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Advances in Palladium-Catalyzed Carbon-Carbon Bond Formation Via Functionalization of Carbon-Hydrogen Bonds

by

Olivier René

B.Sc. (Honours), Université de Sherbrooke, 2007

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Dedicated to Keith Fagnou,

I will always remain tremendously grateful to Keith,
for inspiring my life

ABSTRACT

In the past decade, significant advances have been made in the formation of Csp^2-Csp^2 bonds by direct arylation. However, this process generally requires the use of forcing conditions at temperatures typically above 100 °C, which limits the substrate compatibility as well as large-scale applications. Inspired by the recent advances in the development of milder reaction conditions for the arylation of electon-rich arenes in an aqueous medium, we describe that such reactivity is also possible with electron-deficient polyfluorinated arenes at room temperature under biphasic conditions. Several examples are included, highlighting the application of this method to the preparation of a variety of biaryls using iodides bearing electron-poor, electron-rich and sterically encumbering substituents. Several polyfluoroarenes with different substitution patterns are also tolerated. In addition, the method can be extended to the arylation of halogenated thiophenes in a regioselective fashion.

However, direct arylation conditions that are general for a broad variety of heterocyclic coupling partners are only sparsely reported and the use of a different set of conditions for each type of substrate remains the norm. As part of a program dedicated to the study of the direct arylation mechanism and the development of broadly applicable reaction conditions, we became interested in investigating the effect of electron-deficient biaryl-type phosphine ligands on the C-H bond cleavage step of this process under Pd(0) catalysis. Inspired by previous reports validating the efficiency of these types of ligands in intramomecular direct arylation, we have developed a new electron-deficient fluoroarylphosphine ligand that promotes C-H bond functionalization of a broad variety of heterocycles. The demonstrated ability of these types of ligands to facilitate the C-H bond cleavage step of this process has been assessed and experimental evidence suggests a concerted metalation-deprotonation mechanism in the presence of an electrophilic metal center.

Only recently, nonetheless, has attention been paid to the formation of Csp^3-Csp^2 bonds by the direct arylation strategy. As an alternative to the use of aliphatic halides as an entry point to alkylpalladium(II) intermediates, we describe the use of a Heck-like cyclization of an aryl halide as a means of intercepting the key palladium(II) species, along with the first examples of domino Heck-arylation involving intermolecular capture with heterocyclic arenes via C-H bond cleavage. Several examples are presented, demonstrating the application of this method to the preparation of diverse dihydrobenzofurans, indolines and oxindoles substituted with sulfur-containing heterocycles such as thiazoles, thiophenes and benzothiophene.

ACKNOWLEDGEMENTS

Je tiens, tout d'abord, à remercier mes parents, pour tous leurs encouragements, pour leur support inconditionnel. Bien qu'ils n'aient pas la moindre notion en chimie, toujours ils ont démontré leur intérêt face à mes travaux recherche. Conscient que les mots "molécule" et "palladium" ne fassent pas partie de leur vocabulaire quotidien, leur fascination face aux multiples avancements rendus possibles grâce à la recherche était néamoins réflétée par leurs yeux pétillants de fierté lorsque j'essayais de leur vulgariser les effets de mes ligands sur la vitesse d'arylation.

Lorsqu'il qu'il fut temps de quitter Sherbrooke à la fin de mon baccalauréat, j'étais plus qu'incertain face à mes futurs projets de carrière. Par chance, grâce à l'aide du Prof. Claude Spino, j'ai réussi à obtenir un poste temporaire en chimie médicinale, d'où j'ai fait la rencontre de Louis-David Cantin, un superviseur passioné et dévoué. Grâce à ses nonbreux conseils et son vif intérêt envers le partage de sa science, il a su confirmer en moi ma passion pour la chimie. Sous son aile, mes plans de carrière se sont clarifiés et il a su me guider vers la meilleure decision que j'eût prise, non seulement du plan professionnel, mais aussi du plan personnel: joindre le groupe de Keith pour mes études graduées.

Keith Fagnou; the brilliant scientist, the inspiring supervisor, the awkward giggly guy who shows up behind you at your fume hood and doesn't know how to engage in a conversation, changed my life. Not only did Keith pass on his deep and boundless passion for chemistry to me, he also inspired my life. Thank you Keith for having taken me in your group. I sincerely owe my new career and my passion for chemistry to you.

Moreover, I would like to thank all the Fagnou Factory. All of you made my life enjoyable during these two years that I spent in your company. Un merci tout special se doit à David Lapointe, qui fut mon mentor lorsque j'ai joint le lab. Toujours prêt à répondre à mes multiples questions, David m'a enseigné toutes les bases de la catalyse et m'a toutjours prodigué de précieux conseils. Sans David, ma maîtrise n'aurait de loin pas été aussi fructueuse.

I finally need to thank Malcolm. When I joined the lab, I had no real friends in Ottawa, until I got to know Malcolm Huestis. He became my drinking buddy, my bucca boy. Thanks Malcolm for making these two years in Ottawa so much fun. The party shall now continue in San Francisco, shan't it!

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LIST OF ABBREVIATIONS

Ac	Acetyl
acac	Acetylacetonate
Ad	Adamantyl
Alk	Alkyl
aq	aqueous
Ar	Aryl
Bn	Benzyl
Bu	Butyl
CMD	Concerted matalation-deprotonation
Cy	Cyclohexyl
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	Dibenzylideneacetone
DCC	*N,N'*-Dicyclohexylcarbodiimide
DCE	Dichloroethene
DCM	Dichloromethane
DFT	Density functional theory
DG	Directing group
DMA	Dimethylacetamide
DME	1,2-Dimethoxyethane
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dtbpy	4,4'-Di-*tert*-butyl-2,2'-dipyridyl
equiv	equivalent
Et	Ethyl
F-TOTP	Tris(5-fluoro-2-methylphenyl)-phosphine
GC	Gas chromatography
i-Bu	Isobutyl
IMes	1,3-Dimesitylimidazolin-2-ylidene
i-Pr	Isopropyl
KIE	Kinetic isotope effect

L	Ligand
m	Meta
Me	Methyl
mol	Mole
MS	Mass spectrometry
n-Bu	Normal butyl
NMP	*N*-Methyl-2-pyrrolidone
n-Propyl	Normal propyl
o	Ortho
p	Para
Ph	Phenyl
Piv	Pivaloyl
PMB	Paramethoxybenzyl
r.t.	Room temperature
S_EAr	Electrophilic aromatic substitution
TBAB	Tetra-*N*-butylammonium bromide
TBAC	Tetra-*N*-butylammonium chloride
TBAF	Tetra-*N*-butylammonium fluoride
TBAOAc	Tetra-*N*-butylammonium acetate
t-Bu	Tertiary butyl
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMEDA	*N,N,N',N'*-tetramethyl-ethane-1,2-diamine
Ts	4-Toluenesulfonyl
μW	Microwave

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CHAPTER 1 : BIARYL SYNTHESIS BY DIRECT ARYLATION

1.1. Introduction

The biaryl motif is ubiquitous in very diverse areas of organic chemistry Such motifs are commonly encountered in medicinal chemistry,[1,2,3,4,5] material chemistry[6,7,8] or organic synthesis [9,10,11] For example, in medicinal chemistry, Figure 1 1 shows a variety of biologically active compounds possessing that particular scaffold With the emergence of light-emitting diodes and liquid crystal monitors, the biaryl motif has also been extensively exploited (Figure 1 2) Furthermore, with the recent advancements in transition-metal catalysis, novel high-performance biaryl-type ligands have emerged as a formidable synthetic tool for organic chemists (Figure 1 3)

---

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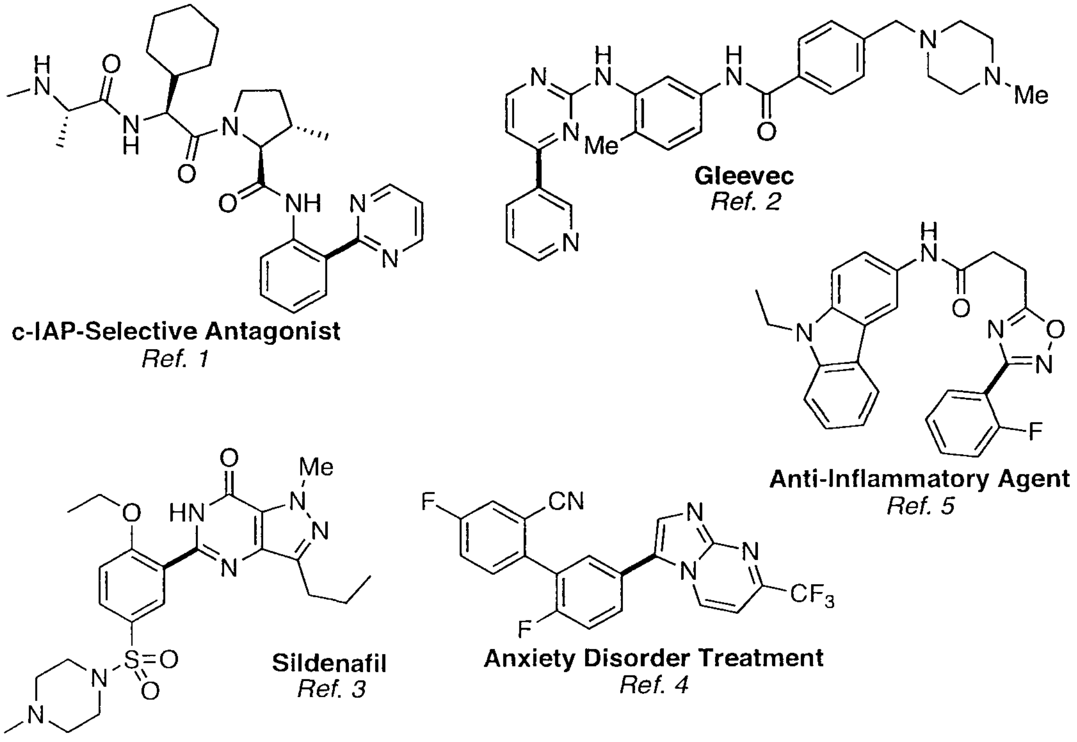
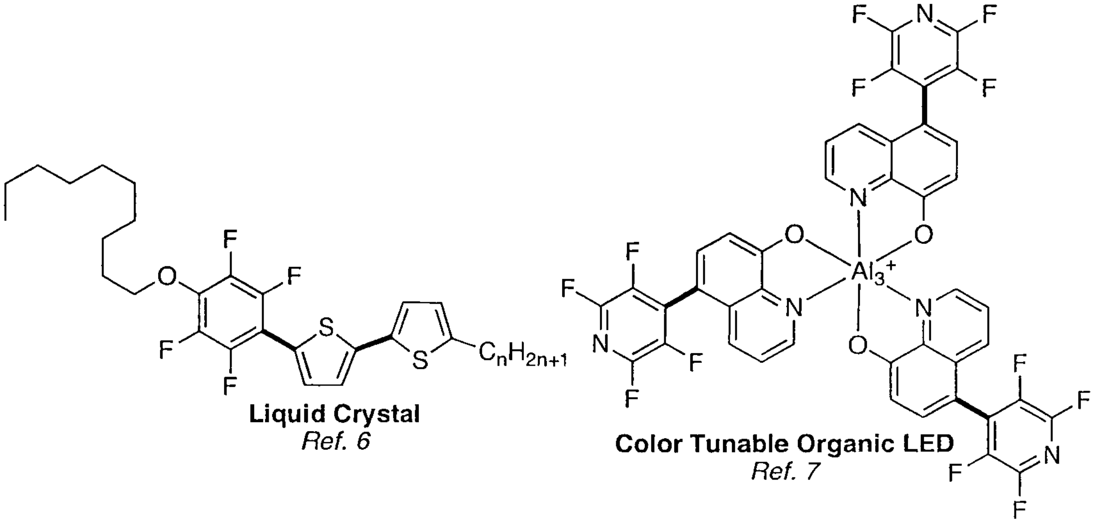
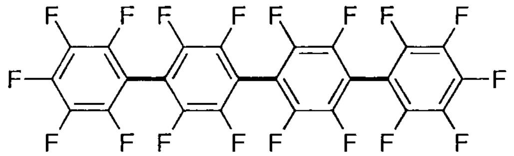


Figure 1.1 – Biologically-Active Compounds Possessing a Biaryl Scaffold



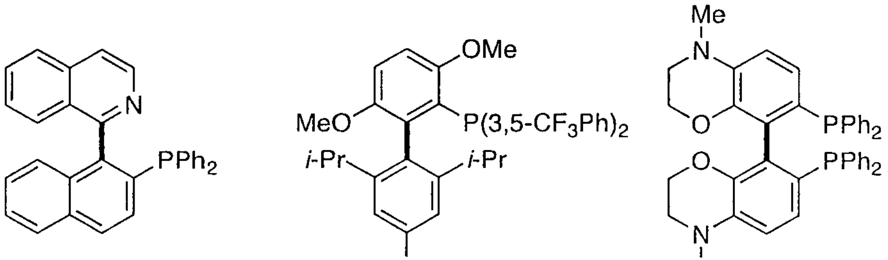
Liquid Crystal
Ref. 6

Color Tunable Organic LED
Ref. 7



Photosensitizer for Splitting of Water
Ref. 8

Figure 1.2 – The Biaryl Motif in Material Chemistry



QUINAP
Ref. 9

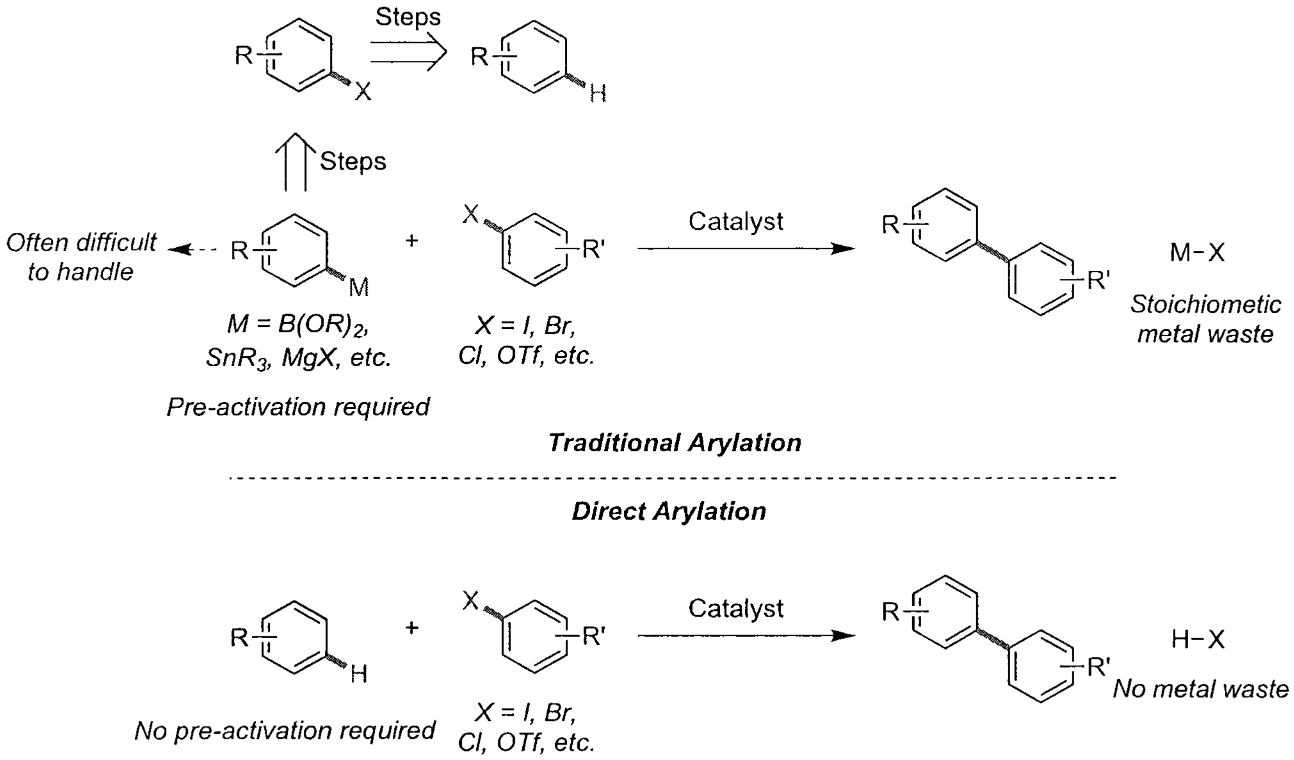
JackiePhos
Ref. 10

SolPhos
Ref. 11

Figure 1.3 – Biaryl-type Phosphine Ligands

Major advancements in palladium-catalyzed cross-coupling chemistry has first emerged in the 70's and 80's which allowed the development of traditional methods to prepare these valuable motifs. Utilizing traditional cross-coupling chemistry, the formation of biaryls can be achieved from aryl halide and aryl organometallic (i.e. Ar-MgX, Ar-ZnX, $Ar\text{-}SnR_3$, $Ar\text{-}B(OR_2)$, $Ar\text{-}SiR_3$)

coupling partners (Scheme 1.1).[12] Although this method has proven to be efficient and high yielding in many cases, several major drawbacks are still associated to this cross-coupling chemistry. For example, due to the nature of the reaction itself, a stoichiometic amount of metallic waste is generated in the reaction. Moreover, the success of this reaction relies on the availability of the organometallic coupling partner, which requires the pre-activating group to be installed in a regioselective and chemoselective fashion. Such pre-activated reagents can thus be difficult to prepare, in several steps, and are often strenuous to handle.



Scheme 1.1 – Summary of the Traditional and Direct Arylation Methods

The past decade, however, has seen the emergence of a tremendously viable alternative, the direct arylation, in which the organometallic coupling partner is replaced by a simple unactivated arene.[13] This new direct approach has the advantage of generating no stoichiometric amount

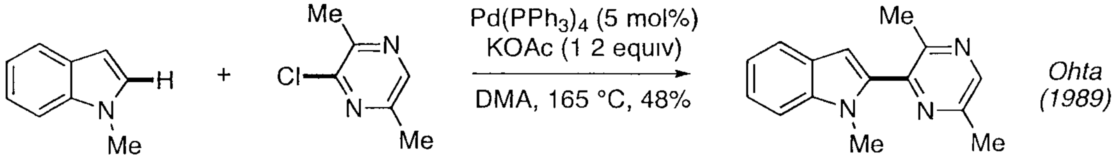
---

[12] For selected reviews on traditional cross-coupling reactions, see: (a) Diederich, F., Stang, P. J., Eds. *Metal-Catalyzed Cross-Coupling Reactions*; Wiley- VCH: New York, 1998. (b) Hassan, J.; Sévignon, M. S.; Gozzi, C.; Shulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359. (c) Baudoin, O. *Eur. J. Org. Chem.* **2005**, *20*, 4223.

[13] For selected reviews on direct arylation, see: (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (b) Campeau, L.-C.; Stuart, D. R.; Fagnou, K. *Aldrichimica Acta* **2007**, *40*, 35. (c) Campeau, L.-C.; Fagnou, K. *Chem.*

of metallic waste, but most of all, no pre-activation of the first coupling partner is required as the reaction proceeds at the carbon-hydrogen bond, which avoids several synthetic manipulations and the handling of often unstable compounds

Since the first report of intermolecular direct arylation of the heteroaromatic indole by Ohta in 1989 (Scheme 1 2),[14] the method has latter been extended to the direct arylation of a plethora of other electron-rich heterocycles, as well as electon-neutral arenes and electron-deficient aromatics [13] In this chapter, a particular focus will be put on the intermolecular variant of the direct arylation of the aforementioned types of aromatic compounds due to its relevance to the work herein presented A brief overview of two proposed mechanistic pathways will also be discussed owing to their predominance in the majority of the work on direct arylation



Scheme 1.2 – Ohta's Seminal Intermolecular Direct Arylation of Indole

1.2. Direct Arylation of Electron-Rich Heterocycles

Since unactivated arenes possess multiple C-H bonds with comparable electronic properties, achieving synthetically useful regioselectivities may appear to be a daunting challenge in direct arylation This is often the case when electronically non-biased arenes are used As a result, strategies involving the utilization of directing groups on the arene capable of coordinating the metal center and favor its approach toward one specific C-H bond have undergone intensive development (Scheme 1 3) [13]

Commun **2006**, 1253 (d) Satoh, T , Miura, M *Chem Lett* **2007**, *36*, 200 (e) Li, B -J , Yang, S -D , Shi, Z -J *Synlett* **2008**, 949 (f) Pascual, S , de Mendoza, P , Echavarren, A M *Org Biomol Chem* **2007**, *5*, 2727 (g) Catellani, M , Motti, E , Della Ca', N , Ferraccioli, R , *Eur J Org Chem* **2007**, 4153 (h) McGlacken, G P , Bateman, L M *Chem Soc Rev* **2009**, *38*, 2447 (i) Ackermann, L , Vicente, R , Kapdi, A R *Angew Chem , Int Ed* **2009**, *48*, 9792

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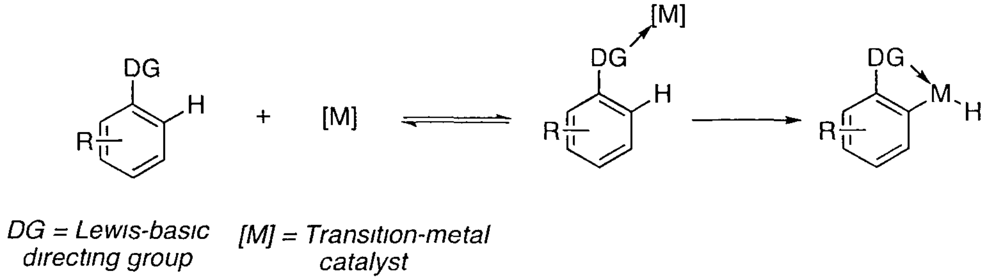

Scheme 1.3 – The Directing-Group Strategy

Conversely, embedding heteroatoms within a cyclic aromatic structure significantly modulates the electronic properties of the different C-H bonds of the heteroarene These inherent differences in the reactivity of C-H bonds of heterocycles are often sufficient to provide high levels of regioselectivity in direct arylation reactions, obviating the necessity for directing groups For that reason, prodigious development in the field of heteroarene arylation has been developed in the past decade, which led to the successful regioselective direct arylation of a broad variety of substrates (Figure 1 4)[15] Of particular importance, examples of direct arylation that employ catalytic metals other than palladium have also been developed Examples that use rhodium[16] have been followed by instances with iridium,[17] as well as more economic catalysts such as copper,[18] nickel,[19] and iron[20] In addition, effects other than the electronic bias of the heterocycle such as the solvent, copper additives and the

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[15] For recent examples, see (a) Seregin, I V , Gevorgyan, V *Chem Soc Rev* **2007,** *36,* 1173-1193 (b) Ackermann, L , Vicente, R , Born, R *Adv Synth Catal* **2008,** *350,* 741 (c) Bellina, F , Cauteruccio, S , Rossi, R *Eur J Org Chem* **2006,** 1379 (d) Bellina, F , Benelli, F , Rossi, R *J Org Chem* **2008,** *73,* 5529 (e) Flegeau, E F , Popkin, M E , Greaney, M F *Org Lett* **2008,** *10,* 2717 (f) Martin, T , Verrier, C , Hoarau, C , Marsais, F *Org Lett* **2008,** *10,* 2909 (g) Ban, I , Sudo, T , Taniguchi, T , Itami, K *Org Lett* **2008,** *10,* 3607 (h) Wang, X , Gribkov, D V , Sames, D *J Org Chem* **2007,** *72,* 1476 (i) Wang, J X , McCubbin, J A , Jin, M , Laufer, R S , Mao, Y , Crew, A P , Mulvihilland, M J , Snieckus, V *Org Lett* **2008,** *10,* 2923 (j) Yang, S - D , Sun, C -L , Fang, Z , Li, B -J , Li, Y -Z , Shi, Z -J *Angew Chem Int Ed* **2008,** *47,* 1473 (k) Goikhman, R , Jacques, T L , Sames, D *J Am Chem Soc* **2009,** *131,* 3042 (l) Jafarpour, F , Rahiminejadan, S , Hazrati, H *J Org Chem* **2010,** *75,* 3109 (m) Hachiya, H , Hirano, K , Satoh, T , Miura, M *Angew Chem Int Ed* **2010,** *49,* 2202 (n) Shibahara, F , Yamaguchi, E , Murai, T *Chem Commun* **2010,** 2471

[16] (a)Lewis, J C , Wiedemann, S H , Bergman, R H , Ellman, J A *Org Lett* **2004,** *6,* 35 (b) Wang, X , Lane, B S , Sames, D *J Am Chem Soc* **2005,** *127,* 4996 (c) Yanagisawa, S , Sudo, T , Noyori, R , Itami, K *J Am Chem Soc* **2006,** *128,* 11748 (d) Yanagisawa, S , Sudo, T , Noyori, R , Itami, K *Tetrahedron* **2008,** *64,* 6073 (e) Yanagisawa, S , Ueda, K , Sekizawa, H , Itami, K *J Am Chem Soc* **2009,** *131,* 14622

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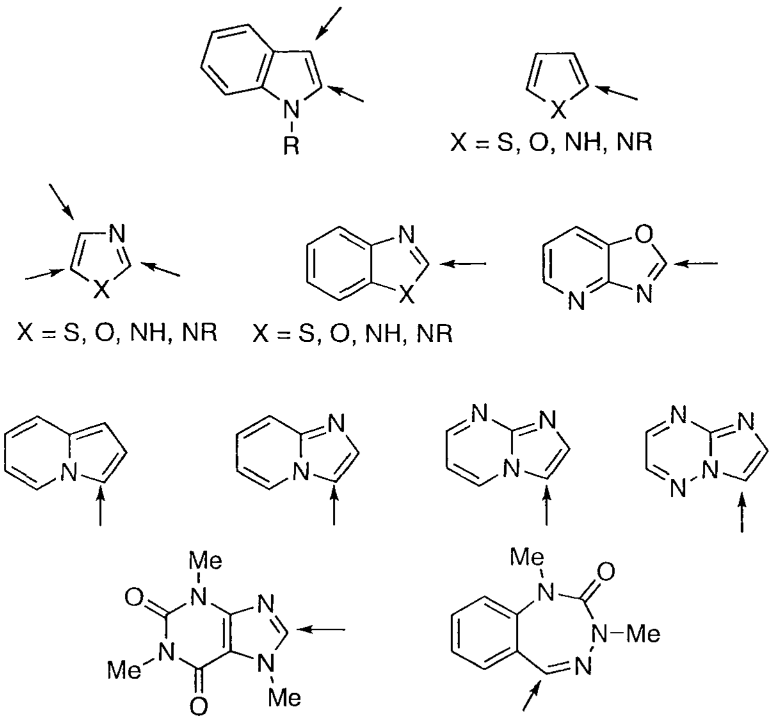
[19] (a) Canivet, J , Yamaguchi, J , Ban, I , Itami, K *Org Lett* **2009,** *11,* 1733 (b) Hachiya, H , Hirano, K , Satoh, T , Miura, M *Org Lett* **2009,** *11,* 1737

[20] Wen, J , Zhang, J , Chen, S -Y , Li, J , Yu, X -Q *Angew Chem Int Ed* **2008,** *47,* 8897

nature of the catalyst can modulate the regioselectivity of the reaction.[13a]



* Possible sites of arylation are denoted by an arrow

Figure 1.4 – Examples of Heteroarenes Employed in Direct Arylation

Of particular interest, the direct arylation of indole, which was pioneered by Ohta in 1989 (Scheme 1.3),[14] had been a troublesome problem in the past due to regioisomeric mixtures often observed resulting from C2 and C3 arylation. In an elegant report published in 2005, Sames disclosed orthogonal conditions allowing the preparation of C2 and C3 arylated indoles with excellent regioselectivities (Scheme 1.4).[21] Under standard conditions developed by Sames, C2 arylation of indole is obtained in a regioselective fashion. Furthermore, they developed a protocol favoring C3 arylation by altering the steric environment of the C2 position. To effect such a reversal in regioselectivity, they resorted to a magnesium base used in conjunction with TMEDA that could complex to the indole nitrogen atom, therefore provoking a regioselective arylation at the C3 position.

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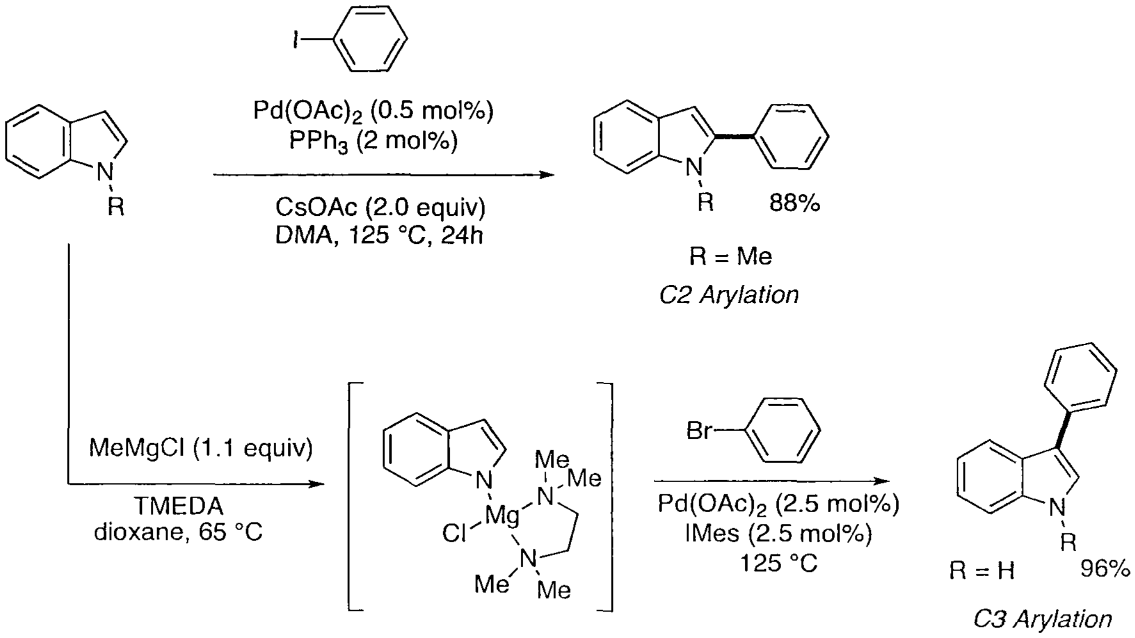
[21] Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050.



Scheme 1.4 – Sames' Orthogonal Direct Arylation of Indole

More recently, the group of Gaunt reported a new site-selective copper(II)-catalyzed direct arylation of indole that can also functionalize the C2 or C3 positions in an orthogonal fashion under mild conditions (Scheme 1.5).[22] The selectivity can be controlled by the nature of the group on the nitrogen atom. Free (NH)- and *N*-alkylindoles deliver the C3-arylated product, whereas *N*-acetylindoles afford the C2 isomer, both with excellent yield and selectivity.

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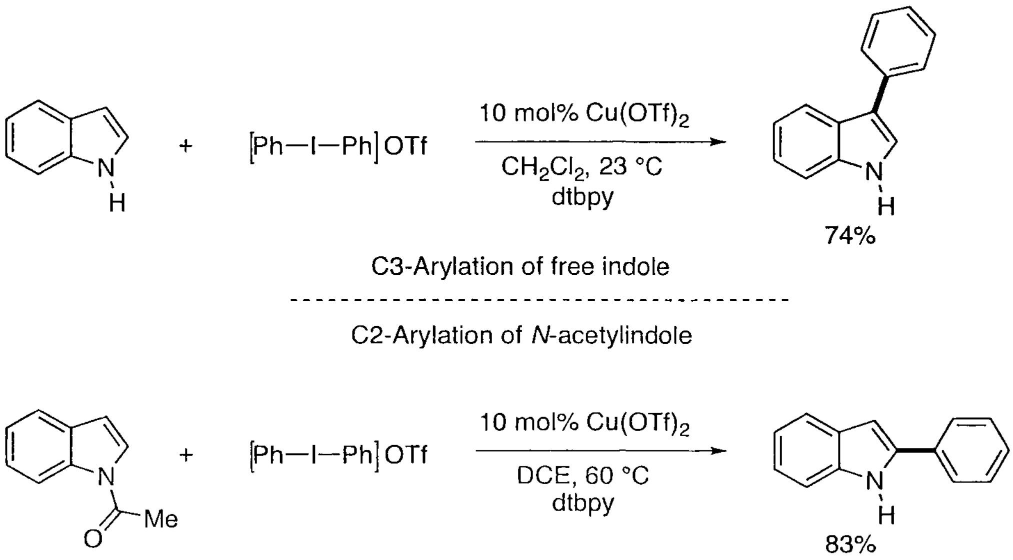
[22] Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 8172.

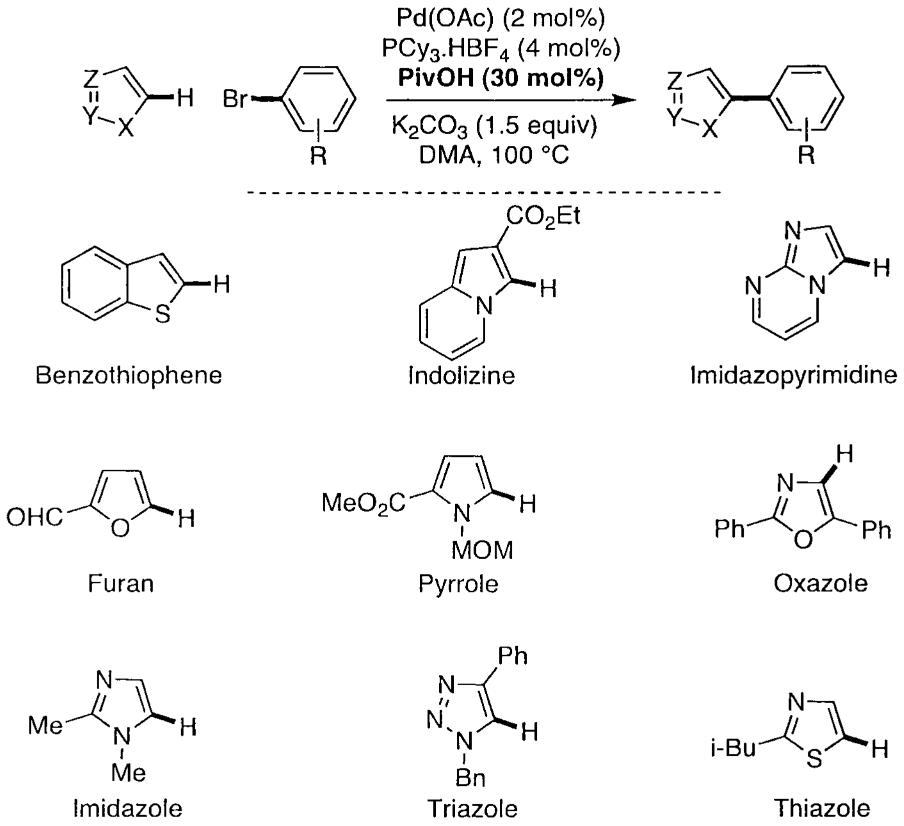


Scheme 1.5 – Gaunt's Orthogonal Direct Arylation of Indole Under Mild Conditions

Although a wide range of heterocycles can now be employed in direct arylation, the establishment of broadly applicable conditions that could enable the reaction to proceed with a vast variety of heterocyclic coupling partners remained elusive until recently.[23] Our group reported in 2009 conditions that were general for the direct arylation of a broad diversity of heterocycles such as benzothiophene, indolizine, imidazopyridine, furan, pyrrole, oxazole, etc. (Scheme 1.6).[23a] The key element in these generally applicable conditions is the presence of a catalytic amount of pivalic acid which has been demonstrated to serve as a proton shuttle for the reaction.

---

[23] For examples of broadly applicable conditions, see (a) Liégault, B.; Lapointe, D.; Caron, L.; Vlassova, A.; Fagnou, K. *J. Org. Chem.* **2009**, *74*, 1826. (b) Chiong, H. A.; Daugulis, O. *Org. Lett.* **2007**, *9*, 1449.



Scheme 1.6 – Fagnou's Generally Applicable Direct Arylation Conditions

1.3. Direct Arylation of Electron-Neutral and Electron-Poor Arenes

The first occurrence of the pivalic acid additive in direct arylation was reported by our group in 2006 for the direct arylation of electron-neutral benzene.[24] In this seminal publication, typically unreactive benzene exhibited unprecedented reactivity in direct arylation, provided that a palladium-pivalic acid co-catalyst system was utilized (Table 1.1). Amongst several acid additives screened, PivOH seemed the exhibit the perfect steric balance for the catalytic system to be effective. Based on experimental evidence with the support of DFT calculations, they demonstrated that this carboxylic acid additive serves as soluble proton shuttle and participates at the C-H bond cleavage step in the catalytic cycle.

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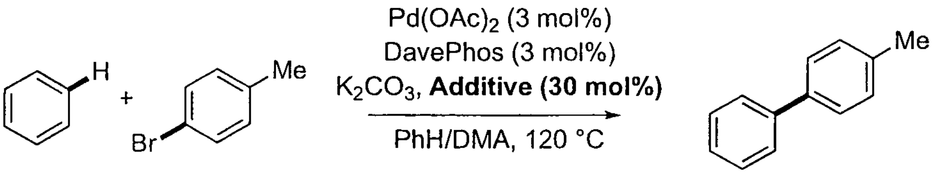
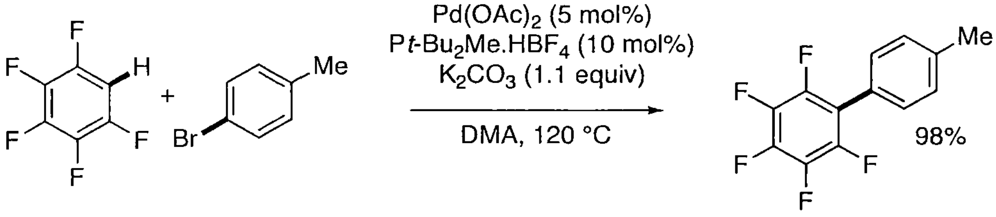
[24] Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496.

Table 1.1. Discovery of the Pivalic Acid Additive



entry	additive	yield (%)
1	None	0
2	AcOH	11
3	EtCO$_2$H	6
4	*i*-PrCO$_2$H	13
5	***t*-BuCO$_2$H**	**82**
6	1-AdCO$_2$H	36

Furthermore, related to reports from Maseras and Echavarren that demonstrated that electron-poor arenes undergo intramolecular direct arylation at a higher rate then electron-neutral arenes,[25] our group disclosed the first intermolecular direct arylation of very electron-deficient polyfluorinated arenes (Scheme 1.7).[26] This breakthrough was in stark contrast with previous direct arylation efforts that had mainly focused on electron-rich arenes.



Scheme 1.7 – Direct Arylation of Polyfluorinated Arenes

Following this work, reports of direct arylation of polyfluoroarenes under copper catalysis by Daugulis[27] as well as direct alkenylation under nickel catalysis by Nakao and Hiyama[28]

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[25] (a) García-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 1066. (b) García-Cuadrado, D.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2007**, *129*, 6880. (c) Pascual, S.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *Tetrahedron* **2008**, *64*, 6021.

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

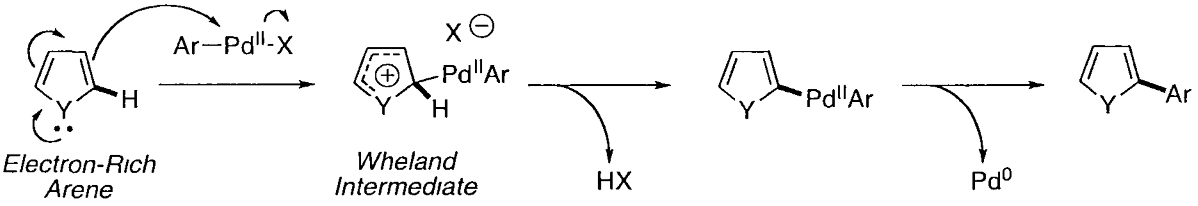
[27] (a) Do, H.-Q.; Khan, R. M. K.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 15185. See also ref. 18b.

