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Direct Arylation of Aromatic Rings Using Palladium Catalysis

Laurence Caron

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for the M. Sc. degree in

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Candidate	Supervisor
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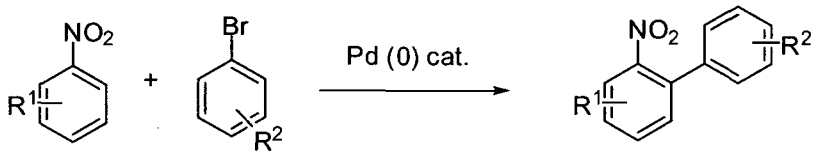
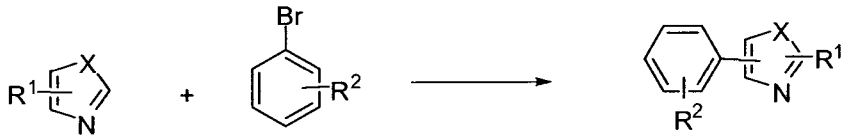
Abstract

The first section illustrates the novel route to access the biphenyl motif. Starting from simple materials, nitroarenes and aryl halides, we are able to obtain different cross-coupled products in good to moderate yields using palladium as a catalyst. The optimization of the reaction conditions as well as the various biaryl motifs obtained are described



The second section summarizes our efforts towards the development of universal reaction conditions that can be used for the arylation of a wide range of heterocycles. Although direct arylation products are available in the literature, no broadly accessible method is available yet. The heterocycles described are limited to azoles and the various motifs obtained are illustrated.



X= O, S, NR

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^{1}H NMR: proton nuclear magnetic resonance

^{13}C NMR: carbon nuclear magnetic resonance

Ac : acyl

Ac_2O: acetic anhydride

acac: acetylacetone

AcOH: Acetic acid

Ad: adamantyl

Ar: aryl

bp: boiling point

cat.: catalytic

C-C: carbon-carbon

C-H: carbon-hydrogen

CN: cyano

Cy: cyclo

DG: directing group

DMA: dimethlyacetamide

DME: dimethoxymethane

DMF: dimethylformamide

dppb: diphenylphosphino butane

dppf: diphenylphosphino ferrocene

dppp: 1,3-bis(diphenylphosphino)propane

equiv: equivalent

Et: ethyl

FG: functional group

GC-MS: gas chromatography-mass spectrometry

GLC: gas-liquid chromatography

h: hour

H_2O : Water

iPr: isopropyl

IR: infrared

K: kelvin

KOAc: potassium acetate

L: ligand

m: meta

M: molar

Me: methyl

MHz: megahertz

mL: millilitres

mol: mole

MS: molecular sieves

n : neo

NBu_3: tributylamine

n-BuLi: neo-butyl lithium

NMP: 1-methyl-2-pyrrolidone

o: ortho

OAc: Acetate

°C : degree Celsius

OPiv: Pivalate

OTf : triflate

o-tol : *ortho*-tolyl

p: para

Ph: phenyl

PhH: benzene

PhMe : Toluene

PivOH: Pivalic acid

p*Ka*: acid dissociation constant

Rf : reference frontline

t-Bu: tert-butyl

TFA: trifluoroacetic acid

THF: tetrahydrofuran

THMD : 2,2,6,6-tetramethyl-3,5-heptanedionate

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One last word of advice for students down the road: you can do whatever you want with chemistry; don't limit yourself to what the majority is doing!

It's not what you can do for chemistry, but what can chemistry do for you?

Chapter 1: Biaryls

1.1 General Introduction

The biaryl motif is found in products that have a wide array of uses, ranging from pharmaceuticals (Telmisartan, Valsartan, Glivec, Celebrex, Losartan), to antibiotics (Biphenomycin), to agrochemicals (Boscalid), to liquid crystals for LCD screens (NCB 807). Figure 1-1 highlights selected examples of these types of compounds. These products are of economic importance and as a result, a substantial amount of research has been focused on their synthesis.[1]

[1] Diovan was the 39th best selling pharmaceutical of 2007 in the US: for a complete list of the 200 top selling pharmaceuticals, see: Lamb, E. *www.pharmacytimes.com* **May 2008**, 20.

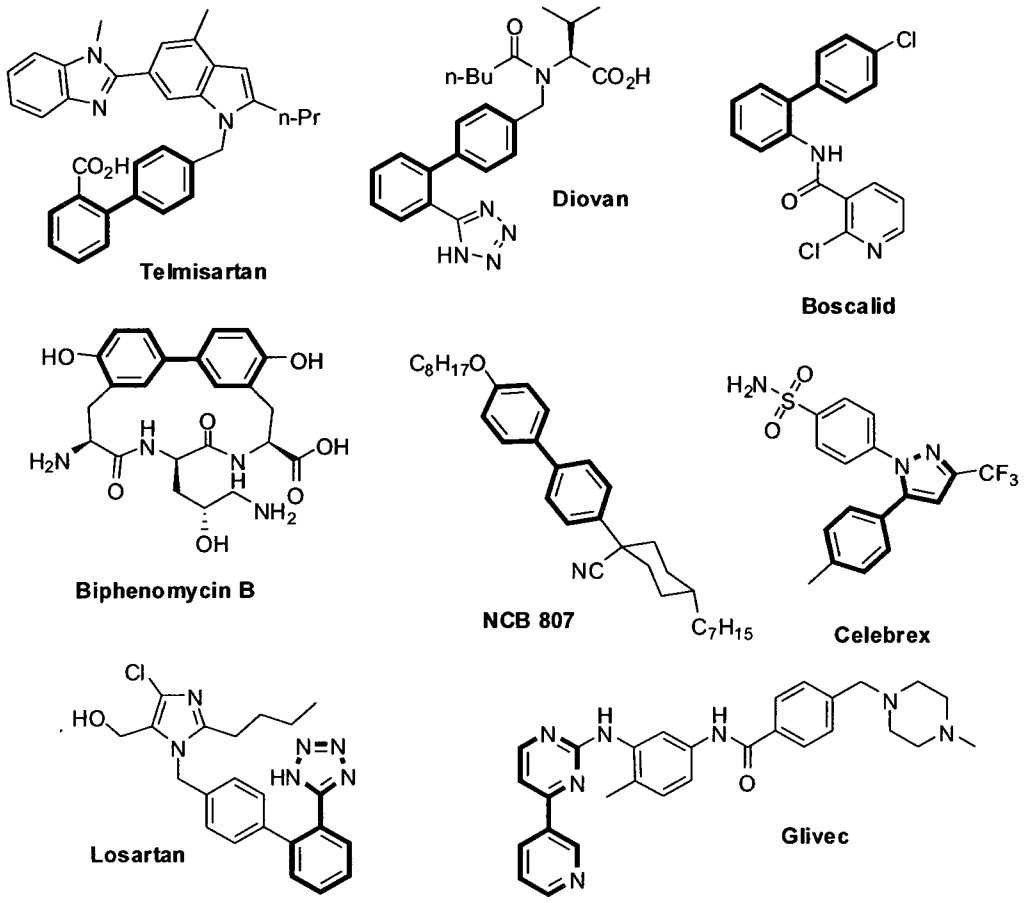


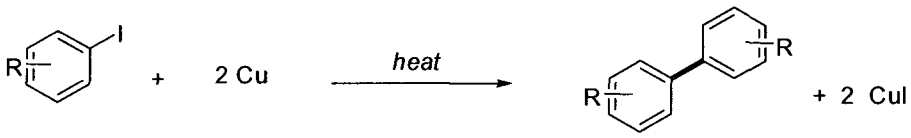
Figure 1-1: Biologically active molecules having the biaryl and heterobiaryl motif

The first part of this thesis will review the evolution of methods used to obtain the biaryl motif in the literature, from the Ullmann coupling to direct arylation. Traditional methods are first described and the transition to more efficient methods is presented afterwards. Representative examples are shown to complement the described methods. Although the direct arylation methods shown in this thesis are based on palladium catalysis, important advances using other transition metals are shown to illustrate the breadth of the field.

1.2 Traditional Methods of Accessing Biaryls

The easiest and most common strategy for synthesizing the biaryl motif is through the formation of the carbon-carbon bond linking the two arenes.[2] This method is the most straight forward and is ultimately the most efficient and economical route.

The first reaction to form a $C(sp^2)$-$C(sp^2)$ bond using stoichiometric copper was developed by Ullmann (Equation 1-1). This method was limited by harsh reaction conditions, like high temperatures, and by the lack of molecular diversity, given that only symmetrical biaryl molecules could be synthesized.[3,4] Since the development of organocuprate chemistry, transition metal catalyzed reactions have emerged as the preferential method of aryl-aryl bond formation and have launched a number of new developments in a rapidly evolving field that has become indispensable to synthetic organic chemistry.



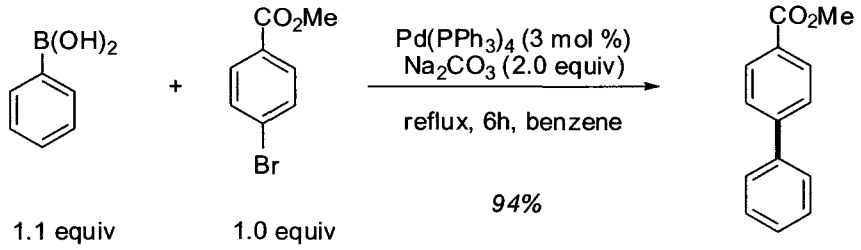
Equation 1-1: Classic Ullmann Reaction

Research is active in the area of transition metal catalyzed reactions.[2,5] Most aryl-aryl bonds are generated through the cross-coupling of an aryl halide or another electrophile with an organometallic reagent. The palladium-catalyzed Suzuki and Stille reactions have received a great deal of attention in the last 30 years as the preferred cross-coupling methodologies.[6]

---

[2] For a general review on aryl-aryl bond formation, see: Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359.
[3] Ley, S. V.; Thomas, A. W. *Angew. Chem. Int. Ed.* **2003**, *42*, 5400.
[4] Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337.
[5] For reviews on the use of transition metals in organic chemistry, see: (a) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127. (b) Rubin, M.; Rubina, M.; Gevorgyaan, V. *Chem. Rev.* **2007**, *107*, 3117. (c) Liu, S.; Xiao, J.; *J. Mol. Catal. A: Chem.* **2007**, *270*, 1. (d) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731.
[6] For selected reviews, see : (a) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed.* **2005**, *44*, 4442. (b) Netherton, M. R.; Fu, G.; *Top. Organomet. Chem.* **2005**, *14*, 85. (c) Stanforth, S. P. *Tetrahedron*, **2008**, *54*, 263. (d) Fairlamb, I. J. S. *Annu. Rep. Prog. Chem., Set. B.* **2006**, *102*, 50.

In the early 1980s, Suzuki revolutionized C-C bond formation by introducing boronic acids as a viable organometallic functionality that can be used in a palladium-catalyzed arylation reaction (Equation 1-2).[7] Unlike previous cross-coupling reactions, the organometallic moiety could be easily coupled to aryl halides using low catalyst loadings. Boronic acids, and their known derivatives, can be accessed from simple starting materials and are, for the most part, stable compounds. The resulting cross-coupled yields are impressive, delivering an efficient and reliable method for the formation of biaryl bonds.

