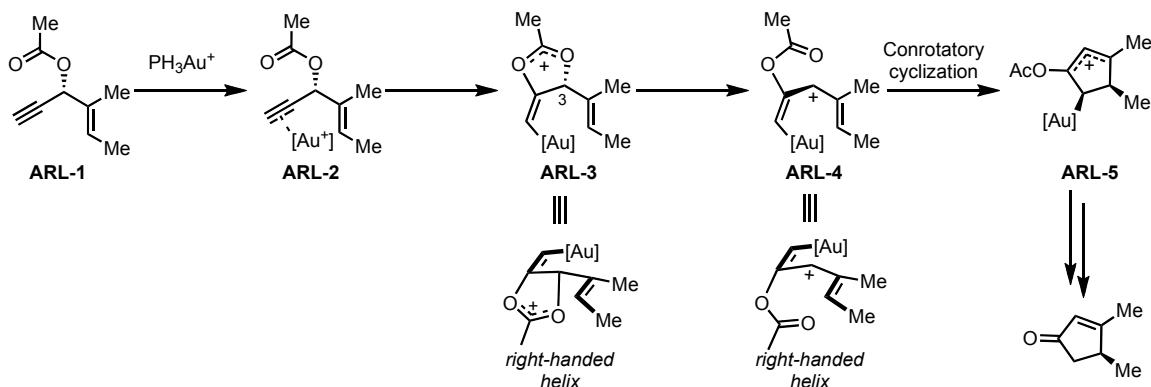
Scheme 7.10 Mechanism for the Au(I)-catalyzed cyclopentenone synthesis proposed by Toste *et al.*¹¹



The DFT evaluation of the mechanism of the Au(I)-catalyzed Rautenstrauch reaction by de Lera *et al.* resulted in a slightly different pathway, particularly in respect to the transfer of the chirality (Scheme 7.11).¹⁵ Their model studies supported most of Toste's catalytic cycle, the principal addition to the mechanism of the reaction was that the C₃-O bond is broken to form the acyclic pentadienyl cation **ARL-4** after the formation of the cyclic vinyl-gold species **ARL-3**. The chiral information of **ARL-1** would have been transferred to the helicity of **ARL-3** and preserved in **ARL-4**. The interconversion between the helices was determined to be higher than the pathway leading to the formation of the cationic cyclopentene intermediate **ARL-5**.

15 Nieto Faza, O.; López, C. S.; Álvarez, R.; de Lera, A. R. *J. Am. Chem. Soc.* **2006**, *128*, 2434.

Scheme 7.11 Mechanism of the Au(I)-catalyzed cyclopentenone synthesis evaluated by DFT proposed by de Lera *et al.*

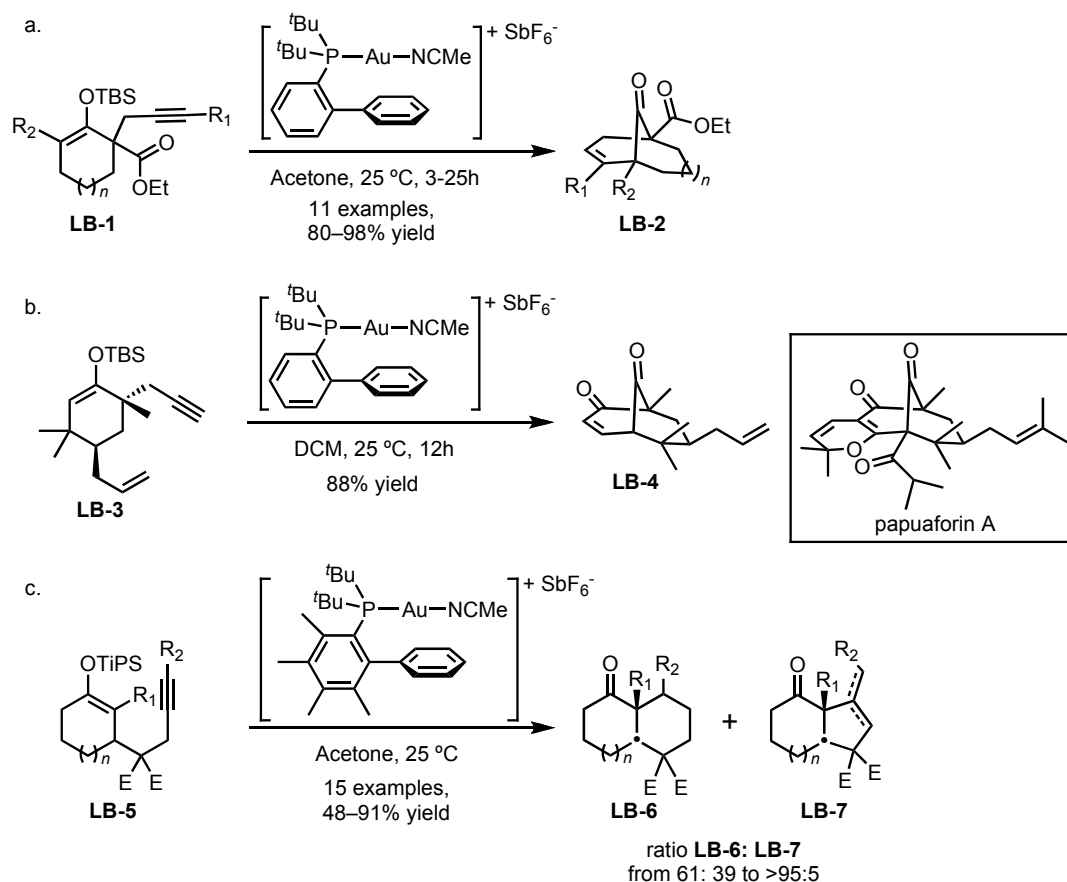


7.3.2 Gold(I) catalyzed 5-*exo-dig* cyclization

In recent years, our group has developed interest in the formation of carbon-bridged medium-sized rings and fused bicycles using gold(I)-catalysis (Scheme 7.12).¹⁶ One of the principal challenges to address was associated with executing 6-*endo-dig* cyclizations instead of the more easily accessible 5-*exo-dig* cyclizations. However, in the context of our to ginkgolide C approach, we envisioned employing a 5-*exo-dig* cyclization to assure the formation of the spiro[4.4]nonane core. To demonstrate the applicability of gold(I)-catalyzed 5-*exo-dig* cyclizations, we selected two recent examples of these reactions employed in the context of total syntheses as well as an example of the formation of spirobicyclic systems.

16 Selected examples: a) Barabé, F.; Bétournay, G.; Bellavance, G.; Barriault, L. *Org. Lett.* **2009**, *11*, 4236. b) Sow, B.; Bellavance, G.; Barabé, F.; Barriault, L. *Beilstein J. Org. Chem.* **2011**, *7*, 1007. c) Barabé, F.; Levesque, P.; Korobkov, I.; Barriault, L. *Org. Lett.* **2011**, *13*, 5580.

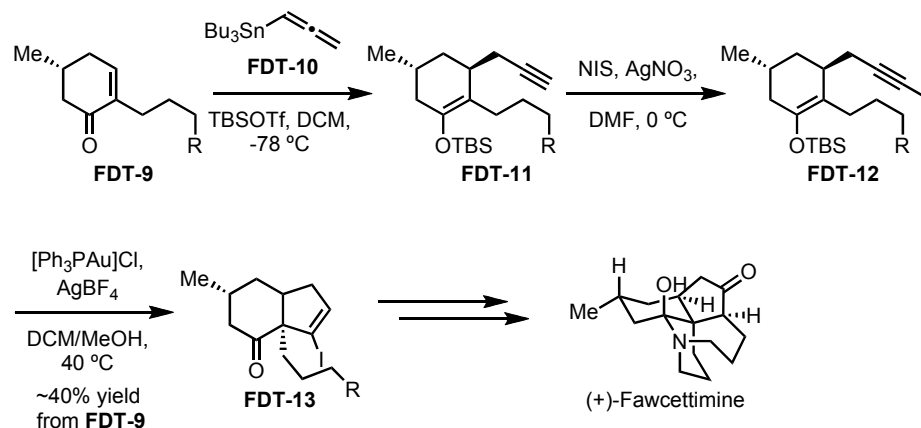
Scheme 7.12 Group precedents on the gold(I)-catalyzed formation of carbon-bridged and fused bicyclic systems.



The first example of the use of a gold(I)-catalyzed 5-*exo-dig* cyclization we selected was from the synthesis of (+)-fawcettimine by Toste *et al.* in 2007.¹⁷ The key sequence of reactions is presented in Scheme 7.13. They began with 1,4-addition of allenyltributylstannane (**FTD-10**) to the enone **FDT-9**, followed by the iodination of the terminal alkyne **FDT-11**. From this intermediate, the key gold(I)-catalyzed cyclization was performed to afford product **FDT-13** in ~40% over these three steps (average of ~74% yield per step). For the cyclization, it is important to emphasize that a quaternary carbon center was formed adjacent to a ketone and an iodide, this underlines the remarkable capacity of gold catalyst to access highly strain systems under mild conditions (40 °C).

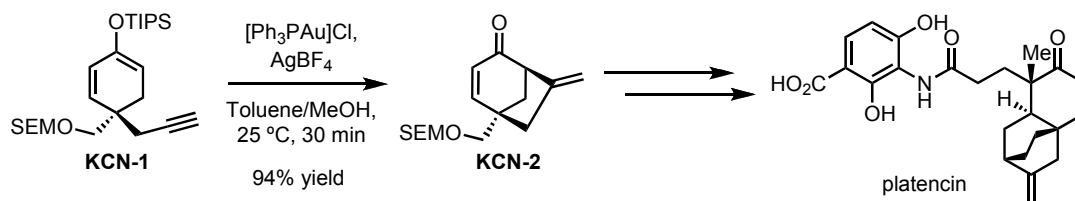
17 Linghu, X.; Kennedy-Smith, J. J.; Toste, F. D. *Angew. Chem. Int. Ed.* **2007**, 46, 7671.

Scheme 7.13 Key sequence of steps of the synthesis of (+)-fawcettimine by Toste *et al.*¹⁷



The second example we selected was from the synthesis of platencin by Nicolaou *et al.* in 2008.¹⁸ In the early stage of the synthesis, the gold(I)-catalyzed cyclization was performed on diene **KCN-1** at ambient temperature and yielded the [3.1.2]-bicyclic intermediate **KCN-2** (94%) in just 30 minutes.

Scheme 7.14 Gold(I)-catalyzed 5-*exo-dig* cyclization step in the synthesis of platencin by Nicolaou *et al.*



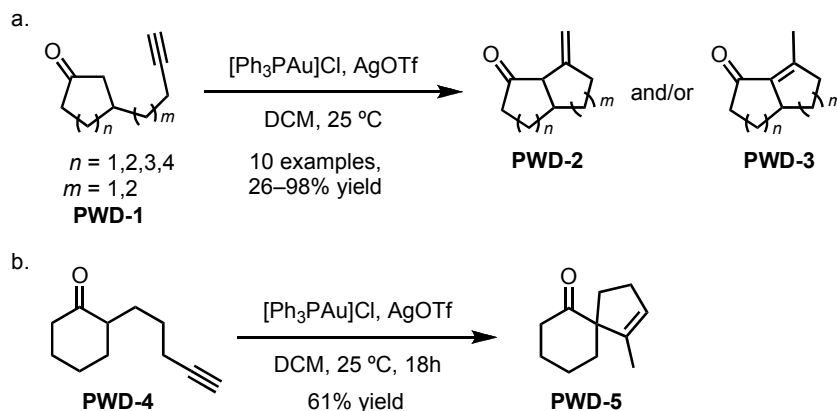
In 2010, Davies *et al.* reported the gold-catalyzed cycloisomerisation reaction of keto-alkynes at ambient temperature (Scheme 7.15).¹⁹ They reported a series of examples where they formed fused and spiro bicyclic compounds through either 5-*exo-dig* or 6-*exo-dig* cyclizations. Moreover, under those conditions, the *exo*-cyclic olefin obtained

18 Nicolaou, K. C.; Tria, G. S.; Edmonds, D. J. *Angew. Chem. Int. Ed.* **2008**, 47, 1780.

19 Davies, P. W.; Detty-Mambo, C. *Org. Biomol. Chem.* **2010**, 8, 2918.

from the *exo-dig* cyclization readily isomerized to either form a more stable (more substituted) alkene or to become conjugated with the ketone.

Scheme 7.15 Keto-alkynes gold(I)-catalyzed 5-*exo-dig* and 6-*exo-dig* cyclizations.



7.4 Efforts toward the preparation of the spirobicyclic core of *Ginkgolide C*

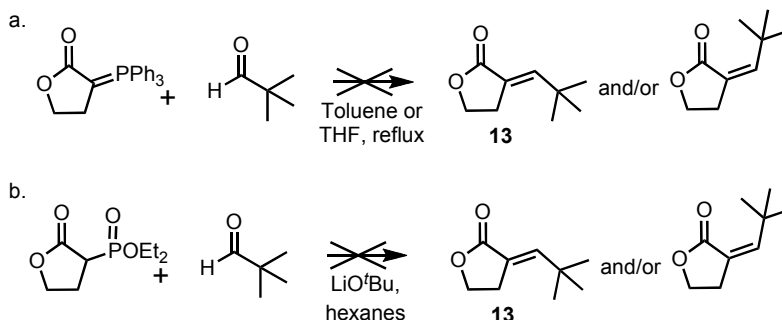
Herein we present our efforts toward the concise preparation of the spirocyclic core of ginkgolide C.

7.4.1 Preparation of enone **11**

The synthesis of **11** was envisioned to start by the formation of enone **13** from γ -butyrolactone (**14**). The initial strategy to obtain the olefin *E* conformation was either the Wittig or the Horner-Wadsworth-Emmons (HWE) olefination reactions (Scheme 7.16). When tested, the Wittig reaction did not yield any products. On the other hand, the HWE resulted in a 1.6: 1 mixture of *E*: *Z* olefins in 46% yield. Some attempts to improve the ratio of products and yield were undertaken, but they were quickly abandoned in favor of a more efficient approach. Instead, we planned to obtain **13** from an aldol reaction followed by a dehydration. We believed that the steric encumbrance between of the *tert*-

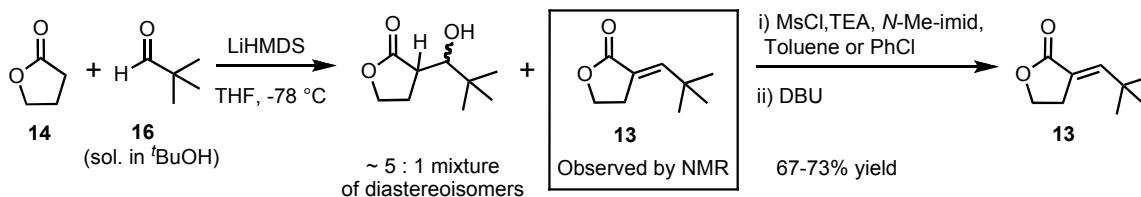
butyl and the carbonyl groups would favor the desired geometry of the olefin during the dehydration step.

Scheme 7.16 Initial attempts to prepare enone **13**.



Following a literature precedent on a similar substrate,²⁰ γ -butyrolactone (**14**) was first treated with lithium hexamethyldisilazide (LiHMDS) in THF at $-78\text{ }^{\circ}\text{C}$ followed by the addition of trimethylacetaldehyde (**16**) as a *tert*-butanol solution. From the NMR of the crude mixture, we observed $\sim 5:1$ mixture of diastereoisomers and small amounts of **13**. The mixture of alcohols were then transformed into mesylate groups and treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to form **13** in $\sim 70\%$ yield as the sole isomer observed. The geometry of the olefin was proven by nOe. Even if this sequence was relatively efficient, the observation of the desired elimination product in the first step suggested that we could obtain **13** in a single step.

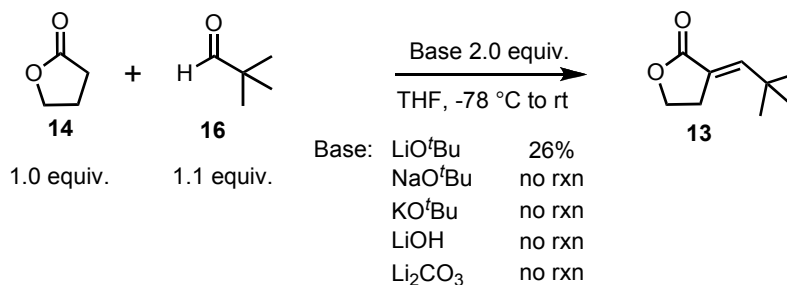
Scheme 7.17 Preparation of **13** by an aldol/dehydration sequence.



20 Choi, Y.; Pu, Y.; Peach, M. L.; Kang, J.-H.; Lewin, N. E.; Sigano, D. M.; Garfield, S. H.; Blumberg, P. M.; Marquez V. E. *J. Med. Chem.* **2007**, 50, 3465.

Before starting the optimization of the reaction conditions, we reasoned that we could replace the LiHMDS by a *tert*-butanoate base since the aldehyde **16** we employed was kept in a *tert*-butanol solution. Also, the pK_a of the corresponding conjugated acids were fairly close, 30 *vs.* 32 for HMDS and *tert*-butanol, respectively. Consequently, we surveyed the most common *tert*-butoxide bases (Scheme 7.18). Surprisingly, only lithium *tert*-butoxide yielded **13** in 26% and both the sodium and potassium analogs did not give any product. In fact, we were initially expecting to observe the opposite trend of reactivity for the different bases. We had incorrectly reasoned that a less coordinating metal, such as K⁺, would accelerate the proton transfers between all the reactants. Moreover, the nature of the base itself was also important, since both lithium hydroxide and carbonate base did not give any products.

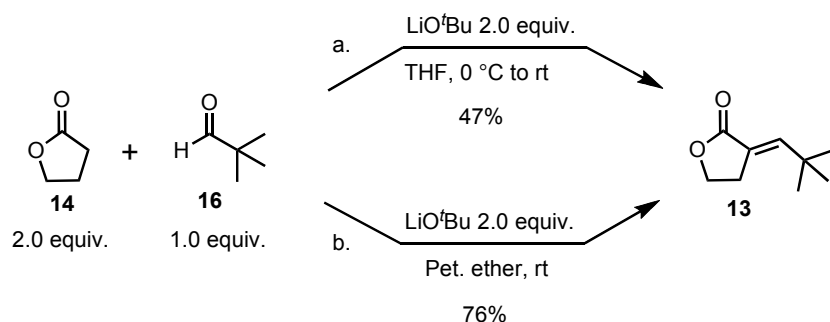
Scheme 7.18 Optimization of the base for the domino adol/dehydration sequence.



The domino adol/dehydration reaction was further improved by adjusting the stoichiometry of the reactants. It was found that the use of an excess of **14** and LiO^tBu, two equivalents each, and performing the reaction at 0 °C to ambient temperature nearly doubled the yield of the reaction (47%, Scheme 7.19a). An evaluation of solvents revealed that petroleum ether efficiently promoted the formation of **13**. Actually, the use of petroleum ether had many advantages over the use of other solvents, for instance: the deprotonated γ -butyrolactone left at the end on the reaction could be removed from the mixture simply by filtration, avoiding a work-up procedure, and product **13** was purified by an easy Krugelrohr distillation to remove traces of the starting γ -butyrolactone left in

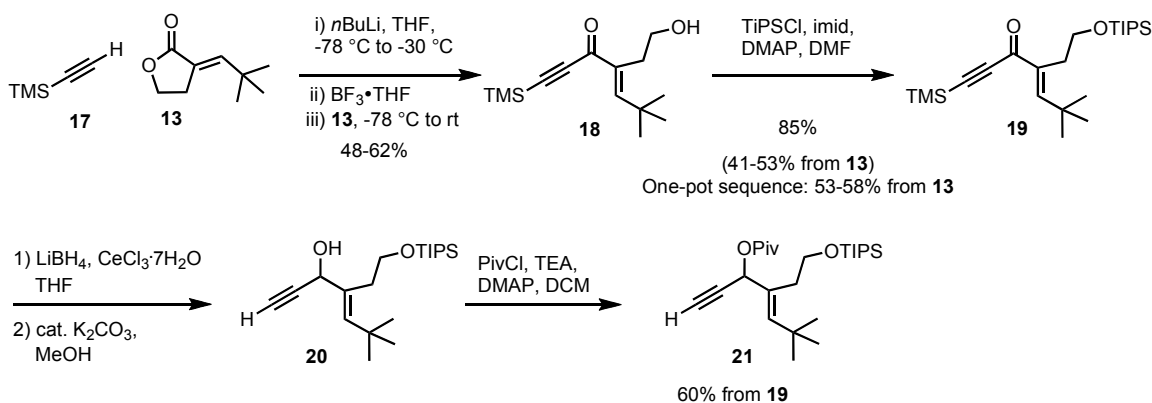
reaction (Scheme 7.19b). From this simple procedure, **13** could reproducibly be obtained in 76 % yield.

Scheme 7.19 Optimization of the stoichiometry, reaction temperature and solvent for the domino aldol/dehydration sequence.



The lactone **13** was then mono-alkylated using TMS-protected acetyltrifluoroborate lithium salts following a literature procedure (Scheme 7.20).²¹ The resulting primary alcohol **21** was then protected with triisopropylsilyl chloride to give **19** in an overall yield of 41–53% for the two steps. However, the overall yield of the sequence could be increased to 53–58% yield if the alcohol **18** was employed crude in the subsequent protection step.

Scheme 7.20 Preparation of the Rautenstrauch precursor **21**.



21 Doudsky, J.; Streinz, L.; Leseticky, L.; Koutek, B. *Synlett* **2003**, 937.

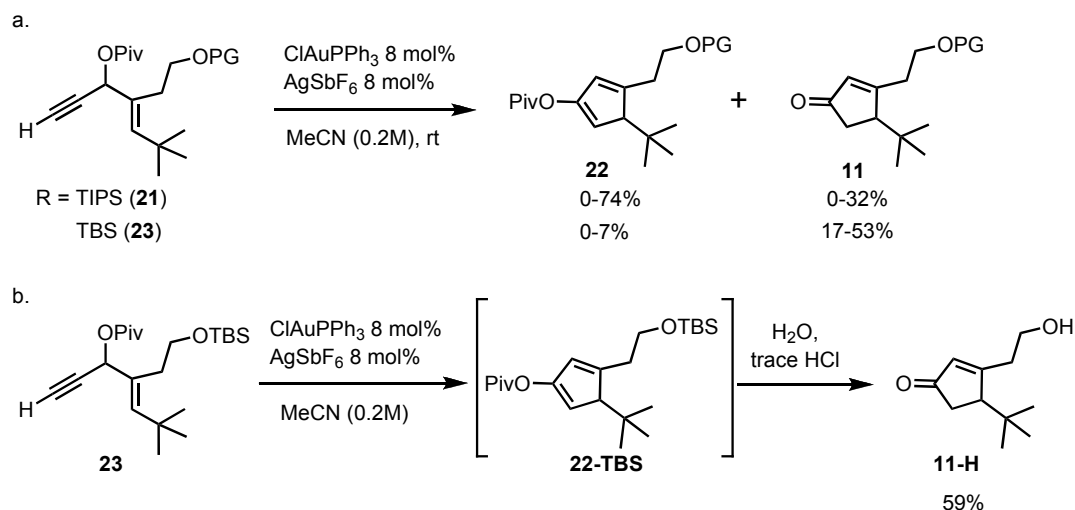
The ketone **19** was then selectively reduced using lithium borohydride in combination with cerium(III) chloride heptahydrate in THF. Then, the resulting crude enyne–alcohol was dissolved in methanol and treated with a catalytic amount of potassium carbonate to efficiently remove the TMS protecting group to afford **20**. The alcohol was then protected as a pivaloate ester (**21**). Starting with **19**, the overall yield for the three steps was 60%. It was noted that for the reduction of **19**, the use of standard Luche conditions (i.e. in methanol) resulted in the rapid cleavage of the TMS protecting followed by a double 1,4-addition of methanoate anion onto the terminal ynone.

The Corey-Bakshi-Shibata-catalyzed asymmetric reduction²² of **19** was attempted under various conditions, however all attempts failed. We observed that for reactions performed at temperature higher than -30 °C only decomposition products were obtained. However, reactions performed at lower temperature were too slow to be of any use. This issue should be addressed in future studies.

The racemic mixture of **21** is then ready to undergo the first key gold-catalyzed Rautenschtrauch reaction.¹³ The treatment of **21** with triphenylphosphinegold(I) hexafluoroantimonate in acetonitrile at ambient temperature resulted in the formation of the diene **22** in 78% yield. Further repetitions of this reaction revealed some reproducibility issues associated with the preparation of the cationic gold(I) catalyst. We later found that the presence of a catalytic amount of acid and sufficient quantity of water provided the desired enone **11** in 32% yield. Even though we added water, the reproducibility problems persisted and seemed related to the lability of the silyl protecting group (Scheme 7.21b). The reaction yields were even less reproducible when the more labile TBS protecting group (**23**) was used. These results are still preliminary, a re-optimization of this transformation was undertaken and included the use of other protecting groups.

22 a) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925. For a review on the subject, see: b) Corey, E. J. *Angew. Chem. Int. Ed.* **2009**, *48*, 2.

Scheme 7.21 Initial attempts to perform the Rautenschtrauch reaction.



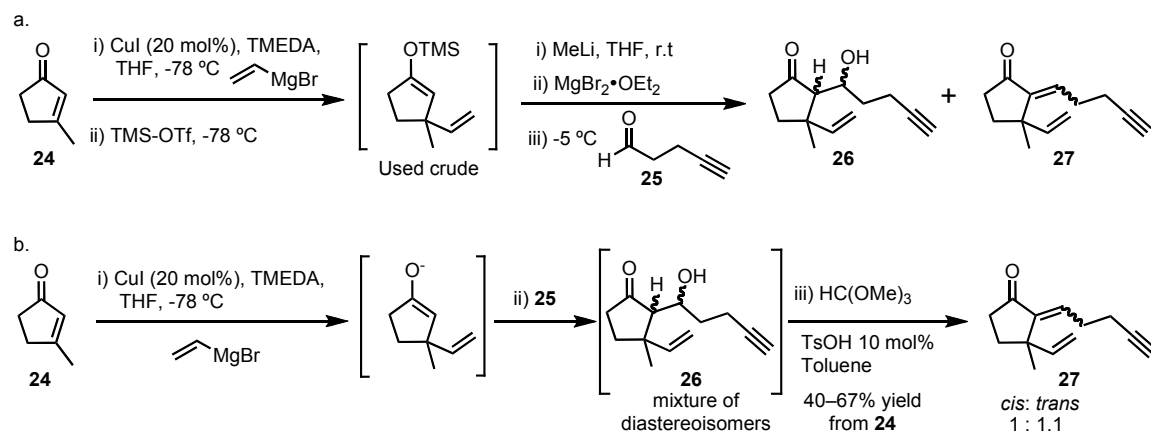
Even though, we were having problems with the Rautenschtrauch reaction, in the meantime, we sought to take a look at the next sequence of steps to test the gold(I)-catalyzed 5-*exo-dig* cyclization. From the beginning, we knew that this sequence also contained some significant challenges, such as the tandem conjugate addition and the enolate capture with an electrophile at the position adjacent to the quaternary center. The following section describes our efforts on the development of this reactions sequence with a model substrate.

7.4.2 Model studies for the 5-*exo-dig* cyclization

To order to develop an efficient route of the formation of the spiro[4.4]nonane core common to the ginkgolide family, we selected the commercially available 3-methylcyclopent-2-enone (**24**) as a model substrate. Initially, our strategy was to perform the conjugate addition on **24** with vinyl magnesium bromide using a copper(I) catalyst and to trap the enolate with TMS-Cl. We tested a variety of copper(I) catalysts, such as: CuI, Cu(PnBu₃), CuBr·DMS, and additives, including: BF₃·THF and HMPA. The procedure that eventually yield the desired silyl-enol ether was to use 20 mol% of CuI, an excess of TMEDA (3.0 equiv.) dissolved in THF at ambient temperature, then the solution was cooled to -78 °C and vinyl magnesium bromide was added followed by a

slow addition of **24** (Scheme 7.22a).²³ When the reaction was judged completed according to TLC analysis, TMS-triflate was added to the solution to trap the enolate. Following the aqueous work-up, the crude silylenol ether was sequentially treated with a methyllithium solution, dry magnesium bromide and the aldehyde **25**. From the mixture of products we isolated after flash chromatography, we identified diastereoisomers of alcohol **26** and the two isomers of alcohol elimination (**27**). Since too many inseparable products were obtained, we have not recorded the yield of this sequence of reactions. Nonetheless, we rapidly realized that we could perform in one-pot sequence and include an orthoformate promoted dehydration reaction at the end (Scheme 7.22b). From this sequence, we efficiently obtained a *cis/trans* mixture of enones **27** in 40–67% yield from **24**.

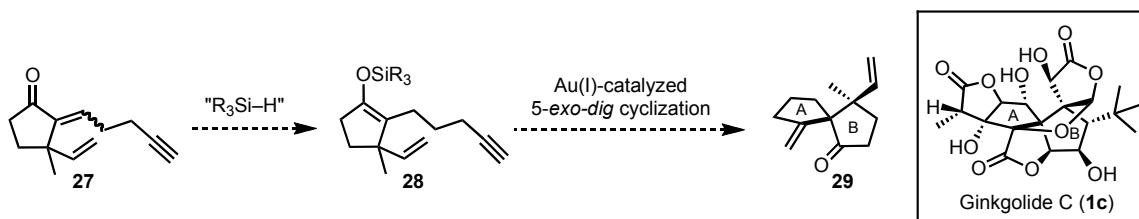
Scheme 7.22 Model studies on the development of the conjugate addition and the enolate C-alkylation sequence.



With the mixture of enones **27** in hand, the next step was to prepare the silyl enol ether preceding the gold catalyzed 5-*exo-dig* cyclization (Scheme 7.23). Even though we found many relevant literature precedents, our efforts to perform a 1,4-hydrosilylation were unsuccessful. Below is an account of the conditions we tried and the alternatives we are considering.

23 Smith, A. B. III; Nolen, E. G. Jr.; Shirai, R.; Blase, F. R.; Ohta, M.; Chida, N.; Hartz, R. A.; Fitch, D. M.; Clark, W. M.; Sprengeler, P. A. *J. Org. Chem.* **1995**, 60, 7837.

Scheme 7.23 Proposed sequence to prepare the spiro[4.4]bicyclic core of ginkgolide C with a model system.



The hydrosilylation of the *trans* isomer of enone **27** was attempted both as a stepwise and one step process. The reduction of the enone, to form **30**, was first tried using a more reactive variant of Stryker's conditions²⁴ using polymethylhydrosiloxane (PMHS) and *tert*-butanol in toluene with a copper–bidentate ligand catalyst, developed by Lipshutz.²⁵ Under those conditions, no reaction was observed even after an extended period of time (Scheme 7.24a). Using two variations of Stryker's conditions to form directly **28**, we were still unable to obtain any reactivity (Scheme 7.24b, entries 1 and 2).^{25,26} When we performed the hydrosilylation reaction using a rhodium catalyst (Scheme 7.24b, entry 3),²⁷ the formation of **31** suggested that the issue we were facing with the enone **27** might be due to the presence of the triple bond. Without surprise, the rhodium-catalyzed hydrosilylation proved that the metal catalysts preferably interacted with the alkyne rather than the enone.²⁸

24 Mahoney, W. S.; Brestensky, D. M.; Stryker, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 291.

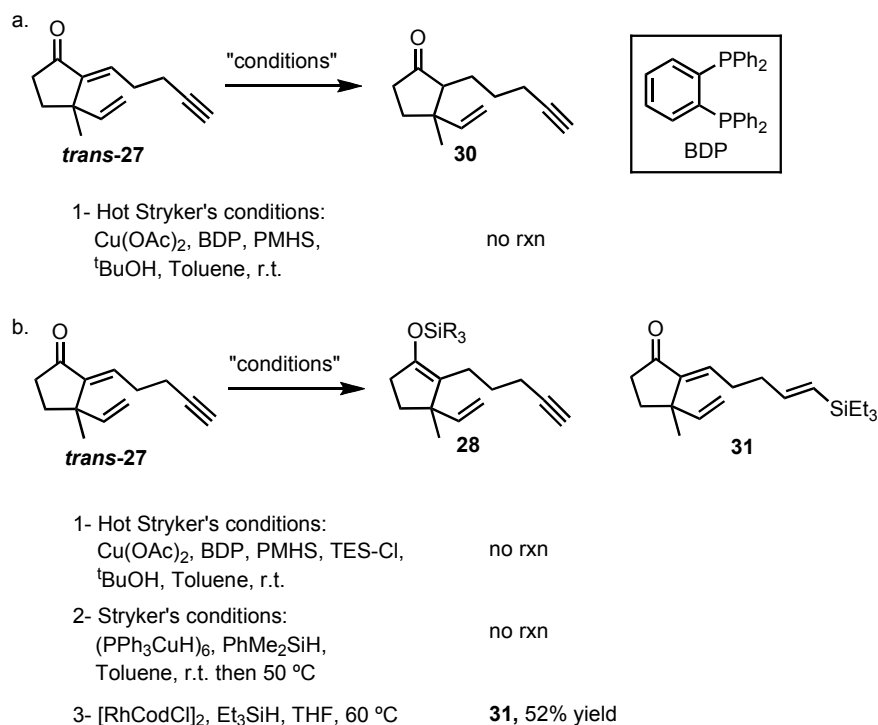
25 Baker, B. A.; Boskovic, Z. V.; Lipshutz, B. H. *Org. Lett.* **2008**, *10*, 289.

26 Lipshutz, B. H.; Chrisman, W.; Noson, K.; Papa, P.; Sclafani, J. A.; Vivian, R. W.; Keith, J. M. *Tetrahedron* **2000**, *56*, 2779.

27 Mori, A.; Kato, T. *Synlett* **2002**, 1167.

28 Both reactions were already known, but to the best of our knowledge they have never been tested simultaneously, see: Sanadaa, T.; Kato, T.; Mitani, M.; Mori, A. *Adv. Synth. Catal.* **2006**, *348*, 51.

Scheme 7.24 Hydrosilylation of enone **27**.



To solve this issue of catalyst poisoning, we envisaged a couple of alternative routes to get to the spiro[4.4]bicyclic core of ginkgolide C. Initially, we considered employing a surrogate of the alkyne, such as an protected alcohol, but this path had the disadvantage of adding unproductive steps to the synthesis: alcohol deprotection, oxidation to the aldehyde and Corey-Fuchs reaction. The potential solution we decided to try was to change the key 5-*exo-dig* cyclization by a 5-*endo-dig* cyclization by removing one carbon in the side chain. If it worked, this approach had the advantage of installing the appropriate functional groups present in the final target by a one-pot Rubottom oxidation and Tamao-Fleming oxidation to form **37** (Scheme 7.25).²⁹

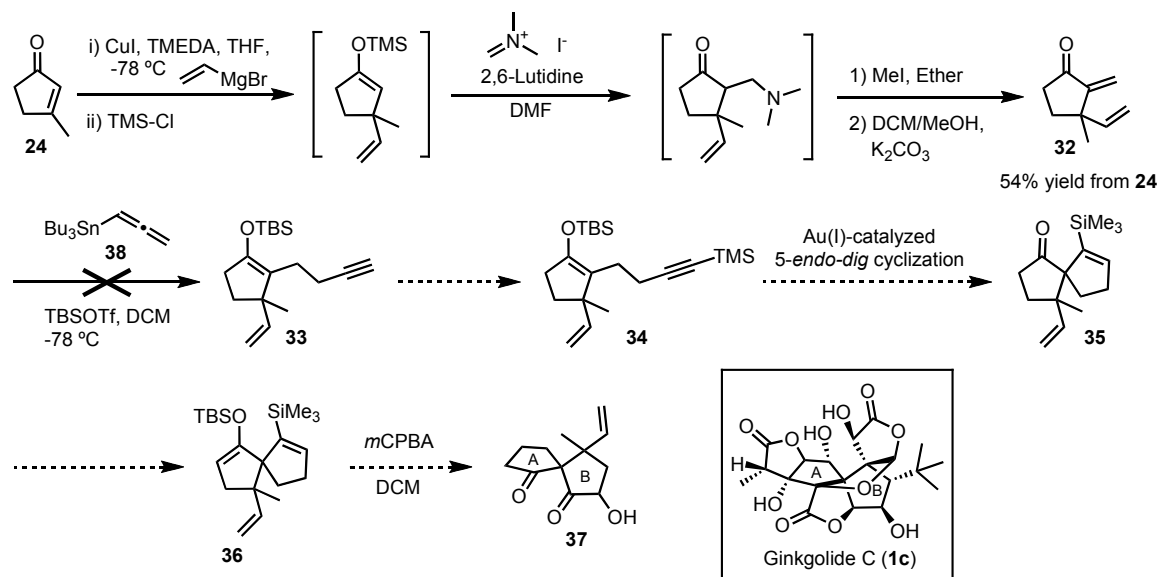
We followed a known procedure to prepare the *exo*-cyclic enone **32** from **24**.^{23,30} The first time we performed this reaction, **32** was isolated in 54% yield. The following

29 For a review on the oxidation of C–Si bonds, see: a) Jones, G. R.; Landais, Y. *Tetrahedron* **1996**, 52, 7599. For seminal publications, see: b) Rubottom, G. M.; Vasquez, M. A.; Pelegrina, D. R. *Tetrahedron*, **1974**, 4319. c) Tamao, K.; Kumada, M.; Maeda, K. *Tetrahedron Lett.* **1984**, 25, 321.

30 Iimura, S.; Overman, L. E.; Paulini, R.; Zakarian, A. *J. Am. Chem. Soc.* **2006**, 128, 13095.

reaction was a TBS-triflate promoted conjugate addition of allenyltributylstannane **38** to **32**.^{17,31} Unfortunately, in our initial and only attempt we only obtained what appeared to be oligomers of **32**. Due to time constraints associated with the redaction of this thesis, our efforts will be reported after its submission.

Scheme 7.25 5-*Endo-dig* cyclization approach to the spiro[4.4]bicyclic core.

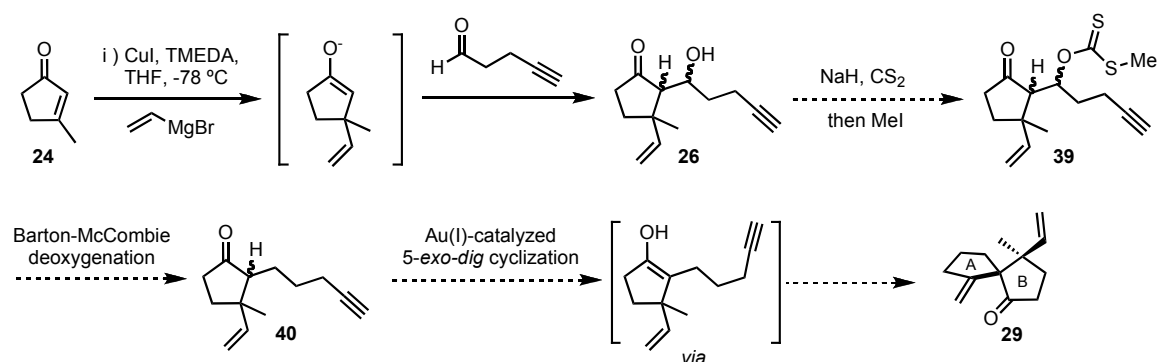


In the event that this alternative route also fails, alcohol **26** could be treated with carbon disulfide (CS_2) and iodomethane to form the xanthate derivative **39** (Scheme 7.26). The Barton-McCombie deoxygenation reaction³² would then yield the ketone **40**, and we have seen in section 7.3.2, examples of gold-catalyzed 5-*exo-dig* from ketones that proceeded *via* the enol tautomer (see Scheme 7.15b).¹⁹ This sequence of reactions would avoid having to deal with the hydrosilylation of the enone in presence of an alkyne. Furthermore, if the cyclization does not work with the ketone, the thermodynamic silyl enol ether could be prepared instead.

31 Haruta, J.; Nishi, S. Matsuda, S.; Akai, S.; Tamaura, Y.; Kita, Y. *J. Org. Chem.* **1990**, 55, 4853.

32 Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.

Scheme 7.26 Proposed Barton-McCombie approach to the spiro[4.4]nonane core.



7.5 Conclusion

In this chapter was presented our strategy toward the total synthesis of ginkgolide C that included two gold(I)-catalyzed reactions as key steps in the preparation of the spiro[4.4]nonane core. We have included short reviews of the syntheses of ginkgolide B by the groups of Corey and Crimmins to illustrate the challenges associated with these family of natural products. We also presented relevant examples to support the feasibility of the targeted gold(I)-catalyzed transformations.

For the synthesis itself, we have presented a robust sequence of reactions to prepare the precursor of the Rautenschtrauch reaction (**21**), though we still have issues with the asymmetric reduction of ketone **19**. We have showed that the gold(I)-catalyzed Rautenschtrauch reaction was compatible with our substrate, although reproducibility problems will require some optimization of the reaction conditions. Using commercially available 3-methylcyclopent-2-enone (**24**) as a model substrate, we have developed the conditions to perform a 1,4-conjugate addition of vinyl magnesium bromide followed by an aldol reaction and elimination sequence to afford the enones **27**. While our efforts to

perform the hydrosilylation on the enone were unsuccessful, we have proposed alternative routes to get to the precursor of the *5-exo-dig* cyclization. Future studies should explore those possible solutions in depth.

Chapter

8

Experimental Information

8.1 Organization and General Considerations

The experimental information section has been organized to coincide with the body of this thesis. Experimental procedure for all new compounds, as well as the procedures that were adapted from literature precedent are included. All spectra data (^1H , ^{13}C , ^{19}F , ^{31}P NMR, IR, R_f , HRMS and MP) are included for all newly reported compounds. References for known compounds for which their syntheses were done from literature precedents are found within this section where the chemistry is described.

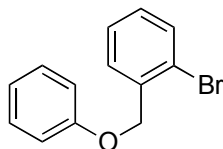
^1H , ^{13}C , ^{19}F , ^{31}P NMR spectra were recorded using Bruker Avance 300 MHz or 400 MHz spectrometers. High-resolution mass spectra were obtained on a Kratos Concept IIIH mass spectrometer. Infrared analysis was performed with a Bruker EQUINOX 55 Fourier-Transform IR spectrometer. Palladium sources and phosphine ligands were stored in the desiccator and were weighed to air. Unless otherwise stated, all other reagents and solvents were used without further purification.

Utilization of Additives in the Development of Mild and Efficient Reactions
Conditions for the Intramolecular Direct Arylation of Simple Arenes

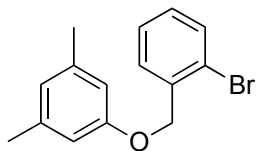
8.2 Chapter 2: Utilization of Additives in the Development of Mild and Efficient Reactions Conditions for the Intramolecular Direct Arylation of Simple Arenes

General Procedure for the preparation of starting materials:

The appropriate phenol, K_2CO_3 (3 equiv.), NaI (0.10 equiv.) and 2-halobenzylbromide (or 2-halobenzylchloride) were placed in a round bottom flask equipped with a refluxed condenser. Reagent grade acetone (0.5 M) was added and the reaction was refluxed overnight. The reaction was allowed to cool and was extracted using Et_2O/H_2O . The organics were dried using $MgSO_4$, filtered and the volatiles were evaporated under reduced pressure. The residues were then purified *via* silica gel column chromatography using Et_2O /hexanes mixtures.