[28] Nakao, Y.; Kashihara, N.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2008**, *130*, 16170.

also appeared in the literature These new instances of arylation of electron-deficient arenes ultimately led to a complete reinvestigation of the reaction mechanism of direct arylation

1.4. Evaluation of the Mechanism of Direct Arylation

Several mechanistic proposals have been put forward for the direct arylation reaction, such as the oxidative C-H insertion,[29] the S$_{\text{E}}$Ar,[30] the Heck-type additions[31] or the concerted-metalation-deprotonation [32] A predominent mechanistic pathway that had been proposed in the past for direct arylation is the aromatic electrophilic palladation (Scheme 1 8) [30] Since early work in this area focused mainly on the arylation of electron-rich heterocycles, it appeared obvious that these types of π-excessive arenes would undergo a Friedel-Crafts-type metalation to generate a Wheland intermediate Rearomatization by loss of HX, followed by a reductive elimination would afford the heterobiaryl product with regeneration of palladium(0)



Scheme 1.8 – S$_{\text{E}}$Ar-Type Mechanism of Direct Arylation

In most cases, this S$_{\text{E}}$Ar mechanism accounted for the regioselectivities observed with several heterocycles Notwithstanding, indole, which would give a C3-arylation product, should a

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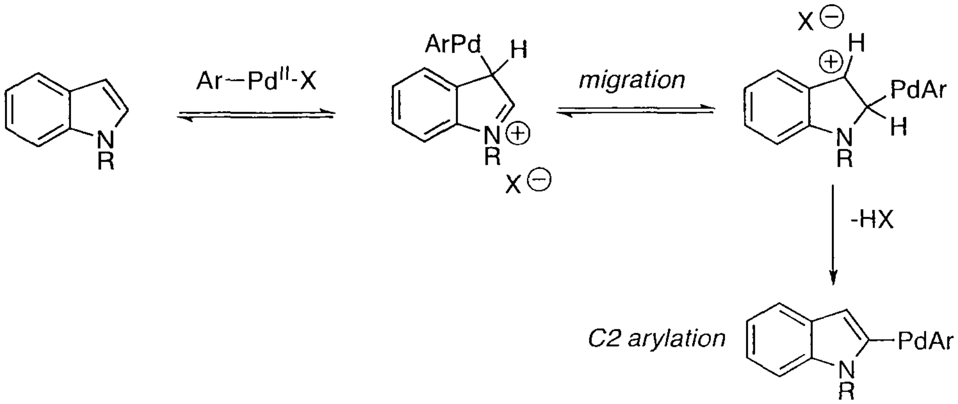
[29] Campo, M A , Huang, Q , Yao, T , Tian, Q , Larock, R C *J Am Chem Soc* **2003**, *125*, 11506

[30] For selected examples, see (a) Catellani, M , Chiusoli, P *J Organomet Chem* **1992**, *425*, 151 (b) Gonzalez, J J , García, N , Gomez-Lor, B , Echavarren, A M *J Org Chem* **1997**, *62*, 1286 (c) Pivsa Art, S , Satoh, T , Kawamura, Y , Miura, M , Nomura, M *Bull Chem Soc Jpn* **1998**, *71*, 467 (d) Martin-Matute, B , Mateo, C , Cardenas, D J , Echavarren, A M *Chem , Eur J.* **2001**, *7*, 2341 (e) Li, W , Nelson, D P , Jensen, M S , Hoerrner, R S , Javadi, G J , Cai, D , Larsen, R D *Org Lett* **2003**, *5*, 4835 (f) Iwasaki, M , Yorimitsu, H , Oshima, K *Chem Asian J* **2007**, *2*, 1430

[31] For selected examples, see (a) Toyota, M , Ilangovan, A , Okamoto, R , Masaki, T , Arakawa, M , Ihara, M *Org Lett* **2002**, *4*, 4293 (b) 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

[32] For selected examples, see (a) Mota, A J , Dedieu, A , Bour, C , Suffert, J *J Am Chem Soc* **2005**, *127*, 7171 (b) Pascual, S , de Mendoza, P , Braga, A A C , Maseras, F , Echavarren, A M *Tetrahedron* **2008**, *64*, 6021 (c) Ackermann, L , Vicente, R , Althammer, A *Org Lett* **2008**, *10*, 2299 (d) Ozdemir, I , Demir, S , Cetinkaya, B , Gourlaouen, C , Maseras, F , Bruneau, C , Dixneuf, P H *J Am Chem Soc.* **2008**, *130*, 1156 See also ref 24, 25 and 26a

S_EAr pathway be operative, gives a C2-arylation product under most reaction conditions. Supporting the electrophilic palladation mechanism, Sames proposed that the C2-arylation product of indole arylation would be the result of a C3 to C2 migration of palladium, from the Wheland intermediate, followed by rearomatization and reductive elimination to provide the observed product (Scheme 1.9).[21]



Scheme 1.9 – Mechanistic Proposal for the Observed C2 arylation of Indole

However, the more recent instances of direct arylation of the tremendously electron-deficient pentafluorobenzene, which cannot possibly undergo an electrophilic attack of palladium, created an intricate mechanistic dichotomy. This conflict between the generally assumed S_EAr pathway and the observed direct arylation of electron-deficient aromatics led the group of Maseras and Echavarren as well as our group to undertake experimental mechanistic studies with the support of DFT calculations of these types of arylations.[33] These studies resulted in remarkable evidence of a concerted metalation-deprotonation (CMD) mechanism in which the proton abstraction and the arene metalation occur simultaneously (Figure 1.5). It has also been demonstrated in our group that the acetate coming from the palladium acetate pre-catalyst participates in the catalytic cycle, thereby facilitating the proton abstraction.[34] Nowadays, considerable experimental and computational evidence also support the CDM mechanism for the direct arylation of electron-neutral and electron-rich arenes.[33a]

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[33] See (a) Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 10848. See also ref. 26 for Fagnou's work. See ref. 25 for Maseras and Echevarren's work.

[34] Sun, H.-Y.; Stuart, D.; Campeau, L.-C.; Fagnou, K. *unpublished results.*

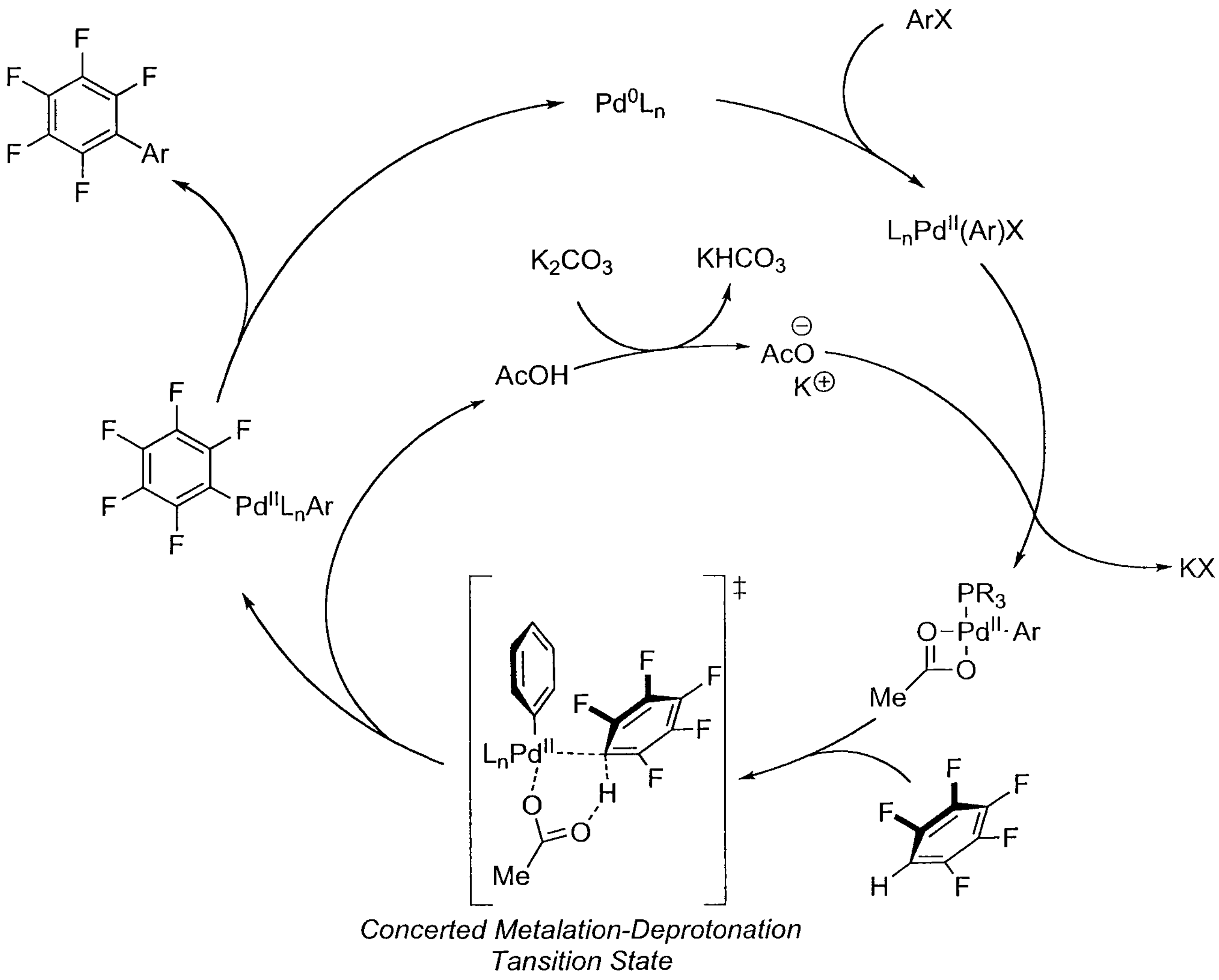

Figure 1.5 – Concerted Metalation-Deprotonation (CMD) Mechanism

CHAPTER 2 : ROOM-TEMPERATURE DIRECT ARYLATION OF POLYFLUORINATED ARENES UNDER BIPHASIC CONDITIONS[35]

2.1. Introduction

Transition metal-catalyzed transformations at C-H bonds have undergone intensive development over the past decade.[36] Tremendous efforts have focused on C-C bond-forming reactions to access biaryl systems using simple arenes in place of preactivated coupling partners.[12] However, these processes require forcing conditions generally associated with the use of high temperatures, typically above 100 °C, which can represent serious limitations for substrate compatibility as well as large scale applications. To broaden the applicability of these transformations, there is a need to develop milder reaction conditions that could proceed at lower temperatures.

An alternative to using traditional organic solvents in palladium-catalyzed direct arylation is to perform the transformation in an aqueous medium.[37] This strategy was employed by Greaney and coworkers and proved to be efficient for the direct arylation of electron-rich heteroarenes at temperatures as low as 50 °C (Scheme 2.1).[38]

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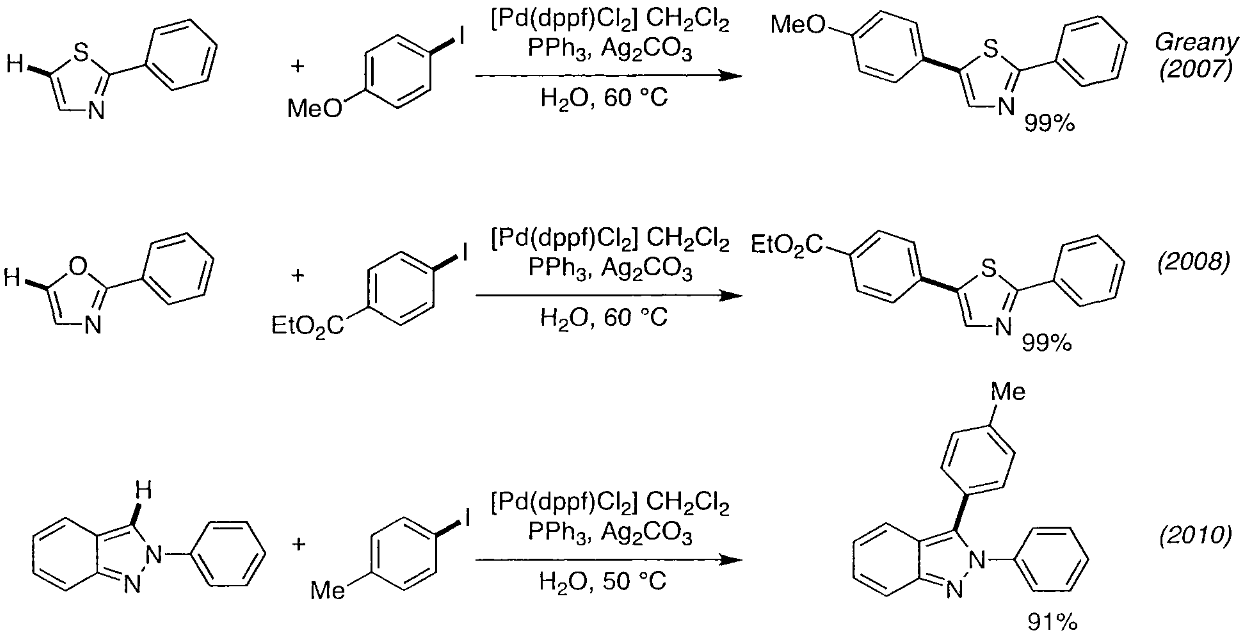
[35] A significant portion of the work described in this chapter has been published in the form of a communication, see: Ref. 26c.

[36] For selected reviews on C-H bond functionalization, see: (a) Lewis, J. C.; Bergman, R. C.; Ellman, J. A.; *Acc. Chem. Res.* **2008**, *41*, 1013. (b) Daugulis, O.; Zaitsev, V. G.; Shabashov, D.; Pham, Q.-N.; Lazareva, A. *Synlett* **2006**, 3382. (c) Ferreira, E. M.; Zhang, H.; Stoltz, B. M.; *Tetrahedron* **2008**, *64*, 5987 (d) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. For selected review on direct arylation, see ref. 13.

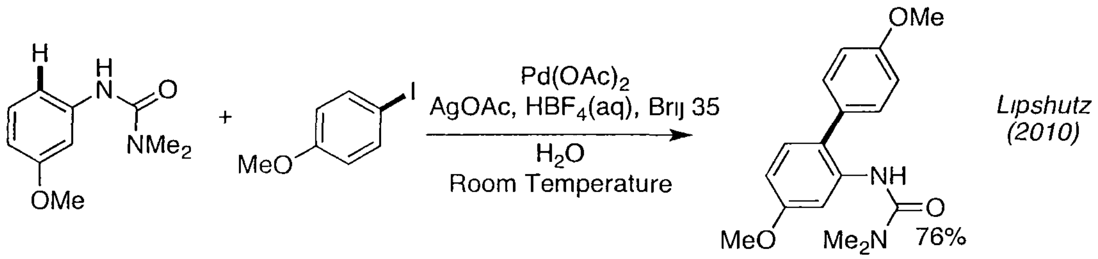
[37] For a review on organic reactions performed on water, see: Chanda, A.; Fokin, V. *Chem. Rev.* **2009**, *109*, 725.

[38] (a) Turner, G. L.; Morris, J. A.; Greaney, M. F. *Angew. Chem., Int. Ed.* **2007**, *46*, 7996. (b) Flegeau, E. F.; Popkin, M. E.; Greaney, M. F. *Org. Lett.* **2008**, *10*, 2717. (c) Ohnmacht, S. A.; Patrizia, M.; Culshaw, A. J.; Greaney, M. F. *Chem Commun.* **2008**, *10*, 1241. (d) Ohnmacht, S. A.; Culshaw, A. J.; Greaney, M. F. *Org Lett.* **2010**, *12*, 224.



Scheme 2.1 – Greany's Direct Arylation of Heteocycles at Low Temperature

More recently, the urea-directed C-H functionalization of electron-rich arenes under Pd(II) catalysis was accomplished at room temperature using water as the reaction solvent (Scheme 2 2) [39]



Scheme 2.2 – Lipshutz's Urea-Directed Arylation of Electron-Rich Arenes at Room Temperature

To our knowledge, no reports have appeared where mild aqueous conditions were successfully employed for the direct arylation of electron-deficient arenes Given the broad applicability

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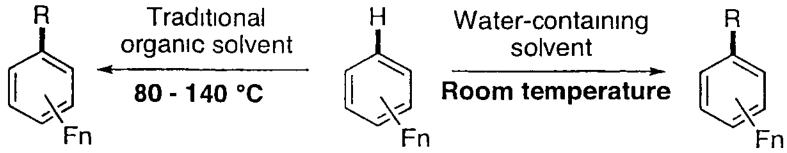
[39] Nishikata, T , Abela, A R , Lipshutz, B H *Angew Chem , Int Ed* **2010**, *49*, 781

of these types of polyarenes in materials chemistry,[40] their synthesis under mild conditions would be valuable (Scheme 2 3)



Scheme 2.3 – Room-Temperature Direct Arylation of Polyfluoroarenes

Drawing inspiration from recent advances in the development of mild C-H functionalization conditions, we decided to investigate new strategies for the direct arylation of electron-deficient polyfluorinated arenes at lower temperature,[41] employing water as a co-solvent in the reaction medium In this chapter, we describe the successful reaction development of a biphasic catalytic system[42] that provides access to a variety of biaryls at ambient temperature We report that the conditions are general and effective for a variety of aryl iodides and polyfluorinated arenes We also demonstrate that, after a preliminary investigation of the applicability of our biphasic conditions to other substrates than polyfluorinated arenes, halogenated thiophenes are also compatible in good yields

2.2. Reaction Development and Optimization

Initial reaction development and optimization was performed with 4-iodotoluene and pentafluorobenzene The aryl iodide was used in order to facilitate oxidative addition of palladium into the carbon-halogen bond Attempts with aryl bromides gave unsatisfactory results at room temperature Under standard conditions, using S-Phos[43] (See Figure 2 1) as the ligand and K_2CO_3 as the base an extensive screening of solvents was performed (Table 2 1)

---

[40] (a) Weck, M , Dunn, A R , Matsumoto, K , Coates, G W , Lobkovsky, E B , Grubbs, R H *Angew Chem , Int Ed* **1999**, *38*, 2741 (b) Tsuzuki, T , Shirasawa, N , Suzuki, T , Tokito, S *Adv Mater* **2003**, *15*, 1455 (c) Montes, V A , Li, G , Pohl, R , Shinar, J , Anzenbacher, P , Jr *Adv Mater* **2004**, *16*, 2001

[41] C-H bond activation of polyfluoroarenes requires high temperatures (80-140 °C), see (a) Nakao, Y , Kashihara, N , Kanyiva, K S , Hiyama, T *J Am Chem Soc* **2008**, *130*, 16170 (b) Wei, Y , Kan, J , Wang, M , Su, W , Hong, M *Org Lett* **2009**, *11*, 3346 (c) Johnson, S A , Huff, C W , Mustafa, F , Saliba, M *J Am Chem Soc* **2008**, *130*, 17278 (d) Xie, K , Yang, Z , Zhou, X , Li, X , Wang, S , Tan, Z , An, X , Guo, C C *Org Lett* **2010**, *12*, 1564 See also ref 18b and 26

[42] For selected examples of transition metal catalyzed reactions under biphasic solvent conditions, see (a) Kurahashi, T , Shinokubo, H , Osuka, A , *Angew Chem , Int Ed* **2006**, *45*, 6336 (b) Bottarelli, P , Costa, M *J Mol Catal A Chem*, **2008**, *289*, 82 (c) Lautens, M , Mancuso, J , Grover, H *Synthesis* **2004**, 2006 (d) Datta, A , Plenio, H *Chem Commun* **2003**, *13*, 1504

[43] Walker, S D , Barder, T E , Martinelli, J R , Buchwald, S L *Angew Chem Int Ed* **2004**, *43*, 1871

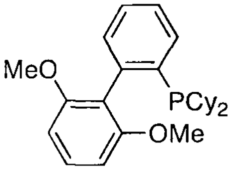
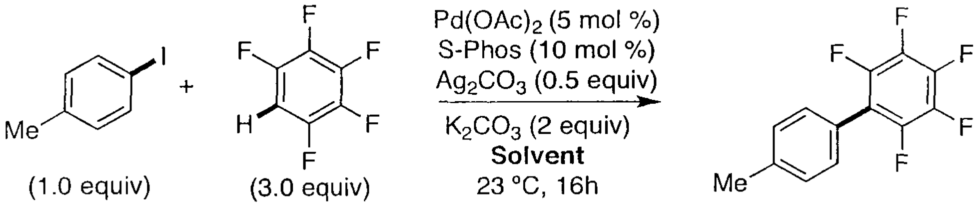


Figure 2.1 – Structure of S-Phos

Table 2.1. Effect of the Solvent



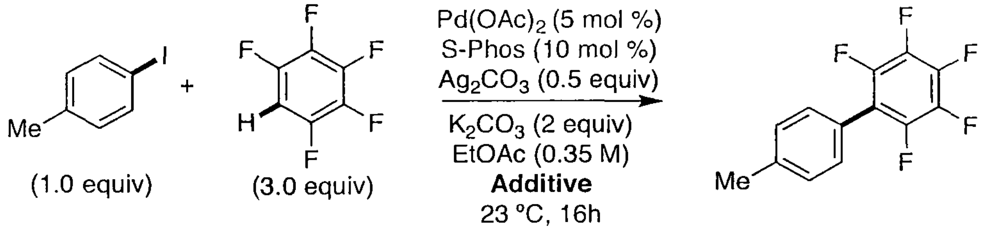
Entry	Solvent	GC-Yield (%)[a]
1	Dimethoxyethane	4
2	Cyclohexanone	6
3	Dioxane	22
4	Acetonitrile	27
5	Methyl Acetate	29
6	Tetrahydrofuran	31
7	Diethyl Ether	45
8	*i*-Propyl Acetate	47
9	Toluene	49
10	Acetone	53
11	*t*-Butyl Acetate	54
12	Dimethylacetamide	57
13	Dimethylformamide	59
14	Ethyl Acetate	68

a) Determinted by GC-MS relative to an internal standard of tetradecane

Solvents such as DME (Table 2.1, entry 1) and cyclohexanone (entry 2) gave only traces of the desired product. A first significant improvement was observed by using dioxane (entry 3), providing the biaryl product in 22% yield. Acetonitrile (entry 4), MeOAc (entry 5), THF (entry 6), Et_2O (entry 7), *i*-PrOAc (entry 8) and toluene (entry 9) gave low to modest yields ranging from 27% to 49%. Also, solvents such as acetone (entry 10), *t*-BuOAc (entry 11), DMA (entry 12) and DMF (entry 13) led to better yields up to 59%. Ultimately, the best results were obtained using EtOAc as the solvent (entry 14). However, under these anhydrous conditions, no yield above 68% could be obtained (entry 14).

The addition of pivalic acid, which has been previously shown to be a beneficial additive for direct arylation was also investigated.[44] Interestingly, Table 2.2 shows that the additive has an inhibitory effect on the room-temperature direct arylation of pentafluorobenzene.

Table 2.2. Effect of Pivalic Acid



Entry	Additive	GC-Yield (%)[a]
1	None	68
2	5 mol% PivOH	56
3	10 mol% PivOH	48

a) Determinted by GC-MS relative to an internal standard of tetradecane

Without the incorporation of the additive, a yield of 68% is obtained (Table 2.2, entry 1). Conversely, by adding 5 mol% pivalic acid, the desired product is obtained in a slightly lower yield of 56% (entry 2). The inhibition is even greater with 10 mol% pivalic acid, yielding only 48% of the biaryl product (entry 3).

Another reaction parameter that was investigated is the effect of the source of palladium. Table 2.3 demonstrates that palladium acetate is the optimal source of palladium.

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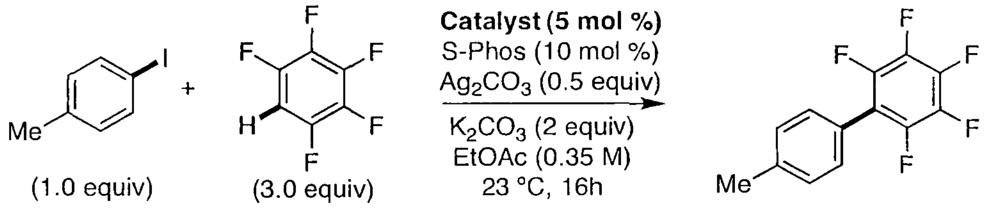
[44] For the seminal discovery of pivalic acid as an additie for direct arylation, see ref. 24.

Table 2.3. Effect of the Source of Palladium



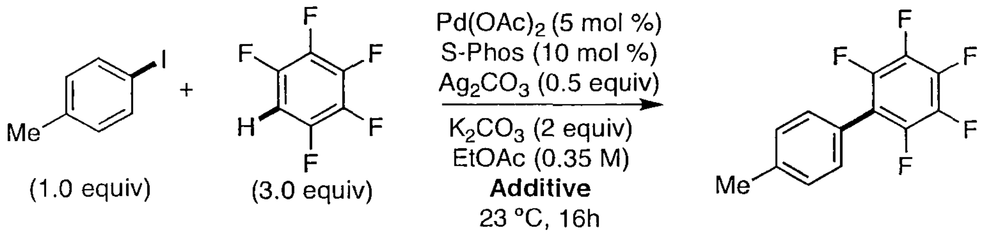
Entry	Palladium Source	GC-Yield (%)[a]
1	$Pd(OAc)_2$	68
2	$PdCl_2$	0
3	$Pd(acac)_2$	0
4	$PdBr_2$	2
5	$Pd(OPiv)_2$	5
6	$Pd_2(dba)_3$	7
7	$Pd(TFA)_2$	27

a) Determinted by GC-MS relative to an internal standard of tetradecane

Compared to $Pd(OAc)_2$, which afforded the product in 68% yield (Table 2.3, entry 1), $PdCl_2$ (entry 2) and $Pd(acac)_2$ (entry 3) are not operative and did not provide any conversion to the biaryl compound. Traces of the desired product could be observed using $PdBr_2$ (entry 4), $Pd(OPiv)_2$ (entry 5) and the $Pd_2(dba)_3$, which is a source of Pd(0) requiring no further reduction in the reaction medium (entry 6). $Pd(TFA)_2$ (entry 7) is the only other source of palladium that provided a significant amount of product, albeit in a low yield of 27%. It has, in fact, been demonstrated experimentally with computational support in our group that the acetate coming the palladium acetate pre-catalyst plays a crucial role in the concerted-metalation deprotonation mechanism in the absence of a pivalic acid additive.[34] This demonstrated ability of acetate to facilitate C-H bond cleavage is therefore in line with the results from Table 2.3 showing that only the $Pd(OAc)_2$ pre-catalyst is competent in direct arylation.

In an effort to help solubilize the base in the reaction medium, which would facilitate a concerted-metalation-deprotonation, the addition of a variety of phase-transfer catalysts was investigated (Table 2.4).

Table 2.4. Effect of Phase-Transfer Catalysts



Entry	Phase Transfer	GC-Yield (%)[a]
1	None	68
2	Tetra-*N*-butylammonium chloride (5 mol%)	69
3	Tetra-*N*-butylammonium chloride (10 mol%)	34
4	Tetra-*N*-butylammonium chloride (20 mol%)	8
5	Tetra-*N*-butylammonium bromide (5 mol%)	50
6	Tetra-*N*-butylammonium fluoride (5 mol%)	37
7	Tetra-*N*-butylammonium acetate (5 mol%)	35
8	Aliquat 336 (5 mol%)	47

a) Determinted by GC-MS relative to an internal standard of tetradecane

The addition of 5 mol% TBAC afforded the product in the same yield as without the additive (Table 2.4, entries 1 and 2). However, by incorporating greater quantities of the same additive, an inhibitory effect was observed, giving the product in 34% and 8% yields with 10 mol% (entry 3) and 20 mol% (entry 4) of the additive, respectively. Moreover, the addition of other phase-transfer catalysts such as TBAB (entry 5), TBAF (entry 6), TBOAc (entry 7) and Aliquat 336 (entry 8) resulted in lower yields in all cases. Therefore, no phase-transfer catalyst was employed in the optimal reaction conditions.

An alternative way to increase the solubility of the base in the reaction medium is the addition of water to the reaction mixture (Figure 2.2).

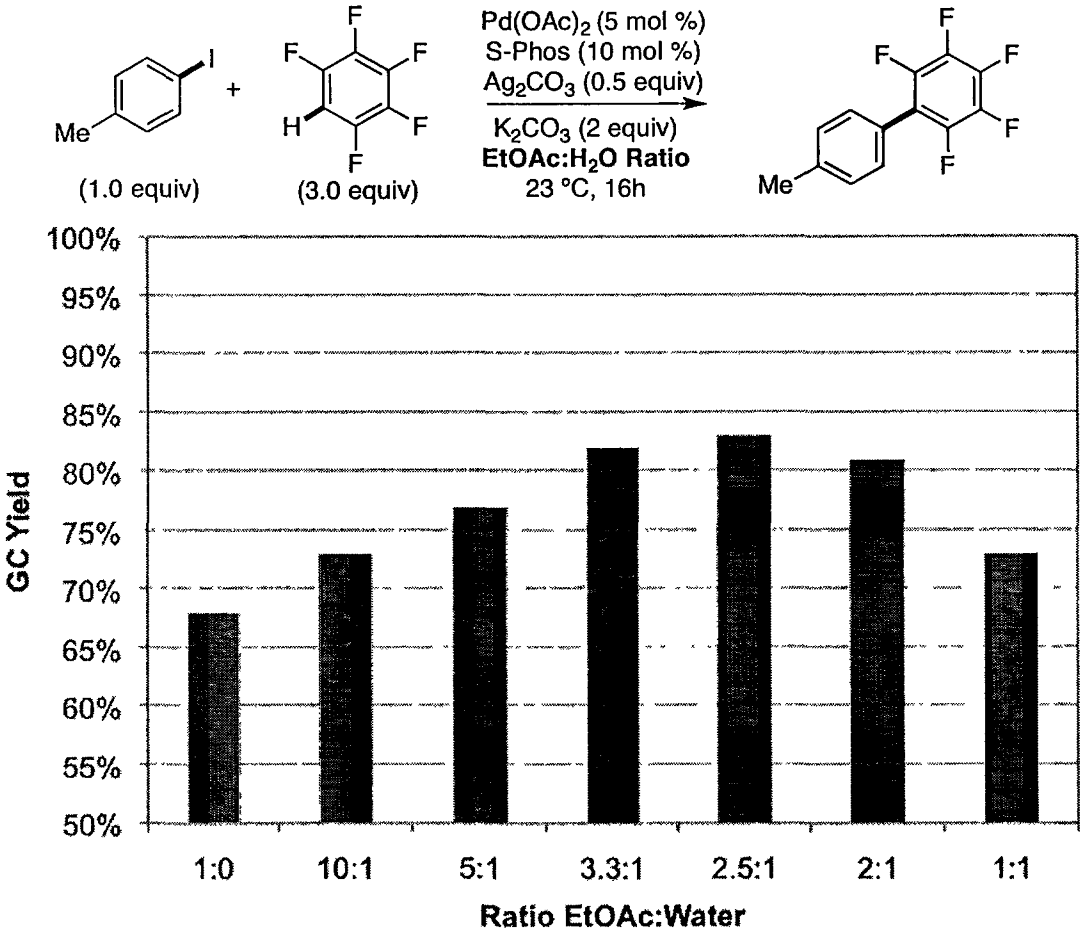


Figure 2.2 – Effect of the ratio of EtOAc to water

To our great delight, we observed that the yield could be significantly increased when using a solvent mixture of water and EtOAc. We were pleased to find that the use of a 2.5:1 mixture of EtOAc and water could improve the reaction yield up to 83% (see Figure 2.2). Taking advantage of biphasic chemistry, it was reasoned that by performing the reaction under such conditions, a complete solubilization of the inorganic components of the reaction could be achieved. In particular, the base, which has been shown to be crucial for the concerted-metalation-deprotonation transition state to occur, is only sparsely soluble in organic solvents.[45] Under these biphasic conditions, the ratio of the two solvent components is crucial to ensure optimal conversion. There is a narrow window around a 2.5:1 ratio of EtOAc and water in which the highest yields are obtained and any deviation from this ratio results in lower conversions.

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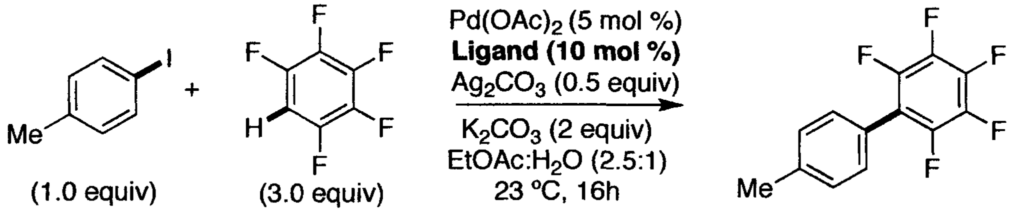
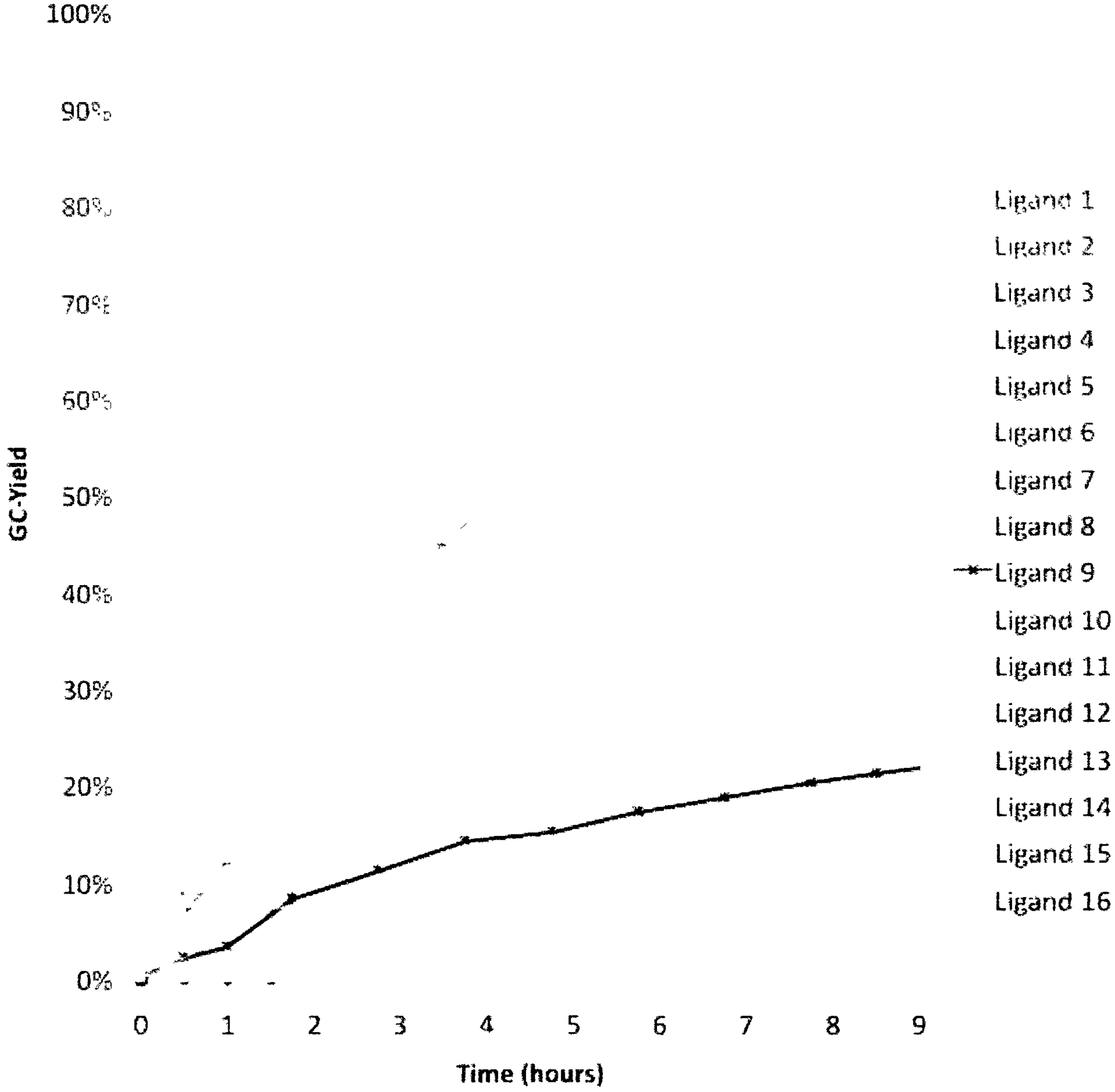
[45] For the solubility of the carbonate base in organic solvents, see ref. 24.

The phosphine ligand also exerted a significant effect on the reaction outcome. In order to thoroughly probe the effect of the ligand, the reaction was monitored with several types of ligands. Figure 2.3 shows the different reaction profiles using a variety of phosphine ligands.