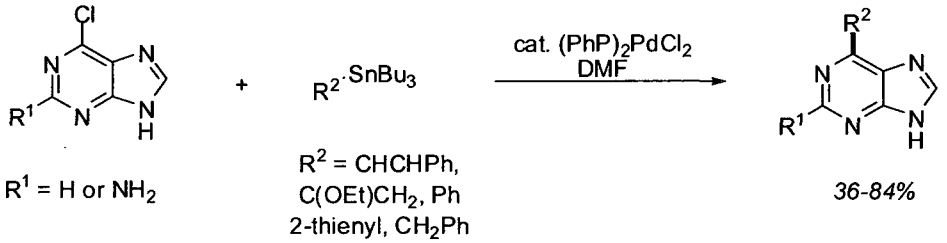


Equation 1-2: Suzuki cross-coupling

In 1986, Stille published his variant of a palladium–catalyzed cross-coupling reaction.[8] For this coupling, the organometallic functionality is an aryl or alkyl tin species (organostanannes).[9,10] These functionalities are stable to moisture, are widely available and are compatible with a wide array of functional groups on either coupling partners. For example, stanannes can be used for the elaboration of heterobiaryls or substituted biaryls. Gundersen demonstrated that 6-chloropurines can be efficiently coupled with a variety of organostanannes in moderate to excellent yields (Equation 1-3).[11]

---

[7] Miyaura, N, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513.
[8] Stille, J. K. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508.
[9] For selected examples of the stille coupling, see: (a) Pattenden, G.; Sinclair, D. J. *J. Organomet. Chem.* **2002**, *653*, 261. (b) Coelho, A. V.; de Souza, A. L. F.; de Lima, P. G.; Wardell, J. L.; Antunes, O. A. C. *Tetrahedron Lett.* **2007**, *48*, 7671. (c) Naber, J. R.; Buchwald, S. L. *Adv. Synth. Catal.* **2008**, *350*, 957. (d)
[10] For a more in depth look at the Stille reaction, see: Espinet, P.; Echavarren, A. M.; *Angew. Chem. Int. Ed.* **2004**, *43*, 4704.
[11] Gundersen, L.-L. *Tetrahedron Lett.* **1994**, *35*, 3155.



Equation 1-3: Stille cross-coupling

1.3 Metal-Catalyzed Cross-Coupling Reactions

Several metal-catalyzed cross-coupling reactions between organometallic functionalities and aryl halides, aryl triflates as well as other leaving groups have been developed to access the biaryl motif. Transition metal catalyzed reactions, such as the ones seen above as well as the Kumada[12] and Negishi[13] cross-coupling reactions all require the preactivation of the desired coupling partners. The term "preactivation" refers to the required transformation of the desired aryl coupling partner into its respective reactive moiety that can undergo the cross-coupling reaction (Scheme 1-1). For example, boronic acids and esters[14], stanannes[15], grignards,[16] and zincates[17] all need to be synthesizes from simpler precursors. Aryl halides and triflates can also be considered as "activated substrates" since they are often synthesized from simpler starting materials (Figure 1-1).

---

[12] Tamao, K. *J. Organomet. Chem.* **2002**, *653*, 23.

[13] For selected examples of the the Negishi coupling reaction, see: (a) Negishi, E.; Hu, Q.; Huang, Z. H. *Aldrichimica Acta,* **2005**, *38*, 71. (b) Abarbri, M.; Thibonnet, J.; Berillon, L.; Dehmel, F.; Rottlander, M.; Knochel, P. *J. Org. Chem.* **2000**, *65*, 4618.

[14] For the synthesis of boronic derivatives, see: (a) Skowronska-Ptasinska, M.; Aarts, V. M. L. J.; Egberink, R. J. M.; van Eerden, J.; Harkema, S.; Reinhoudt, D. N. *J. Org. Chem.* **1988**, *53*, 5484. (b) Browne, D. L.; Helm, M. F.; Plant, A.; Harrity, J. P. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 8656.

[15] For selected examples of the synthesis of stanannes, see: (a) Fleming, I.; Rowley, M. *Tetrahedron Lett.* **1986**, *27*, 5417. (b) Ito, S.; Okujima, T.; Morita, N. J. Chem. Soc. Perkin Trans. 1 2002, 16, 1896.

[16] For selected examples of the synthesis of grignards, see: (a) Sato, F. *J. Organomet. Chem.* **1985**, *285*, 53. (b) Burns, T. P.; Rieke, R. D. *J. Org. Chem.* **1983**, *48*, 4141. (c) Hoffmann, R. W. *Chem. Soc. Rev.* **2003**, *32*, 225.

[17] For selected examples of the synthesis of zincates, see: (a) Petrier, C.; de Souza Barbosa, J. C.; Dupuy, C.; Luche, J.-L. *J. Org. Chem.* **1985**, *50*, 5761. (b) Uchiyama, M.; Koike, M.; Kameda, M.; Kondo, Y.; Sakamoto, T. *J. Am. Chem. Soc.* **1996**, *118*, 8733.

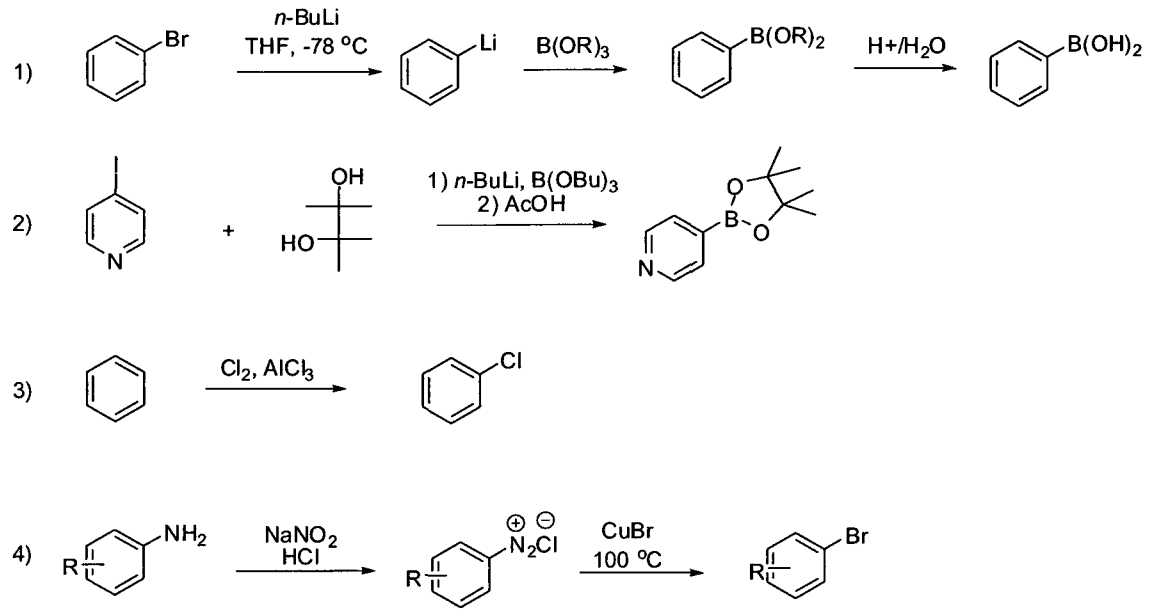
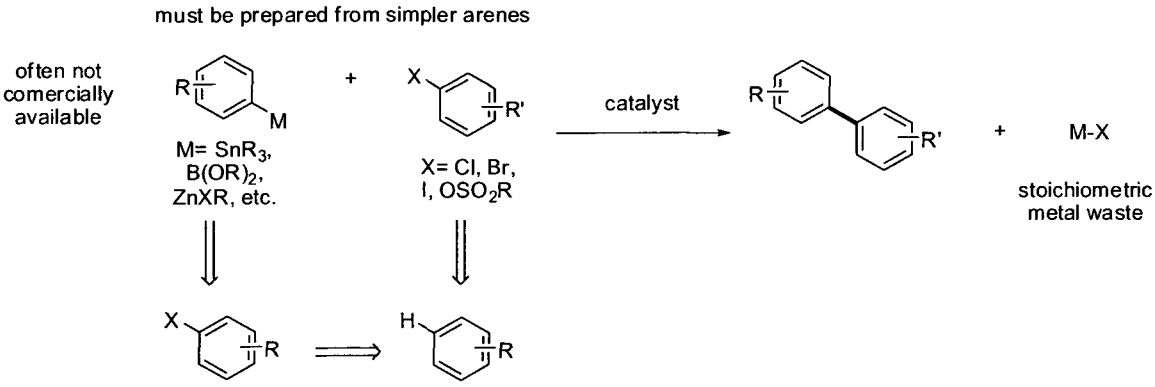


Figure 1-1: Multiple steps necessary for preactivation

Even with advances in the field of cross-coupling, certain limitations still accompany these metal-catalyzed reactions.[18] The inconveniences observed are due mainly to the organometallic preactivation. Organometallic reagents are often: (1) not commercially available for all regioisomers; (2) synthesized prior to the coupling reaction (Figure 1-1); (3) not compatible with all types of reaction conditions and (4) toxic. This reduces the synthetic utility and versatility of these reactions as well as creating unnecessary waste from reagents, solvents and purification (Scheme 1-1).



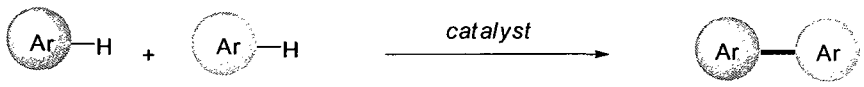
Scheme 1-1: Preactivation in cross-coupling reactions

[18] Alonso, F.; Beletskaya, I. P.; Yus, M. *Tetrahedron* **2008**, *64*, 3047.

Furthermore, the side products resulting from aryl-aryl bond formation are often overlooked. One of these by-products is a stoichiometric amount of metal waste, which is ultimately wasteful and toxic to the environment.[19] When efficacy of these types of cross-coupling reactions is considered, it is important to take into consideration the synthesis and/or preactivation of the coupling partners as well as the waste that is produced.

1.3.1 Oxidative Arene Cross-Coupling Reactions

In terms of atom economy, the most economical strategy is to couple two C-H bonds together (Equation 1-4). Until recently, this proposed reaction seemed unlikely. Since C-H bonds are often considered inert when compared to other functional groups, their possible lack of reactivity could be a problem.



Equation 1-4: Coupling of two unactivated arenes

Selectivity could also be difficult since the catalyst must distinguish between numerous C-H bonds on each arene and between the two starting aryls (Figure 1-1). The catalyst must avoid arene homocoupling and consumption of only one of the starting materials. Few reactions meet all of these demands. A few oxidative arene cross-coupling reactions have been developed, but the scope of these reactions is still very limited.[20]

---

[19] Sheldon, R. A. *Chem. Commun.* **2008**, 3352.