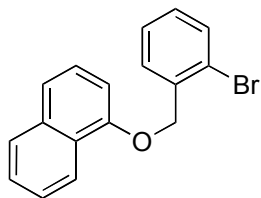
1-Bromo-2-(phenoxymethyl)benzene (1a): The compound was prepared according to the general procedure and exhibited spectral data identical to previous reports (93%).¹



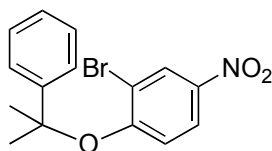
1-((3,5-Dimethylphenoxy)methyl)-2-bromobenzene (1b): The compound was prepared according to the general procedure (97%) and exhibited spectral data identical to previous reports.¹ R_f = 0.31 (5% ether/hexane); 1H NMR (400MHz, $CDCl_3$, 293K, TMS): 2.29 (6H, s), 5.08 (2H, s), 6.62 (3H, s), 7.16 (1H, td, J = 1.8, 7.5 Hz), 7.32 (1H, td, J = 1.2, 7.5 Hz), 7.58-7.53 (2H, m); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 21.5, 69.1, 112.5,

¹ Ames, D.E.; Opalko, A. *Tetrahedron* **1984**, 40, 1919.

122.2, 123.0, 127.5, 128.8, 129.1, 132.5, 136.5, 139.3, 158.0; **IR** ($\nu_{\max}/\text{cm}^{-1}$): 2917, 1595, 1322, 1154; **HRMS** calculated for $\text{C}_{15}\text{H}_{15}\text{OBr}$ (M^+): 290.0306, Found: 290.0324.



1-(2-Bromo-benzyloxy)-naphthalene (1c): The compound was prepared according to the general procedure (91%) and exhibited spectral data identical to previous reports.¹ R_f = 0.55 (5% EtOAc/hexanes); **^1H NMR (400MHz, CDCl_3 , 293K, TMS):** 5.33 (2H, s), 6.89 (1H, d, J = 8.0 Hz), 7.24 (1H, d, J = 3.0 Hz), 7.38 (2H, m), 7.49 (3H, m), 7.62 (1H, d, J = 8.0 Hz), 7.69 (1H, d, J = 8.0 Hz), 7.82 (1H, m), 8.38 (2H, m); **^{13}C NMR (100MHz, CDCl_3 , 293K, TMS):** 69.5, 105.4, 120.8, 122.3, 125.3, 125.7, 125.8, 126.5, 127.5, 127.6, 128.7, 129.2, 129.2, 132.6, 134.6, 136.4, 154.0; **IR** ($\nu_{\max}/\text{cm}^{-1}$): 2924, 1364, 1246, 1096; **HRMS** calculated for $\text{C}_{17}\text{H}_{13}\text{OBr}$ (M^+): 312.0046, Found: 312.0150.

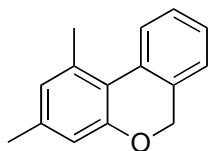


1-(2-(2-Bromo-5-nitrophenoxy)propan-2-yl)benzene (1e): To a flask containing a suspension of potassium hydride (0.27 g, 2.0 mmol, 1.1 equiv.) in THF (3 mL) at 0 °C was added slowly the 2-phenylpropan-2-ol (0.4g, 2.0mmol, 1.1 equiv.) and the solution was stirred for 10mins. This solution was then added slowly to a solution of 2-bromo-1-fluoro-4-nitrobenzene (0.4 g, 1.8 mmol, 1.0 equiv.) in THF (9 mL) at 0 °C. The solution was then allowed to warm to room temperature and was stirred for an additional 2 hours. Saturated aqueous ammonium chloride was then added and the solution was extracted with DCM and dried over magnesium sulfate. The product was then purified by column chromatography on silica gel using 5% ether/hexanes as the eluant. (83%): R_f = 0.30 (5% ether/hexane); **^1H NMR (400MHz, CDCl_3 , 293K, TMS):** 1.85 (6H, s), 6.36 (1H, d, J = 9.2 Hz), 7.28–7.41 (5H, m), 7.80 (1H, dd, J = 9.2, 2.8 Hz), 8.42 (1H, d, J = 2.8Hz); **^{13}C NMR (100MHz, CDCl_3 , 293K, TMS):** 29.3, 83.9, 114.5, 116.8, 123.4, 124.9, 127.8,

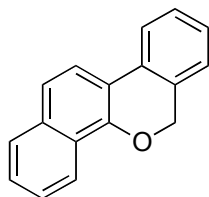
128.9, 128.9, 141.0, 144.1, 158.4; **IR** ($\nu_{\max}/\text{cm}^{-1}$): 2984, 1516, 1473, 1341, 1275, 1138; **HRMS** calculated for $\text{C}_{15}\text{H}_{14}\text{O}_3\text{NBr}$ (M^+) 335.0157; found: 335.0105.

General Cyclization Procedure:

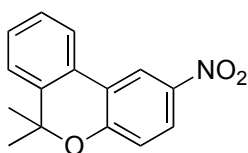
K_2CO_3 (1.7mmol, 3.0eq.), $\text{Pd}(\text{OPiv})_2$ (0.03, 0.05 equiv.), $\text{P}(p\text{-FPh})_3$ (0.03, 0.05 equiv.) and pivalic acid (0.17mmol, 0.3 equiv.) were weighed to air and placed in a screw capped vial (4 mL) with a magnetic stir bar. The reaction vessel was purged with argon for ~5 minutes. The cyclization precursor (0.57 mmol, 1.0 equiv.) was then added to the reaction vessel as a solution in *N,N*-dimethylacetamide (3 mL). The reaction was heated to indicate temperature for 12 hours. Upon completion, the reaction was cooled to room temperature. The products were loaded directly onto a silica gel packed column and eluted using ether/hexane mixtures.



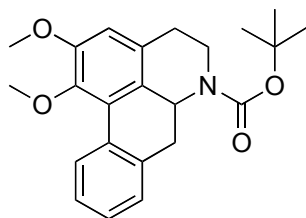
1,3-Dimethyl-6H-benzo[c]chromene (2b): The compound was prepared according to the general cyclization procedure but the reaction was performed at 60°C (96%) and exhibited spectral data identical to previous reports.¹ **Mp** = 82–83°C (CHCl_3); **R_f** = 0.29 (3% ether/hexanes); **¹H NMR (400MHz, CDCl_3 , 293K, TMS):** 2.31 (3H, s), 2.64 (3H, s), 4.92 (2H, s), 6.75 (2H, d, J = 9.3 Hz), 7.20–7.29 (2H, m), 7.36 (1H, td, J = 1.2, 7.5 Hz), 7.73 (1H, d, J = 7.8 Hz); **¹³C NMR (100MHz, CDCl_3 , 293K, TMS):** 21.6, 23.0, 69.5, 115.8, 120.9, 125.2, 126.4, 126.8, 126.9, 128.2, 131.2, 133.8, 135.6, 139.1, 156.8; **IR** ($\nu_{\max}/\text{cm}^{-1}$): 2924, 1615, 1284, 1151, 1064; **HRMS** Calculated for $\text{C}_{15}\text{H}_{14}\text{O}$ (M^+): 210.1045; Found: 210.1056.



6H-Dibenzo[*c,h*]chromene (2c): The compound was prepared according to the general cyclization procedure (97%) and exhibited spectral data identical to previous reports.¹ **R_f** = 0.47 (5% EtOAc/hexane); **¹H NMR (400MHz, CDCl₃, 293K, TMS):** 5.23 (2H, s), 7.11 (1H, d, *J*= 7.0 Hz), 7.22 (1H, t, *J*= 2.0 Hz), 7.33 (1H, t, *J*= 3.0 Hz), 7.45 (3H, m), 7.65 (1H, d, *J*= 3.0 Hz), 7.75 (2H, m), 8.25 (1H, m); **¹³C NMR (100MHz, CDCl₃, 293K, TMS):** 68.7, 117.1, 120.9, 121.5, 121.9, 122.2, 124.5, 125.3, 125.7, 126.6, 127.3, 127.6, 128.5, 130.6, 130.6, 134.3, 150.2; **IR (ν_{max}/cm⁻¹):** 2870, 1395, 1351, 1096; **HRMS** Calculated for C₁₇H₁₂O (M⁺): 232.0871; Found: 232.0888.

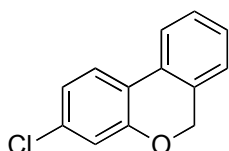


6,6-Dimethyl-2-nitro-6H-benzo[*c*]chromene (2e): The compound was prepared following the general cyclization procedure at 50 °C (94%) and exhibited spectral data identical to previous reports.¹ **Mp** = 92–95°C (ether); **R_f** = 0.23 (3% ether/hexane); **¹H NMR (400MHz, CDCl₃, 293K, TMS):** 1.67 (6H, s), 7.00 (1H, d, *J*= 8.9 Hz), 7.25–7.27 (1H, m), 7.36–7.43 (2H, m), 7.76–7.79 (1H, s), 8.10 (1H, dd, *J*= 8.9, 2.7 Hz), 8.64 (1H, d, *J*= 2.7 Hz); **¹³C NMR (100MHz, CDCl₃, 293K, TMS):** 27.9, 79.5, 118.4, 118.9, 122.4, 122.5, 123.4, 124.9, 126.3, 128.2, 129.4, 138.7, 142.2, 158.2; **IR (ν_{max}/cm⁻¹):** 2982, 1518, 1339, 1266, 1106; **HRMS** Calculated for C₁₅H₁₃O₃N (M⁺) 255.0895; found: 255.0873.

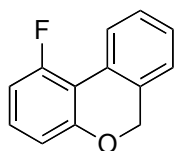


1-(1,2-Dimethoxy-4,5,6a,7-tetrahydro-dibenzoquinoline-6-carboxylic acid tert-butyl ester (2f): The compound was prepared according to the general cyclization procedure but the reaction was performed at 70 °C (70%) and exhibited spectral data identical to previous reports.¹ **R_f** = 0.57 (100% EtOAc); **mp** = 149–151 °C (CHCl₃); **¹H NMR (300MHz, CDCl₃, 293K, TMS):** 1.49 (9H, s), 2.63–3.00 (5H, m), 3.66 (3H, s), 3.89 (3H,

s), 4.41–4.44 (1H, m), 4.64–4.69 (1H, m), 6.67 (1H, s), 7.21–7.34 (3H, m), 8.44 (1H, d, $J = 7.8$ Hz); ^{13}C NMR (75MHz, CDCl_3 , 293K, TMS): 28.8, 30.7, 35.7, 38.7, 51.9, 56.2, 60.3, 80.2, 111.7, 126.8, 127.3, 127.9, 128.0, 128.4, 128.7, 130.1, 132.0, 137.3, 145.8, 152.2, 155.0; IR ($\nu_{\text{max}}/\text{cm}^{-1}$): 3070, 2930, 1687, 1406, 1249, 1163, 1106; HRMS calculated for $\text{C}_{23}\text{H}_{27}\text{NO}_4$ (M^+) 381.1940; found: 381.1943.



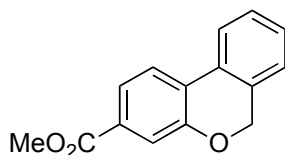
3-Chloro-6H-benzo[c]chromene (2i): The compound was prepared according to the general cyclization procedure and isolated with 1-chloro-6H-benzo[c]chromene as a minor contaminant in a 15:1 ratio (96%) and exhibited spectral data identical to previous reports.¹ $R_f = 0.28$ (3% ether/hexane); ^1H NMR (400MHz, CDCl_3 , 293K, TMS): 5.16 (2H, s), 6.99 (1H, d, $J = 2.0$ Hz), 7.08 (1H, dd, $J = 8.0, 2.0$ Hz), 7.26 (1H, d, $J = 7.5$ Hz), 7.34 (1H, td, $J = 7.5, 1.0$ Hz), 7.40 (1H, t, $J = 7.5$ Hz), 7.79 (1H, d, $J = 7.5$ Hz), 7.84 (1H, d, $J = 8.0$ Hz); ^{13}C NMR (100MHz, CDCl_3 , 293K, TMS, mixture): 70.0, 70.6, 119.0, 123.7, 123.8, 124.0, 126.6, 126.7, 126.8, 126.9, 127.9, 129.7, 130.0, 130.0, 130.5, 130.8, 131.2, 133.0, 135.7, 157.4, 159.5; IR ($\nu_{\text{max}}/\text{cm}^{-1}$): 2850, 1479, 1198, 1017; HRMS Calculated for $\text{C}_{15}\text{H}_{12}\text{O}_3$ (M^+) 240.0786; Found: 240.0789.



1-Fluoro-6H-benzo[c]chromene (2j):² The compound was prepared according to the general cyclization procedure and isolated with 3-fluoro-6H-benzo[c]chromene as a minor contaminant in a 1.2:1 ratio (93%). $R_f = 0.28$ (3% ether/hexane); ^1H NMR (400MHz, CDCl_3 , 293K, TMS): Major: 5.11 (2H, s), 6.84–6.91 (2H, m), 7.26 (1H, m), 7.32 (1H, d, $J = 7.5$ Hz), 7.36 (1H, td, $J = 1.0, 7.0$ Hz), 7.43 (1H, t, $J = 8.0$ Hz), 8.00 (1H, d, $J = 8.0$ Hz), Minor: 5.16 (2H, s), 6.75 (1H, dd, $J = 2.5, 10.0$ Hz), 6.84 (1H, m,

2 Campeau, L.-C; Parisien, M.; Jean, A.; Fagnou, F. *J. Am. Chem. Soc.* **2006**, 128, 581.

overlapping with major), 7.76 (1H, d, $J = 7.5$ Hz), 7.87 (1H, d, $J = 6.5, 9.0$ Hz), 3H complete overlap with major isomer; ^{13}C NMR (100MHz, CDCl_3 , 293K, TMS): Major only: 70.2, 111.3 (d, $J_{\text{CF}} = 22.9$ Hz), 113.9 (d, $J_{\text{CF}} = 13.3$), 115.1 (d, $J_{\text{CF}} = 3.9$ Hz), 127.6, 127.7, 128.5, 130.0, 130.4, 131.3 (d, $J_{\text{CF}} = 11.5$ Hz), 133.8, 158.7 (d, $J_{\text{CF}} = 7.6$ Hz), 162.4 (d, $J_{\text{CF}} = 247.9$); **IR** (ν_{max} / cm^{-1}): 3063, 2839, 1619, 1294, 1228; **HRMS** Calculated for $\text{C}_{13}\text{H}_9\text{OF}$ (M^+) 200.0637; Found: 200.0650.



Methyl 6H-benzo[c]chromene-3-carboxylate (2k): The compound was prepared according to the general cyclization procedure and isolated with 1-methyl-6H-benzo[c]chromene as a minor contaminant in a >30:1 ratio (92%) and exhibited spectral data identical to previous reports.¹ **Mp** = 93–94 °C (acetone); **R_f** = 0.36 (5% ether/hexane); ^1H NMR (400MHz, CDCl_3 , 293K, TMS): 3.88 (3H, s), 5.19 (2H, s), 7.29 (1H, d, $J = 7.8$ Hz), 7.39 (1H, td, $J = 7.5$ Hz, 1.0 Hz), 7.43 (1H, t, $J = 7.5$ Hz), 7.53 (1H, d, $J = 1.5$ Hz), 7.68 (1H, dd, $J = 8.5, 2.0$ Hz), 7.86 (1H, d, $J = 8$ Hz), 7.94 (1H, d, $J = 8.5$ Hz); ^{13}C NMR (100MHz, CDCl_3 , 293K, TMS): 53.4, 65.1, 69.9, 119.7, 119.8, 124.6, 127.9, 125.4, 126.8, 130.5, 130.7, 130.8, 134.0, 156.5, 167.6; **IR** (ν_{max} / cm^{-1}): 2947, 1707, 1412, 1308, 1233, 1197; **HRMS** Calculated for $\text{C}_{15}\text{H}_{12}\text{O}_3$ (M^+) 240.0786; Found: 240.0788.

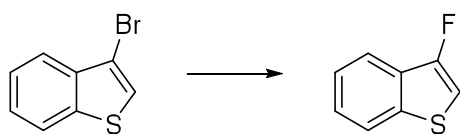
8.3 Chapter 3: Analysis of the CMD mechanism in Palladium-catalyzed direct arylation across a broad range of aromatic substrates and examples of its application

General procedure for the direct arylation of heterocycles:

$\text{Pd}(\text{OAc})_2$ (5 mol%), tricyclohexylphosphonium tetrafluoroborate (10 mol%), K_2CO_3 (1.5 equiv.) and PivOH (30 mol%) were weighed to air and placed in a screw-cap vial equipped with a magnetic stir bar. The heteroarene (1.0 equiv.) and the aryl bromide (1.0 equiv.), if a solid, were then added at that point. The vial was purged with argon and a

solution of the coupling partners, if liquid, in dimethylacetamide (DMA) (0.3 M) was added to the mixture. The reaction mixture was then stirred vigorously at 100 °C for 16 hours. The solution was then cooled to ambient temperature and loaded directly on the column or was diluted with ethyl acetate, then filtered and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography to afford the corresponding product.

Section 3.2.1: Procedure for the preparation of 3-fluorobenzothiophene

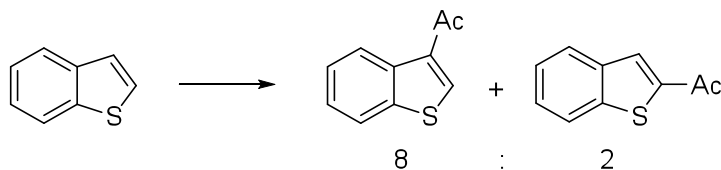


3-Fluorobenzothiophene: This procedure is an adaptation of a previously reported protocol.³ Lithium chloride (7.0 mmol, 2.33 equiv.) was added to a 10 mL flask equipped with a magnetic stir bar and a septum. The flask was flame-dried under vacuum, backfilled with argon and kept under a positive pressure of argon. A solution of *i*-PrMgCl 2.0M in THF (4.0 mmol, 1.33 equiv.) was added to the lithium chloride and the mixture was stirred at room temperature for an hour. The reaction mixture was cooled to -15 °C and 3-bromobenzothiophene (3.0 mmol, 1.0 equiv) was added dropwise to the mixture (over a period of a minute). The reaction temperature was increased to 10 °C over a period of one hour and the formation of the Grignard reagent was checked by GC analysis after a mini work up in water (generally no more than 85% conversion were obtained). Once the Grignard reagent was obtained, the reaction mixture was cooled to 0 °C and a solution of N-Fluorobenzenesulfonimide (NFSI, 4.1 mmol, 1.4 equiv.) in THF was added in a single portion. The solution was then warmed to room temperature and stirred for an additional 30 minutes. After this, water was added and the mixture was transferred to a separator funnel. The aqueous layer was extracted five times with 15 mL of pentane. The combined organic layers were dried over anhydrous magnesium sulfate and evaporated under reduced pressure (Caution: the final compound seems to be volatile). The crude product was purified by flash chromatography in pentane to isolated

3 Krasovskiy, A.; Knochel, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 3333.

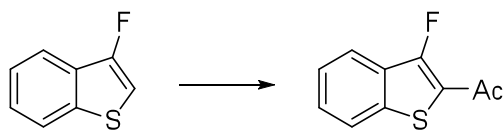
the final product and the unreacted 3-bromobenzothiophene from the other side products. The unreacted 3-bromobenzothiophene was separated from the 3-fluorobenzothiophene by submitting the mixture of products to hydrogenation conditions with activated Pd/C in DMF under an H₂ atmosphere at room temperature. 3-fluorobenzothiophene was obtained in a 29% yield as colorless oil. **¹H NMR (400MHz, CDCl₃, 293K, TMS):** 7.80–7.75 (m, 2H), 7.45–7.37 (m, 2H), 6.85 (d, *J* = 2.1 Hz, 1H); **¹³C NMR (100MHz, CDCl₃, 293K, TMS):** 152.0 (d, *J*_{CF} = 262 Hz), 136.9, 129.0 (d, *J*_{CF} = 23.8 Hz), 125.5, 124.4, 123.1 (d, *J*_{CF} = 1.3 Hz), 120.1 (d, *J*_{CF} = 2.2 Hz), 103.5 (d, *J*_{CF} = 20.0 Hz); **¹⁹F NMR (377MHz, CDCl₃, 293K, TMS):** -135.6; **IR (ν_{max}/cm⁻¹):** 3093, 1371, 1148, 1096; **HRMS** calculated for C₈H₅SF (M⁺) 152.0096; Found: 152.0100.

Friedel-Crafts acylation:



The final compounds were obtained in a 57% yield as non-separable 4:1 mixture of regioisomers by following a procedure described in the literature.⁴

The ¹H NMR of the mixture was found to correspond to the reported spectrum.

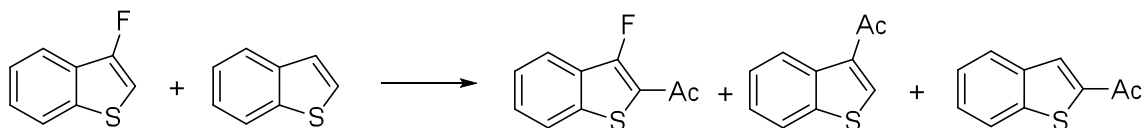


The final compound was obtained in a 63% yield as a solid by following a procedure described in the literature.⁴ **Mp** : 64 °C; **¹H NMR (400MHz, CDCl₃, 293K, TMS):** 7.86 (ddd, *J* = 8.1, 1.3, 0.8 Hz, 1H), 7.77 (dm, *J* = 8.2 Hz, 1H), 7.53 (td, *J* = 7.1, 1.2 Hz, 1H), 7.45 (dd, *J* = 8.1, 1.0 Hz, 1H), 2.71 (d, *J* = 3.1 Hz, 3H); **¹³C NMR (100MHz, CDCl₃, 293K, TMS):** 190.4, 152.0 (d, *J*_{CF} = 279 Hz), 137.8 (d, *J*_{CF} = 9.0 Hz), 129.2 (d, *J*_{CF} = 23.9 Hz), 128.8, 125.2, 123.4 (d, *J*_{CF} = 1.6 Hz), 123.0 (d, *J*_{CF} = 12.3 Hz), 122.2 (d, *J*_{CF} = 2.0 Hz),

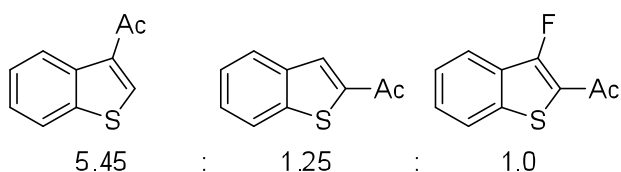
4 Okuyama, T.; Tani, Y.; Miyake, K.; Yokoyama, Y. *J. Org. Chem.* **2007**, 72, 1634.

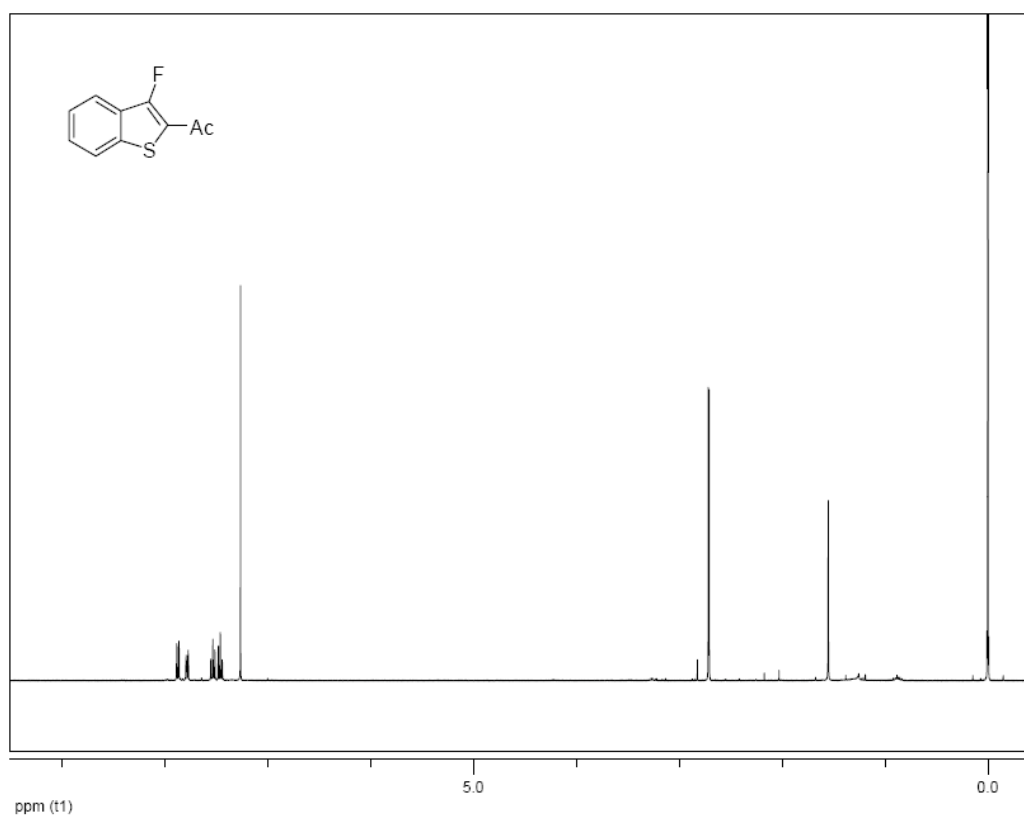
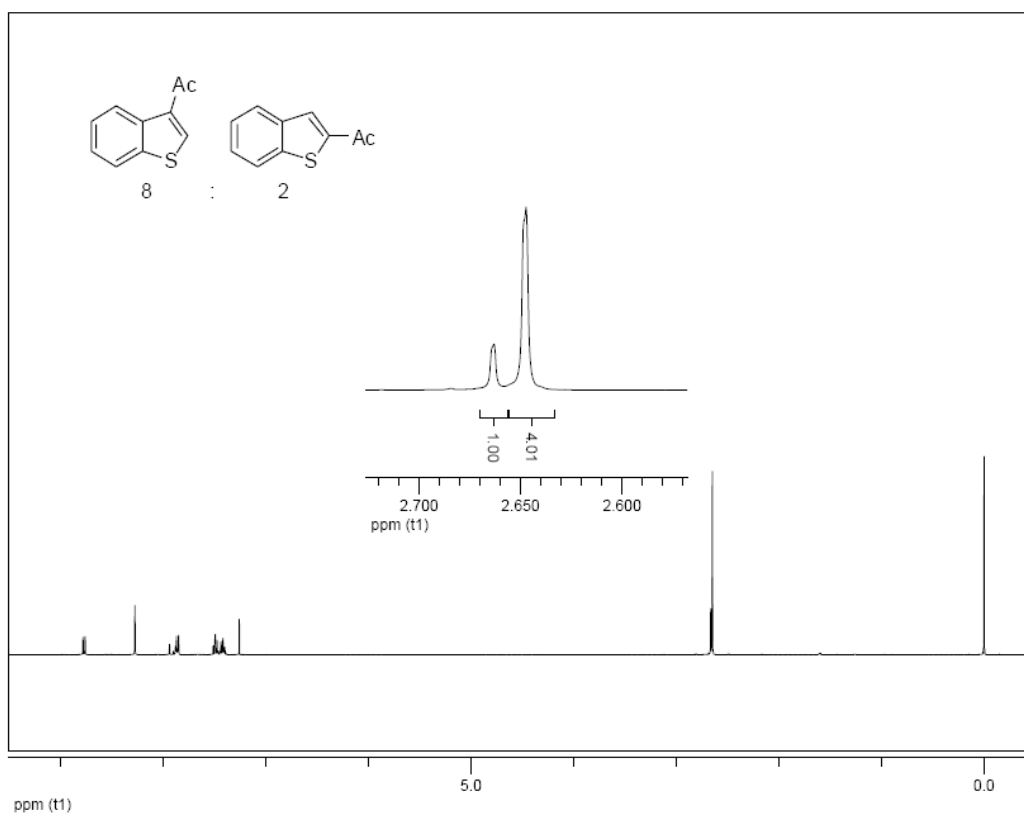
103.5 (d, J_{CF} = 20.0 Hz), 29.5 (d, J_{CF} = 5.1 Hz); ^{19}F NMR (377MHz, CDCl_3 , 293K, TMS): -119.1; IR ($\nu_{\text{max}}/\text{cm}^{-1}$): 3092, 2921, 1665, 1380, 1278; HRMS calculated for $\text{C}_{10}\text{H}_7\text{OSF}$ (M^+) 194.0202; Found: 194.0195;

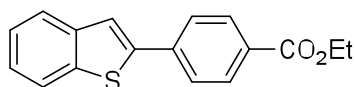
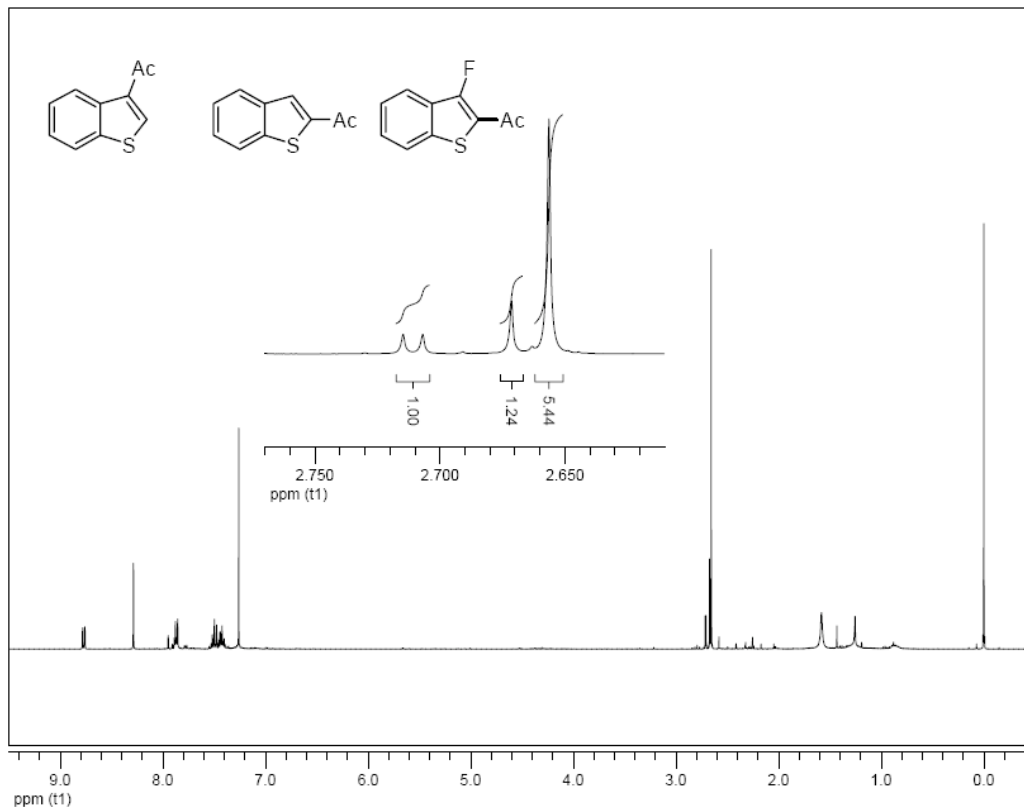
Procedure for the Friedel-Crafts competition reaction:



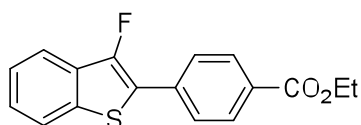
To a flame-dried vial equipped with a magnetic stir bar and a septum was added AlCl_3 (0.10 mmol, 0.12 equiv.) and the vial was kept under an argon atmosphere. Freshly distilled DCM (1 mL) was added to the flask followed by acetyl chloride (0.80 mmol, 0.10 equiv.) *via* syringe. The mixture was mixed at room temperature for 30 minutes then it was cooled to $-41\text{ }^\circ\text{C}$. To a flame-dried flask equipped with a magnetic stir bar and a septum was added benzothiophene (0.40 mmol, 0.5 equiv.), and 3-fluorobenzothiophene (0.40 mmol, 0.50 equiv.), the mixture was diluted with 3 mL of freshly distilled DCM, then it was cooled to $-41\text{ }^\circ\text{C}$ under an argon atmosphere. At this point, the $\text{AlCl}_3/\text{AcCl}$ mixture was slowly canulated into the benzothiophene/3-fluorobenzothiophene mixture and the reaction was then allowed to slowly warm to room temperature. Water was added to the reaction and the aqueous layer was extracted four times with DCM. The combined organic layers were dried over anhydrous magnesium sulfate. The acetylated product were separated from the unreacted starting material by flash chromatography using a gradient of 5% to 20% of diethyl ether in petroleum ether. GC-MS analysis confirmed complete recovery of acetylated products. The following product distribution was observed by ^1H NMR.







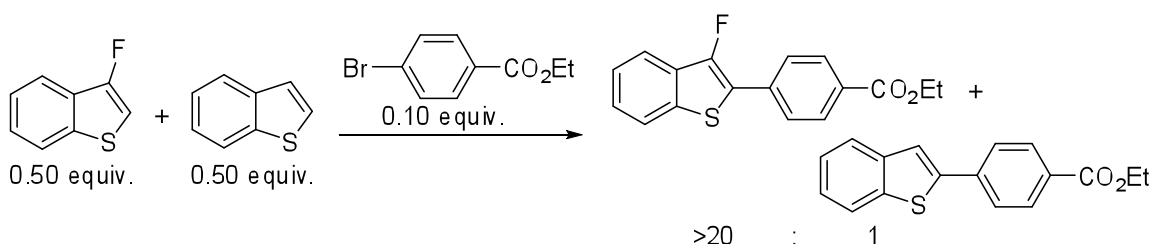
Ethyl 4-(benzo[b]thiophen-2-yl)benzoate: This compound was obtained in a 53% yield as a solid by following the general procedure for the direct arylation of heterocycles. **Mp:** 162 °C; **¹H NMR (400MHz, CDCl₃, 293K, TMS):** 8.09 (d, *J*= 8.6Hz, 2H), 7.87-7.76 (m, 4H), 7.65 (s, 1H), 7.40-7.31 (m, 2H), 4.40 (q, *J*= 7.1Hz, 2H), 1.42 (t, *J*= 7.1Hz, 3H); **¹³C NMR (100MHz, CDCl₃, 293K, TMS):** 166.2, 142.8, 140.5, 139.9, 138.4, 130.2, 129.9, 126.1, 124.9, 124.7, 123.9, 122.3, 121.0, 61.1, 14.4; **IR (ν_{max}/cm⁻¹):** 3029, 2989, 2937, 1698, 1637, 1287; **HRMS** calculated for C₁₇H₁₄SO₂ (M⁺) 282.0715; Found: 282.0714.



Ethyl 4-(3-fluorobenzo[b]thiophen-2-yl)benzoate: This compound was obtained in 87% yield as a solid by following the general procedure for the direct arylation of

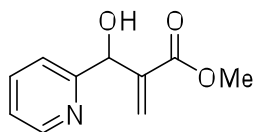
heterocycles. **Mp**: 142 °C; **¹H NMR (400MHz, CDCl₃, 293K, TMS)**: 8.11 (d, *J* = 8.6Hz, 2H), 7.83 (d, *J* = 8.6 Hz, 2H), 7.81–7.74 (m, 2H), 7.46–7.40 (m, 2H), 4.40 (q, *J* = 7.1 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H); **¹³C NMR (100MHz, CDCl₃, 293K, TMS)**: 166.1, 148.5 (d, *J*_{CF} = 268.6 Hz), 135.5 (d, *J*_{CF} = 4.1Hz), 134.6 (d, *J*_{CF} = 8.7Hz), 130.5 (d, *J*_{CF} = 24.3Hz), 130.1, 129.6, 127.1 (d, *J*_{CF} = 5.8Hz), 126.2, 125.0, 122.7 (d, *J*_{CF} = 1.5), 120.4 (d, *J*_{CF} = 1.8Hz), 119.6 (d, *J*_{CF} = 11.1Hz), 61.1, 14.4; **¹⁹F NMR (377MHz, CDCl₃, 293K, TMS)**: -132.3; **IR (ν_{max}/cm⁻¹)**: 3028, 2984, 1707, 1645, 1368, 1279; **HRMS** calculated for C₁₇H₁₃SO₂F (M⁺) 300.0620; Found: 300.0613;

Procedure for the arylation competition of benzothiophene vs. 3-fluorobenzothiophene with an aryl-bromide:

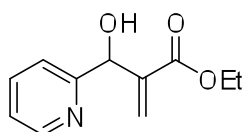


Benzothiophene (0.35 mmol, 0.50 equiv.), 3-fluorobenzothiophene (0.35 mmol, 0.50 equiv.), Pd(OAc)₂ (5 mol%), PCy₃·HBF₄ (10 mol%), pivalic acid (PivOH, 30 mol%), potassium carbonate (2.0 equiv.) were weighed to air and placed in a vial equipped with a magnetic stir bar and purged with argon. The aryl halide (0.10 equiv.) was added *via* syringe as a DMA solution (to produce a reaction concentration of 0.3 M relative to the mixture of benzothiophenes). The mixture was then stirred at 100 °C for 2 hours. An aliquot of the reaction was taken after 2 hours and the GC-MS trace of showed the complete conversion of the aryl-bromide to the 2-aryl-3-fluorobenzothiophene and only trace amount of 2-arylbenzothiophene were detected.

Section 3.2.2: Re-examination of the reactivity of indolizine toward direct arylation and Friedel-Crafts acylation reactions

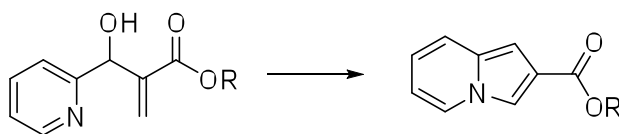


Methyl 2-(hydroxy(pyridin-2-yl)methyl)acrylate: This compound was obtained in a 77% yield as a solid by following the published procedure.⁵ **Mp:** 69 °C. **¹H NMR (400MHz, CDCl₃, 293K, TMS):** 8.55 (dt, *J*= 4.4 1.0 Hz, 1H), 7.68 (td, *J*= 7.7, 1.8 Hz, 1H), 7.42 (d, *J*= 7.9 Hz, 1H), 7.21 (ddd, *J*= 7.4, 4.9, 1.0 Hz, 1H), 6.36 (s, 1H), 5.97 (t, *J*= 1.0 Hz, 1H), 5.63 (d, *J*= 6.4 Hz, 1H), 4.81 (d, *J*= 6.4 Hz, 1H), 3.74 (s, 3H); **¹³C NMR (100MHz, CDCl₃, 293K, TMS):** 166.6, 159.4, 148.3, 141.8, 136.8, 126.9, 122.7, 121.3, 72.1, 51.9; **IR (*v*_{max}/cm⁻¹):** 3281, 2960, 1717, 1438, 1046; **HRMS** calculated for C₁₀H₁₁NO₃ (M⁺) 193.0739; Found: 193.07416.



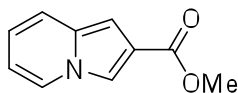
Ethyl 2-(hydroxy(pyridin-2-yl)methyl)acrylate: This compound was obtained in a 94% yield as a solid by following the published procedure.⁵ **Mp:** 66 °C; **¹H NMR (400MHz, CDCl₃, 293K, TMS):** 8.55 (dq, *J*= 4.9, 0.5 Hz, 1H), 7.67 (td, *J*= 7.7, 1.7 Hz, 1H), 7.42 (dq, *J*= 7.9, 0.5 Hz, 1H), 7.21 (dd, *J*= 6.8, 4.9 Hz, 1H), 6.37 (d, *J*= 0.6 Hz, 1H), 5.95 (d, *J*= 1.1 Hz, 1H), 5.61 (d, *J*= 6.5 Hz, 1H), 4.82 (d, *J*= 6.6 Hz, 1H), 4.18 (q, *J*= 7.1 Hz, 2H), 1.24 (t, *J*= 7.1 Hz, 3H); **¹³C NMR (100MHz, CDCl₃, 293K, TMS):** 166.1, 159.6, 148.2, 142.0, 136.8, 126.7, 122.6, 121.2, 72.2, 60.8, 14.0; **IR (*v*_{max}/cm⁻¹):** 3370, 2983, 1716, 1268, 1150, 1047; **HRMS** calculated for C₁₁H₁₃NO₃ (M⁺) 207.0895; Found: 207.0879.

General procedure for the formation of indolizines:

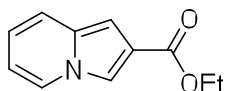


⁵ Bode, M. L.; Kaye, P. T. *J. Chem. Soc., Perkin Trans I* **1993**, 1809.

The ester (14.5 mmol) was weighed open to air and placed in a microwave tube with a magnetic stir bar. The flask was capped with a rubber septum and purged with argon. The acetic anhydride (2.5 equiv.) was added *via* syringe. The rubber septum was replaced by a microwave tube cap and the mixture was then placed in the CEM Discover microwave reactor at 130 °C for 30 minutes (conditions: max. power: 200W; T°: 110 °C; max. pressure: 250 psi). The reaction was diluted with 30 mL of diethyl ether and transferred to a 250 mL Erlenmeyer flask. A saturated solution of ammonium hydroxide was added slowly until the pH of the aqueous layer became basic. Then the aqueous layer was extracted three times with 30 mL of diethyl ether. The combined organic layers were dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure. The residue was loaded onto a silica gel column for chromatography, typically using a gradient of 5% to 20% of diethyl ether in petroleum ether.

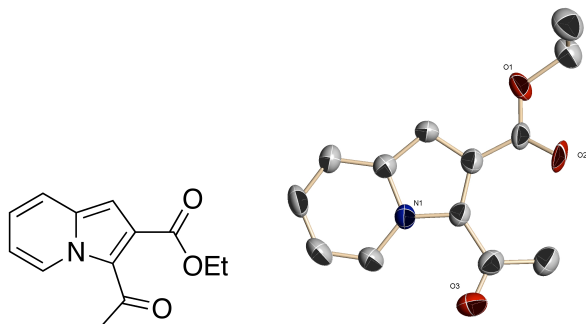


Methyl indolizine-2-carboxylate: This compound was obtained in a 46% yield as a solid by following the general procedure for the formation of the indolizines. **Mp** : 118 °C. **¹H NMR (400MHz, CDCl₃, 293K, TMS):** 7.85 (d, *J*= 7.0 Hz, 1H), 7.79 (s, 1H), 7.35 (d, *J*= 9.1 Hz, 1H), 6.82 (s, 1H), 6.68 (dd, *J*= 9.1 Hz, 6.5 Hz, 1H), 6.53 (t, *J*= 6.4 Hz, 1H), 3.88 (s, 3H); **¹³C NMR (100MHz, CDCl₃, 293K, TMS):** 165.6, 125.4, 120.3, 119.7, 118.1, 115.9, 112.3, 100.4, 51.5; **IR (*v*_{max}/cm⁻¹):** 2948, 1714, 1217; **HRMS** calculated for C₁₀H₉NO₂ (M⁺) 175.0633; Found: 175.0627.