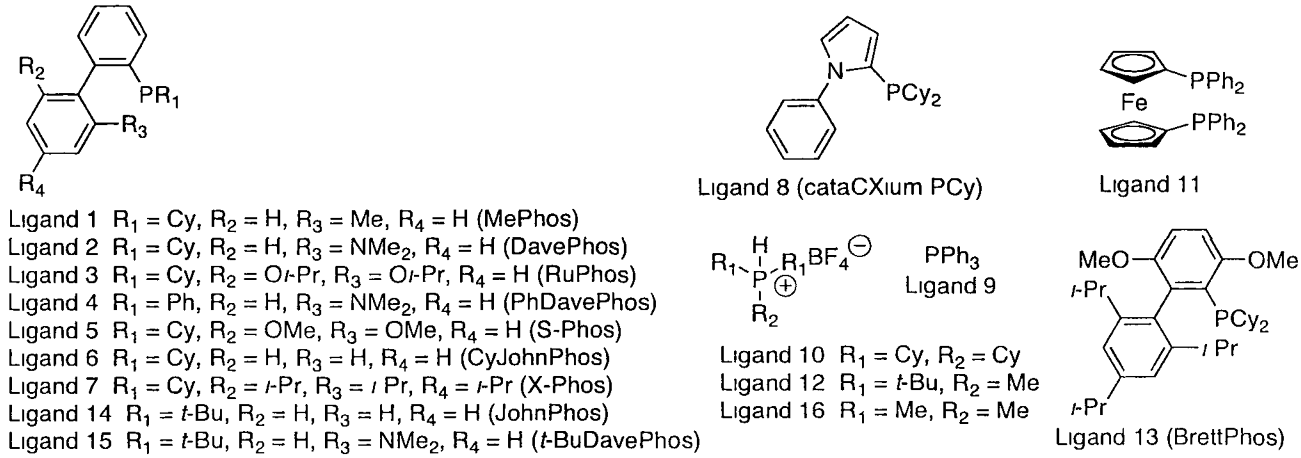


Figure 2.3 – Reaction Profiles with Various Ligands

From the different reaction profiles in Figure 2 3, we observed that superior results were obtained with biaryl-type phosphine ligands bearing two cyclohexyl groups on the phosphine, such as MePhos, DavePhos, RuPhos, S-Phos, CyJohnPhos and X-Phos Ultimately, the best two ligands were DavePhos and MePhos, providing almost complete conversion in 5 and 2 hours, respectively All other types of ligands were less effective For example, cataCXium PCy, PPh_3, PCy_3, dppf, P*t*-Bu_2Me and BrettPhos all gave low conversions after 9 hours Finally, JohnPhos and *t*-BuDavePhos, both bearing two *tert*-butyl goups on the phosphine, as well as PMe_3 were not operative for the reaction

To conclude the reaction development, we noted that a silver carbonate additive was required for the coupling reaction to proceed[46] Indeed, without the addition of Ag_2CO_3, no conversion to the biaryl product was observed and only the starting materials were recovered The role of silver(I) is attributed to a plausible abstraction of the iodide ligand from the Pd(II) complex, thereby generating an electrophilic cationic palladium intermediate[47]

In summary, the reaction development and optimization led to the following optimal conditions featuring a biphasic solvent system 4-iodotoluene (1 0 equiv), pentafluorobenzene

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[46] For examples of silver(I) used in direct arylation, see (a) Lebrasseur, N , Larrosa, I *J Am Chem Soc* **2008**, *130*, 2926 (b) Campeau, L -C , Parisien, M , Jean, A , Fagnou, K *J Am Chem Soc* **2006**, *128*, 581 (c) Daugulis, O , Zaitsev, V G *Angew Chem , Int Ed* **2005**, *44*, 4046

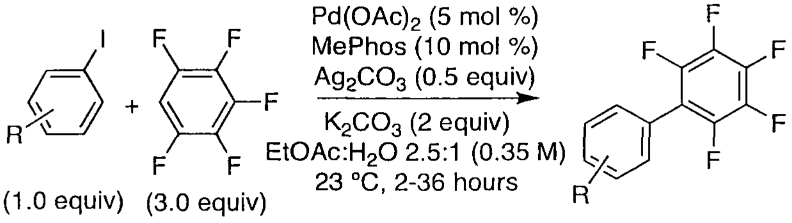
[47] For examples of cationic Pd(II) complexes generated by Ag(I) abstraction of the iodide ligand, see (a) Grove, D M , van Koten, G , Louwen, J N , Noltes, J G , Spec, A L *J Am Chem Soc* **1982**, *104*, 6609 (b) Denmark, S E , Schnute, M E *J Org Chem* **1995**, *60*, 1013 (c) Hirabayashi, K , Mori, A , Kawashima, J , Suguro, M , Nishihara, Y , Hiyama, T *J Org Chem* **2000**, *65*, 5342 (d) Overman, L E , Poon, D J *Angew Chem , Int Ed* **1997**, *36*, 518

(3.0 equiv), $Pd(OAc)_2$ (5 mol%), MePhos (10 mol%), Ag_2CO_3 (0.5 equiv), K_2CO_3 (2.0 equiv), $EtOAc{:}H_2O$ (2.5:1, 0.35 M), 23 °C, 2 hours.

2.3. Applicability of the Transformation

Illustrative examples with respect to the aryl iodide are shown in Table 2.5. In addition to 4-iodotoluene, which possesses a minimal steric and electronic bias, (Table 2.5, entry 1), electron-withdrawing groups such as a ketone, an ester or a trifluoromethyl group are well tolerated, giving rise to the coupling products in 85% to 96% yields (entries 2 to 4). Aryl iodides bearing electron-donating groups at the *para* and *ortho* positions also give excellent yields of 92% and 99% (entries 5 and 6). Sterically demanding substrates are compatible as exemplified by products **2.7** and **2.8** obtained in 78% and 95% yields, respectively (entries 7 and 8). Interestingly, 5-iodoindole is also tolerated, giving biaryl **2.9** in 93% yield without arylation of the azole ring (entry 9).

Table 2.5. Scope of Aryl Iodides with Pentafluorobenzene



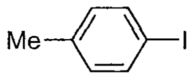
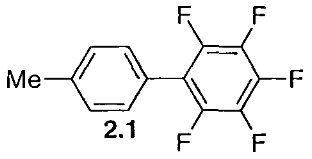
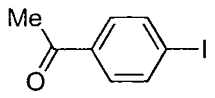
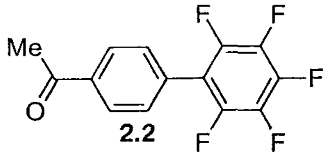
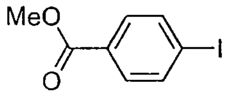
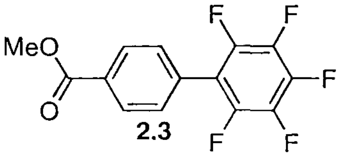
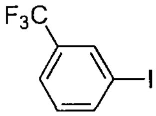
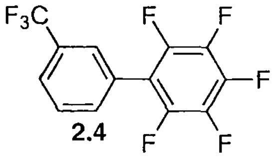
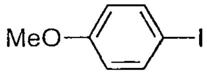
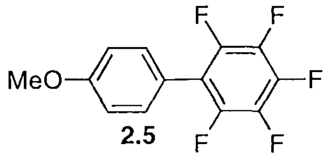
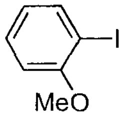
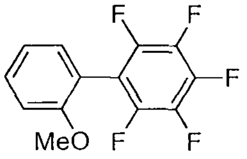
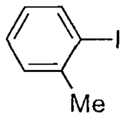
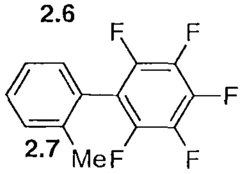
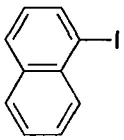
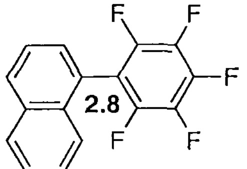
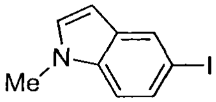
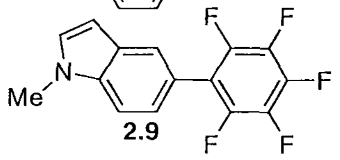
entry	aryl iodide	product	isolated yield
1		 **2.1**	90%
2		 **2.2**	95%
3		 **2.3**	96%

Table 2.5 continued.

4		 **2.4**	85%
5		 **2.5**	92%
6		 **2.6**	99%
7		 **2.7**	78%
8		 **2.8**	95%
9		 **2.9**	93%

Other aryl iodides that were tested under the room-temperature biphasic conditions showed to be unreactive, providing no product or only traces of the desired material (Figure 2.4).

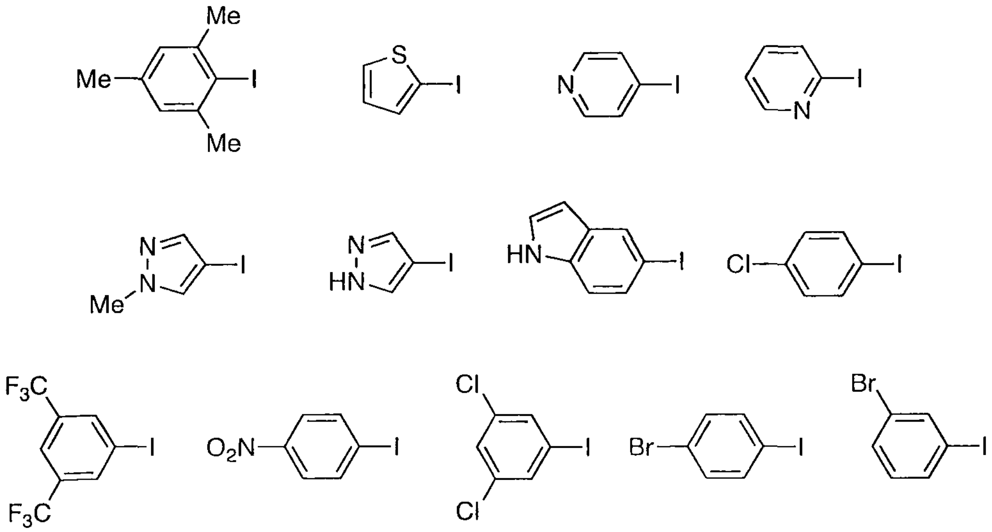
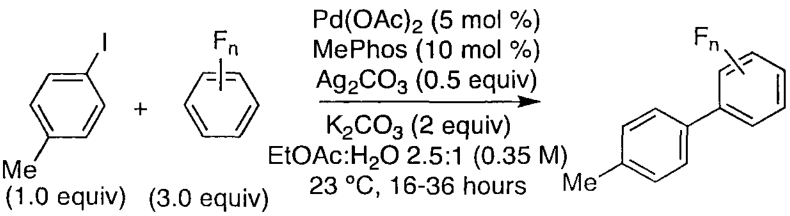


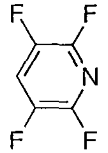
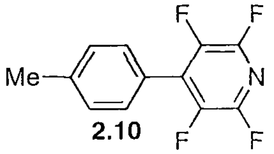
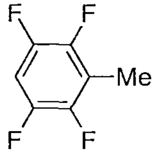
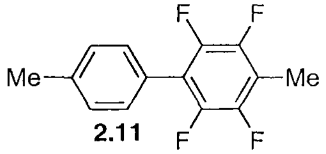
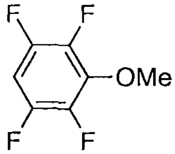
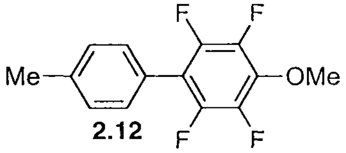
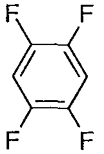
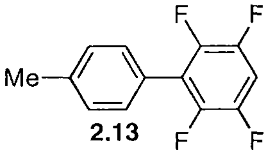
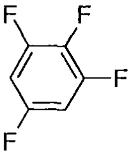
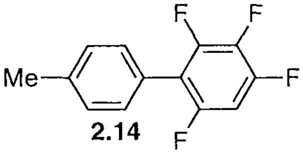
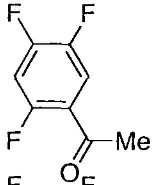
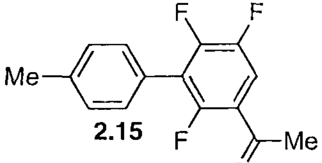
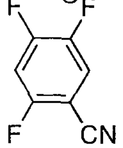
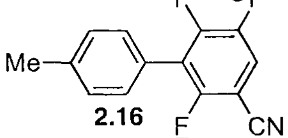
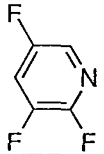
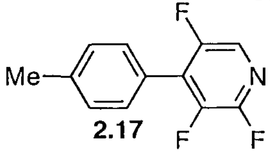
Figure 2.4 – Incompatible Aryl Iodides

For example, aryl iodides that are too encumbered, such as iodomesitylene, were unreactive. Several heterocyclic iodides, such as 2-iodothiophene, 4-iodopyridine, 2-iodopyridine and 4-iodo-1-methylpyrazole were also incompatible. Unprotected 4-iodopyrazole and 5-iodoindole failed to provide the desired product. Furthermore, chloro and bromo-substituted aryl iodides gave low conversion to the desired coupling product and a mixture of polyarylation was often observed. In addition, iodoarenes bearing strongly electron-withdrawing groups, such as *p*-iodonitrobenzene and 1-iodo-3,5-bis(trifluoromethyl)benzene reacted very slowly and no significant amount of product could be isolated.

With regard to the polyfluoroarene coupling partner, tetrafluoro and trifluoroarenes were found to be efficient for the coupling reaction (Table 2.6). For example, tetrafluorinated biaryls **2.10**, **2.11** and **2.12** (Table 2.6, entries 1 to 3), bearing different substitution patterns can be obtained in excellent yields ranging from 91% to 98%. Symmetrical tetrafluoroarenes having more than one potential site of arylation require a larger excess of the polyfluoroarene component in order for the monoarylated product **2.13** and **2.14** to be obtained in 90% and 88% yields, respectively (entries 4 and 5). Attempts to favor diarylation of these symmetrical fluorinated arenes by using an excess of the aryl iodide failed and gave a mixture of mono and diarylation in low yields. Furthermore, less activated trifluorinated arenes bearing various substituents can also be coupled efficiently and selectively to give only monoarylation products in 81% to 99% yields (entries 6 to 8).

Table 2.6. Scope of Polyfluoroarenes with 4-Iodotoluene



entry	perfluoroarene	product	isolated yield
1		 **2.10**	95%
2		 **2.11**	91%
3		 **2.12**	98%
4[a]		 **2.13**	90%
5[a]		 **2.14**	88%
6		 **2.15**	99%
7		 **2.16**	81%
8		 **2.17**	98%

[a] 10.0 equiv of tetrafluoroarene used

Although the conditions are general for a variety of polyfluoroarenes, some of the less activated substrates or coupling partner bearing incompatible functionalities proved to be reluctant to undergo direct arylation (Figure 2.5).

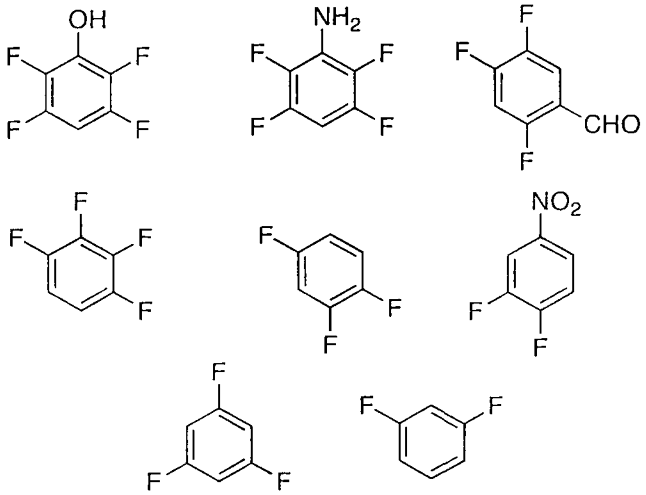


Figure 2.5 – Incompatible Polyfluoroarenes

For example, unprotected tetrafluorophenol and aniline were incompatible coupling partners under the biphasic conditions. The aldehyde functionality was also not tolerated and gave low conversion of the biaryl product. Less activated 1,2,3,4-tetrafluorobenzene, 1,2,4-trifluorobenzene, 1,3,5-trifluorobenzene and 1,3-difluorobenzene gave product in very low conversion and no significant amount of product could be isolated. The nitro functionality also seemed to be detrimental to the reactivity of the fluoroarene coupling partner.

We also wanted to investigate the applicability of our room-temperature biphasic conditions to the aylation of other types of substrates than polyfluorinated arenes. In order to determine other compatible coupling partners, several electron-deficient and electron-neutral arenes as well as electron-rich heterocycles were screened using the optimal reaction conditions (Figure 2.6).

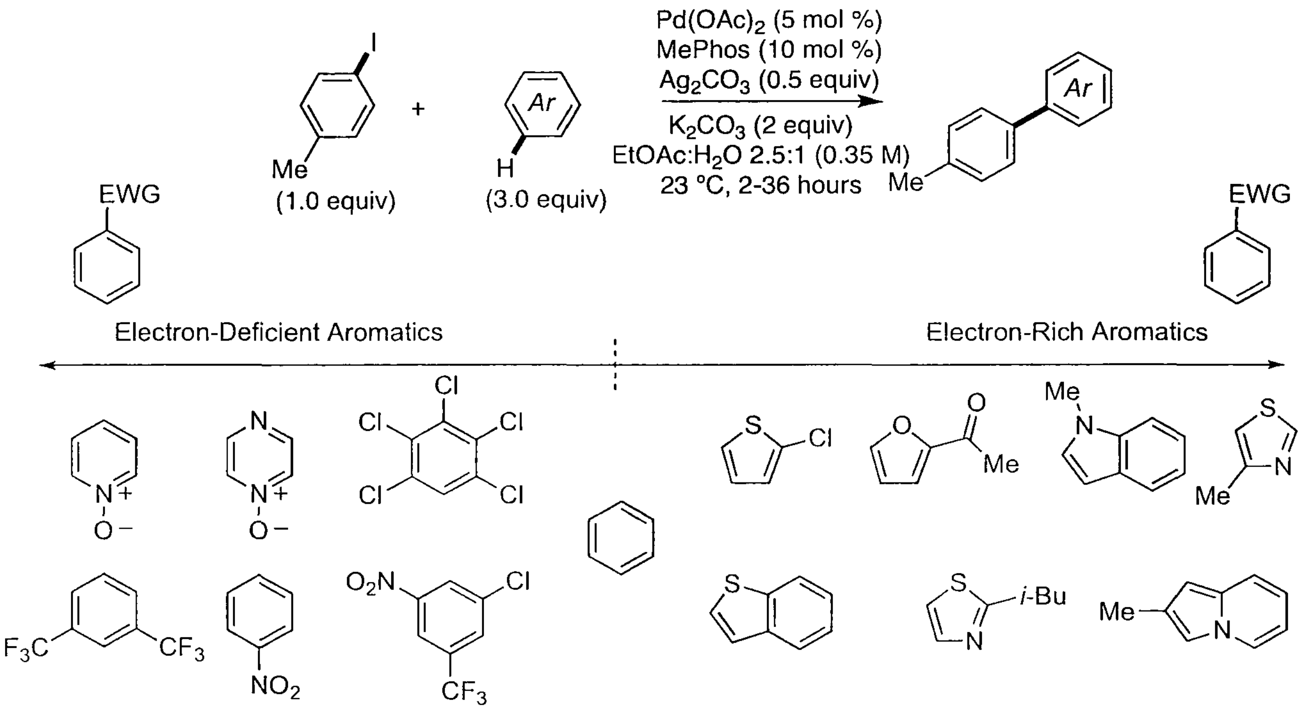


Figure 2.6 – Other types of Arenes Screened Under the Room-Temperature Conditions

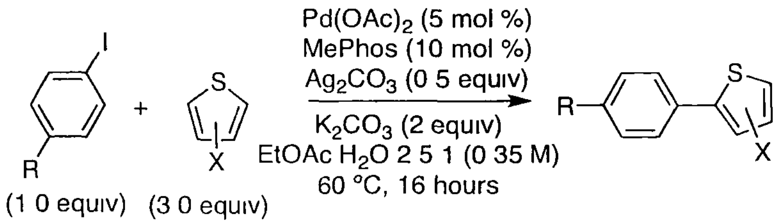
Amongst all the electron-deficients arenes, electron-neutral benzene and electron-rich heterocycles that were tested for the reaction, 2-chlorothiophene was the first type of substrate other than fluorinated arenes that showed to be a compatible coupling partner, giving the desired product in 37% yield after 16 hours.

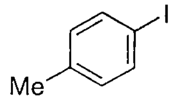
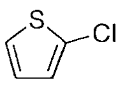
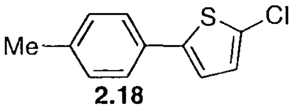
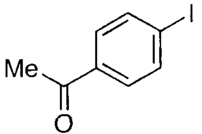
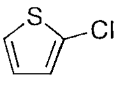
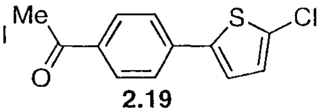
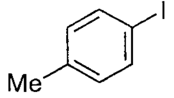
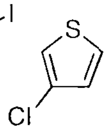
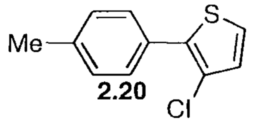
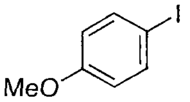
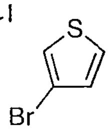
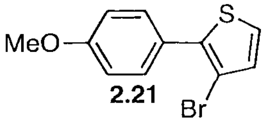
In the Fagnou group, it has recently been demonstrated that introduction of a chlorine atom enhances the propensity for heteroarenes to undergo C-H bond functionalization.[48] For that reason, we decided to investigate these types of substrates in greater detail. We were pleased to observe that, by slightly elevating the temperature to 60 °C, good yields could be obtained with different halogenated thiophenes (Table 2.7).

---

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

Table 2.7. Arylation of Halogenated Thiophenes



entry	aryl iodide	thiophene	product	isolated yield
1			 **2.18**	77%
2			 **2.19**	61%
3			 **2.20**	73%
4			 **2.21**	72%

Indeed, 2-chlorothiophene reacts regioselectively at the C5 position at only 60 °C to afford products **2.18** and **2.19** in 77% and 61% yields, respectively (Table 2.7, entries 1 and 2). 3-Chlorothiophene also reacts selectively at the C2 position, providing biaryl product **2.20** in good yield (entry 3). More interestingly, 3-bromothiophene is a compatible coupling partner and C-H bond cleavage occurs in the presence of a reactive C-Br bond (entry 4).[49] The presence of the chlorine and bromine substituents on these products is a valuable synthetic handle that can be used for subsequent transformations.

In summary, we have developed mild biphasic conditions for the direct arylation of electron-deficient arenes at room temperature. The conditions are general and effective for a variety of aryl iodides and polyfluorinated arenes as coupling partners and excellent yields are generally obtained. Other halogenated thiophenes are also compatible and led to the heterobiaryl products in good yields.

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[49] Traces of another regioisomer were observed by GC MS with the use of 3-chloro and 3-bromothiophene.

CHAPTER 3 : EVALUATION OF A NEW CLASS OF ELECTRON-DEFICIENT PHOSPHINE LIGANDS FOR DIRECT ARYLATION

3.1. Introduction

Heterocyclic biaryl compounds are predominant in natural products[50] and medicinal compounds [51] Although the traditional methods to prepare these valuable motifs necessitate the use of a stoichiometric amount of organometallic coupling partner through transition-metal catalysis,[12] more efficient processes in which the organometallic species can be replaced by a simple heteroarene have proven to be a viable alternative for the preparation of heteroatom-containing biaryls [13,15] However, general conditions that are widely compatible with all classes of heterocyclic coupling partners are only sparsely reported[23] and the use of a different set of conditions for each class of substrate remains the norm In order to further improve direct arylation and establish more broadly applicable reaction conditions, a better understanding of the reaction mechanism and the development of novel high-performance ligands are essential

As part of a program dedicated to the study of the direct arylation mechanism and the development of broadly applicable reaction conditions, we became interested in investigating the effect of electron-deficient phosphine ligands[52] on the C-H bond cleavage step of this process under Pd(0) catalysis Whilst most of the focus has traditionally been on the study of electron-rich ligands, few studies on the effect of electron-deficient phosphine ligands are described in the literature [13]

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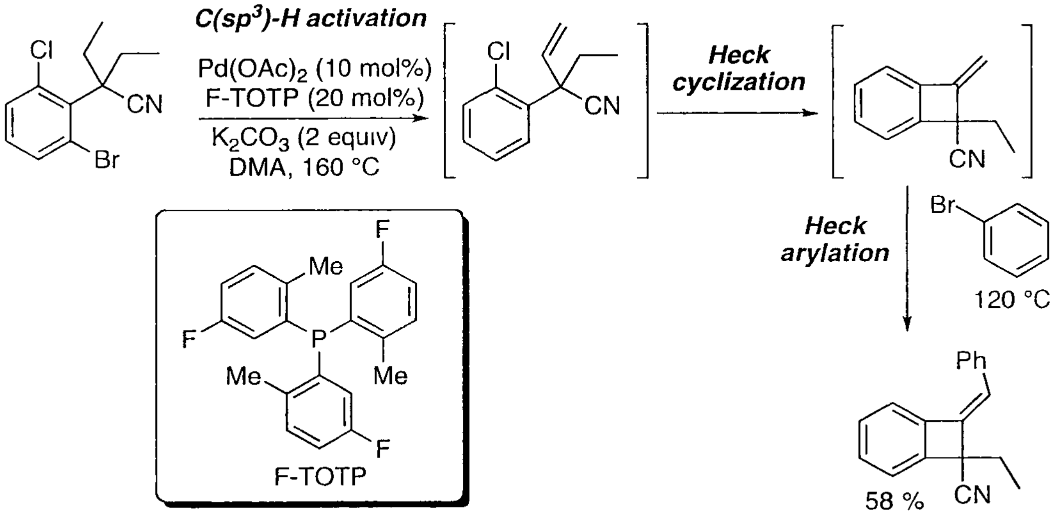
[50] For examples, see (a) Faulkner, D J *Nat Prod Rep* **2001**, *18*, 1 (b) Davies, R J , Kane, P D , Moody, C J , Slawin, A M Z *J Org Chem* **2005**, *70*, 5840 (c) Yang, C G , Huang, H , Jiang, B *Curr Org Chem* **2004**, *8*, 1691

[51] For examples, see a) Chimenti, F , Maccioni, E , Secci, D , Bolasco, A , Chimenti, P , Granese, A , Carradori, S , Alcaro, S , Ortuso, F , Yáñez, M , Orallo, F , Cirilli, R , Ferretti, R , La Torre, F *J Med Chem* **2008**, *51*, 4874 (b) Armistead, D M , Badia, M C , Bemis, G W , Bethiel, R S , Frank, C A , Novak, P M , Ronkin, S M , Saunders, J O WO9740028, 1997 See also, ref 1, 2, 3, 4 and 5

[52] For a review on electron deficient fluoroarylphosphine ligands, see Pollock, C L, Saunders, G C , Smyth, E M C S , Sorokin, V *J Fluorine Chem* **2008**, *129*, 142

Reports by Baudoin,[53] Gevorgyan[54] as well as our group[55] have validated the efficiency of electron-deficient ligands in intramolecular processes with Pd(0) catalysts

For example, the group of Baudoin performed the synthesis of substituted benzocarbocycles *via* an elegant cascade reaction featuring a C(sp^3)-H activation step followed by two subsequent Heck additions, using the electron-deficient fluorine-containing F-TOTP ligand (Scheme 3 1) [53a]



Scheme 3.1 – Formation of Benzocarbocycles by a Cascade Reaction Featuring a C(sp^3)-H Activation Step

For the C-H activation step of this transformation, Baudoin and co-workers proposed a catalytic cycle implicating a cyclopalladation of the Pd(II) intermediate resulting from oxidative insertion into the C-Br bond Thereafter, β-hydride elimination followed by reductive elimination affords the dehydrogenated product (Scheme 3 2) [53b]

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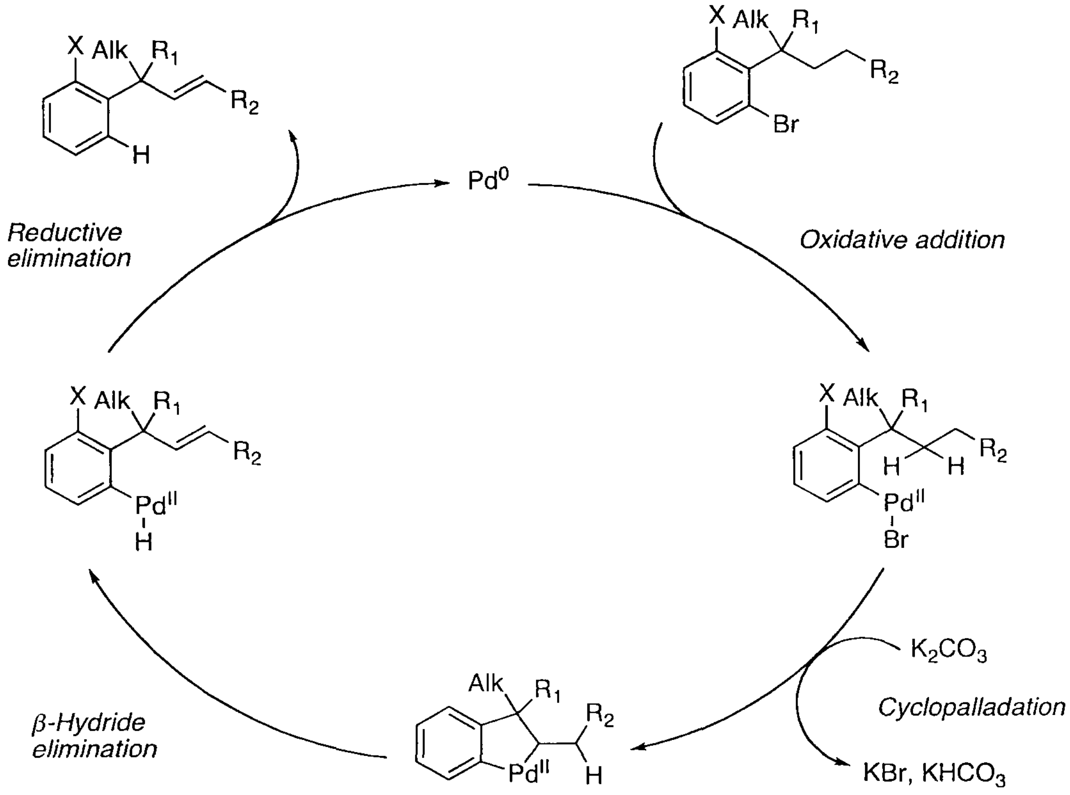
[53] (a) Hitce, J , Baudoin, O *Adv Synth Catal* **2007**, *349*, 2054 (b) Hitce, J , Retailleau, P , Baudoin, O *Chem Eur J* **2007**, *13*, 792

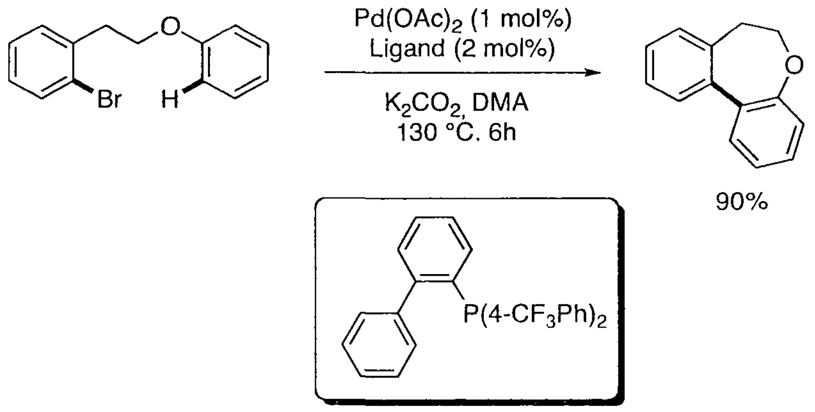
[54] Huang, C , Gevorgyan, V *Org Lett* **2010**, *12*, 2442

[55] (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



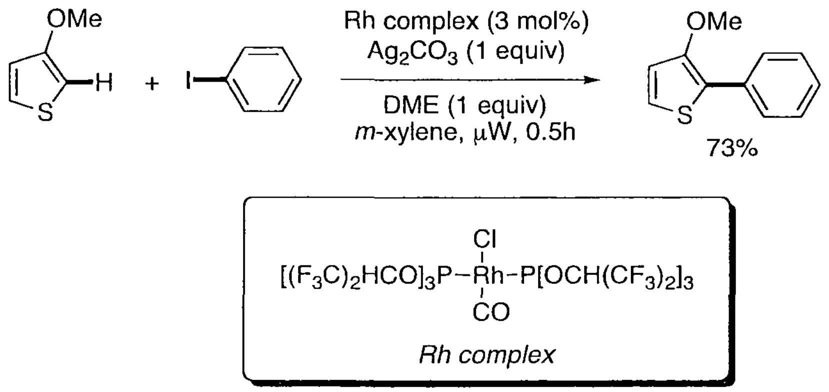
Scheme 3.2 – Mechanism of Baudoin's C(sp^3)-H Activation

Similarly, the group of Fagnou resorted to using an electron-deficient biaryl-type ligand for the formation of 7-membered rings by intramolecular direct arylation (Scheme 3.3).[55a] The formation of these types of large rings by direct arylation is a difficult process when standard electron-rich ligands are utilized. Interestingly, the discovery of this new ligands induced complete conversion to the desired product in excellent yield. Furthermore, the group of Gevorgyan recently disclosed the synthesis of unsymmetrical *o*-biphenols *via* a silicon-tethered palladium-catalyzed direct arylation utilizing the exceptionally electron-poor tris(pentafluorophenyl)phosphine ligand.[54]



Scheme 3.3 – Formation of 7-Membered Rings (Fagnou)

Additionally, new intermolecular reactions using π-accepting phosphite ligands have also been observed by Itami and coworkers under Rh(I) catalysis.[56] For example, using a preformed Rh(I) complex bearing very electron-deficient polyfluorinated phosphite ligands, they performed the direct arylation of different heterocycles with aryl iodides (Scheme 3.4).



Scheme 3.4 – Rh(I)-Catalyzed Intermolecular Direct Arylation of Heterocycles (Itami)

In this chapter, we report the synthesis and the development of a new class of electron-poor fluoroarylphosphine ligands that is compatible with a broad variety of heterocycles. We demonstrate that a more electron-deficient metal center accelerates the direct arylation reaction and also

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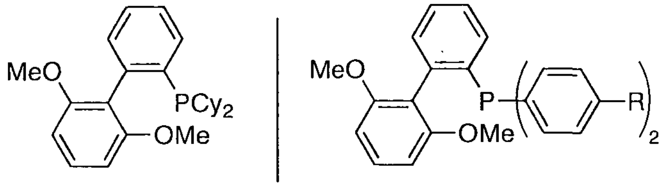
[56] (a) Yanagisawa, S.; Sudo, T.; Noyori, R.; Itami, K. *J. Am. Chem. Soc.* **2006**, *128*, 11748. (b) Yanagisawa, S.; Sudo, T.; Noyori, R.; Itami, K. *Tetrahedron* **2008**, *64*, 6073. (c) Yanagisawa, S.; Ueda, K.; Sekizawa, H.; Itami, K. *J. Am. Chem. Soc.* **2009**, *131*, 14622.

report mechanistic evidence that a concerted metalation-deprotonation (CMD) parthway[33] is operative, even in the presence of an electrophilic metal center. Based on these mechanistic studies, a rationale for the acceleration of the C-H bond cleavage step in the presence of electron-deficient ligands is provided. These results should encourage further investigation of electron-deficient ligands in new transition-metal catalyzed transformations.

3.2. Synthesis of the Ligands

In our initial ligand design studies, we focused our efforts toward the synthesis of biaryl-type phosphine ligands bearing electron-withdrawing fluoro and trifluoromethyl groups (Figure 3.1). "Buchwald-type" biaryl ligands have shown to be efficient for C-H bond functionalization reactions[57] as well as several other processes[58] and were therefore selected as a starting point for our studies. We were pleased to observe that substitution of the cyclohexyl groups by electron-deficient arenes on the S-Phos ligand[43] provided promising results.



S-Phos

Ligand **3.1**: R = H
Ligand **3.2**: R = F
Ligand **3.3**: R = CF_3

Figure 3.1 – Electron-Deficient Variants of S-Phos

These electron-deficient variants of S-Phos could be easily obtained *via* a straightforward phosphonite intermediate approach developed by the group of Straub for the synthesis of particularly bulky unsymmetrical phosphines.[59] Using this approach, they could synthesize

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[57] For selected examples of biaryl phosphine ligands used in direct arylation, see: (a) Ackermann, L.; Althammer, A.; Fenner, S. *Angew. Chem., Int. Ed.* **2009,** *48*, 201. (b) Huestis, M. P.; Fagnou, K. *Org. Lett.* **2009,** *11*, 1357. (c) Watanabe, T.; Oishi, S.; Fujii, N.; Ohno, H. *J. Org. Chem.* **2009**, *74*, 4720. (d) Campeau, L.-C.; Bertrand-Laperle, M.; Leclerc, J.-P.; Villemure, E.; Gorelsky, S.; Fagnou, K. *J. Am. Chem. Soc.* **2008,** *130*, 3276.

[58] For selected examples of biaryl phosphine ligands used in other processes, see: a) Fors, B. P.; Watson, D. A.; Biscoe, M. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 13552. (b) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550. (c) Watson, D. A.; Su, M.; Teverovskiy, G.; Zhang, Y.; García-Fortanet, J.; Kinzel, T.; Buchwald, S. L. *Science* **2009,** *325*, 1661.

[59] Keller, J.; Schlierf, C.; Nolte, C.; Mayer, P.; Straub, B. F. *Synthesis* **2006,** 354.

triarylphosphines such as 9-anthryl(1-naphthyl)phenylphosphine and other bulkier variants of this ligand (Figure 3.2).

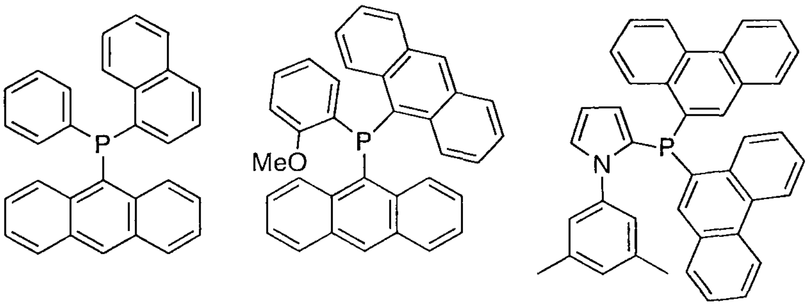
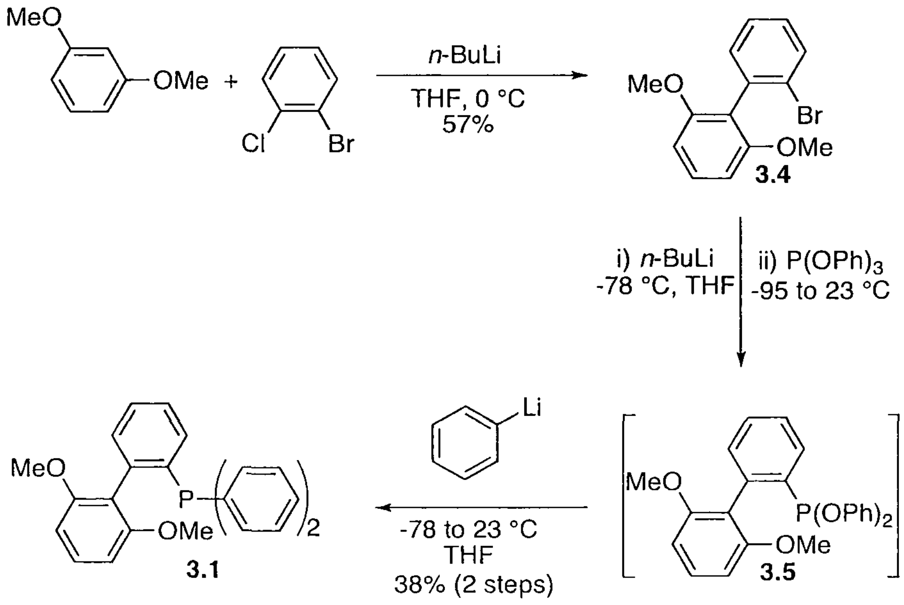


Figure 3.2 – Bulky Triarylphosphines Synthesized Using a Phosphonite Intermediate Approach (Straub)

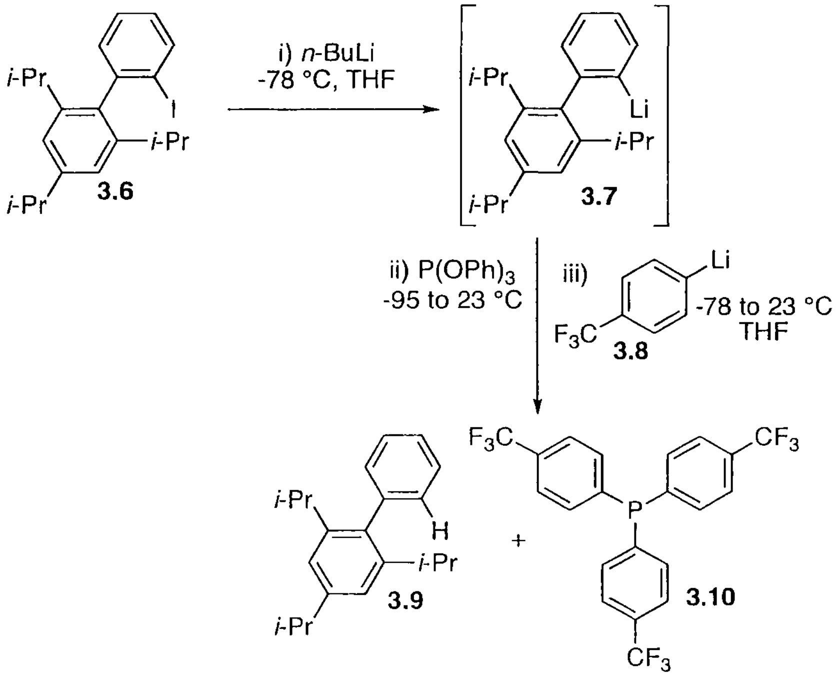
Since remarkably encumbered phosphines could be obtained *via* the chemistry developed by Straub, we envisaged that the method would be also applicable to the synthesis of the electron-deficient triaryl variants of the S-Phos ligand (Figure 3.1). Indeed, biaryl bromide **3.4**, which was obtained by a nucleophilic aromatic substitution reaction, underwent lithium-halogen exchange and reacted with triphenyl phosphite at low temperature (-95 °C) to afford phosphonite intermediate **3.5**. This intermediate was immediately reacted with an excess of phenyllithium to provide the desired ligands **3.1** in a moderate yield of 38% (Scheme 3.5).