[20] For examples of cross-couplings with two C-H bonds, see: (a) Stuart, D. R.; Villemure, E.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 12072. (b) Dwight, T. A.; Rue, N. R.; Charyk, D.; Josselyn, R.; DeBoef, B.; *Org. Lett.* **2007**, *9*, 3137. (c) Hull, K. L.; Lanni, E. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 14047. (d) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 11904. (e) Li, R.; Jiang, L.; Lu, W. *Organometallics* **2006**, *25*, 5973. (f) Liégault, B.; Lee, D.; Huestis, M. P.; Stuart, D. R.; Fagnou, K. *J. Org. Chem.* **2008**, *73*, 5022.

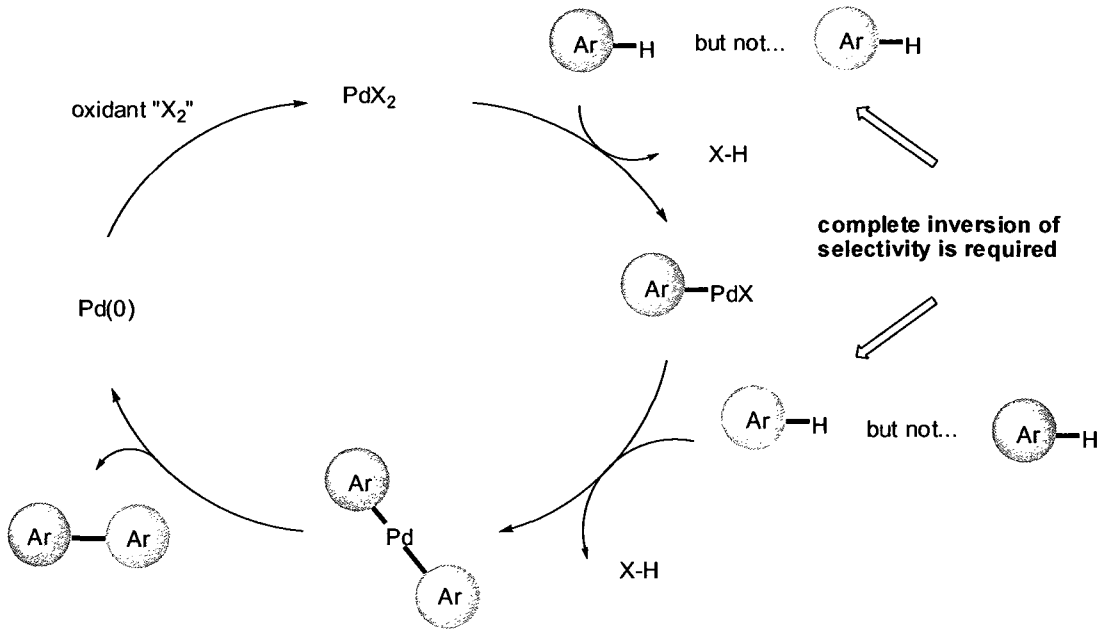


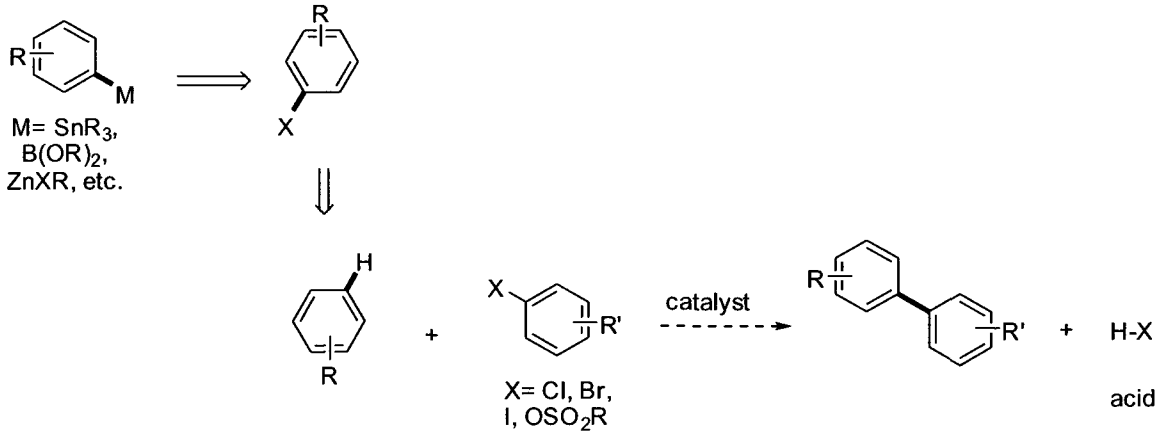
Figure 1-2: Prototypical arene catalytic cycle demonstrating the challenges associated with the coupling of two C-H bonds

In recent years, direct arylation or C-H bond functionalization has emerged as an attractive alternative to traditional cross-coupling methods as a way to access unsymmetrical biaryls. The reactions strive to improve the efficacy of aryl-aryl bond formation by only removing one of the preactivated coupling partners and replacing it with a simple arene. By treating the C-H bond as a functional group, just like the carbon-halogen or carbon-metal bond, the toxic waste of the reaction is greatly reduced. Efficacy is gained since the multiple chemical steps required for arene preactivation are eliminated. This strategy can be described by the term "direct arylation" (Scheme 1-2).[20d,21,22,23]

[21] For general 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) Seregin, I.V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. (d) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200. (e) Lewis, J. C.; Bergman, R. C.; Ellman, J. A. *Acc. Chem. Res.* **2008**, *41*, 1013.

[22] For recent examples of direct arylation using Pd(0), see: (a) Ackermann, L.; Vicente, R.; Born, R. *Adv. Synth. Catal.* **2008**, *350*, 741. (b) Lebrasseur, N.; Larrosa, I. *J. Am. Chem. Soc.* **2008**, *130*, 2926. (c) Shabazhov, D.; Daugulis, O. *J. Org. Chem.* **2007**, *72*, 7720. (d) Campeau, L.-C.; Bertrand-Laperle, M.; Leclerc, J.-P.; Villemure, E.; Gorelsky, S.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3276. (e) Derridj, F.; Gottumukkala, A. L.; Djebbar, S.; Doucet, H. *Eur. J. Inorg. Chem.* **2008**, 2250. (f) Chuprakov, S.; Chernyak, N.; Dudnik, A.; Gevorgyan, V. *Org. Lett.* **2007**, *9*, 2333.

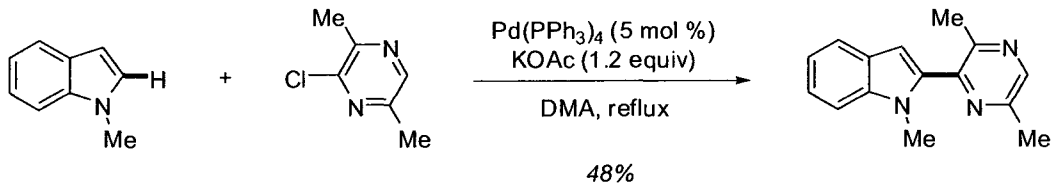
[23] For recent examples of direct arylation using Pd(II), see: (a) Beck, E. M.; Hatley, R.; Gaunt, M. J. *Angew. Chem. Int. Ed.* **2008**, *47*, 3004. (b) Wang, D.-H.; Wasa, M.; Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 7190. (c) Chiong, H. A.; Pham, Q.-N.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 9879.



Scheme 1-2: Replacement of the organometallic moiety with a simple C-H bond

Most research in this area is focused on the replacement of the problematic carbon-metal bond with a C-H bond. It is usually the most difficult partner to prepare and can be expensive, as complexity of the substitution pattern increases, or altogether unavailable. Aryl halides are most commonly used as the activated partner because of their ease of preparation and commercial availability. Furthermore, the waste generated with the replacement of the organometallic moiety, rather then the replacement of the halide, is a simple acid, which can easily be removed and disposed of without a great impact on the environment (Scheme 1-2).

To achieve direct arylation, a good starting point is to create or use an arene having the same reactivity as the preactivated arene. The first examples of direct-arylation were achieved with electron-rich heterocycles, such as indoles, over twenty years ago. Ohta observed that unsubstituted indole reacted at C2 with chlorodiazine under palladium catalysis (Equation 1-5).[24]

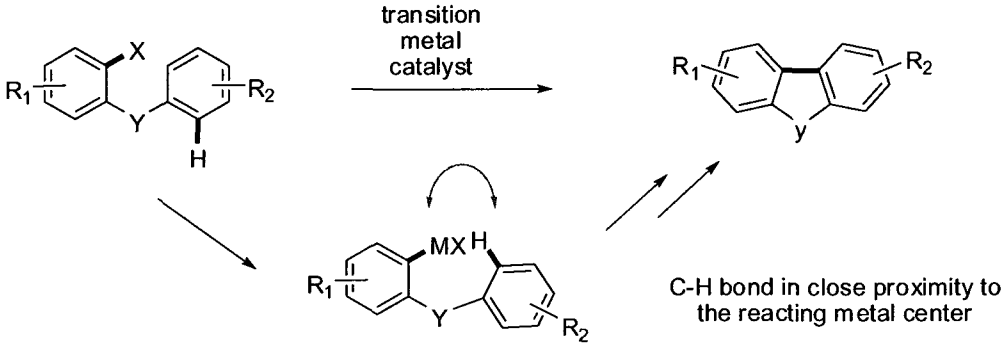


Equation 1-5: First direct arylation reaction of heterocycles

[24] Akita, Y.; Itagaki, Y.; Takizawa, S.; Ohta, A. *Chem. Pharm. Bull.* **1989**, *37*, 1477.

1.3.2 Direct Arylation

Intramolecular cross-coupling reactions were first developed. These reactions employ a tether to link the two reacting arenes and to limit the degree of freedom in the reaction media. The close proximity controls regioselectivity by bringing together the two reaction site and the catalyst so they can react selectively (Scheme 1-3).



Scheme 1-3: Intramolecular reactions bring the metal center in close proximity to the C-H bond that is to be functionalized

In the developmental stages, theses types of reactions typically suffered from a limited substrate scope as well as the use of high, even stoichiometric, catalyst loadings.[25] To overcome these challenges, new catalysts were developed. Recent advances are discussed in chapter 2.

Intermolecular reactions pose more potential problems than intramolecular reactions because of the metal catalyst's reactional freedom. This is a significant challenge to overcome and achieving regioselective arylation is difficult. The two factors that have an impact on regioselectivity are the electronics of the arene being functionalized and the presence of a directing group (Figure 1-3). Directing group-assisted direct arylation reactions are prevalent in the literature and usually employ a Lewis-basic heteroatom that can coordinate the metal catalyst and bring it into close proximity with the desired C-H bond.

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[25] For examples using 30 mol % of catalyst, see: (a) Kitamura, M.; Ohmori, K.; Kawase, T.; Suzuki, K. *Angew. Chem. Int. Ed.* **1999**, *38*, 1229. (b) Rice, J. E.; Cai, Z.-W.; He, Z.-M.; LaVaoie, E. J. *J. Org. Chem.* **1995**, *60*, 8101. For examples using 25 mol %, see: (c) Matsumoto, T.; Hosoya, T.; Suzuki, K. *J. Am. Chem. Soc.* **1992**, *114*, 3568.