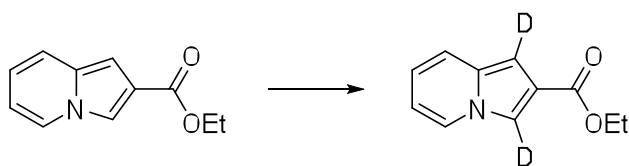
Ethyl indolizine-2-carboxylate: This compound was obtained in a 66% yield as a white solid by following the general procedure for the formation of indolizines. **Mp**: 70-71 °C; **¹H NMR (400MHz, CDCl₃, 293K, TMS):** 7.85 (d, *J*= 7.9 Hz, 1H), 7.80 (s, 1H), 7.35 (d, *J*= 9.1 Hz, 1H), 6.83 (s, 1H), 6.67 (dd, *J*= 9.1, 6.5 Hz, 1H), 6.52 (t, *J*= 7.0 Hz, 1H), 4.35 (q, *J*= 7.1 Hz, 2H), 1.38 (t, 7.1 Hz, 3H); **¹³C NMR (100MHz, CDCl₃, 293K, TMS):**

165.2, 132.8, 125.4, 120.3, 118.1, 115.8, 112.2, 100.4, 60.2, 14.5; **IR** ($\nu_{\max}/\text{cm}^{-1}$): 2980, 1686, 1089; **HRMS** calculated for $\text{C}_{11}\text{H}_{11}\text{NO}_2$ (M^+) 189.0790; Found: 189.0792.



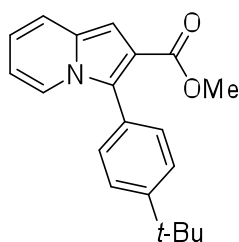
3-Acetyl-2-(ethoxycarbonyl)indolizin-6-ylum: This compound was obtained as colorless crystals in a 10–30% yield as the sole side product of the indolizine formation. **Mp:** 83–84 °C; **^1H NMR** (400MHz, CDCl_3 , 293K, TMS): δ 9.81 (dq, $J = 7.3, 0.9$ Hz, 1H), 7.53 (dt, $J = 8.9, 1.2$ Hz, 1H), 7.13 (ddd, $J = 8.8, 6.7, 1.1$ Hz, 1H), 6.91 (ddd, $J = 7.2, 6.8, 1.4$ Hz, 1H), 6.82 (d, $J = 0.5$ Hz, 1H), 4.43 (q, $J = 7.1$ Hz, 2H), 2.64 (s, 3H), 1.42 (t, $J = 7.1$ Hz, 3H); **^{13}C NMR** (100MHz, CDCl_3 , 293K, TMS): δ 189.0, 166.1, 136.0, 128.5, 127.6, 124.0, 119.3, 115.3, 104.9, 61.7, 30.2, 14.3; **HRMS** calculated for $\text{C}_{13}\text{H}_{13}\text{NO}_3$ (M^+) 231.0895; Found: 231.0908.

Procedure for the H/D exchange at the C1 and C3 position of the indolizine ring:

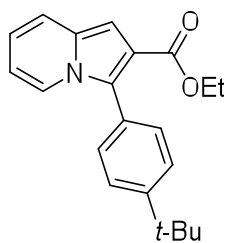


The indolizine (1.0 mmol) was weighed open to air, placed in a vial with a magnetic stir bar and purged with argon. Acetic acid OD (1 mL) and deuterium oxide (1 mL) were then added via syringe. The mixture was heated to 70 °C for 20 hours. The reaction mixture was diluted with 10 mL of ethyl acetate. Portions of potassium carbonate were carefully added to the mixture until the gas production stopped and the aqueous layer became saturated. The organic layer was removed and the aqueous layer was extracted three times with 10 mL of ethyl acetate. The combined organic layers were evaporated under reduced pressure. The residue was loaded onto a base treated silica gel column for

chromatography, typically using a gradient of 10% to 20% of diethyl ether in petroleum ether. The product obtained was re-subjected to the same conditions to maximize deuterium incorporation. The final compound was obtained in a 74% yield as a solid with 95% of deuterium incorporation at both C1 and C3 positions of the indolizine. **Mp:** 70 °C; **¹H NMR (400MHz, CDCl₃, 293K, TMS):** 7.85 (d, *J*= 7.9Hz, 1H), 7.35 (d, *J*= 9.1 Hz, 1H), 6.67 (dd, *J*= 9.1, 6.5 Hz, 1H), 6.52 (t, *J*= 7.0 Hz, 1H), 4.35 (q, *J*= 7.1 Hz, 2H), 1.38 (t, *J*= 7.1 Hz, 3H); **¹³C NMR (100MHz, CDCl₃, 293K, TMS):** 165.1, 132.6, 125.3, 120.3, 118.0, 112.2, 60.2, 14.5; **IR (ν_{max} /cm⁻¹):** 2981, 1701, 1089; **HRMS** calculated for C₁₁H₉D₂NO₂ (M⁺) 191.0915; Found: 191.0904.



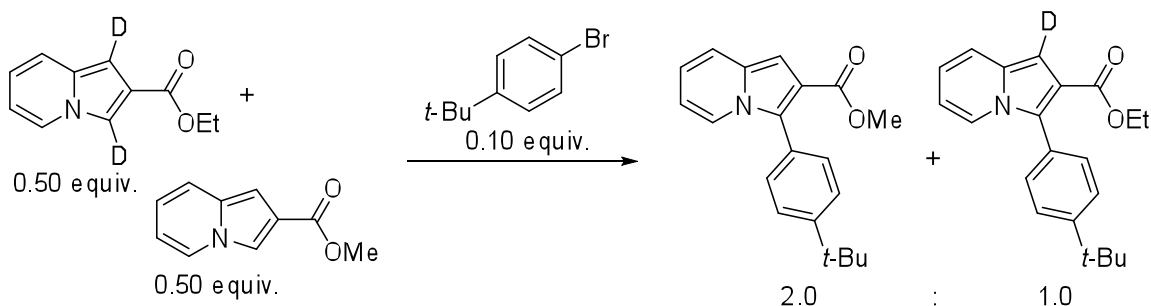
Methyl 3-(4-tert-butylphenyl)indolizine-2-carboxylate: This compound was obtained in a 95% yield as a solid by following the general procedure for the direct arylation of heterocycles. **Mp:** 103-104 °C; **¹H NMR (400MHz, CDCl₃, 293K, TMS):** 7.82 (dd, *J*= 7.3, 1.0 Hz, 1H), 7.54–7.49 (m, 2H), 7.43–7.37 (m, 3H), 6.94 (s, 1H), 6.69 (ddd, *J*=9.1, 6.4, 1.0 Hz, 1H), 6.44 (ddd, *J*= 7.4, 6.4, 1.3 Hz, 1H), 3.76 (s, 3H), 1.39 (s, 9H); **¹³C NMR (100MHz, CDCl₃, 293K, TMS):** 165.5, 151.4, 131.7, 130.4, 128.0, 127.4, 125.5, 1230, 120.2, 118.2, 116.9, 112.0, 101.3, 51.3, 34.8, 31.3; **IR (ν_{max} /cm⁻¹):** 2960, 1717, 1236, 1174; **HRMS** calculated for C₂₀H₂₁NO₂ (M⁺) 307.1572; Found: 307.1561.



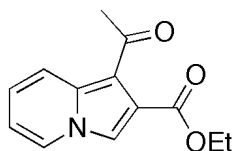
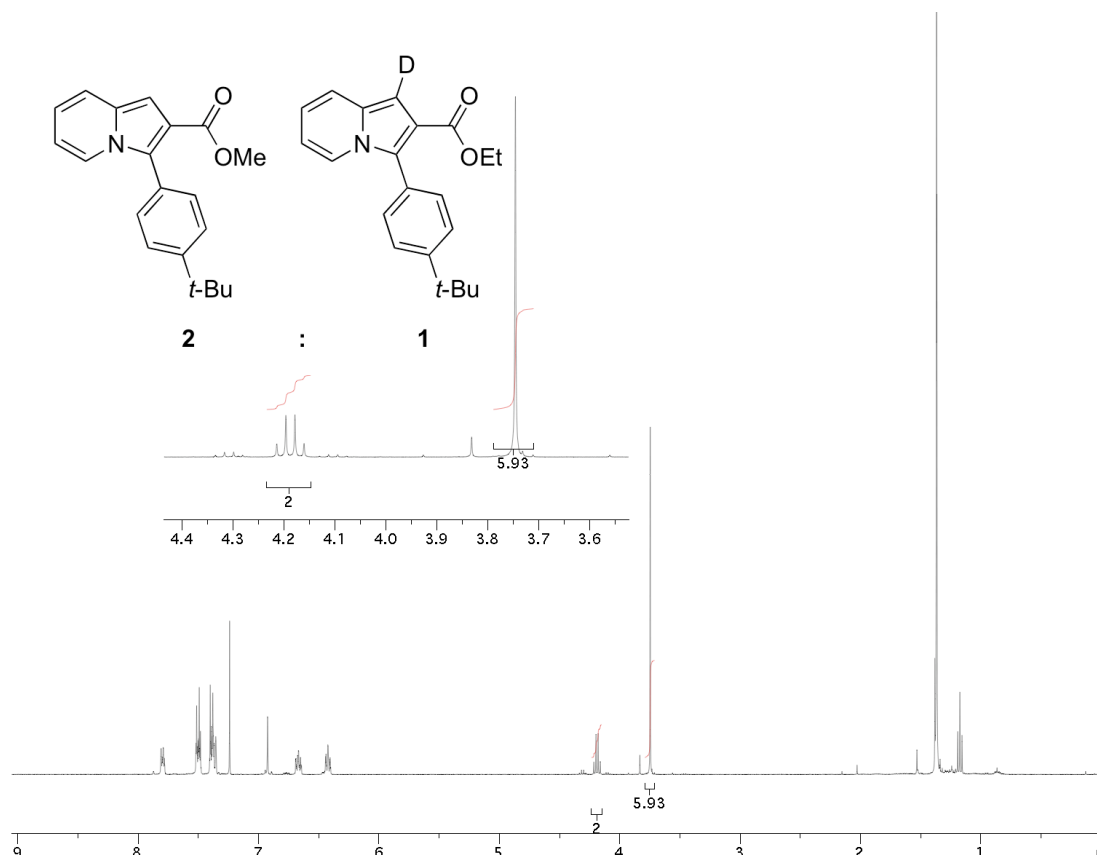
Ethyl 3-(4-tert-butylphenyl)indolizine-2-carboxylate: This compound was obtained in a 94% yield as a solid by following the general procedure for the direct arylation of

heterocycles. **Mp**: 104–105 °C; **¹H NMR (400MHz, CDCl₃, 293K, TMS)**: 7.81 (dd, *J*= 7.3, 1.0 Hz, 1H), 7.55–7.48 (m, 2H), 7.44–7.35 (m, 3H), 6.96 (s, 1H), 6.69 (ddd, *J*= 9.0, 6.3, 0.9 Hz, 1H), 6.44 (ddd, *J*= 7.4, 6.5, 1.3 Hz, 1H), 4.20 (q, *J*= 7.1 Hz, 2H), 1.39 (s, 9H), 1.19 (t, *J*= 7.1 Hz, 3H); **¹³C NMR (100MHz, CDCl₃, 293K, TMS)**: 165.1, 151.4, 131.7, 130.5, 127.8, 127.6, 125.4, 123.0, 120.2, 118.1, 117.4, 111.9, 101.3, 59.9, 34.7, 31.3, 14.1; **IR (ν_{max}/cm⁻¹)**: 2963, 1713, 1235, 1175; **HRMS** calculated for C₂₁H₂₃NO₂ (M⁺) 321.1729; Found: 321.1716.

Procedure for the kinetic isotope effect (KIE) experiment:



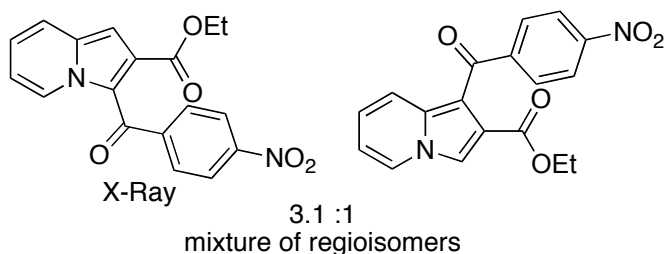
The indolizine-CO₂Me (0.30 mmol, 0.50 equiv.), indolizine-CO₂Et (0.30 mmol, 0.50 equiv.), Pd(OAc)₂ (5 mol%), PCy₃·HBF₄ (10 mol%), pivalic acid (PivOH, 30 mol%), potassium carbonate (2.0 equiv.) were weighed to air and placed in a vial equipped with a magnetic stir bar and purged with argon. The aryl halide (0.10 equiv.) was added *via* syringe as a DMA solution (to produce a reaction concentration of 0.3 M relative to the mixture of indolizine). The mixture was then stirred at 100 °C for 1–2 hours. The reaction mixture was then loaded directly onto a silica gel column for chromatography using a gradient of 10% to 20% of diethyl ether in petroleum ether. A control reaction (without deuterium label indolizine) was also run to confirm that the starting compounds reacted at the same rate. A kinetic isotope effect of 2.0 was confirmed by NMR.



Ethyl indolizine-2-carboxylate: Procedure adapted from a literature procedure.⁶ In an oven dried 10 mL flask equipped with a stir bar and a reflux condenser was premixed acetyl chloride (142 μ L, 2.0 mmol) and AlCl_3 (266 mg, 2.0 mmol) in DCM (2 mL) under argon atmosphere for $\sim$ 10 minutes at room temperature. After this period of time, the mixture was heated to reflux and at this point a solution of the indolizine (189 mg, 1.0 mmol) in DCM (1 mL) was added. After few minutes, the reaction was quenched by pouring it over ice and the mixture was extracted with EtOAc. The extract was washed with sat. NaHCO_3 and brine, then dried over MgSO_4 . After evaporation of the solvent, the

⁶ Sawada, K.; Okada, S.; Kuroda, A.; Watanabe, S.; Sawada, Y.; Tanaka, H. *Chem. Pharm. Bull.* **2001**, *49*, 799.

residue was flashed on silica gel (hexane: EtOAc 3:2). The crude NMR revealed 75% conversion to a single product that corresponded to the product isolated by Gevorgyan *et al.*⁷



Ethyl 3-(4-nitrobenzoyl)indolizine-2-carboxylate: In an oven dried 10 mL flask equipped with a stir bar and a reflux condenser was premixed *para*-nitrobenzoyl chloride (185 mg, 1.0 mmol) and AlCl₃ (133 mg, 1.0 mmol) in DCM (1 mL) under argon atmosphere for ~10 minutes at room temperature. After this period of time, the mixture was heated to reflux and at this point a solution of the indolizine (95 mg, 0.50 mmol) in DCM (0.7 mL) was added. After few minutes, the reaction was quenched by pouring it over ice and the mixture was extracted with DCM. The extract was washed with sat. NaHCO₃ and brine, then dried over MgSO₄. After evaporation of the solvent, the residue was flashed on silica gel (20% DCM in Pet. Ether) from which were isolated a mixture of 3.1 to 1 of isomers in a combined yield of 35%. A second purification allowed the separation of the isomers. **Major Isomer** (X-Ray structure): **Mp**: 125-128 °C (CHCl₃); **Rf**: 0.15 (20% EtOAc, petroleum ether); **¹H NMR (400 MHz, CDCl₃)**: δ 9.56 (dd, *J* = 7.2, 0.8 Hz, 1H), 8.28-8.26 (m, 2H), 7.87-7.85 (m, 2H), 7.62 (dd, *J* = 8.9, 1.1 Hz, 1H), 7.25-7.20 (m, 1H), 7.02-6.99 (m, 1H), 6.94 (s, 1H), 3.76 (q, *J* = 7.2 Hz, 2H), 0.98 (t, *J* = 7.1 Hz, 3H). **¹³C NMR (101 MHz, CDCl₃)**: δ 183.9, 164.6, 149.3, 147.1, 137.1, 129.6, 128.6, 127.7, 125.0, 123.5, 120.2, 119.9, 116.0, 105.8, 61.4, 13.9; **IR (ν_{max}/cm⁻¹)**: 2931, 1702, 1515, 1506, 1487, 1170; **HRMS** calculated for C₁₈H₁₄N₂O₅ (M⁺) 338.0903; Found: 338.0910. **Minor Isomer**: **Mp**: 130-131 °C (CHCl₃); **Rf**: 0.15 (20% EtOAc, petroleum ether); **¹H NMR (400 MHz, CDCl₃)**: δ 8.27 (d, *J* = 8.7 Hz, 2H), 8.07 (t, *J* = 9.0 Hz, 2H), 7.90 (d, *J* = 8.7 Hz, 2H), 7.82 (s, 1H), 7.17 (t, *J* = 7.8 Hz, 1H), 6.87 (t, *J* = 6.7 Hz, 1H),

7 Park, C.-H.; Ryabova, V.; Seregin, I. V.; Sromek, A. W.; Gevorgyan, V. *Org. Lett.* **2004**, 6, 1159.

3.89 (q, $J = 7.1$ Hz, 2H), 0.98 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (101 MHz; CDCl_3): δ 189.4, 163.9, 149.4, 146.8, 137.2, 129.7, 126.1, 124.8, 123.5, 121.5, 120.5, 118.4, 114.9, 61.0, 14.0; IR ($\nu_{\text{max}}/\text{cm}^{-1}$): 2954, 1692, 1500, 1170; HRMS calculated for $\text{C}_{18}\text{H}_{14}\text{N}_2\text{O}_5$ (M^+) 338.0903; Found: 338.0910.

8.3.1 Section 3.4: Establishment of broadly applicable reaction conditions for the palladium-catalyzed direct arylation of heteroaromatic compounds

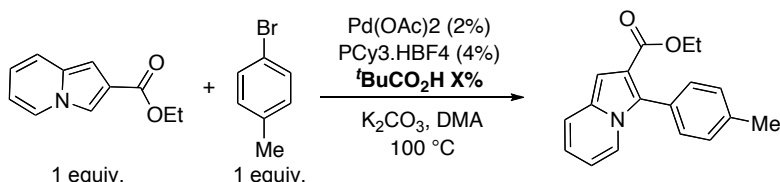
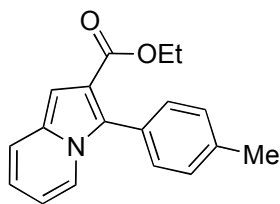
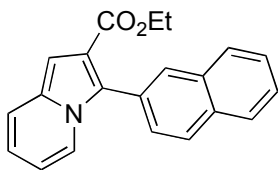


Table 8.1 Data of the evaluation of the effect of pivalic acid on the rate of arylation of indolizine (Figure 3.10)

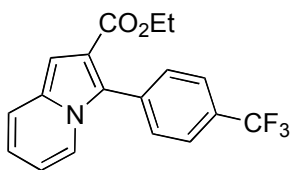
No PivOH		10 mol% PivOH		30 mol% PivOH	
Time (min)	GC-Yield (%)	Time (min)	GC-Yield (%)	Time (min)	GC-Yield (%)
0	0	0	0	0	0
5	0	5	7	5	0
10	14	10	42	10	0
15	28	15	52	15	3
20	36	20	56	20	26
25	42	25	59	25	51
30	49	30	61	30	64
40	57	60	70	50	78
50	63			60	81
60	65				



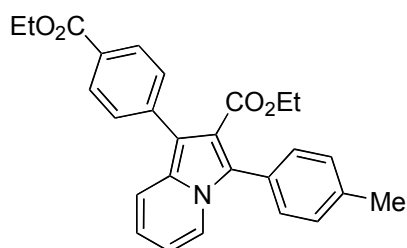
Ethyl 3-(*p*-tolyl)indolizine-2-carboxylate 1a: Synthesized according to the general procedure. Yellow solid; **mp** 83–85°C; **R_f** 0.55 (petroleum ether/ethyl acetate 80/20); **¹H NMR (400 MHz, CDCl₃)** δ 7.76 (dd, *J* = 7.3, 1.0 Hz, 1H), 7.41–7.28 (m, 5H), 6.95 (s, 1H), 6.68 (ddd, *J* = 9.1, 6.4, 1.0 Hz, 1H), 6.43 (ddd, *J* = 7.5, 6.5, 1.3 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 2.43 (s, 3H), 1.21 (t, *J* = 7.1 Hz, 3H); **¹³C NMR (100 MHz, CDCl₃)** δ 165.1, 138.3, 131.6, 130.7, 129.2, 127.8, 127.7, 122.9, 120.2, 118.0, 117.4, 111.9, 101.2, 59.8, 21.4, 14.2; **IR (ν_{max}/cm⁻¹)** 2976, 2931, 1717, 1490, 1234, 1173; **HRMS** Calculated for C₁₈H₁₇NO₂ (M⁺) 279.1259, Found 279.1262.



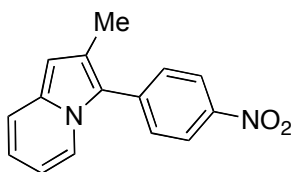
Ethyl 3-(naphthalen-2-yl)indolizine-2-carboxylate 1b: Synthesized according to the general procedure. White solid; **mp** 116–118 °C; **R_f** 0.53 (petroleum ether/ethyl acetate 80/20); **¹H NMR (400 MHz, CDCl₃)** δ 7.96 (m, 2H), 7.93–7.85 (m, 2H), 7.83 (dd, *J* = 7.3, 0.9 Hz, 1H), 7.58–7.49 (m, 3H), 7.43 (dt, *J* = 9.1, 1.2 Hz, 1H), 7.02 (s, 1H), 6.72 (ddd, *J* = 9.1, 6.4, 1.0 Hz, 1H), 6.46 (ddd, *J* = 7.6, 6.4, 1.3 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 1.14 (t, *J* = 7.1 Hz, 3H); **¹³C NMR (100 MHz, CDCl₃)** δ 165.1, 133.3, 133.2, 131.9, 130.1, 128.6, 128.2, 128.2, 128.0, 127.8, 127.4, 126.6, 126.2, 122.9, 120.2, 118.3, 117.9, 112.2, 101.6, 60.0, 14.1; **IR (ν_{max}/cm⁻¹)**: 3061, 3024, 2979, 1709, 1225, 1198, 1170, 764; **HRMS** Calculated for C₂₁H₁₇NO₂ (M⁺) 315.1259, Found 315.1270.



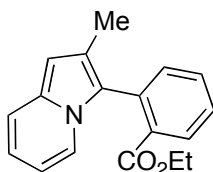
Ethyl 3-(4-(trifluoromethyl)phenyl)indolizine-2-carboxylate 1c: Synthesized according to the general procedure. Yellow solid; **mp** 92–94 °C; **R_f** 0.5 (petroleum ether/ethyl acetate 80/20); **¹H NMR (400 MHz, CDCl₃)** δ 7.79–7.72 (m, 3H), 7.62 (d, *J* = 7.9 Hz, 2H), 7.43 (dt, *J* = 9.1, 1.1 Hz, 1H), 7.00 (s, 1H), 6.74 (ddd, *J* = 9.1, 6.5, 1.0 Hz, 1H), 6.51 (ddd, *J* = 7.6, 6.5, 1.3 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 1.21 (t, *J* = 7.1 Hz, 3H); **¹³C NMR (100 MHz, CDCl₃)** δ 164.8, 134.6, 132.3, 131.5, 130.4 (q, *J_{CF}* = 33 Hz), 125.6, 125.5 (q, *J_{CF}* = 4 Hz), 122.8, 122.5, 120.4, 118.7, 118.2, 112.7, 102.0, 60.2, 14.1; **¹⁹F NMR (377 MHz, CDCl₃)** δ -62.7; **IR (ν_{max}/cm⁻¹)** 2986, 2962, 2900, 1695, 1235, 1176, 1161, 1107; **HRMS** Calculated for C₁₈H₁₄F₃NO₂ (M⁺) 333.0977, Found 333.0979.



Ethyl 1-(4-(ethoxycarbonyl)phenyl)-3-(p-tolyl)indolizine-2-carboxylate 1d: Synthesized according to the general procedure. Green solid; **mp** 78–84 °C; **R_f** 0.3 (petroleum ether/ethyl acetate 80/20); **¹H NMR (400 MHz, CDCl₃)** δ 8.11 (d, *J* = 8.2 Hz, 2H), 7.81 (d, *J* = 7.3 Hz, 1H), 7.55 (d, *J* = 8.2 Hz, 2H), 7.48–7.29 (m, 5H), 6.74 (dd, *J* = 9.2, 6.4 Hz, 1H), 6.51 (t, *J* = 6.8 Hz, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 4.05 (q, *J* = 7.1 Hz, 2H), 2.45 (s, 3H), 1.42 (t, *J* = 7.1 Hz, 3H), 0.94 (t, *J* = 7.1 Hz, 3H); **¹³C NMR (100 MHz, CDCl₃)** δ 166.8, 165.4, 139.8, 138.6, 130.6, 130.2, 130.2, 129.5, 129.3, 128.1, 127.9, 127.5, 123.0, 119.5, 118.6, 116.9, 114.5, 112.6, 60.8, 60.2, 21.5, 14.4, 13.7; **IR (ν_{max}/cm⁻¹)**: 3025, 2981, 2934, 2903, 2871, 1713, 1607, 1272, 1175, 1101, 1016; **HRMS** Calculated for C₂₇H₂₅NO₄ (M⁺) 427.1784, Found 427.1799.

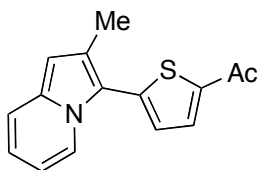


2-Methyl-3-(4-nitrophenyl)indolizine 2a. Synthesized according to the general procedure. Exhibited identical spectral data according to previous report.⁸ Red solid; **R_f** 0.5 (petroleum ether/ethyl acetate 80/20); **¹H NMR (400 MHz, CDCl₃)** δ 8.37–8.32 (m, 2H), 8.10 (dd, J = 7.2, 0.9 Hz, 1H), 7.65–7.61 (m, 2H), 7.35 (dt, J = 8.9, 1.1 Hz, 1H), 6.74 (ddd, J = 8.9, 6.5, 1.0 Hz, 1H), 6.48 (td, J = 7.1, 1.3 Hz, 1H), 6.42 (s, 1H), 2.36 (s, 3H); **¹³C NMR (100 MHz, CDCl₃)** δ 145.8, 138.6, 133.9, 129.2, 125.3, 124.3, 121.9, 120.4, 118.8, 118.5, 110.8, 102.3, 12.7.

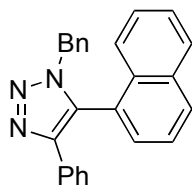


Methyl 2-(2-methylindolizin-3-yl)benzoate 2b. Synthesized according to the general procedure. Green solid; **mp** 78–82 °C; **R_f** 0.22 (petroleum ether/ethyl acetate 80/20); **¹H NMR (400 MHz, CDCl₃)** δ 8.03 (dd, J = 7.8, 1.4 Hz, 1H), 7.61 (td, J = 7.6, 1.4 Hz, 1H), 7.48 (dt, J = 7.7, 1.4 Hz, 1H), 7.46 (dd, J = 7.1, 0.9 Hz, 1H), 7.41 (dd, J = 7.6, 1.3 Hz, 1H), 7.29 (d, J = 8.9 Hz, 1H), 6.59 (ddd, J = 8.9, 6.5, 1.0 Hz, 1H), 6.36 (s, 1H), 6.31 (td, J = 7.1, 1.3 Hz, 1H), 3.52 (s, 3H), 2.15 (s, 3H); **¹³C NMR (100 MHz, CDCl₃)** δ 167.6, 133.0, 132.2, 132.1, 130.8, 128.1, 123.2, 122.2, 121.2, 118.3, 116.5, 109.4, 100.1, 52.2, 12.0; **IR (ν_{max} /cm⁻¹):** 3070, 2949, 2928, 2863, 1731, 1716, 1428, 1291, 1251, 1084; **HRMS** Calculated for C₁₇H₁₅NO₂ (M⁺) 265.1103, Found 265.1124.

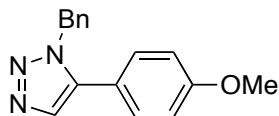
8 Park, C.-H.; Ryabova, V.; Seregin, I. V.; Sromek, A. W.; Gevorgyan, V. *Org. Lett.* **2004**, 6, 1159.



1-(5-(2-Methylindolizin-3-yl)thiophen-2-yl)ethanone 2c: Synthesized according to the general procedure. Yellow oil; **R_f** 0.25 (petroleum ether/ethyl acetate 80/20); **¹H NMR (400 MHz, CDCl₃)** δ 8.36 (d, J = 7.2 Hz, 1H), 7.75 (d, J = 3.9 Hz, 1H), 7.33 (d, J = 8.9 Hz, 1H), 7.18 (d, J = 3.8 Hz, 1H), 6.75 (dd, J = 8.7, 6.7 Hz, 1H), 6.53 (t, J = 6.8 Hz, 1H), 6.40 (s, 3H), 2.60 (s, 1H), 2.44 (s, 3H); **¹³C NMR (100 MHz, CDCl₃)**: δ 190.3, 142.1, 141.9, 134.1, 133.0, 126.6, 126.1, 122.8, 118.6, 118.5, 115.4, 110.9, 102.3, 26.5, 13.3; **IR (ν_{max} /cm⁻¹)**: 2956, 2926, 2856, 1652, 1489, 1456, 1436, 1350, 1295, 1273, 1253; **HRMS** Calculated for C₁₅H₁₃NOS (M⁺) 255.0718, Found 255.0704.



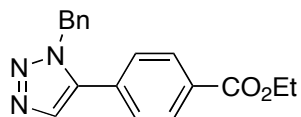
1-Benzyl-5-(naphthalen-1-yl)-4-phenyl-1,2,3-triazole 3a: Synthesized according to the general procedure. Exhibited identical spectral data according to previous report.⁹ White solid; **R_f** 0.45 (petroleum ether/ethyl acetate 60/40); **¹H NMR (400 MHz, CDCl₃)** δ 7.99 (d, J = 8.3 Hz, 1H), 7.92 (d, J = 8.2 Hz, 1H), 7.52–7.43 (m, 4H), 7.30–7.15 (m, 3H), 7.14–7.03 (m, 6H), 6.79 (d, J = 6.9 Hz, 2H), 5.37 (d, J = 14.9 Hz, 1H), 5.08 (d, J = 14.9 Hz, 1H); **¹³C NMR (100 MHz, CDCl₃)** δ 145.5, 134.8, 133.6, 131.9, 131.8, 130.9, 130.4, 129.2, 128.5, 128.4, 128.3, 128.1, 127.8, 127.7, 127.4, 126.7, 126.2, 125.4, 125.3, 124.6, 52.5.



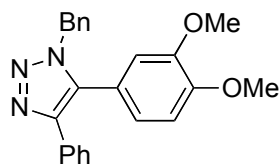
1-Benzyl-5-(4-methoxyphenyl)-1,2,3-triazole 4a: Synthesized according to the general procedure. Exhibited identical spectral data according to previous report.⁹ White solid; **R_f**

⁹ Chuprakov, S.; Chernyak, N.; Dudnik, A. S.; Gevorgyan, V. *Org. Lett.* **2007**, 2, 2333.

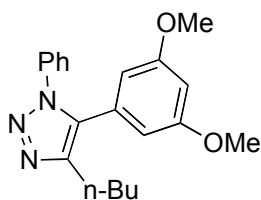
0.35 (petroleum ether/ethyl acetate 50/50); **¹H NMR (400 MHz, CDCl₃)** δ 7.69 (s, 1H), 7.33–7.26 (m, 3H), 7.19–7.15 (m, 2H), 7.11–7.07 (m, 2H), 6.96–6.90 (m, 2H), 5.53 (s, 2H), 3.84 (s, 3H); **¹³C NMR (100 MHz, CDCl₃)** δ 160.5, 138.0, 135.7, 133.0, 130.2, 128.8, 128.1, 127.1, 118.9, 114.4, 55.4, 51.6.



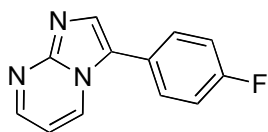
Ethyl 4-(1-benzyl-1,2,3-triazol-5-yl)benzoate 4b. Synthesized according to the general procedure. Exhibited identical spectral data according to previous report.⁹ Pale green solid; **R_f** 0.45 (petroleum ether/ethyl acetate 50/50); **¹H NMR (400 MHz, CDCl₃)** δ 8.08 (d, *J* = 8.6 Hz, 2H), 7.80 (s, 1H), 7.34 (d, *J* = 8.6 Hz, 2H), 7.31–7.27 (m, 3H), 7.07 (dd, *J* = 6.8, 2.8 Hz, 2H), 5.58 (s, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 1.41 (t, *J* = 7.1 Hz, 3H); **¹³C NMR (100 MHz, CDCl₃)** δ 165.7, 137.2, 135.2, 133.7, 131.4, 131.2, 130.1, 128.9, 128.8, 128.3, 127.1, 61.4, 52.1, 14.3.



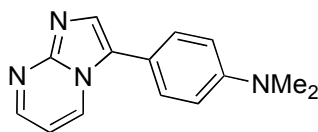
1-Benzyl-5-(3,4-dimethoxyphenyl)-4-phenyl-1,2,3-triazole 3b: Synthesized according to the general procedure. Pale yellow solid; **mp** 121–124 °C; **R_f** 0.4 (dichloromethane); **¹H NMR (400 MHz, CDCl₃)** δ 7.60 (d, *J* = 7.6 Hz, 2H), 7.32–7.19 (m, 6H), 7.06 (dd, *J* = 6.0, 2.4 Hz, 2H), 6.92 (d, *J* = 8.3 Hz, 1H), 6.77 (dd, *J* = 8.3, 1.7 Hz, 1H), 6.46 (d, *J* = 1.6 Hz, 1H), 5.41 (s, 2H), 3.94 (s, 3H), 3.57 (s, 3H); **¹³C NMR (100 MHz, CDCl₃)** δ 150.0, 149.2, 144.4, 135.8, 133.8, 131.0, 128.7, 128.4, 128.1, 127.7, 127.4, 126.5, 122.8, 119.8, 112.8, 111.5, 55.9, 55.7, 52.0; **IR (ν_{max}/cm⁻¹):** 3005, 2965, 2940, 2840, 1606, 1587, 1513, 1491, 1254, 1233, 1021; **HRMS** Calculated for C₂₃H₂₁N₃O₂ (M⁺) 371.1634, Found 371.1614.



4-*n*-Butyl-5-(3,5-dimethoxyphenyl)-1-phenyl-1,2,3-triazole 5: Synthesized according to the general procedure. White solid; **mp** 95–96 °C; **R_f** 0.15 (petroleum ether/ethyl acetate 80/20); **¹H NMR (400 MHz, CDCl₃)** δ 7.40–7.30 (m, 5H), 6.45 (t, *J* = 2.3 Hz, 2H), 6.28 (d, *J* = 2.3 Hz, 2H), 3.68 (s, 6H), 2.77 (dd, *J* = 7.6, 7.6 Hz, 2H), 1.73 (q, *J* = 7.6 Hz, 2H), 1.39 (sext, *J* = 7.4 Hz, 2H), 0.91 (t, *J* = 7.4 Hz, 1H); **¹³C NMR (100 MHz, CDCl₃)** δ 160.8, 146.2, 136.9, 133.7, 129.4, 129.1, 128.7, 124.8, 107.8, 100.9, 55.3, 31.8, 24.9, 22.5, 13.9; **IR (ν_{max}/cm⁻¹):** 3005, 2960, 2932, 2862, 2838, 1590, 1498, 1456, 1425, 1202, 1157, 1059; **HRMS** Calculated for C₂₀H₂₃NO₂ (M⁺ - N₂) 309.1729, Found 309.1733.



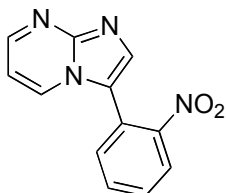
3-(4-Fluorophenyl)imidazo[1,2-a]pyrimidine 6a. Synthesized according to the general procedure. Exhibited identical spectral data according to previous report.¹⁰ Yellow solid; **R_f** 0.25 (dichloromethane/methanol 90/10); **¹H NMR (400 MHz, CDCl₃)** δ 8.59 (dd, *J* = 11.9, 2.0 Hz, 1H), 8.57 (dd, *J* = 14.8, 2.0 Hz, 1H), 7.87 (s, 1H), 7.56–7.49 (m, 2H), 7.29–7.22 (m, 2H), 6.91 (dd, *J* = 6.9, 4.0 Hz, 1H); **¹³C NMR (100 MHz, CDCl₃)** δ 162.8 (d, *J_{CF}* = 250 Hz), 149.6, 149.0, 133.9, 130.8, 130.0 (d, *J_{CF}* = 8 Hz), 124.4 (d, *J_{CF}* = 3 Hz), 123.3, 116.7 (d, *J_{CF}* = 22 Hz), 108.9; **¹⁹F NMR (377 MHz, CDCl₃)** δ -111.7.



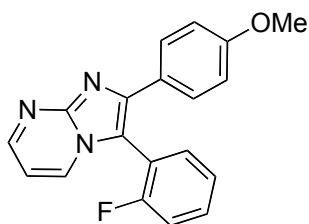
3-(4-*N,N*-dimethylaniline)imidazo[1,2-a]pyrimidine 6b: Synthesized according to the general procedure. Exhibited identical spectral data according to previous report.¹⁰

¹⁰ Li, W.; Nelson, D. P.; Jensen, M. S.; Hoerrner, R. S.; Javadi, G. J.; Cai, D.; Larsen, R. D. *Org. Lett.* **2003**, 5, 4835

Yellow solid; **R_f** 0.28 (dichloromethane/methanol 90/10); **¹H NMR (400 MHz, CDCl₃)** δ 8.59 (dd, *J* = 6.9, 2.0 Hz, 1H), 8.53 (dd, *J* = 4.0, 2.0 Hz, 1H), 7.80 (s, 1H), 7.41–7.37 (m, 2H), 6.88–6.82 (m, 3H), 3.04 (s, 6H); **¹³C NMR (100 MHz, CDCl₃)** δ 150.6, 148.8, 148.5, 132.9, 131.0, 129.1, 124.8, 115.4, 112.7, 108.4, 40.4.



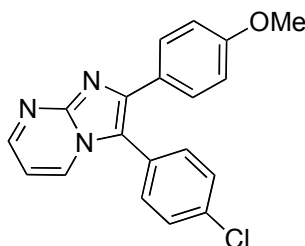
3-(2-Nitrophenyl)imidazo[1,2-a]pyrimidine 6c: Synthesized according to the general procedure. Exhibited identical spectral data according to previous report.¹⁰ Yellow solid; **R_f** 0.25 (dichloromethane/methanol 90/10); **¹H NMR (400 MHz, CDCl₃)** δ 8.65 (dd, *J* = 4.1, 2.0 Hz, 1H), 8.25 (dd, *J* = 8.2, 1.3 Hz, 1H), 8.02 (dd, *J* = 6.9, 2.0 Hz, 1H), 7.88 (s, 1H), 7.81 (td, *J* = 7.6, 1.4 Hz, 1H), 7.72 (ddd, *J* = 8.0, 7.6, 1.6 Hz, 1H), 7.60 (dd, *J* = 7.6, 1.5 Hz, 1H), 6.91 (dd, *J* = 6.9, 4.1 Hz, 1H); **¹³C NMR (100 MHz, CDCl₃)** δ 150.2, 149.2, 148.7, 135.3, 134.3, 133.9, 131.8, 130.7, 125.4, 122.9, 119.6, 108.9.



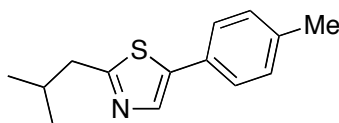
3-(2-Fluorophenyl)-2-(4-methoxyphenyl)imidazo[1,2-a]pyrimidine 7a. Synthesized according to the general procedure. Exhibited identical spectral data according to previous report.¹¹ Yellow solid; **R_f** 0.4 (dichloromethane/methanol 95/5); **¹H NMR (400 MHz, CDCl₃)** δ 8.57 (dd, *J* = 4.1, 2.0 Hz, 1H), 8.05 (dt, *J* = 6.8, 2.3 Hz, 1H), 7.72–7.67 (m, 2H), 7.54 (m, 1H), 7.40 (td, *J* = 7.4, 1.8 Hz, 1H), 7.36–7.24 (m, 2H), 6.89–6.81 (m, 3H), 3.81 (s, 3H); **¹³C NMR (100 MHz, CDCl₃)** δ 160.6 (d, *J_{CF}* = 249 Hz), 159.7, 149.7, 148.4, 145.1, 133.3 (d, *J_{CF}* = 3 Hz), 131.7 (d, *J_{CF}* = 8 Hz), 131.3 (d, *J_{CF}* = 3 Hz), 129.5,

11 Ermolat'ev, D. S.; Giménez, V. N.; Babaev, E. V.; Van der Eycken, E. *J. Comb. Chem.* **2006**, 8, 659.

125.9, 125.3 (d, $J_{CF} = 4$ Hz), 116.8, 116.6, 113.9, 112.7, 108.6, 55.2; ^{19}F NMR (377 MHz, CDCl_3) δ -110.7.

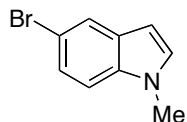


3-(4-Chlorophenyl)-2-(4-methoxyphenyl)imidazo[1,2-a]pyrimidine 7b: Synthesized according to the general procedure. Exhibited identical spectral data according to previous report.¹¹ Pale yellow solid; R_f 0.4 (dichloromethane/methanol 95/5); ^1H NMR (400 MHz, CDCl_3) δ 8.54 (m, 1H), 8.20 (m, 1H), 7.67 (d, $J = 8.4$ Hz, 2H), 7.53 (d, $J = 8.0$ Hz, 2H), 7.40 (d, $J = 8.1$ Hz, 2H), 6.90–6.77 (m, 3H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 159.7, 149.7, 148.1, 144.2, 135.3, 131.9, 130.2, 130.1, 129.6, 127.5, 125.8, 117.1, 113.9, 108.6, 55.2.

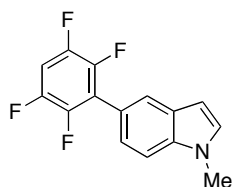


2-(iso-Butyl)-5-(p-tolyl)thiazole 8: Synthesized according to the general procedure. White solid; mp 30 °C; R_f 0.3 (petroleum ether/diethyl ether 90/10); ^1H NMR (400 MHz, CDCl_3) δ 7.78 (s, 1H), 7.42 (d, $J = 8.1$ Hz, 2H), 7.18 (d, $J = 7.9$ Hz, 2H), 2.87 (d, $J = 7.2$ Hz, 2H), 2.36 (s, 3H), 2.13 (sept, $J = 6.8$ Hz, 1H), 1.02 (d, $J = 6.6$ Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 169.1, 138.6, 137.9, 137.1, 129.7, 128.8, 126.5, 42.5, 29.8, 22.3, 21.2; IR ($\nu_{\text{max}}/\text{cm}^{-1}$): 2957, 2929, 2871, 1498, 1446, 1427, 1122; HRMS Calculated for $\text{C}_{14}\text{H}_{17}\text{NS}$ (M^+) 231.1082, Found 231.1072.