Scheme 3.5 – Synthesis of Ligand 3.1

Using the same phosphonite intermediate method, ligands **3.2** and **3.3** could be synthesized in 12% and 46% yields, respectively. It is also important to discuss the purification procedure of these ligands, which required extensive optimization. Indeed, the simple purification procedure reported by Srtaub for his synthesis of bulky phosphines, which is essentially a single recrystallization of the crude reaction mixture in acetone, proved to be utterly ineffective with our ligands **3.1** to **3.3**. The procedure that was privileged after a thorough investigation of different purification procedures was to first concentrate to dryness the crude reaction mixture under high vacuum. Thereafter, the resulting solid was quickly filtered through a short pad of silica gel, eluting with a mixture of EtOAc/hexanes (25:75). After concentration under reduced pressure, MeOH was added and sonicated until precipitation of the product occurred. The collected precipitate was recrystallized from acetone for ligand **3.1** or ethanol for ligands **3.2** and **3.3**. Also, for the recrystallization to give rise to analytically pure product, the solid had to be carefully dissolved in the boiling solvent, and slowly cooled down to ambient temperature over the course of the night. This laborious purification procedure is potentially the reason for the very low yields obtained in some instances.

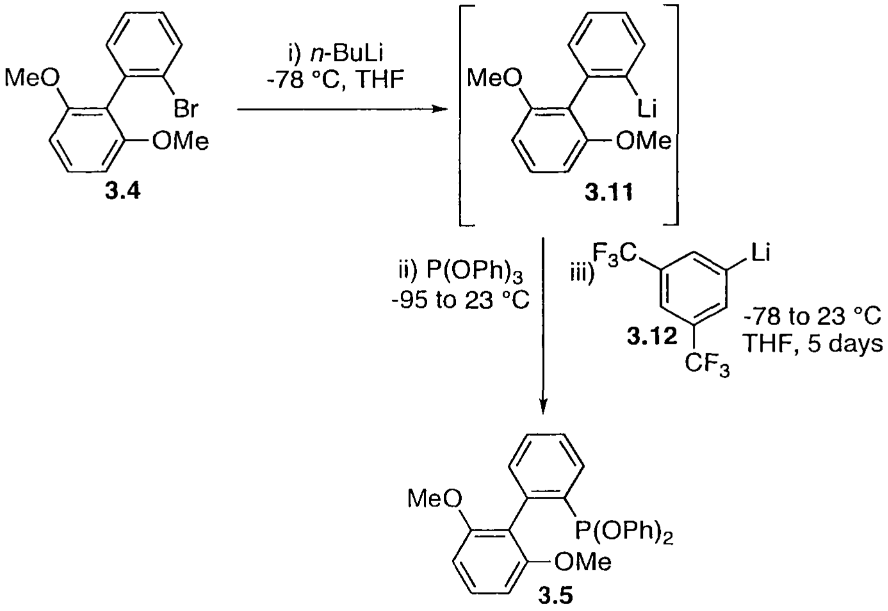
Some limitations are associated to the synthetic approach. For example too much steric encumbrance on the biaryl portion of the ligand is not tolerated. For example, biaryl aryllithium bearing *iso*-propyl substituents **3.7** was unreactive toward triphenyl phosphite (Scheme 3.6).



Scheme 3.6 – Formation of Byproduct 3.8 and 3.9

Indeed, by reacting biaryllithium **3.7**, generated from lithium-halogen exchange with biaryl iodide **3.6**, with triphenylphosphite, followed by addition of *p*-trifluoromethylphenyllithium **3.8**, no desired product was obtained. The dehalogenated biaryl **3.9** and tris(trifluoromethyl)phenylphosphine **3.10** were the only two reaction products isolated.

Moreover, the exceedingly electron-poor bis(trifluoromethyl)phenyllithium **3.12** also showed to be reluctant to undergo reaction with phosphonite **3.5** due to poor nucluophilicity (Scheme 3.7).



Scheme 3.7 – Lack of Reactivity of Aryllithium 3.12

For example, after generating biaryllithium **3.11**, it was reacted with thiphenylphosphite to give phosphonite **3.5**, which was followed by addition of aryllithium **3.12**. Even after a reaction time of 5 days, the sole product isolated was phosphonite **3.5**, indicating that the aryllithium **3.12** was not nucleophilic enough to undergo a substitution reaction on the phosphonite. Attempts to perform the reaction at higher temperature up to reflux temperature led to decomposition of the reaction products and the desired product could not be isolated.

3.3. Kinetic Analyses With Ligands 3.1, 3.2 and 3.3

Ligands **3.1**, **3.2** and **3.3** were first tested for the direct arylation of the electron-deficient pentafluorobenzene with 4-bromotoluene under standard conditions established in our group in 2006 and the kinetics were compared to those obtained with S-Phos as the ligand (Figure 3.3).[26b]

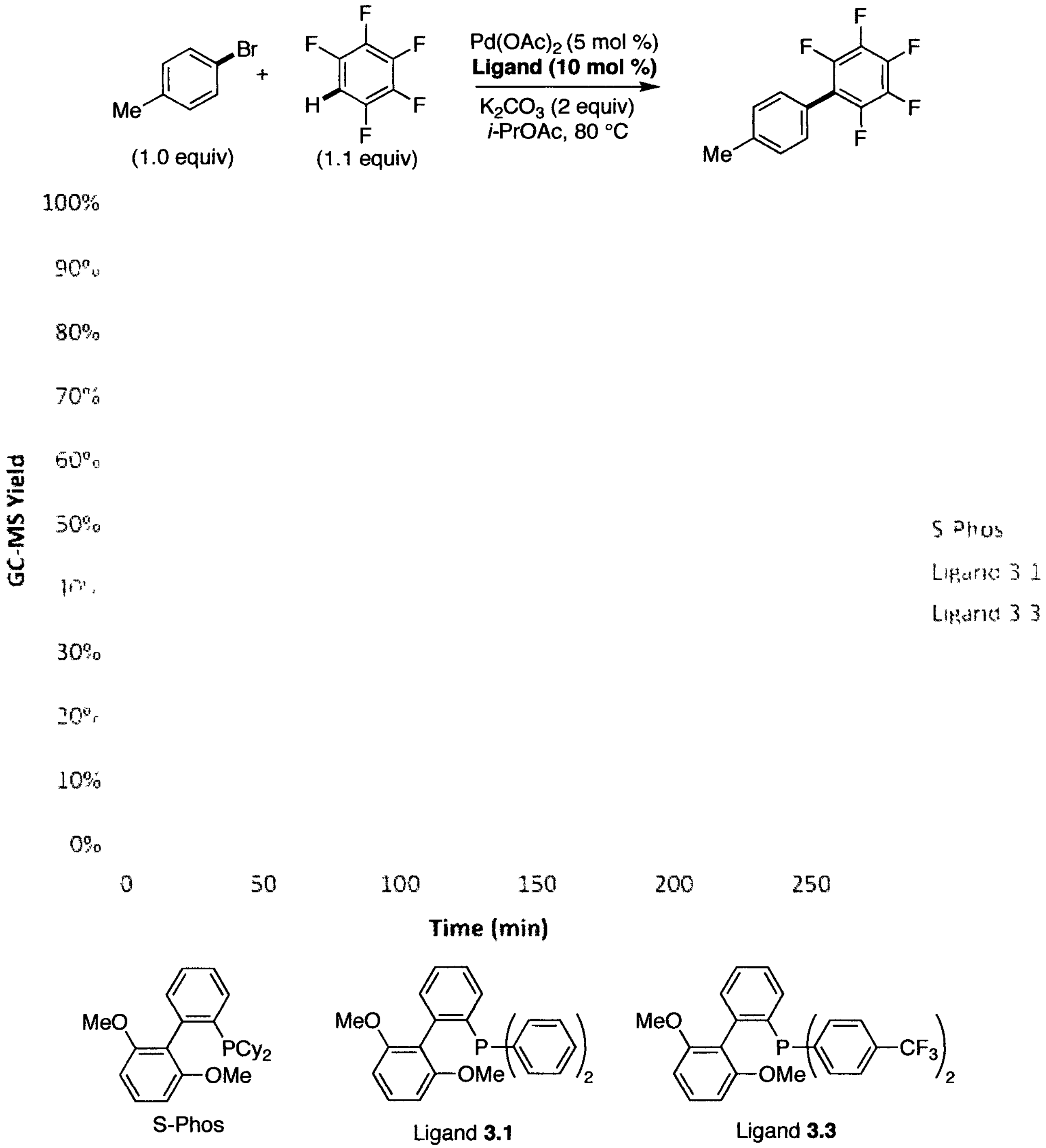
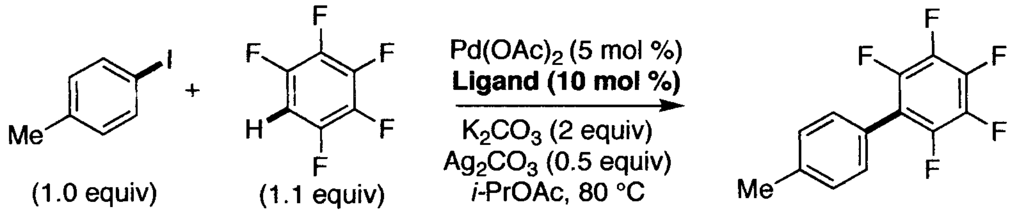
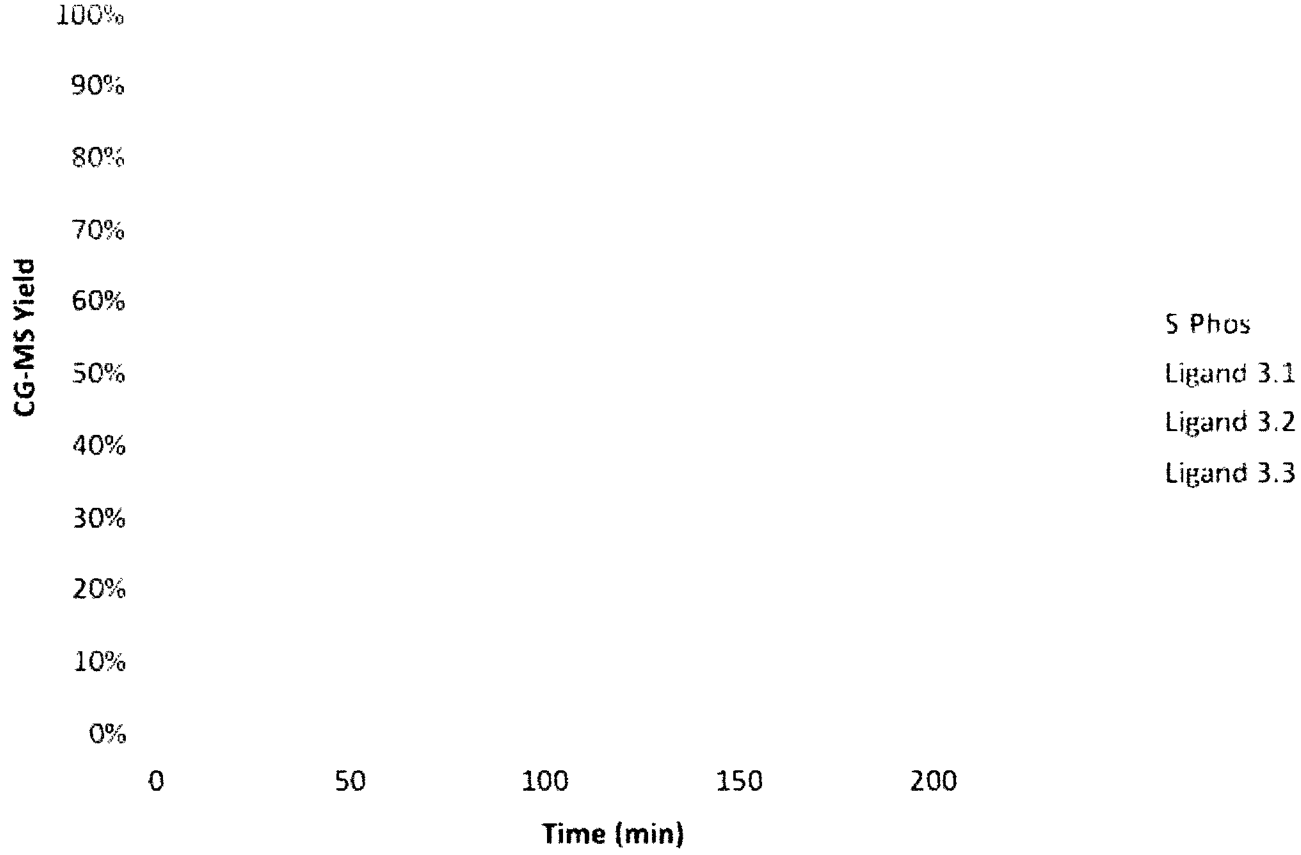


Figure 3.3 – Kinetics With Pentafluorobenzene and 4-Bromotoluene

From Figure 3.3, we can observe that electron-rich S-Phos provides the best results, giving complete conversion in approximately 3 hours. These reaction profiles reveal that more electron-deficient ligands indeed decelerate the reaction. It is plausible that this diminution of the reaction rate arises from a slower oxidative insertion into the carbon-bromine bond in the presence of more electron-deficient ligands.

In order to circumvent the difficulty for palladium bearing electron-deficient ligands to undergo oxidative insertion, the same kinetics were measured with 4-iodotoluene instead of 4-bromotoluene (Figure 3.4). In this case, a silver carbonate additive was also added in order to sequester the iodide anion. These types of silver additives have shown to overcome an inhibitory effect of iodide on direct arylation that had been previously observed in our group.[60]





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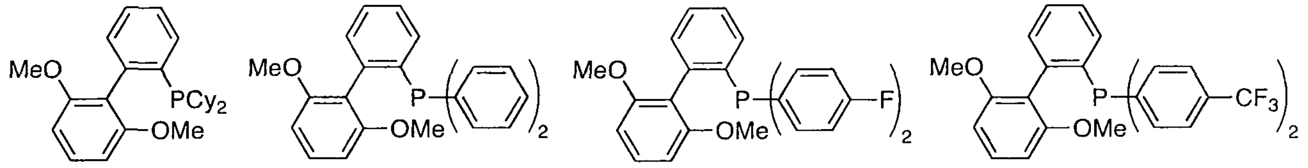
[60] Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581.



S-Phos Ligand **3.1** Ligand **3.2** Ligand **3.3**

Figure 3.4 – Kinetics With Pentafluorobenzene and 4-Iodotoluene

The outcome of these kinetics with 4-iodotoluene is in stark contrast with the results obtained with 4-bromotoluene. The more electron-rich S-Phos ligand now gives rise to the slowest reaction rate. The fastest conversion to the biaryl product occurs with the use of ligand **3.1**, bearing two phenyl groups on the phosphine. It is also notable to mention that the addition of electron-withdrawing groups on the two phenyl substituent still slows down the reaction. Indeed, although ligands **3.2** and **3.3**, bearing a fluoro and a trifluoromethyl substituent are still better than S-Phos, they provide slower converstion than ligand **3.1**. It is presumed that ligand **3.1** pocesses the proper electron-withdrawing character to allow C-H bond cleavage at an appreciable rate whilst it is not electron-deficient enough to affect the rate of oxidative insertion.

In order to further probe the effect of the electronic properties of the ligand on the rate of C-H bond cleavage, the same ligands were then tested for the direct arylation of the electron-rich heterocyclic benzothiophene using standard conditions for the direct arylation of a broad variety of heterocycles.[23a] Preliminary results with 4-bromotoluene were again unsatisfactory due to presumed slow oxidative insertion into the carbon-bromide bond (Figure 3.5).

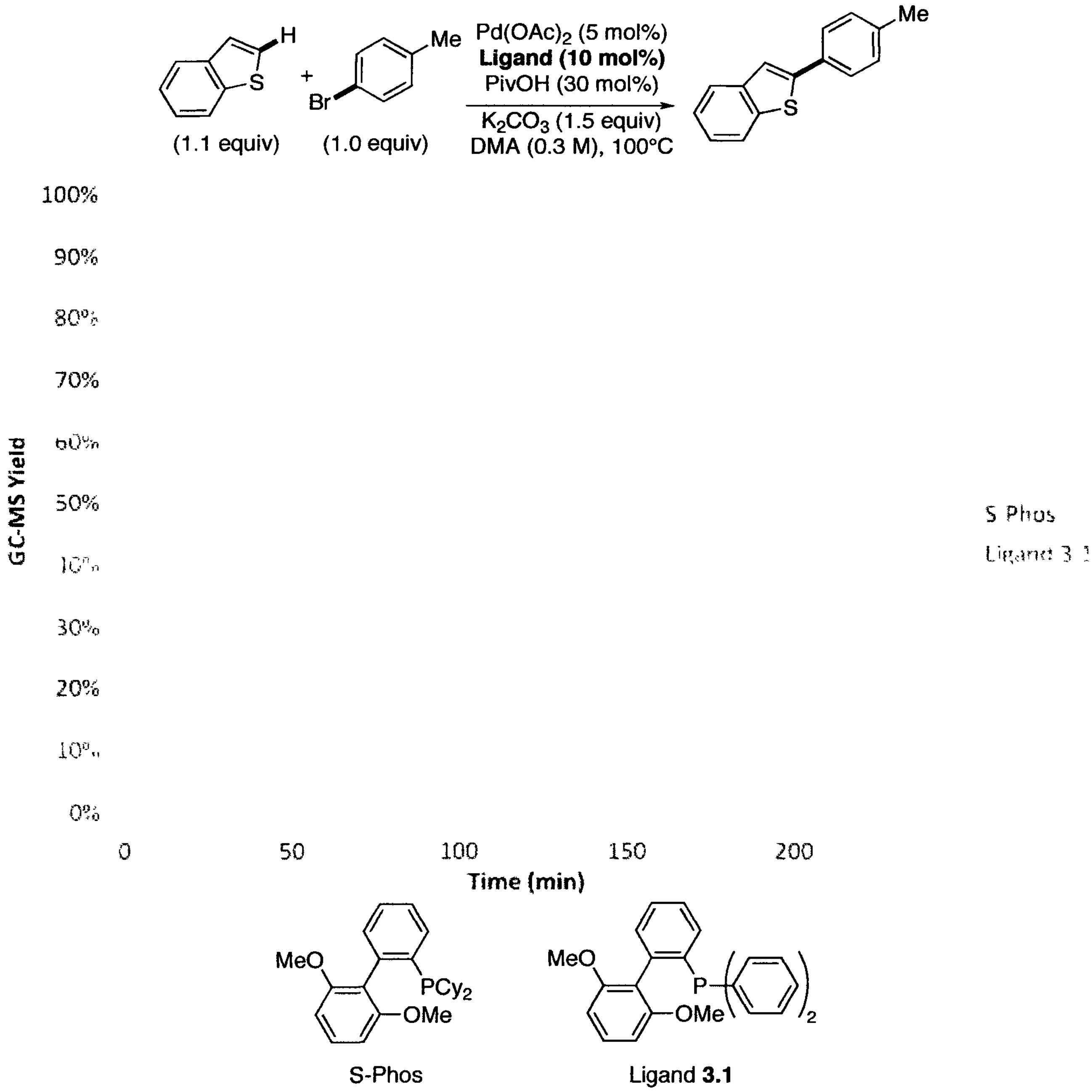


Figure 3.5 – Kinetics With Benzothiophene and 4-Bromotoluene

As shown on Figure 3.5, S-Phos provided significantly more promising results than ligand **3.1**. For this experiment, other more electron-deficient ligands were not tried due to the apparent detrimental effect of these types of ligands on the rate of the reaction.

Interestingly, provided that a silver carbonate additive was added to the reaction, the use of aryl iodides, which are typically incompatible in direct arylation of heterocycles due to potential catalyst poisoning, led to very promising results (Figure 3.6). Furthermore, in the previously reported broadly applicable conditions for direct arylation, aryl iodides remained unreactive even in the presence of silver additives.[23a]

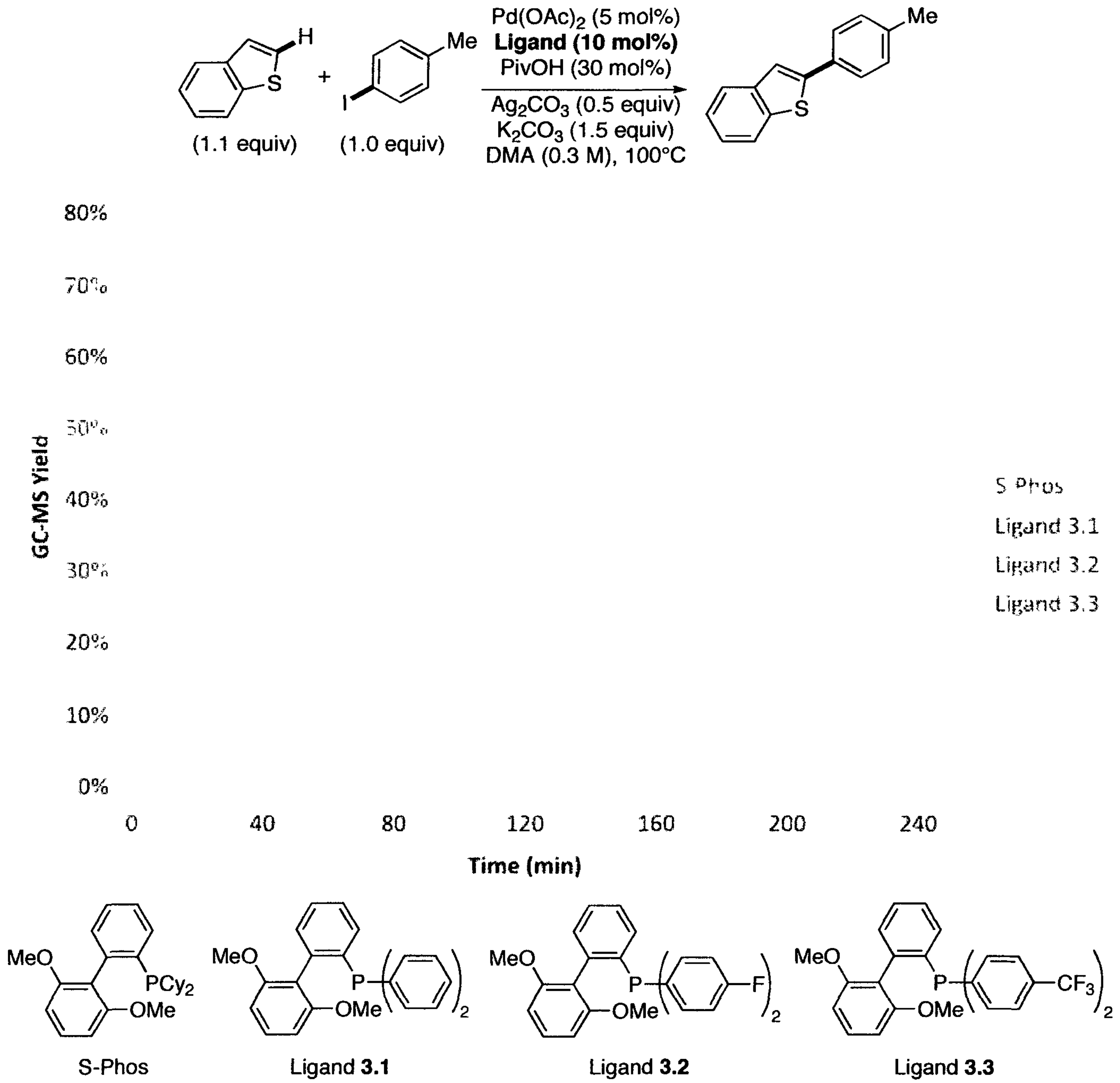


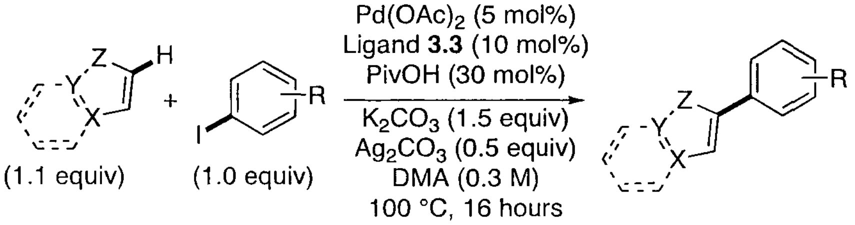
Figure 3.6 – Kinetics With Benzothiophene and 4-Iodootoluene

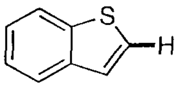
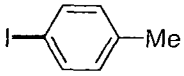
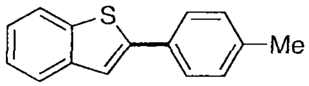
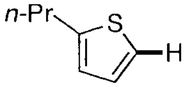
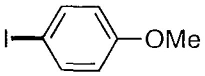
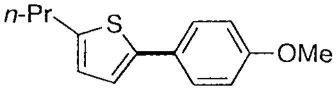
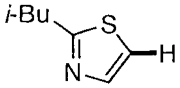
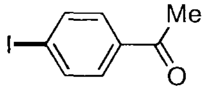
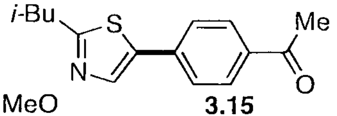
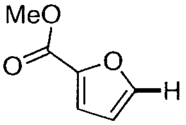
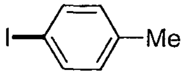
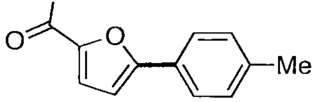
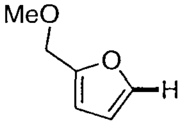
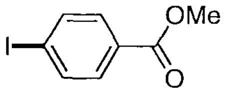
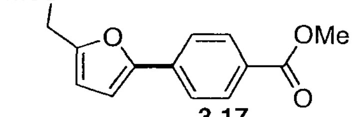
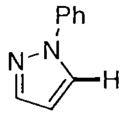
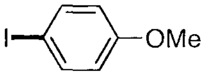
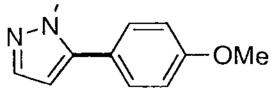
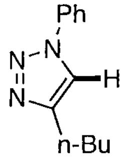
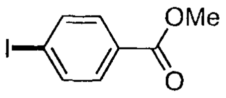
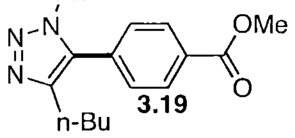
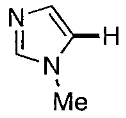
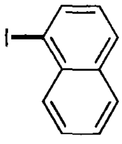
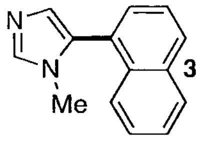
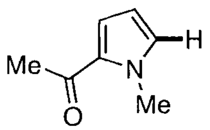
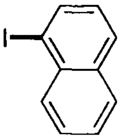
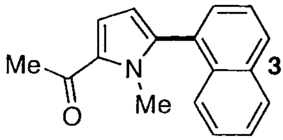
For example, the use of the electron-rich S-Phos ligand led to very low conversion after 4 hours. In contrast, ligand **3.1**, and ligand **3.2** gave rise to substantially more promising results, providing heterobiaryl product in 33% and 39% yield, respectively. Ultimately, the more electron-deficient ligand **3.3**, bearing two *p*-trifluoromethylphenyl substituents, led to a remarkable acceleration of the reaction rate, affording the desired product in 75% GC yield after 4 hours and was therefore selected as an optimal ligand for the direct arylation of heterocycles.

3.4. Applicability of Ligand 3.3 in Direct Arylation

Due to the very promising results obtained with ligand **3.3** for the direct arylation of electron-rich heterocycles, allowing the reaction to proceed smoothly and effectively with aryl iodides for the first time, the applicability of this ligand was investigated with a broad variety of substrates. Illustrative examples of the scope of the transformation are presented in Table 3.1.

Table 3.1. Scope of the Direct Arylation of Heterocycles With Ligand **3.3**



entry	heterocycle	aryl iodide	product	isolated yield
1			 **3.13**	78%
2			 **3.14**	89%
3			 **3.15**	84%
4			 **3.16**	46%
5			 **3.17**	43%
6			 **3.18**	72%
7			 **3.19**	93%
8			 **3.20**	52%
9			 **3.21**	43%

The transformation proceeds smoothly and selectively with various sulfur, oxygen and nitrogen-containing heterocycles. For example, benzothiophene (Table 3.1, entry 1), 2-propylthiophene (entry 2) and 2-*iso*-butylthiazole (entry 3) led to the coupling products using electron-rich and electron-poor aryl iodides in yields ranging from 78% to 89%. Furan heterocycles bearing electron-withdrawing (entry 4) and slightly electron-donating groups (entry 5) are also compatible providing heterobiaryl products, albeit in modest yields. Moreover, several nitrogen-containing heterocycles such as pyrazole (entry 6), triazole (entry 7), imidazole (entry 8), and pyrrole (entry 9) proved to be efficient coupling partners, providing the desired product in a regioselective fashion in yields up to 93%. It is noteworthy to mention that iodides bearing electron-donating (entries 2 and 6) and electron-withdrawing substituents (entry 3, 5 and 7) as well as sterically encumbered iodides (entries 8 and 9) are tolerated with these heterocycles.

Other heterocycles that were tested with the use of the electron-deficient ligand **3.3** showed to be unreactive, providing no product or only traces of the desired material (Figure 3.7).

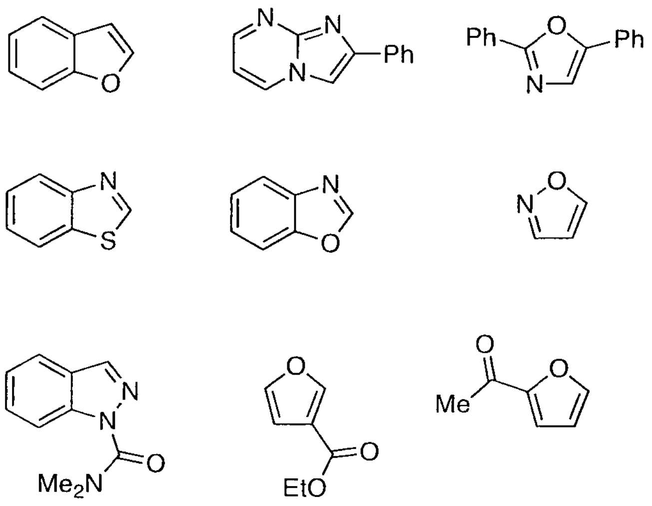
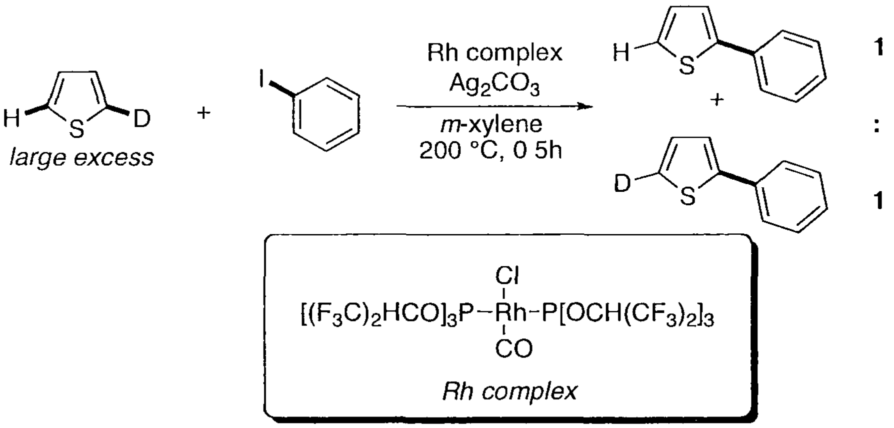


Figure 3.7 – Incompatible Heterocycles

For example, heterocycles such as benzofuran, imidazopyrimidine, oxazole, benzothiazole, benzoxazole, isoxazole and indazole did not give rise to any product formation under the reaction conditions. Also, furan heterocycles bearing an ethyl ester substituent at the C3 position or a methyl ketone at the C2 position led to very low conversions and mixtures of regioisomers were observed.

3.4. Mechanistic Studies for the Direct Arylation of Benzothiophene With Ligand 3.3

In a previous report on the effect of electron-deficient ligands, Itami and coworkers described a trend similar to ours for the Rh(I)-catalyzed arylation of thiophene wherein more electron-deficient ligands better facilitated C-H bond cleavage[61] They proposed that π-accepting phosptite ligands render the rhodium center more electron-deficient, thereby facilitating electrophilic-metalation This was supported by a kinetic isotope effect (k_H/k_D) of 1 measured in a one-pot competition, indicating a kinetically insignificant C-H bond cleavage step (Scheme 3 8)



Scheme 3.8 – Primary KIE With π-Accepting Phosptite Ligands (Itami)

To better assess the mechanism of this transformation in the presence of our electron-deficient palladium catalyst, a kinetic isotope effect was measured by comparing the initial rate of C-H bond funtionalization of benzothiophene *vs* benzothiophene-*d* in side-by-side experiments (Scheme 3 9)[62]

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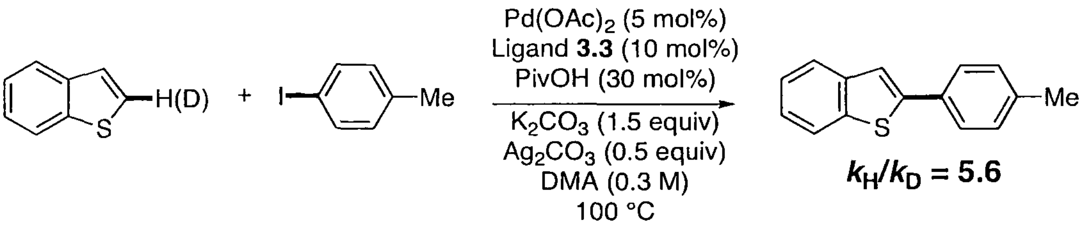
[61] For a mechanistic analysis, see ref 56b

[62] For experimental details concerting the measurement and comparison of initial rates, see supporting information



Scheme 3.9 – Primary KIE With Electron-Deficient Ligand 3.3 by Initial Rate Comparison

A pronounced primary KIE of 5.6 was obtained, thereby implicating C-H bond cleavage at the rate-determining step. The magnitude of the KIE is in line with previously observed KIEs of 3.08 and 5.59 for intermolecular direct arylation reactions with polyfluoroarenes[26a] and benzene,[24] respectively, both known to proceed *via* the CMD mechanism for C-H bond cleavage. It is also consistent with large KIEs reported by Echavarren and Maseras with the intramolecular variant of the direct arylation reaction.[25b]

To provide additional evidence for a CMD pathway, a one-pot competition experiment performed with an equimolar mixture of 2-methylthiophene and 2-chlorothiophene was conducted.[63] This experiment demonstrated that arylation of the more electron-deficient 2-chlorothiophene was favored over the more nucleophilic 2-methylthiophene in a 3.9:1 ratio (Scheme 3.10).

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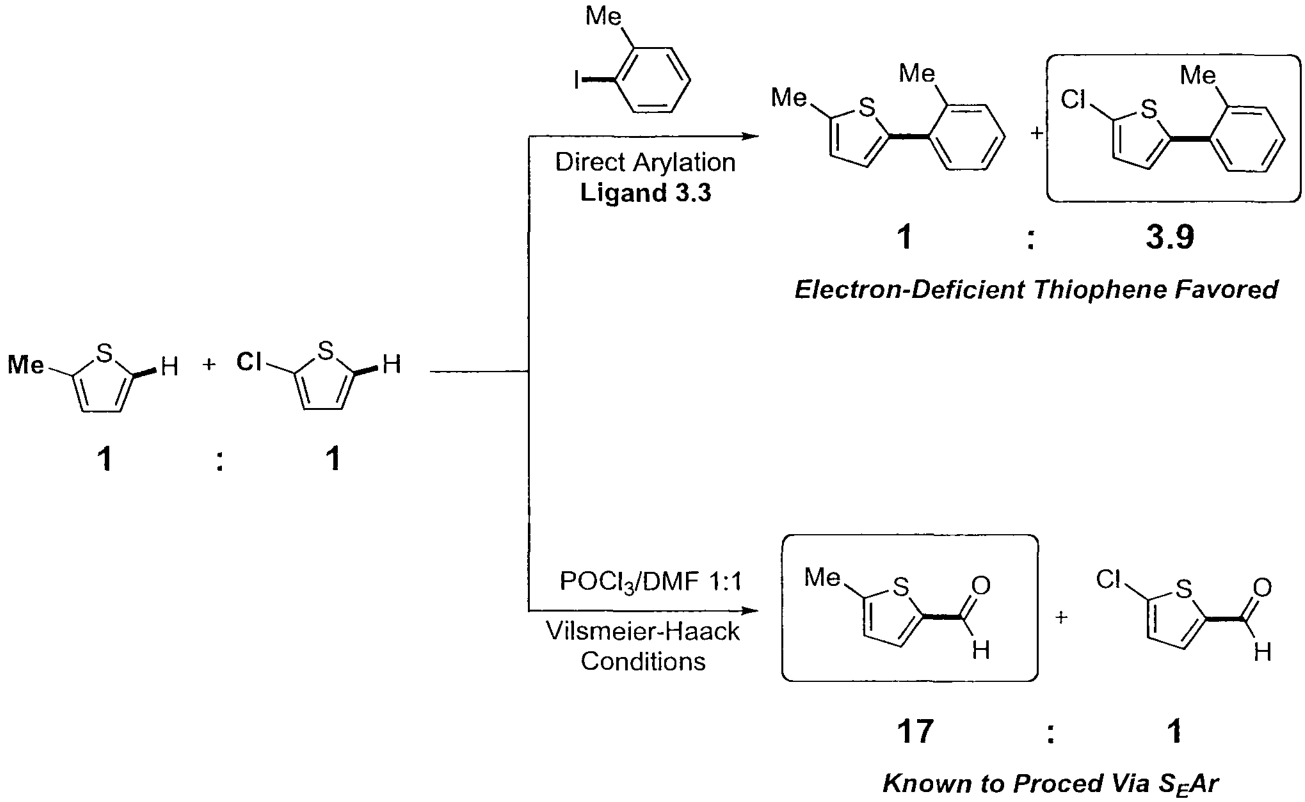
[63] For experimental details concerning the competition experiment and the measurement of the ratio of products, see supporting information.