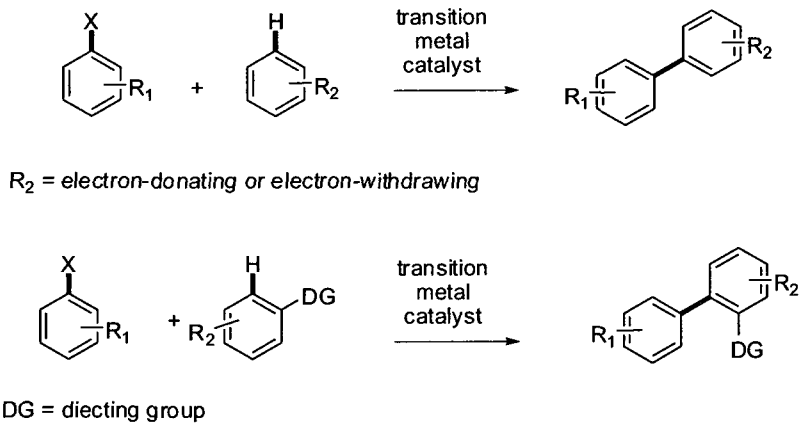


Figure 1-3: The two approaches that favour regioselective reactions

Whether it is for heteroarenes or simple arenes, regioselectivity is arguably the most important challenge in direct arylation. Heterocycles, however, have an advantage over simple arenes since they possess an inherent electronic bias due to the presence of heteroatoms in the aromatic ring. Heterocycles rarely need a directing group to control regioselectivity because the electronic properties are well known. This means that for most heteroarenes, reactivity is well established and can be correctly predicted.[26] A conscientious choice of reagents and additives is decisive in controlling regioselectivity.

1.4 Transition Metals Used in Direct Arylation

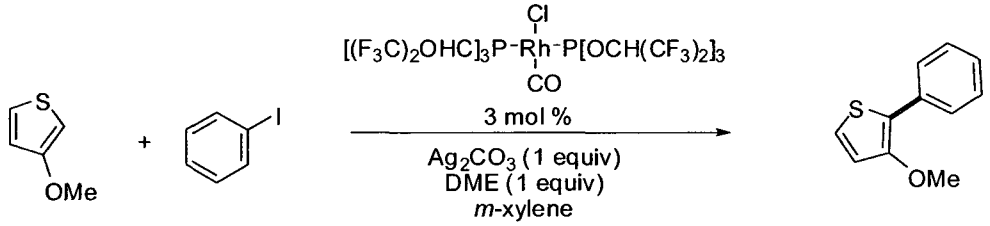
Palladium is the metal that has seen the most widespread use in C-C bond forming reactions and this thesis will be limited to reactions involving this metal..[27] Several reasons can explain its extensive use.[28] First of all, Pd catalysts and reagents are tolerant of a wide array of functional groups, relieving the usual efforts necessary for functional groups manipulation such as protecting group manipulations. Second, Pd

[26] *Heterocyclic Chemistry*; Joule, J.; Mills, K; Blackwell Publishing; USA, 2000.
[27] *Palladium Reagents and Catalysts;* Tsuji, J.; John Wiley & Sons: England, 2004.
[28] For reviews on the use of Pd in cross-coupling, see: (a) King, A. O.; Yasuda, N. *Top. Organomet. Chem.* **2004**, *6*, 205. (b) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed.* **2005**, *44*, 4442. (c) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

catalysts and reagents are not exceptionally sensitive and most reactions can be carried out without too many precautions due to oxygen and ambient moisture.[29]

Various other transition metals are used successfully in direct arylation such as rhodium[21e,30] ruthenium[31] and copper[32]. Relevant and recent examples using these metals are described to show the current progress in the field of direct arylation.

Various rhodium complexes are reactive in direct arylation. Itami and co-workers have shown that thiophene and other heterocycles can be arylated with iodobenzene via rhodium catalysis (Equation 1-6).[30g] Rhodium demonstrates surprising reactivity, but its widespread use is limited by its elevated cost.



75%

Equation 1-6: Direct arylation using a Rh catalyst

The use of ruthenium in direct arylation reactions is being investigated for ecological and economical reasons. Ackermann and co-workers recently presented

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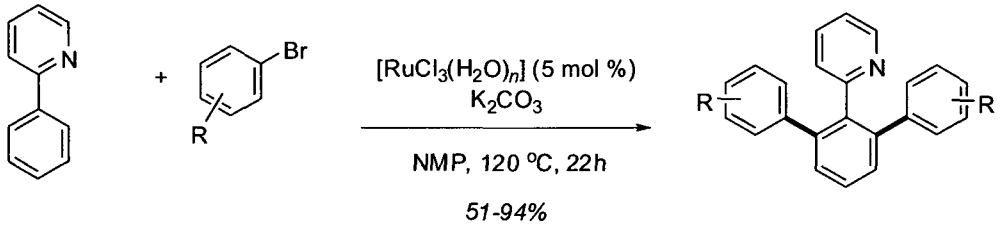
[29] For Pd-catalyzed reactions in aqueous media, see: Shaughnessy, K. H.; DeVasher, R. B *Curr. Org. Chem,* **2005**, *9*, 585.

[30] For recent examples of direct arylation using Rh, see: (a) Bedford, R. B.; Coles, S. J.; Hursthouse, M. B.; Limmert, M. E. *Angew. Chem. Int. Ed.* **2003**, *42*, 112. (b) Bedford, R. B.; Limmert, M. E. *J. Org. Chem.* **2003**, *68*, 8669. (c) Oi, S.; Watanabe, S.-I.; Fukita, S.; Inoue, Y. *Tetrahedron Lett.* **2003**, *44*, 8665. (d) Zhao, X.; Yu, Z. *J. Am. Chem. Soc.* **2008**, *130*, 8136. (e) Proch, S.; Kempe, R. *Angew. Chem. Int. Ed.* **2007**, *46*, 3135. (f) Lewis, J. C.; Berman, A. M.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 2493. (g) Yanagisawa, S.; Sudo, T.; Noyori, R.; Itami, K. *J. Am. Chem. Soc.* **2006**, *128*, 11748.

[31] For recent examples using Ru, see: (a) Ozdemir, I.; Demir, S.; Çetinkaya, B.; Gourlaouen, C.; Maseras, F.; Bruneau, C.; Dixneuf, P. H. *J. Am. Chem. Soc.* **2008**, *130*, 1156. (b) Ackermann, L.; Vicente, R.; Althammer, A. *Org. Lett.* **2008**, *10*, 2299. (c) Ackermann, L.; Althammer, A.; Born, R. *Tetrahedron*, **2008**, *64*, 6115. (d) Ackermann, L.; Althammer, A.; Born, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 2619. (e) Ackermann, L. *Org. Lett.* **2005**, *7*, 3123. (f) Oi, S.; Aizawa, E.; Ogino, Y.; Inoue, Y. *J. Org. Chem.* **2005**, *70*, 3113.

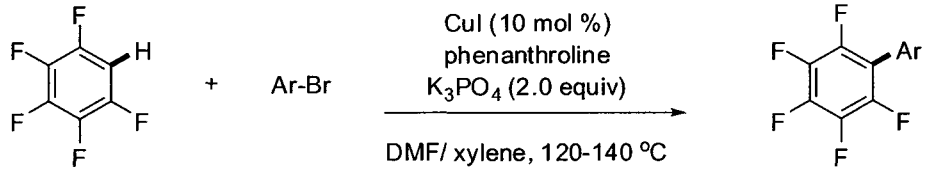
[32] For recent examples using Cu, see: (a) Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 8172. (b) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 1128. (c) Ackermann, L.; Potukuchi, H. K.; Landsberg, D.; Vicente, R. *Org. Lett.* **2008**, *10*, 3081.

direct arylation methodologies employing pyridine derivatives and simple ruthenium salts without the need for additional phosphorus-based ligands (Equation 1-7).[31c] These simple ruthenium salts are inexpensive and commercially available.



Equation 1-7: Direct arylation using a Ru catalyst

Although copper has long been employed as a stoichiometric reagent in the Ullman coupling reaction, its use as a catalyst is now being developed. Copper has the advantage of being less expensive than other transition metals. Daugulis and co-workers recently published the arylation of perfluorobenzene using only CuI and phenanthroline as an efficient catalyst system (Equation 1-8).[32b] Daugulis has also extended this methodology to the arylation of heterocycles.[33]



Equation 1-8: Direct arylation using Cu catalyst

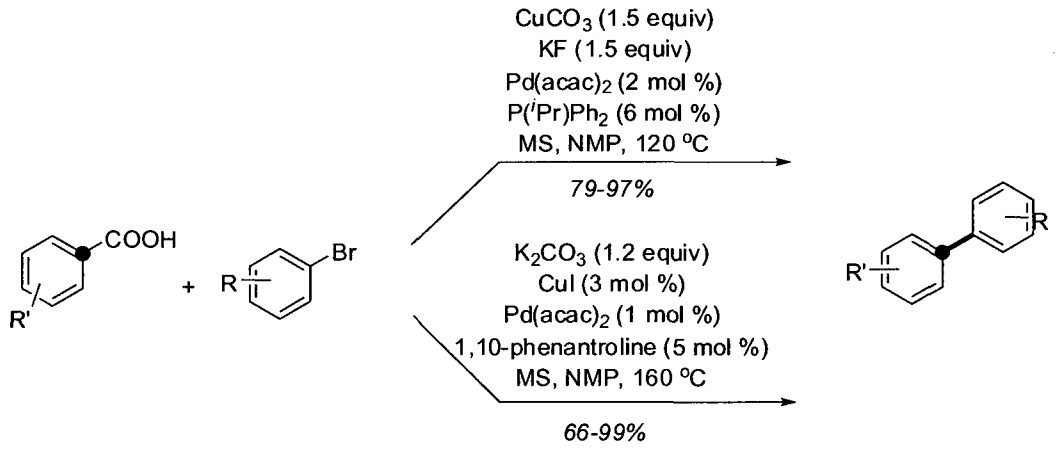
1.5 Alternative to Organometallic Functionalized Arenes

One major problem C-C bond forming reactions still face is site selectivity and how to arylate at one particular C-H bond. An emerging strategy is to replace the organometallic functionality with a more environmentally benign functional group, such

[33] Do, H.-Q.; Khan, R. M. K.; Daugulis, O. *J. Am. Chem. Soc.* **2008,** *ASAP Article* (DOI: 10.1021/ja805688p)

as carboxylic acids.[34] The decarboxylation reaction creates a powerful nucleophile with a static negative charge that can react regioselectively with a metal to form the desired biaryl compound. Benzoic acids are inexpensive and commercially available. Although the starting materials are stable and can easily be derived, the presence of the carboxylic acid can still be described as an activating group, since it is removed in the cross-coupling step and does not appear in the final biaryl molecule. Fortunately, the side product is the naturally occurring carbon dioxide.