8.3.2 Section 3.5: Predictable and Site-Selective Functionalization of Poly-(Hetero)Arene Compounds by Palladium Catalysis



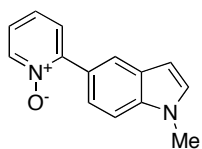
5-Bromo-*N*-methylindole: To a solution of 5-bromoindole (3.00 g, 15.30 mmol, 1 equiv.) in acetone (46.0 mL, 0.33 M) cooled to 0 °C was added freshly powdered potassium hydroxide (4.29 g, 77 mmol, 5 equiv.). After being stirred at 0 °C for 30 minutes, iodomethane (4.34 g, 30.6 mmol, 2 equiv.) was added dropwise while the solution was vigorously stirred. The reaction was slowly raised to room temperature and stirred overnight. The reaction was filtered and the solvent removed under reduced pressure. The crude product was purified by distillation on a Kugelrhor apparatus (115–125 °C) and isolated as a pale yellow solid in 94% yield and exhibited spectral data identical to previous reports.¹² **¹H NMR (400MHz, CDCl₃, 297K, TMS):** δ ppm 7.74 (dd, *J* = 1.9, 0.5 Hz, 1H), 7.29 (dd, *J* = 8.7, 1.9 Hz, 1H), 7.18 (d, *J* = 8.7 Hz, 1H), 7.04 (d, *J* = 3.1 Hz, 1H), 6.41 (dd, *J* = 3.1, 0.8 Hz, 1H), 3.76 (s, 3H).



***N*-Methyl-5-(2,3,5,6-tetrafluorophenyl)indole (9):** In a 4 mL screw cap vial was added potassium carbonate (658 mg, 4.76 mmol, 2 equiv.), SPhos (98 mg, 0.238 mmol, 10 mol%) and palladium(II) acetate (26.7 mg, 0.119 mmol, 5 mol%). The vial was purged with argon before a stock solution of 5-bromo-*N*-methylindole (500 mg, 2.380 mmol, 1 equiv.) in isopropyl acetate (2.4 mL) was added. The solution was stirred for 1 minute before 1,2,4,5-tetrafluorobenzene (1072 mg, 7.14 mmol, 3 equiv.) was added. The reaction was heated to 80 °C and stirred for 18 hours. Upon cooling, the reaction was

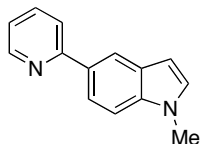
12 Soll, R. M.; Parks, J. A.; Rimele, T. J.; Heaslip, R. J.; Wojdan, A.; Oshiro, G.; Grimes, D.; Asselin, A. *Eur. J. Org. Chem.* **1990**, 25, 191.

diluted with ethyl acetate and filtered over celite. The filtrate was concentrated and the residues were purified by silica gel chromatography using 2% ether in petroleum ether as the eluent. The product was isolated as a white solid in 52% yield. **Mp**: 125–128 °C (CHCl₃); **R_f**: 0.55 (2% ether, petroleum ether); **¹H NMR (400MHz, CDCl₃, 296K, TMS)**: δ ppm 7.74–7.71 (m, 1H), 7.43 (d, *J* = 8.5 Hz, 1H), 7.30 (dddd, *J* = 8.5, 1.5, 1.5, 1.5 Hz, 1H), 7.12 (d, *J* = 3.1 Hz, 1H), 7.03 (dddd, *J* = 9.7, 9.7, 7.3, 7.3 Hz, 1H), 6.56 (dd, *J* = 3.1, 0.8 Hz, 1H), 3.84 (s, 3H); **¹³C NMR (100MHz, CDCl₃, 297K, TMS)**: δ ppm 147.7–144.80 (m), 145.4–142.5 (m), 136.7, 129.8, 128.5, 123.3 (t, *J* = 1.8 Hz), 123.0 (t, *J* = 1.9 Hz), 122.9 (t, *J* = 16.7 Hz), 118.2 (t, *J* = 2.3 Hz), 109.4, 103.9 (t, *J* = 22.8 Hz), 101.6, 32.9; **IR (ν_{max}/cm⁻¹)**: 2931, 1515, 1506, 1487, 1170, 931, 887, 738, 708; **HRMS** calculated for C₁₅H₉F₄N (M⁺) 279.0671; Found: 279.0665.



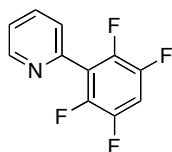
2-(N-Methylindol-5-yl)pyridine N-oxide (10). In a test tube was added potassium carbonate (214 mg, 1.55 mmol, 1.3 equiv.), tri-*tert*-butylphosphonium tetrafluoroborate (20.7 mg, 0.071 mmol, 10 mol%), palladium(II) acetate (13.4 mg, 0.060 mmol, 5 mol%) and pyridine *N*-oxide (453 mg, 4.76 mmol, 4 equiv.). The tube was fitted with a septum, purged with argon before a solution of 5-bromo-*N*-methylindole (250 mg, 1.190 mmol, 1 equiv.) in toluene (4 mL, 0.3 M) was added. The septum was covered in parafilm and the reaction was heated to 110 °C and stirred for 18 hours. Upon cooling, the reaction was diluted with dichloromethane and filtered over celite. The filtrate was concentrated and the residues were purified by silica gel chromatography using 3% methanol and 5% acetone in chloroform as the eluent. The product was isolated as an off-white solid in 63% yield. **Mp**: 138–142 °C (CHCl₃); **R_f**: 0.25 (3% MeOH, 5% Me₂CO, CHCl₃) **¹H NMR (400MHz, CDCl₃, 296K, TMS)**: δ ppm 8.35 (d, *J* = 5.6 Hz, 1H), 8.05 (s, 1H), 7.73 (d, *J* = 8.5 Hz, 1H), 7.48 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.40 (d, *J* = 8.4 Hz, 1H), 7.28 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.17 (dd, *J* = 5.7, 5.7 Hz, 1H), 7.09 (d, *J* = 3.1 Hz, 1H), 6.55 (d, *J* = 3.1 Hz, 1H), 3.81 (s, 3H); **¹³C NMR (100MHz, CDCl₃, 298K, TMS)**: δ ppm 150.7, 140.6, 137.1, 129.6, 128.2, 127.6, 125.7, 123.8, 123.6, 122.8, 122.5, 109.0, 101.9,

33.0; **IR** ($\nu_{\max}$ / cm^{-1}): 3102, 2948, 1606, 1513, 1476, 1421, 1339, 1245, 842, 763, 734; **HRMS** calculated for $\text{C}_{14}\text{H}_{12}\text{N}_2\text{O}$ (M^+) 224.0950; Found: 224.0930.



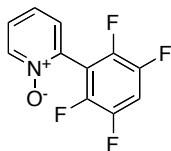
N-Methyl-5-(pyridin-2-yl)indole (11): In a round bottom flask was dissolved the pyridine-*N*-oxide in methanol and to the solution was added palladium on carbon, the flask was purged with hydrogen gas and vigorously stir under hydrogen atmosphere until the reaction was judged completed by TLC.

Alternatively, **11** was prepared by mixing in a flask, equip with a stir bar, zinc dust <10 micron (~4 to 5 equiv.), the starting pyridine-*N*-oxide and a 1:1 mixture of THF and a saturated aqueous solution of NH_4Cl . The mixture was vigorously stirred at ambient temperature for ~30 minutes. The crude is extracted with ethyl acetate and purified by silica gel chromatography. Pale yellow solid; **mp**: 54–58 °C; **R_f**: 0.49 (MeOH/DCM 5/95); **¹H NMR (400 MHz, CDCl_3)** δ ppm 8.68 (ddd, $J = 4.8, 1.8, 1.0$ Hz, 1H), 8.26 (dd, $J = 1.7, 0.6$ Hz, 1H), 7.92 (dd, $J = 8.6, 1.6$ Hz, 1H), 7.78 (dt, $J = 8.0, 1.1$ Hz, 1H), 7.72 (ddd, $J = 8.0, 7.3, 1.8$ Hz, 1H), 7.40 (dt, $J = 8.6, 0.7$ Hz, 1H), 7.16 (ddd, $J = 7.3, 4.8, 1.2$ Hz, 1H), 7.08 (d, $J = 3.1$ Hz, 1H), 6.56 (dd, $J = 3.1, 0.8$ Hz, 1H), 3.82 (s, 3H); **¹³C NMR (100 MHz, CDCl_3)** δ ppm 158.9, 149.6, 137.4, 136.7, 131.1, 129.7, 128.9, 121.15, 121.0, 120.5, 119.8, 109.5, 102.0, 33.1; **IR** ($\nu_{\max}$ / cm^{-1}): 3086, 3002, 2939, 1583, 1512, 1462, 1422, 1341, 1304, 1247, 1150, 777, 761, 686; **HRMS** Calculated for $\text{C}_{14}\text{H}_{12}\text{N}_2$ (M^+) 208.1000, found 208.0975.

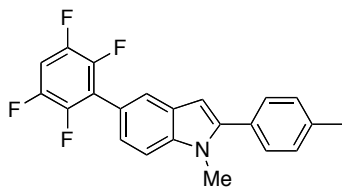


2-(2,3,5,6-Tetrafluorophenyl)pyridine (12): $\text{Pd}(\text{OAc})_2$ (5 mol%), di-*tert*-butylmethylphosphonium tetrafluoroborate (10 mol%), K_2CO_3 (1.1 equiv.) were weighed to air and placed in a screw-cap vial equipped with a magnetic stir bar. 2-Bromopyridine (1.0 equiv.) was added at this point. The vial was purged with argon and a solution of 1,2,4,5-

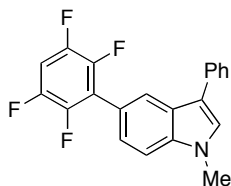
tetrafluorobenzene (3.0 equiv.) in dimethylacetamide (DMA) (3.0 M) was added to the mixture. The reaction mixture was then stirred vigorously at 120 °C for 16 hours. The solution was then cooled to ambient temperature and diluted with ethyl acetate, then filtered and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography to afford the corresponding product. Yellow solid; **mp**: 74–76 °C; **R_f**: 0.36 (petroleum ether/ethyl acetate 80/20); **¹H NMR (400 MHz, CDCl₃)** δ ppm 8.79 (ddd, $J = 4.9, 1.8, 0.9$ Hz, 1H), 7.85 (td, $J = 7.8, 1.8$ Hz, 1H), 7.51 (dt, $J = 7.9, 1.2$ Hz, 1H), 7.39 (ddd, $J = 7.7, 4.9, 1.2$ Hz, 1H), 7.14 (tt, $J_{\text{HF}} = 9.6, 7.3$ Hz, 1H); **¹³C NMR (100 MHz, CDCl₃)** δ ppm 150.2, 147.9, 146.3 (dddd, $J_{\text{CF}} = 248.2, 14.6, 10.2, 4.2$ Hz), 144.4 (dtd, $J_{\text{CF}} = 249.5, 9.3, 5.2$ Hz), 136.8, 126.0, 123.9, 120.9 (t, $J_{\text{CF}} = 16.3$ Hz), 106.2 (t, $J_{\text{CF}} = 22.6$ Hz); **IR** (ν_{max} /cm⁻¹): 3032, 2926, 1590, 1572, 1511, 1499, 1297, 1198, 939; **HRMS** Calculated for C₁₁H₅NF₄ (M⁺) 227.0358, found 227.0349.



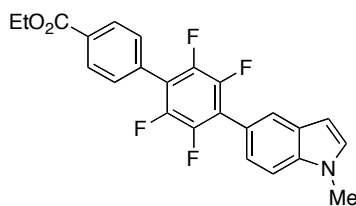
2-(2,3,5,6-Tetrafluorophenyl)pyridine N-oxide (13). 2-(2,3,5,6-Tetrafluorophenyl)pyridine (**12**) was dissolved in DCM (~0.3 M), few mg of MeReO₄ was added to the solution. Then a 50% solution of H₂O₂ in water (approximately 1/5 of the volume of DCM) was added, the mixture was stirred vigorously at ambient temperature until the reaction was judge completed by TLC. The solution was then extracted with ethyl acetate, dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography to afford the corresponding product. White solid; **mp**: 167–168 °C; **R_f**: 0.36 (MeOH/DCM 5/95); **¹H NMR (400 MHz, CDCl₃)** δ ppm 8.39 (d, $J = 6.4$ Hz, 1H), 7.43–7.34 (m, 3H), 7.21 (quin, $J = 8.4$ Hz, 1H); **¹³C NMR (100 MHz, CDCl₃)** δ ppm 146.3 (dm, $J_{\text{CF}} = 252$ Hz), 144.5 (dm, $J_{\text{CF}} = 252$ Hz), 140.5, 138.5 129.2, 126.9, 124.9, 107.7 (m); **IR** (ν_{max} /cm⁻¹): 3052, 3024, 3007, 1500, 1432, 1257, 1188, 940, 896, 763; **HRMS** Calculated for C₁₁H₅NOF₄ (M⁺) 243.0307, found 243.0327.



N-Methyl-5-(2,3,5,6-tetrafluorophenyl)-2-p-tolylindole (CW-1): Synthesized according to the general procedure of Conditions A. The product was isolated as a white solid in 64% yield. **mp:** 152–155 °C (CHCl₃); **R_f:** 0.45 (2% ether, petroleum ether); **¹H NMR (400MHz, CDCl₃, 296K, TMS):** δ ppm 7.72 (d, *J* = 0.9 Hz, 1H), 7.46 (d, *J* = 8.5 Hz, 1H), 7.43–7.40 (m, 2H), 7.33–7.28 (m, 3H), 7.03 (dddd, *J*_{HF} = 9.7, 9.7, 7.3, 7.3 Hz, 1H), 6.60 (d, *J* = 0.7 Hz, 1H), 3.78 (s, 3H), 2.44 (s, 3H); **¹³C NMR (100MHz, CDCl₃, 298K, TMS):** δ ppm 147.9–144.6 (m), 145.4–142.8 (m), 142.7, 138.3, 138.2, 129.5, 129.3 (two overlapping carbon signals), 128.0, 123.3 (dd, *J* = 1.8, 1.8 Hz), 122.9 (dd, *J* = 17.3, 17.3 Hz), 122.5 (dd, *J* = 1.8, 1.8 Hz), 118.6 (dd, *J* = 2.4, 2.4 Hz), 109.7, 103.9 (dd, *J* = 22.5, 22.5 Hz), 101.7, 31.3, 21.3; **IR (ν_{max} /cm⁻¹):** 3075, 2928, 1493, 1171, 939; **HRMS** calculated for C₂₂H₁₅F₄N (M⁺) 369.1141; Found: 369.1116.

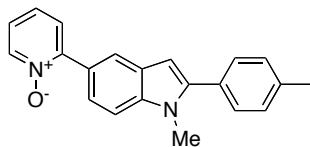


N-Methyl-3-phenyl-5-(2,3,5,6-tetrafluorophenyl)indole (CW-2): Synthesized according to the procedure of Conditions B. Yellow solid; **mp:** 123–125 °C (CHCl₃); **R_f:** 0.27 (2% ether, petroleum ether); **¹H NMR (400MHz, CDCl₃, 296K, TMS):** δ ppm 8.01 (d, *J* = 0.7 Hz, 1H), 7.63 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.49–7.41 (m, 3H), 7.35 (ddd, *J* = 8.5, 2.9, 1.4 Hz, 1H), 7.30–7.26 (m, 1H), 7.29 (s, 1H), 7.04 (dddd, *J* = 9.7, 9.7, 7.3, 7.3 Hz, 1H), 3.89 (s, 3H); **¹³C NMR (100MHz, CDCl₃, 297K, TMS):** δ ppm 147.8–144.7 (m), 145.4–142.4 (m), 137.5, 135.0, 128.9, 127.4, 127.4, 126.2, 126.1, 123.8 (dd, *J*_{CF} = 1.7, 1.7 Hz), 122.8 (dd, *J*_{CF} = 17.1, 17.1 Hz), 122.1 (dd, *J*_{CF} = 1.8, 1.8 Hz), 118.8 (dd, *J*_{CF} = 2.2, 2.2 Hz), 109.7, 117.4, 104.0 (dd, *J*_{CF} = 22.9, 22.9 Hz), 33.0; **IR (ν_{max} /cm⁻¹):** 3075, 2948, 1604, 1491, 1456, 1223, 1171, 939, 751, 710; **HRMS** calculated for C₂₁H₁₃F₄N (M⁺) 355.0984; Found: 355.0990.

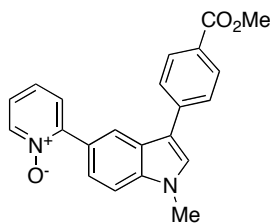


Ethyl *N*-methyl-5-(2,3,5,6-tetrafluoro-4'-carboxylatebiphenyl-4-yl)indole (14):

Synthesized according to the procedure of Conditions C and D. The product was isolated as a white solid in 54% yield with conditions C and in 58% yield with conditions D. **Mp**: 177–179 °C (CHCl₃); **R_f**: 0.21 (5% ether, petroleum ether); **¹H NMR (400MHz, CDCl₃, 296K, TMS)**: δ ppm 1.43 (t, *J* = 7.1 Hz, 3H), 3.86 (s, 3H), 4.43 (q, *J* = 7.1 Hz, 2H), 6.58 (dd, *J* = 3.1, 0.7 Hz, 1H), 7.14 (d, *J* = 3.1 Hz, 1H), 7.36 (ddd, *J* = 8.4, 2.9, 1.4 Hz, 1H), 7.46 (d, *J* = 8.6 Hz, 1H), 7.62 (ddd, *J* = 8.6, 1.4, 1.4 Hz, 2H), 7.79 (d, *J* = 0.8 Hz, 1H), 8.19 (ddd, *J* = 8.6, 1.8 Hz, 2H); **¹³C NMR (100MHz, CDCl₃, 298K, TMS)**: δ ppm 14.3, 33.0, 61.2, 101.7, 109.4, 117.6 (dd, *J*_{CF} = 16.5, 16.5 Hz), 118.0 (dd, *J*_{CF} = 2.0, 2.0 Hz), 121.9 (dd, *J*_{CF} = 16.8, 16.8 Hz), 123.1 (dd, *J*_{CF} = 1.7, 1.7 Hz), 123.4 (dd, *J*_{CF} = 1.6, 1.6 Hz), 128.5, 129.7, 129.9, 130.3 (dd, *J*_{CF} = 2.0, 2.0 Hz), 130.9, 132.3 (dd, *J*_{CF} = 2.0, 2.0 Hz), 136.8, 145.4–142.6 (m), 145.8–143.0 (m), 166.1; **IR (ν_{max}/cm⁻¹)**: 2958, 2908, 1710, 1479, 1271, 1100; **HRMS** calculated for C₂₄H₁₇F₄NO₂ (M⁺) 427.1195; Found: 427.1180.

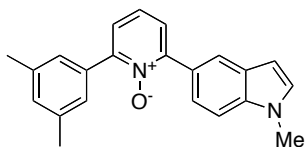


2-(*N*-Methyl-2-*p*-tolylindol-5-yl)pyridine *N*-oxide (15): Synthesized according to the general procedure of Conditions A. The product was isolated as a white solid in 53% yield. Beige solid; **mp** 156–160 °C; **R_f** 0.27 (MeOH/Acetone/DCM 5:30:65); **¹H NMR (400 MHz, CDCl₃)** δ ppm 8.42–8.40 (m, 1H), 8.06 (d, *J* = 0.8 Hz, 1H), 7.78–7.74 (m, 1H), 7.54–7.40 (m, 4H), 7.36–7.18 (m, 4H), 6.60 (s, 1H), 3.77 (s, 3H), 2.43 (s, 3H); **¹³C NMR (100 MHz, CDCl₃)** δ ppm 150.9, 142.6, 140.7, 138.8, 138.1, 132.5, 129.6, 129.4 (2 carbons), 127.8, 126.4, 124.2, 123.7, 122.9, 122.1, 109.4, 102.2, 31.4, 21.4; **IR (ν_{max}/cm⁻¹)**: 3024, 2950, 2920, 1616, 1472, 1233, 759; **HRMS** Calculated for C₂₁H₁₈N₂O (M⁺) 314.1419, found 314.1391.



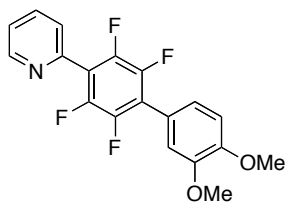
2-(3-(4-(Methoxycarbonyl)phenyl)-1-methyl-1H-indol-5-yl)pyridine-N-oxide (17):

Synthesized according to the general procedure of Conditions B. The product was isolated as a white solid in 55% yield. Yellow solid; decomposed at ~210 °C; **R_f** 0.58 (MeOH/DCM 2/98); **¹H NMR (400 MHz, CDCl₃)** δ ppm 8.69 (d, *J* = 4.7 Hz, 1H), 8.17 (d, *J* = 1.1 Hz, 1H), 7.99 (dd, *J* = 8.7, 1.6 Hz, 1H), 7.74 (td, *J* = 8.0, 1.7 Hz, 1H), 7.72 (d, *J* = 1.4 Hz, 1H), 7.52 (d, *J* = 10.2 Hz, 2H), 7.42 (d, *J* = 8.6 Hz, 1H), 7.20 (ddd, *J* = 6.5, 4.7, 1.9 Hz, 1H), 6.98 (s, 1H), 6.43 (d, *J* = 10.2 Hz, 2H), 3.84 (s, 3H), 3.80 (s, 3H); **¹³C NMR (100 MHz, CDCl₃)** δ ppm 185.1, 170.2, 158.3, 149.7, 147.6, 143.4, 138.0, 136.8, 132.0, 128.7, 127.4, 125.6, 122.0, 121.5, 120.5, 117.9, 110.9, 110.4, 53.6, 33.2; **IR (ν_{max}/cm⁻¹):** 3057, 2961, 2871, 1714, 1589, 1466, 1278, 1162, 773; **HRMS** Calculated for C₂₂H₁₈N₂O₃ (M⁺) 358.1317, found 358.1310.



2-(3,5-Dimethylphenyl)-6-(N-methylindol-5-yl)pyridine N-oxide (13):

Synthesized according to the procedure of Conditions E and F. The product was isolated as a white solid in 24% yield with conditions E and in 51% yield with conditions F. Off-white solid; **mp:** 195–198 °C (CHCl₃); **R_f:** 0.45 (3% Me₂CO, CHCl₃); **¹H NMR (400MHz, CDCl₃, 296K, TMS):** δ ppm 8.10 (dd, *J* = 1.6, 0.4 Hz, 1H), 7.78 (dd, *J* = 8.7, 1.6 Hz, 1H), 7.47–7.42 (m, 3H), 7.37 (d, *J* = 8.7 Hz, 1H), 7.33 (dd, *J* = 7.8, 2.4 Hz, 1H), 7.28 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.05 (m, 2H), 6.52 (dd, *J* = 3.1, 0.8 Hz, 1H), 3.80 (s, 3H), 2.36 (s, 6H); **¹³C NMR (100MHz, CDCl₃, 298K, TMS):** δ ppm 151.1, 150.2, 137.5, 137.0, 133.6, 130.8, 129.4, 128.1, 127.3, 126.2, 125.3, 124.8, 124.5, 123.2, 122.8, 108.6, 101.8, 32.9, 21.3; **IR (ν_{max}/cm⁻¹):** 3005, 2951, 1556, 1476, 1358, 1246, 1226, 786, 721; **HRMS** calculated for C₂₂H₂₀N₂O (M⁺) 328.1576; Found 328.1556.

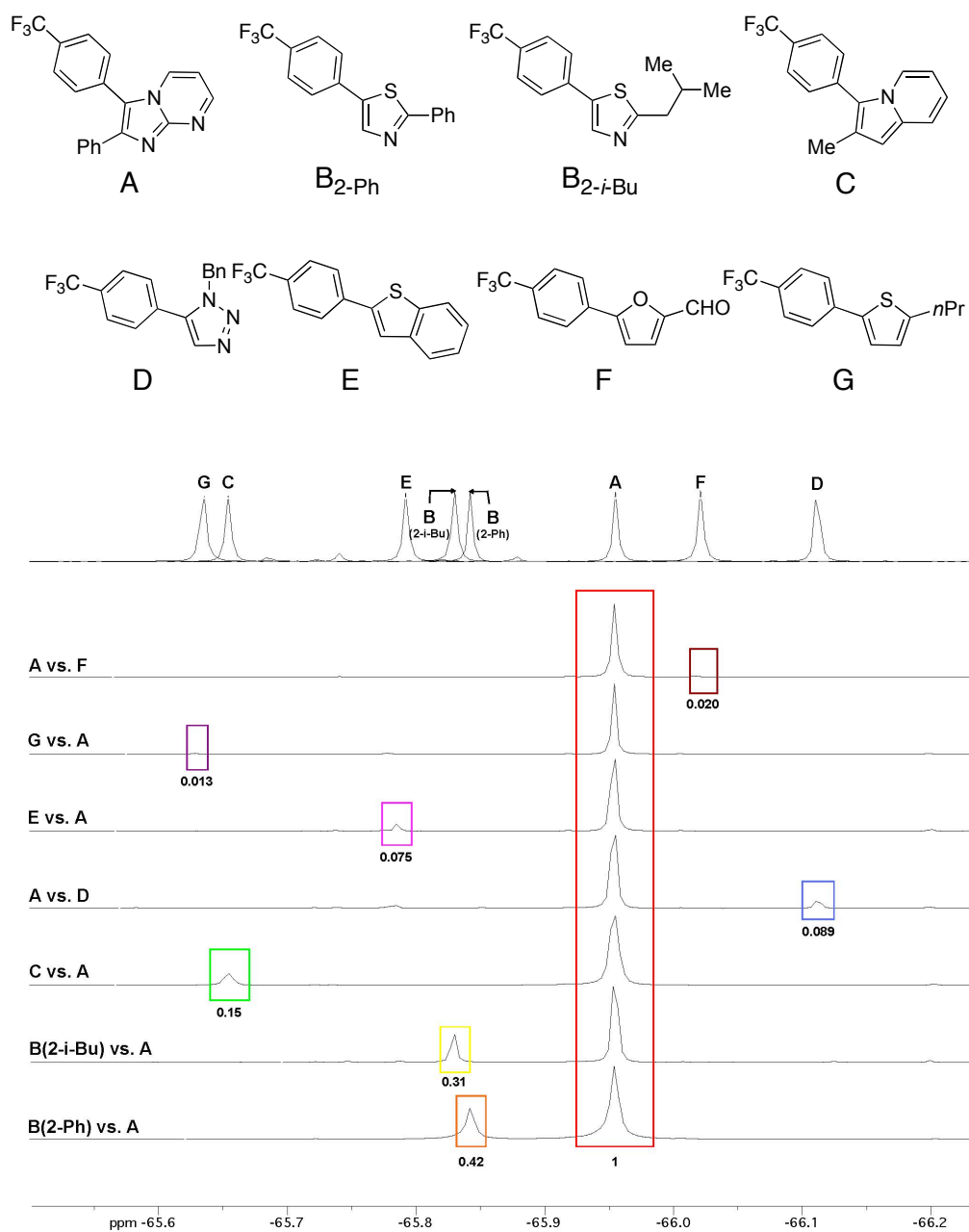


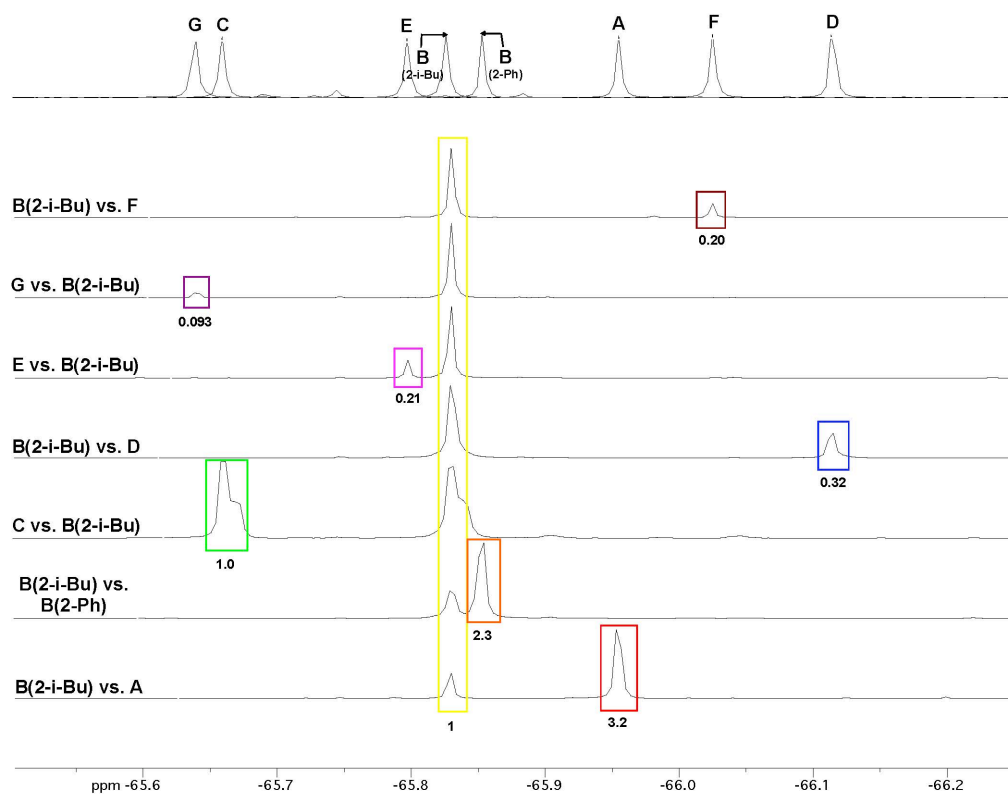
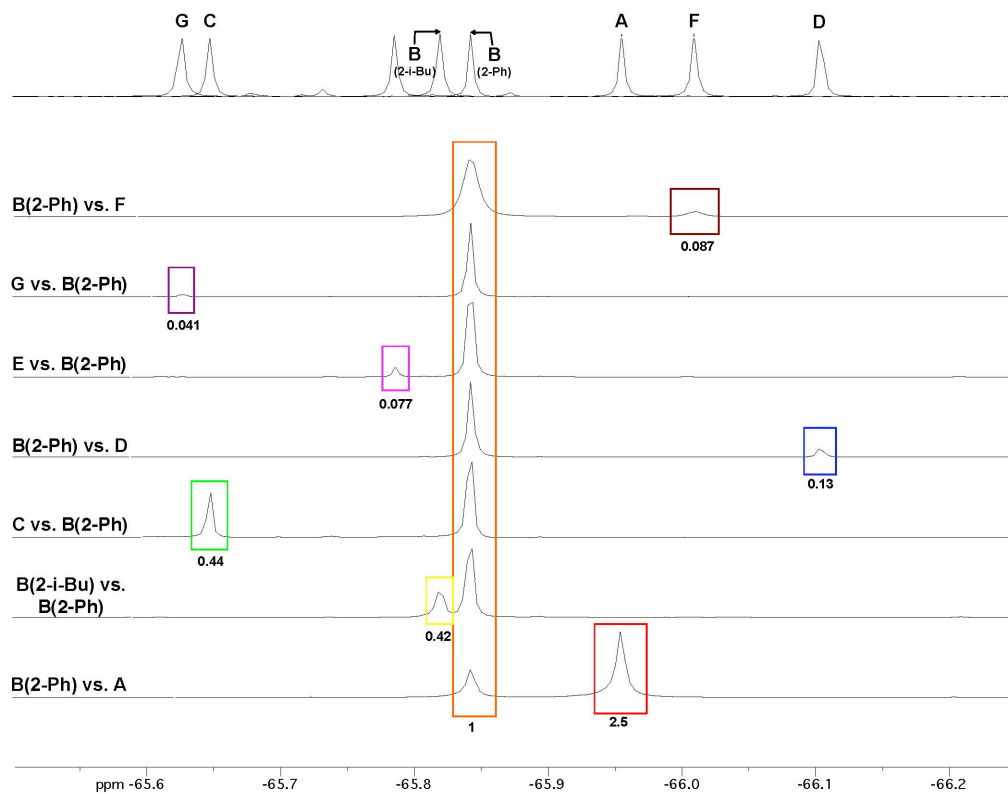
2-(2,3,5,6-Tetrafluoro-3',4'-dimethoxybiphenyl-4-yl)pyridine (21): Synthesized according to the general procedure of Conditions C. White solid; **mp**: 154–156 °C; **R_f**: 0.21 (petroleum ether/ethyl acetate 80/20); **¹H NMR (400 MHz, CDCl₃)** δ ppm 8.81 (ddd, *J* = 4.9, 1.8, 0.9 Hz, 1H), 7.86 (td, *J* = 7.8, 1.8 Hz, 1H), 7.56 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.39 (ddd, *J* = 7.7, 4.9, 1.1 Hz, 1H), 7.11 (dq, *J* = 8.3, 1.6 Hz, 1H), 7.03 (q, *J* = 1.6 Hz, 1H), 7.01 (d, *J* = 8.4 Hz, 1H), 3.96 (s, 3H), 3.93 (s, 3H); **¹³C NMR (100 MHz, CDCl₃)** δ ppm 150.2, 149.9, 149.0, 148.0, 136.7, 126.1, 123.7, 123.3, 120.8 (t, *J_{CF}* = 16.7 Hz), 119.6, 118.6 (t, *J_{CF}* = 16.2 Hz), 113.3, 111.2, 56.1, 56.0; **IR (ν_{max} /cm⁻¹)**: 3015, 2987, 2949, 2914, 2844, 1586, 1524, 1482, 1456, 1261, 980; **HRMS** Calculated for C₁₉H₁₃NO₂F₄ (M⁺) 363.0882, found 363.0887.

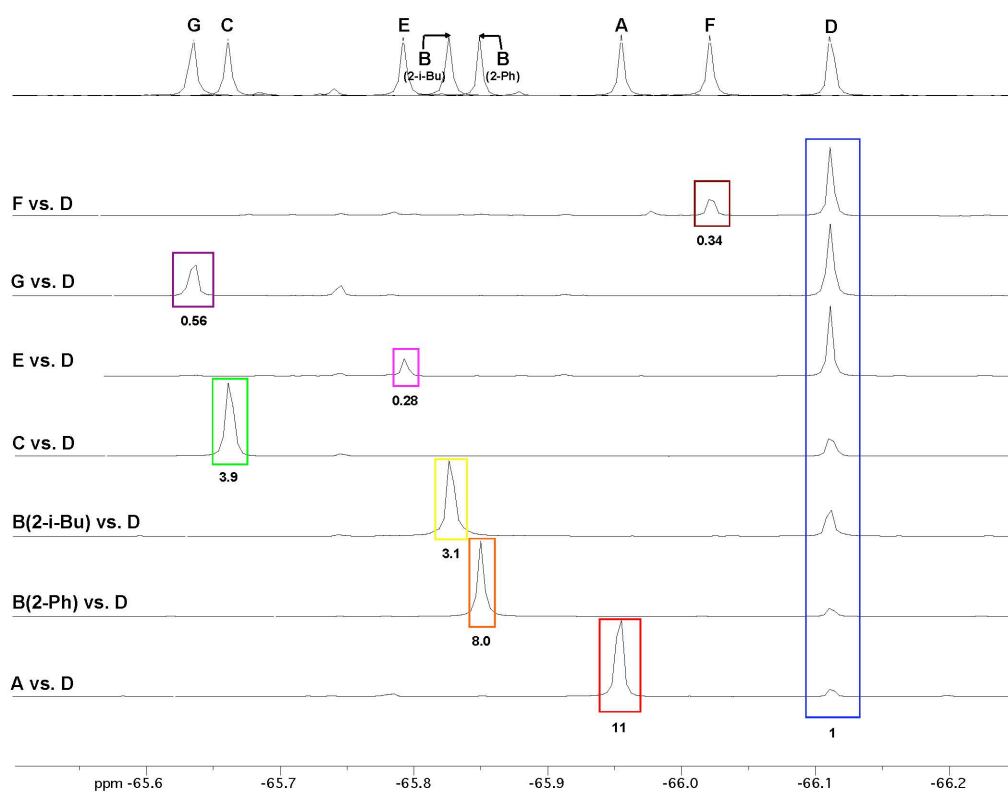
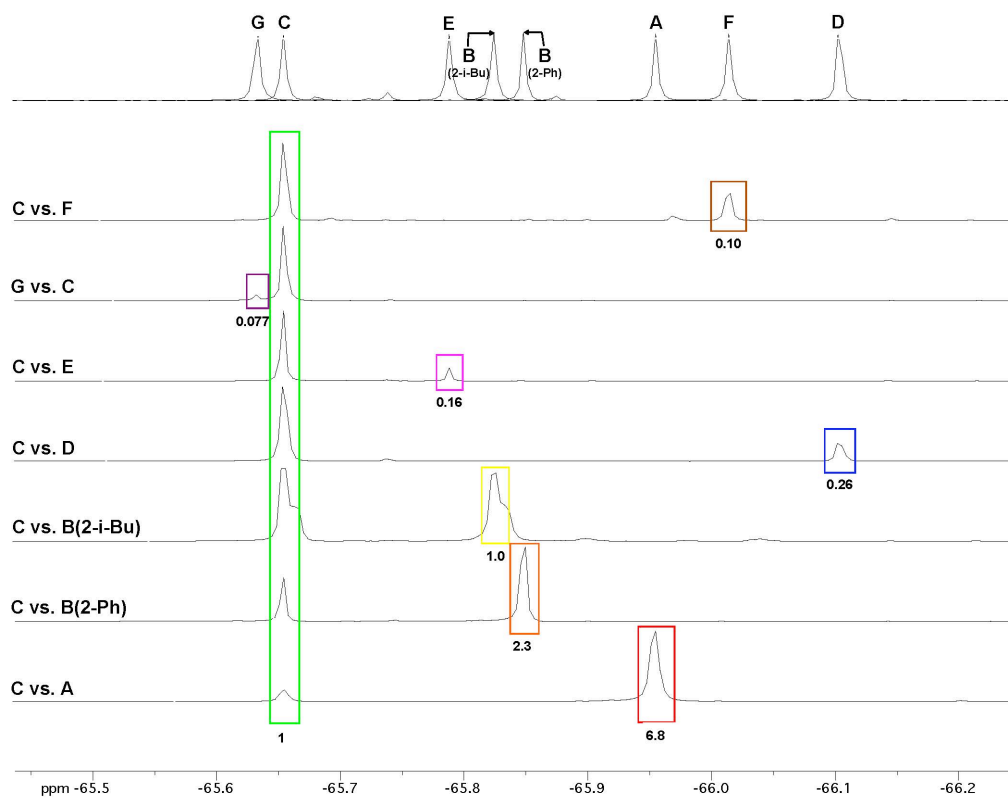
Section 3.5.2: General procedure and NMR spectra of the Competition Experiments of Figure 3.13

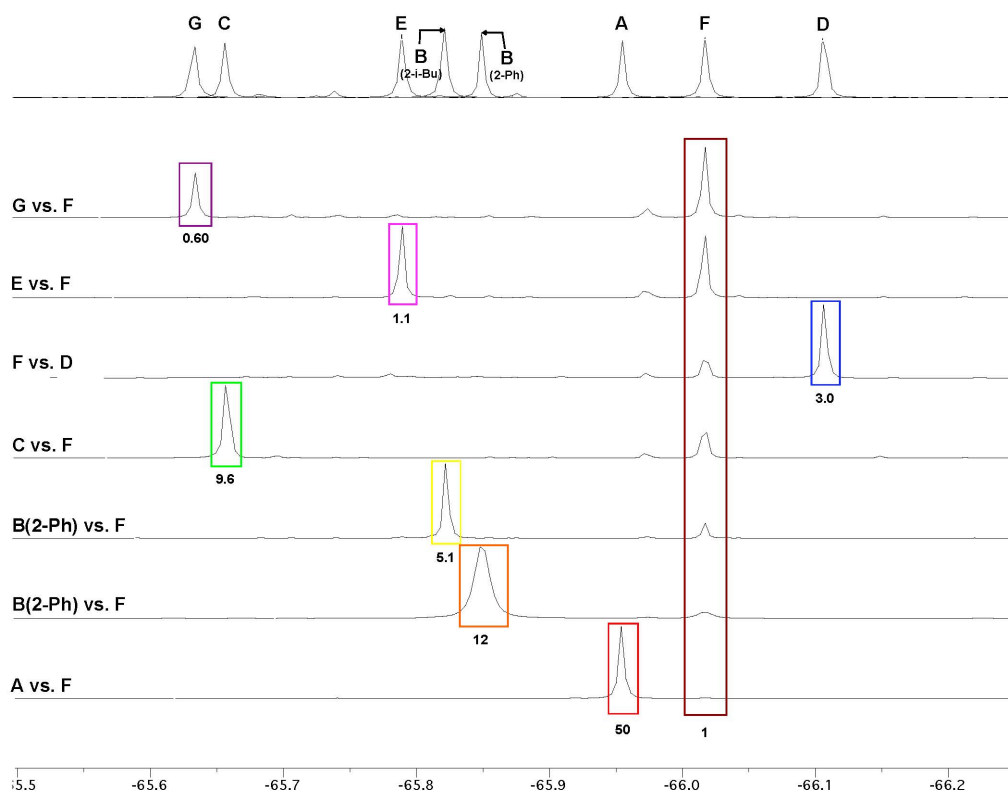
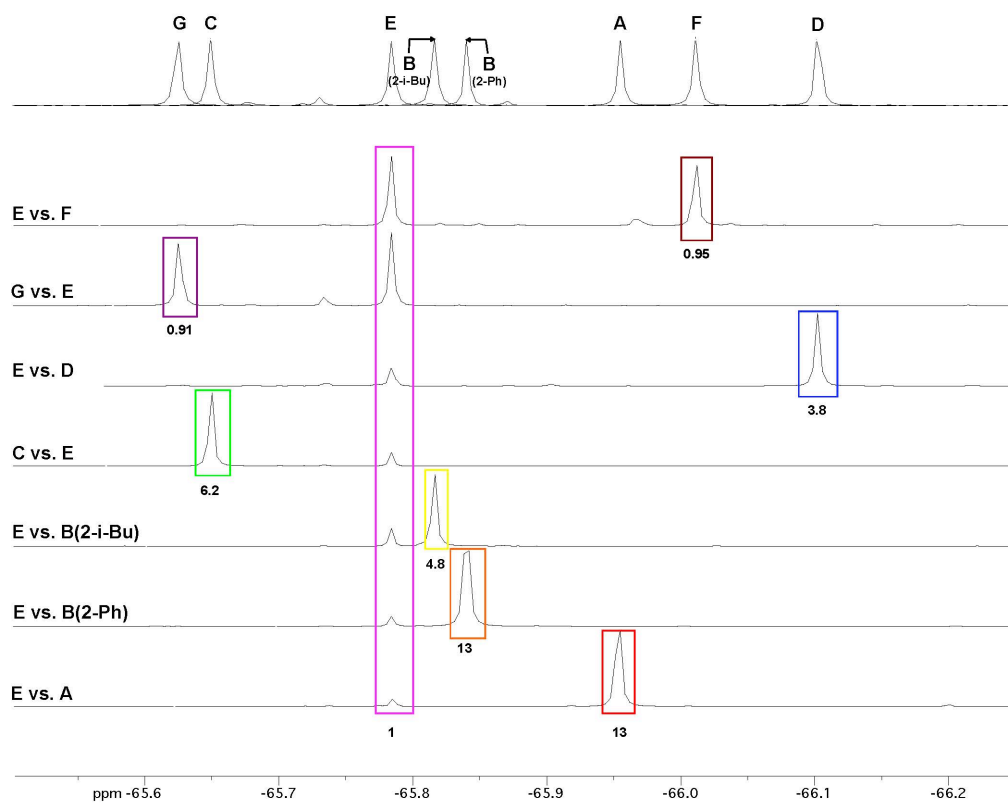
General procedure for the direct arylation of heterocycles: Pd(OAc)₂ (6.7 mg, 0.030 mmol, 5 mol%), tricyclohexylphosphonium tetrafluoroborate (22.1 mg, 0.060 mmol, 10 mol%), K₂CO₃ (124 mg, 0.90 mmol, 1.5 equiv.) and PivOH (18.4 mg, 0.18 mmol, 30 mol%) were weighed to air and placed in a screw-cap vial equipped with a magnetic stir bar. The heteroarenes (0.30 mmol, 0.5 equiv. each), if a solid, were then added at that point. The vial was purged with argon and a solution of the *p*-CF₃-bromobenzene (16.9 mg, 0.075 mmol, 0.125 equiv.) and the heteroarenes (0.30 mmol, 0.5 equiv. each), if liquid, in dimethylacetamide (2.0 mL, 0.3 M) was added to the mixture. The reaction mixture was then stirred vigorously at 100 °C overnight. The solution was then cooled to ambient temperature and then filtered and evaporated under reduced pressure. The remaining solvent was then removed under reduced pressure using a Kugelrohr apparatus. The crude mixture was then analyzed by ¹⁹F NMR spectroscopy.