Scheme 3.9 – Competition Experiment Between 2-Methylthiophene and 2-Chlorothiophene

This outcome is in agreement with previous results for a reaction demonstrated to proceed through a CMD mechanism for which arylation of the less nucleophilic 2-chlorothiophene was favored in an 11:1 ratio.[48] In contrast, Vilsmeier-Haack formylation competition (which is know to proceed *via* an S_EAr mechanism)[64] with the same system reacts preferentially with the more nucleophilic 2-methylthiophene in a 17:1 ratio.[48]

This experimental evidence is in agreement with a CMD mechanism where metalation of the heterocycle and C-H bond cleavage occur simultaneously at the turnover-limiting step of the reaction. It also indicates that electrophilic aromatic palladation is unlikely to occur even in the presence of an electrophilic catalyst system. It is plausible that a more electrophilic palladium center might facilitate interaction with the heterocycle by promoting binding through π orbitals between the arene and the metal.[65] It was also demonstrated by DFT calculations that a better interaction between

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[64] Vilsmeier, A.; Haack, A. *Ber. Dtsch. Chem. Ges.* **1927**, *60*, 119.

[65] Biswas, B.; Sugimoto, M.; Sakaki, S. *Organometallics* **2000**, *19*, 3895.

the palladium center and the heterocycle prior to the formation of the CMD transition state results in an overall lower energetic barrier for the reaction to proceed.[66] Additionally, a more facile displacement of a labile electron-deficient ligand from a palladium center bearing two ligands might liberate a vacant coordination site on the metal for arene binding.

In summary, we have developed a new electron-deficient fluoroarylphosphine ligand that promotes C-H bond functionalization of a broad variety of heterocycles. The demonstrated ability of these types of ligands to facilitate the C-H bond cleavage step of this process has been assessed and experimental evidence suggests a concerted metalation-deprotonation mechanism in the presence of an electrophilic metal center. These results should prompt interest amongst the scientific community in pursing development of electron-deficient ligands in an ever-widening range of transition-metal catalyzed transformations.

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[66] For details concerning the DFT calculations, see ref. 33a.

CHAPTER 4 : DOMINO PALLADIUM-CATALYZED HECK-INTERMOLECULAR DIRECT ARYLATION REACTIONS[67]

4.1. Introduction

Although the use of aryl halide and organometallic coupling partners is the norm in metal-catalyzed cross-coupling reactions,[12] more efficient processes that can replace the aryl organometallic with a simple arene are emerging as valuable alternatives.[13] The majority of studies done in the past decade have focused on the formation of C*sp*^{2}-C*sp*^{2} bonds.[13] Recently, however, important steps have been made dealing with the formation of C*sp*^{3}-C*sp*^{2} (alkane-arene) bonds. Building on the first reports that validated this reactivity in intramolecular processes,[68] new intermolecular reactions have been realized with aliphatic and benzylic halides with Pd(0) catalysts[69] as well as with aliphatic halides and Pd(II)[70] or Ru(II) catalysts.[71]

For example, our group recently disclosed a broadly applicable Pd(0)-catalyzed heteroarene benzylation reaction wherein a unique focus was put on the most challenging heterocyclic classes under traditional benzylation techniques such as sulfur-containing heterocycles (Scheme 4.1).[69b]

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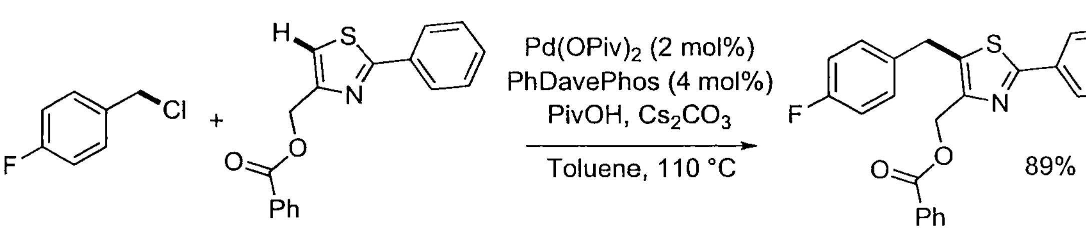
[67] A significant portion of the work described in this chapter has been published in the form of a communication, see: René, O.; Lapointe, D.; Fagnou, K. *Org. Lett.* **2009**, *11*, 4560.

[68] (a) Song, Z. Z.; Wong, H. N. C. *J. Org. Chem.* **1994**, *59*, 33. (b) Hwang, S. J.; Cho, S. H.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 16158.

[69] (a) Verrier, C.; Hoarau, C.; Marsais, F. *Org. Biomol. Chem.* **2009**, *7*, 647. (b) Lapointe, D.; Fagnou, K. *Org. Lett.* **2009**, *11*, 4160.

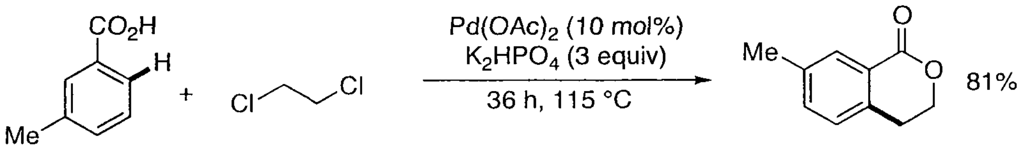
[70] Zhang, Y.-H.; Shi, B.-F.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2009**, *48*, 6097.

[71] Ackermann, L.; Novák, P.; Vicente, R.; Hofmann, N. *Angew. Chem. Int. Ed.* **2009**, *48*, 6045.

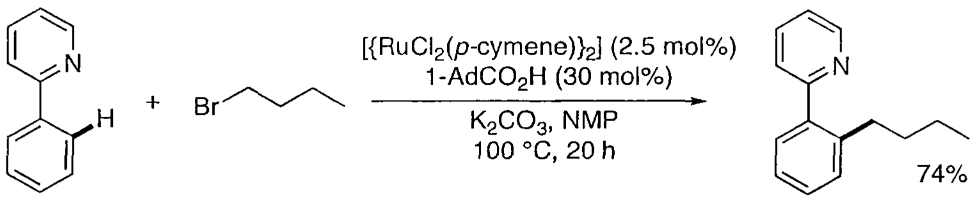


Scheme 4.1 – Direct Benzylation of Heterocyclic Compounds (Fagnou)

Aditionnally, Yu and Ackermann recently reported complementary conditions for the direct alkylation of arenes under Pd(II) and Ru(II) catalysis (Scheme 4.2). Taking advantage of the κ^2 coordination of a cation with a carboxylate group,[72] Yu showed that the Pd(II) center can chelate in the proximity of the ortho C-H bond of benzoic acid enabling a geometry that is essential for facile C-H bond cleavage.[70] On the other hand, Ackermann capitalized on the ability of the lewis basic pyridine to *ortho*-direct ruthenation on the adjacent arene, which allowed the development of a C-H bond functionalization reaction featuring the conversion of primary and secondary alkyl halides into the corresponding alkylated arene products.[71]



Yu's Pd(II)-Catalyzed ortho-Directed Alkylation of Benzoic Acids



Ackermann's Ru(II)-Catalyzed ortho-Directed Alkylation of Arylpyridines

Scheme 4.2 – Complementary Conditions for the Direct Alkylation of Arenes (Yu and Ackermann)

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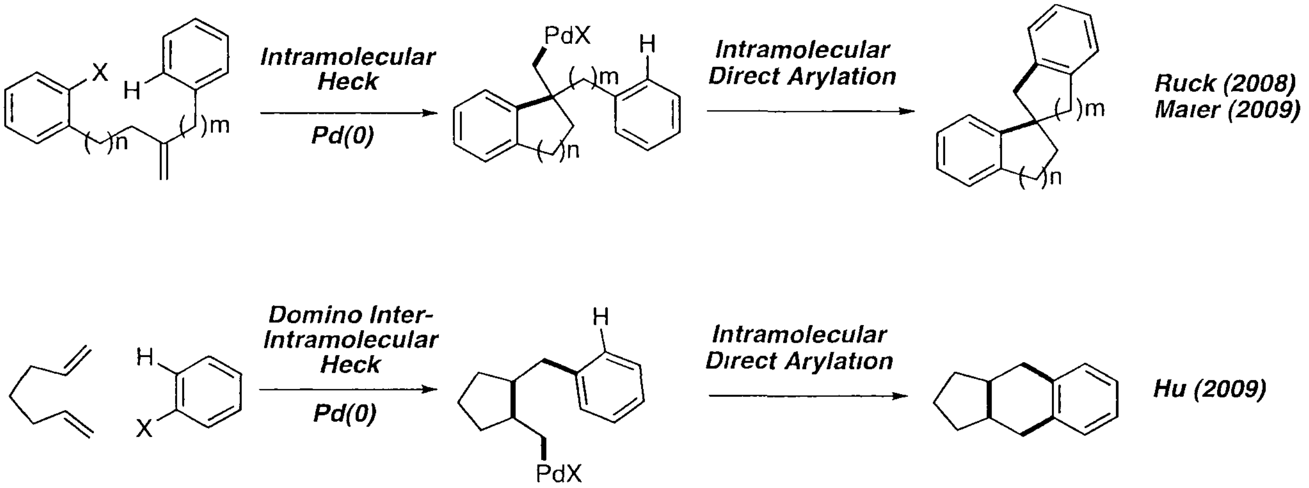
[72] For detailed discussion and evidence for cation-promoted Pd insertion into C-H bonds see: Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 14082.

An alternative to the use of aliphatic halides as a means of accessing the alkylpalladium(II) intermediates is to employ a Heck coupling of an aryl halide with an alkene in a domino sequence with a direct arylation step[73] This strategy has been successfully employed in the preparation of complex organic molecules using traditional techniques,[74] and the first examples of successful Heck-intramolecular direct arylation involving alkyl palladium(II) intermediates have recently been described (Scheme 4 3)[75]



Scheme 4.2 – First Examples of Domino Reactions Featuring an Intramolecular Direct Arylation Step

For example, the group of Ruck first reported an efficient preparation of spiro-fused indane-oxindoles by performing an intramolecular Heck-type carbopalladation to form an alkylpalladium intermediate, which underwent a subsequent intramolecular C-H bond functionalization

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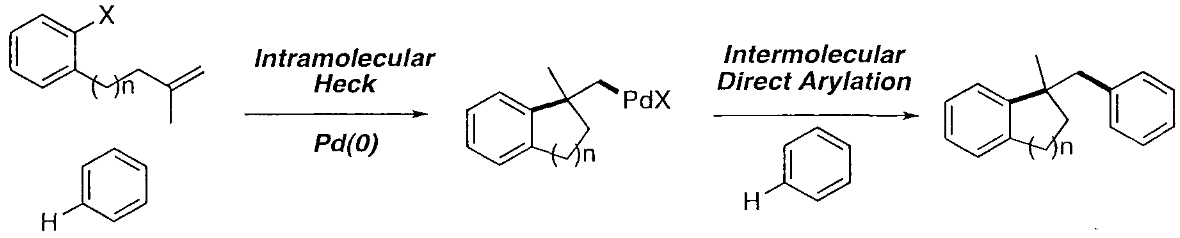
[73] For reviews on domino palladium catalyzed reactions, see (a) Patil, N T , Yamamoto, Y *Top Organomet Chem* **2006**, *19*, 91 (b) Balme, G , Bossharth, E , Monteiro, N *Eur J Org Chem* **2003**, *21*, 4101 (c) De Meijere, A , Von Zezschwitz, P , Brase, S *Acc Chem Res*, **2005**, *38*, 412 (d) Patil,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

[74] For selected examples, see (a) Grigg, R , Sridharan W , Zhang, J *Tetrahedron Lett* **1999**, *40*, 8227 (b) Grigg, R , Sansano, J M , Santhakumar, V , Sridharan, V , Thangavelanthum, R , Thornton-Pett, M , Wilson, D *Tetrahedron* **1997**, *53*, 34, 11803 (c) Sukanthini, S , Wilson, D , Redpath, J *Tetrahedron* **2000**, *38*, 7525 (d) Lee, C -W , Oh, K S , Kim, K S , Ahn, K H *Org Lett* **2000**, *2*, 1213 (e) Arthuis, M , Pontikis, R , Florent, J -C *Tetrahedron Lett* **2007**, *48*, 6397 (f) Ishikura, M , Takahashi, N , Yamada, K , Yanada, R *Tetrahedron*, **2006**, *62*, 11580

[75] (a) Ruck, R T , Huffman, M A , Kim, M M , Shevlin, M , Kandur, W V , Davies, I W *Angew Chem Int Ed* **2008**, *47*, 4711 (b) Satyanarayana, G , Maichle-Mossmer, C , Maier, M E *Chem Commun* **2009**, *12*, 1571 (c) Hu, Y , Yu, C , Ren, D , Hu, Q , Zhang, L , Cheng, D *Angew Chem Int Ed* **2009**, *48*, 5448 (d) For a slightly different variant of this process where the direct arylation occurs at the aryl halide fragment, see Beaudoin, M , Wolfe, J P *Org Lett* **2007**, *9*, 3073

step to provide the corresponding spiro cycles.[75a] Thereafter, Hu reported an efficient one-step synthesis of the benzocyclo[penta- to octa-]isoindole core using a novel domino cyclization method involving an intermolecular Heck-type carbopalladation and the subsequent regioselective intramolecular functionalization of an unactivated C-H bond.[75c]

To our knowledge, no reports have appeared where a challenging intermolecular direct arylation-terminating step has been used (Scheme 4.3).



Scheme 4.3 – Domino Heck-Intermolecular Direct Arylation

For this reaction class to function, the catalyst must undergo selective intermolecular direct arylation in the presence of unreacted alkene that may participate in a competitive intermolecular Heck-type addition to give unwanted by-products. By building on previous advances in catalyst design in palladium-catalyzed direct arylation, our hope was that intermolecular direct arylation at an alkylpalladium(II) intermediate may become a favored process.

In this chapter, we report the successful development of a domino palladium-catalyzed Heck-type cyclization followed by an intermolecular direct arylation step. We also describe several examples demonstrating that such reactivity is indeed possible, providing rapid access to highly functionalized heterocyclic compounds. These results build on past success and should further inspire confidence in the use of direct arylation techniques as a viable alternative to the use of stoichiometric organometallic reagents in an ever widening range of commonly employed palladium(0)-catalyzed organic transformations.

4.2. Synthesis of the Starting Alkenes

During the course of the investigation of the domino Heck-intermolecular direct arylation, alkenes **4.1** to **4.5** were synthesized and evaluated as coupling partners for the reaction (Figure 4.1).

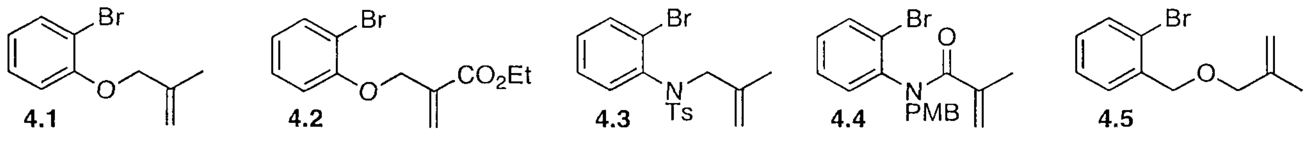
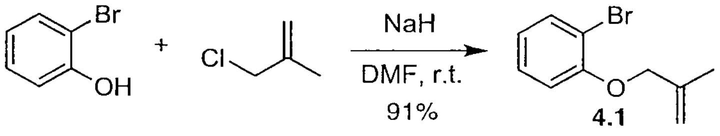


Figure 4.1 – Alkenes Investigated for the Domino Reaction

Alkene **4.1** was utilized as our standard coupling partner for the development and optimization of the reaction conditions. Starting from 2-bromophenol, deprotonation with sodium hydride in DMF, followed by addition of 3-chloro-2-methyl-1-propene afforded the Williamson ether synthesis product in 91% yield (Scheme 4.4). The use of DMF as the solvent appeared to be crucial as other solvents such as THF gave rise to no product formation due to the low availability of sparsely soluble phenoxide anion in other solvents.



Scheme 4.4 – Synthesis of Alkene 4.1

Conversion of the methyl substituent of alkene **4.1** to an ethyl ester generates coupling partner **4.2**. To perform such a transformation, the synthesis of allylic bromide **4.7** was first required according to a literature procedure (Scheme 4.5).[76] Following the decomposition of paraformaldehyde under acidic conditions, reaction of ethyl acrylate with *in situ* formed formaldehyde under Baylis-Hillman reaction conditions with catalytic DABCO led to allylic alcohol **4.6**. The alcohol was subsequently converted to bromide **4.7** under the action of phosphorus tribromide in 18% yield

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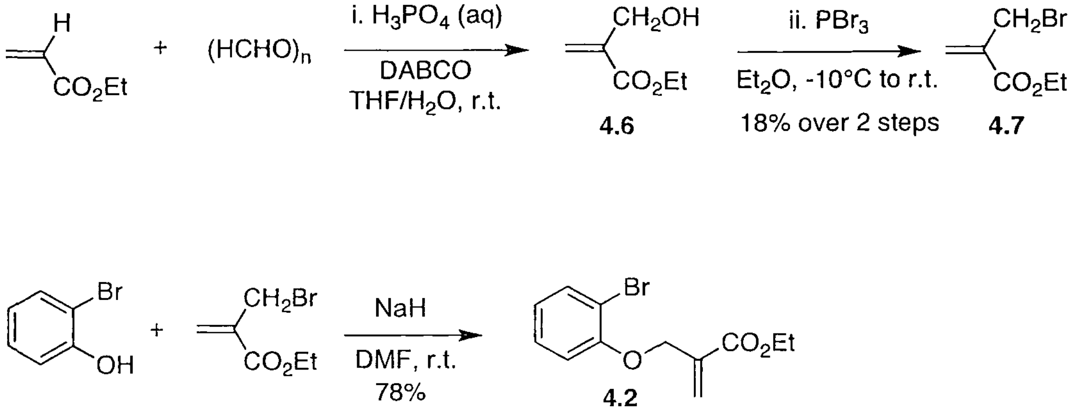
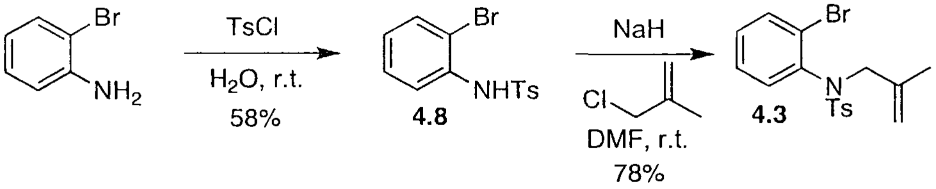
[76] Hediger, M. E. *Bioorg. Med. Chem.* **2004**, *12*, 4995.

over 2 steps. Bromide **4.7** was then reacted with 2-bromophenol under standard Williamson ether synthesis conditions to give alkene **4.2** in 78% yield.



Scheme 4.5 – Synthesis of Alkene 4.2

Aniline-derived alkene **4.3** was prepared in two steps starting from 2-bromoaniline (Scheme 4.6). Tosyl protection of the bromoaniline was first accomplished resorting to a literature procedure in which water was used as the solvent.[77] This interesting procedure allowed to preparation of the monotolysated aniline **4.8** in 58% yield. Other tosylation procedures using traditional organic solvents resulted in mainly ditosylated product and all attempts to remove one of the tosyl groups were unsuccessful. Thereafter, tosylaniline **4.8** was deprotonated with sodium hydride and underwent a nucleophilic substitution on 3-chloro-2-methyl-1-propene to generate alkene **4.3** in 78% yield.



Scheme 4.6 – Synthesis of Alkene 4.3

The PMB-protected anilide **4.4** was also showed be an efficient coupling partner during the course of the development of the domino reaction. By using a modified literature procedure (Scheme 4.6),[75a] 2-bromoaniline was reacted with 4-methoxybenzaldehyde under reductive amination

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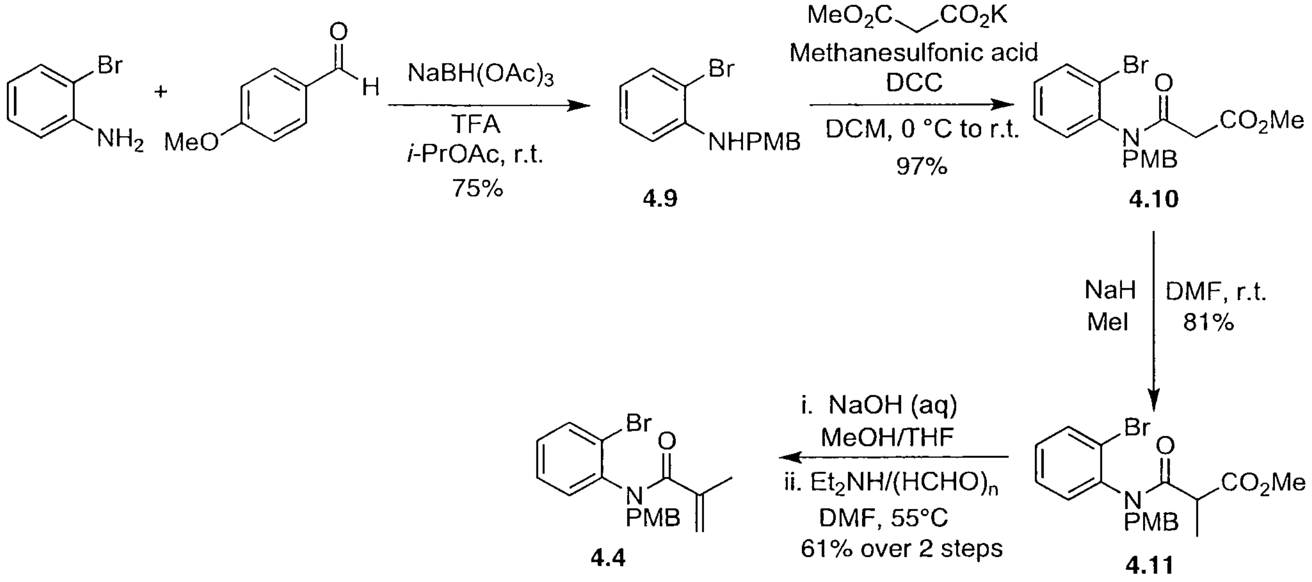
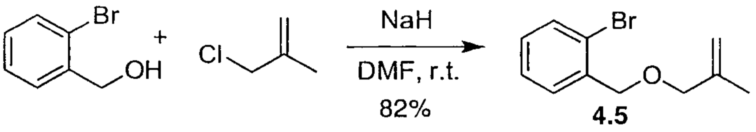
[77] Kamal, A.; Reddy, J. S.; Bharathi, E. V.; Dastagiri, D. *Tetrahedron Lett.* **2008**, 348.

conditions to give PMB-protected aniline **4.9** in 75% yield. Subsequent peptide coupling with malonic acid monomethyl ester in the presence of DCC led to the formation of anilide **4.10** in 97% yield, which then underwent a methylation event with iodomethane in 81% yield to give rise to methylated anilide **4.11**. Thereafter, decarboxylation of the methylester under basic conditions, followed by trapping of the intermediate enolate with formaldehyde allowed the formation of an unstable alcohol. Under the reaction conditions, dehydration of the intermediate alcohol afforded the desired alkene **4.4** in 62% over 2 steps.



Scheme 4.6 – Synthesis of Alkene 4.4

Homologation of phenyl ether **4.1** to a benzyl ether leads to alkene **4.5**, which was investigated for the formation of isochromans under the domino reaction conditions. To synthesize this alkene, 2-bromobenzylalcohol was reacted with 3-chloro-2-methyl-1-propene under Williamson ether synthesis conditions to give product **4.4** in 82% yield (Scheme 4.7).

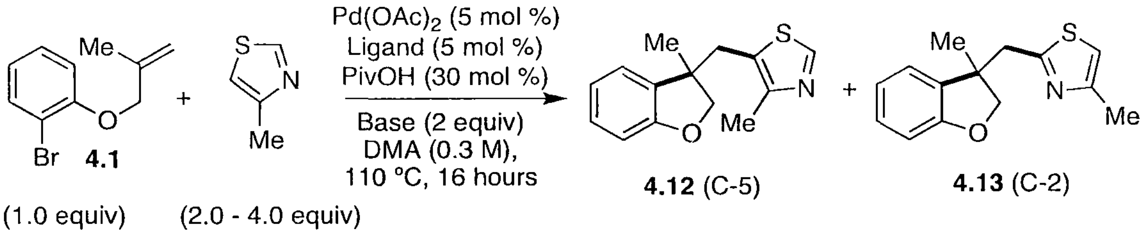


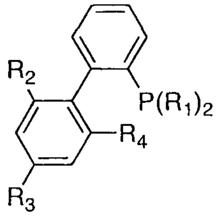
Scheme 4.7 – Synthesis of Alkene 4.5

4.3. Reaction Development and Optimization

Initial reaction development and optimization was performed with bromoarene **4.1** and 4-methylthiazole. The heterocyclic 4-methylthioazole was used as the second coupling partner because of its general reluctance to undergo direct arylation. Indeed, because of the steric encumbrance generated by the methyl substituent at the C4 position, rendering arylation at the C5 position more difficult, it was reasoned that the development of reaction conditions that would be effective for such an arduous coupling partner should enable the reaction to function with a broader variety of substrates. Two factors were found to exert a dramatic influence on both the yield and the regioselectivity of arylation: the base and the ligand (Table 4.1).

Table 4.1. Optimization of the Reaction with 4-Methylthiazole[a]





DavePhos: R_1 = Cy, $R_2 = R_3$ = H, R_4 = NMe_2
JohnPhos: R_1 = *t*-Bu, $R_2 = R_3 = R_4$ = H
X-Phos: R_1 Cy, $R_2 = R_3 = R_4$ = *i*-Pr

entry	base	ligand	equiv. HetAr	Yield [%] (**4.12**:**4.13**)[b]
1	Cs_2CO_3	DavePhos	2.0	2:2
2	K_3PO_4	DavePhos	2.0	4:1
3	K_2CO_3	DavePhos	2.0	21:9
4	K_2CO_3	JohnPhos	2.0	22:6
5	K_2CO_3	$P^tBu_3 HBF_4$	2.0	10:31
6	K_2CO_3	X-Phos	2.0	33:4
7	K_2CO_3	X-Phos	4.0	57:5

a) Reaction conditions : Aryl bromide (1.0 equiv), Heterocycle (2 or 4 equiv), $Pd(OAc)_2$ (5 mol %), Ligand (5 mol %), PivOH (30 mol %), Base (2.0 equiv), DMA (0.3 M), 110 °C, 16 h. b) Determined by GC analysis relative to tetradecane as an internal standard.

For example, with DavePhos, the use of Cs_2CO_3 or K_3PO_4 as the base did not yield significant amounts of desired product (Table 4 1, entries 1-2) A noteworthy improvement was observed with K_2CO_3, giving rise to product **4.12** in 21% yield with low regioselectivity (entry 3) While the use of JohnPhos did not provide any notable change on the reaction outcome (entry 4), the use of tri-*tert*-butylphosphine gave an inversion in direct arylation regioselectivity at the thiazole, providing regioisomer **4.13** in 31% yield with a 3 1 regioisomeric ratio (entry 5) X-Phos, on the other hand, gave a slightly improved yield of 33%, but favoring the formation of regioisomer **4.12** in an 8 1 ratio (entry 6) We also found that by using 4 equivalents of the heterocyclic coupling partner,[78] the isolated yield of **4.12** could be further improved to 57% with an 11 1 regioselectivity (entry 7)

Pivalic acid, which has previously been shown to be a beneficial additive in palladium-catalyzed direct arylation[79] also results in increased yields and reproducibility in these reactions (Table 4 2)

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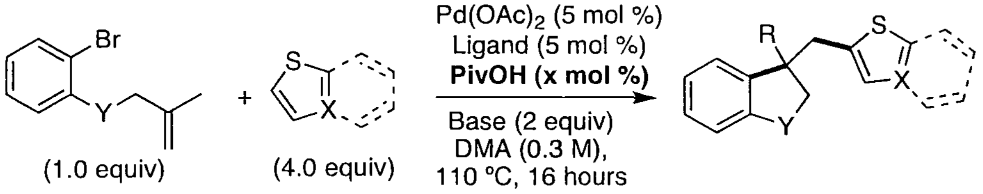
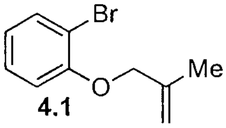
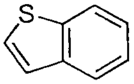
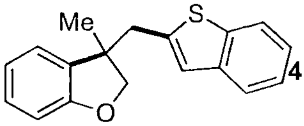
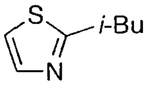
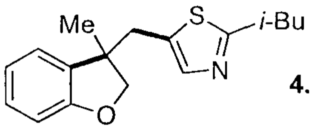
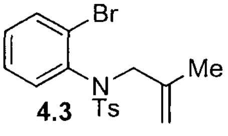
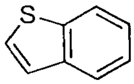
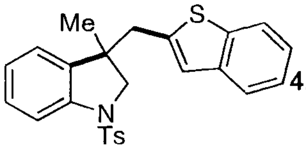
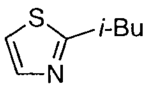
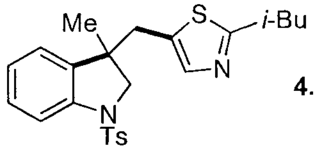
[78] The excess heterocycle remains unreacted and can be recovered in the purification process

[79] (a) Lafrance, M , Gorelsky, S I , Fagnou, K *J Am Chem Soc* **2007**, *129*, 14570 (b) Watanabe, T , Oishi, S , Fujii, N , Ohno, H *Org Lett* **2008**, *10*, 1759 See also ref 15k, 23a, 24, 32d, 55b and 57b (c) Ackermann has found that other carboxylic acid additives improve outcomes in Ru-catalyzed direct arylation, See ref 57a

Table 4.2. Effect of Pivalic Acid on the Yield of the Reaction



entry	aryl bromide	heterocycle	product	isolated yield (0 mol% PivOH)	isolated yield (30 mol% PivOH)
1	 **4.1**		 **4.14**	66%	76%
2	**4.1**		 **4.15**	50%	72%
3	 **4.3**		 **4.16**	40%	84%
4	**4.3**		 **4.17**	48%	75%

For example, dihydrobenzofurans **4.14** and **4.15** (Table 4.2, entries 1 and 2) are obtained in 76% and 72% yields in the presence of 30 mol % PivOH, while 66% and 50% yields, respectively, are observed in its absence. The beneficial effect of pivalic acid is even more marked in the preparation of indolines **4.16** and **4.17** where yields of 84% and 75% are reduced to 40% and 48% when the use of pivalic acid is omitted (entries 3 and 4).

The addition of pivalic acid has also shown a benificial effect on the rate of the reaction (Figure 4.2).

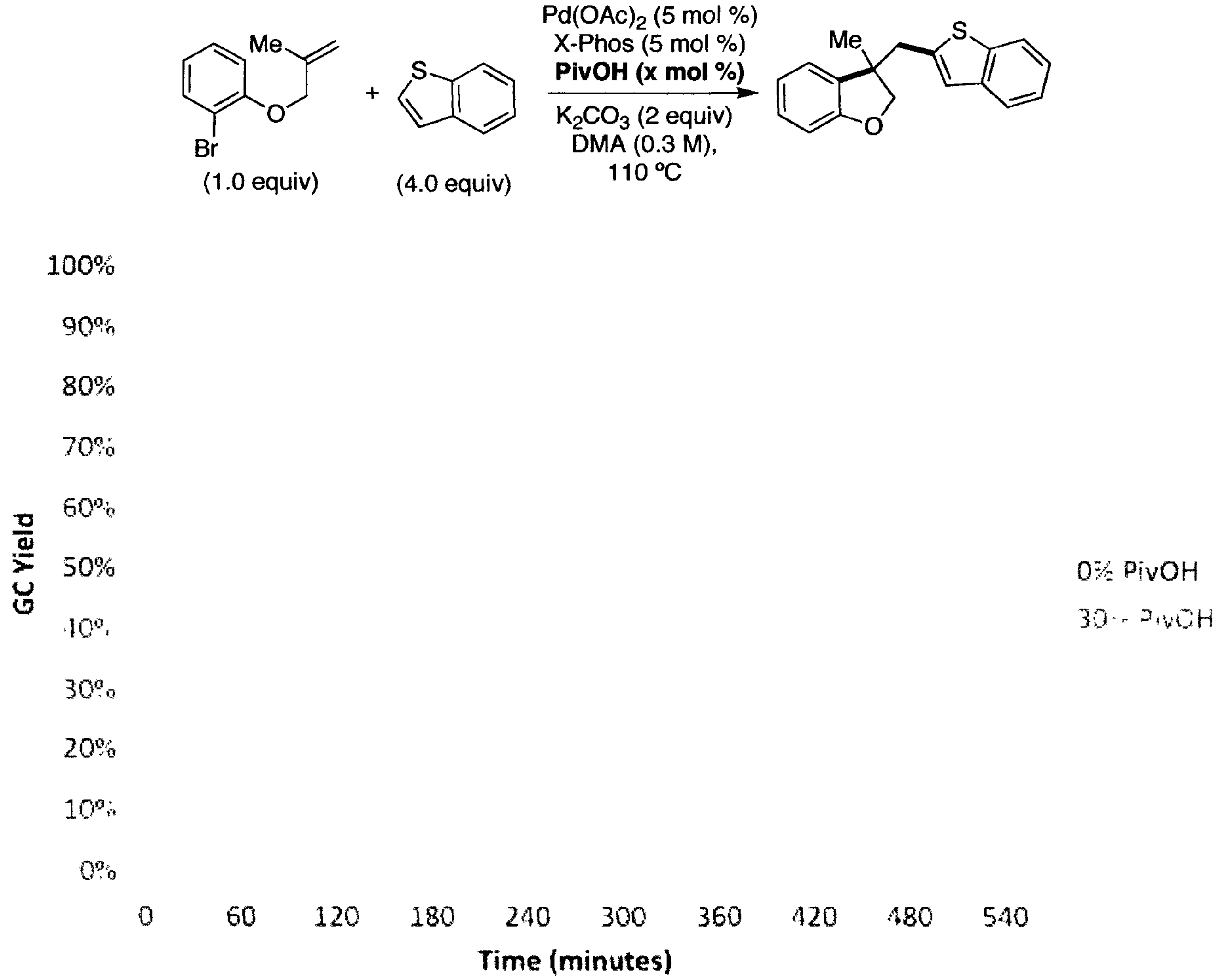


Figure 4.2 – Effect of Pivalic Acid on the Rate of the Reaction

For example, without the addition of PivOH, after 9 hours, the reaction reaches 64% conversion. At this point, the catalytic system is no longer operative and the reaction stops progressing. In contrast, in the presence of 30 mol % PivOH, a similar yield of 63% is obtained in only 3 hours. Although the catalytic system stops being operative after 5 hours in the presence of the additve, the yield of the reaction remain higher. At 9 hours, a 76% conversion is achieved with 30 mol % pivalic acid. While the addition of pivalic acid is not a crucial prerequisite for product formation, given the improved outcomes associated with its use, we adopted the addition of 30 mol % pivalic acid as a standard procedure in the evaluation of scope. The role of the potassium pivalate, generated *in situ* from

from the stoichiometric potassium carbonate base, is plausibly that of a ligand on the palladium metal that is involved in the transition state for heterocycle C-H bond cleavage [80]

In summary, the reaction development and optimization led to the following optimal conditions aryl bromide (1 0 equiv), heterocycle (4 0 equiv), Pd(OAc)$_2$ (5 mol%), X-Phos (5 mol%), K$_2$CO$_2$ (2 0 equiv), DMA (0 3 M), 110 °C, 16 hours

4.4. Applicability of the Transformation

Illustrative examples of the scope are shown in Tables 4 3 and 4 4 Using aryl bromides **4.1** and **4.2**, the reaction affords 3,3-disubstituted dihydrobenzofurans with a variety of sulfur-containing heterocycles in yields up to 92% (Table 4 3) The transformation is compatible with benzothiophene (Table 4 3, entry 1) alkyl-substituted thiazoles at the 2 or 4 positions (entries 2 and 3) and 2-propylthiophene (entry 4) producing the dihydrobenzofuran products in good yields ranging from 58% to 76% Chlorothiophene is also an excellent substrate resulting in a 92% yield (entry 5) Electron-withdrawing substituents on the thiophene such as a methyl ester and an aldehyde are also tolerated, albeit in more modest yields of 47% and 41%, respectively (entries 6-7) Entries 8 and 9 show that dihydrobenzofurans can also be substituted by an ester at the 3 position in yields ranging from 55% to 61% using 2-chlorothiophene and benzothiophene as the second coupling partner

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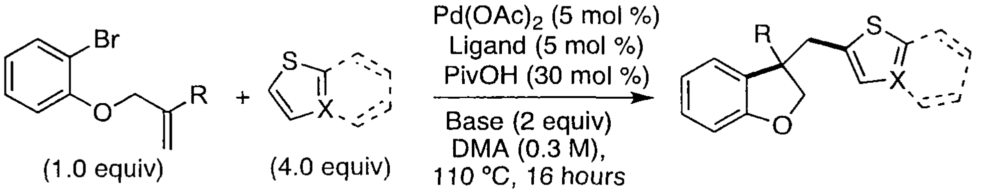
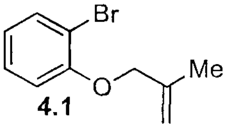
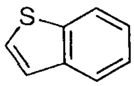
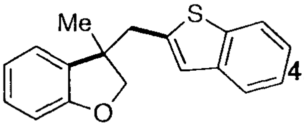
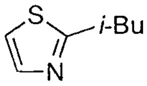
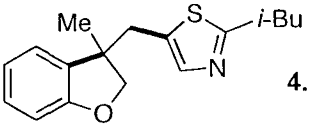
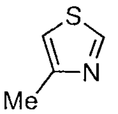
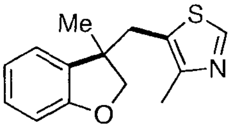
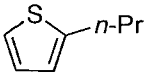
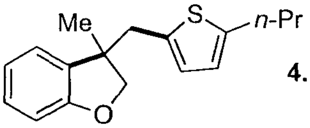
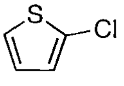
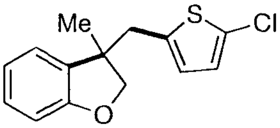
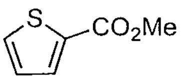
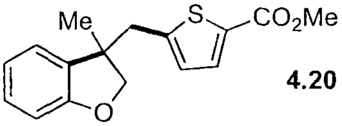
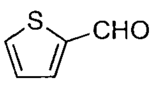
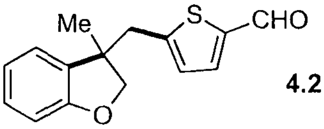
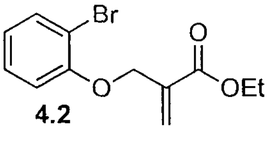
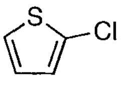
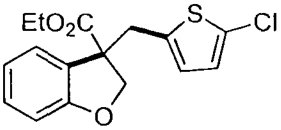
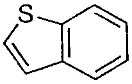
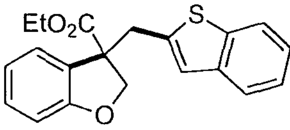
[80] For a discussion about the CMD mechanism, see ref 33

Table 4.3. Scope of the Reaction for the Formation of Dihydrobenzofurans



entry	aryl bromide	heterocycle	product	isolated yield
1	 **4.1**		 **4.14**	76%
2	**4.1**		 **4.15**	72%
3	**4.1**		 **4.12**	58%
4	**4.1**		 **4.18**	76%
5	**4.1**		 **4.19**	92%
6	**4.1**		 **4.20**	47%
7	**4.1**		 **4.21**	41%
8	 **4.2**		 **4.22**	55%
9	**4.2**		 **4.23**	61%

Indolines and oxindoles are prevalent in natural products and medicinal compounds,[81] therefore the establishment of methods enabling their rapid access remains an important goal We were pleased to find that the domino Heck-direct arylation reaction may be used to access a variety of 3,3-disubstituted indoline and oxindole compounds (Table 4 4) For the formation of indolines, the reaction is compatible with benzothiophene (Table 4 4, entry 1), alkyl-substituted thiazoles (entries 2 and 3) and 2-propylthiophene (entry 4) with yields ranging from 64% to 84%. 2-Chlorothiophene is an ideal coupling partner, providing the desired indoline product in 99% yield (entry 5) The formation of oxindoles is also possible with yields ranging from 47% with 2-propylthiophene (entry 6) to 82% with 2-chlorothiophene (entry 7) Benzothiophene and thiazole both gave product in 67% yield (entries 8 and 9)

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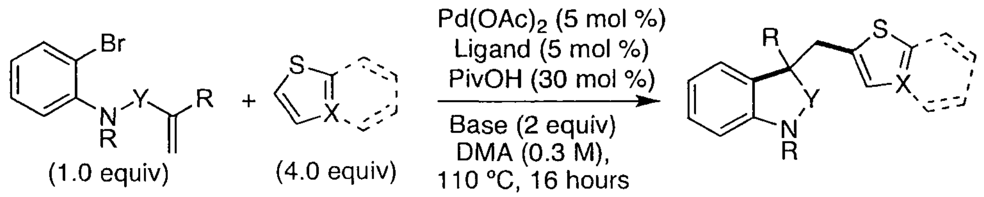
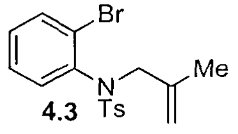
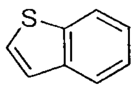
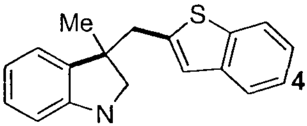
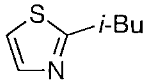
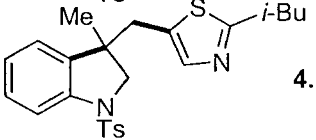
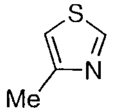
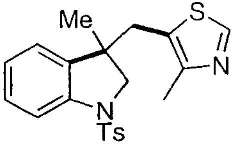
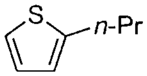
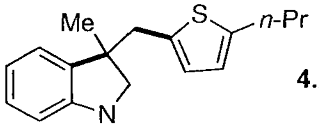
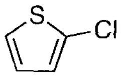
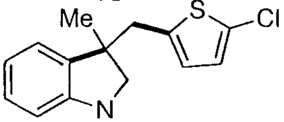
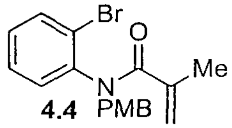
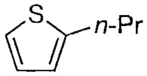
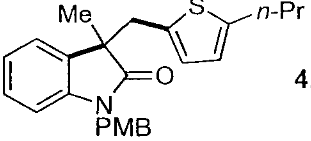
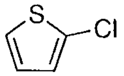
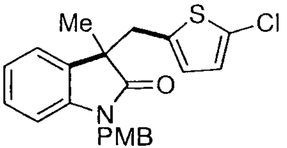
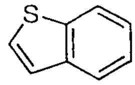
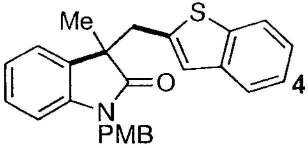
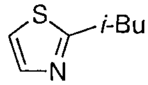
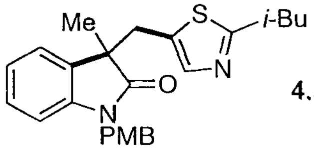
[81] For selected examples of 3,3-disubstituted indolines in natural products, see (a) Zhang, H , Boonsombat, J , Padwa, A *Org Lett* **2007**, *9*, 279 (b) Kobayashi, S , Ueda, T , Fukuyama, T *Synlett* **2000**, 883 (c) Yokoshima, S , Ueda, T , Kobayashi, S , Sato, A , Kuboyama, T , Tokuyama, H , Fukuyama, T *J Am Chem Soc* **2002**, *124*, 2137

For selected examples of 3,3-disubstituted oxindoles in natural products, see (a) Jossang, A , Jossang, P , Hadi, H A , Sevenet, T , Bodo, B *J Org Chem* **1991**, *56*, 6527 (b) Cui, C B , Kakeya, H , Osada, H *J Antibiot* **1996**, *49*, 832 (c) Pellegrini, C , Weber, M , Borschberg, H J *Helv Chim Acta* **1996**, *79*, 151

Table 4.4. Scope of the Reaction for the Formation of Indolines and Oxindoles



entry	aryl bromide	heterocycle	product	isolated yield
1	 **4.3**		 **4.16**	84%
2	**4.3**		 **4.17**	75%
3	**4.3**		 **4.24**	64%
4	**4.3**		 **4.25**	67%
5	**4.3**		 **4.26**	99%
6	 **4.4**		 **4.27**	47%
7	**4.4**		 **4.28**	82%
8	**4.4**		 **4.29**	67%
9	**4.4**		 **4.30**	67%

Other types of (hetero)arenes were tested under the domino reaction conditions and showed to be unsuccessful coupling partners, giving no product and only traces of product (Figure 4.3).