Goossen and co-workers have developed two efficient sets of reaction conditions that promote decarbloxylation followed by arylation (Scheme 1-4).[34C] Low catalyst loading can be used to obtain biaryls in good to excellent yields.



Scheme 1-4: Two different pathways can be used in decarboxylative arylation

[34] For examples of decarboxylative cross-coupling reactions, see: (a) Becht, J.-M.; Catala, C.; Le Drian, C.; Wagner, A. *Org. Lett.* **2007**, *9*, 1781. (b) Becht, J.-M.; Le Drian, C. *Org. Lett.* **2008**, *10*, 3161. (c) Goossen, L. J.; Deng, G.; Levy, L. M. *Science* **2006**, *313*, 662. (c) Goossen, L. J.; Rodríguez, N.; Melzer, B.; Linder, C.; Deng, G.; Levy, L. M. *J. Am. Chem. Soc.* **2007**, *129*, 4824. (e) Goossen, L. J.; Melzer, B. *J. Org. Chem.* **2007**, *72*, 7473. (f) Forgione, P.; Brochu, M.-C.; St-Onge, M.; Thesen, K. H.; Bailey, M. D.; Bilodeau, F. *J. Am. Chem. Soc.* **2006**, *128*, 11350. (g) Beaudoin, O. *Angew. Chem. Int. Ed.* **2007**, *49*, 1373.

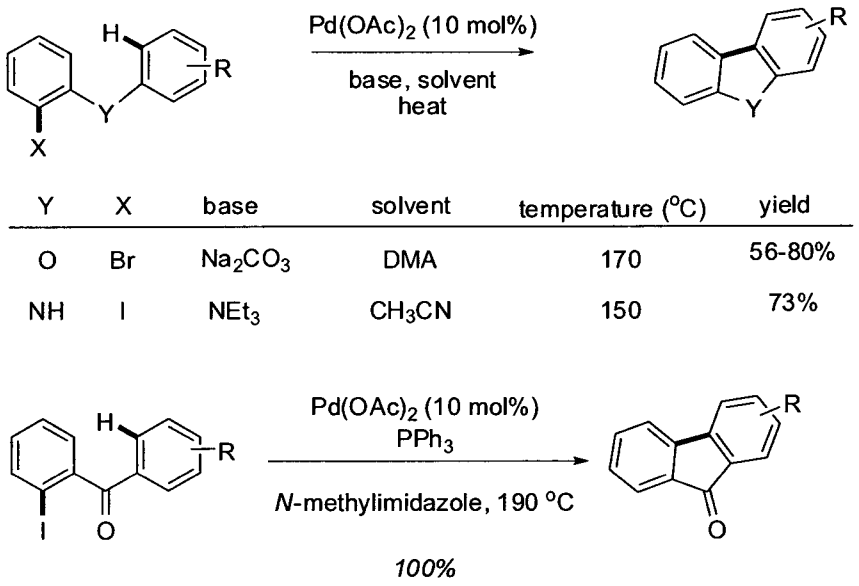
Chapter 2: Direct Arylation of Simple Arenes

2.1 Intramolecular Direct Arylation

Chemists are relying more and more on the economical direct arylation strategy. The removal of activating groups used in traditional carbon-carbon bond forming reactions has simplified chemistry and given rapid access to a wide variety of compounds. Intramolecular direct arylation reactions were the first to appear and they are considered to be a stepping stone for intermolecular reactions. Intramolecular reactions permit rapid development of potent catalyst systems. The developed methodologies have the possibility to then be applied to an intermolecular direct arylation approach. [35]

The first published work demonstrating intramolecular palladium-catalyzed direct arylation reactions was completed by Ames and Opalko in the 1980's. A multitude of dibenzofurans are obtained using 10% $Pd(OAc)_2$ and Na_2CO_3 in DMA at a 170 °C. The polycyclic compounds are achieved in moderate to good yields. Following these attractive results, the authors were able to vary the tether from oxygen to nitrogen and carbonyl, and obtain various five-membered fused polycyclic compounds in good yields (Scheme 2-1).[36]

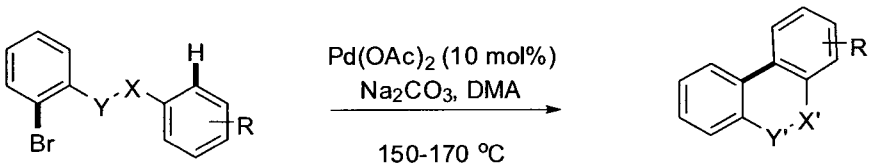
[35] Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581.
[36] Ames, D. E.; Opalko, A. *Synthesis* **1983**, 234.



Y	X	base	solvent	temperature (°C)	yield
O	Br	Na_2CO_3	DMA	170	56-80%
NH	I	NEt_3	CH_3CN	150	73%

Scheme 2-1: Intramolecular direct arylation using Ames and Opalko's conditions

The fused ring was expanded to a six-membered ring and methyl amides, amides, esters, and sulphonamides were used as tethers (Scheme 2-2).[37] Although the yields vary from poor to excellent, the novelty of these reactions was a turning point for intramolecular reactions.



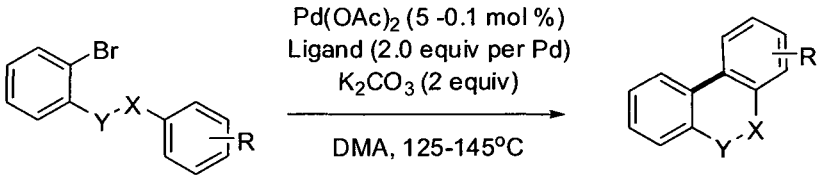
Y	X	Y'	X'	yield
CO	O	CO	O	41%
NH	CO	NH	CO	53%
CO	NMe	CO	NMe	50%
NSO_2Ph	SO_2	NH	SO_2	56%

Scheme 2-2: Variation of the tether to access various polycyclic compounds

Following these benchmark results, intramolecular reactions evolved. Fagnou and co-workers have developed de novo reaction conditions with enhance catalyst

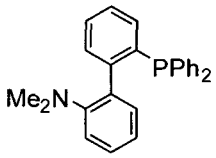
[37] Ames, D. E.; Opalko, A. *Tetrahedron* **1984**, *40*, 1919.

activity and an extensive scope. In their first report, the catalyst loading could be lowered to 0.1 mol % (Scheme 2-3).[38] Ten polycyclic compounds were obtained in higher then 80 % yield, using various tethers, including carbon, oxygen and carbonyl functional group.



as low as 0.1 mol% Pd

Y	X	yield
O	CH_2	90-98%
CH_2	O	91%
NMe	CO	83%
CH_2	CH_2	79%

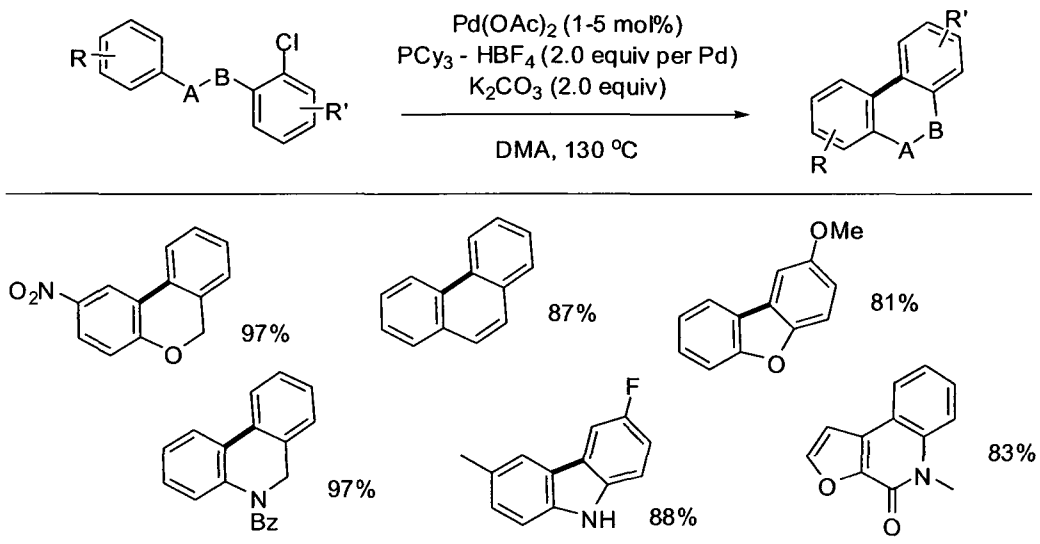


Ligand

Scheme 2-3: Intramolecular direct arylation using Fagnou and co-workers' conditions is possible with a wide range of tethers

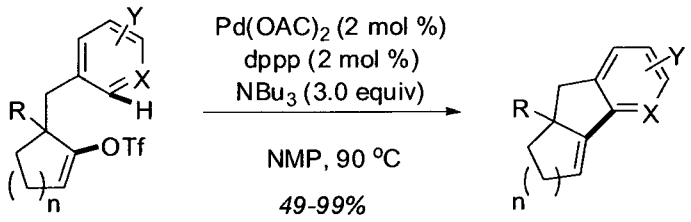
Following their initial investigation, the group was able to extend the system to couple aryl iodides and chlorides.[35] Although aryl iodides are often regarded as the most reactive halide in arylation, poor results were obtained using this halogen. Addition of an iodide-sequestering agent had to be used to achieve complete conversion. More interestingly, the less expensive and readily available aryl chlorides reacted in high yield and selectivity. A wide array of tethers could be used including carbon, oxygen, and nitrogen. Scheme 2-4 illustrates some of the polycyclic compounds obtained using this methodology.

[38] Campeau, L.-C.; Parisien, M.; Leblanc, M.; Fagnou, K. *J. Am. Chem. Soc.* **2004**, *126*, 9186.



Scheme 2-4: Intramolecular direct arylation of aryl chlorides using Fagnou and co-workers' conditions

Aryl halides can be substituted by pseudo-halides in palladium-catalyzed direct arylation. In 2007, Willis and co-workers showed that alkenyl triflates could be used instead of aryl halides in the formation of carbocycles (Equation 2-1).[39] Good to excellent yields were obtained using a relatively low catalyst loading. Only 2 mol % of $Pd(OAc)_2$ and 2 mol % of 1,3-bis(diphenylphosphino)propane (dppp) were needed. A variety of functional groups was tolerated on the benzene ring. The benzene ring can be substituted by various heterocycles. The use of polar non-protic solvents, like NMP, was necessary to achieve complete conversion.