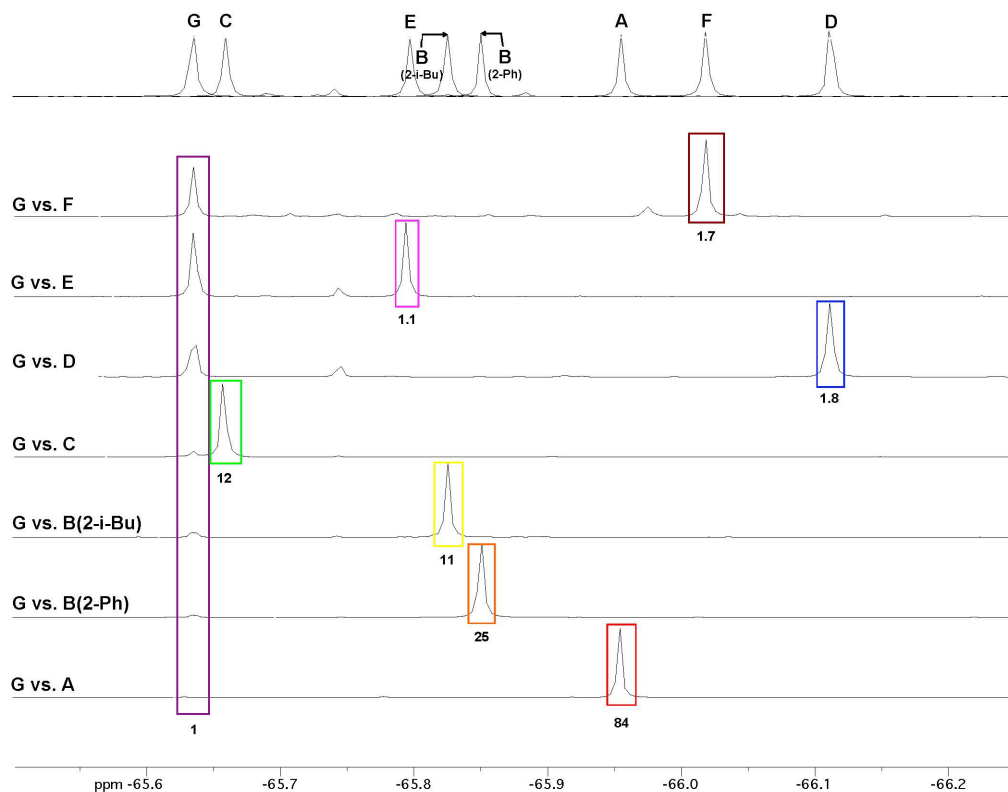
Figure 8.1 Label compounds for the competition experiments.



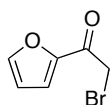






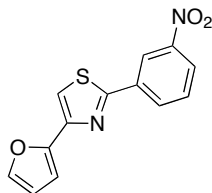


Preparation of the model substrates:

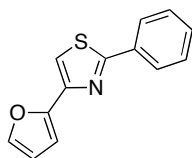


2-Bromo-1-(furan-2-yl)ethanone (22): A solution of 2-acetylfuran (1.0 equiv.) in ethyl acetate (0.1 M) was added to a reaction flask equipped with a magnetic stir bar, followed by the addition of copper(II) bromide (1.7 equiv.). The reaction mixture was then stirred vigorously and heated to reflux. When the reaction reached completion, as judged by TLC, the reaction mixture was allowed to cool to room temperature, filtered and evaporated under reduced pressure. The crude product was purified using silica gel column chromatography to afford furan-2-carbonyl bromide as a white solid in 70% yield. R_f 0.21 (petroleum ether/ethyl acetate 90/10); ^1H NMR matched the previously

reported spectrum.¹³ **¹H NMR (400MHz, CDCl₃, 296K, TMS):** δ ppm 7.65 (dd, J = 1.7, 0.8 Hz, 1H), 7.35 (dd, J = 3.6, 0.8 Hz, 1H), 6.61 (dd, J = 3.6, 1.7 Hz, 1H), 4.33 (s, 2H).



Synthesis of 4-(furan-2-yl)-2-(3-nitrophenyl)thiazole (16). Synthesized following a literature procedure.¹⁴ To a solution of furan-2-carbonyl bromide (1.0 equiv.) and 3-nitrobenzothioamide (1.0 equiv.) in tetrahydrofuran (1.0 M) was added to a reaction flask equipped with a magnetic stir bar. The reaction mixture was stirred vigorously and heated to reflux until judged complete by TLC. The solution was then evaporated under reduced pressure, and the crude product purified by silica gel column chromatography in 10 – 20% ethyl acetate/petroleum ether to afford 4-(furan-2-yl)-2-(3-nitrophenyl)thiazole (**16**) in 92% yield. Yellow solid; **mp**: 116–118 °C; **R_f**: 0.47 (petroleum ether/ethyl acetate 80/20); **¹H NMR (400 MHz, CDCl₃)** δ ppm 8.85 (t, J = 2.0 Hz, 1H), 8.33 (ddd, J = 7.8, 1.7, 1.0 Hz, 1H), 8.28 (ddd, J = 8.2, 2.3, 1.0 Hz, 1H), 7.65 (t, J = 8.0 Hz, 1H), 7.51 (s, 1H), 7.49 (dd, J = 1.8, 0.8 Hz, 1H), 6.94 (dd, J = 3.4, 0.5 Hz, 1H), 6.53 (dd, J = 3.4, 1.8 Hz, 1H); **¹³C NMR (100 MHz, CDCl₃)** δ ppm 165.5, 149.9, 148.8, 148.7, 142.7, 135.1, 132.3, 130.1, 124.6, 121.6, 113.0, 111.8, 107.9; **IR (ν_{max} /cm⁻¹):** 3116, 3093, 1531, 1348, 1024; **HRMS** Calculated for C₁₃H₈N₂O₃S (M⁺) 272.0256, found 272.0271.

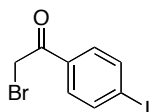


4-(Furan-2-yl)-2-phenylthiazole: Synthesized using the same procedure as compound **16**, isolated in 74 % yield. Orange solid; **mp**: 56–57 °C; **R_f**: 0.44 (petroleum ether/ethyl acetate 90/10); **¹H NMR (400 MHz, CDCl₃)** δ ppm 8.01–7.99 (m, 2H), 7.46–7.43 (m, 4H), 7.40 (s, 1H), 6.89 (dd, J = 3.2, 0.5 Hz, 1H), 6.50 (dd, J = 3.3, 1.8 Hz, 1H); **¹³C NMR**

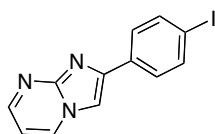
13 Taikyun, R.; Lankin, M. E.; Shih, D. H.; Lankin, C. M. Synthesis of 2-(2-furoyl)-4(5)-(2-furanyl)-1H-imidazole and analogs thereof. U.S. Patent 4665192, May 1987.

14 Turner, G. L.; Morris, J. A.; Greaney, M. F. *Angew. Chem., Int. Ed.* **2007**, 46, 7996.

(100 MHz, CDCl₃) δ ppm 168.6, 150.4, 148.1, 142.4, 133.5, 130.3, 129.1, 126.8, 112.0, 111.7, 107.4; **IR** (ν_{max} /cm⁻¹): 3115, 3066, 3025, 1616, 1515, 1469, 1201, 1007; **HRMS** Calculated for C₁₃H₉NOS (M⁺) 227.0405, found 227.0387.



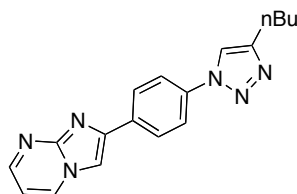
2-Bromo-1-(4-iodophenyl)ethanone (24): Synthesized following the same procedure described for 2-bromo-1-(furan-2-yl)ethanone, isolated in 72 % yield. White solid; **mp**: 102–106 °C; **R_f**: 0.47 (petroleum ether/diethyl ether 90/10); **¹H NMR (400 MHz, CDCl₃)** δ ppm 7.89–7.86 (m, 2H), 7.71–7.68 (m, 2H), 4.39 (s, 2H); **¹³C NMR (100 MHz, CDCl₃)** δ ppm 190.9, 138.4, 133.3, 130.4, 102.4, 30.4; **IR** (ν_{max} /cm⁻¹): 2997, 2948, 1692, 1580, 1395, 1196, 803; **HRMS** Calculated for C₈H₆NBrI (M⁺) 323.8647, found 323.8657.



2-(4-Iodophenyl)imidazo[1,2-*a*]pyrimidine (25): Synthesized following a literature procedure.¹⁵ In a round bottom flask were mixed 2-aminopyrimidine (1.0 equiv.) and 2-Bromo-1-(4-iodophenyl)ethanone. Acetone (0.4 M) was added and the mixture was heated to reflux for 2–3 hours. At this point significant amount of precipitate had formed, the mixture was cooled down to ambient temperature and decanted. Then a 1.5:1 mixture of ethanol and water (~0.4M) were added to the precipitate as well as NaHCO₃ (~1.4 equiv.). The resulting solution was heated to 80 °C for an additional 2–3 hours. The reaction mixture was the cooled to ambient temperature and extracted with dichloromethane. The combined organic layer were dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure. The crude product was purified using silica gel column chromatography to afford 2-(4-iodophenyl)imidazo[1,2-*a*]pyrimidine as a pale brown solid in 50 to 78 % yield. No melting point found, it decomposed ~270 °C; **R_f**: 0.53 (MeOH/DCM 5/95); **¹H NMR (400 MHz; DMSO-*d*₆)** δ

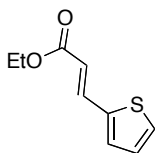
15 Rivall, Y.; Grassy, G.; Taudou, A.; Ecalle, R. *J. Med. Chem.* **1991**, 26, 13.

ppm 8.96 (dd, $J = 6.8, 1.9$ Hz, 1H), 8.54 (dd, $J = 4.1, 1.9$ Hz, 1H), 8.42 (s, 1H), 7.85–7.80 (m, 4H), 7.06 (dd, $J = 6.7, 4.2$ Hz, 1H); ^{13}C NMR (101 MHz; 383 K; DMSO- d_6) δ ppm 149.9, 144.4, 144.1, 137.1, 134.4, 132.8, 127.4, 108.4, 107.3, 93.2; IR (ν_{max} / cm^{-1}): 3114, 3073, 2922, 2854, 1499, 1469, 1350, 1200; HRMS Calculated for $\text{C}_{12}\text{H}_8\text{N}_3\text{I}$ (M^+) 320.9763, found 320.9780.



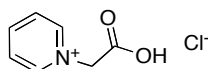
2-(4-(4-Butyl-1H-1,2,3-triazole)phenyl)imidazo[1,2-a]pyrimidine (26). Synthesized following a literature procedure.¹⁶ In a flask equipped with a stir bar were mixed: (1.0 equiv.), sodium azide (1.05 equiv.), CuI (10 mol%), sodium ascorbate (10 mol%). To this mixture was added a solution of DMF (0.3 M) containing 1-hexyne (1.05 equiv.) and *N,N'*-dimethylethane-1,2-diamine (15 mol%). The mixture was stirred at ambient temperature until it was judged completed by TLC. Water and dichloromethane were added to the reaction mixture and the aqueous layer was extracted a few times with dichloromethane. The combined organic layer were dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure. The crude product was purified using silica gel column chromatography to afford **26** as a pale brown solid in 82 to 90 % yield. Pale brown solid; decomposed at ~ 270 °C; R_f : 0.20 (MeOH/DCM 5/95); ^1H NMR (400 MHz, CDCl_3) δ ppm 8.57 (dd, $J = 4.1, 2.0$ Hz, 1H), 8.47 (dd, $J = 6.7, 2.0$ Hz, 1H), 8.20–8.15 (m, 2H), 7.89 (s, 1H), 7.84–7.81 (m, 2H), 7.77 (s, 1H), 6.90 (dd, $J = 6.7, 4.1$ Hz, 1H), 2.82 (t, $J = 7.7$ Hz, 2H), 1.74 (dt, $J = 15.3, 7.6$ Hz, 2H), 1.45 (dq, $J = 14.9, 7.4$ Hz, 2H), 0.97 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (100 MHz, 383 K, DMSO- d_6) δ ppm 150.0, 147.9, 147.7, 144.7, 144.0, 134.4, 133.1, 126.6, 119.8, 119.3, 108.4, 107.5, 30.3, 24.2, 21.1, 12.9; IR (ν_{max} / cm^{-1}): 3131, 2953, 2923, 2856, 1614, 1521, 1492, 1225, 762; HRMS Calculated for $\text{C}_{18}\text{H}_{18}\text{N}_4$ ($\text{M}^+ - \text{N}_2$) 290.1531, found 290.1525.

16 Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596.

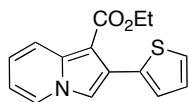


(E)-Ethyl 3-(thiophen-2-yl)acrylate (27): Synthesized following a literature procedure.¹⁷

¹H NMR of the final product matched the previously reported spectrum. Light sensitive clear oil; **R_f**: 0.279 (petroleum ether/ethyl acetate 90/10); **¹H NMR (400 MHz, CDCl₃)** δ ppm 7.78 (d, *J* = 15.7 Hz, 1H), 7.37 (d, *J* = 5.1 Hz, 1H), 7.25–7.24 (m, 1H), 7.05 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.24 (d, *J* = 15.7 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H); **¹³C NMR (100 MHz, CDCl₃)** δ ppm 166.9, 139.6, 137.1, 130.9, 128.4, 128.1, 117.1, 60.5, 14.4; **IR (ν_{max}/cm⁻¹):** 3106, 2981, 2903, 1709, 1627, 1370, 1267, 1170, 1043, 706; **HRMS** Calculated for C₉H₁₀O₂S (M⁺) 182.0402, found 182.0383.



1-(Carboxymethyl)pyridinium chloride (28): Synthesized following a literature procedure.¹⁸ To a solution of pyridine (1.0 equiv.) in ethyl acetate (0.66 M) was added α-chloroacetic acid and the mixture was stirred at ambient temperature overnight. A white precipitate was formed. The solution was filtered, washed with ethyl acetate and dried under vacuum. The product was used crude. ¹H NMR of the final product matched the previously reported spectrum. **¹H NMR (400 MHz; DMSO-*d*₆)** δ ppm 9.09 (dd, *J* = 6.7, 1.3 Hz, 2H), 8.67 (tt, *J* = 7.8, 1.3 Hz, 1H), 8.20 (dd, *J* = 7.8, 6.8 Hz, 2H), 5.58 (s, 2H).



Ethyl 2-(thiophen-2-yl)indolizine-1-carboxylate (29). Synthesized according to the general procedure.¹⁸ In a round bottom flask equipped with a stir bar was added 1-(carboxymethyl)pyridinium chloride (1.0 equiv.), MnO₂ (~8 equiv.) and 1,4-dioxane (0.25 M). To the suspension was added triethylamine (3.0 equiv.) and (*E*)-ethyl 3-

17 Bonini, C.; Chiummiento, L.; De Bonis, M.; Funicello, M.; Lupattelli, P.; Pandolfo, R. *Tetrahedron: Asymmetry* **2006**, 17, 2919.

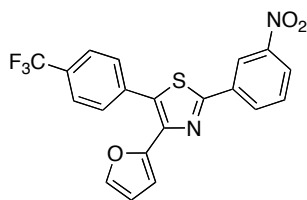
18 Zhang, L.; Liang, F.; Sun, L.; Hu, Y.; Hu, H *Synthesis* **2000**, 12, 1733.

(thiophen-2-yl)acrylate (4.0 equiv.). The resulting mixture was stirred at 120 °C overnight. After the mixture was cooled to ambient temperature, filtered and wash with ethyl acetate. The filtrate was evaporated and the crude residue was purified by silica gel column chromatography. The remaining starting olefin was recovered along with the desired product in 25 % yield. Pale green and light sensitive solid; **mp**: 62–66 °C; **R_f**: 0.19 (petroleum ether/ethyl acetate 90/10); **¹H NMR (400 MHz, CDCl₃)** δ ppm 8.22 (d, J = 9.1 Hz, 1H), 7.96 (d, J = 6.8 Hz, 1H), 7.43 (dd, J = 3.6, 1.1 Hz, 1H), 7.39 (s, 1H), 7.31 (dd, J = 5.1, 1.1 Hz, 1H), 7.08 (t, J = 4.4 Hz, 1H), 7.06 (ddd, J = 9.3, 6.9, 1.0 Hz, 1H), 6.73 (td, J = 6.8, 1.1 Hz, 1H), 4.35 (q, J = 7.1 Hz, 2H), 1.35 (t, J = 7.1 Hz, 3H); **¹³C NMR (100 MHz, CDCl₃)** δ ppm 164.9, 137.0, 135.7, 127.8, 127.1, 125.5, 125.4, 125.0, 122.7, 120.6, 114.2, 113.0, 101.6, 59.7, 14.6; **IR (v_{max} /cm⁻¹)**: 3111, 2979, 2903, 1696, 1507, 1437, 1419, 1237, 1218, 1103, 782; **HRMS** Calculated for C₁₅H₁₃NO₂S (M⁺) 271.0667, found 271.0697.

Section 3.5.2: Selective functionalization of the *bis*-heterocycles

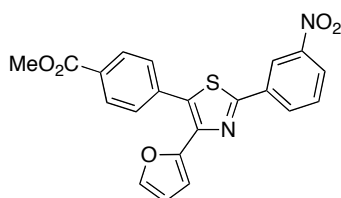
General procedure for the direct arylation of *bis*-heterocycles:¹⁹ Pd(OAc)₂ (5 mol%), tricyclohexylphosphonium tetrafluoroborate (10 mol%), K₂CO₃ (1.5 equiv.) and PivOH (30 mol%) were weighed to air and placed in a screw-cap vial equipped with a magnetic stir bar. The *bis*-heteroarene (1.1 equiv.) and the aryl bromide (1.0 equiv.), if a solid, were then added at that point. The vial was purged with argon and a solution of the coupling partners, if liquid, in dimethylacetamide (DMA) (0.3 M) was added to the mixture. The reaction mixture was then stirred vigorously at 100 °C for 16 hours. The solution was then cooled to ambient temperature and loaded directly on the column or was diluted with ethyl acetate, then filtered and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography to afford the corresponding product.

19 Liégault, B.; Lapointe, D.; Caron, L.; Vlassova, A.; Fagnou, K. *J. Org. Chem.* **2009**, *74*, 1826.

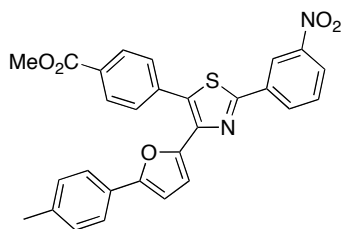


4-(Furan-2-yl)-2-(3-nitrophenyl)-5-(4-(trifluoromethyl)phenyl)thiazole (30):

Synthesized according to the general procedure for the direct arylation. Pale brown solid; **mp**: 157–159 °C; **R_f**: 0.41 (petroleum ether/ethyl acetate 80/20); **¹H NMR (400 MHz, CDCl₃)** δ ppm 8.83 (t, J = 1.9 Hz, 1H), 8.31 (dddd, J = 7.8, 7.8, 1.5, 1.0 Hz, 2H), 7.71–7.64 (m, 5H), 7.38 (dd, J = 1.7, 0.7 Hz, 1H), 6.79 (dd, J = 3.4, 0.7 Hz, 1H), 6.48 (dd, J = 3.4, 1.8 Hz, 1H); **¹³C NMR (100 MHz, CDCl₃)** δ ppm 164.1, 149.1, 148.9, 143.0, 142.9, 134.7, 132.2, 131.6, 130.9 (q, J_{CF} = 32.8 Hz), 130.4, 130.2, 125.6 (q, J_{CF} = 3.8 Hz), 124.9, 124.0 (q, J_{CF} = 272 Hz), 121.4, 111.6, 110.6; **IR (ν_{max} /cm⁻¹)**: 3094, 2932, 1534, 1353, 1324, 1168, 1125, 1068, 1013, 734; **HRMS** Calculated for C₂₀H₁₁N₂O₃SF₃ (M⁺) 416.0442, found 416.0398.

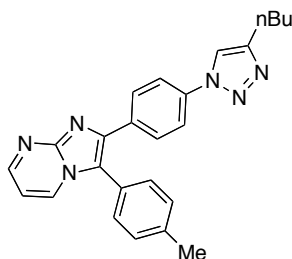


Methyl 4-(2-(3-nitrophenyl)-4-(furan-2-yl)thiazol-5-yl)benzoate (31): Synthesized according to the general procedure for the direct arylation. Yellow solid; **mp**: 166–168 °C; **R_f**: 0.42 (petroleum ether/ethyl acetate 80/20); **¹H NMR (400 MHz, CDCl₃)** δ ppm 8.83 (t, J = 1.9 Hz, 1H), 8.32–8.26 (m, 2H), 8.10 (d, J = 8.6 Hz, 2H), 7.67 (t, J = 7.9 Hz, 1H), 7.60 (d, J = 8.6 Hz, 2H), 7.37 (dd, J = 1.8 and 0.8 Hz, 1H), 6.76 (dd, J = 3.4, 0.8 Hz, 1H), 6.46 (dd, J = 3.4, 1.8 Hz, 1H), 3.96 (s, 3H); **¹³C NMR (100 MHz, CDCl₃)** δ ppm 166.7, 164.1, 149.0, 148.7, 142.8, 142.6, 135.5, 134.7, 132.2, 132.0, 130.3, 130.1, 129.9, 129.7, 124.7, 121.3, 111.5, 110.4, 52.3; **IR (ν_{max} /cm⁻¹)**: 3094, 2952, 2857, 1724, 1607, 1534, 1353, 1279; **HRMS** Calculated for C₂₁H₁₄N₂O₅S (M⁺) 406.0623, found 406.0618.



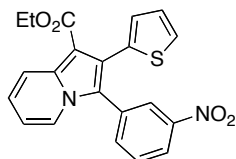
Methyl 4-(2-(3-nitrophenyl)-4-(5-*p*-tolylfuran-2-yl)thiazol-5-yl)benzoate (32):

Synthesized according to the general procedure for the direct arylation. Bright yellow solid; **mp**: 194–202 °C; **R_f**: 0.26 (petroleum ether/ethyl acetate 80/20); **¹H NMR (400 MHz, CDCl₃)** δ ppm 8.86 (t, J = 1.8 Hz, 1H), 8.34–8.29 (m, 2H), 8.16–8.13 (m, 2H), 7.72 (d, J = 8.4 Hz, 2H), 7.67 (t, J = 8.0 Hz, 1H), 7.22 (d, J = 8.2 Hz, 2H), 7.08 (d, J = 8.0 Hz, 2H), 7.00 (d, J = 3.5 Hz, 1H), 6.67 (d, J = 3.5 Hz, 1H), 4.00 (s, 3H), 2.33 (s, 3H); **¹³C NMR (100 MHz, CDCl₃)** δ ppm 166.8, 164.1, 154.5, 148.9, 148.7, 142.9, 137.8, 136.1, 134.8, 132.2, 131.2, 130.3, 130.3, 130.2, 129.8, 129.5, 127.6, 124.8, 123.7, 121.4, 112.7, 106.2, 52.5, 21.4; **IR ($\nu_{\max}$ /cm⁻¹)**: 3028, 2957, 2921, 2859, 1716, 1532, 1351, 1277, 1112; **HRMS** Calculated for C₂₈H₂₀N₂O₅S (M⁺) 496.1093, found 496.1104.



2-(4-(4-Butyl-1H-1,2,3-triazol-1-yl)phenyl)-3-*p*-tolylimidazo[1,2-*a*]pyrimidine (33):

Synthesized according to the general procedure for the direct arylation. Yellow solid; **mp**: 192–194°C; **R_f**: 0.50 (MeOH/DCM 5/95); **¹H NMR (400 MHz, CDCl₃)** δ ppm 8.58 (dd, J = 4.0, 2.0 Hz, 1H), 8.24 (dd, J = 6.9, 2.0 Hz, 1H), 7.92 (d, J = 8.8 Hz, 2H), 7.71 (s, 1H), 7.66 (d, J = 8.8 Hz, 2H), 7.40–7.33 (m, 4H), 6.83 (dd, J = 6.9, 4.1 Hz, 1H), 2.80 (t, J = 7.6 Hz, 2H), 2.49 (d, J = 2.4 Hz, 3H), 1.76–1.66 (m, 2H), 1.49–1.36 (m, 2H), 0.96 (t, J = 7.3 Hz, 3H); **¹³C NMR (100 MHz, CDCl₃)** δ ppm 150.3, 149.3, 148.0, 142.2, 140.0, 136.7, 134.0, 131.0, 130.8, 130.5, 129.5, 125.4, 120.2, 120.1, 118.7, 108.9, 31.6, 25.5, 22.4, 21.6, 14.0; **IR ($\nu_{\max}$ /cm⁻¹)**: 2956, 2927, 2869, 2859, 1617, 1525, 1517, 1496, 1223, 1203; **HRMS** Calculated for C₂₅H₂₄N₆ (M⁺) 408.2062, found 408.2053.

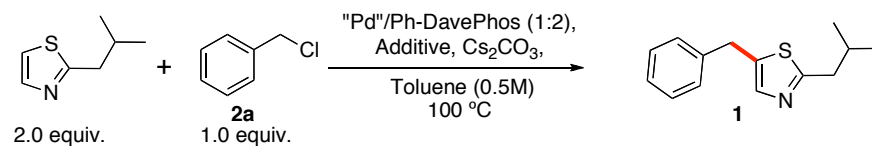


Ethyl 3-(3-nitrophenyl)-2-(thiophen-2-yl)indolizine-1-carboxylate (34). Synthesized according to the general procedure for the direct arylation. Bright yellow solid; **mp**: 136–137 °C; **R_f**: 0.18 (petroleum ether/ethyl acetate 90/10); **¹H NMR (400 MHz, CDCl₃)** δ ppm 8.36 (dt, J = 9.1, 1.2 Hz, 1H), 8.27 (t, J = 1.8 Hz, 1H), 8.20 (ddd, J = 8.2, 2.3, 1.2 Hz, 1H), 8.00 (dt, J = 7.1, 1.1 Hz, 1H), 7.64 (dt, J = 7.7, 1.4 Hz, 1H), 7.56 (t, J = 7.9 Hz, 1H), 7.28 (dd, J = 5.0, 1.4 Hz, 1H), 7.16 (ddd, J = 9.2, 6.7, 1.1 Hz, 1H), 6.96–6.92 (m, 2H), 6.77 (td, J = 6.9, 1.3 Hz, 1H), 4.26 (q, J = 7.1 Hz, 2H), 1.22 (d, J = 14.3 Hz, 3H); **¹³C NMR (100 MHz, CDCl₃)** δ ppm 164.6, 148.7, 137.0, 136.5, 134.5, 131.9, 130.0, 129.1, 126.5, 126.3, 125.5, 123.9, 123.5, 123.3, 123.1, 122.7, 120.7, 113.7, 104.3, 59.7, 14.3; **IR ($\nu_{\max}$ /cm⁻¹)**: 3077, 2981, 1685, 1534, 1507, 1348, 1199, 1129, 739; **HRMS** Calculated for C₂₁H₁₆N₂O₄S (M⁺) 392.0831, found 392.0847.

8.4 Chapter 4: Palladium-Catalyzed sp^3 - sp^2 C–C bond Formation by C–H Functionalization Reactions

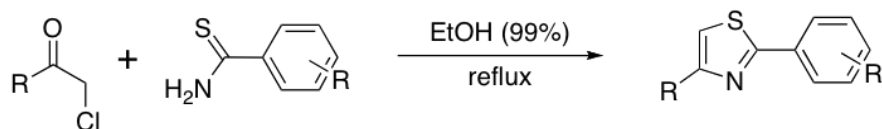
General procedure for the direct benzylation of heterocycles: Pd(OPiv)₂ (2 or 5 mol%), 2-Ph₂P-2'-(Me₂N)biphenyl (4 or 10 mol%), Cs₂CO₃ (1.5 equiv.) and PivOH (20 mol%) are weighed to air and placed in a screw-cap vial equipped with a magnetic stir bar. The heterocycle (1 equiv.), if a solid is then added at that point. The vial is purged with argon and a solution of the benzyl chloride (1.5 or 2.0 equiv.) in degassed toluene (0.5 M) is added to the mixture. The reaction mixture is then stirred vigorously at 110 °C for 16 to 24 hours. The solution is then cooled to ambient temperature, diluted with ethyl acetate, then filtered and evaporated under reduced pressure. The crude product is purified by silica gel column chromatography to afford the corresponding product.

Table 8.2 Data of the evaluation of pivalic acid on the rate of direct benzylation of thiazole. (Figure 4.2)



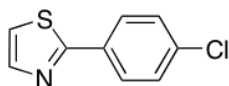
No PivOH		20 mol% PivOH	
Time (min)	GC-Yield (%)	Time (min)	GC-Yield (%)
0	0	0	3
30	1	40	7
60	2	60	14
90	5	90	19
128	10	120	24
157	14	150	30
235	27	180	36
300	33	210	42
395	36	240	46
495	38	270	51
		300	61
		360	3

Section 4.2.2: Synthesis and characterization of Starting Materials

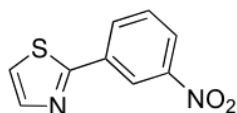


General procedure for the preparation of the 2-aryl and 3- substituted thiazole:²⁰

Thioamide (3,0 mmol), α -chloro ketone (3,6 mmol) are weighed to air and placed in a round bottom flask equipped with a magnetic stir bar and a reflux condenser. Ethanol (99%, 1 M) is then added and the mixture is heated to reflux until full consumption of the thioamide as judge by TLC (~ 1 hour). The mixture is then evaporated under reduced pressure. The crude product is purified by silica gel column chromatography to afford the corresponding product.

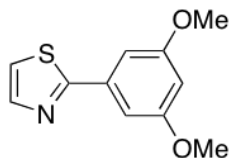


2-(4-Chlorophenyl)thiazole: Synthesized according to the general procedure of thiazole synthesis. Brown solid; **mp** 32–34 °C; **R_f** 0.35 (petroleum ether/ethyl acetate 80/20); **¹H NMR (400 MHz, CDCl₃)** δ 7.90 (dt, J = 8.7, 2.0 Hz, 2H), 7.86 (d, J = 3.3 Hz, 1H), 7.42 (dt, J = 8.7, 2.0 Hz, 1H), 7.34 (d, J = 3.3 Hz, 1H); **¹³C NMR (100 MHz, CDCl₃)** δ 166.9, 143.7, 135.8, 132.0, 129.1, 127.7, 119.0; **IR (ν_{max} /cm⁻¹):** 3121, 3081, 2047, 1249, 1146, 1014; **HRMS** Calculated for C₉H₆ClNS (M⁺) 194.9909, Found 194.9924.

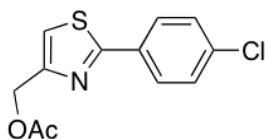


2-(3-Nitrophenyl)thiazole: Synthesized according to the general procedure of thiazole synthesis. Yellow solid; **mp** 94–97 °C; **R_f** 0.33 (petroleum ether/ethyl acetate 80/20); **¹H NMR (400 MHz, CDCl₃)** δ 8.82 (t, J = 2.0 Hz, 1H), 8.31 (dt, J = 6.6, 1.2 Hz, 1H), 8.28 (ddd, J = 8.2, 2.1, 0.9 Hz, 1H), 7.95 (d, J = 3.2 Hz, 1H), 7.65 (t, J = 8.0 Hz, 1H), 7.46 (d, J = 3.2 Hz, 1H); **¹³C NMR (100 MHz, CDCl₃)** δ 165.4, 148.7, 144.2, 135.1, 132.1, 130.0, 124.3, 121.4, 120.2; **IR (ν_{max} /cm⁻¹):** 3128, 3039, 2049, 1534, 1249; **HRMS** Calculated for C₉H₆N₂O₂S (M⁺) 206.0150, Found 206.0166.

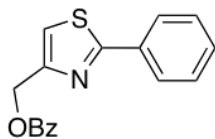
²⁰ Turner, G. L.; Morris, J. A.; Greaney, M. F. *Angew. Chem., Int. Ed.* **2007**, *46*, 7996.



2-(3,5-Dimethoxyphenyl)thiazole: Synthesized according to the general procedure of thiazole synthesis. Pale yellow oil; **R_f** 0.30 (petroleum ether/ethyl acetate 80/20); **¹H NMR (400 MHz, CDCl₃)** δ 7.86 (d, J = 3.3 Hz, 1H), 7.32 (d, J = 3.3 Hz, 1H), 7.13 (d, J = 2.3 Hz, 2H), 6.53 (t, J = 2.3 Hz, 1H), 3.86 (s, 6H); **¹³C NMR (100 MHz, CDCl₃)** δ 168.3, 161.1, 143.5, 135.3, 119.0, 104.5, 102.5, 55.6; **IR (ν_{max} /cm⁻¹):** 1595, 1457, 1427, 1206, 1157, 1062, 1024; **HRMS** Calculated for C₉H₆N₂O₂S (M⁺) 221.0510, Found 221.0492.

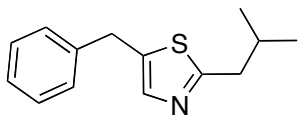


(2-(4-Chlorophenyl)thiazol-4-yl)methyl acetate: Synthesized according to the general procedure of thiazole synthesis. Pale yellow solid; **mp** 52–55 °C; **R_f** 0.41 (petroleum ether/ethyl acetate 80/20); **¹H NMR (400 MHz, CDCl₃)** δ 7.89 (d, J = 8.8 Hz, 2H), 7.41 (d, J = 8.8 Hz, 2H), 7.30 (s, 1H), 5.25 (s, 2H), 2.14 (s, 3H); **¹³C NMR (100 MHz, CDCl₃)** δ 170.6, 167.3, 152.3, 136.1, 131.8, 129.1, 127.8, 117.7, 61.7, 20.9; **IR (ν_{max} /cm⁻¹):** 3106, 3036, 1737, 1247; **HRMS** Calculated for C₁₂H₁₀ClNO₂S (M⁺) 267.0121, Found 267.0069.

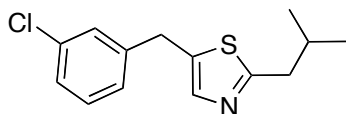


(2-Phenylthiazol-4-yl)methyl benzoate: Synthesized according to the general procedure of thiazole synthesis. Yellow solid; **mp** 68–70 °C; **R_f** 0.39 (petroleum ether/ethyl acetate 80/20); **¹H NMR (400 MHz, CDCl₃)** δ 8.11 (d, J = 7.2 Hz, 2H), 8.01–7.90 (m, 2H), 7.57 (t, J = 7.4 Hz, 1H), 7.51–7.40 (m, 5H), 7.36 (s, 1H), 5.54 (s, 2H); **¹³C NMR (100 MHz, CDCl₃)** δ 168.6, 166.2, 152.3, 133.4, 133.1, 130.1, 129.9, 129.7, 128.9, 128.3, 126.6, 117.3, 62.3; **IR (ν_{max} /cm⁻¹):** 3120, 3069, 3037, 2972, 1790, 1725, 1266, 1104; **HRMS** Calculated for C₁₇H₁₃NO₂S (M⁺) 295.0667, Found 295.0653.

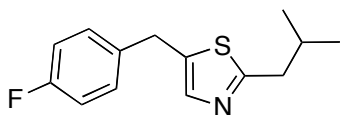
Section 4.2.2: Characterization of Coupling Products



5-Benzyl-2-iso-butylthiazole (1): Synthesized according to the general procedure. Colorless oil; R_f 0.31 (petroleum ether/ethyl acetate 80/20); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.36 (s, 1H), 7.34–7.27 (m, 2H), 7.23 (m, 3H), 4.10 (s, 2H), 2.79 (d, $J = 7.2$ Hz, 2H), 2.05 (hept, $J = 6.8$ Hz, 1H), 0.97 (d, $J = 6.6$ Hz, 6H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 169.8, 139.6, 139.5, 137.5, 128.7, 128.5, 126.8, 42.5, 33.3, 29.7, 22.3; IR (ν_{max} / cm^{-1}): 3032, 2960, 2928, 2869, 1225; HRMS Calculated for $\text{C}_{14}\text{H}_{17}\text{NS}$ (M^+) 231.1082, Found 231.1076.

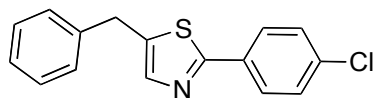


5-(3-Chlorobenzyl)-2-isobutylthiazole (5): Synthesized according to the general procedure. Colorless oil; R_f 0.20 (petroleum ether/ethyl acetate 90/10); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.37 (s, 1H), 7.25 (d, $J = 8.1$ Hz, 1H), 7.22 (dt, $J = 4.1, 2.0$ Hz, 3H), 7.10 (d, $J = 6.6$ Hz, 1H), 4.08 (s, 2H), 2.80 (d, $J = 7.2$ Hz, 2H), 2.06 (hept, $J = 6.8$ Hz, 1H), 0.97 (d, $J = 6.6$ Hz, 7H); $^{13}\text{C NMR}$ (75 MHz, CDCl_3): δ 170.2, 141.6, 139.9, 136.4, 134.5, 130.0, 128.7, 127.1, 126.7, 42.6, 32.9, 29.8, 22.4; IR (ν_{max} / cm^{-1}): 3019, 2956, 2931, 2871, 1472, 1153, 1047; HRMS Calculated for $\text{C}_{14}\text{H}_{16}\text{ClNS}$ (M^+) 265.0692, Found 265.0708.

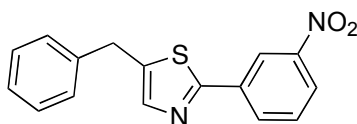


5-(4-Fluorobenzyl)-2-isobutylthiazole (6): Synthesized according to the general procedure. Colorless oil; R_f 0.31 (petroleum ether/ethyl acetate 80/20); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.35 (s, 1H), 7.21–7.14 (m, 2H), 7.03–6.95 (m, 2H), 4.07 (s, 2H), 2.79 (d, $J = 7.2$ Hz, 2H), 2.06 (hept, $J = 6.8$ Hz, 1H), 0.97 (d, $J = 6.6$ Hz, 6H); $^{13}\text{C NMR}$

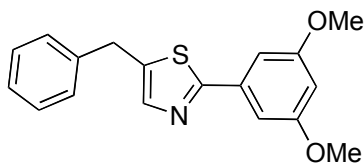
(100 MHz, CDCl₃) δ 169.9, 161.7 (d, J = 245.0 Hz), 139.6, 137.3, 135.3 (d, J = 3.2 Hz), 129.9 (d, J = 8.0 Hz), 115.5 (d, J = 21.4 Hz), 42.5, 32.4, 29.7, 22.3; ¹⁹F NMR (377 MHz, CDCl₃) δ -116.2; IR (ν_{max} /cm⁻¹): 2963, 2931, 2869, 834; HRMS Calculated for C₁₄H₁₆FNS (M⁺) 249.0987, Found 249.1013.



5-Benzyl-2-(4-chlorophenyl)thiazole (7): Synthesized according to the general procedure. Yellow solid; mp 80–81 °C; R_f 0.50 (petroleum ether/ethyl acetate 80/20); ¹H NMR (400 MHz, CDCl₃) δ 7.80 (d, J = 8.5 Hz, 2H), 7.57 (s, 1H), 7.37 (d, J = 8.6 Hz, 2H), 7.35–7.30 (m, 2H), 7.26 (m, 3H), 4.18 (s, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 166.2, 141.3, 139.3, 139.1, 135.6, 132.3, 129.1, 128.8, 128.4, 127.4, 126.9, 33.3; IR (ν_{max} /cm⁻¹): 3022, 2932, 2907, 972; HRMS Calculated for C₁₆H₁₂ClNS (M⁺) 285.0379, Found 285.0357.

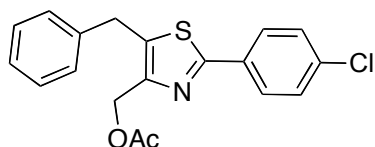


5-Benzyl-2-(3-nitrophenyl)thiazole (8): Synthesized according to the general procedure. Pale yellow solid; mp 100–103 °C; R_f 0.18 (petroleum ether/ethyl acetate 80/20); ¹H NMR (400 MHz, CDCl₃) δ 8.71 (s, 1H), 8.21 (t, J = 8.0 Hz, 2H), 7.65 (s, 1H), 7.59 (t, J = 8.0 Hz, 1H), 7.39–7.32 (m, 2H), 7.31–7.25 (m, 3H), 4.22 (s, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 164.4, 148.7, 141.7, 140.6, 139.0, 135.4, 131.7, 129.9, 128.9, 128.5, 127.1, 124.0, 121.0, 33.4; IR (ν_{max} /cm⁻¹): 3066, 3035, 2925, 2863, 1226; HRMS Calculated for C₁₆H₁₂N₂O₂S (M⁺) 296.0619, Found 296.0612.