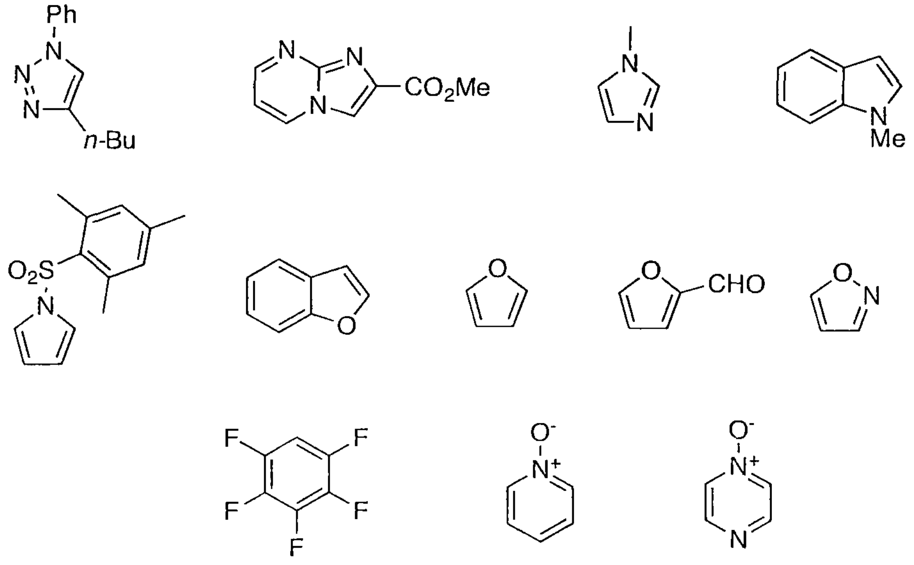
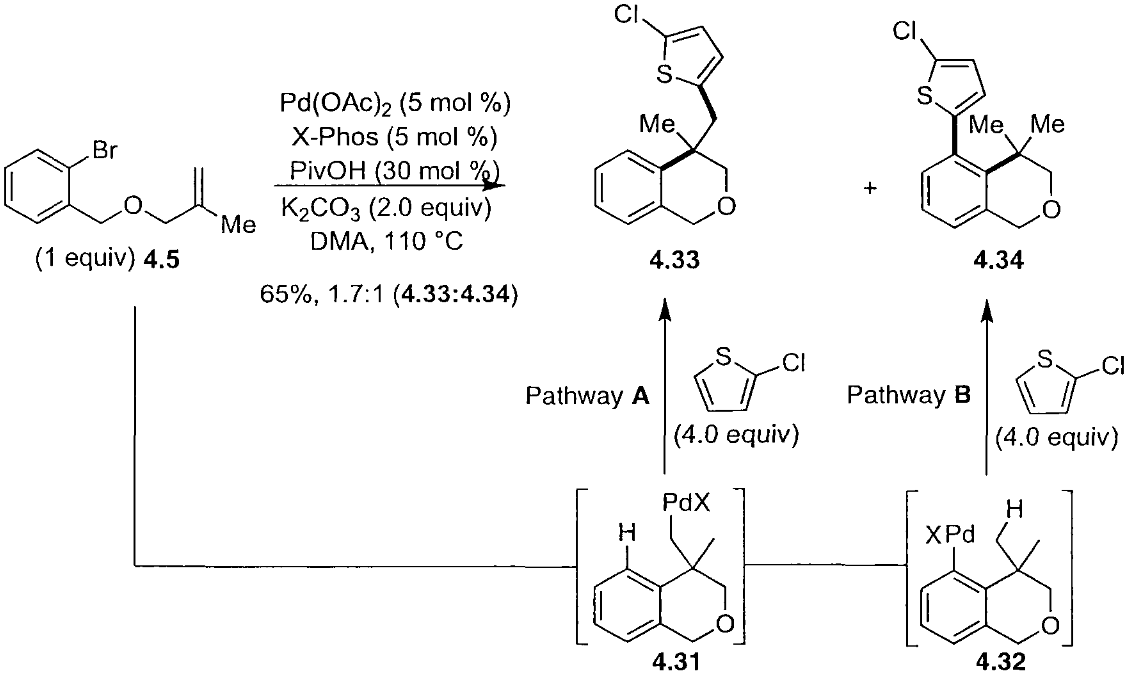


Figure 4.3 – Incompatible Coupling Partners

For example, nitrogen-containing heterocycles, such as triazole, imidazopyrimidine, imidazole, indole and pyrrole led to either traces of product or sluggish mixtures of regioisomers. Similarly, oxygen-containing heterocycles such as benzofuran, furan or isoxazole were also unsuccessful. Electron-deficient arenes such as pentafluorobenzene, pyridine-*N*-oxide and pyrazine-*N*-oxide were also incompatible coupling partners, providing the desired products in very low yields.

The formation of isochroman heterocycles was also investigated by the homologation of the phenyl ether to benzyl ether **4.5**. In this case, the formation of the two regioisomers **4.33** and **4.34** in a 1.7:1 ratio was obtained in 65% isolated yield for the mixture (Scheme 4.8). This outcome is most likely the result of palladium migration from the alkyl group to the adjacent aromatic ring. As shown in Scheme 4.8, intermediate **4.31**, produced after the intramolecular Heck reaction may undergo two competitive processes: intermolecular direct arylation to give product **4.33** or migration to the neighboring aromatic ring to form a new arylpalladium(II) intermediate **4.32**. Once formed, **4.32** may then participate in an arylation process with the thiophene coupling partner to give regioisomer **4.34**. Larock and co-workers have demonstrated that such migratory processes can occur when the alkylpalladium intermediate and the adjacent C-H bond on the aromatic ring are in a favorable geometry.[82]



Scheme 4.8 – Regioselectivity of the Formation of Isochromans

We also wanted to determine if it would be possible to control the regioselectvity of the reaction by modulating the concentration of 2-chlorothiophene in the reaction (Figure 4.4). Increasing the concentration of the heterocycle would have the effect of accelerating the rate of the direct arylation step *vs* the rate of palladium migration, resulting in a greater proportion of the non-migrated product **4.33**. Conversely, by incorporating less 2-chlorothiophene in the reaction, palladium migration should become a more favored process and the migrated product **4.34** should become the major product.

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[82] (a) Huang, Q.; Fazio, A.; Dai, G.; Campo, M. A.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 7460. (b) Kesharwani, T.; Larock, R. C. *Tetrahedron* **2008**, *64*, 5963.

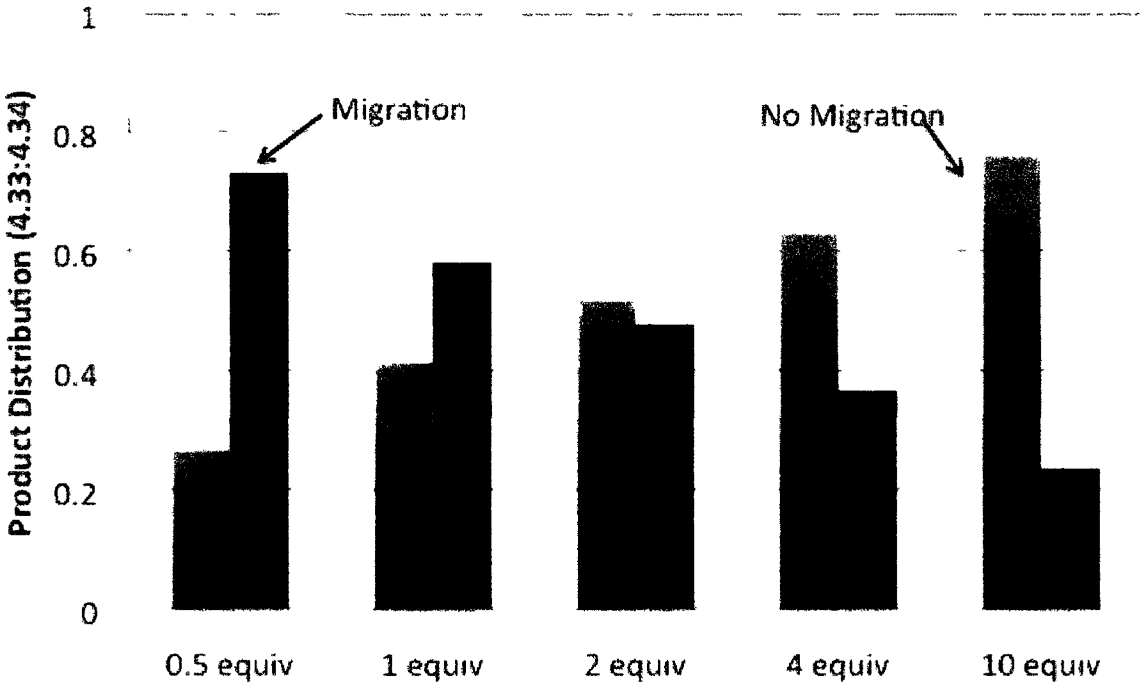


Figure 4.4 – Influence of the Concentration of Heterocycle on the Regioselectivity

As shown in Figure 4.3, when only 0.5 equiv of 2-chlorothiophene are used, **4.34** is the major product in a 0.7:0.3 ratio. This is the result of a more favored palladium migration at low concentration of the direct arylation coupling partner. In contrast, when 10 equiv of the heterocycle are used, the regioselectivity is reversed and **4.33**, the non-migrated product, becomes the major isomer. This confirms that a more facile direct arylation step *vs* palladium migration will result in a greater proportion of the non-migrated isomer.

In conclusion, we have developed a domino Heck-intermolecular direct arylation to furnish a variety of dihydrobenzofurans, indolines and oxindoles. The reaction conditions are general for a variety of sulfur-containing heterocycles as the direct arylation coupling partner and excellent yields can be obtained. In addition to synthetic utility, the demonstrated ability to combine direct arylation into this class of tandem process should raise confidence in the viability of other domino processes involving alkyl palladium(II) reactive intermediates.

FINAL CONCLUSION

Given the timeliness of catalytic methods capable of achieving reactivity at unactivated C-H bonds and the rarity of such a mild approach for electron-deficient arenes, the beneficial effect of our new biphasic conditions should demonstrate the viability of water in the development new mild direct arylations.

Additionaly, considering the scarcity of broadly applicable direct arylation conditions for various heterocycles, the observed increased rates of C-H bond functionalization with our new electron-deficient fluoroarylphosphine ligand should prompt interest amongst the scientific community in pursing development of electron-deficient ligands for direct arylation.

Finally, a novel approach for the direct formation of Csp^3-Csp^2 bonds in a domino sequence has been developed. This chemistry should prompt the investigation of other processes involving alkylpalladium(II) intermediates in an ever widening range of commonly employed palladium(0)-catalyzed organic transformations.

SECTION CLAIMS

Publications :

1) René, O.; Fagnou, K. *Org. Lett.* **2010**, *12*, 2116.
2) René, O.; Fagnou, K. *Adv. Synth. Catal.* **2010**, *Accepted.*
3) René, O.; Lapointe, D.; Fagnou, K. *Org. Lett.* **2009**, *11*, 4560.

This work was highlighted in *Org. Process Res. Dev.* **2009**, *13*, 1038.
This work was highlighted in *Chem. Commun.* **2010**, *46*, 4866.

Oral Presentations :

1) Olivier René, David Lapointe, Keith Fagnou (2009) Domino Palladium-Catalyzed Heck-Intermolecular Direct Arylation Reactions, *Catalysis Conference, Francophone Association for Knowledge (ACFAS), Ottawa, ON, Canada.*

Poster Presentations :

1) Olivier René, Keith Fagnou (2010) New Strategies for the Palladium-Catalyzed Direct Arylation Allowing Milder and More Broadly Applicable Conditions, *37th Northeast Regional Meeting of the American Chemical Society, Potsdam, NY, USA.*
2) Olivier René, Keith Fagnou (2010) New Strategies for the Palladium-Catalyzed Direct Arylation Allowing Milder and More Broadly Applicable Conditions, *93rd Canadian Chemistry Conference and Exhibition, Toronto, ON, Canada.*
3) Olivier René, Keith Fagnou (2010) New Strategies for the Palladium-Catalyzed Direct Arylation Allowing Milder and More Broadly Applicable Conditions, *Keith Fagnou Organic Chemistry Symposium (KFOS), Ottawa, ON, Canada.*
4) Olivier René, David Lapointe, Keith Fagnou (2009) Domino Palladium-Catalyzed Heck-Direct Arylation Reactions, Quebec-Ontario Mini Symposium of Bioorganic and Organic Chemistry 2009, Laval University, Quebec City, QC, Canada.
5) Olivier René, David Lapointe, Keith Fagnou (2009) Pd-Catalyzed Tandem 1,2 Migratory Insertion / Intermolecular Direct Alkylation, *39th Spring Organic Synthesis Symposium (Synthesis Day), University of Ottawa, Ottawa, ON, Canada*

SUPPORTING INFORMATION

General Considerations

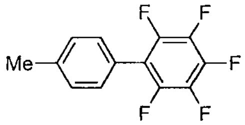
All reactions were performed under an atmosphere of argon. HPLC grade THF, Et_2O and CH_2Cl_2 were dried and purified using an MBraun solvent purification system. DMF, DMA, EtOAc, and H_2O were kept in a Wheaton bottle, dried with molecular sieves (4 Å) and degassed by bubbling argon while sonicating. Unless otherwise stated, all other solvents and reagents were purchased at > 98% purity and used as is. All palladium sources, ligands and bases were purchased from Strem Chemicals and stored in a desiccator (weighing to air). Thin-layer chromatograms were performed on EMD TLC Silica gel 60 F_{254} aluminum-backed plates and visualized with UV light or $KMnO_4$ solution (3 g $KMnO_4$, 20 g Na_2CO_3, 5 mL 5% aqueous NaOH, 300 mL distilled water). Flash purification was performed on Silicycle SilicaFlash F60 60-63 μm (230-400 mesh) silica gel.

Pentafluorobenzene and 1,2,4,5-tetrafluoro-3-methoxybenzene were purchased from Alfa Aesar. 2,3,5,6-Tetrafluoropyridine, 1,2,4,5-tetrafluoro-3-methylbenzene, 1,2,4,5-tetrafluorobenzene, 1-(2,4,5-trifluorophenyl)ethanone, 2,4,5-trifluorobenzonitrile and 2,3,5-trifluoropyridine were purchased from Matrix Scientific. 1,2,3,5-Tetrafluorobenzene was purchased from SynQuest Fluorochemicals.

Melting points were measured on an Electrothermal MEL-TEMP instrument. IR spectra were recorded on an ABB Bomem Arid-Zone spectrometer. Nuclear magnetic resonance spectra (^{1}H, ^{13}C, ^{31}P, ^{19}F) were recorded on a Bruker AV- 400 spectrometer. The internal standard is TMS (0.00 ppm) for the resonance of protons and residual chloroform (77.16 ppm) for the resonance of carbons. Phosphoric acid (0.00 ppm) was used as an external standard in the ^{31}P spectra. Trifluorotoluene (-67.73 ppm) was employed as an external standard in the ^{19}F NMR spectra. High resolution mass spectra were obtained on a Kratos Concept IIH using electron impact ionization in positive mode.

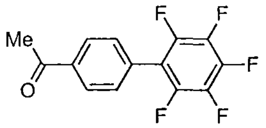
General Procedure for the Direct Arylation of Polyfluoroarenes (A)

K_2CO_3 (83.0 mg, 0.60 mmol, 2.0 equiv), Ag_2CO_3 (41.3 mg, 0.15 mmol, 0.5 equiv), MePhos (dicyclohexyl(2'-methylbiphenyl-2-yl)phosphine) (11.0 mg, 0.03 mmol, 10 mol%) and $Pd(OAc)_2$ (3.4 mg, 0.015 mmol, 5 mol%) were weighed to air in a screw cap vial equipped with a magnetic stir bar. The aryl iodide (0.3 mmol, 1.0 equiv) and the perfluoroarene (0.9 mmol, 3.0 equiv) were introduced at this moment if solid. The vial was purged with argon for 10 minutes. EtOAc (600 μL) and H_2O (240 μL) were then added to the reaction mixture using a syringe and a 23G1 needle. The aryl iodide and the perfluoroarene were introduced at this moment if liquid. The reaction mixture was stirred at 23 °C for 2 to 36 hours until the reaction was judged complete by TLC analysis. The reaction mixture was diluted with CH_2Cl_2, filtered through Celite® and concentrated under reduced pressure. The residual solid was purified by silica gel column chromatography to afford the corresponding product.



2,3,4,5,6-Pentafluoro-4'-methylbiphenyl (2.1)

Prepared according to general procedure A. The title compound was obtained as a white solid (90% yield). Reaction time: 2 hours. Exhibited spectral data in accordance with previous report.[83] ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (s, 4H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.2 (dm, J_F = 244.2 Hz), 140.3 (dm, J_F = 236.6 Hz), 139.4, 137.7 (dm, J_F = 237.9 Hz), 130.0, 129.5, 123.4, 116.0 (td, J_F = 17.8, 4.0 Hz), 21.4; ^{19}F NMR (377 MHz, $CDCl_3$) δ -143.4 (dd, J_F = 22.6, 8.3 Hz, 2F), -156.2 (t, J_F = 21.2 Hz, 1F), -162.5 (td, J_F = 22.2, 8.3 Hz, 2F).



1-(2',3',4',5',6'-Pentafluorobiphenyl-4-yl)ethanone (2.2)

Prepared according to general procedure A. The title compound was obtained as a white solid (95% yield). Reaction time: 16 hours. Exhibited spectral data in accordance with previous report.[26b] 1H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 8.4 Hz, 2H), 7.52 (d, J = 8.3 Hz, 2H), 2.63, (s, 3H); ^{13}C NMR (100

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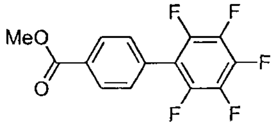
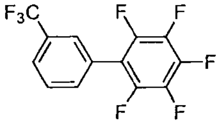
[83] Korenaga, T.; Kosaki, T.; Fukumura, R.; Ema, T. ; Sakai, T. *Org. Lett.* **2005**, *7*, 4915.

MHz, $CDCl_3$) δ 197.4, 144.1 (dm, J_F = 248.7 Hz), 140.9 (dm, J_F = 255.1 Hz), 138.0 (dm, J_F = 253.3 Hz), 137.6, 131.1, 130.6, 128.6, 115.0 (td, J_F = 16.8, 4.1 Hz), 26.7; ^{19}F NMR (377 MHz, CDC13) δ -142.8 (dd, J_F = 22.9, 8.2 Hz, 2F), -154.0 (t, J_F = 20.9 Hz, 1F), -161.6 (td, J_F = 22.6, 7.9 Hz, 2F).



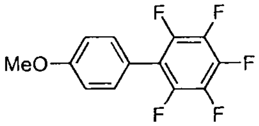
Methyl 2',3',4',5',6'-pentafluorobiphenyl-4-carboxylate (2.3)

Prepared according to general procedure A. The title compound was obtained as a white solid (96% yield). Reaction time: 16 hours. Exhibited spectral data in accordance with previous report.[26b] ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.96, (s, 3H), 7.52 (d, J = 8.6 Hz, 2H), 8.16 (d, J = 8.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 144.2 (dm, J_F = 248.8 Hz), 140.9 (dm, J_F = 255.1 Hz), 138.0 (dm, J_F = 253.3 Hz), 131.0, 130.3, 129.9, 115.0 (td, J_F = 17.0, 4.0 Hz), 52.4; ^{19}F NMR (377 MHz, $CDCl_3$) δ -142.8 (dd, J_F = 23.1, 8.4Hz, 2F), -154.2 (t, J_F = 20.8Hz, 1F), -161.7 (td, J_F = 22.2, 7.9, 2F).



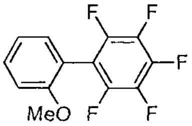
2,3,4,5,6-Pentafluoro-3'-(trifluoromethyl)biphenyl (2.4)

Prepared according to general procedure A. The title compound was obtained as a colorless oil (85% yield). Reaction time: 36 hours. R_f 0.56 (100% Hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73-7.69 (m, 2H), 7.68-7.59 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.3 (dm, J_F = 247.1 Hz), 141.1 (dm, J_F = 253.6 Hz), 138.1 (dm, J_F = 251.7 Hz), 133.6, 131.6 (q, J_F = 32.5 Hz), 129.5, 127.4, 127.2, 126.3 (q, J_F = 3.7 Hz), 123.9 (q, J_F = 270.8 Hz), 114.6 (td, J_F = 16.6, 4.0 Hz); ^{19}F NMR (377 MHz, $CDCl_3$) δ -62.9 (s, 3F), -143.1 (dd, J_F = 22.6, 8.0 Hz, 2F), -153.9 (t, J_F = 20.9 Hz, 1F), -161.5 (td, J_F = 21.7, 7.8 Hz, 2F); IR (ν_{max}) 2958, 2927, 2853, 1524, 1502, 1339, 1066, 990, 677 cm^{-1}; HRMS Calcd for $C_{13}H_4F_8$ $[M]^+$ 312.0185, Found 312.0162.



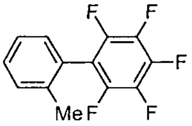
2,3,4,5,6-Pentafluoro-4'-methoxybiphenyl (2.5)

Prepared according to general procedure A. The title compound was obtained as a white solid (92% yield). Reaction time: 2 hours. Exhibited spectral data in accordance with previous report.[84] ^{1}H NMR (400 MHz, CDCl3) δ 7.36 (ddd, *J* = 8.9, 1.3, 1.3 Hz, 2H), 7.01 (d, *J* = 8.9 Hz, 2H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 144.2 (dm, J_F = 244.9 Hz), 140.2 (dm, J_F = 217.8 Hz), 137.7 (dm, J_F = 15.2), 131.4, 118.4, 115.7 (td, J_F = 17.0, 4.4), 114.2, 55.4; ^{19}F NMR (377 MHz, $CDCl_3$) δ -143.6 (dd, J_F = 23.1, 8.1 Hz, 2F), -156.5 (t, J_F = 21.1 Hz, 1F), -162.5 (td, J_F = 22.0, 7.4 Hz, 2F).



2,3,4,5,6-Pentafluoro-2'-methoxybiphenyl (2.6)

Prepared according to general procedure A. The title compound was obtained as a white solid (99% yield). Reaction time: 16 hours. Exhibited spectral data in accordance with previous report.[85] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (ddd, *J* = 8.0, 8.0, 1.6 Hz, 1H), 7.23 (d, *J* = 7.2 Hz, 1H), 7.07-7.01 (m, 2H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2, 144.6 (dm, J_F = 241.5 Hz), 140.6 (dm, J_F = 250.8 Hz), 137.7 (dm, J_F = 250.8 Hz), 131.8, 131.3, 120.7, 115.4 (d, J_F = 1.4 Hz), 113.0 (td, J_F = 19.1, 4.1 Hz), 111.4, 55.8; ^{19}F NMR (377 MHz $CDCl_3$) δ -140.2 (dd, J_F = 23.0, 7.8 Hz, 2F), -156.2 (t, J_F = 20.9 Hz, 1F), -163.2 (td, J_F = 22.0, 7.2 Hz, 2F).



2,3,4,5,6-Pentafluoro-2'-methylbiphenyl (2.7)

Prepared according to general procedure A. The title compound was obtained as a colorless oil (78% yield). Reaction time: 36 hours. Exhibited spectral data in accordance with previous report.[83] ^{1}H NMR (400 MHz, CDCl3) δ 7.40-7.33 (m, 2H), 7.28 (ddd, *J* = 7.3, 7.3, 1.6 Hz, 1H), 7.18 (d, *J* = 7.6 Hz, 1H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.2 (dm, J_F = 248.4 Hz), 140.1 (dm, J_F = 251.6 Hz), 137.8 (dm, J_F = 251.5 Hz), 137.5, 130.7, 130.6, 129.8, 126.1, 126.0, 115.6 (td, J_F = 19.9, 3.7 Hz), 19.8; ^{19}F NMR (377 MHz, $CDCl_3$) δ -140.5 (dd, J_F = 23.2, 8.3 Hz, 2F), -155.4 (t, J_F = 20.8 Hz, 1F), -162.2 (td, J_F = 22.1, 7.6 Hz, 2F).

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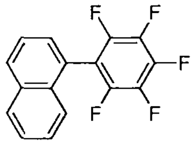
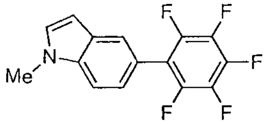
[84] Wei, Y.; Kan, J.; Wang, M.; Su, W.; Hong, M. *Org. Lett.* **2009**, *11*, 3346.

[85] Chen, Q.-Y. and Li, Z.-T. *J. Org. Chem.* **1993**, *58*, 2599.



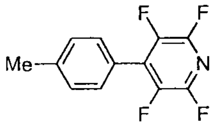
1-(Perfluorophenyl)naphthalene (2.8)

Prepared according to general procedure A. The title compound was obtained as a white solid (95% yield). Reaction time: 16 hours. Exhibited spectral data in accordance with previous report.[26b] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 8.2 Hz, 1H), 7.93 (d, J = 7.8 Hz, 1H), 7.58-7.48 (m, 4H), 7.44 (d, J = 6.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.6 (dm, J_F = 247.4 Hz), 141.0 (dm, J_F = 254.0 Hz), 137.8 (dm, J_F = 253.5 Hz), 133.7, 131.6, 130.2, 129.0, 128.7, 127.1, 126.4, 125.2, 124.6, 123.8, 114.4 (td, J_F = 19.6, 3.9 Hz); ^{19}F NMR (377 MHz, $CDCl_3$) δ -139.4 (d, J_F = 31.2 Hz, 2F), -154.6 (t, J_F = 20.8 Hz, 1F), -161.8 (td, JF = 21.5, 11.0 Hz, 2F).



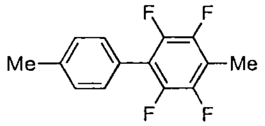
1-Methyl-5-(perfluorophenyl)-1*H*-indole (2.9)

Prepared according to general procedure A. The title compound was obtained as a yellow solid (93% yield). Reaction time: 16 hours. Rf 0.41 (EtOAc/Hexanes 1/9); mp: 152-154 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 0.8 Hz, 1H), 7.41 (d, J = 8.5 Hz, 1H), 7.23 (dq, J = 8.4, 1.6 Hz, 1H), 7.11 (d, J = 3.1 Hz, 1H), 6.54 (dd, J = 3.1, 0.8 Hz, 1H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.5 (dm, J_F = 240.4 Hz), 140.2 (dm, J_F = 202.1 Hz), 137.7 (dm, J_F = 202.2 Hz), 136.9, 130.0, 128.7, 123.4, 123.2, 117.4 (td, J_F = 17.5, 4.3 Hz), 117.2 (d, J_F = 1.2 Hz), 109.6, 101.7, 33.1; ^{19}F NMR (377 MHz, $CDCl_3$) δ -143.4 (dd, J_F = 23.3, 7.7 Hz, 2F), -157.2 (t, J_F = 20.9 Hz, 1F), -162.9 (td, J_F = 22.2, 7.3 Hz, 2F); IR (ν_{max}) 2956, 2921, 2853, 1495, 983, 756 cm^{-1}; HRMS Calcd for $C_{15}H_8F_5N$ $[M]^+$ 297.0577, Found 297.0568.



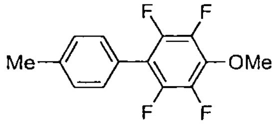
2,3,5,6-Tetrafluoro-4-*p*-tolylpyridine (2.10)

Prepared according to general procedure A. The title compound was obtained as a white solid (95% yield). Reaction time: 16 hours. Exhibited spectral data in accordance with previous report.[26a] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (dt, J = 8.3, 1.6 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.2 (dm, J_F = 243.6 Hz), 141.1, 139.4 (dm, J_F = 257.9 Hz), 133.6 (m), 129.8, 129.7, 123.1, 21.6; ^{19}F NMR (377 MHz, $CDCl_3$) δ -91.09 (td, J_F = 24.4, 13.1 Hz, 2F), -145.37 (td, J_F = 24.5, 13.0 Hz, 2F).



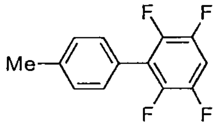
2,3,5,6-Tetrafluoro-4,4'-dimethylbiphenyl (2.11)

Prepared according to general procedure A. The title compound was obtained as a white solid (91% yield). Reaction time: 16 hours. Exhibited spectral data in accordance with previous report.[6] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, J = 8.2 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 2.41 (s, 3H), 2.30 (t, J = 2.1 Hz, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 145.8 (dm, J_F = 169.8 Hz), 143.4 (dm, J_F = 169.7 Hz), 139.0, 130.1 (t, J_F = 2.1 Hz), 129.4, 124.9 (t, J_F = 2.3 Hz), 118.1 (t, J_F = 16.8 Hz), 114.9 (t, J_F = 19.2 Hz), 21.5, 7.7 (m); ^{19}F NMR (377 MHz, $CDCl_3$) δ -144.3 (dd, J_F = 22.7, 12.6 Hz, 2F), -145.7 (dd, J_F = 22.6, 12.7 Hz, 2F).



2,3,5,6-Tetrafluoro-4-methoxy-4'-methylbiphenyl (2.12)

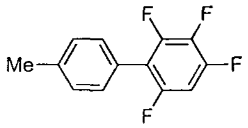
Prepared according to general procedure A. The title compound was obtained as a white solid (98% yield). Reaction time: 16 hours. Exhibited spectral data in accordance with previous report.[26a] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.1 Hz, 2H), 4.10 (t, J = 1.3 Hz, 3H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.4 (dm, J_F = 243.8 Hz), 141.3 (ddt, J_F = 245.4, 16.0, 4.4 Hz), 139.0, 137.4 (m), 130.2 (t, J_F = 4.9 Hz), 129.4, 124.4, 114.4 (t, J_F = 17.0 Hz), 62.3, 21.5; ^{19}F NMR (377 MHz, $CDCl_3$) δ -145.3 (dd, J_F = 22.2, 8.8 Hz, 2F), -158.4 (dd, J_F = 22.2, 8.8 Hz, 2F).



2,3,5,6-Tetrafluoro-4'-methylbiphenyl (2.13)

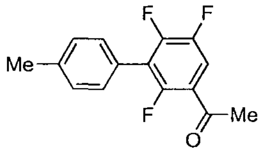
Prepared according to general procedure A using 10.0 equiv of 1,2,4,5-tetrafluorobenzene. The title compound was obtained as a white solid (90% yield). Reaction time: 16 hours. Exhibited spectral data in accordance with previous report.[26a] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.28 (m, 4H), 7.03 (tt, J = 9.7, 7.3 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.4 (dm, J_F = 242.0 Hz), 143.8 (dm, J_F

= 240.3 Hz), 139.4, 130.1, 129.5, 124.6 (t, J_F = 2.3 Hz), 121.7 (t, J_F = 16.7 Hz), 104.7 (t, J_F = 22.6 Hz), 21.5; ^{19}F NMR (377 MHz, $CDCl_3$) δ -139.3 (dd, J_F = 22.2, 12.7 Hz, 2F), -144.0 (dd, J_F = 22.5, 12.8 Hz, 2F).



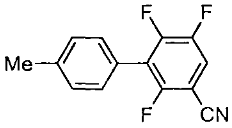
2,3,4,6-Tetrafluoro-4'-methylbiphenyl (2.14)

Prepared according to general procedure A using 10.0 equiv of 1,2,3,5-tetrafluorobenzene. The title compound was obtained as a white solid (88% yield). Reaction time: 16 hours. Exhibited spectral data in accordance with previous report.[26a] 1H NMR (400 MHz, $CDCl_3$) δ 7.32-7.27 (m, 4H), 6.85 (dddd, J = 10.1, 9.5, 6.2, 2.4 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4 (dm, J_F = 245.4 Hz), 149.7 (dm, J_F = 248.7 Hz), 149.1 (dm, J_F = 244.1 Hz), 139.0, 137.6 (dm, J_F = 246.0 Hz), 130.1, 129.4, 124.6, 116.1 (m), 101.0 (ddd, J_F = 29.0, 21.2, 3.9 Hz), 21.5; ^{19}F NMR (377 MHz, $CDCl_3$) δ -118.2 (d, J_F = 11.0 Hz, 1F), -133.9 (dd, J_F = 21.2, 4.8 Hz, 1F), -135.5 (dt, J_F = 21.8, 2.7 Hz, 1F), -165.0 (m, 1F).



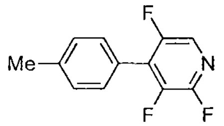
1-(2,5,6-Trifluoro-4'-methylbiphenyl-3-yl)ethanone (2.15)

Prepared according to general procedure A. The title compound was obtained as a white solid (99% yield). Reaction time: 16 hours. R_f 0.47 (100% Toluene); mp: 47-49 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (ddd, J = 10.3, 8.9, 6.5 Hz, 1H), 7.34-7.29 (m, 4H), 2.62 (d, J = 5.7 Hz, 3H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.8 (d, J_F = 4.3 Hz), 155.5 (ddd, J_F = 251.5, 5.3, 2.6 Hz), 151.0 (ddd, J_F = 256.4, 14.6, 7.2 Hz), 147.5 (ddd, J_F = 246.2, 13.8, 3.0 Hz), 139.4, 130.1, 129.5, 124.6 (d, J_F = 2.0 Hz), 122.0 (dt, J_F = 16.8, 3.9 Hz), 121.4 (dd, J_F = 23.3, 15.5 Hz), 116.2 (ddd, J_F = 20.3, 4.3, 2.2 Hz), 31.6 (d, J_F = 7.9 Hz), 21.5; ^{19}F NMR (377 MHz, $CDCl_3$) δ -113.9 (dd, J_F = 16.2, 9.7 Hz, 1F), -128.5 (dd, J_F = 22.4, 9.7 Hz, 1F), -140.1 (dd, J_F = 22.7, 16.2 Hz, 1F); IR (ν_{max}) 2964, 2925, 2852, 1690, 1481, 1370, 904, 810 cm^{-1}; HRMS Calcd for $C_{15}H_{11}F_3O$ $[M]^+$ 264.0762, Found 264.0784.



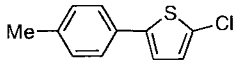
2,5,6-Trifluoro-4'-methylbiphenyl-3-carbonitrile (2.16)

Prepared according to general procedure A. The title compound was obtained as a white solid (81% yield). Reaction time: 16 hours. R_f 0.60 (100% Toluene); mp: 168-170 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (td, J = 8.3, 5.7 Hz, 1H), 7.33 (s, 4H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2 (ddd, J_F = 255.9, 5.7, 2.8 Hz), 151.6 (ddd, J_F = 258.6, 13.8, 6.7 Hz), 147.4 (ddd, J_F = 248.6, 14.2, 3.7 Hz), 140.1, 129.9 (t, J_F = 2.0 Hz), 129.7, 123.2 (d, J_F = 1.9 Hz), 122.3 (dd, J_F = 19.2, 16.1 Hz), 118.8 (dd, J_F = 21.8, 2.0 Hz), 112.7 (t, J_F = 2.1 Hz), 97.6 (m), 21.5; ^{19}F NMR (377 MHz, $CDCl_3$) δ -110.8 (dd, J_F = 14.1, 9.1 Hz, 1F), -125.9 (dd, J_F = 21.8, 9.4 Hz, 1F), -137.7 (dd, J_F = 21.8, 13.9 Hz, 1F); IR (ν_{max}) 2956, 2922, 1480, 1354, 914, 814 cm^{-1}; HRMS Calcd for $C_{14}H_8F_3N$ [M]$^+$ 247.0609, Found 247.0605.