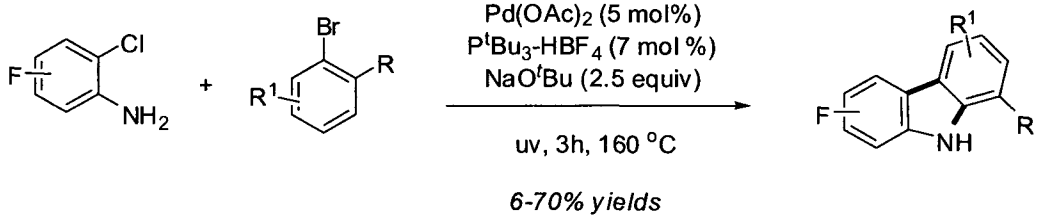


Equation 2-1: Intramolecular direct arylation using alkenyl triflates

A popular motif for intramolecular direct arylation is carbazoles. The formation of the nitrogen-tethered arenes is well documented in the literature, providing easy access

[39] Cruz, A. C. F.; Miller, N. D.; Willis, M. C. *Org. Lett.* **2007**, *9*, 4391.

to the starting materials. Carbazoles are present in many pharmaceuticals, natural product and other chemical products.[40] Various groups have described the formation of carbazole-type compounds using transition metals.[41] Recently, Bedford and co-workers described a one-step synthesis of fluorocarbazoles via sequential amination and C-H insertion (Equation 2-2).[42] Moderate to good yields are obtained with aryl chlorides but the methodology is limited to *ortho*-substituted aryl halides.



Equation 2-2: One-pot synthesis of carbazoles from simple staring materials

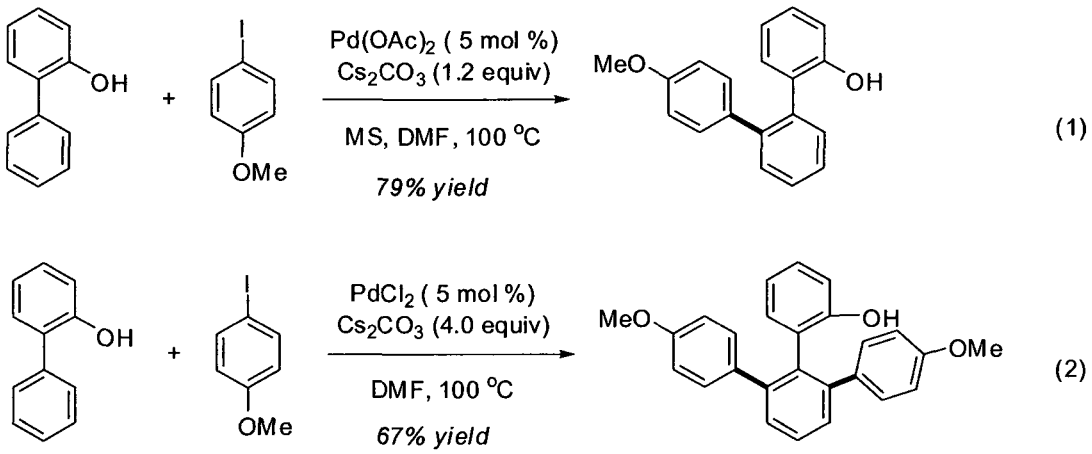
2.2 Directing Group-Assisted Arylation

2.2.1 Oxygenated Directing Groups

The first example of intermolecular direct arylation was demonstrated by Miura and co-workers in 1997. Using an alcohol as a directing group, 2-phenylphenols and naphthols were arylated in good yield using a palladium catalyst (Scheme 2-5).[43] Two sets of conditions were elaborated, creating the opportunity to selectively choose between mono or diarylated products. The authors propose that regioselectivity is

[40] Tsang, W. C. P.; Munday, R. H.; Brasche, G.; Zheng, N.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 7603.
[41] For selected examples of the synthesis of carbazole through direct arylation, see: (a) Franck, P.; Hostyn, S.; Dajka-Halász, B.; Polonka-Bálint, A.; Monsieurs, K.; Mátyus, P.; Maes, B. U. W. *Tetrahedron* **2008**, *64*, 6030. (b) Liu, Z.; Larock, R. *Org. Lett.* **2007**, *6*, 3739. (c) Liu, Z.; Larock, R. *Tetrahedron* **2007**, *63*, 347.
[42] Bedford, R. B.; Betham, M.; Charmant, J. P. H.; Weeks, A. L. *Tetrahedron* **2008**, *64*, 6038.
[43] (a) Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1740. (b) Satoh, T.; Inoh, J.-I.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem Soc. Jpn.* **1998**, *71*, 2239.

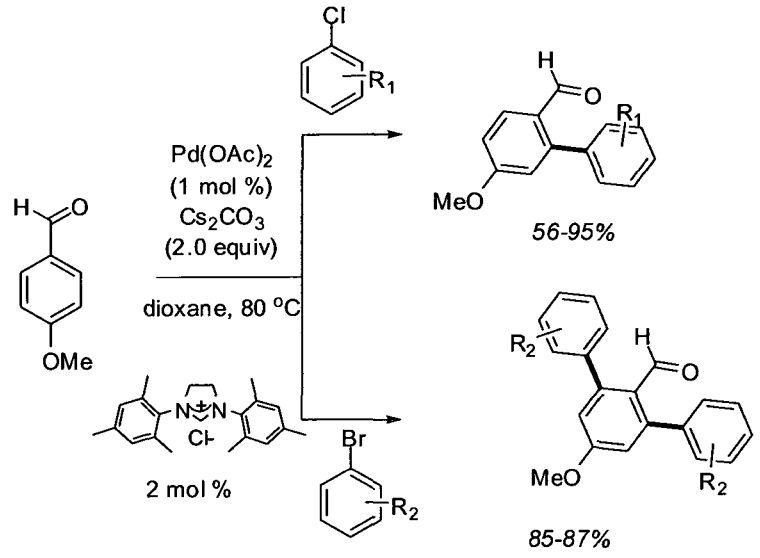
controlled by the interaction between the phenolate and the palladium catalyst. This brings the metal center in close proximity to the ortho C-H bond.



Scheme 2-5: Phenols can be used as efficient directing group for direct arylation

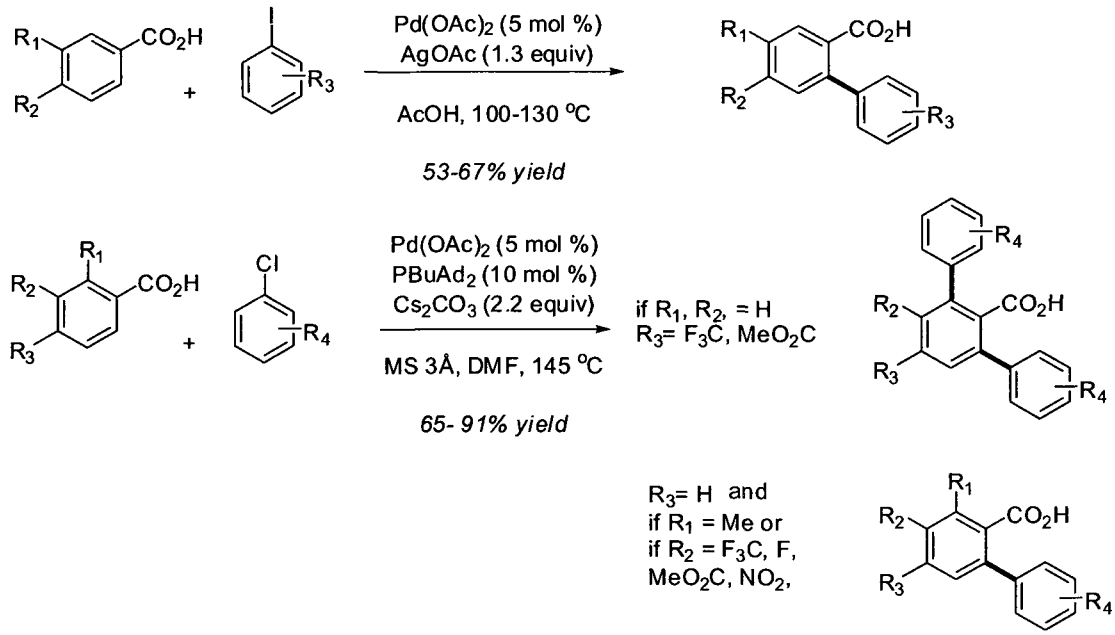
Others oxidation states of oxygen are used as directing groups. In 2005, Çetinkaya and co-workers reported the use of the aldehyde functionality as a directing group.[44] The authors were able to selectively arylate a variety of benzaldehyde derivatives using $Pd(OAc)_2$, an *N*-heterocyclic carbene ligand, and Cs_2CO_3 (Scheme 2-6). Good selectivity between mono and diarylated products is possible by varying the aryl halide while using the same set of reaction condition. If aryl chlorides are used, the monoarylated product can be achieved, while aryl bromides provide the diarylated product in excellent yield.

[44] Gürbüz, N.; Özdemir, I.; Çetinkaya, B. *Tetrahedron Lett.* **2005**, *46*, 2273.



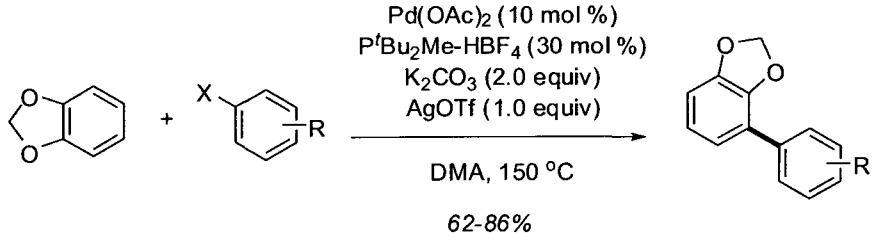
Scheme 2-6: Aldehydes can be used as efficient directing group for direct arylation

Carboxylic acids are also used as directing groups. In 2007, Daugulis and co-workers described the arylation of benzoic acid using either aryl iodides or aryl chlorides (Scheme 2-7).[23c] For arylation using aryl iodides, the conditions are: $Pd(OAc)_2$, AgOAc in acetic acid at 100-130 °C. $Pd(OAc)_2$, $PBuAd_2$, Cs_2CO_3 and molecular sieves in DMF at 145 °C are used with aryl chlorides. Diarylated products were often present unless there was substitution in the *ortho* or the *meta* position of benzoic acid. The authors believe that the carboxylic acid forms a metallacyle with the Pd catalyst which induces the observed regioselectivity. Furthermore, the removal of the carboxylic acid post-arylation can easily be achieved, removing any trace of the directing group.



Scheme 2-7: Carboxylic acids can be used as efficient directing group for direct arylation

Fagnou and co-workers demonstrated the use of another type of oxygen containing directing group. An ether directing group is employed to selectively arylate benzodioxole (Equation 2-3).[35] With aryl chlorides and bromides, biphenyls can be obtained in moderate to good yields. Arylation occurs selectively using $Pd(OAc)_2$, $P^tBu_2Me\text{-}HBF_4$, K_2CO_3 and AgOTf at 150 °C.

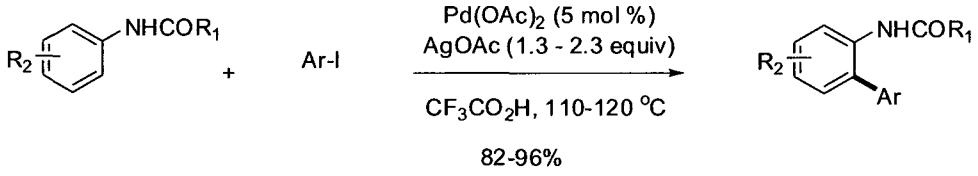


Equation 2-3: Ethers can be used as efficient directing group for direct arylation.