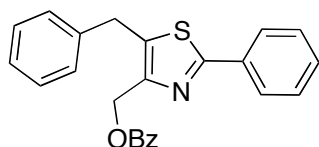


5-Benzyl-2-(3,5-dimethoxyphenyl)thiazole (9): Synthesized according to the general procedure. Yellow solid; mp 56–58 °C; R_f 0.24 (petroleum ether/ethyl acetate 80/20); ¹H

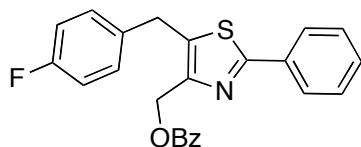
NMR (400 MHz, CDCl₃) δ 7.57 (s, 1H), 7.38–7.30 (m, 2H), 7.29–7.23 (m, 3H), 7.04 (d, J = 2.0 Hz, 2H), 6.49 (d, J = 2.0 Hz, 1H), 4.18 (s, 2H), 3.83 (s, 6H); **¹³C NMR (100 MHz, CDCl₃)** δ 167.5, 161.1, 141.1, 139.4, 138.9, 135.6, 128.8, 128.5, 126.9, 104.1, 102.5, 55.5, 33.3; **IR** ($\nu_{\max}$ /cm⁻¹): 2969, 2935, 2835, 1204, 1026; **HRMS** Calculated for C₁₈H₁₇NO₂S (M⁺) 311.0980, Found 311.0976.



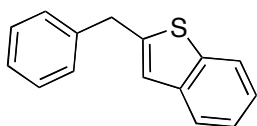
(5-Benzyl-2-(4-chlorophenyl)thiazol-4-yl)methyl acetate (10): Synthesized according to the general procedure. Pale yellow solid; **mp** 88–92°C; **R_f** 0.48 (petroleum ether/ethyl acetate 80/20); **¹H NMR (400 MHz, CDCl₃)** δ 7.84–7.75 (m, 2H), 7.39–7.34 (m, 2H), 7.34–7.29 (m, 2H), 7.28–7.21 (m, 3H), 5.24 (s, 2H), 4.23 (s, 2H), 2.08 (s, 3H); **¹³C NMR (100 MHz, CDCl₃)** δ 170.8, 164.6, 147.3, 139.2, 138.3, 135.9, 131.9, 129.1, 128.8, 128.4, 127.5, 127.0, 59.5, 32.3, 20.9; **IR** ($\nu_{\max}$ /cm⁻¹): 3032, 2966, 2935, 2052, 1710; **HRMS** Calculated for C₁₉H₁₆ClNO₂S (M⁺) 357.0590, Found 357.0564.



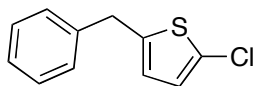
(5-Benzyl-2-phenylthiazol-4-yl)methyl benzoate (11): Synthesized according to the general procedure. White solid; **mp** 78–80 °C; **R_f** 0.55 (petroleum ether/ethyl acetate 80/20); **¹H NMR (400 MHz, CDCl₃)** δ 8.08–8.01 (m, 2H), 7.90–7.86 (m, 2H), 7.58–7.51 (m, 1H), 7.45–7.37 (m, 5H), 7.32–7.20 (m, 5H), 5.50 (s, 2H), 4.31 (s, 2H); **¹³C NMR (100 MHz, CDCl₃)** δ 166.5, 165.8, 147.3, 139.4, 138.1, 133.5, 133.0, 123.0, 129.9, 129.8, 128.9, 128.8, 128.4, 128.3, 126.9, 126.4, 60.2, 32.4; **IR** ($\nu_{\max}$ /cm⁻¹): 3067, 3028, 2964, 1718, 1266; **HRMS** Calculated for C₂₄H₁₉NO₂S (M⁺) 385.1136, Found 385.1143.



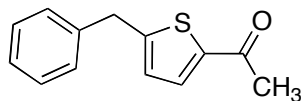
(5-(4-Fluorobenzyl)-2-phenylthiazol-4-yl)methyl benzoate (12): Synthesized according to the general procedure. White solid; **mp** 80–83 °C; **R_f** 0.52 (petroleum ether/ethyl acetate 80/20); **¹H NMR (400 MHz, CDCl₃)** δ 8.03 (d, J = 7.2 Hz, 2H), 7.88 (dd, J = 6.7, 3.0 Hz, 2H), 7.55 (t, J = 7.4 Hz, 1H), 7.46–7.36 (m, 5H), 7.22 (dd, J = 8.5, 5.4 Hz, 2H), 6.97 (t, J = 8.6 Hz, 2H), 5.49 (s, 2H), 4.28 (s, 2H) ; **¹³C NMR (100 MHz, CDCl₃)** δ 166.3, 165.8, 161.7 (d, J_{CF} = 245.4 Hz), 147.3, 137.8, 135.1 (d, J_{CF} = 3.3 Hz), 133.3, 133.0, 123.0, 129.8 (d, J_{CF} = 8.0 Hz), 129.8, 129.7, 128.8, 128.3, 126.3, 115.6, 115.4, 60.0, 31.5; **¹⁹F NMR (377 MHz, CDCl₃)** δ -115.7; **IR (ν_{max} /cm⁻¹):** 3068, 3040, 2960, 2915, 1720, 1504, 1268, 1219; **HRMS** Calculated for C₂₄H₁₈FNO₂S (M⁺) 403.1042, Found 403.1069.



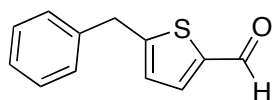
2-Benzylbenzothiophene (13): Synthesized according to the general procedure. White solid; **mp** 76–78 °C; **R_f** 0.30 (petroleum ether/diethyl ether 90/10); **¹H NMR (400 MHz, CDCl₃)** δ 7.73 (d, J = 7.8 Hz, 1H), 7.65 (d, J = 7.8 Hz, 1H), 7.39–7.16 (m, 7H), 7.00 (s, 1H), 4.22 (s, 2H); **¹³C NMR (100 MHz, CDCl₃)** δ 145.1, 140.0, 139.5, 128.8, 128.6, 126.7, 124.1, 123.6, 122.9, 122.1, 121.6, 37.0; **IR (ν_{max} /cm⁻¹):** 3060, 3032, 2966; **HRMS** Calculated for C₁₅H₁₂S (M⁺) 224.0660, Found 224.0636.



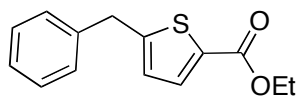
2-Benzyl-5-chlorothiophene (14): Synthesized according to the general procedure. Oil; **R_f** 0.46 (petroleum ether 100%); **¹H NMR (400 MHz, CDCl₃)** δ 7.36–7.27 (m, 2H), 7.27–7.18 (m, 3H), 6.71 (d, J = 3.7 Hz, 1H), 6.56 (dt, J = 3.7, 1.0 Hz, 1H), 4.04 (s, 2H); **¹³C NMR (100 MHz, CDCl₃)** δ 142.9, 139.5, 128.6, 128.5, 127.9, 126.7, 125.7, 124.3, 36.4; **IR (ν_{max} /cm⁻¹):** 3090, 3067, 3034, 2906, 2843, 1453, 1219; **HRMS** Calculated for C₁₁H₉ClS (M⁺) 208.0113, Found 208.0115.



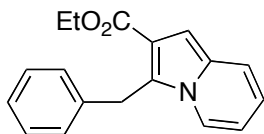
1-(5-Benzylthiophen-2-yl)ethanone (15): Synthesized according to the general procedure. Oil; R_f 0.46 (petroleum ether/ethyl acetate 80/20); ^1H NMR (400 MHz, CDCl_3) δ 7.51 (d, $J = 3.8$ Hz, 1H), 7.35–7.27 (m, 2H), 7.27–7.20 (m, 3H), 6.81 (dt, $J = 3.8, 0.9$ Hz, 1H), 4.14 (s, 2H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 190.3, 153.9, 142.8, 138.9, 132.7, 128.6, 128.5, 126.8, 126.3, 36.6, 26.3; IR (ν_{max} / cm^{-1}): 3063, 3032, 2925, 1655, 1276; HRMS Calculated for $\text{C}_{13}\text{H}_{12}\text{OS}$ (M^+) 216.0609, Found 216.0612.



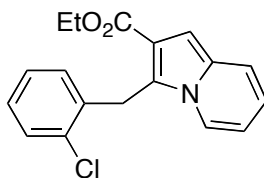
5-Benzylthiophene-2-carbaldehyde (16): Synthesized according to the general procedure. Pale brown oil; R_f 0.20 (petroleum ether/ethyl acetate 90/10); ^1H NMR (400 MHz, CDCl_3) δ 9.80 (s, 1H), 7.60 (d, $J = 3.8$ Hz, 1H), 7.37–7.29 (m, 2H), 7.29–7.21 (m, 3H), 6.90 (dt, $J = 3.7, 0.8$ Hz, 1H), 4.18 (s, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 182.7, 155.8, 142.4, 138.7, 136.9, 128.8, 128.7, 127.1, 126.6, 36.9; IR (ν_{max} / cm^{-1}): 3091, 3066, 3032, 2926, 2847, 2810, 1664, 1451; HRMS Calculated for $\text{C}_{12}\text{H}_{10}\text{OS}$ (M^+) 202.0452, Found 202.0451.



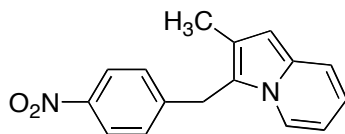
Ethyl 5-benzylthiophene-2-carboxylate (17): Synthesized according to the general procedure. Colorless oil; R_f 0.64 (petroleum ether/ethyl acetate 80/20); ^1H NMR (400 MHz, CDCl_3) δ 7.63 (d, $J = 3.7$ Hz, 1H), 7.35–7.28 (m, 2H), 7.28–7.19 (m, 3H), 6.79 (d, $J = 3.6$ Hz, 1H), 4.30 (q, $J = 7.1$ Hz, 2H), 4.14 (s, 2H), 1.33 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 162.3, 152.0, 139.2, 133.5, 132.1, 128.7, 128.6, 126.9, 126.0, 60.9, 36.5, 14.3; IR (ν_{max} / cm^{-1}): 3032, 2985, 2935, 1698, 1279, 1254, 1223; HRMS Calculated for $\text{C}_{14}\text{H}_{14}\text{O}_2\text{S}$ (M^+) 246.0715, Found 246.0714.



Ethyl 3-benzylindolizine-2-carboxylate (18): Synthesized according to the general procedure. Gray solid; **mp** 70–73 °C; **R_f** 0.56 (petroleum ether/ethyl acetate 80/20); **¹H NMR (400 MHz, CDCl₃)** δ 7.63 (d, J = 7.2 Hz, 1H), 7.37 (d, J = 9.0 Hz, 1H), 7.29–7.20 (m, 2H), 7.20–7.08 (m, 3H), 6.92 (s, 1H), 6.65 (dd, J = 9.0, 6.5 Hz, 1H), 6.46 (t, J = 6.8 Hz, 1H), 4.70 (s, 2H), 4.36 (q, J = 7.1 Hz, 2H), 1.37 (t, J = 7.1 Hz, 3H); **¹³C NMR (100 MHz, CDCl₃)** δ 165.8, 137.6, 131.6, 128.6, 128.0, 126.3, 126.1, 122.4, 120.4, 117.5, 117.4, 112.0, 100.7, 60.1, 30.4, 14.4; **IR (ν_{max} /cm⁻¹):** 3069, 3032, 2985, 2903, 2049, 1226, 1163, 1031; **HRMS** Calculated for C₁₈H₁₇NO₂ (M⁺) 279.1259, Found 279.1247.

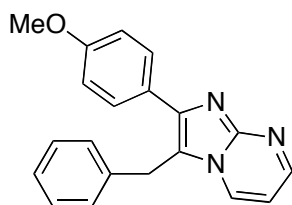


Ethyl 3-(2-chlorobenzyl)indolizine-2-carboxylate (19): Synthesized according to the general procedure. Gray solid; **mp** 53–56 °C; **R_f** 0.67 (petroleum ether/ethyl acetate 80/20); **¹H NMR (400 MHz, CDCl₃)** δ 7.53 (d, J = 7.2 Hz, 1H), 7.45–7.35 (m, 2H), 7.12 (td, J = 7.8, 1.2 Hz, 1H), 7.01 (td, J = 7.7, 0.8 Hz, 1H), 6.95 (s, 1H), 6.68 (dd, J = 8.8, 6.5 Hz, 1H), 6.59 (d, J = 7.6 Hz, 1H), 6.53–6.43 (m, 1H), 4.79 (s, 2H), 4.33 (q, J = 7.1 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H); **¹³C NMR (100 MHz, CDCl₃)** δ 165.6, 135.1, 133.7, 131.8, 129.4, 128.8, 127.7, 127.0, 124.8, 122.3, 120.4, 118.0, 117.7, 112.3, 100.8, 60.1, 27.7, 14.3; **IR (ν_{max} /cm⁻¹):** 3060, 2988, 2932, 1701, 1232, 1163; **HRMS** Calculated for C₁₈H₁₆ClNO₂ (M⁺) 313.0870, Found 313.0877.

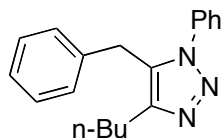


2-Methyl-3-(4-nitrobenzyl)indolizine (20): Synthesized according to the general procedure. Orange solid (light sensitive); **mp** 100–104 °C; **R_f** 0.55 (petroleum ether/ethyl

acetate 80/20); **¹H NMR (400 MHz, CDCl₃)** δ 8.10 (d, *J* = 8.5 Hz, 2H), 7.41 (d, *J* = 7.0 Hz, 1H), 7.32 (d, *J* = 8.9 Hz, 1H), 7.19 (d, *J* = 8.4 Hz, 2H), 6.61 (t, *J* = 7.7 Hz 1H), 6.41–6.30 (m, 2H), 4.32 (s, 2H), 2.35 (s, 3H); **¹³C NMR (100 MHz, CDCl₃)** δ 146.7, 146.2, 132.3, 128.6, 123.9, 123.5, 121.3, 118.5, 117.1, 116.2, 109.9, 99.8, 29.7, 11.8; **IR (ν_{max}/cm⁻¹):** 2931, 2866, 1345, 1223; **HRMS** Calculated for C₁₆H₁₄N₂O₂ (M⁺) 266.1055, Found 266.1070.

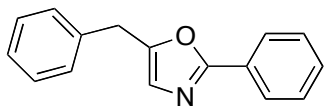


3-Benzyl-2-(4-methoxyphenyl)imidazo[1,2-*a*]pyrimidine (21): Synthesized according to the general procedure. Brown solid; **mp** 124–129°C; **R_f** 0.46 (Dichloromethane/methanol 95/5); **¹H NMR (400 MHz, CDCl₃)** δ 8.50 (dd, *J* = 4.1, 2.0 Hz, 1H), 7.96 (dd, *J* = 6.8, 1.9 Hz, 1H), 7.80 (d, *J* = 8.8 Hz, 2H), 7.36–7.21 (m, 3H), 7.13 (d, *J* = 6.9 Hz, 2H), 6.97 (d, *J* = 8.8 Hz, 2H), 6.73 (dd, *J* = 6.8, 4.1 Hz, 1H), 4.49 (s, 2H), 3.83 (s, 3H); **¹³C NMR (100 MHz, CDCl₃)** δ 159.7, 149.0, 148.0, 145.6, 136.1, 130.6, 129.6, 129.2, 127.6, 127.2, 126.5, 115.5, 114.1, 108.2, 55.3, 29.7; **IR (ν_{max}/cm⁻¹):** 3032, 2960, 2938, 2841, 1251, 1176; **HRMS** Calculated for C₂₀H₁₇N₃O (M⁺) 315.1372, Found 315.1373.

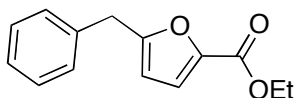


5-Benzyl-4-butyl-1-phenyl-1H-1,2,3-triazole (22): Synthesized according to the general procedure. White solid; **mp** 46–47 °C; **R_f** 0.36 (chloroform/diethyl ether 90/10); **¹H NMR (400 MHz, CDCl₃)** δ 7.47–7.38 (m, 3H), 7.32–7.27 (m, 2H), 7.27–7.16 (m, 3H), 6.92 (d, *J* = 6.5 Hz, 2H), 4.01 (s, 2H), 2.71–2.60 (m, 2H), 1.69 (dt, *J* = 15.4, 7.6 Hz, 2H), 1.45–1.31 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H); **¹³C NMR (100 MHz, CDCl₃)** δ 146.2, 136.9, 136.6, 131.9, 129.3, 129.2, 128.6, 127.9, 126.7, 125.4, 77.0, 31.5, 28.6, 24.9, 22.5, 13.8;

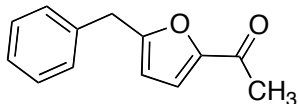
IR ($\nu_{\max}$ / cm^{-1}): 3032, 2960, 2935, 2869; **HRMS** Calculated for $\text{C}_{19}\text{H}_{21}\text{N}_3$ (M^+) 291.1735, Found 291.1726.



2-Benzyl-2-phenyloxazole (23): Synthesized according to the general procedure. Pale yellow oil; R_f 0.52 (petroleum ether/ethyl acetate 80/20); **^1H NMR (400 MHz, CDCl_3)** δ 8.01–7.96 (m, 2H), 7.45–7.37 (m, 3H), 7.37–7.21 (m, 5H), 6.86 (t, $J = 1.0$ Hz, 1H), 4.06 (s, 2H); **^{13}C NMR (100 MHz, CDCl_3)** δ 161.2, 151.4, 136.6, 130.1, 128.7, 128.7, 127.6, 126.9, 126.1, 124.8, 32.1; **IR** ($\nu_{\max}$ / cm^{-1}): 3066, 3035, 2922, 1701, 1241; **HRMS** Calculated for $\text{C}_{16}\text{H}_{13}\text{NO}$ (M^+) 235.0997, Found 235.0996.

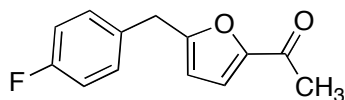


Ethyl 5-benzylfuran-2-carboxylate (24): Synthesized according to the general procedure. Colorless oil; R_f 0.58 (petroleum ether/ethyl acetate 80/20); **^1H NMR (400 MHz, CDCl_3)** δ 7.35–7.28 (m, 2H), 7.28–7.20 (m, 3H), 7.08 (d, $J = 3.4$ Hz, 1H), 6.05 (d, $J = 3.4$ Hz, 1H), 4.34 (q, $J = 7.1$ Hz, 2H), 4.04 (s, 2H), 1.36 (t, $J = 7.1$ Hz, 3H); **^{13}C NMR (100 MHz, CDCl_3)** δ 159.6, 158.9, 143.7, 136.7, 128.9, 128.7, 126.9, 119.0, 108.8, 60.8, 34.8, 14.4; **IR** ($\nu_{\max}$ / cm^{-1}): 3031, 2985, 2931, 1701, 1029; **HRMS** Calculated for $\text{C}_{14}\text{H}_{14}\text{O}_3$ (M^+) 230.0943, Found 230.0969.



1-(5-Benzylfuran-2-yl)ethanone (25): Synthesized according to the general procedure. Yellow oil; R_f 0.42 (petroleum ether/ethyl acetate 80/20); **^1H NMR (400 MHz, CDCl_3)** δ 7.36–7.29 (m, 2H), 7.29–7.22 (m, 3H), 7.09 (d, $J = 3.5$ Hz, 1H), 6.10 (d, $J = 3.5$ Hz, 1H), 4.04 (s, 2H), 2.43 (s, 3H); **^{13}C NMR (100 MHz, CDCl_3)** δ 186.2, 160.1, 151.8, 136.4, 128.7, 128.6, 126.8, 119.0, 109.2, 34.7, 25.6; **IR** ($\nu_{\max}$ / cm^{-1}): 3126, 3088, 3066,

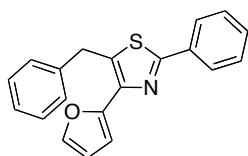
3035, 2925, 1673, 1507, 1295; **HRMS** Calculated for C₁₃H₁₂O₂ (M⁺) 200.0837, Found 200.0851.



1-(5-(4-Fluorobenzyl)furan-2-yl)ethanone (26): Synthesized according to the general procedure. Colorless oil; *R_f* 0.35 (petroleum ether/ethyl acetate 80/20); **¹H NMR (400 MHz, CDCl₃)** δ 7.25–7.17 (m, 2H), 7.10 (d, *J* = 3.5 Hz, 1H), 7.06–6.96 (m, 2H), 6.10 (dt, *J* = 3.5, 0.8 Hz, 1H), 4.01 (s, 2H), 2.43 (s, 3H); **¹³C NMR (100 MHz, CDCl₃)** δ 186.2, 161.9 (d, *J_{CF}* = 245.2 Hz), 159.8, 152.0, 132.2 (d, *J_{CF}* = 3.3 Hz), 130.4 (d, *J_{CF}* = 8.0 Hz), 119.0, 115.6 (d, *J_{CF}* = 21.5 Hz), 109.3, 34.0, 25.8; **¹⁹F NMR (377 MHz, CDCl₃)** δ -115.8; **IR (ν_{max} /cm⁻¹):** 312, 3076, 3048, 3013, 2929, 1677, 1507, 1298, 1223; **HRMS** Calculated for C₁₃H₁₁FO₂ (M⁺) 218.0743, Found 218.0734.

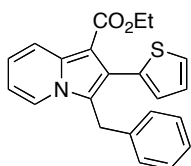
8.4.1 Section 4.2.3: *Post facto* improvement of the reaction conditions

General procedure for the direct benzylation of *bis*-heterocycles:²¹ Pd(OAc)₂ (5 mol%), triphenylphosphine (10 mol%), K₂CO₃ (1.5 equiv.) and PivOH (20 mol%) were weighed to air and placed in a screw-cap vial equipped with a magnetic stir bar. The heteroarene (1.1 equiv.) was then added at that point. The vial was purged with argon and a solution of the benzyl chloride (1.0 equiv.) in toluene (0.5 M) was added to the mixture. The reaction mixture was then stirred vigorously at 110 °C for 16 to 24 hours. The solution was then cooled to ambient temperature, diluted with ethyl acetate, then filtered and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography to afford the desired product.

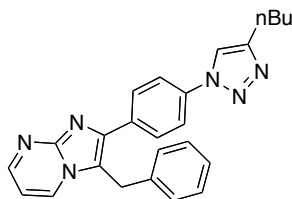


21 Lapointe, D.; Fagnou, K. *Org. Lett.* **2009**, *11*, 4160.

5-Benzyl-4-(furan-2-yl)-2-phenylthiazole (30): Synthesized according to the general procedure for the direct benzylation. Beige solid; **mp** 120–121 °C; **R_f**: 0.46 (petroleum ether/ethyl acetate 90/10); **¹H NMR (400 MHz, CDCl₃)** δ ppm 7.93–7.90 (m, 2H), 7.52 (dd, J = 1.1, 0.5 Hz, 1H), 7.41–7.39 (m, 3H), 7.33–7.25 (m, 5H), 6.85 (d, J = 3.3 Hz, 1H), 6.53 (dd, J = 3.4, 1.9 Hz, 1H), 4.50 (s, 2H); **¹³C NMR (100 MHz, CDCl₃)** δ ppm 165.8, 150.8, 142.9, 142.2, 140.1, 133.6, 133.2, 130.1, 128.9, 128.9, 128.7, 126.9, 126.5, 111.5, 108.8, 33.1; **IR ($\nu_{\max}$ /cm⁻¹):** 3062, 3027, 2919, 2852, 1680, 1601, 1494, 1474, 1310, 1253, 1171, 1009; **HRMS** Calculated for C₂₀H₁₅NOS (M⁺) 317.0874, found 317.0864.



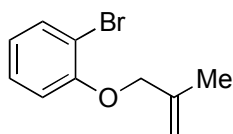
Ethyl 3-benzyl-2-(thiophen-2-yl)indolizine-1-carboxylate (31): Synthesized according to the general procedure for the direct benzylation. Yellow solid; **mp**: 154–156 °C; **R_f**: 0.48 (petroleum ether/ethyl acetate 90/10); **¹H NMR (400 MHz, CDCl₃)** δ ppm 8.29 (dt, J = 9.1, 1.1 Hz, 1H), 7.64 (dt, J = 7.0, 0.9 Hz, 1H), 7.37 (dd, J = 4.6, 1.8 Hz, 1H), 7.31–7.18 (m, 3H), 7.08–7.04 (m, 5H), 6.64 (td, J = 6.8, 1.3 Hz, 1H), 4.25 (q, J = 7.1 Hz, 2H), 4.24 (s, 2H), 1.22 (t, J = 7.1 Hz, 3H); **¹³C NMR (100 MHz, CDCl₃)** δ ppm 164.9, 137.3, 136.2, 135.7, 128.9, 128.0, 127.9, 126.8, 126.6, 126.1, 123.4, 123.3, 123.1, 122.4, 120.3, 112.9, 102.9, 59.4, 30.4, 14.4; **IR ($\nu_{\max}$ /cm⁻¹):** 3105, 3026, 2979, 2928, 2901, 1683, 1501, 1243, 1038; **HRMS** Calculated for C₂₂H₁₉NO₂S (M⁺) 361.1136, found 361.1138.



3-Benzyl-2-(4-(4-butyl-1H-1,2,3-triazol-1-yl)phenyl)imidazo[1,2-a]pyrimidine (27): Synthesized according to the general procedure for the direct benzylation. Pale yellow solid; **mp**: 178–180 °C; **R_f**: 0.11 (MeOH/DCM 2/98); **¹H NMR (400 MHz, CDCl₃)** δ ppm 8.58 (dd, J = 4.1, 2.0 Hz, 1H), 8.03 (td, J = 7.0, 2.8 Hz, 1H), 8.02 (d, J = 8.7 Hz, 2H), 7.82 (d, J = 8.8 Hz, 2H), 7.76 (s, 1H), 7.36–7.29 (m, 3H), 7.16 (d, J = 6.8 Hz, 2H),

6.81 (dd, $J = 6.8, 4.1$ Hz, 1H), 4.55 (s, 2H), 2.81 (t, $J = 7.7$ Hz, 2H), 1.74 (q, $J = 6.8$ Hz, 2H), 1.44 (sex, $J = 7.4$ Hz, 2H), 0.97 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ ppm 149.9, 149.4, 148.2, 144.3, 137.0, 135.8, 134.2, 131.1, 129.7, 129.5, 127.7, 127.5, 120.6, 118.8, 116.9, 108.8, 31.6, 29.8, 25.5, 22.5, 14.0; IR (ν_{max} / cm^{-1}): 2958, 2932, 2864, 1507, 1498, 1346, 1225, 1097, 1042, 843; HRMS Calculated for $\text{C}_{25}\text{H}_{24}\text{N}_6$ (M^+) 408.2062, found 408.2072.

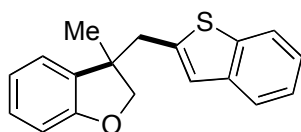
8.4.2 Section 4.3: Tandem 1,2-migratory insertion–Direct arylation



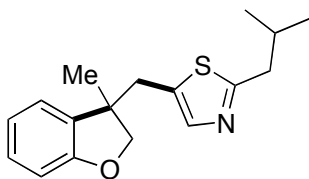
1-Bromo-2-(2-methylallyloxy)benzene (33): To a solution of 2-bromophenol (3.39 g, 19.6 mmol, 1.0 equiv.) in DMF (65 mL, 0.3 M) was added 60% sodium hydride (864 mg, 21.6 mmol, 1.1 equiv) and the mixture was stirred at room temperature for 30 minutes. 3-Chloro-2-methylprop-1-ene (2.11 mL, 21.6 mmol, 1.1 equiv) was then added and the mixture was stirred until the reaction was judged completed by TLC analysis. Water was added and the mixture was diluted with ethyl acetate. The layers were separated and the organic layer was washed with water (x3) and brine, dried over anhydrous MgSO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to afford the corresponding product. The title compound was obtained as a colorless liquid (4.07 g, 91% yield). Exhibited spectral data in accordance with previous report.²² ^1H NMR (400 MHz, CDCl_3) δ 7.54 (dd, $J = 7.6, 1.6$ Hz, 1H), 7.25–7.21 (m, 1H), 6.87 (dd, $J = 8.0, 1.2$ Hz, 1H), 6.82 (ddd, $J = 7.6, 7.6, 1.2$ Hz, 1H), 5.17 (dd, $J = 1.6, 0.8$ Hz, 1H), 5.02 (dd, $J = 2.8, 1.2$ Hz, 1H), 4.49 (s, 2H), 1.86 (d, $J = 0.4$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 155.0, 140.2, 133.3, 128.3, 121.9, 113.4, 112.8, 112.2, 72.4, 19.3.

22 Stanetty, P.; Koller, H.; Pürstinger, G. *Monatshefter für Chemie* **1990**, 53, 1170.

Procedure for the 1,2-Migratory Insertion–Direct Arylation domino sequence: K₃PO₄ (170 mg, 0.8 mmol, 2.0 equiv), DavePhos (2-Dicyclohexylphosphino-2'-dimethylaminebiphenyl) (7.9 mg, 0.02 mmol, 5 mol%) and Pd(OAc)₂ (4.5 mg, 0.02 mmol, 5 mol%) were weighed to air in a screw cap vial equipped with a magnetic stir bar. The vial was purged with argon for 10 minutes. In a separate vial, the aryl bromide (0.4 mmol, 1.0 equiv), the heterocycle (0.8 mmol, 2.0 equiv) and pivalic acid (12.3 mg, 0.12 mmol, 30 mol%) were dissolved in DMA (1.3 mL) and the solution was added to the reaction mixture using a syringe. The reaction mixture was stirred at 100 °C for 16 hours. Volatiles were then removed by horizontal distillation under reduced pressure and the residual solid was purified by silica gel column chromatography without prior removal of insoluble salts to afford the corresponding product.

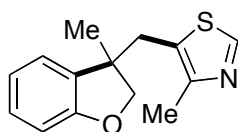


3-(Benzo[*b*]thiophen-2-ylmethyl)-3-methyl-2,3-dihydrobenzofuran (34): Prepared according to procedure the 1,2-migratory insertion–direct arylation domino sequence. The title compound was obtained as a beige solid (85% yield). **Mp:** 62–63 °C; **R_f** 0.30 (EtOAc/Hexanes 5/95); **¹H NMR (400 MHz, CDCl₃)** δ 7.73 (d, *J* = 7.8 Hz, 1H), 7.66 (d, *J* = 7.5 Hz, 1H), 7.33–7.24 (m, 2H), 7.17 (ddd, *J* = 8.0, 8.0, 0.8 Hz, 1H), 7.11 (d, *J* = 7.4 Hz, 1H), 6.92–6.89 (m, 2H), 6.78 (d, *J* = 8.0, 1H), 4.58 (d, *J* = 8.9 Hz, 1H), 4.16 (d, *J* = 8.9 Hz, 1H), 3.19 (d, *J* = 4.8 Hz, 2H), 1.46 (s, 3H); **¹³C NMR (100 MHz, CDCl₃)** δ 159.5, 140.6, 139.8, 139.6, 134.3, 128.5, 124.1, 123.7, 123.75, 123.0, 122.9, 122.0, 120.5, 109.8, 81.6, 46.1, 41.5, 25.4; **IR (ν_{max}/cm⁻¹):** 3068, 3028, 2962, 2928, 2879, 1596, 1480, 1457, 1228; **HRMS** Calculated for C₁₈H₁₆OS [M]⁺ 280.0922, Found 280.0901.



2-Isobutyl-5-((3-methyl-2,3-dihydrobenzofuran-3-yl)methyl)thiazole (35): Prepared according to procedure the 1,2-migratory insertion–direct arylation domino sequence.

The title compound was obtained as a colorless oil (80% yield). **R_f** 0.30 (EtOAc/Hexanes 25/75); **¹H NMR (400 MHz, CDCl₃)** δ 7.26 (s, 1H), 7.16 (ddd, *J* = 7.2, 7.2, 1.6 Hz, 1H), 7.05 (ddd, *J* = 7.6, 1.2, 0.4 Hz, 1H), 6.90 (ddd, *J* = 7.6, 7.6, 0.8 Hz, 1H), 6.75 (d, *J* = 7.6 Hz, 1H), 4.45 (d, *J* = 8.8 Hz, 1H), 4.14 (d, *J* = 8.8 Hz, 1H), 3.06 (d, *J* = 0.4 Hz, 2H), 2.04 (non, *J* = 6.8 Hz, 1H), 1.43 (s, 3H), 0.94 (dd, *J* = 6.8, 1.2 Hz, 6H); **¹³C NMR (100 MHz, CDCl₃)** δ 169.9, 159.7, 141.4, 133.7, 132.7, 128.7, 123.0, 120.6, 116.3, 109.9, 81.5, 46.0, 42.3, 38.2, 29.7, 25.3, 22.25, 22.2; **IR (ν_{max} /cm⁻¹)**: 2959, 2931, 2872, 1745; **HRMS** Calculated for C₁₇H₂₁NOS [M]⁺ 287.1344, Found 287.1283.

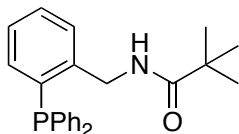


4-Methyl-5-((3-methyl-2,3-dihydrobenzofuran-3-yl)methyl)thiazole (36): Prepared according to procedure the 1,2-migratory insertion–direct arylation domino sequence. The title compound was obtained as a yellow oil (14% yield). **R_f** 0.15 (EtOAc/Hexanes 20/80); **¹H NMR (400 MHz, CDCl₃)** δ 8.54 (s, 1H), 7.16 (ddd, *J* = 8.0, 7.4, 1.5 Hz, 1H), 6.93 (dd, *J* = 7.4, 1.2 Hz, 1H), 6.87 (ddd, *J* = 7.4, 7.4, 0.9 Hz, 1H), 6.77 (d, *J* = 8.0 Hz, 1H), 4.40 (d, *J* = 8.8 Hz, 1H), 4.15 (d, *J* = 8.8 Hz, 1H), 3.10 (d, *J* = 14.8 Hz, 1H), 3.00 (d, *J* = 14.8 Hz, 1H), 2.18 (s, 3H), 1.44 (s, 3H); **¹³C NMR (100 MHz, CDCl₃)** δ 159.7, 151.0, 150.0, 133.4, 128.7, 126.4, 123.1, 120.7, 109.9, 81.8, 46.6, 37.0, 24.6, 15.0; **IR (ν_{max} /cm⁻¹)**: 3054, 2964, 2931, 2886, 1480, 1228; **HRMS** Calculated for C₁₄H₁₅NOS [M]⁺ 245.0874, Found 245.0810.

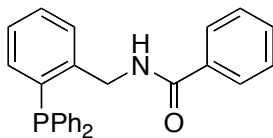
8.5 Chapter 5: Development of ligands to promote the CMD pathway in C–H bond functionalization reactions.

Section 5.1.1: General procedure for the amidation of the (2-Ph₂P-phenyl)methanamine: To a flask containing a solution of acyl chloride (1.5 equiv) in DCM under inert atmosphere was added K₂CO₃ (2.0 equiv.). Then to this mixture was added *via* syringe a solution of 2'-(Ph₂P)-benzylamine in DCM (0.3 M total) at ambient temperature. The mixture was stirred until the reaction was judged completed by TLC

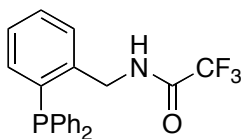
analysis. Water was added and the mixture was diluted with ethyl acetate. The layers were separated and the organic layer was washed with water (x3) and brine, dried over anhydrous MgSO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to afford the corresponding product.



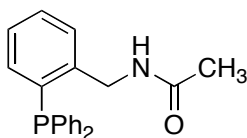
***N*-(2-(Diphenylphosphino)benzyl)pivalamide (1):** Prepared according to procedure for the amidation of 2'-(Ph_2P)-benzylamine (82% yield). White solid; **mp**: 87–89 °C; **R_f** 0.55 (EtOAc/Hexanes 40/60); **^1H NMR (400 MHz, CDCl_3)**: δ 7.46–7.43 (m, 1H), 7.34 (t, J = 6.9 Hz, 7H), 7.27–7.18 (m, 5H), 6.90 (dd, J = 6.8, 4.8 Hz, 1H), 5.82 (s, 1H), 4.65 (d, J = 5.7 Hz, 2H), 0.98 (s, 9H); **^{13}C NMR (101 MHz, CDCl_3)**: δ 178.1, 143.1 (d, J_{CP} = 25 Hz), 136.3 (d, J_{CP} = 9 Hz), 135.8 (d, J_{CP} = 14 Hz), 134.0 (d, J_{CP} = 19 Hz), 130.0 (d, J_{CP} = 5 Hz), 129.6, 129.1, 128.9, 128.8, 127.9, 42.6 (d, J_{CP} = 21 Hz), 38.6, 27.4; **IR (ν_{max} / cm^{-1})**: 3250, 2956, 2869, 1710, 1263; **HRMS** Calculated for $\text{C}_{24}\text{H}_{26}\text{NOP} [\text{M}]^+ - \text{CH}_3$ 360.1517, Found 360.1502.



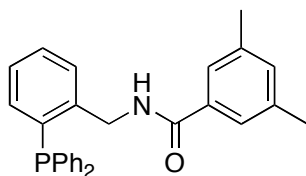
***N*-(2-(Diphenylphosphino)benzyl)benzamide (2):** Prepared according to procedure for the amidation of 2'-(Ph_2P)-benzylamine (79% yield). White solid; **mp**: 112–114 °C; **R_f** 0.25 (EtOAc/Hexanes 40/60); **^1H NMR (400 MHz, CDCl_3)**: δ 7.55 (ddd, J = 7.6, 4.5, 1.0 Hz, 1H), 7.42–7.38 (m, 1H), 7.37–7.31 (m, 9H), 7.30–7.25 (m, 6H), 7.22 (td, J = 7.5, 1.2 Hz, 1H), 6.93 (ddd, J = 7.6, 4.5, 1.2 Hz, 1H), 6.25 (t, J = 4.3 Hz, 1H), 4.87 (d, J = 5.9 Hz, 2H); **^{13}C NMR (101 MHz; CDCl_3)**: δ 166.8, 142.6 (d, J_{CP} = 25 Hz), 136.2 (d, J_{CP} = 9 Hz), 136.1 (d, J_{CP} = 14 Hz), 134.1 (d, J_{CP} = 23 Hz), 134.0 (d, J_{CP} = 20 Hz), 131.3, 130.5 (d, J_{CP} = 5 Hz), 129.7, 129.2, 129.0, 128.9, 128.4, 128.2, 126.9, 43.2 (d, J_{CP} = 20 Hz); **IR (ν_{max} / cm^{-1})**: 3250, 2986, 2959, 1710, 1263; **HRMS** Calculated for $\text{C}_{26}\text{H}_{22}\text{NOP} [\text{M}]^+ - \text{C}_6\text{H}_5$ 318.1048, Found 318.1077.



N-(2-(Diphenylphosphino)benzyl)-2,2,2-trifluoroacetamide (3): Prepared according to procedure for the amidation of 2'-(Ph₂P)-benzylamine (92% yield). White solid; **mp**: 95–96 °C; **R_f** 0.20 (MeOH/DCM 10/90); **¹H NMR (400 MHz, CDCl₃)**: δ 7.43 (ddd, *J* = 7.5, 4.4, 1.1 Hz, 1H), 7.39–7.34 (m, 7H), 7.29–7.23 (m, 5H), 6.94 (ddd, *J* = 7.6, 4.6, 1.1 Hz, 1H), 6.41 (s, 1H), 4.72 (d, *J* = 6.1 Hz, 2H); **¹³C NMR (101 MHz, CDCl₃)**: δ 156.9 (q, *J_{CF}* = 37.1 Hz), 140.1 (d, *J_{CP}* = 24.3 Hz), 136.6 (d, *J* = 14.0 Hz), 135.4 (d, *J* = 8.5 Hz), 134.2, 133.97 (d, *J_{CP}* = 2.8 Hz), 132.1 (d, *J_{CP}* = 10.2 Hz), 130.4 (d, *J* = 4.7 Hz), 129.8, 129.5, 115.8 (q, *J_{CF}* = 288 Hz), 42.8 (d, *J_{CP}* = 20.7 Hz); **IR (ν_{max}/cm⁻¹)**: 3250, 2981, 2965, 1690, 1283; **HRMS** Calculated for C₂₁H₁₇NOPF₃ [M]⁺ 387.1000, Found 387.0996.

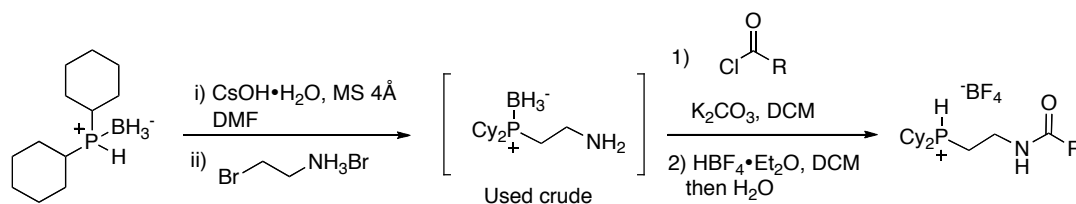


N-(2-(Diphenylphosphino)benzyl)acetamide (4): Prepared according to procedure for the amidation of 2'-(Ph₂P)-benzylamine (85% yield). White solid; **mp**: 89–90 °C; **R_f** 0.20 (MeOH/DCM 10/90); **¹H NMR (400 MHz, CDCl₃)**: δ 7.45 (ddd, *J* = 7.6, 4.5, 1.2 Hz, 1H), 7.37–7.32 (m, 7H), 7.29–7.24 (m, 4H), 7.20 (td, *J* = 7.5, 1.3 Hz, 1H), 6.90 (ddd, *J* = 7.6, 4.6, 1.2 Hz, 1H), 5.48 (s, 1H), 4.61 (d, *J* = 5.9 Hz, 2H), 1.66 (s, 4H); **¹³C NMR (101 MHz, CDCl₃)**: δ 169.6, 142.6 (d, *J_{CP}* = 24.3 Hz), 136.2 (d, *J_{CP}* = 9.0 Hz), 136.0 (d, *J_{CP}* = 14.1 Hz), 134.1 (d, *J* = 19.8 Hz), 133.8, 130.2 (d, *J* = 5.2 Hz), 129.6, 129.1 (d, *J_{CP}* = 27.4 Hz), 128.9, 128.1, 42.8 (d, *J_{CP}* = 20.0 Hz), 23.1; **IR (ν_{max}/cm⁻¹)**: 3250, 2956, 2894, 1683, 1249; **HRMS** Calculated for C₂₁H₂₀NOP [M]⁺–C₂H₃O 290.1099, Found 290.1101.



***N*-(2-(Diphenylphosphino)benzyl)-3,5-dimethylbenzamide (5):** Prepared according to procedure for the amidation of 2'-(Ph₂P)-benzylamine (61% yield). White solid; **mp**: 110–111 °C; **R_f** 0.25 (EtOAc/Hexanes 40/60); Mixture of rotamers observed by NMR, Major rotamer: **¹H NMR (300 MHz, CDCl₃)**: δ 7.65–7.46 (m, 3H), 7.40–7.20 (m, 11H), 7.04 (s, 2H), 6.94 (t, *J* = 5.7 Hz, 1H), 6.33 (s, 1H), 4.87 (d, *J* = 5.7 Hz, 2H), 2.27 (s, 6H); Minor **¹H NMR (300 MHz, CDCl₃)**: δ 7.65–7.47 (m, 3H), 7.30 (q, *J* = 18.5 Hz, 11H), 7.08–7.00 (m, 3H), 6.33 (s, 1H), 4.69 (s, 2H), 2.34 (s, 6H). Major only **¹³C NMR (101 MHz, CDCl₃)**: δ 167.2, 142.8 (d, *J_{CP}* = 24.8 Hz), 138.0, 136.3 (d, *J_{CP}* = 9.4 Hz), 136.1 (d, *J_{CP}* = 13.4 Hz), 134.0 (d, *J_{CP}* = 19.7 Hz), 130.5 (d, *J_{CP}* = 5.2 Hz), 129.6, 129.2, 128.9 (d, *J_{CP}* = 6.9 Hz), 128.1, 124.6, 43.0 (d, *J_{CP}* = 21.1 Hz), 21.3; **IR (ν_{max}/cm⁻¹)**: 3250, 2954, 2886, 1652, 1247; **HRMS** Calculated for C₂₈H₂₆NOP [M]⁺–C₉H₉O 290.1099, Found 290.1071.