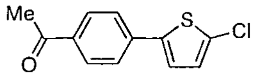
2,3,5-Trifluoro-4-*p*-tolylpyridine (2.17)

Prepared according to general procedure A. The title compound was obtained as a white solid (98% yield). Reaction time: 16 hours. R_f 0.44 (EtOAc/Hexanes 1/9) mp: 47-48 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (dd, J = 1.5, 1.5 Hz, 1H), 7.43-7.41 (m, 2H), 7.33 (d, J = 8.0 Hz, 2H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0 (dd, J_F = 253.8, 4.0 Hz), 148.9 (ddd, J_F = 234.1, 15.4, 2.1 Hz), 142.2 (ddd, J_F = 262.3, 30.7, 3.2 Hz), 140.4, 129.9 (m), 129.8 (t, J_F = 2.3 Hz), 129.5, 128.5 (ddd, J_F = 29.0, 14.4, 6.3 Hz), 123.3 (m), 21.5; ^{19}F NMR (377 MHz, $CDCl_3$) δ -89.4 (t, J_F = 27.2 Hz, 1F), -132.8 (dd, J_F = 28.6, 3.8 Hz, 1F), -141.1 (dd, J_F = 25.9, 3.8 Hz, 1F); IR (ν_{max}) 3050, 2927, 2851, 1470, 1442, 815, 753 cm^{-1}; HRMS Calcd for $C_{12}H_8F_3N$ [M]$^+$ 223.0609, Found 223.0603.



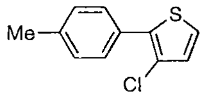
2-Chloro-5-*p*-tolylthiophene (2.18)

Prepared according to general procedure A at 60°C. The title compound was obtained as a white solid (77% yield). Reaction time: 16 hours. Exhibited spectral data in accordance with previous report.[48] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, J = 8.2 Hz, 2H), 7.17 (d, J = 7.9 Hz, 2H), 7.01 (d, J = 3.9 Hz, 1H), 6.86 (d, J = 3.9 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3, 137.9, 131.1, 129.8, 128.6, 127.1, 125.6, 121.8, 21.3.



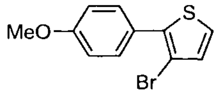
1-(4-(5-Chlorothiophen-2-yl)phenyl)ethanone (2.19)

Prepared according to general procedure A at 60°C. The title compound was obtained as a white solid (61% yield). Reaction time: 16 hours. R_f 0.31 (EtOAc/Hexanes 1/9); mp: 118-120 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.97-7.94 (m, 2H), 7.59-7.56 (m, 2H), 7.19 (d, J = 3.9 Hz, 1H), 6.92 (d, J = 3.9 Hz, 1H), 2.60 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 197.2, 141.5, 138.0, 136.1, 131.2, 129.3, 127.6, 125.3, 123.9, 26.7; IR (ν_{max}) 2957, 2926, 2853, 1675, 1433, 798 cm^{-1}; HRMS Calcd for $C_{12}H_9OSCl$ [M]$^+$ 236.0063, Found 236.0058.



3-Chloro-2-*p*-tolylthiophene (2.20)

Prepared according to general procedure A at 60°C. The crude product was purified by preparative HPLC (Varian Polaris C18-A 5 μm column, flow = 20.0 mL/min, MeCN:Water 65:35) to give the title compound as a colorless oil (73% yield) Reaction time: 16 hours. R_f 0.53 (100% Hexanes); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.56-7.54 (m, 2H), 7.25-7.22 (m, 2H), 7.22 (d, J = 5.2 Hz, 1H), 6.98 (d, J = 5.4 Hz, 1H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 138.2, 136.5, 129.5, 129.4, 129.3, 128.7, 123.6, 121.1, 21.4; IR (ν_{max}) 3116, 2955, 2927, 1498, 885, 811, 701 cm^{-1}; HRMS Calcd for $C_{11}H_9SCl$ [M]$^+$ 208.0113, Found 208.0125.

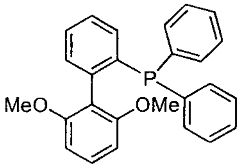


3-Bromo-2-(4-methoxyphenyl)thiophene (2.23)

Prepared according to general procedure A at 60°C. The crude product was purified by preparative HPLC (Varian Polaris C18-A 5 μm column, flow = 20.0 mL/min, MeCN:Water 60:40) to give the title compound as a colorless oil (72% yield) Reaction time: 16 hours. R_f 0.38 (Toluene/Hexanes 2/8); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.58-7.56 (m, 2H), 7.23 (d, J = 5.4 Hz, 1H), 7.03 (d, J = 5.4 Hz, 1H), 6.97-6.95 (m, 2H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 159.8, 138.3, 131.6, 130.5, 125.4, 124.5, 114.1, 107.2, 55.5; IR (ν_{max}) 2960, 2928, 2851, 1495, 1247, 830 cm^{-1}; HRMS Calcd for $C_{11}H_9OSBr$ [M]$^+$ 267.9557, Found 267.9542.

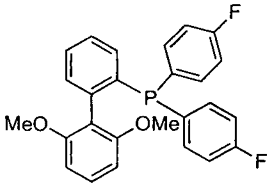
General Procedure for the Synthesis of Phosphine Ligands (B)

To a solution of 2'-Bromo-2,6-dimethoxybiphenyl (1.90 g, 6.48 mmol, 1.0 equiv) in THF (100 mL) was added *n*-butyllithium (2.7 mL, 2.5 M in hexanes, 1.05 equiv) dropwise at -78 °C. The resulting mixture was stirred at -78 °C for 1 hour and then cooled down to -95 °C using an acetone/liquid N_2 bath. A solution of triphenylphosphite (2.01 g, 6.48 mmol, 1.0 equiv) in THF (8 mL) was added with vigorous stirring. The reaction was allowed to slowly warm up to ambient temperature and was stirred for 1 more hour until a clear solution was obtained. The resulting solution was then cooled down to -78 °C and a freshly made solution of phenyllithium (32.4 mmol, 5.0 equiv) [made from phenyl bromide (32.4 mmol, 5.0 equiv) and *n*-butyllithium (13.2 mL, 2.5 M in hexanes, 5.1 equiv) in THF (100 mL)] was cannulated into the reaction mixture. The resulting solution was warmed to ambient temperature and stirred for 5 days. When the reaction was considered to be complete by ^{31}P NMR analysis, water (10 mL) was added and THF was removed under reduced pressure. Water (100 mL) was added and the product was extracted with Et_2O (3 x 50 mL), dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude product was then rapidly subjected to a short column of silica gel eluting with a mixture of EtOAc/Hexanes (25:75). After concentration under reduced pressure, MeOH was added and sonicated until precipitation of the product occurred. The collected precipitate was recrystallized from acetone or ethanol [the boiling solution was slowly cooled down to 25 °C and let stand at ambient temperature for 24 hours]. The pure product was obtained as white crystalline needles.



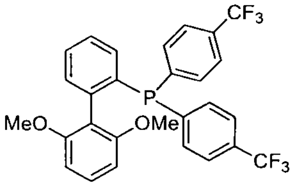
(2',6'-Dimethoxybiphenyl-2-yl)diphenylphosphine (3.1)

Prepared according to general procedure B and recrystallized from acetone. The title compound was obtained as a white solid (38% yield). R_f 0.53 (EtOAc/Hexanes 25/75); mp : 125-127 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (ddd, J = 7.5, 7.5, 1.1 Hz, 1H), 7.29-7.17 (m, 13H), 7.14 (ddd, J = 7.7, 3.7, 1.0 Hz, 1H), 6.52 (d, J = 8.4 Hz, 2H), 3.44 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) 157.9, 141.5 (d, J_P = 33.5 Hz), 138.3 (d, J_P = 12.6 Hz), 137.9 (d, J_P = 9.7 Hz), 134.2 (d, J_P = 2.0 Hz), 133.7 (d, J_P = 19.6 Hz), 131.0 (d, J_P = 6.0 Hz), 129.3, 128.9, 128.1 (d, J_P = 6.5 Hz), 128.0, 127.4, 119.2 (d, J_P = 7.9 Hz), 103.6, 55.5; ^{31}P NMR (162 MHz, $CDCl_3$) δ -11.98; IR (ν_{max}) 3067, 3001, 2964, 2832, 1590, 1471, 1246, 1111, 745 cm^{-1}; HRMS Calcd for $C_{26}H_{23}O_2P_1$ $[M - OCH_3]^+$ 367.1252, Found 367.1241.



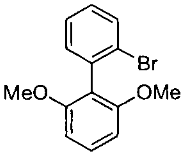
(2',6'-Dimethoxybiphenyl-2-yl)bis(4-fluorophenyl)phosphine (3.2)

Prepared according to general procedure B and recrystallized from EtOH. The title compound was obtained as a white solid (12% yield). R_f 0.53 (EtOAc/Hexanes 25/75); mp : 136-138 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.42 (ddd, J = 7.5, 7.5, 1.1 Hz, 1H), 7.28 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H), 7.27 (dd, J = 8.4, 8.4 Hz, 1H), 7.22 (ddd, J = 7.5, 4.2, 0.9 Hz, 1H), 7.17-7.11 (m, 4H), 7.06 (ddd, J = 7.7, 3.8, 0.9 Hz, 1H), 7.00-6.94 (m, 4H), 6.51 (d, J = 8.4 Hz, 2H), 3.46 (s, 6H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 163.1 (d, J_F = 246.4 Hz), 157.8 (d, J_P = 1.3 Hz), 141.3 (d, J_P = 32.9 Hz), 137.7 (d, J_P = 9.3 Hz), 135.5 (dd, J_F = 21.3, J_P = 7.6 Hz), 133.6, 133.5 (dd, J_P = 12.8, J_F = 3.5 Hz), 131.2 (d, J_P = 5.8 Hz), 129.4, 129.1, 127.5, 118.8 (d, J_P = 7.7 Hz), 115.4 (dd, J_P = 20.6, J_F = 7.3 Hz), 103.6, 55.4; ^{31}P NMR (162 MHz, CDCl$_3$) δ -14.63; ^{19}F NMR (377 MHz, CDCl3) δ -113.51 (d, J = 4.2 Hz, 2F); IR (ν_{max}) 3061, 2934, 2839, 1592, 1491, 1473, 1253, 1223, 1108, 822 cm^{-1}; HRMS Calcd for $C_{26}H_{21}F_2O_2P_1$ [M – OCH$_3$]$^+$ 403.1063, Found 403.1048.



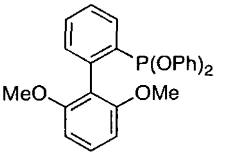
(2',6'-Dimethoxybiphenyl-2-yl)bis(4-(trifluoromethyl)phenyl)phosphine (3.3)

Prepared according to general procedure B and recrystallized from EtOH. The title compound was obtained as a white solid (46% yield). R_f 0.55 (EtOAc/Hexanes 25/75); mp : 122-124 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.51 (ddd, J = 7.9, 0.6, 0.6 Hz, 4H), 7.44 (ddd, J = 7.5, 1.3, 0.5 Hz, 1H), 7.32-7.23 (m, 7H), 7.08 (dddd, J = 7.6, 4.0, 1.2, 0.4 Hz, 1H), 6.51 (d, J = 8.4 Hz, 2H), 3.45 (s, 6H); ^{13}C NMR (100 MHz, CDCl$_3$) 157.6, 142.5 (br d, J_P = 16.0 Hz), 141.7 (d, J_P = 34.2 Hz), 135.9 (d, J_P = 7.8 Hz), 133.8 (d, J_P = 21.0 Hz), 133.7 (d, J_P = 19.7 Hz), 131.3 (d, J_P = 6.4 Hz), 130.3 (q, J_F = 32.1 Hz), 129.6, 129.5, 127.7, 124.8 (m), 124.1 (q, J_F = 270.4 Hz), 118.5 (d, J_P = 7.9 Hz), 103.5, 55.2; ^{31}P NMR (162 MHz, CDCl$_3$) δ -12.02; ^{19}F NMR (377 MHz, CDCl3) δ -62.75 (s, 6F); IR (ν_{max}) 2961, 2916, 2846, 1592, 1471, 1322, 1113, 1063, 769 cm^{-1}; HRMS Calcd for $C_{28}H_{21}F_6O_2P_1$ [M – OCH$_3$]$^+$ 503.0999, Found 503.0998.



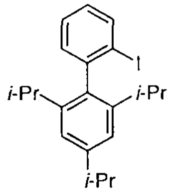
2'-Bromo-2,6-dimethoxybiphenyl (3.4)

To a solution of 1,3-dimethoxybenzene (7.77 mL, 60.0 mmol, 1.2 equiv) in THF (150 mL) was added *n*-butyllithium (24 mL, 2.5 M in hexanes, 1.2 equiv) dropwise at 0 °C. The reaction mixture was stirred at ambiant temperature for 3 hours and then cooled down to 0 °C. 1-Bromo-2-chlorobenzene (5.80 mL, 50.0 mmol, 1.0 equiv) was added dropwise over 15 minutes and the reaction was stirred for another 15 minutes followed by a quench with methanol. The reaction was concentration under reduced pressure and diluted with diethylether (150 mL). The crude material was washed with water (2 x 50 mL) and brine (50 mL), dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. The product was recrystallized from boiling methanol to give the title compound as yellow crystalline solid (57% yield). Exhibited spectral data in accordance with previous report.[86] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (ddd, *J* = 8.0, 1.2, 0.4 Hz, 1H), 7.34 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H), 7.33 (dd, *J* = 8.4, 8.4 Hz, 1H), 7.23 (ddd, *J* = 7.6, 2.0, 0.4 Hz, 1H), 7.19 (ddd, *J* = 8.0, 7.3, 1.8 Hz, 1H), 6.65 (d, *J* = 8.4 Hz, 2H), 3.73 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 136.2, 132.43, 132.41, 129.6, 128.7, 127.0, 125.3, 119.0, 104.2, 56.1.



Diphenyl 2-(2',6'-Dimethoxybiphenylyl)phosphonite (3.6)

By-product isolated from Scheme 3.7. Exhibited spectral data in accordance with previous report.[59]



2'-Iodo-2,4,6-triisopropylbiphenyl (3.6)

Prepared according to the method reported by Hartmann *et al.*[87] (20.0 mmol scale). The title compound was obtained as a yellow crystalline solid (4.04 g, 50% yield). Exhibited spectral data in accordance with previous report.[86] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.37 (ddd, *J* = 7.5,

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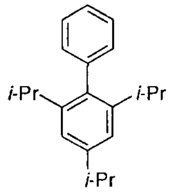
[86] Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685.

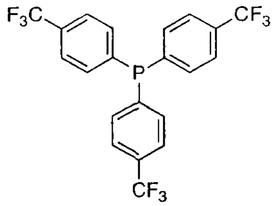
[87] Hartmann, N.; Niemeyer, M. *Synth. Commun.* **2001**, *31*, 3839.

7.5, 1.2 Hz, 1H), 7.19 (dd, J = 7.6, 1.6 Hz, 1H), 7.05-7.00 (m, 3H), 2.95 (t, J = 6.9 Hz, 1H), 2.39 (quintet, J = 6.9 Hz, 2H), 1.31 (d, J = 6.9 Hz, 6H), 1.22 (t, J = 6.8 Hz, 6H), 1.01 (d, J = 6.8 Hz, 6H) ; ^{13}C NMR (100 MHz) δ 148.6, 146.0, 145.8, 139.3, 138.9, 130.6, 128.3, 127.8, 120.8, 102.5, 34.4, 30.7, 25.0, 24.2, 23.3.



2,4,6-Triisopropylbiphenyl (3.9)

By-product isolated from Scheme 3.6. Exhibited spectral data in accordance with previous report.[86]

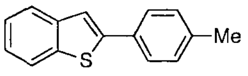


Tris(4-trifluoromethylphenyl)phosphine (3.10)

By-product isolated from Scheme 3.6. Exhibited spectral data in accordance with corresponding commercial material.

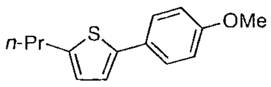
General Procedure for the Direct Arylation of Heterocycles (C)

K_2CO_3 (62.2 mg, 0.45 mmol, 1.5 equiv), Ag_2CO_3 (41.4 mg, 0.15 mmol, 0.5 equiv), phosphine **4.3** (16.0 mg, 0.03 mmol, 10 mol%), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol, 5 mol%) and pivalic acid (9.2 mg, 0.09 mmol, 30 mol%) were weighed to air in a screw cap vial equipped with a magnetic stir bar. The aryl iodide (0.3 mmol, 1.0 equiv) and the heterocycle (0.33 mmol, 1.1 equiv) were introduced at this moment if solid. The vial was purged with argon for 10 minutes. DMA (1 mL) was then added to the reaction mixture using a syringe and a 23G1 needle. The aryl iodide and the heterocycle were introduced at this moment if liquid. The reaction mixture was stirred at 100 °C for 16 hours. Upon completion of the reaction, the mixture was filtered and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography to afford the corresponding product.



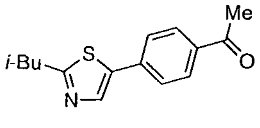
2-*p*-Tolylbenzo[*b*]thiophene (3.13)

Prepared according to general procedure C. The title compound was obtained as a white solid (78% yield). Exhibited spectral data in accordance with previous report.[23a] ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.84 (br d, J = 7.8 Hz, 1H), 7.75 (br d, J = 7.6 Hz, 1H), 7.60 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 0.5 Hz, 1H), 7.33 (ddd, J = 6.8, 6.8, 1.6 Hz, 1H), 7.29 (ddd, J = 6.8, 6.8, 1.6 Hz, 1H), 7.22 (br d, J = 8.0 Hz, 2H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) 144.5, 140.9, 139.4, 138.4, 131.6, 129.7, 126.5, 124.5, 124.2, 123.5, 122.3, 118.9, 21.4.



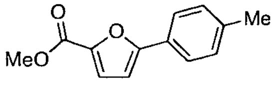
2-(4-Methoxyphenyl)-5-propylthiophene (3.14)

Prepared according to general procedure C. The title compound was obtained as a colorless oil (89% yield). Exhibited spectral data in accordance with previous report.[88] ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.48 (d, J = 8.8 Hz, 2H), 7.00 (d, J = 3.5 Hz, 1H), 6.89 (d, J = 8.8 Hz, 2H), 6.71 (ddd, J = 3.5, 1.2, 1.2 Hz, 1H), 3.82 (s, 3H), 2.78 (t, J = 8.0 Hz, 2H), 1.72 (sex, J = 7.5 Hz, 2H), 1.00 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) 158.8, 144.4, 141.6, 127.7, 126.7, 124.9, 121.6, 114.2, 55.3, 32.3, 24.9, 13.7.



1-(4-(2-Isobutylthiazol-5-yl)phenyl)ethanone (3.15)

Prepared according to general procedure C. The title compound was obtained as a white solid (84% yield). R$_f$ 0.20 (EtOAc/Hexanes 25/75); mp : 42-44 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.97 (d, J = 8.6 Hz, 2H), 7.95 (s, 1H), 7.62 (d, J = 8.6 Hz, 2H), 2.90 (d, J = 7.2 Hz, 2H), 2.62 (s, 3H), 2.15 (non, J = 6.7 Hz, 1H), 1.03 (d, J = 6.6 Hz, 6H); ^{13}C NMR (100 MHz, CDCl$_3$) 197.2, 171.2, 139.1, 137.3, 136.3, 136.2, 129.2, 126.5, 42.7, 29.9, 26.6, 22.4; IR (ν_{max}) 3053, 2963, 2879, 1677, 1602, 1356, 1263, 823 cm^{-1}; HRMS Calcd for $C_{15}H_{17}N_1O_1S_1$ $[M]^+$ 259.1027, Found 259.1031.



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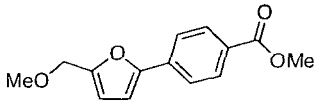
[88] Campbell, N. L.; Duffy, W. L.; Thomas, G. I.; Wild, J. H.; Kelly, S. M.; Bartle, K.; O'Neil, M.; Minter, V.; Tuffin, R. P. *J. Mater. Chem.* **2002**, *12*, 2706.

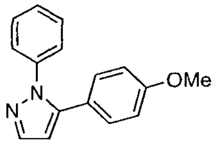
Methyl 5-*p*-tolylfuran-2-carboxylate (3.16)

Prepared according to general procedure C. The crude product was purified by preparative HPLC (Varian Polaris C18-A 5 μm column, flow = 20.0 mL/min, MeCN:Water 10:90 to 90:10 gradient over 30 minutes) to give the title compound as a yellow oil (46% yield). Exhibited spectral data in accordance with previous report.[89] ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.66 (d, *J* = 8.4 Hz, 2H), 7.23-7.20 (m, 3H), 6.66 (d, *J* = 3.6 Hz, 1H), 3.89 (s, 3H), 2.36 (d, *J* = 3.5 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) 159.2, 157.9, 143.2, 139.1, 129.5, 126.8, 124.8, 120.1, 106.2, 51.8, 21.4.



Methyl 4-(5-(methoxymethyl)furan-2-yl)benzoate (3.17)

Prepared according to general procedure C. The title compound was obtained as a colorless oil (43% yield). R$_f$ 0.27 (EtOAc/Toluene 7/93); ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.04 (d, *J* = 8.8 Hz, 2H), 7.74 (d, *J* = 8.8 Hz, 2H), 6.75 (d, *J* = 3.3 Hz, 1H), 6.45 (d, *J* = 3.4 Hz, 1H), 4.47 (s, 2H), 3.92 (s, 3H), 3.42 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) 166.8, 153.1, 152.4, 134.6, 130.0, 128.6, 123.4, 111.7, 107.8, 66.4, 58.0, 52.1; IR (ν_{max}) 2949, 2927, 1718, 1611, 1432, 1278, 1110, 766 cm^{-1}; HRMS Calcd for C$_{14}$H$_{14}$O$_4$ [M]$^+$ 246.0864, Found 246.0892.



5-(4-Methoxyphenyl)-1-phenyl-1*H*-pyrazole (3.18)

Prepared according to general procedure C. The title compound was obtained as a colorless oil (72% yield). R$_f$ 0.42 (EtOAc/Toluene 1/9); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.68 (d, *J* = 1.8 Hz, 1H), 7.34-7.25 (m, 5H), 7.13 (d, *J* = 8.8 Hz, 2H), 6.81 (d, *J* = 8.8 Hz, 2H), 6.43 (d, *J* = 1.8 Hz, 1H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) 159.6, 142.9, 140.3, 130.1, 128.9, 127.4, 125.3, 123.1, 114.0, 107.4, 55.3; IR (ν_{max}) 3050, 2935, 2837, 1616, 1501, 1451, 1250, 759 cm^{-1}; HRMS Calcd for C$_{16}$H$_{14}$N$_2$O$_1$ [M]$^+$ 250.1100, Found 250.1106.

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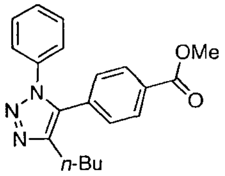
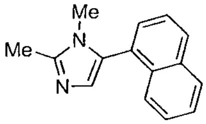
[89] Lee, S.; Yi, K. Y.; Hwang, S. K.; Lee, B. H.; Yoo, S.-E.; Lee, K. *J. Med. Chem.* **2005**, *48*, 2882.



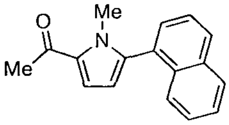
Methyl 4-(4-butyl-1-phenyl-1*H*-1,2,3-triazol-5-yl)benzoate (3.19)

Prepared according to general procedure C. The title compound was obtained as a colorless oil (93% yield). R_f 0.25 (EtOAc/Hexanes 25/75); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (m, *J* = 8.4 Hz, 2H), 7.39-7.36 (m, 3H), 7.29-7.24 (m, 4H), 3.93 (s, 3H), 2.76 (t, *J* = 7.8 Hz, 2H), 1.71 (quint, *J* = 7.2 Hz, 2H), 1.41-1.31 (m, 2H), 0.89 (t, *J* = 9.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 166.4, 146.7, 136.6, 132.9, 132.3, 130.5, 130.0, 129.6, 129.3, 129.0, 124.9, 52.4, 31.7, 24.9, 22.5, 13.8; IR (ν_{max}) 3015, 2955, 2857, 1727, 1504, 1274, 1112, 760 cm^{-1}; HRMS Calcd for $C_{20}H_{21}N_3O_2$ $[M - N_2]^+$ 307.1572, Found 307.1571.



1,2-Dimethyl-5-(naphthalen-1-yl)-1*H*-imidazole (3.20)

Prepared according to general procedure C. The title compound was obtained as a yellow oil (52% yield). Exhibited spectral data in accordance with previous report.[90] ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.89 (br d, *J* = 8.0 Hz, 2H), 7.66 (br d, *J* = 8.0 Hz, 1H), 7.52-7.40 (m, 4H), 7.00 (s, 1H), 3.25 (s, 3H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 145.4, 133.6, 132.8, 131.0, 129.0, 128.9, 128.3, 128.0, 127.1, 126.5, 126.0, 125.5, 125.2, 30.9, 13.7.



1-(1-Methyl-5-(naphthalen-1-yl)-1*H*-pyrrol-2-yl)ethanone (3.21)

Prepared according to general procedure C. The crude product was purified by preparative HPLC (Varian Polaris C18-A 5 μm column, flow = 20.0 mL/min, MeCN:Water 10:90 to 90:10 gradient over 30 minutes) to give the title compound as a colorless oil (43% yield). Exhibited spectral data in accordance with previous report.[91] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (dd, *J* = 8.4, 8.4 Hz, 2H), 7.55-7.42 (m, 5H), 7.12 (d, *J* = 4.0 Hz, 1H), 6.26 (d, *J* = 4.0 Hz, 1H), 3.63 (s, 3H), 2.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 188.7, 141.1, 133.6, 132.7, 131.5, 129.7, 129.4, 128.9, 128.5, 126.9, 126.3, 125.7, 125.3, 119.6, 110.6, 35.0, 27.5.

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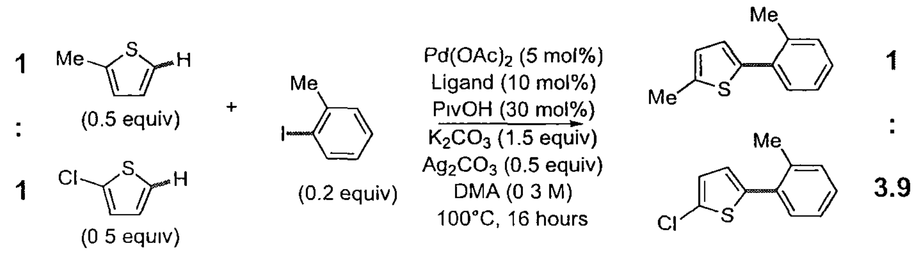
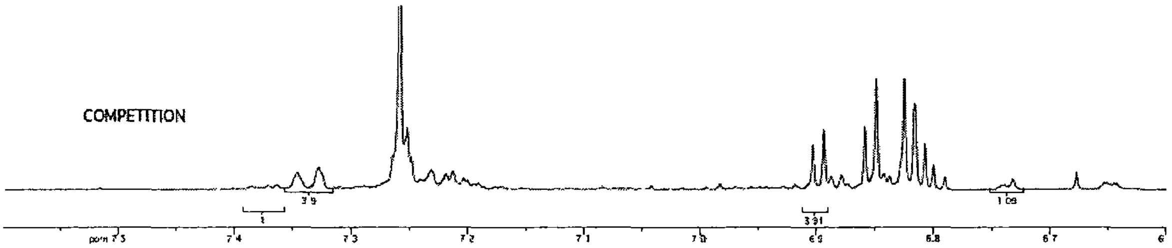
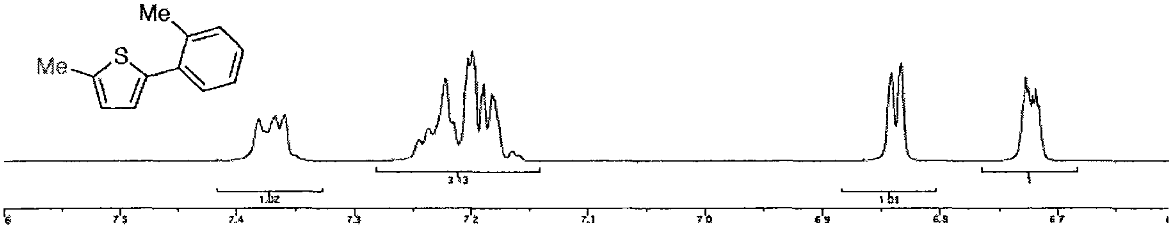
[90] Roger, J.; Doucet, H. *Tetrahedron*, **2009**, *65*, 9772.

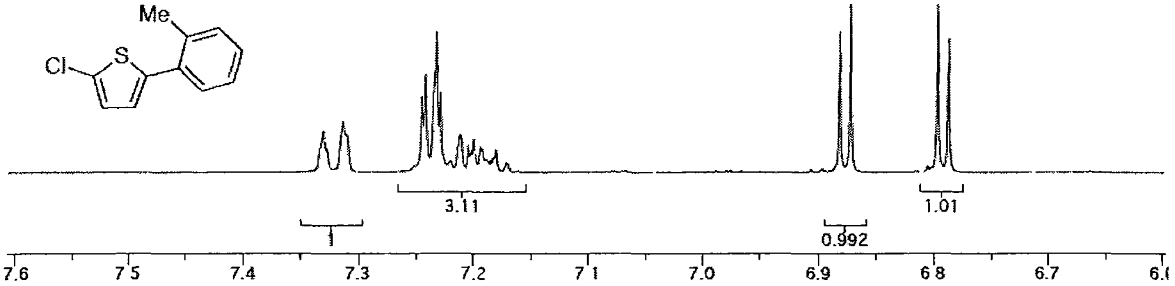
[91] Roger, J.; Doucet, H. *Adv. Synth. Catal.* **2009**, *351*, 1977.

Competition Experiment With Ligand 4.3



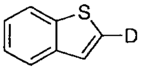






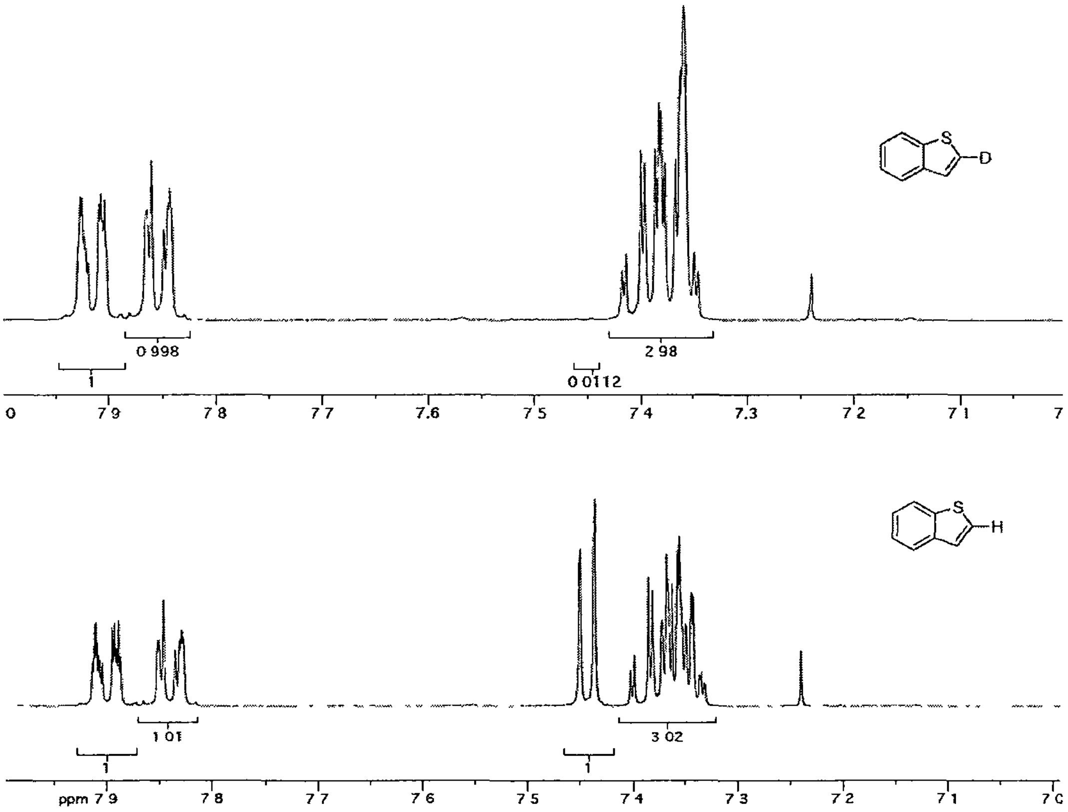
A 1:1 mixture of 2-methylthiophene and 2-chlorothiophene was reacted with 2-iodobenzene according to general procedure B using the equivalents of reactants shown above. After 16 hours, volatiles were removed under vacuum and the crude mixture was filtered through a short plug of silica gel eluting with hexanes. The resulting mixture was concentrated and analyzed by ^{1}H NMR. Complete characterization of the pure isolated products is available in a previous report.[48]

Kinetic Isotope Effect Experiment With Ligand 4.3

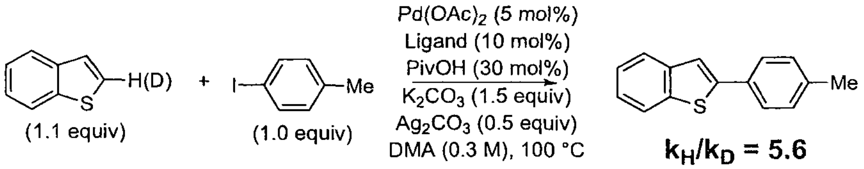


Benzo[*b*]thiophene-*d*

To a solution of benzo[*b*]thiophene (1.00 g, 7.45 mmol, 1.0 equiv) in THF (20 mL) at -78 °C was added *n*-butyllithium (4.5 mL, 2.5 M in hexanes, 1.5 equiv) dropwise. The resulting mixture was stirred at -78 °C for 2 hours and D_2O (5 mL) was added. The mixture was warmed to ambient temperature and THF was removed under reduced pressure. Water (50 mL) was added and the product was extracted with Et_2O (3 x 20 mL), dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was filtered through a short plug of silica gel eluting with hexanes to give the corresponding product as a white solid (980 mg, 98% yield). ^1H NMR analysis shows 99% incorporation.

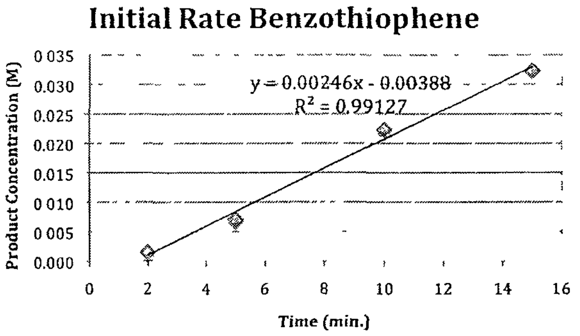


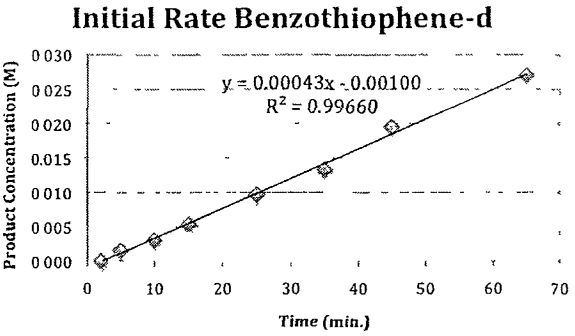
KIE Measurement



Benzo[*b*]thiophene and benzo[*b*]thiophene-*d* were reacted with 4-iodotoluene according to general procedure B in two side-by-side experiments. The progression of the reaction was monitored by GC-MS analysis relative to an internal standard of tetradecane until ~10-20% conversion and initial rates were calculated.

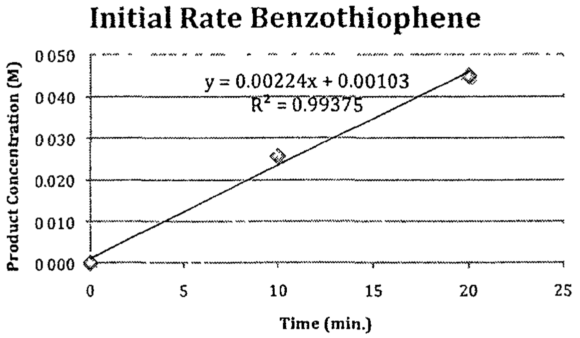
Trial 1

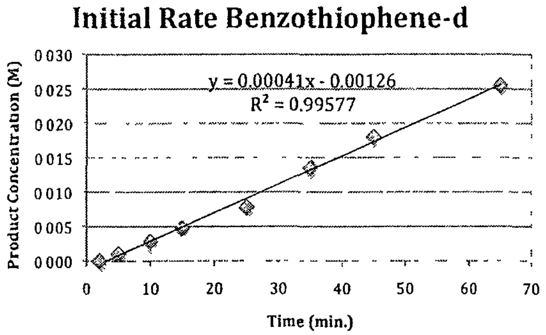




KIE = 0.00246 M/min / 0.00043 M/min = 5.7

Trial 2

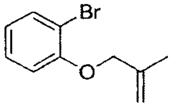




KIE = 0.00224 M/min / 0.00041 M/min = 5.5

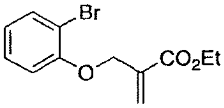
General Procedure for the Preparation of Starting Alkenes (D)

To a solution of aryl bromide (1 0 equiv) in DMF (0 5 M) was added 60% sodium hydride (1 1 equiv) and the mixture was stirred at room temperature for 30 minutes Allyl halide (1 2 equiv) was then added and the mixture was stirred until the reaction was judged to be 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



1-Bromo-2-(2-methylallyloxy)benzene (4.1)

Prepared according to general procedure D (15 0 mmol scale) The title compound was obtained as a colourless liquid (3 41 g, 91% yield) Exhibited spectral data in accordance with previous report [92] ^{1}H 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



Ethyl 2-((2-bromophenoxy)methyl)acrylate (4.2)

Prepared according to general procedure D (7 5 mmol scale) The title compound was obtained as a colourless liquid (1 67 g, 78% yield) R_f 0 85 (EtOAc/Hexanes 10/90), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7 55 (dd, J = 8 0, 1 6 Hz, 1H), 7 26 (ddd, J = 8 4, 7 2, 1 6 Hz, 1H), 6 93 (dd, J = 8 4, 1 2 Hz, 1H), 6 86 (ddd, J = 7 6, 7 6, 1 2 Hz, 1H), 6 44 (dt, J = 1 6, 1 6 Hz, 1H), 6 18 (dt, J = 2 0, 2 0 Hz, 1H), 4 81 (dd, J

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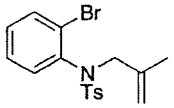
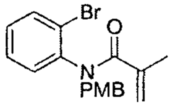
[92] Stanetty, P , Koller, H , Purstinger, G *Monatshefte fur Chemie* **1990**, *121*, 883

= 2.0, 2.0 Hz, 2H), 4.27 (q, J = 7.2 Hz, 2H), 1.33 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 154.6, 135.4, 133.4, 128.5, 126.3, 122.3, 113.5, 112.3, 66.8, 61.0, 14.2; IR (ν_{max}) 3071, 2985, 2906, 2872, 1718, 1591, 1477, 1282, 1158, 753, 649 cm^{-1}; HRMS Calcd for $C_{12}H_{13}O_3Br_1$ $[M]^+$ 284.0048, Found 284.0040.