2.2.2 Nitrated Directing Groups

Arguably, the most widely used directing groups include a nitrogen atom. The element can easily bind to the metal catalyst because of its Lewis basic properties. Nitrogen-containing directing groups include amides, imines and pyridine heterocycles. In the last couple of years, new methods employing a vast choice of nitrogen directing groups have appeared.

Daugulis and co-workers used various nitrogen containing functional groups for direct arylation.[22d,45] Amides were shown to be potent directing group that can cross-couple anilides with aryl iodides (Equation 2-4). The amide can either be methyl (R_1 = Me) or ethyl (R_1 = Et). The anilide group can be easily removed through base hydrolysis affording aniline derivatives.



Equation 2-4: Anilides can be used as efficient directing group for direct arylation

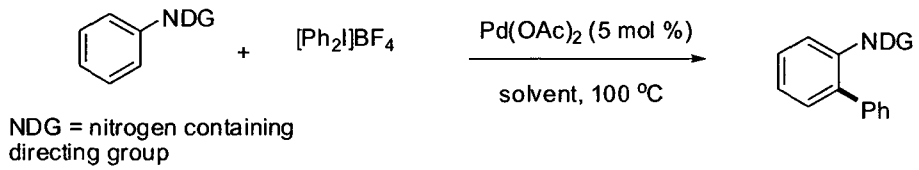
Sanford and co-workers have described the use of nitrogen containing directing groups that include amides and a diverse array of heterocycles.[46] Pyridines, quinolines, pyrrolidinones and methyl anilides can be used to selectively direct mono-arylation (Scheme 2-8). The authors also offer an alternative to aryl halides or alkyl triflates by using hypervalent iodide species as the activated coupling partner. Although iodide arylating agents are less common, they have proven efficacy[47] and can be used as their air-stable tetrafluoroborate salt. The direct arylation conditions use $Pd(OAc)_2$, $NaHCO_3$ (or no base) and AcOH, $AcOH/Ac_2O$, C_6H_6, or toluene as the solvent at 100 °C. A wide variety of functionalities are tolerated, ranging from aldehydes to alkyls to halides. The method is regioselective and translates to good isolated yields.

---

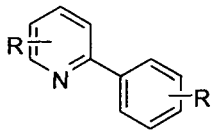
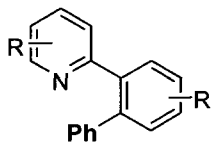
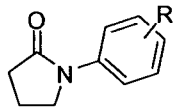
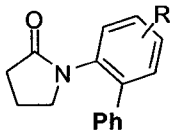
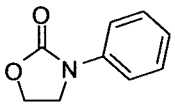
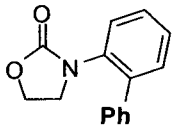
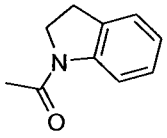
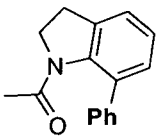
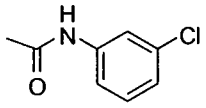
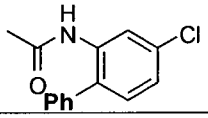
[45] For other examples using amide directing groups, see: (a) Zaitsev, V. G.; Daugulis, O. *Angew. Chem. Int. Ed.* **2005**, *44*, 4046. (b) Shabashov, D.; Daugulis, O. *Org.Lett.* **2006**, *8*, 4947. (c) Lazareva, A.; Daugulis, O. *Org. Lett.* **2006**, *8*, 5211.

[46] Kalyani, D.; Depres, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330.

[47] Richardson, R. D.; Wirth, T. *Angew. Chem. Int. Ed.* **2006**, *45*, 4402.



NDG = nitrogen containing directing group

substrate	product	yields
		51-91%
		75-84%
		83%
		49%
		67%

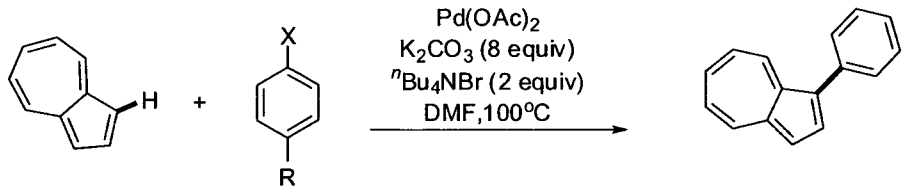
Scheme 2-8: Various nitrated directing groups can be used with the same Pd catalyst

2.3 Non-directed Arylation

Highly regioselective intermolecular reactions that use a directing group have been widely developed, but reactions utilizing the electronics of the arene being functionalized are less common. There are only a few examples of simple arenes that are reactive to a palladium-catalyzed direct arylation reaction. The first direct arylation reaction was achieved in 2000 by Dyker and co-workers.[48] Using $Pd(OAc)_2$, K_2CO_3 and *n*-Bu_4NBr, azulene and aryl halides were cross-coupled in DMF at 100 °C (Scheme 2-9).

[48] Dyker, G.; Borowski, S.; Heiermann, J.; Körning, J.; Opwis, K.; Henkel, G.; Köckerling, M. *J. Organomet. Chem.* **2000**, *606*, 106.

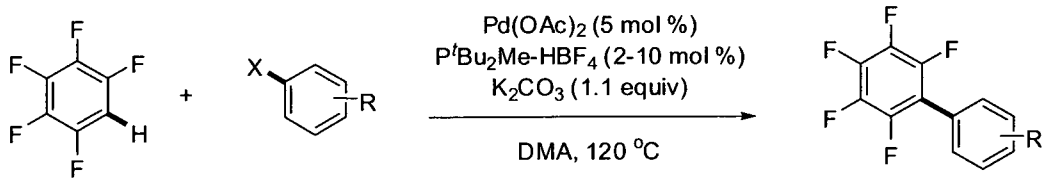
Very low yields were obtained and 8 equivalents of base was used. Arylation proceeds at the most nucleophilic position and the authors proposed that the reactivity of azulene was due to its dipolar nature.



X	R	equiv Ar-X	$Pd(OAc)_2$	yield
I	H	5	5 mol %	5%
I	H	30	5 mol %	13%
Cl	NO_2	5	5 mol %	16%
Cl	NO_2	5	15 mol %	28%

Scheme 2-9: Arylation of azulene

In 2006, Fagnou and co-workers demonstrated that fluorinated benzene rings could be coupled with various aryl bromides under Pd catalysis.[49] Using $Pd(OAc)_2$, $P(^tBu)_2Me$ and K_2CO_3 in DMA at 120 °C, good to excellent isolated yields were obtained (Equation 2-5). Perfluorobenzenes have only one C-H bond available, limiting regioselectivity and reactivity issues. Aryl chlorides and iodides are tolerated as well as a various fluorine substitution patterns on the simple arene.

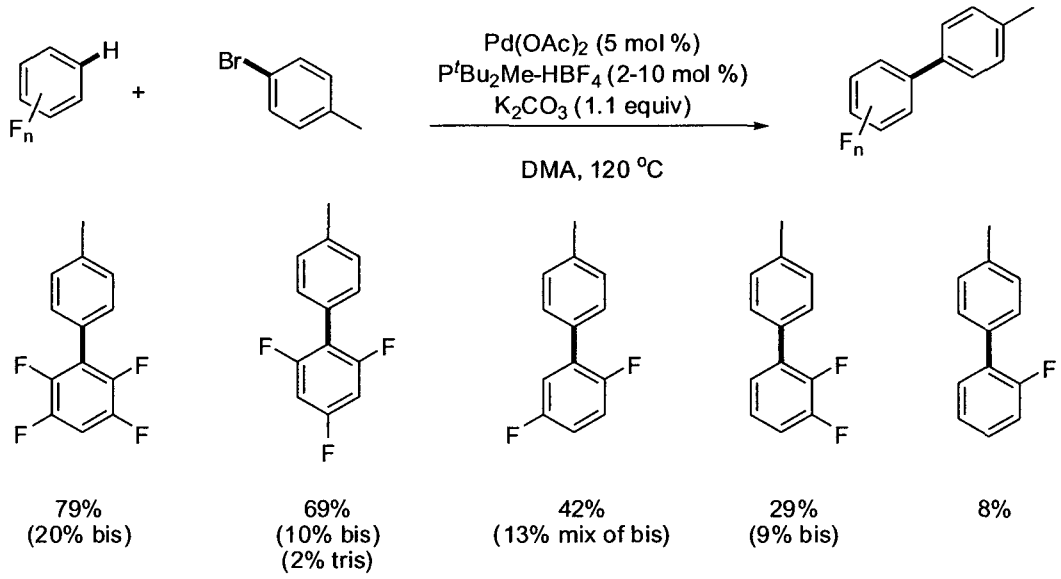


Equation 2-5: Direct arylation of perfluorobenzene with various aryl bromides

When the number of fluorine atoms present on the aryl ring is reduced, the yield of monoarylated product is reduced (Scheme 2-10). Diarylated and triarylated products can be observed, albeit in low yield. During that same year, the authors described new

[49] Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128,* 8754.

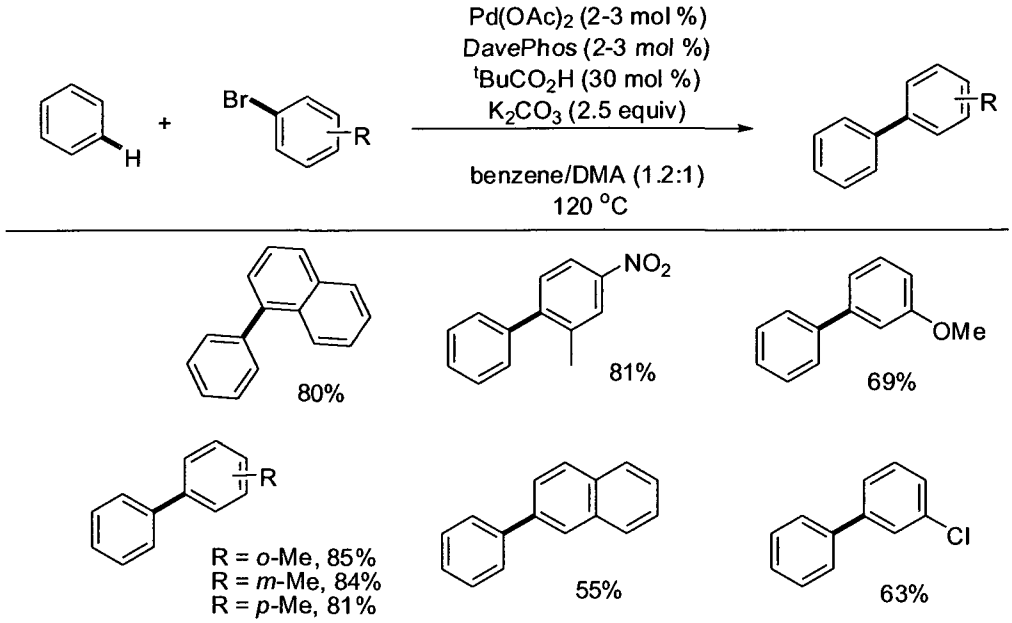
sets of conditions for the arylation of penta- and perfluorobenzene that allow a wider array of halide coupling partners.[50]



Scheme 2-10: Various fluorinated benzene are reactive the same Pd catalyst

Fagnou and co-workers applied their methodology to the most neutral arene: benzene (Scheme 2-11).[51] No electronic bias favours a particular C-H bond on the aromatic ring. Incredibly, monoarylated products were obtained in moderate to high yield. $^{t}BuCO_2H$ (PivOH) was used as an effective additive that improved reactivity when combined to $Pd(OAc)_2$, DavePhos[52] and K_2CO_3.