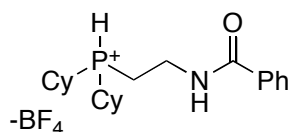
Preparation of ligands 6–8:



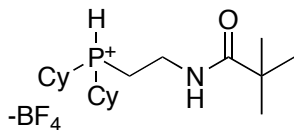
General procedure: To a suspension containing activated 4 Å molecular sieves (600 mg/mmol of starting material) in anhydrous DMF (0.125 M), cesium hydroxide monohydrate (3 equiv) was added and the mixture was stirred under inert atmosphere for a few minutes. After R₂P·BH₃²³ (1.0 equiv) was added and the mixture was stirred for 1 hour. To the resulting mixture, was added 2-bromoethanamine·HBr (1.2 equiv) in one portion. The reaction was stirred at room temperature for 24 hours. Once completed, water was added and the mixture was diluted with ethyl acetate. The layers were separated and the organic layer was washed with water (x3) and brine, dried over anhydrous MgSO₄ and concentrated under reduced pressure. The crude product was used in the next step. To a flask containing a solution of acyl chloride (2.0 equiv) in DCM

²³ Procedure from: He, Y.; Hinklin, R. J.; Chang, J.; Kiessling, L. L. Org. Lett. 2004, 6, 4479.

under inert atmosphere was added K_2CO_3 (2.0 equiv.). Then to this mixture was added at ambient temperature portion wise the crude phosphino-amine. The mixture was stirred until the reaction was judged completed by TLC analysis. Water was added and the mixture was diluted with ethyl acetate. The layers were separated and the organic layer was washed with water (x3) and brine, dried over anhydrous MgSO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography. The phosphine was deprotected by adding $\text{HBF}_4 \cdot \text{OEt}_2$ (10 equiv) to a solution of the phosphine-borane complex in DCM (0.08 M) under inert atmosphere. After few minutes, water was added (1:1 ratio with water), the mixture was then transferred to an extraction funnel and the aqueous layer was extracted 3X with DCM, dried over anhydrous MgSO_4 and concentrated under reduced pressure yielding the phosphonium HBF_4 salt.

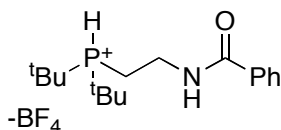


N-(2-(Dicyclohexylphosphino)ethyl)benzamide* HBF_4 (6): White solid; **mp:** 94–96 °C; **^1H NMR (300 MHz, CDCl_3):** 7.96–7.88 (m, 2H), 7.54–7.42 (m, 3H), 6.60 (s, 0.5H), 5.02 (s, 0.5H), 3.90 (dt, $J = 11.2, 5.8$ Hz, 2H), 2.75–2.64 (m, 2H), 2.58–2.45 (m, 2H), 2.05–1.74 (m, 10H), 1.57–1.24 (m, 10H). **^{13}C NMR (101 MHz, CDCl_3):** δ 168.7, 133.0, 132.1, 128.8, 127.4, 34.9 (d, $J_{\text{CP}} = 4.6$ Hz), 28.7 (d, $J_{\text{CP}} = 42.0$ Hz), 27.2 (dd, $J_{\text{CP}} = 40.8, 3.4$ Hz), 26.0 (dd, $J_{\text{CP}} = 13.5, 6.7$ Hz), 25.1 (d, $J_{\text{CP}} = 1.1$ Hz), 14.8 (d, $J_{\text{CP}} = 43.2$ Hz); **IR (ν_{max} / cm^{-1}):** 2956, 2931, 2894, 1652, 1558; **Electrospray Ionisation** Calculated for $\text{C}_{21}\text{H}_{33}\text{NOP}^+$ 346.2294, BF_4^- 87.0035, found C^+ (346.5), $\text{C}^+\text{C}^+\text{B}^-$ (779.5).



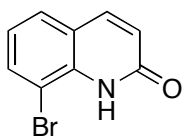
N-(2-(Dicyclohexylphosphino)ethyl)pivalamide* HBF_4 (7): White solid; **mp:** 94–96 °C; **^1H NMR (400 MHz, CDCl_3):** δ 7.23 (broad peak, 0.5H), 6.58 (broad peak, 0.5H), 6.30 (broad peak, 0.5H), 5.12 (broad peak, 0.5H), 3.65 (broad peak, 2H), 2.53 (broad peak, 2H), 2.32–1.78 (m, 12H), 1.49–1.29 (m, 10H), 1.20 (s, 9H); **^{13}C NMR (101 MHz,**

CDCl₃): δ 164.4, 38.9, 34.6, 28.7 (d, J_{CP} = 42.1 Hz), 27.5, 27.0 (d, J_{CP} = 3.3 Hz), 26.32–25.77 (m), 25.5 (d, J_{CP} = 2.3 Hz), 25.1;); **IR** (ν_{max} /cm⁻¹): 2982, 2894, 1652, 1558; **Electrospray Ionisation** Calculated for C₁₉H₃₇NOP⁺ 326.2613, BF₄⁻ 87.0035, found C⁺ (326.3), C⁺C⁺B⁻ (739.6).



N-(2-(Di-tert-butylphosphino)ethyl)pivalamide*HBF₄ (8): White solid; **mp**: 94–96 °C; **¹H NMR** (400 MHz, CDCl₃): δ 8.11 (t, J = 5.4 Hz, 1H), 7.91 (d, J = 7.1 Hz, 2H), 7.50 (t, J = 7.3 Hz, 1H), 7.43 (t, J = 7.4 Hz, 2H), 6.58 (t, J = 3.9 Hz,), 5.41 (t, J = 3.8 Hz,), 3.96–3.87 (m, 2H), 2.65 (dq, J = 10.4, 5.2 Hz, 2H), 1.50 (d, J = 16.6 Hz, 18H); **¹³C NMR** (101 MHz, CDCl₃): δ 169.0, 132.8, 132.2, 128.8, 127.4, 37.0 (d, J_{CP} = 5.9 Hz), 32.9 (d, J_{CP} = 35.8 Hz), 27.1, 15.4 (d, J_{CP} = 41.1 Hz); **IR** (ν_{max} /cm⁻¹): 2956, 2931, 2894, 1652, 1558; **Electrospray Ionisation** Calculated for C₁₇H₁₉NOP⁺ 294.1981, BF₄⁻ 87.0035, found C⁺ (294.2), C⁺C⁺B⁻ (675.4).

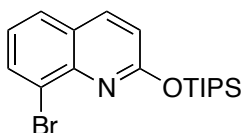
Section 5.1.2:



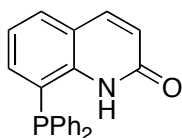
8-Bromoquinolin-2(1H)-one (10): This compound was prepared following a literature procedure.²⁴ To an ice-cooled solution of 2-bromoaniline (2.71 g, 15.75 mmol, 1.05 equiv) in benzene (15 mL) containing pyridine (1.25 mL) was added freshly prepared cinnamoyl chloride (2.5 g, 15.0 mmol, 1.0 equiv) in benzene (15 mL, 0.6 M total) dropwise with stirring. Once the addition completed, the reaction was allowed to warm to ambient temperature. After 12 hours, EtOAc was added until dissolution occurred, and the mixture was washed with water, dilute hydrochloric acid (2 X 75 mL), and aqueous NaHCO₃. The dried organic layer on concentration gave the amide **9**, which was used as

24 Leclerc, G.; Marciniak, G.; Decker, N.; Schwartz, J. *J. Med. Chem.* **1986**, 29, 2433.

such in the next step. To a solution of **9** (1.34 g, 4.44 mmol) in chlorobenzene (7.5 mL, 0.6 M) was added portionwise under stirring AlCl_3 (2.82 g, 21.5 mmol, 5 equiv). The mixture was heated to 130 °C and maintained at this temperature for 3 hour. Then, the solution was carefully poured onto ice; the precipitate formed was triturated with hexane and filtered to give **10** in 66–81% yield; **mp** 208–210 °C; **R_f** 0.40 (MeOH/DCM 5/95); **¹H NMR (400 MHz, CDCl₃)**: δ 9.03 (s, 1H), 7.74–7.71 (m, 2H), 7.53 (dd, J = 7.9, 1.0 Hz, 1H), 7.11 (t, J = 7.9 Hz, 1H), 6.68 (d, J = 9.5 Hz, 1H); **¹³C NMR (101 MHz; CDCl₃)**: δ 162.2, 140.5, 135.8, 133.7, 127.7, 123.4, 123.1, 121.2, 109.2; **IR (ν_{max} /cm⁻¹)**: 3350, 2989, 2889, 1652, 1506, 1276; **HRMS** Calculated for C₉H₆NOBr [M]⁺ 222.9633, Found 222.9624.

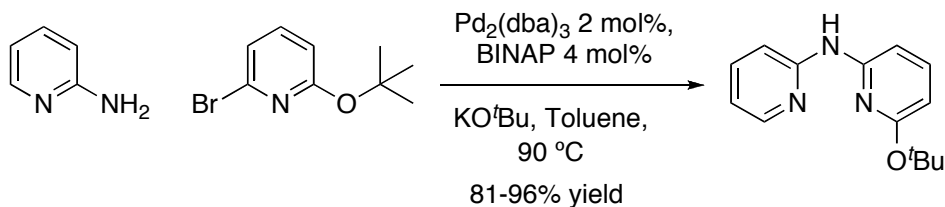


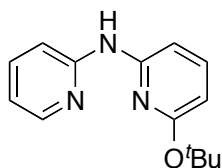
8-Bromo-2-(tri-isopropylsilyloxy)quinoline (11): To a solution of **10** (672 mg, 3.0 mmol, 1.0 equiv), imidazole (490 mg, 7.2 mmol, 2.4 equiv), DMAP (~40g, 5 mmol%) in DMF at room temperature was added dropwise TIPSCl (0.77 mL, 3.6 mmol, 1.2 equiv). The mixture was stirred until the reaction was judged completed by TLC analysis. Water was added and the mixture was diluted with ethyl acetate. The layers were separated and the organic layer was washed with water (x3) and brine, dried over anhydrous MgSO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to afford the corresponding product. The product was obtained as a white solid in 72% yield, **mp** 224–227 °C; **R_f** 0.40 (EtOAc/Pet. ether 20/80); **¹H NMR (400 MHz, CDCl₃)**: δ 7.97 (d, J = 8.7 Hz, 1H), 7.90 (dd, J = 7.5, 1.3 Hz, 1H), 7.64 (dd, J = 8.0, 1.2 Hz, 1H), 7.19 (t, J = 7.8 Hz, 1H), 6.94 (d, J = 8.7 Hz, 1H), 1.70 (sept, J = 7.5 Hz, 3H), 1.15 (d, J = 7.5 Hz, 18H); **¹³C NMR (101 MHz; CDCl₃)**: δ 161.9, 144.4, 139.7, 133.1, 127.1, 126.3, 124.3, 122.5, 115.9, 18.4, 12.8; **IR (ν_{max} /cm⁻¹)**: 2943, 2864, 1652, 1600, 1284; **HRMS** Calculated for C₁₈H₂₆NOBrSi [M]⁺ 379.0967, Found 379.0925.



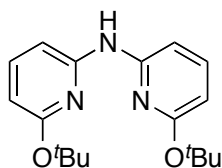
8-(Diphenylphosphino)quinolin-2(1H)-one (12): To a solution of **11** (1.80 g, 4.73 mmol, 1.0 equiv) in dry THF (16 mL, 0.3M) at -78 °C was added 2.31 mL of butyl lithium (2.45 M, 1.2 equiv). After ~10 minutes at this temperature, chlorodiphenylphosphine (1.13 mL, 6.15 mmol, 1.3 equiv) was added slowly to the reaction mixture, once the addition completed, the reaction was allowed to warm up to ambient temperature. The mixture was stirred until the reaction was judged completed by TLC analysis. Methanol followed by water were added and the mixture was diluted with ethyl acetate. The layers were separated and the organic layer was washed with water (x3) and brine, dried over anhydrous MgSO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to afford the corresponding product. The product was obtained as a white solid in 72% yield, **mp** 154–160 °C; R_f 0.65 (MeOH/DCM 5/95); ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 9.92 (s, 1H), 8.00 (d, $J = 9.4$ Hz, 1H), 7.78 (d, $J = 7.7$ Hz, 1H), 7.42 (s, 6H), 7.28–7.20 (m, 5H), 7.10 (s, 1H), 6.59 (d, $J = 9.2$ Hz, 1H); ^{13}C NMR (101 MHz, $\text{DMSO}-d_6$): δ 161.2, 141.2, 136.0, 134.2, 133.3 (d, $J_{CP} = 19.4$ Hz), 130.1, 129.4, 129.0 (d, $J_{CP} = 7.0$ Hz), 122.6, 121.9, two quaternary carbons missing; **IR** (ν_{max} / cm^{-1}): 3340, 3064, 3022, 2987, 1652, 1506; **HRMS** Calculated for $\text{C}_{21}\text{H}_{16}\text{NOP}$ $[\text{M}]^+$ 329.0970, Found 329.0994.

Section 5.2:



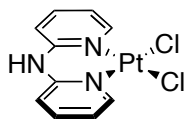


6-*tert*-Butoxy-*N*-(pyridin-2-yl)pyridin-2-amine: In a flask was added 2-aminopyridine (94 mg, 1.2 mmol, 1.2 equiv), 2-bromo-6-*tert*-butoxypyridine (230 mg, 1.0 mmol, 1.0 equiv), Pd₂(dba)₃ (18 mg, 2 mol%), BINAP (25 mg, 4 mol%) and potassium *tert*-butoxide (168 mg, 1.5 mmol, 1.5 equiv). Once all the powders were added, the flask was thoroughly purged with argon, then toluene (9 mL, 0.11 M) was added and the solvent was then degassed with argon. After being thoroughly degassed, the flask was sealed and heat to 90 °C for a couple of hours. The mixture was stirred until the reaction was judged completed by TLC analysis. Once completed, the reaction mixture was filtered through a pad of celite and the solvent remove under reduce pressure. The crude product was purified by silica gel column chromatography to afford the corresponding product. The product was obtained as a orange solid in 96% yield, **mp** 154–160 °C; **R_f** 0.20 (MeOH/DCM 10/90); **¹H NMR (400 MHz, CDCl₃):** δ 8.26 (d, *J* = 3.9 Hz, 1H), 7.57 (t, *J* = 6.9 Hz, 1H), 7.50–7.42 (m, 2H), 7.37 (s, 1H), 7.02 (d, *J* = 7.8 Hz, 1H), 6.82 (t, *J* = 5.9 Hz, 1H), 6.26 (d, *J* = 7.9 Hz, 1H), 1.58 (s, 9H); **¹³C NMR (101 MHz; CDCl₃):** δ 162.8, 154.1, 151.8, 148.1, 140.1, 137.6, 116.3, 111.5, 105.7, 103.0, 79.4, 29.0; **IR (ν_{max}/cm⁻¹):** 3250, 2977, 2931, 1436; **HRMS** Calculated for C₁₄H₁₇N₃O [M]⁺ 243.1372, Found 243.1362.



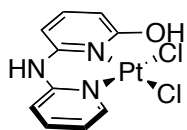
Bis(6-*tert*-butoxypyridin-2-yl)amine: This compound was prepared similarly to previous compound (85% yield). Yellow oil; **R_f** 0.45 (EtOAc/Pet. ether 20/80); **¹H NMR (400 MHz, CDCl₃):** δ 7.44 (t, *J* = 7.9 Hz, 2H), 6.94 (d, *J* = 7.8 Hz, 2H), 6.82 (s, 1H), 6.24 (dd, *J* = 7.9, 0.3 Hz, 2H), 1.59 (s, 19H); **¹³C NMR (101 MHz; CDCl₃):** δ 162.9,

151.8, 139.9, 105.3, 102.7, 79.4, 29.0; **IR** ($\nu_{\max}$ / cm^{-1}): 3250, 2989, 2931, 1430; **HRMS**
Calculated for $\text{C}_{14}\text{H}_{17}\text{N}_3\text{O}$ $[\text{M}]^+$ 243.1372, Found 243.1362.



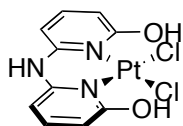
MS-6

Complex **MS-6**: This complex was prepared from 2,2'-dipyridyl amine (Aldrich) and *cis*-(Me_2SO) $_2\text{Pt}(\text{Cl})_2$ ²⁵ following the procedure of Tu *et al.*²⁶ Exhibited identical spectral data according to previous report.²⁷



14

This complex was prepared from 2,2'-dipyridyl amine (Aldrich) and *cis*-(Me_2SO) $_2\text{Pt}(\text{Cl})_2$ ²⁵ following the procedure of Tu *et al.*²⁶ **¹H NMR (400 MHz, DMSO-*d*₆)**: δ 12.21 (s, 1H), 10.76 (s, 1H), 8.56 (d, J = 5.3 Hz, 1H), 7.93 (t, J = 7.4 Hz, 1H), 7.72 (t, J = 8.0 Hz, 1H), 7.22 (d, J = 8.2 Hz, 1H), 7.12 (t, J = 6.6 Hz, 1H), 6.71 (d, J = 7.7 Hz, 1H), 6.45 (d, J = 8.0 Hz, 1H); **¹³C NMR (101 MHz; DMSO)**: δ 165.4, 151.4, 150.6, 142.8, 140.6, 119.6, 116.7, 113.3, 105.1, 102.6. Not fully characterized.



15

This complex was prepared from 2,2'-dipyridyl amine (Aldrich) and *cis*-(Me_2SO) $_2\text{Pt}(\text{Cl})_2$ ²⁵ following the procedure of Tu *et al.*²⁶ **¹H NMR (300 MHz, DMSO-**

²⁵ Hill, G. S.; Irwin, M. J.; Levy, C. J.; Rendina, L. M.; Puddephatt, R. J. *Inorg. Synth.* **1998**, 32, 149.

²⁶ Tu, C.; Wu, X.; Liu, Q.; Wang, X.; Xu, Q.; Guo, Z. *Inorg. Chim. Acta.*, 2004, 357, 95.

²⁷ Hickman, A. J.; Villalobos, J. M.; Sanford, M. S. *Organometallics*, **2009**, 28, 5316.

d_6): δ 10.54 (s, 1H), 7.68 (t, $J = 8.0$ Hz, 2H), 6.70 (d, $J = 8.0$ Hz, 2H), 6.47 (d, $J = 8.1$ Hz, 2H). Not fully characterized.

H/D exchange reactions:

All glassware and stir bars were dried before each use. A 0.04 M stock solution of the appropriate Ag salt in TFA- d_1 was prepared immediately before use. Of this solution (0.25 mL) was added to a 2 mL screw cap vial fitted with a plastic cap containing the appropriate Pt complex. An additional 0.25 mL of TFA- d_1 was added, this mixture was stirred for 1 min, and then benzene (50 μ L, 0.56 mmol) was added. The reaction vessel was sealed and submerged in a preheated sand bath at 150 °C. At the completion of the reaction, the mixture was cooled to room temperature, filtered through a plug of Celite, and the Celite plug was washed with ether (2 mL). Aqueous K_2CO_3 (2 x 1 mL of a saturated solution in deionized H_2O) was added slowly to quench the TFA- d_1 . The organic layer was then separated and diluted with ether to generate a sample for analysis by GCMS. The % deuterium incorporation is defined as the area of C–H bonds converted to C–D bonds.

8.6 Chapter 6: Analysis of the Palladium-Catalyzed (Aromatic)C–H Bond Metallation-Deprotonation Mechanism Spanning the Entire Spectrum of Arenes

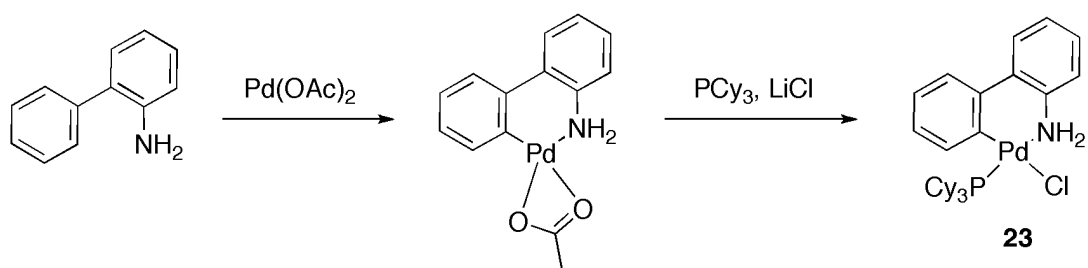
Table 8.3 Gibbs free energies and electronic energies of the CMD transition states for the ArH substrates with the $Pd(C_6H_5)(PMe_3)(OAc)$ catalyst, the catalyst and substrate preparation energies and the catalyst-substrate interaction energies ($kcal\ mol^{-1}$). (Data collected by Serge Gorelsky)

	ArH		ΔG_{TS}	ΔE_{TS}	E_{prep} PdL	E_{prep} ArH	E_{int}
Class I	1	C_6F_5H	21.9	11.9	15.3	28.8	-32.2
	2	$m\text{-}C_6F_2H_4$	25.4	16.3	16.3	32.2	-32.0
			29.0	19.2	16.4	39.9	-37.1
			32.4	23.1	15.9	41.7	-34.6
	3	C_6FH_5	30.3	20.7	16.8	38.9	-35.1

			34.3	24.1	16.2	43.0	-35.1
			34.2	23.8	16.5	44.7	-37.5
	4	<i>m</i> -C ₆ Cl ₂ H ₄	28.9	19.4	16.1	34.3	-31.0
			30.9	20.9	15.8	39.6	-34.5
			32.1	22.6	15.9	41.0	-34.3
	5	C ₅ H ₅ NO	27.2	16.5	15.5	36.8	-35.7
			31.1	21.6	15.7	40.1	-34.2
			30.5	20.8	16.5	42.8	-38.5
	6	C ₆ H ₅ OCH ₃	32.7	22.6	17.4	42.5	-37.3
			35.1	24.7	16.3	44.4	-35.9
			34.4	23.9	17.5	45.8	-39.4
	7	C ₈ H ₆ S	26.5	16.7	16.7	37.5	-37.6
			29.2	19.3	17.2	39.6	-37.4
	8	C ₈ H ₅ SF	22.6	12.3	17.2	32.4	-37.3
	9	C ₃ H ₃ N ₂ Me	27.3	16.9	17.5	41.3	-41.9
			28.5	18.3	18.0	45.3	-45.0
			31.3	21.5	16.6	43.6	-38.6
	10	C ₈ H ₆ O	26.3	16.5	16.9	39.6	-40.0
			27.5	17.6	17.0	40.7	-40.0
Class II	11	C ₄ H ₄ O	25.3	15.6	17.8	42.5	-44.8
			28.7	19.5	17.4	42.1	-40.0
	12	C ₃ H ₃ SN	23.7	14.5	17.0	36.8	-39.2
			26.4	16.6	16.2	34.8	-34.4
			29.7	20.0	16.3	39.8	-36.1
	13	Ph-C ₃ H ₂ SNO	23.8	12.4	16.6	33.9	-38.1
			25.5	13.1	15.4	32.3	-34.6
	14	MeC ₃ H ₃ NN	25.0	14.3	18.7	44.8	-49.3
			26.5	15.9	17.5	41.0	-42.6
			29.6	20.2	17.6	45.1	-42.5
	15	C ₈ H ₇ N	22.5	13.1	19.9	48.1	-54.9
			30.9	21.1	17.2	44.3	-40.3
			27.1	17.1	19.1	49.1	-51.1
	16	C ₆ H ₅ N ₃	21.4	11.1	18.5	42.2	-49.4
			30.6	20.5	16.0	40.4	-35.9
Class III	17	C ₆ H ₆	33.9	25.1	16.4	44.6	-35.9
	18	<i>p</i> -NC ₄ H ₄ NO	24.9	14.7	15.3	34.3	-34.9
			32.2	22.2	14.8	37.5	-30.2
	19	C ₉ H ₇ NO	26.7	15.4	15.8	35.9	-36.2
			27.4	16.7	15.4	36.7	-35.4
			31.5	20.9	16.0	40.0	-35.2

	20	C ₃ H ₃ SNO	16.7	5.8	16.6	29.3	-40.1
			22.7	12.6	16.8	33.7	-37.9
			23.3	12.5	15.5	32.2	-35.2
	21		23.2	12.5	20.4	50.1	-58.0
			26.8	16.6	19.8	50.8	-53.9
	22h	C ₄ H ₄ S	25.6	15.9	17.3	39.9	-41.4
			29.9	20.7	16.8	41.8	-37.8

Section 6.2.3: Reactivity of C2 substituted thiophenes:

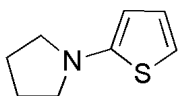


Preparation of the 2'-(PdPCy_3Cl)-2-aminobiphenyl (23**) precatalyst:** The preparation of the precatalyst was made following the procedures reported by Buchwald *et al.*²⁸ A mixture of $\text{Pd}(\text{OAc})_2$ (420 mg, 1.87 mmol, 1.0 equiv.) and freshly purified 2-aminobiphenyl (331 mg, 1.96 mmol, 1.05 equiv.) in anhydrous toluene (12 mL, 0.15 M) was heated at 60 °C for 30 min under an argon atmosphere, at which point the initial red color of the solution faded and a grey precipitate had formed. After the reaction cooled to room temperature, the toluene was removed with a pipette. The remaining solid was washed twice with toluene (~3 mL) and then suspended in dry acetone (12 mL). After addition of lithium chloride (226 mg, 5.34 mmol, 3.0 equiv., stored in a desiccator), the resulting slurry was stirred at room temperature under argon for 1 hour to give a homogenous solution. PCy_3 (500 mg, 1.78 mmol, 1.0 equiv.) was then added portionwise over 5 min. The PCy_3 was stored in the glovebox and weighted in the glovebox, although PCy_3 can be stored on bench top if kept under inert atmosphere. The mixture was stirred at room temperature for a couple of hours (3-4 hours), at which point a significant amount of a grey precipitate in suspension had formed. The precipitate in suspension was then

28 Kinzel, T.; Zhang, Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, 14073.

separated from solid LiCl by decantation and the remaining LiCl was washed with dry acetone once. The acetone suspension was then stored for some time to let the precipitate settled. Most of the solvent was removed with a pipette and washed twice with ether (~5 mL). When most of the solvent was removed with a pipette, the remaining solvent was removed with a rotary vacuum evaporator and dried under vacuum. Yield: 850 mg, 1.44 mmol (80%). ^{31}P NMR (121 MHz CDCl_3): 36.0, 33.8. (Rotamers).

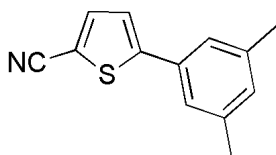
General procedure for the direct arylation of heterocycles:²⁹ 2'-(PdPCy₃Cl)-2-aminobiphenyl (5 mol%), K_2CO_3 (1.5 equiv.) and PivOH (30 mol%) were weighed to air and placed in a screw-cap vial equipped with a magnetic stir bar. The heteroarene (1.1 equiv.) and the aryl bromide (1.0 equiv.), if a solid, were then added at that point. The vial was purged with argon and a solution of the coupling partners, if liquid, in dimethylacetamide (DMA) (0.3 M) was added to the mixture. The reaction mixture was then stirred vigorously at 100 °C for 4–16 hours. The solution was then cooled to ambient temperature and loaded directly on the column or was diluted with ethyl acetate, then filtered and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography to afford the corresponding product.



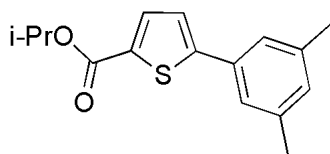
1-(Thiophene-2-yl)pyrrolidine (22a). Synthesized following a known procedure from 2-iodothiophene.³⁰ Light sensitive oil; **R_f** 0.35 (petroleum ether/ethyl acetate 80/20); **^1H NMR (400 MHz, CDCl_3)** δ ppm 6.78 (ddd, $J = 5.2, 3.8, 1.2$ Hz, 1H), 6.38 (dd, $J = 5.4, 1.2$ Hz, 1H), 5.75 (dd, $J = 3.7, 1.2$ Hz, 1H), 3.25 (dq, $J = 6.5, 3.4$ Hz, 4H), 2.05–1.97 (m, 4H); **^{13}C NMR (100 MHz, CDCl_3)** δ ppm 155.9, 126.9, 108.3, 100.0, 51.2, 25.8; **IR (ν_{max} / cm^{-1})** 2966, 2889, 2837, 1533, 1471, 1456, 1362 cm^{-1} ; **HRMS** Calculated for $\text{C}_8\text{H}_{11}\text{NS}$ (M^+) 153.0612, Found 153.0614.

29 Liégault, B.; Lapointe, D.; Caron, L.; Vlassova, A.; Fagnou, K. *J. Org. Chem.* **2009**, 74, 1826.

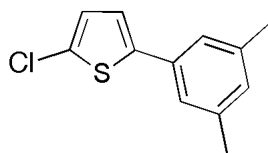
30 Lu, Z.; Twieg, R. J. *Tetrahedron* **2005**, 61, 903.



5-(3,5-Dimethylphenyl)thiophene-2-carbonitrile. Synthesized according to the general procedure for the direct arylation. Yellow solid; **Mp**: 68-70 °C (CHCl₃); **Rf** 0.60 (petroleum ether/ethyl acetate 80/20); **¹H NMR (400 MHz, CDCl₃)** δ ppm 7.57 (d, *J* = 3.9 Hz, 1H), 7.24 (d, *J* = 3.9 Hz, 1H), 7.21 (s, 2H), 7.04 (s, 1H), 2.36 (s, 6H); **¹³C NMR (100 MHz, CDCl₃)** δ ppm 152.4, 139.1, 138.4, 132.3, 131.3, 129.8, 124.4, 123.2, 114.7, 21.4; **IR (ν_{max}/cm⁻¹)** 3084, 2961, 2358, 2331, 2219, 1652 cm⁻¹; **HRMS** Calculated for C₁₃H₁₁NS (M⁺) 213.0612, Found 213.0618.

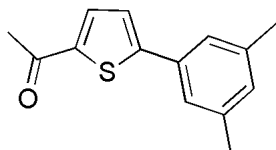


Isopropyl 5-(3,5-dimethylphenyl)thiophene-2-carboxylate. Synthesized according to the general procedure for the direct arylation, 96 % yield. Pale oil; **Rf** 0.50 (petroleum ether/ethyl acetate 80/20); **¹H NMR (400 MHz, CDCl₃)** δ ppm 7.73 (d, *J* = 3.9 Hz, 1H), 7.25 (s, 2H), 7.25 (d, *J* = 4.1 Hz, 1H), 6.99 (s, 1H), 5.22 (septuplet, *J* = 6.3 Hz, 1H), 2.35 (s, 6H), 1.36 (d, *J* = 6.3 Hz, 6H); **¹³C NMR (100 MHz, CDCl₃)** δ ppm 162.0, 151.5, 138.8, 134.1, 133.5, 132.8, 130.6, 124.2, 123.4, 68.8, 22.1, 21.4; **IR (ν_{max}/cm⁻¹)** 2979, 2926, 2875, 1697, 1276 cm⁻¹; **HRMS** Calculated for C₁₆H₁₈O₂S (M⁺) 274.1028, Found 274.1050.

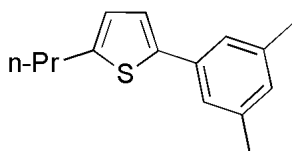


2-Chloro-5-(3,5-dimethylphenyl)thiophene. Synthesized according to the general procedure for the direct arylation. Green solid; **Mp**: 70-71 °C (CHCl₃); **Rf** 0.65

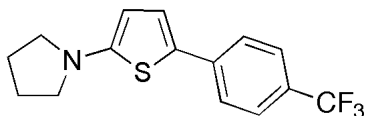
(petroleum ether/ethyl acetate 80/20); **¹H NMR (400 MHz, CDCl₃)** δ ppm 7.12 (wide s, 2H), 7.02 (d, *J* = 3.9 Hz, 1H), 6.93 (wide s, 1H), 6.86 (d, *J* = 3.9 Hz, 1H), 2.33 (s, 6H); **¹³C NMR (100 MHz, CDCl₃)** δ ppm 143.4, 138.7, 133.7, 129.7, 128.8, 127.1, 123.6, 122.1, 21.4; **IR** (*v*_{max} /cm⁻¹) 2914, 2850, 1598, 1431 cm⁻¹; **HRMS** Calculated for C₁₂H₁₁ClS (M⁺) 222.0270, Found 222.0254.



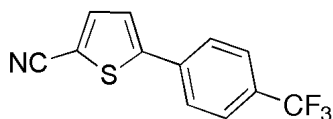
1-(5-(3,5-Dimethylphenyl)thiophen-2-yl)ethanone. Synthesized according to the general procedure for the direct arylation. Oil; **R_f** 0.30 (petroleum ether/ethyl acetate 80/20); **¹H NMR (400 MHz, CDCl₃)** δ ppm 7.64 (d, *J* = 4.0 Hz, 1H), 7.28 (d, *J* = 4.0 Hz, 1H), 7.27 (wide s, 2H), 7.00 (wide s, 1H), 2.55 (s, 3H), 2.35 (d, *J* = 0.6 Hz, 6H); **¹³C NMR (100 MHz, CDCl₃)** δ ppm 153.4, 142.8, 138.8, 133.5, 133.3, 130.9, 127.3, 124.3, 123.8, 26.7, 21.4; **IR** (*v*_{max} /cm⁻¹) 3004, 2921, 2864, 1647, 1436 cm⁻¹; **HRMS** Calculated for C₁₄H₁₄OS (M⁺) 230.0765, Found 230.0761.



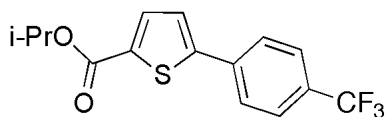
2-(3,5-Dimethylphenyl)-5-propylthiophene. Synthesized according to the general procedure for the direct arylation, 73 % yield. oil; **R_f** 0.70 (petroleum ether/ethyl acetate 80/20); **¹H NMR (400 MHz, CDCl₃)** δ ppm 7.18 (s, 2H), 7.09 (d, *J* = 3.5 Hz, 1H), 6.88 (s, 1H), 6.72 (dd, *J* = 3.5, 1.9 Hz, 1H), 2.79 (t, *J* = 7.5 Hz, 2H), 2.33 (s, 6H), 1.72 (sextet, *J* = 7.4 Hz, 2H), 1.00 (t, *J* = 7.3 Hz, 3H); **¹³C NMR (100 MHz, CDCl₃)** δ ppm 145.2, 142.1, 138.4, 134.7, 128.9, 125.1, 123.6, 122.6, 32.5, 25.0, 21.5, 13.8; **IR** (*v*_{max} /cm⁻¹) 2962, 2922, 2870, 1652, 1558 cm⁻¹; **HRMS** Calculated for C₁₅H₁₈S (M⁺) 230.1129, Found 230.1121.



1-(5-(4-(Trifluoromethyl)phenyl)thiophen-2-yl)pyrrolidine. Synthesized according to the general procedure for the direct arylation. Green solid; **Mp**: 142-144 °C (CHCl₃); **Rf** 0.25 (petroleum ether/ethyl acetate 80/20); ¹H NMR (300 MHz, CDCl₃) δ ppm 7.53-7.47 (m, 4H), 7.16 (d, *J* = 3.9 Hz, 1H), 5.73 (d, *J* = 4.0 Hz, 1H), 3.34-3.30 (m, 4H), 2.08-2.03 (m, 4H); ¹³C NMR (100 MHz, CDCl₃) δ ppm 156.2, 139.1, 126.5 (q, *J*_{C-F} = 32.0 Hz), 125.8 (q, *J*_{C-F} = 3.9 Hz), 125.1, 124.6 (q, *J*_{C-F} = 272.1 Hz), 124.1, 123.6, 101.6, 51.0, 25.9; **IR** (*v*_{max} /cm⁻¹) 3055, 2985, 2856, 1610, 1517, 1481, 1326, 1107 cm⁻¹; **HRMS** Calculated for C₁₅H₁₄F₃NS (M⁺) 297.0799, Found 297.0792.



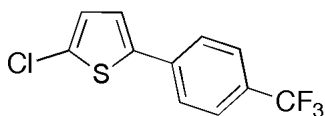
5-(4-(Trifluoromethyl)phenyl)thiophene-2-carbonitrile. Synthesized according to the general procedure for the direct arylation, 73% yield. ¹H NMR of the final product matched the previously reported spectrum.³¹ Yellow solid; **Rf** 0.10 (petroleum ether/diethyl ether 95/5); ¹H NMR (400 MHz, CDCl₃) δ ppm 7.73-7.68 (m, 4H), 7.63 (d, *J* = 3.9 Hz, 1H), 7.36 (d, *J* = 3.9 Hz, 1H).



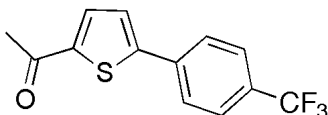
Isopropyl 5-(4-(trifluoromethyl)phenyl)thiophene-2-carboxylate. Synthesized according to the general procedure for the direct arylation, 67% yield. White solid; **Mp**: 96-98 °C (CHCl₃); **Rf** 0.60 (petroleum ether/ethyl acetate 80/20); ¹H NMR (400 MHz, CDCl₃) δ ppm 7.77 (d, *J* = 3.9 Hz, 1H), 7.74 (d, *J* = 8.1 Hz, 2H), 7.66 (d, *J* = 8.3 Hz, 2H), 7.36 (d, *J* = 3.9 Hz, 1H), 5.24 (7, *J* = 6.3 Hz, 1H), 1.38 (d, *J* = 6.3 Hz, 6H); ¹³C

31 Battace, A.; Lemhadri, M.; Zair, T.; Doucet, H.; Santelli, M. *Adv. Synth. Catal.* **2007**, 349, 2507.

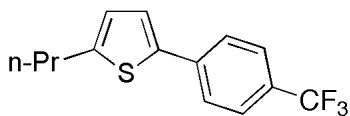
NMR (100 MHz, CDCl₃) δ ppm 161.7, 148.8, 137.0, 134.7, 134.1, 130.5 (q, J_{C-F} = 33.0 Hz), 126.5 (q, J_{C-F} = 3.8 Hz), 126.2, 124.9, 124.2 (q, J_{C-F} = 272.1 Hz), 69.2, 22.1; **IR** (ν_{max} /cm⁻¹) 3002, 2993, 1679, 1653, 1276 cm⁻¹; **HRMS** Calculated for C₁₅H₁₃F₃NO₂S (M⁺) 314.0588, Found 314.0589.



2-Chloro-5-(4-(trifluoromethyl)phenyl)thiophene. Synthesized according to the general procedure for the direct arylation. ¹H NMR of the final product matched the previously reported spectrum.³² Pale yellow solid; **Rf** 0.60 (petroleum ether/ethyl acetate 95/5); **¹H NMR (400 MHz, CDCl₃)** δ ppm 7.64-7.59 (m, 4H), 7.16 (d, J = 3.9 Hz, 1H), 6.93 (d, J = 3.9 Hz, 1H).



1-(5-(4-(Trifluoromethyl)phenyl)thiophen-2-yl)ethanone. Synthesized according to the general procedure for the direct arylation, 50% yield. ¹H NMR of the final product matched the previously reported spectrum.³¹ White solid; **Rf** 0.35 (petroleum ether/ethyl acetate 70/30); **¹H NMR (400 MHz, CDCl₃)** δ ppm 7.76 (d, J = 8.2 Hz, 2H), 7.68 (d, J = 3.9 Hz, 2H), 7.67 (d, J = 8.3 Hz, 3H), 7.40 (d, J = 4.0 Hz, 1H), 2.59 (s, 3H).



2-Propyl-5-(4-(trifluoromethyl)phenyl)thiophene. Synthesized according to the general procedure for the direct arylation. ¹H NMR of the final product matched the previously reported spectrum.¹⁹ **¹H NMR (400 MHz, CDCl₃)** δ ppm 7.64 (d, J = 8.4 Hz, 2H), 7.59

32 Liégault, B.; Petrov, I.; Gorelsky, S. I.; Fagnou, K. *J. Org. Chem.* **2010**, 75, 1047.

(d, $J = 8.4$ Hz, 2H), 7.21 (d, $J = 3.6$ Hz, 1H), 6.78 (d, $J = 3.5$ Hz, 1H), 2.81 (t, $J = 7.5$ Hz, 2H), 1.74 (sext, $J = 7.5$ Hz, 2H), 1.01 (t, $J = 7.3$ Hz, 3H).

General procedure of the Competition Experiments of Figure 6.3, with the exception of the competitions involving 1-(thiophene-2-yl)pyrrolidine (22a): 2'-(PdPCy₃Cl)-2-aminobiphenyl (3.5 mg, 0.006 mmol, 1 mol%), K₂CO₃ (83 mg, 0.60 mmol, 1.0 equiv.) and PivOH (9.2 mg, 0.09 mmol, 15 mol%) were weighed to air and placed in a screw-cap vial equipped with a magnetic stir bar. The heteroarenes (0.30 mmol, 0.50 equiv. each), if a solid, were then added at that point. The vial was purged with argon and a solution of the 5-bromo-*m*-xylene (11.1 mg, 0.060 mmol, 10 mol%) and the heteroarenes (0.30 mmol, 0.5 equiv. each), if liquid, in dimethylacetamide (2.0 mL, 0.3 M) was added to the mixture. The reaction mixture was then stirred vigorously at 100 °C overnight. The solution was then cooled to ambient temperature and then filtered and evaporated under reduced pressure. The remaining solvent was then removed under reduced pressure using a Kugelrohr apparatus. The crude mixture was then analyzed by ¹H NMR spectroscopy.

General procedure of the Competition Experiments of Figure 6.3 involving 1-(thiophene-2-yl)pyrrolidine (22a). Due to the instability of **22a**, an electron-deficient aryl bromide needed to be employed to give a greater stability to the arylation product. 2'-(PdPCy₃Cl)-2-aminobiphenyl (3.5 mg, 0.006 mmol, 1 mol%), K₂CO₃ (83 mg, 0.60 mmol, 1.0 equiv.) and PivOH (9.2 mg, 0.09 mmol, 15 mol%) were weighed to air and placed in a screw-cap vial equipped with a magnetic stir bar. The heteroarenes (0.30 mmol, 0.50 equiv. each), if a solid, were then added at that point. The vial was purged with argon and a solution of the 1-bromo-4-(trifluoromethyl)benzene (13.5 mg, 0.060 mmol, 10 mol%) and the heteroarenes (0.30 mmol, 0.5 equiv. each), if liquid, in dimethylacetamide (2.0 mL, 0.3 M) was added to the mixture. The reaction mixture was then stirred vigorously at 100 °C overnight. The solution was then cooled to ambient temperature and then filtered and evaporated under reduced pressure. The remaining

solvent was then remove under reduce pressure using a Kugelrohr apparatus. The crude mixture was then analyzed by ^1H NMR spectroscopy.