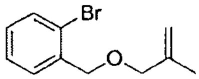
2-Bromo-N-tosyl-N-(2-methylallyl)aniline (4.3)

Prepared according to general procedure D (10.0 mmol scale). The title compound was obtained as a pale yellow solid (2.83 g, 78% yield). R_f 0.5 (EtOAc/Hexanes 25/75); mp: 99-100 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62-7.59 (m, 2H), 7.56 (dd, J = 7.6, 1.2 Hz, 1H), 7.28-7.24 (m, 3H), 7.18-7.13 (m, 2H), 4.74 (t, J = 1.2 Hz, 1H), 4.66 (q, J = 0.8 Hz, 1H), 4.15 (d, J = 4.4 Hz, 2H), 2.43 (s, 2H), 1.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.6, 139.9, 137.7, 136.5, 134.1, 132.3, 129.6, 129.5, 128.0, 127.7, 125.2, 115.9, 57.1, 21.6, 20.5; IR (ν_{max}) 3076, 2979, 2924, 1472, 1343, 1156, 1092, 718, 660, 570, 541 cm^{-1}; HRMS Calcd for $C_{17}H_{18}NO_2SBr$ $[M]^+$ 379.0242, Found 379.0205.



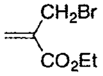
***N*-(2-Bromophenyl)-*N*-(4-methoxybenzyl)methacrylamide (4.4)**

Prepared according to the method reported Ruck *et al.*[99] (1.8 mmole scale). The title compound was obtained as a white solid (395 mg, 61% yield over 2 steps). R_f 0.20 (EtOAc/Petroleum Ether 10/90); mp: 45-46 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (ddd, J = 10.0, 4.0, 4.0 Hz, 1H), 7.14-7.10 (m, 4H), 6.79-6.75 (m, 2H), 6.70 (dd, J = 5.6, 3.6 Hz, 1H), 5.56 (d, J = 14.0 Hz, 1H), 4.97 (d, J = 20.0 Hz, 2H), 4.14 (d, J = 14.0 Hz, 1H), 3.77 (s, 3H), 1.82 (br s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 158.9, 141.2, 140.2, 133.6, 131.7, 130.6, 129.1, 128.9, 127.7, 123.4, 118.2, 113.6, 55.1, 50.8, 20.3; IR (ν_{max}) 3065, 2954, 2928, 2837, 1655, 1628, 1512, 1475, 1247, 1030, 756 cm^{-1}; HRMS Calcd for $C_{18}H_{18}NO_2Br$ $[M]^+$ 359.0521, Found 359.0522.



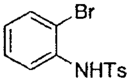
1-Bromo-2-((2-methylallyloxy)methyl)benzene (4.5)

Prepared according to general procedure D (20.0 mmol scale). The title compound was obtained as a colourless liquid (3.95 g, 82% yield). Exhibited spectral data in accordance with previous report.[93] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54-7.50 (m, 2H), 7.31 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H), 7.16-7.11 (m, 1H), 5.04 (br s, 1H), 4.94 (br s, 1H), 4.55 (s, 2H), 4.01 (d, *J* = 0.4 Hz, 2H), 1.79 (br s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.0, 137.8, 132.4, 128.9, 128.7, 127.3, 122.5, 112.4, 74.6, 71.2, 19.5.



Ethyl 2-(bromomethyl)acrylate (4.7)

A mixture of paraformaldehyde (1.65 g, 55.5 mmol) in H_3PO_4 (0.2 mL, 1N) and water (5 mL) was stirred at 90 °C for 1.5 hours, until the reaction formed a clear solution. After cooling down to room temperature, THF (5 mL), ethyl acrylate (5.43 mL, 50.0 mmol) and DABCO (1,4-diazabicyclo[2.2.2]octane) (550 mg, 5.0 mmol) were added and the mixture was stirred for 16 hours. Brine was added and the product was extracted with Et_2O (x3), washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was dissolved in Et_2O (50 mL) and cooled down to -10 °C. Phosphorus tribromide (25 mL, 1 M in DCM, 25.0 mmoles) was then slowly added and the mixture was stirred at room temperature for 3 hours. The mixture was cooled to 0 °C and water was added. The product was extracted with hexanes (x3), concentrated and purified by horizontal distillation under reduced pressure to give the corresponding product as a colourless liquid (1.73 g, 18% yield over 2 steps). Exhibited spectral data in accordance with previous report.[94] ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.33 (d, *J* = 0.8 Hz, 1H), 5.95 (d, *J* = 0.8 Hz, 1H), 4.28 (q, *J* = 7.2 Hz, 2H), 4.19 (d, *J* = 0.8 Hz, 2H), 1.35 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 137.5, 128,8, 61.2, 29.3, 14.1.



2-Bromo-N-tosylaniline (4.8)

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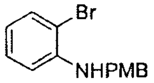
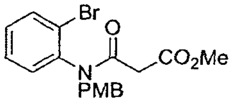
[93] Liron, F.; Knochel, P. *Tetrahedron Lett.* **2007**, *48*, 4943.
[94] Hediger, M. E. *Bioorg. Med. Chem.* **2004**, *12*, 4995.

Prepared according to the method reported by Kamal *et al.*[95] (10.0 mmol scale). The title compound was obtained as a pale yellow solid (1.85 g, 58% yield). Exhibited spectral data in accordance with previous report.[96] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.63 (m, 3H), 7.40 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.26 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H), 7.21 (d, *J* = 8.0 Hz, 2H), 6.98-6.94 (m, 3H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.2, 135.8, 134.7, 132.6, 129.7, 128.6, 127.3, 126.3, 122.5, 115.7, 21.6.



2-Bromo-*N*-(4-methoxybenzyl)aniline (4.9)

Prepared according to the method reported by McLaughlin *et al.*[97] (20.0 mmol scale). The title compound was obtained as a yellow oil (4.38 g, 75% yield). Exhibited spectral data in accordance with previous report.[98] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.30-7.26 (m, 2H), 7.13 (ddd, *J* = 8.4, 7.6, 1.6 Hz, 1H), 6.89 (m, 2H), 6.62 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.56 (ddd, *J* = 7.6, 7.6, 1.6 Hz, 1H), 4.66 (br s, 1H), 4.32 (d, *J* = 5.2 Hz, 2H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, CDCl3) δ 158.9, 144.8, 132.3, 130.6, 128.5, 128.4, 117.9, 114.1, 111.6, 109.6, 55.3, 47.5.



Methyl 3-((2-bromophenyl)(4-methoxybenzyl)amino)-3-oxopropanoate (4.10)

Prepared according to the method reported by Ruck *et al.*[99] (4.6 mmol scale). The title compound was obtained as a colourless oil (1.74 g, 97% yield). Exhibited spectral data in accordance with previous report.[99] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69-7.67 (m, 1H), 7.24-7.17 (m, 2H), 7.15-7.11 (m, 2H), 6.82-6.77 (m, 3H), 5.56 (d, *J* = 14.0 Hz, 1H), 4.02 (d, *J* = 14.0 Hz, 1H), 3.77 (s, 3H), 3.66 (s, 3H), 3.18 (d, *J* = 15.6 Hz, 1H), 3.08 (d, *J* = 16.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 165.7, 159.1, 139.8, 133.9, 131.6, 130.6, 130.2, 128.5, 128.4, 123.7, 113.7, 55.2, 52.3, 51.0, 41.6.

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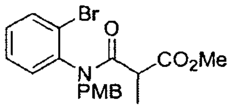
[95] Kamal, A.; Reddy, J. S.; Bharathi, E. V.; Dastagiri, D. *Tetrahedron Lett.* **2008**, 348.

[96] Krolski, M. E.; Renaldo, A. F.; Rudissil, D. E.; Stille J. K. *J. Org. Chem.* **1988**, *53*, 1170.

[97] McLaughlin, M.; Palucki, M.; Davies, I. W. *Org. Lett.* **2006**, *8*, 3307.

[98] Reisman, S. E.; Ready, J. M.; Weiss, M. M.; Hasuoka, A.; Hirata, M.; Tamaki, K.; Ovaska, T. V.; Smith, C. J.; Wood, J. L. *J. Am. Chem. Soc.* **2008**, *130*, 2087.

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

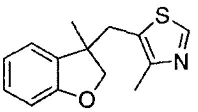


Methyl 3-((2-bromophenyl)(4-methoxybenzyl)amino)-2-methyl-3-oxopropanoate (4.11)

Prepared according to the method reported Ruck *et al.*[99] (2.2 mmol scale). The title compound was obtained as a colourless oil (735 mg, 81%, yield). The compound exists as a 1:3 mixture of rotamers. R_f 0.35 (EtOAc/Hexanes 25/75); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (dd, J = 8.0, 2.0 Hz, 0.25H), 7.66 (dd, J = 8.0, 2.0 Hz, 0.75H), 7.25-7.17 (m, 2H), 7.16-7.12 (m, 1.5H), 7.10-7.07 (m, 0.5H), 6.83-6.76 (m, 2.75H), 6.69 (dd, J = 7.2, 2.0 Hz, 0.25H), 5.65 (d, J = 14.4 Hz, 0.25H), 5.64 (d, J = 14.4 Hz, 0.75H), 3.96 (d, J= 14.4 Hz, 0.75H), 3.95 (d, J= 14.4 Hz, 0.25H), 3.78 (s, 2.25H), 3.77 (s, 0.75H), 3.70 (s, 0.75H), 3.61 (s, 2.25H), 3.15 (q, J = 7.2 Hz, 1H), 1.42 (d, J = 6.8 Hz, 2.25H), 1.29 (d, J = 7.2 Hz, 0.75H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 170.5, 169.9, 169.5, 159.0, 158.9, 139.9, 139.8, 134.1, 133.7, 131.9, 131.6, 130.6, 130.4, 130.0, 128.8, 128.2, 128.1, 123.8, 113.7, 113.6, 55.1, 52.3, 52.2, 51.0, 50.8, 44.1, 44.0, 14.5, 14.1; IR (ν_{max}) 3063, 2997, 2950, 2837, 1748, 1667, 1247, 1031, 659 cm^{-1}; HRMS Calcd for $C_{19}H_{20}NO_4Br$ $[M]^+$ 405.0576, Found 405.0551.

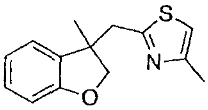
General Procedure for The Domino Heck-Direct Arylation Reaction (E)

K_2CO_3 (111 mg, 0.80 mmol, 2.0 equiv), XPhos (2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl) (9.5mg, 0.02 mmol, 5 mol%) and $Pd(OAc)_2$ (4.7 mg, 0.02 mmole, 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 (1.6 mmol, 4.0 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 and a 23G1 needle. The reaction mixture was stirred at 110 °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.



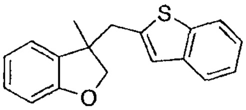
4-Methyl-5-((3-methyl-2,3-dihydrobenzofuran-3-yl)methyl)thiazole (4.12)

Prepared according to general procedure E. The title compound was obtained as a yellow oil (58% yield). R_f 0.15 (EtOAc/Hexanes 20/80); ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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}) 3054, 2964, 2931, 2886, 1480, 1228, 974, 751 cm^{-1}; HRMS Calcd for $C_{14}H_{15}NOS$ $[M]^+$ 245.0874, Found 245.0810



4-Methyl-2-((3-methyl-2,3-dihydrobenzofuran-3-yl)methyl)thiazole (4.13)

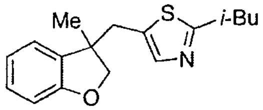
Prepared according to general procedure E using $P^tBu_3 \cdot HBF_4$ as the ligand. The title compound was obtained as a yellow oil (33%). R_f 0.50 (EtOAc/Toluene 25/75); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (ddd, *J* = 8.0, 7.6, 1.6 Hz, 1H), 7.11 (dd, *J* = 7.6, 0.8 Hz, 1H), 6.90 (ddd, *J* = 7.6, 7.6, 0.8 Hz, 1H), 6.76 (d, *J* = 8.0 Hz, 1H), 6.69 (s, 1H), 4.70 (d, *J* = 8.8 Hz, 1H), 4.17 (d, *J* = 9.2 Hz, 1H), 3.29 (d, *J* = 14.0 Hz, 1H), 3.24 (d, *J* = 14.4Hz, 1H), 2.42 (d, *J* = 1.2 Hz, 3H), 1.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 159.7, 152.3, 133.9, 128.6, 122.9, 120.6, 113.5, 109.9, 81.4, 46.0, 43.6, 25.5, 17.1; IR (ν_{max}) 3108, 2963, 2924, 2877, 1596, 1480, 1229, 974, 751 cm^{-1}; HRMS Calcd for $C_{14}H_{15}NOS$ $[M]^+$ 245.0874, Found 245.0839



3-(Benzo[*b*]thiophen-2-ylmethyl)-3-methyl-2,3-dihydrobenzofuran (4.14)

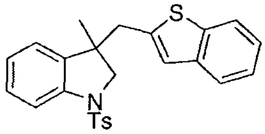
Prepared according to general procedure E. The title compound was obtained as a beige solid (76% yield). R_f 0.30 (EtOAc/Hexanes 5/95); mp: 62-63 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.8 Hz, 1H), 7.66 (d, *J* = 7.5 Hz, 1H), 7.33-7.24 (m, 2H), 7.17 (ddd, *J* = 8.0, 8.0, 0.8 Hz, 1H), 7.11(d, *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); ^{13}C NMR (100 MHz, $CDCl_3$) 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})

3068, 3028, 2962, 2928, 2879, 1596, 1480, 1457, 1228, 978, 748 cm^{-1}; HRMS Calcd for $C_{18}H_{16}OS$ $[M]^+$ 280.0922, Found 280.0901.



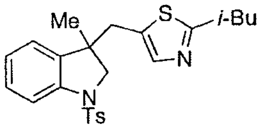
2-*Iso*butyl-5-((3-methyl-2,3-dihydrobenzofuran-3-yl)methyl)thiazole (4.15)

Prepared according to general procedure E. The title compound was obtained as a colourless oil (72% yield). R_f 0.30 (EtOAc/Hexanes 25/75); ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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}) 2959, 2931, 2872, 1745, 979 cm^{-1}; HRMS Calcd for $C_{17}H_{21}NOS$ $[M]^+$ 287.1344, Found 287.1283.



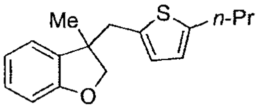
3-(Benzo[*b*]thiophen-2-ylmethyl)-3-methyl-1-tosylindoline (4.16)

Prepared according to general procedure E. The title compound was obtained as a white solid (84% yield). R_f 0.10 (EtOAc/Hexanes 10/90); mp: 121-122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65-7.60 (m, 3H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.32-7.23 (m, 3H), 7.08-7.00 (m, 2H), 6.97 (d, *J* = 8.0 Hz, 2H), 6.82 (s, 1H), 3.98 (d, *J* = 10.4 Hz, 1H), 3.60 (d, *J* = 10.4 Hz, 1H), 3.07 (d, *J* = 14.4 Hz, 1H), 3.00 (d, *J* = 14.4 Hz, 1H), 2.23 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9, 141.4, 140.3, 140.0, 139.4, 138.0, 133.9, 129.4, 128.5, 127.1, 124.1, 124.0, 123.8, 123.4, 123.2, 122.9, 121.9, 114.3, 60.5, 44.3, 41.3, 27.1, 21.5; IR (ν_{max}) 3057, 3034, 2967, 2929, 2871 1477, 1354, 1168, 1093, 750, 661, 578, 544 cm^{-1}; HRMS Calcd for $C_{25}H_{23}N_1O_2S_2$ $[M]^+$ 433.1170, Found 433.1120.



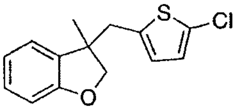
2-*Iso*butyl-5-((3-methyl-1-tosylindolin-3-yl)methyl)thiazole (4.17)

Prepared according to general procedure E. The title compound was obtained as a colourless oil (75% yield). R_f 0.10 (EtOAc/Hexanes 25/75); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.66 (m, 2H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.26-7.21 (m, 3H), 7.14 (s, 1H), 7.00 (ddd, *J* = 7.2, 7.2, 0.8 Hz, 1H), 6.94 (dd, *J* = 7.6, 0.8 Hz, 1H), 3.87 (d, *J* = 10.8 Hz, 1H), 3.51 (d, *J* = 10.8 Hz, 1H), 2.88 (d, *J* = 15.2 Hz, 1H), 2.83 (d, *J* = 15.2 Hz, 1H), 2.76- 2.67 (m, 2H), 2.36 (s, 3H), 2.01 (non, *J* = 6.4 Hz, 1H), 1.22 (s, 3H), 0.94 (dd, *J* = 6.4, 0.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.1, 141.6, 141.3, 137.7, 133.9, 132.2, 129.7, 128.6, 127.2, 123.5, 123.2, 114.4, 60.7, 44.1, 42.3, 37.9, 29.7, 26.1, 22.3, 22.2, 21.5; IR (ν_{max}) 3068, 2959, 2929, 2874, 1478, 1355, 1167, 1092, 746 cm^{-1}; HRMS Calcd for $C_{24}H_{28}N_2O_2S_2$ $[M]^+$ 440.1592, Found 440.1566.



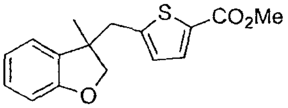
3-Methyl-3-((5-propylthiophen-2-yl)methyl)-2,3-dihydrobenzofuran (4.18)

Prepared according to general procedure E. The title compound was obtained as a colourless oil (76% yield). R_f 0.30 (EtOAc/Hexanes 5/95); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (ddd, *J* = 8.0, 8.0, 1.6 Hz, 1H), 7.06 (dd, *J* = 7.6, 1.2 Hz, 1H), 6.89 (t, *J* = 7.2 Hz, 1H), 6.77 (d, *J* = 8.0 Hz, 1H), 6.56 (d, *J* = 3.2 Hz, 1H), 6.49 (d, *J* = 3.6 Hz, 1H), 4.53 (d, *J* = 8.8 Hz, 1H), 4.12 (d, *J* = 8.8 Hz, 1H), 3.06 (d, *J* = 14.4 Hz, 1H), 3.00 (d, *J* = 14.4 Hz, 1H), 2.70 (t, *J* = 7.6 Hz, 2H), 1.64 (sex, 7.2 Hz, 2H), 1.40 (s, 3H), 0.95 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 144.5, 136.9, 134.7, 128.3, 126.6, 123.5, 123.0, 120.4, 109.7, 81.7, 46.1, 40.9, 32.1, 25.1, 24.8, 13.7; IR (ν_{max}) 3064, 2925, 2873, 2842, 1595, 1480, 1456, 977, 749 cm^{-1}; HRMS Calcd for $C_{17}H_{20}O_1S_1$ $[M]^+$ 272.1235, Found 272.1218.



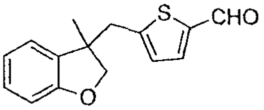
3-((5-Chlorothiophen-2-yl)methyl)-3-methyl-2,3-dihydrobenzofuran (4.19)

Prepared according to general procedure E. The title compound was obtained as a yellow oil (92% yield). R_f 0.40 (EtOAc/Hexanes 25/75); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (ddd, *J* = 7.2, 7.2, 1.2 Hz, 1H), 7.05 (ddd, *J* = 7.2, 1.2, 0.4 Hz, 1H), 6.89 (dd, *J* = 7.6, 7.6, 1.2 Hz, 1H), 6.77 (dd, *J* = 8.0, 0.4 Hz, 1H), 6.69 (d, *J* = 4.0 Hz, 1H), 6.43 (ddd, *J* = 3.6, 0.8, 0.8 Hz, 1H), 4.46 (d, *J* = 8.8 Hz, 1H), 4.13 (d, *J* = 8.8 Hz, 1H), 3.03 (dd, *J* = 14.8, 0.8 Hz, 1H), 2.97 (dd, *J* = 14.8, 0.4 Hz, 1H), 1.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 138.4, 133.8, 128.6, 128.0, 126.4, 125.6, 123.0, 120.6, 109.9, 81.4, 46.0, 41.3, 25.3; IR (ν_{max}) 3079, 3048, 2962, 2927, 2882, 1596, 1480, 1451, 1231, 990, 831, 750 cm^{-1}; HRMS Calcd for $C_{14}H_{13}OSCl$ $[M]^+$ 264.0376, Found 264.0347.



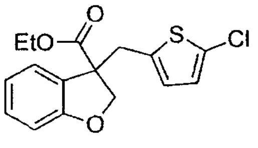
Methyl 5-((3-methyl-2,3-dihydrobenzofuran-3-yl)methyl)thiophene-2-carboxylate (4.20)

Prepared according to general procedure E. The title compound was obtained as a white solid (47% yield). R_f 0.50 (EtOAc/Hexanes 25/75); mp: 97-98 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 4.0 Hz, 1H), 7.16 (ddd, *J* = 8.0, 8.0, 1.6 Hz, 1H), 7.03 (dd, *J* = 7.2, 0.8 Hz, 1H), 6.89 (ddd, *J* = 7.2, 7.2, 0.8 Hz, 1H), 6.77 (d, *J* = 8.0 Hz, 1H), 6.61 (d, *J* = 4.0 Hz, 1H), 4.49 (d, *J* = 8.8 Hz, 1H), 4.14 (d, *J* = 8.8 Hz, 1H), 3.84 (s, 3H), 3.12 (d, *J* = 14.4 Hz, 1H), 3.08 (d, *J* = 14.4 Hz, 1H), 1.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 159.6, 147.4, 133.6, 133.3, 132.0, 128.7, 128.0, 123.0, 120.6, 109.9, 81.5, 52.0, 46.2, 41.3, 25.0; IR (ν_{max}) 3057, 2956, 2883, 1711, 1480, 1458, 1290, 1094, 748 cm^{-1}; HRMS Calcd for $C_{16}H_{16}O_3S$ $[M - C_7H_7O_2S]^+$ 133.0653, Found 133.0648.



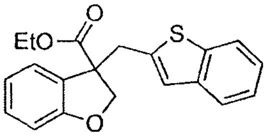
5-((3-Methyl-2,3-dihydrobenzofuran-3-yl)methyl)thiophene-2-carbaldehyde (4.21)

Prepared according to general procedure E. The title compound was obtained as a yellow oil (41% yield). R_f 0.35 (EtOAc/Toluene 5/95); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (s, 1H), 7.56 (d, *J* = 3.6 Hz, 1H), 7.16 (ddd, *J* = 7.2, 7.2, 1.2 Hz, 1H), 7.04 (dd, *J* = 7.6, 1.2 Hz, 1H), 6.90 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H), 6.76 (d, *J* = 8.0 Hz, 1H), 6.70 (d, *J* = 3.6 Hz, 1H), 4.49 (d, *J* = 8.8 Hz, 1H), 4.15 (d, *J* = 9.2 Hz, 1H), 3.14 (d, *J* = 1.2 Hz, 2H), 1.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.6, 159.6, 150.9, 142.8, 136.4, 133.3, 128.9, 128.5, 123.0, 120.7, 110.0, 81.4, 46.3, 41.7, 25.2; IR (ν_{max}) 3050, 2968, 2879, 2807, 1663, 1596, 1480, 1455, 1233, 753 cm^{-1}; HRMS Calcd for $C_{15}H_{14}O_2S_1$ $[M]^+$ 258.0715, Found 258.0698.



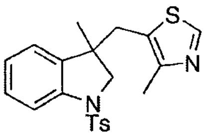
Ethyl 3-((5-chlorothiophen-2-yl)methyl)-2,3-dihydrobenzofuran-3-carboxylate (4.22)

Prepared according to general procedure E. The title compound was obtained as a yellow oil (55% yield). R_f 0.30 (100% Toluene); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (ddd, J = 7.6, 1.6, 0.4 Hz, 1H), 7.22 (ddd, J = 8.0, 7.6, 1.6 Hz, 1H), 6.92 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H), 6.81 (d, J = 8.0 Hz, 1H), 6.70 (d, J = 4.0 Hz, 1H), 6.52 (d, J = 3.6 Hz, 1H), 4.98 (dd, J = 9.6, 0.4 Hz, 1H), 4.48 (d, J = 9.2 Hz, 1H), 4.30-4.18 (m, 2H), 3.57 (d, J = 15.2 Hz, 1H), 3.19 (dd, J = 14.8, 0.8 Hz, 1H), 1.30 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 159.6, 137.0, 130.0, 128.9, 127.9, 126.7, 125.7, 124.4, 120.8, 110.2, 76.6, 61.9, 57.5, 38.6, 14.1; IR (ν_{max}) 3068, 2987, 2935, 2904, 1730, 1596, 1480, 1219, 1018, 750 cm^{-1}; HRMS Calcd for $C_{16}H_{15}O_3S_1Cl_1$ $[M]^+$ 322.0430, Found 322.0425.



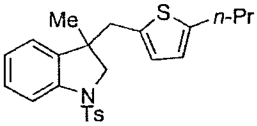
Ethyl 3-(benzo[b]thiophen-2-ylmethyl)-2,3-dihydrobenzofuran-3-carboxylate (4.23)

Prepared according to general procedure E. The title compound was obtained as a yellow oil (61% yield). R_f 0.35 (100% Toluene); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (dd, J = 8.0, 0.8 Hz, 1H), 7.67 (dd, J = 6.8, 1.2 Hz, 1H), 7.41 (dd, J = 7.2, 1.2 Hz, 1H), 7.33-7.21 (m, 3H), 6.99 (s, 1H), 6.93 (ddd, J = 7.6, 7.6, 0.8 Hz, 1H), 6.82 (d, J = 8.0 Hz, 1H), 5.04 (d, J = 9.6 Hz, 1H), 4.58 (d, J = 9.6 Hz, 1H), 4.32-4.20 (m, 2H), 3.82 (d, J = 14.8 Hz, 1H), 3.35 (dd, J = 14.8, 0.8 Hz, 1H), 1.30 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 159.6, 139.9, 139.5, 139.3, 129.9, 128.2, 124.4, 124.3, 124.1, 123.8, 123.1, 122.1, 120.8, 110.2, 76.6, 61.9, 57.4, 39.1, 14.1; IR (ν_{max}) 3056, 2983, 2904, 1730, 1594, 1480, 1214, 748 cm^{-1}; HRMS Calcd for $C_{20}H_{18}O_3S_1$ $[M]^+$ 338.0977, Found 338.0964.



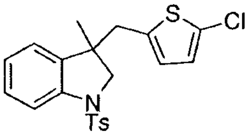
4-Methyl-5-((3-methyl-1-tosylindolin-3-yl)methyl)thiazole (4.24)

Prepared according to general procedure E. The title compound was obtained as a yellow oil (64% yield). R_f 0.05 (EtOAc/Hexanes 5/95); ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.43 (s, 1H), 7.67-7.62 (m, 3H), 7.27-7.20 (m, 3H), 6.98 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H), 6.83 (dd, J = 7.6, 0.8 Hz, 1H), 3.80 (d, J = 10.4 Hz, 1H), 3.51 (d, J = 10.0 Hz, 1H), 2.92 (d, J = 14.8 Hz, 1H), 2.86 (d, J = 14.8 Hz, 1H), 2.37 (s, 3H), 2.08 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 151.2, 150.0, 144.2, 141.4, 137.1, 133.7, 129.7, 128.6, 127.3, 125.9, 123.5, 123.3, 114.3, 61.0, 44.6, 36.9, 25.8, 21.5, 15.0; IR (ν_{max}) 3067, 3031, 2969, 2923, 2873, 1602, 1477, 1353, 1169, 756 cm^{-1}; HRMS Calcd for $C_{21}H_{22}N_2O_2S_2$ [M]$^+$ 398.1123, Found 398.10484.



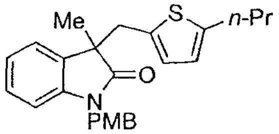
3-Methyl-3-((5-propylthiophen-2-yl)methyl)-1-tosylindoline (4.25)

Prepared according to general procedure E. The title compound was obtained as a yellow oil (67% yield). R_f 0.50 (EtOAc/Hexanes 10/90); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.69 (dd, J = 6.4, 1.6 Hz, 2H), 7.62 (d, J = 8.0 Hz, 1H), 7.24-7.20 (m, 3H), 7.01-6.96 (m, 2H), 6.51 (d, J = 3.6 Hz, 1H), 6.4 (d, J = 3.2 Hz, 1H), 3.96 (d, J = 10.4 Hz, 1H), 3.48 (d, J = 10.4 Hz, 1H), 2.82 (s, 2H), 2.67 (t, J = 7.6 Hz, 2H), 2.36 (s, 3H), 1.63 (sex, J = 7.6 Hz, 2H), 1.19 (s, 3H), 0.95 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 144.6, 143.9, 141.2, 138.6, 136.2, 134.0, 129.6, 128.2, 127.2, 126.8, 123.5, 123.4, 123.2, 114.3, 60.8, 44.3, 40.8, 32.0, 26.0, 24.8, 21.5, 13.6; IR (ν_{max}) 3066, 2962, 2926, 2869, 1476, 1455, 1351, 1169, 743 cm^{-1}; HRMS Calcd for $C_{24}H_{27}N_1O_2S_2$ [M - $C_8H_{11}S_1$]$^+$ 286.0902, Found 286.0890.



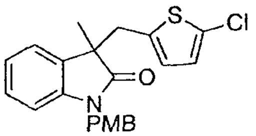
3-((5-Chlorothiophen-2-yl)methyl)-3-methyl-1-tosylindoline (4.26)

Prepared according to general procedure E. The title compound was obtained as a yellow solid (99% yield). R_f 0.35 (100% Toluene); mp: 85-86 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.63-7.61 (m, 3H), 7.26-7.19 (m, 3H), 7.03-6.98 (m, 2H), 6.57 (d, J = 4.0 Hz, 1H), 6.31 (d, J = 3.6 Hz, 1H), 3.82 (d, J = 10.0 Hz, 1H), 3.54 (d, J = 10.4 Hz, 1H), 2.90 (d, J = 14.8 Hz, 1H), 2.80 (d, J = 15.2 Hz, 1H), 2.37 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 144.1, 141.5, 138.0, 137.5, 133.7, 129.6, 128.6, 128.3, 127.2, 126.6, 125.3, 123.5, 123.2, 114.2, 60.2, 44.2, 40.9, 26.9, 21.6; IR (ν_{max}) 3066, 2966, 2923, 1598, 1477, 1354, 1167, 1091, 751, 662, 578, 544 cm^{-1}; HRMS Calcd for $C_{21}H_{20}NO_2S_2Cl$ $[M - C_5H_4S_1Cl_1]^+$ 286.0902, Found 286.0872.



1-(4-Methoxybenzyl)-3-methyl-3-((5-propylthiophen-2-yl)methyl)indolin-2-one (4.27)

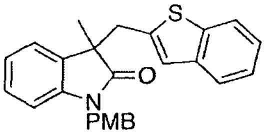
Prepared according to general procedure E. The title compound was obtained as a yellow solid (47% yield). R_f 0.35 (EtOAc/Toluene 10/90); mp: 96-97 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.24 (dd, J = 7.2, 0.8 Hz, 1H), 7.12 (ddd, J = 7.6, 7.6, 1.2, Hz, 1H), 7.04 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H), 6.78-6.75 (m, 2H), 6.72-6.69 (m, 2H), 6.53 (d, J = 8.4 Hz, 1H), 6.43 (d, J = 3.2 Hz, 1H), 6.38 (d, J = 3.6 Hz, 1H), 4.98 (d, J = 15.6 Hz, 1H), 4.48 (d, J = 15.6 Hz, 1H), 3.75 (s, 3H), 3.40 (d, J = 14.0 Hz, 1H), 3.22 (d, J = 14.0 Hz, 1H), 2.60-2.56 (m, 2H), 1.57-1.48 (m, 5H), 0.85 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 179.6, 158.7, 144.4, 142.8, 135.5, 133.1, 128.1, 128.0, 127.6, 126.6, 123.2, 123.0, 122.3, 113.9, 109.2, 55.2, 49.9, 43.0, 38.7, 32.1, 24.7, 23.7, 13.6; IR (ν_{max})3059, 2965, 2926, 2871, 2838, 1713, 1612, 1513, 1247, 1178, 747 cm^{-1}; HRMS Calcd for $C_{25}H_{27}NO_2S$ $[M]^+$ 405.1762, Found 405.1789.



3-((5-Chlorothiophen-2-yl)methyl)-1-(4-methoxybenzyl)-3-methylindolin-2-one (4.28)

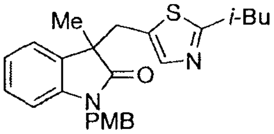
Prepared according to general procedure E. The title compound was obtained as a yellow oil (82% yield). R_f 0.45 (EtOAc/Toluene 10/90); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.26 (ddd, J = 7.2, 1.2, 0.4 Hz, 1H), 7.16 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H), 7.07 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H), 6.76-6.69 (m, 4H), 6.58-

6.56 (m, 2H), 6.39 (d, J = 4.0 Hz, 1H), 5.06 (d, J = 15.6 Hz, 1H), 4.41 (d, J = 15.6 Hz, 1H), 3.76 (s, 3H), 3.40 (d, J = 14.4 Hz, 1H), 3.18 (dd, J = 14.4, 0.8 Hz, 1H), 1.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.1, 158.8, 142.9, 137.0, 132.5, 128.4, 128.05, 128.0, 127.3, 126.5, 125.3, 122.8, 122.5, 114.0, 109.5, 55.2, 49.7, 43.0, 39.0, 23.8; IR (ν_{max}) 3058, 3006, 2965, 2926, 2835, 1711, 1612, 1513, 1248, 1034, 749 cm^{-1}; HRMS Calcd for $C_{22}H_{20}NO_2SCl$ $[M]^+$397.0903, Found 397.0929.



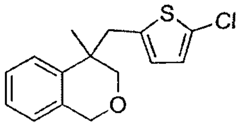
3-(Benzo[*b*]thiophen-2-ylmethyl)-1-(4-methoxybenzyl)-3-methylindolin-2-one (4.29)

Prepared according to general procedure E. The title compound was obtained as a yellow solid (67% yield). R_f 0.40 (EtOAc/Hexanes 25/75); mp: 111-113 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (t, J = 7.2 Hz, 2H), 7.37 (dd, J = 6.8, 1.6 Hz, 1H), 7.28 (dd, J = 7.6, 1.2 Hz, 1H), 7.22 (dd, J = 8.4, 1.2 Hz, 1H), 7.17- 7.09 (m, 2H), 6.94 (s, 1H), 6.48 (dd, J = 8.0, 1.2 Hz, 1H), 6.36 (d, J = 8.4 Hz, 2H), 5.99 (d, J = 8.8 Hz, 2H), 5.12 (d, J = 16.0 Hz, 1H), 4.27 (d, J = 15.6 Hz, 1H), 3.63 (d, J = 14.0 Hz, 1H), 3.53 (s, 3H), 3.37 (d, J = 14.4 Hz, 1H), 1.58 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.1, 158.4, 142.9, 140.0, 139.5, 139.45, 132.8, 128.4, 127.7, 126.9, 123.9, 123.8, 123.6, 123.3, 122.8, 122.5, 122.1, 113.4, 109.5, 55.1, 49.9, 42.9, 39.4, 24.2; IR (ν_{max}) 3056, 3013, 2967, 2927, 2838, 1711, 1612, 1513, 1247, 1177, 747 cm^{-1}; HRMS Calcd for $C_{26}H_{23}NO_2S$ $[M]^+$ 413.1449, Found 413.1454.



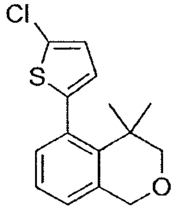
3-((2-*Iso*butylthiazol-5-yl)methyl)-1-(4-methoxybenzyl)-3-methylindolin-2-one (4.30)

Prepared according to general procedure E. The title compound was obtained as a yellowish solid (67% yield). R_f 0.35 (EtOAc/Toluene 25/75); mp: 81-82 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (dd, J = 7.2, 0.8 Hz, 1H), 7.21 (s, 1H), 7.14 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H), 7.05 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H), 6.89-6.87 (m, 2H), 6.76-6.73 (m, 2H), 6.60 (d, J = 7.2 Hz, 1H), 4.83 (d, J = 15.6 Hz, 1H), 4.56 (d, J = 15.2 Hz, 1H), 3.75 (s, 3H), 3.47 (d, J = 14.4 Hz, 1H), 3.20 (dd, J = 14.4, 0.8 Hz, 1H), 2.66-2.56 (m, 2H), 1.88 (non, J= 6.8 Hz, 1H), 1.53 (s, 3H), 0.84 (d, J = 6.8 Hz, 3H), 0.82 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.2, 169.6, 158.9, 142.8, 141.3, 132.5, 131.5, 128.4, 128.3, 127.6, 122.9, 122.5, 114.0, 109.3, 55.2, 49.5, 43.2, 42.2, 35.7, 29.6, 23.6, 22.2, 22.1; IR (ν_{max}) 3055, 2959, 2930, 2907, 2866, 2834, 1711, 1612, 1513, 1247, 1177, 747 cm^{-1}; HRMS Calcd for $C_{25}H_{28}N_2O_2S_1$ $[M]^+$ 420.1871, Found 420.1857.



4-((5-Chlorothiophen-2-yl)methyl)-4-methylisochroman (4.33)

Prepared according to general procedure E. Title compound is reported as a 6.5:1 molar ratio mixture with compound **21**. (65% yield for the mixture of **4.33** and **4.34**) Characterization of the major isomer is reported. R_f 0.25 (100% Toluene); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.18 (m, 3H), 7.00-6.97 (m, 1H), 6.71 (d, J = 3.6 Hz, 1H), 6.48 (ddd, J = 3.6, 0.8, 0.8 Hz, 1H), 4.88 (s, 2H), 3.82 (d, J = 11.6 Hz, 1H), 3.48 (d, J = 11.2 Hz, 1H), 3.19 (d, J = 14.8 Hz, 1H), 2.94 (d, J = 14.8 Hz, 1H), 1.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.8, 138.8, 134.0, 127.6, 126.7, 126.6, 126.3, 126.1, 125.1, 124.2, 73.4, 68.9, 40.9, 37.1, 23.5; IR (ν_{max}) 3069, 3019, 2964, 2940, 2838, 1447, 1101, 987, 762 cm^{-1}; HRMS Calcd for $C_{15}H_{15}OSCl$ $[M]^+$ 278.0532, Found 278.0528.



5-(5-Chlorothiophen-2-yl)-4,4-dimethylisochroman (4.34)

Prepared according to general procedure E. (65% yield for the mixture of **4.33** and **4.34**) A small amount of the compound was isolated by semi-prep HPLC for characterization only. R_f 0.25 (100% toluene); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (dd, J = 7.6, 7.6 Hz, 1H), 7.07 (ddd, J = 7.6, 1.2, 1.2 Hz, 1H), 6.99 (ddd, J = 7.6, 0.8, 0.8 Hz, 1H), 6.85 (d, J = 3.6 Hz, 1H), 6.75 (d, J = 3.6 Hz, 1H), 4.88 (s, 2H), 3.50 (s, 2H), 1.10 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3, 142.5, 134.8, 133.2, 132.6, 129.2, 126.9, 125.4, 125.25, 125.2, 78.5, 69.4, 34.8, 26.8; IR (ν_{max}) 3066, 2965, 2928, 2870, 1732, 1461, 1096, 798, 754 cm^{-1}; HRMS Calcd for $C_{15}H_{15}OSCl$ $[M]^+$ 278.0532, Found 278.0536.

ATTACHED ^{1}H AND ^{13}C NMR SPECTRA