Figure 8.2 Results of the competition experiments between C2 substituted thiophenes.

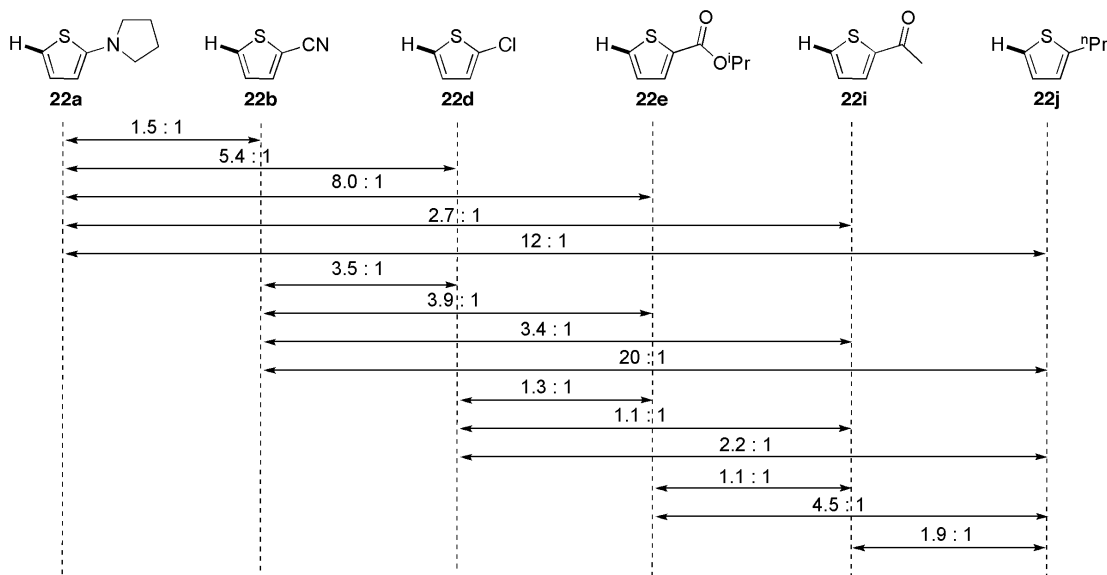


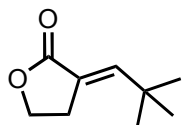
Table S3. The C-H bond orders for free (hetero)arenes with the “reactive” C-H bonds (bold C-H bonds in Figure 1) at their bond lengths in the lowest-energy CMD TS structures.

Table 8.4 The C-H bond orders for free (hetero)arenes with the “reactive” C-H bonds (bold C-H bonds in Figure 1) at their bond lengths in the lowest-energy CMD TS structures. (Data collected by Serge Gorelsky)

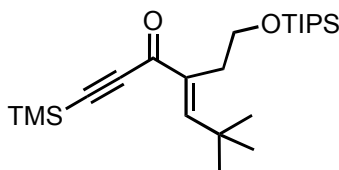
ArH	C-H bond order
1	0.920
2	0.941
3	0.936
4	0.922
5	0.958
6	0.954
7	0.900
8	0.879
9	0.911

10	0.940
11	0.939
12	0.890
13	0.875
14	0.916
15	0.916
16	0.909
17	0.926
18	0.934
19	0.982
20	0.903
21	0.915
22h	0.901

8.7 Part B, Chapter 7: Studies Toward the Synthesis of Ginkgolide C Spirobicyclic Core by Au(I)-Catalyzed Cyclizations



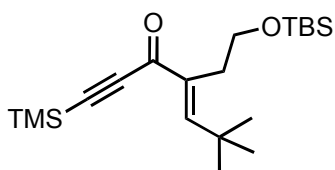
(E)-3-(2,2-Dimethylpropylidene)dihydrofuran-2(3H)-one (13). In a 500 mL round bottom flask equipped with a stir bar was added lithium *tert*-butoxide (9.64 g, 120.4 mmol, 2 equiv.) and 200 mL of petroleum ether (0.3 M). To this suspension, was added via syringe trimethylacetaldehyde 75 mol% in *tert*-butanol (8.56 mL, 60.2 mmol, 1 equiv.). The flask was then placed in a ice bath and to the mixture was added in one portion γ -butyrolactone (9.2 mL, 120.4 mmol, 2 equiv.). An exothermic reaction follows the additions of γ -butyrolactone, therefore the ice bath was kept under the flask to avoid any reaction runaways. After 10-15 minutes, the ice bath was removed and the reaction was allowed to stir at ambient temperature overnight. The reaction mixture appearance changed from a heterogeneous suspension to a pale yellow milky solution. After being stirred overnight, the reaction solution was filtered over fritted filter and the remaining solid was washed with diethylether. The filtrate was then evaporate under reduce pressure dried under high vacuum. The crude oil was then purified with the KugelRohr apparatus at approximately 80-85 °C and 0.1 Torr, this distillation should remove any un-reacted γ -butyrolactone. 7.05 g of **6** were isolated as clear oil in a yield of 76%. **Rf**: 0.30 (30% ether, petroleum ether, KMnO₄); **¹H NMR (300MHz, CDCl₃, 296K)**: δ ppm 6.74 (t, J = 2.8 Hz, 1H), 4.33 (t, J = 7.4 Hz, 2H), 3.02 (td, J = 7.4, 2.8 Hz, 2H), 1.16 (s, 9H); **¹³C NMR (101MHz, CDCl₃, 296K, TMS)**: δ ppm 150.5, 121.4, 65.3, 34.0, 29.4, 25.5; **IR (ν_{max} /cm⁻¹)**: 2960, 2870, 1757, 1667, 1223, 1177, 1038, 726; **HRMS** calculated for C₉H₁₄O₂ (M⁺) 154.0994; Found: 154.0983.



(E)-6,6-Dimethyl-4-(2-(triisopropylsilyloxy)ethyl)-1-(trimethylsilyl)hept-4-en-1-yn-3-one (19). This reaction was performed following a known literature procedure.³⁴ In a flame dried 250 mL round bottom flask equipped with a stir bar and under an argon atmosphere was added ethynyltrimethylsilane (2.94 mL, 20.8 mmol, 1.2 equiv.) and 40 mL of freshly distilled THF. The solution was cooled to -78 °C, then a solution *n*-butyllithium 2.5 M in hexanes (8.3 mL, 20.8 mmol, 1.2 equiv.) was slowly added. The solution was allowed to slowly warm to approximately -30 °C for 30 minutes. Then reaction mixture was then cooled to -78 °C again, then BF₃·THF (2.2 mL, 19.9 mmol, 1.15 equiv.) was added in one portion. The mixture was then stirred for an additional 10 minutes at -78 °C, then the lactone **13** (2.67 g, 17.33 mmol, 1.0 equiv.) was added to the mixture as a THF solution (20 mL). The resulting mixture was allowed to warm to ambient temperature and stirred for 1-2 hours. When judged completed by TLC, the reaction mixture was quenched by the addition of 40 mL of a 2:1 mixture of saturated solution of ammonium chloride and concentrated ammonium hydroxide. Then more water was poured into the mixture and the aqueous layer was extracted with ether (4X). The combined organic layer were dried over sodium sulfate, filtered and concentrated under vacuum. The 4.52 g of crude alcohol **18** was recovered as a colorless oil, the product was used without further purification in the next step. **Rf**: 0.19 (15% EtOAc/petroleum ether, UV and KMnO₄); **¹H NMR (300 MHz; CDCl₃)**: δ 7.37 (s, 1H), 3.66 (q, *J* = 6.2 Hz, 2H), 2.75 (t, *J* = 6.7 Hz, 2H), 1.92 (t, *J* = 5.7 Hz, 1H), 1.25 (s, 9H), 0.28-0.25 (m, 9H); **¹³C NMR (101 MHz; CDCl₃)**: δ 182.3, 163.1, 138.0, 100.3, 99.9, 62.3, 34.6, 30.5, 28.9, -0.6. **IR (ν_{max} /cm⁻¹)**: 2959, 2933, 2876, 2158, 1763, 1636, 846; **HRMS** calculated for C₁₄H₂₄O₂Si (M⁺-CH₃) 237.1311; Found: 237.1317. The crude alcohol dissolved in DMF (85 mL, 0.2 M) in a 250 mL flask equipped with a stir bar, to this solution were added imidazole (2.36 g, 34.7 mmol, 2.4 equiv.) and *N,N*-4-dimethylaminopyridine (DMAP, 200 mg, 1.7 mmol, 10 mol%). To this solution was

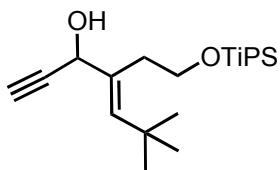
³⁴ Doudsky, J.; Streinz, L.; Leseticky, L.; Koutek, B. *Synlett* **2003**, 937.

added slowly triisopropylsilyl chloride (4.0 mL, 20.8 mmol, 1.2 equiv.) at ambient temperature. When the reaction was judged completed by TLC,³⁵ approximately 50 mL of ether was poured into the reaction and it was transfer into an extraction funnel, in which approx. 400 mL of water were added. The aqueous layer was extracted with ether (~ 4X, 50-100 mL), the combined organic layer where then wash 3X with water, then brine, concentrated under reduce pressure. The crude product was purified by flash chromatography (5% ether/ petroleum ether). The product was isolated as colourless oil in 53% yield starting from γ -butyrolactone, an average of 73% yield per steps. **Rf**: 0.60 (5% Et₂O/Petroleum ether, UV and KMnO₄) **¹H NMR (400MHz, CDCl₃, 296K, TMS)**: 7.27 (s, 1H), 3.64 (t, *J* = 7.4 Hz, 2H), 2.72 (t, *J* = 7.3 Hz, 2H), 1.23 (s, 9H), 1.03 (m, 21H), 0.24-0.22 (m, 9H); **¹³C NMR (100MHz, CDCl₃, 298K, TMS)**: δ ppm 181.5, 162.0, 137.8, 100.6, 98.6, 62.3, 34.5, 30.6, 29.3, 18.2, 12.1, -0.6; **IR (ν_{max} /cm⁻¹)**: 2960, 2867, 1636, 1465, 1365, 1252, 1106, 1086, 846; **HRMS** calculated for C₂₃H₄₄O₂Si₂ (M⁺-C₃H₇) 365.2332; Found: 365.2346.



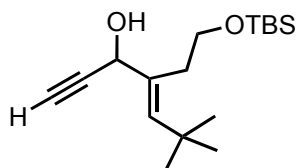
(E)-4-(2-(tert-Butyldimethylsilyloxy)ethyl)-6,6-dimethyl-1-(trimethylsilyl)hept-4-en-1-yn-3-one (19-TBS): Prepared with the same method as **22**. Oil; **Rf**: 0.75 (15% EtOAc/Petroleum ether, UV); **¹H NMR (400 MHz, CDCl₃)**: δ 7.30 (s, 1H), 3.59 (t, *J* = 7.4 Hz, 2H), 2.71 (s, 2H), 1.25 (s, 9H), 0.90-0.86 (m, 12H), 0.26-0.25 (m, 9H), 0.04 (d, *J* = 2.0 Hz, 6H); **¹³C NMR (101 MHz; CDCl₃)**: δ 181.4, 162.2, 137.6, 100.6, 98.6, 62.1, 34.5, 30.6, 29.2, 26.2, 18.6, -0.6, -5.1; **IR (ν_{max} /cm⁻¹)**: 2958, 2929, 2858, 1636, 1463, 1253; **HRMS** calculated for C₂₀H₃₈O₂Si (M⁺-CH₃) 351.2176; Found: 351.2168.

³⁵ The reaction might be completed after a few hours, but generally it was left overnight.

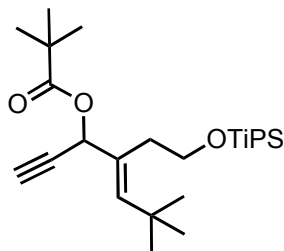


(E)-6,6-Dimethyl-4-(2-(triisopropylsilyloxy)ethyl)-1-(trimethylsilyl)hept-4-en-1-yn-3-ol (20): In a 25 mL round bottom flask equipped with a stir bar, was added lithium borohydride (430 mg, 8.81 mmol, 3.6 equiv.) and 5 mL of THF then cooled to 0 °C. To the stirring suspension was added portion wise cerium chloride heptahydrate (1.37 g, 3.67 mmol, 1.5 equiv.), hydrogen gas bubbled-off the solution. After the reaction stopped bubbling, ketone **19** (1.0 g, 2.45 mmol, 1.0 equiv.) was dissolved in 3 mL of THF (0.3 M in total) and the solution was added to the LiBH₄/CeCl₃ mixture. The reaction was allowed to warm to ambient temperature and it was stirred until it was judged complete by TLC. Once completed, a saturated solution of ammonium chloride was added to reaction mixture. The heterogeneous mixture was poured into an extraction funnel and extracted with ether. The combined organic layers were dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was used without purification in the next step. **Rf**: 0.25 (5% Et₂O/Petroleum ether, KMnO₄); **¹H NMR (400MHz, CDCl₃, 296K, TMS)**: 5.70 (s, 1H), 4.87 (d, *J* = 8.4 Hz, 1H), 4.63 (d, *J* = 8.1 Hz, 1H), 3.98 (ddd, *J* = 9.7, 5.4, 4.3 Hz, 1H), 3.76 (td, *J* = 9.4, 3.4 Hz, 1H), 2.76 (ddd, *J* = 14.8, 5.2, 3.4 Hz, 1H), 2.66 (ddd, *J* = 14.7, 9.0, 4.1 Hz, 1H), 1.12 (s, 9H), 1.12-1.08 (m, 21H), 0.16 (s, 9H); **¹³C NMR (100MHz, CDCl₃, 298K, TMS)**: δ ppm 142.3, 135.8, 106.6, 90.4, 70.4, 64.5, 33.0, 31.3, 30.8, 18.1, 12.0, -0.02. The crude alcohol was diluted in approximately 10 mL of methanol and to the solution was added a stir bar and a ~50 mg of potassium carbonate. The mixture was stirred at ambient temperature for ~15 minutes. When the reaction is completed, the base was filtered off the solution and the product concentrated under reduced pressure. The crude product was purified by flash chromatography and yielded the terminal alkyne as a colorless oil in 74% yield. **Rf**: 0.50 (20% EtOAc/Petroleum ether, KMnO₄); **¹H NMR (400MHz, CDCl₃, 296K, TMS)**: 5.69 (s, 1H), 4.92 (d, *J* = 8.0 Hz, 1H), 4.66 (ddd, *J* = 8.0, 2.2, 0.4 Hz, 1H), 3.99 (ddd, *J* = 9.7, 5.3, 4.2 Hz, 1H), 3.78 (td, *J* = 9.4, 3.3 Hz, 1H), 2.78 (ddd, *J* = 14.9, 5.2, 3.3 Hz, 1H), 2.65 (ddd, *J* = 14.8, 9.1, 4.1 Hz, 1H), 2.50 (d, *J* = 2.2 Hz, 1H), 1.14 (s, 9H), 1.16-1.07 (m, 21H); **¹³C NMR (100MHz, CDCl₃, 298K, TMS)**: δ ppm 142.3, 135.4, 84.9, 73.7, 69.8,

64.4, 33.1, 31.3, 30.6, 18.1, 12.0; **IR** ($\nu_{\max}$ / cm^{-1}): 3390, 3312, 2945, 2868, 2723, 2108, 1715, 1668, 1464, 1092; **HRMS** calculated for $\text{C}_{20}\text{H}_{38}\text{O}_2\text{Si}$ ($\text{M}^+ - \text{C}_3\text{H}_7$) 295.2093; Found: 295.2102.

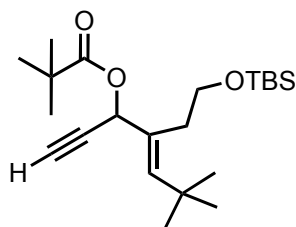


(E)-4-(2-(tert-Butyldimethylsilyloxy)ethyl)-6,6-dimethylhept-4-en-1-yn-3-ol: Prepared with the same method as **23**. Oil; **Rf**: 0.25 (20% EtOAc/Petroleum ether, KMnO_4); **^1H NMR (300 MHz, CDCl_3)**: δ 5.69 (s, 1H), 4.83 (d, $J = 7.9$ Hz, 1H), 4.65 (d, $J = 7.8$ Hz, 1H), 3.91 (dt, $J = 9.8, 4.9$ Hz, 1H), 3.71 (td, $J = 9.4, 3.5$ Hz, 1H), 2.76 (ddd, $J = 14.8, 4.9, 3.7$ Hz, 1H), 2.62 (ddd, $J = 14.4, 9.4, 4.7$ Hz, 1H), 2.50 (d, $J = 2.2$ Hz, 1H), 1.19-1.16 (m, 9H), 0.96-0.89 (m, 9H), 0.11 (d, $J = 4.2$ Hz, 6H); **^{13}C NMR (75 MHz, CDCl_3)**: δ 142.5, 135.2, 84.9, 73.7, 69.8, 64.0, 33.1, 31.2, 30.5, 26.0, 18.5, -5.3; **IR** ($\nu_{\max}$ / cm^{-1}): 2958, 1683, 1558, 1251.



(E)-6,6-Dimethyl-4-(2-(triisopropylsilyloxy)ethyl)-1-(trimethylsilyl)hept-4-en-1-yn-3-one (21): In a 10 mL round bottom flask was dissolved the alcohol **20** (310 mg, 0.91 mmol, 1.0 equiv.) in 5mL of dry dichloromethane (~ 0.2 M). To this solution was added TEA (440 μL , 3.2 mmol, 3.0 equiv.) and DMAP (~ 10 mg, 0.05 mmol, 5 mol%). To the stirring solution was added drop-wise trimethylacetyl chloride (163 μL , 1.32 mmol, 1.25 equiv.). **Rf**: 0.50 (20% EtOAc/Petroleum ether, KMnO_4) **^1H NMR (400MHz, CDCl_3 , 296K, TMS)**: 5.80 (d, $J = 0.6$ Hz, 1H), 5.75 (dd, $J = 2.2, 0.9$ Hz, 1H), 3.83 (dt, $J = 29.0, 10.4, 5.5$ Hz, 2H), 2.68 (ddd, $J = 13.6, 10.0, 5.6$ Hz, 1H), 2.57 (ddd, $J = 13.5, 9.9, 6.0$ Hz, 1H), 2.50 (d, $J = 2.2$ Hz, 1H), 1.21 (s, 9H), 1.15 (s, 9H), 1.09-1.04 (m, $J = 2.7$ Hz, 21H); **^{13}C NMR (100MHz, CDCl_3 , 298K, TMS)**: δ ppm 177.1, 143.6, 130.2, 80.6, 74.7, 69.3,

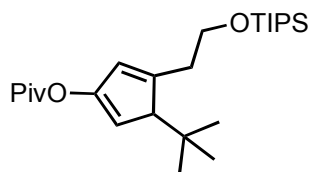
63.0, 38.8, 33.1, 32.1, 31.1, 27.1, 18.2, 12.1; **IR** ($\nu_{\max}$ / cm^{-1}): 2900, 2868, 1738, 1464, 1141, 1098, 882; **HRMS** calculated for $\text{C}_{25}\text{H}_{46}\text{O}_3\text{Si}$ ($\text{M}^+ - \text{C}_3\text{H}_7$) 379.2668; Found: 379.9746.



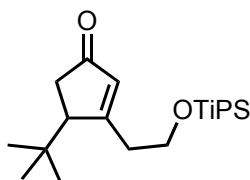
(E)-4-(2-(tert-Butyldimethylsilyloxy)ethyl)-6,6-dimethylhept-4-en-1-yn-3-yl pivalate (23): Prepared with the same method as **21**. Oil; **Rf**: 0.75 (20% EtOAc/Petroleum ether, KMnO_4); **^1H NMR** (400 MHz, CDCl_3): δ 5.80 (s, 1H), 5.74 (dd, $J = 2.2, 0.8$ Hz, 1H), 3.80 (td, $J = 9.9, 6.0$ Hz, 1H), 3.71 (td, $J = 9.9, 5.8$ Hz, 1H), 2.65 (ddd, $J = 13.6, 9.9, 5.8$ Hz, 1H), 2.50 (d, $J = 2.3$ Hz, 1H), 1.22 (s, 9H), 1.15 (s, 9H), 0.90 (s, 9H), 0.06 (s, 6H); **^{13}C NMR** (101 MHz; CDCl_3): δ 177.0, 143.7, 130.1, 80.6, 74.8, 69.3, 62.8, 38.8, 33.1, 32.0, 31.1, 27.1, 26.1, 18.5; **IR** ($\nu_{\max}$ / cm^{-1}): 2960, 2908, 1733, 1683, 1139.

Rautenschtrauch reaction: This reaction was performed following a known literature procedure.³⁶ In a 3 mL flask were premixed triphenylphosphinegold(I) chloride (12 mg, 0.06 mmol, 6 mol%) and silver hexafluoroantimonate (8.8 mg, 0.06 mmol, 6 mol%) in 0.5 mL of acetonitrile and the mixture was stirred at ambient temperature for 10 minutes. In another 3 mL vial, was dissolved pivalate **21** (108 mg, 0.255 mmol, 1 equiv.) in 2.5 mL of acetonitrile (~0.1 M). The $[\text{PPh}_3\text{Au}]^+\text{SbF}_6^-$ was filtered and added to reaction mixture and it was stirred overnight at ambient temperature. From this reaction, two products were observed by TLC, although reproducibility of the reaction is an issue.

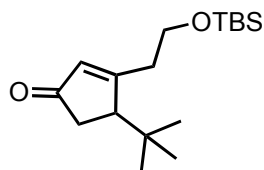
36 Shi, X.; Gorin, D. J.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 5802.



3-tert-Butyl-4-(2-(triisopropylsilyloxy)ethyl)cyclopenta-1,4-dienyl pivalate (22): Rf: 0.60 (3% Et₂O/Petroleum ether, UV and KMnO₄) **¹H NMR (400MHz, CDCl₃, 296K, TMS):** 6.00 (dq, *J* = 2.8, 1.4 Hz, 1H), 5.86 (t, *J* = 1.8 Hz, 1H), 3.84 (t, *J* = 7.6 Hz, 2H), 2.85-2.79 (m, 1H), 2.78-2.54 (m, 2H), 1.28 (s, 9H), 1.08-1.05 (m, 22H), 1.02 (s, 8H); **IR (ν_{max} /cm⁻¹):** 2960, 2867, 1735, 1464, 1105, 883; **HRMS** calculated for C₂₅H₄₆O₃Si (M⁺-C₃H₇) 379.2668; Found: 379.2662.



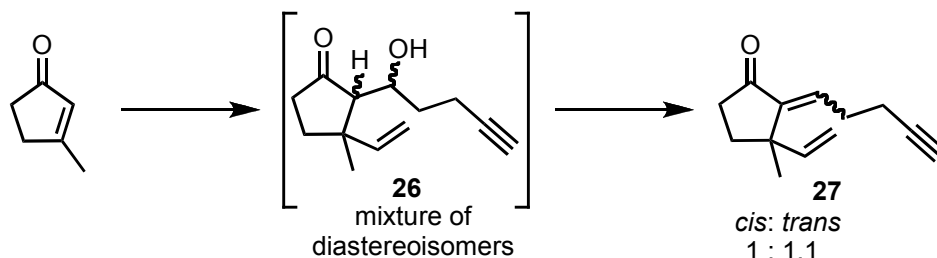
4-tert-Butyl-3-(2-(triisopropylsilyloxy)ethyl)cyclopent-2-enone (11). Rf: 0.35 (15% EtOAc/Petroleum ether, UV and KMnO₄) **¹H NMR (400MHz, CDCl₃, 296K, TMS):** 6.08 (d, *J* = 1.3 Hz, 1H), 3.92 (qt, *J* = 9.3, 6.6 Hz, 2H), 2.86-2.78 (m, 1H), 2.77-2.75 (m, 1H), 2.62 (dt, *J* = 16.3, 6.3 Hz, 1H), 2.42 (dd, *J* = 18.6, 6.5 Hz, 1H), 2.28 (dd, *J* = 18.6, 2.0 Hz, 1H), 1.08-1.04 (m, 21H), 0.98 (s, 9H); **¹³C NMR (100MHz, CDCl₃, 298K, TMS):** δ ppm 209.0, 181.7, 132.4, 61.8, 54.7, 40.3, 38.0, 34.3, 28.5, 18.1, 12.0; **IR (ν_{max} /cm⁻¹):** 2960, 2867, 1705, 1605, 1464, 1103, 680; **HRMS** calculated for C₂₀H₃₈O₂Si (M⁺-C₃H₇) 295.2093; Found: 295.2095.



4-tert-Butyl-3-(2-(tert-butyldimethylsilyloxy)ethyl)cyclopent-2-enone:

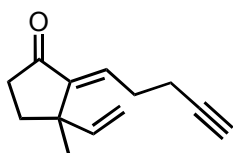
¹H NMR (400 MHz, CDCl₃): δ 6.06 (s, 1H), 3.89-3.78 (m, 2H), 2.83-2.73 (m, 2H), 2.63-2.52 (m, 1H), 2.41 (dd, *J* = 18.6, 6.5 Hz, 1H), 2.28 (dd, *J* = 18.6, 2.1 Hz, 1H), 1.24 (d, *J* = 2.7 Hz, 3H), 0.98 (s, 9H), 0.88 (s, 9H), 0.06 (d, *J* = 1.2 Hz, 6H); **¹³C NMR (101 MHz;**

CDCl_3): δ 209.1, 181.7, 132.3, 61.4, 54.6, 40.3, 37.8, 34.3, 29.9, 28.5, 27.2, 26.0, 18.3; **IR** (ν_{max} / cm^{-1}): 2956, 2929, 1697, 1683, 1095; **HRMS** calculated for $\text{C}_{17}\text{H}_{32}\text{O}_2\text{Si}$ ($\text{M}^+ - \text{C}_4\text{H}_9$) 239.1467; Found: 239.1452.

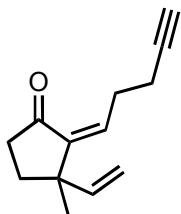


2-(1-Hydroxypent-4-ynyl)-3-methyl-3-vinylcyclopentanone (26): In a flame-dried flask under argon atmosphere was prepared a slurry of CuI (160 mg, 0.83 mmol, 20 mol%) in 5 mL of THF, to this mixture was then added freshly distilled TMEDA (1.9 mL, 12.5 mmol, 3.0 equiv) at room temperature. The solution became translucent, at this point, a 1.0 M solution of vinyl magnesium bromide (4.6 mL, 1.1 equiv) was added to the solution. The reaction mixture was then cooled to $-78\text{ }^{\circ}\text{C}$ and the 3-methylcyclopent-2-enone (400 mg, 4.16 mmol, 1.0 equiv) as a 5 mL THF solution was then added dropwise. We TLC analysis indicated the completion of the consumption of the enone, 4-pentynal (895 mg, 5.41 mmol, 1.3 equiv) was then added neat into the reaction solution. The reaction was then allowed to warm to ambient temperature and was followed frequently by TLC. Once the reaction intermediate has been completely consumed, water was poured into the reaction followed by a saturated solution of NH_4Cl . The aqueous layer was then extracted 4 times with ether, the combined organic layers were dried over MgSO_4 and evaporated under reduce pressure. The crude product was purified by flash chromatography to yield an inseparable mixture of diastereoisomers of alcohol. Oil, **Rf**: 0.45 (20% EtOAc/Petroleum ether, vanillin); **^1H NMR (400 MHz, CDCl_3)**: δ One diastereoisomer 6.08 (dd, $J = 17.4, 10.8$ Hz, 1H), two diastereoisomers 5.92 (ddd, $J = 17.6, 15.3, 10.5$ Hz, 1H), overlapping signals 5.18-5.09 (m, 4H), overlapping signals 4.09-3.97 (m, 2H), overlapping signals 3.93-3.87 (m, 1H), 3.71 (s, 1H), overlapping signals 2.42-2.20 (m, 11H), overlapping signals 2.12-1.55 (m, 15H), One diastereoisomer 1.41 (s, 3H), One diastereoisomer 1.35 (s, 3H), One diastereoisomer 1.21 (s, 3H), One diastereoisomer 1.09 (s, 3H); **HRMS** calculated for $\text{C}_{13}\text{H}_{16}\text{OSi}$ (M^+) 188.1201; Found:

188.1157. **Dehydration of alcohol 26:** To a solution of the mixture of diastereoisomers of alcohol **30** (510 mg, 2.47 mmol, 1.0 equiv) in DCM (8.5 mL, 0.3 M) was added *p*-TsOH (43 mg, 10 mol%) followed by methyl-orthoformate (0.325 mL, 2.97 mmol, 1.2 equiv). The reaction was stirred at ambient temperature until TLC analysis indicated the reaction was completed. Water was then added and the aqueous layer was extracted with DCM. The combined organic layers were dried over MgSO₄ and evaporated under reduce pressure. The crude product was purified by flash chromatography to yield a mixture of olefin isomers in 40-67% from two steps.

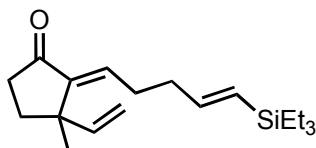


(E)-3-Methyl-2-(pent-4-ynylidene)-3-vinylcyclopentanone (27-trans): *E* geometry confirmed by nOe; ¹H NMR (300 MHz, CDCl₃): δ 6.66 (t, *J* = 7.5 Hz, 1H), 5.94 (dd, *J* = 17.2, 10.6 Hz, 1H), 5.09 (q, *J* = 1.3 Hz, 1H), 5.04 (dd, *J* = 9.1, 1.0 Hz, 1H), 2.47 (dq, *J* = 14.0, 7.0 Hz, 2H), 2.38-2.28 (m, 4H), 1.98 (t, *J* = 2.6 Hz, 1H), 1.89 (dt, *J* = 12.9, 8.1 Hz, 1H), 1.74 (ddd, *J* = 12.9, 8.2, 7.2 Hz, 1H), 1.39 (s, 3H); ¹³C NMR (101 MHz; CDCl₃): δ 206.6, 144.6, 143.4, 136.8, 112.4, 83.1, 69.5, 46.1, 35.9, 35.4, 27.0, 24.6, 18.1; IR (*ν*_{max} /cm⁻¹): 2937, 1716, 1259; HRMS calculated for C₁₃H₁₆O (M⁺) 188.1201; Found: 188.1157.



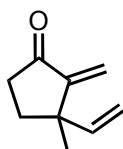
(Z)-3-Methyl-2-(pent-4-ynylidene)-3-vinylcyclopentanone (27-cis): *Z* geometry confirmed by nOe; ¹H NMR (300 MHz, CDCl₃): δ 5.91 (t, *J* = 7.4 Hz, 1H), 5.84 (dd, *J* = 17.3, 10.5 Hz, 1H), 5.06-4.97 (m, 2H), 3.05-2.83 (m, 2H), 2.35-2.28 (m, 4H), 2.00-1.91 (m, 2H), 1.75 (dt, *J* = 12.7, 8.4 Hz, 1H), 1.27 (s, 3H); ¹³C NMR (101 MHz; CDCl₃): δ 208.3, 145.5, 143.2, 138.7, 112.9, 83.6, 69.1, 47.3, 36.6, 33.9, 26.5, 26.0, 18.4; IR (*ν*_{max}

$/\text{cm}^{-1}$): 2937, 1716, 1259; **HRMS** calculated for $\text{C}_{13}\text{H}_{16}\text{OSi}$ (M^+) 188.1201; Found: 188.1118.



(E)-3-Methyl-2-((E)-5-(triethylsilyl)pent-4-enylidene)-3-vinylcyclopentanone (31):

This product was obtained as an undesired product. The procedure to obtain this product can be found in the literature.³⁷ **Rf**: 0.20 (5% Ether/Petroleum ether, UV and Vanilin); **¹H NMR (400 MHz, CDCl₃)**: δ 6.64 (t, $J = 7.5$ Hz, 1H), 6.33 (dt, $J = 14.1, 7.0$ Hz, 1H), 5.93 (dd, $J = 17.2, 10.6$ Hz, 1H), 5.46 (dt, $J = 14.1, 1.2$ Hz, 1H), 5.06 (dd, $J = 3.9, 1.0$ Hz, 1H), 5.02 (dd, $J = 10.6, 1.0$ Hz, 1H), 2.36-2.22 (m, 6H), 1.88 (dt, $J = 12.9, 8.1$ Hz, 1H), 1.73 (ddd, $J = 12.9, 8.2, 7.2$ Hz, 1H), 1.38 (s, 3H), 0.93 (t, $J = 7.8$ Hz, 10H), 0.61 (t, $J = 7.9$ Hz, 6H); **¹³C NMR (101 MHz, CDCl₃)**: δ 206.8, 148.2, 144.7, 142.5, 138.7, 126.8, 112.1, 46.0, 35.9, 35.4, 33.3, 28.3, 24.7, 7.7, 4.8; **IR (ν_{max} /cm⁻¹)**: 2956, 2937, 2910, 1718, 1276; **HRMS** calculated for $\text{C}_{19}\text{H}_{32}\text{OSi}$ ($\text{M}^+ - \text{C}_2\text{H}_5$) 275.1831; Found: 275.1839.



3-Methyl-2-methylene-3-vinylcyclopentanone (32): This product was prepared following a literature procedure.³⁸ In a flame-dried flask under argon atmosphere was prepared a slurry of CuI (380 mg, 20 mol%) in 20 mL of THF, to this mixture was then added freshly distilled TMEDA (9 mL, 3.0 equiv) at room temperature. The solution became translucent, at this point a 1.0 M solution of vinyl magnesium bromide (22 mL, 1.1 equiv) was added to the solution. The reaction mixture was then cooled to -78 °C and the 3-methylcyclopent-2-enone (1.93 g, 20 mmol, 1.0 equiv) as a 20 mL THF solution was then added slowly. When TLC analysis indicated the complete consumption of the enone, TMSCl (3.03 mL, 24 mmol, 1.2 equiv) was then added neat into the reaction

³⁷ Mori, A.; Kato, T. *Synlett* **2002**, 1167.

³⁸ Iimura, S.; Overman, L. E.; Paulini, R.; Zakarian, A. *J. Am. Chem. Soc.* **2006**, 128, 13095.

solution. The reaction was then allowed to warm to ambient temperature and was followed frequently by TLC. Once the reaction intermediate has been completely consumed, water was poured into the reaction followed by ether and a saturated solution of NH_4Cl . The aqueous layer was then extracted 4 times with ether, the combined organic layers were dried over MgSO_4 and evaporated under reduce pressure. The crude product was purified by flash chromatography to yield the volatile silyl enol ether. The product was then dissolved in dry DMF (100 mL) and 2,6-lutidine (7.2 mL, 62 mmol, 3.0 equiv) was added. This solution was then added dropwise to a solution of Eschenmoser's salt ($\text{Me}_2\text{NCH}_2^+\text{Cl}^-$) (11.33 g, 61.25 mmol, 3.05 equiv) and DMF (100 mL) at 0 °C.³⁹ The resulting mixture was stirred at 0 °C for 1 h and then diluted with EtOAc (500 mL). This solution was washed with saturated aqueous NaHCO_3 solution (500 mL), and then brine, dried over anhydrous MgSO_4 , and concentrated. The resulting residue was taken up in Et_2O (150 mL) and MeI (13.7 mL, 220 mmol, 11 equiv) was added. After 12 h at room temperature, the solution was concentrated and the residue was dissolved in DCM (150 mL). Methanol (50 mL) and aqueous K_2CO_3 solution (~15%, 100 mL) were added, and the mixture was stirred vigorously for 3 h. The reaction mixture was extracted with DCM, and the combined organic phases were washed with brine, dried over MgSO_4 , and concentrated. The residue was purified by column chromatography to afford the desired product in 54% yield over three steps. Oil; **Rf**: 0.55 (20% EtOAc/Petroleum ether, UV and KMnO_4); **^1H NMR (400 MHz, CDCl_3)**: δ 6.11 (s, 1H), 5.85 (dd, J = 17.3, 10.4 Hz, 1H), 5.23 (d, J = 0.4 Hz, 1H), 5.06-4.96 (m, 2H), 2.35 (dd, J = 8.4, 7.1 Hz, 2H), 2.01 (td, J = 12.5, 5.6 Hz, 1H), 1.77 (dt, J = 12.7, 8.6 Hz, 1H), 1.30 (s, 3H); **^{13}C NMR (101 MHz; CDCl_3)**: δ 207.1, 151.6, 144.7, 117.7, 113.2, 46.6, 35.6, 33.8, 25.8; **IR (ν_{max} / cm^{-1})**: 2968, 2931, 2869, 1724, 1635; **HRMS** calculated for $\text{C}_9\text{H}_{12}\text{O}$ (M^+) 136.0888; Found: 136.0883.

39 Schreiber, J.; Maag, H.; Hashimoto, N.; Eschenmoser, A. *Angew. Chem., Int. Ed.* **1971**, *10*, 330.

Claims to Original Research

1. Development of mild reaction conditions for the intramolecular direct arylation reaction.
2. Mechanistic studies on the palladium-catalyzed C–H bond cleavage of various (hetero)arenes.
3. Development of a general methodology for the direct arylation of a wide range of electron-rich heteroarenes.
4. Development of a general methodology for the direct benzylation and tandem 1,2-migratory insertion–direct arylation for a wide range of electron-rich heteroarenes.
5. Development of general guidelines for the predictable and selective functionalization of complex *bis*-heteroarenes.
6. Development of ligands specific for the direct arylation.
7. Development of a synthetic strategy potentially applicable to the synthesis of ginkgolide C.

Publications

7. Predictable and Site-Selective Functionalization of Poly-(Hetero)Arene Compounds by Palladium Catalysis **Lapointe, D.**; Markiewicz, T.; Whipp, C. J.; Toderian, A.; Fagnou, K. *J. Org. Chem.* **2011**, 76, 749. (*Featured Article*)
6. Overview of the Mechanistic Work on the Concerted Metallation-Deprotonation Pathway. (Highlight) **Lapointe, D.**; Fagnou, K. *Chem. Lett.* **2010**, 39, 1118. (*Invited Contribution*)
5. Domino Palladium-Catalyzed Heck-Intermolecular Direct Arylation Reactions. René, O.; **Lapointe, D.**; Fagnou, K. *Org. Lett.* **2009**, 11, 4560.
4. Palladium-Catalyzed Benzylation of Heterocyclic Aromatic Compounds. **Lapointe, D.**; Fagnou, K. *Org. Lett.* **2009**, 11, 4160.
3. Establishment of Broadly Applicable Reaction Conditions for the Palladium-Catalyzed Direct Arylation of Heteroatom-Containing Aromatic Compounds. Liégault, B.; **Lapointe, D.**; Caron, L.; Vlassova, A.; Fagnou, K. *J. Org. Chem.* **2009**, 74, 1826. (*Featured Article*)
2. Analysis of the Concerted Metalation-Deprotonation Mechanism in Palladium-Catalyzed Direct Arylation Across a Broad Range of Aromatic Substrates. Gorelsky, S. I.; **Lapointe, D.**; Fagnou, K. *J. Am. Chem. Soc.* **2008**, 130, 10848.
1. Mild and Efficient Palladium-Catalyzed Intramolecular Direct Arylation Reactions. Lafrance, M.; **Lapointe, D.**; Fagnou, K. *Tetrahedron* **2008**, 64, 6015.

Presentations

Oral presentations:

3. Lapointe, D; Gorelsky, S.; Markiewicz, T.; Toderian, A.; Fagnou, K. (2010) Toward a Better Understanding of the Underlying Parameters Governing the Concerted Metallation-Deprotonation Mechanism. Pacifichem, Honolulu, Hawaii.
2. Lapointe, D; Fagnou, K. (2009) Arylation d'halogénures benzyliques catalysée par le palladium. Association francophone pour le savoir, University of Ottawa.
1. Lapointe, D; Liégault, B.; Caron, L.; Vlassova, A; Gorelsky, S. I.; Fagnou, K. (2008) Palladium-Catalyzed Direct Arylation: Mechanistic Studies and Reaction Development. Quebec Ontario Minisymposium in Synthetic and Bioorganic Chemistry, University of Toronto.

Poster presentations:

13. Lapointe, D.; Markiewicz, T.; Whipp, C. J.; Toderian, A.; Fagnou, K (2010) Predictable and Site-Selective Functionalization of Poly-(Hetero)Arene Compounds by Palladium Catalysis, Quebec Ontario Minisymposium in Synthetic and Bioorganic Chemistry, Brock University.
12. Lapointe, D.; Markiewicz, T.; Whipp, C. J.; Toderian, A.; Fagnou, K. (2010) Predictable and Site-Selective Functionalization of Poly-(Hetero)Arenes Compounds by Palladium Catalysis , Astra Zeneca Symposium, Montréal.
11. Lapointe, D.; Markiewicz, T.; Toderian, A.; Fagnou, K. (2010) Toward a better understanding of the concerted metallation-deprotonation mechanism and its application in the regioselective C-H bond functionalization, Keith Fagnou Organic chemistry Symposium, University of Ottawa.

10. Lapointe, D.; René, O.; Fagnou, K. (2010) Palladium-Catalyzed $\text{sp}^3\text{-sp}^2$ C-C bond Formation by Direct Arylation, 14th Biennial Lilly grantee Symposium, Indianapolis.
9. Lapointe, D.; Fagnou, K. (2009) Palladium-catalyzed benzylation of heteroaromatic compounds, Quebec Ontario Minisymposium in Synthetic and Bioorganic Chemistry, Laval University.
8. Lapointe, D.; Fagnou, K. (2009) Novel Ligands Specifically Designed for Direct Arylation, Synthesis day, University of Ottawa.
7. Lapointe, D.; Fagnou, K. (2009) Non-Friedel Crafts Benzylation of Aromatic Heterocycles Catalyzed by Palladium, OCCI, University of Ottawa.
6. Lapointe, D.; René, O.; Fagnou, K. (2009) Palladium-Catalyzed $\text{sp}^3\text{-sp}^2$ C-C bond Formation by Direct Arylation, 92nd Canadian Chemistry Conference and Exhibition, Hamilton.
5. Lapointe, D.; Liégault, B.; Caron, L.; Vlassova, A.; Gorelsky, S. I.; Fagnou, K. (2008) General method for the direct arylation of unactivated heterocycles, Astra Zeneca Symposium, Montréal.
4. Lapointe, D.; Lafrance, M.; Fagnou, K. (2008) Mild and Efficient Palladium-Catalyzed Intramolecular Direct Arylation Reactions, OCCI, University of Ottawa.
3. Lapointe, D.; Lafrance, M.; Fagnou, K. (2007) Mild and Efficient Palladium-Catalyzed Intramolecular Direct Arylation Reactions, Quebec Ontario Minisymposium in Synthetic and Bioorganic Chemistry, University of Montréal.

2. Lapointe, D.; Fagnou, K. (2007) Novel Ligands Specifically Designed for Direct Arylation, Synthesis day, University of Ottawa.
1. Lapointe, D.; Fagnou, K. (2007) Novel Ligands Specifically Designed for Direct Arylation, OCCI, University of Carleton.