[50] Lafrance, M.; Shore, D.; Fagnou, K. *Org. Lett.* **2006**, *8*, 5097.
[51] Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496.
[52] Buchwald's phosphine ligand : 2-Dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl.



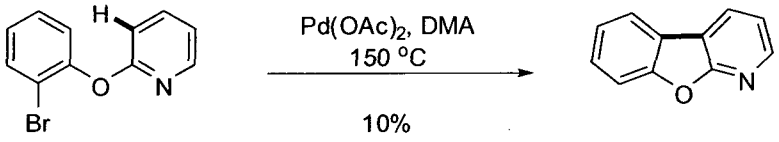
Scheme 2-11: Direct arylation of benzene with various aryl bromides

Chapter 3: Pd-Catalyzed Direct Arylation of Nitro-Substituted Aromatics with Aryl Halides

3.1 Non-Directed Direct Arylation of Simple Arenes

3.1.1 Electron-Deficient and Electron-Neutral Arenes

In 1984, Ames was the first to introduce the Pd-catalyzed direct arylation of electron-deficient arenes (Equation 3-1). It was achieved via an intramolecular reaction in low yield.



Equation 3-1: The first example of direct arylation of electron poor arenes

The direct arylation of electron-deficient arenes was revolutionary because it opposed the widely accepted electrophilic aromatic substitution (S_EAr) mechanism favoured for electron-rich aromatics.

In the last few years, intermolecular direct arylation of electron-poor arenes has emerged (Figure 3-1).[53] Biaryl compounds can now be obtained in excellent yield. Of particular interest is the arylation of azines, diazines, and thiazoles. Direct arylation of

[53] (a) Jonckers, T. H. M.; Maes, B. U. W.; Lemières, G. L. F.; Rombouts, G.; Pieters, L.; Haemers, A.; Dommisse, R. A. *Synlett* **2003**, *5*, 615. (b) Hostyn, S.; Maes, B. U. W.; Pieters, L.; Lemières, G. L. F.; Mátyus, P; Hajós, G.; Dommiss, R. A. *Tetrahedron* **2005**, *61*, 1571.

their *N*-oxides was shown to proceed under palladium catalysis with aryl halides in good to high yields, allowing an entry point into a novel reactivity profile. [22d,54]

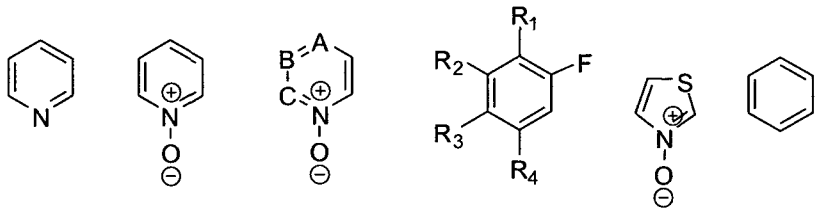
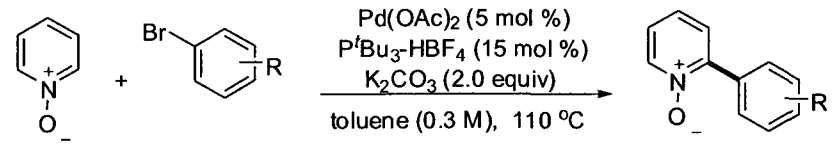


Figure 3-1: Electron-deficient and neutral arenes that can undergo direct arylation

The ease of direct arylation for pyridine *N*-oxide was first exposed. Using $Pd(OAc)_2$, P^tBu_3-HBF_4, K_2CO_3 in toluene at 110 °C, various substituted pyridine *N*-oxides could be coupled with aryl bromides. Removal of the *N*-oxide is achieved through Pd-catalyzed hydrogenolysis. Table 3-1 illustrates the versatility of the arylation method. Electron-poor and electron-rich functional groups are tolerated on either coupling partners.

[54] (a) Campeau, L.-C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *127*, 18020. (b) Leclerc, J.-P.; Fagnou, K. *Angew. Chem. Int. Ed.* **2006**, *45*, 7781. (c) Campeau, L.-C.; Schipper, D, Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3266.



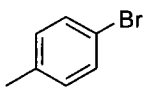
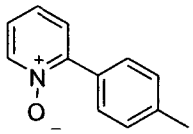
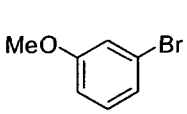
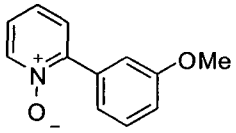
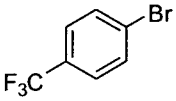
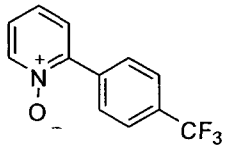
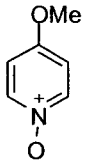
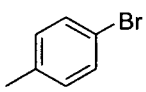
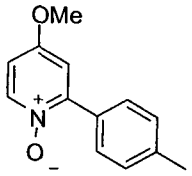
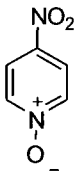
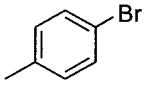
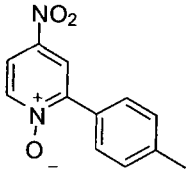
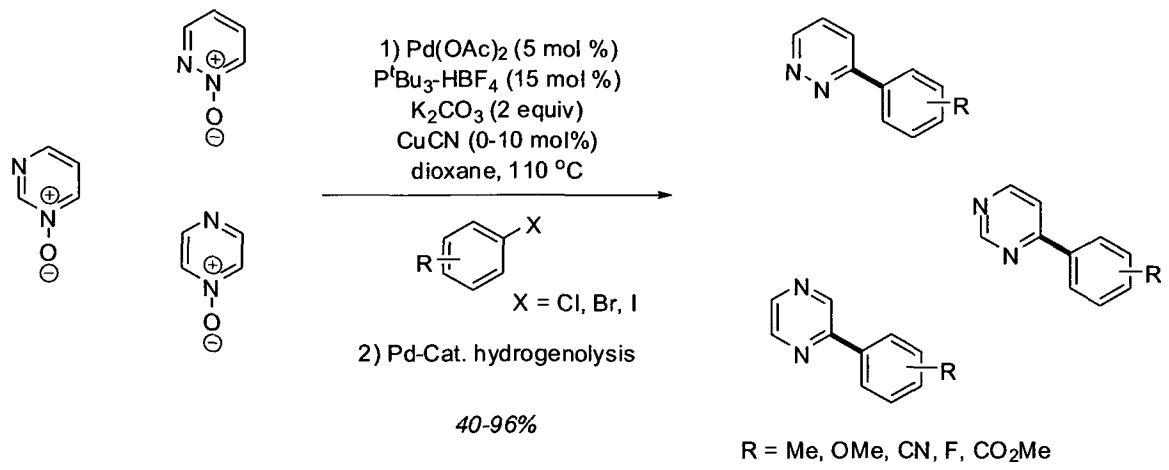
entry	*N*-oxide	aryl halide	product	yield
1	**1a**			91
2	**1a**			97
3	**1a**			76
4				80
5				78

Table 3-1: Regioselective Direct Arylation of Pyridine N-Oxides

In that same year, Fagnou and Leclerc achieved the direct arylation of various forms of diazines (including pyrazines, pyrimidine and pyridazine) through arylation of the corresponding *N*-oxides (Scheme 3-1).[54b] Only one nitrogen atom was oxidized. Using the same catalyst, ligand and base previously described for pyridine *N*-oxide, diazine *N*-oxides can be arylated in good to excellent yields with an assortment of aryl halides. This type of substrate class can be challenging, since free nitrogen atoms can often bind very strongly to the metal catalyst and inhibit catalysis.



Scheme 3-1: Direct arylation of diazines

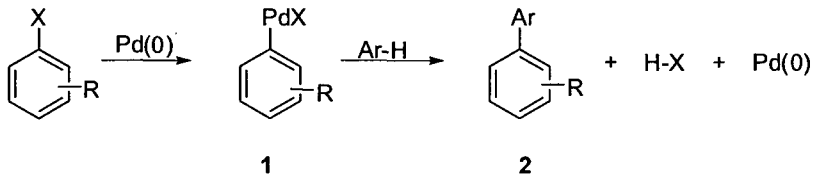
When aryl iodides are used, a silver source is necessary to sequester the iodide anion. For pyrimidine *N*-oxide, the addition of CuCN is necessary to overcome catalyst inhibition. Electron-donating and -withdrawing groups are tolerated on the aryl halide.

3.1.2 Proposed Mechanisms for Direct Arylation of Electron-Deficient and Electron-Neutral Arenes

Several mechanisms, such as oxidative C-H insertion, S_EAr, a Heck-like mechanism and σ-bond metathesis have been proposed for Pd-catalyzed reactions (Figure 3-2). Unambiguous mechanistic insight that differentiates one or more of these pathways is still lacking. Certainly, the S_EAr pathway has attracted the most support and many arylation reactions can be successfully explained by this mechanism.[55] Mechanistically, the first step should be the oxidative insertion of the metal catalyst into the carbon-halogen bond. As for the next step, different mechanisms have been proposed to explain the formation of the carbon-carbon bond. For the S_EAr pathway, the first step would most likely be the attack of the nucleophilic arene on the electrophilic

[55] (a) Wang, X.; Lane, B. S.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 4996. (b) Lewis, J. C.; Wiedemann, S. H.; Bergmann, R. G.; Ellman, J. A. *Org. Lett.* **2004**, *6*, 36. (c) Park, C.-H.; Ryabova, V.; Seregin, I. V.; Sromeck, A. W.; Gevorgyan, V. *Org. Lett.* **2004**, *6*, 1159. (d) Li, W.; Nelson, D. P.; Jensen, M. S.; Hoerner, R. S.; Javadi, G. J.; Cai, D.; Larsen, R. D. *Org. Lett.* **2003**, *5*, 4835.

metal species. The resulting Wheland intermediate then under goes deprotonation to give an organometallic intermediate. Reductive elimination gives the biaryl product. While the exact nature of this key step has been examined for most of the described pathways, the exact mechanism is still unknown and could be dependent on the on substrates and reagents used.



Scheme 3-2: Typical direct arylation pathway

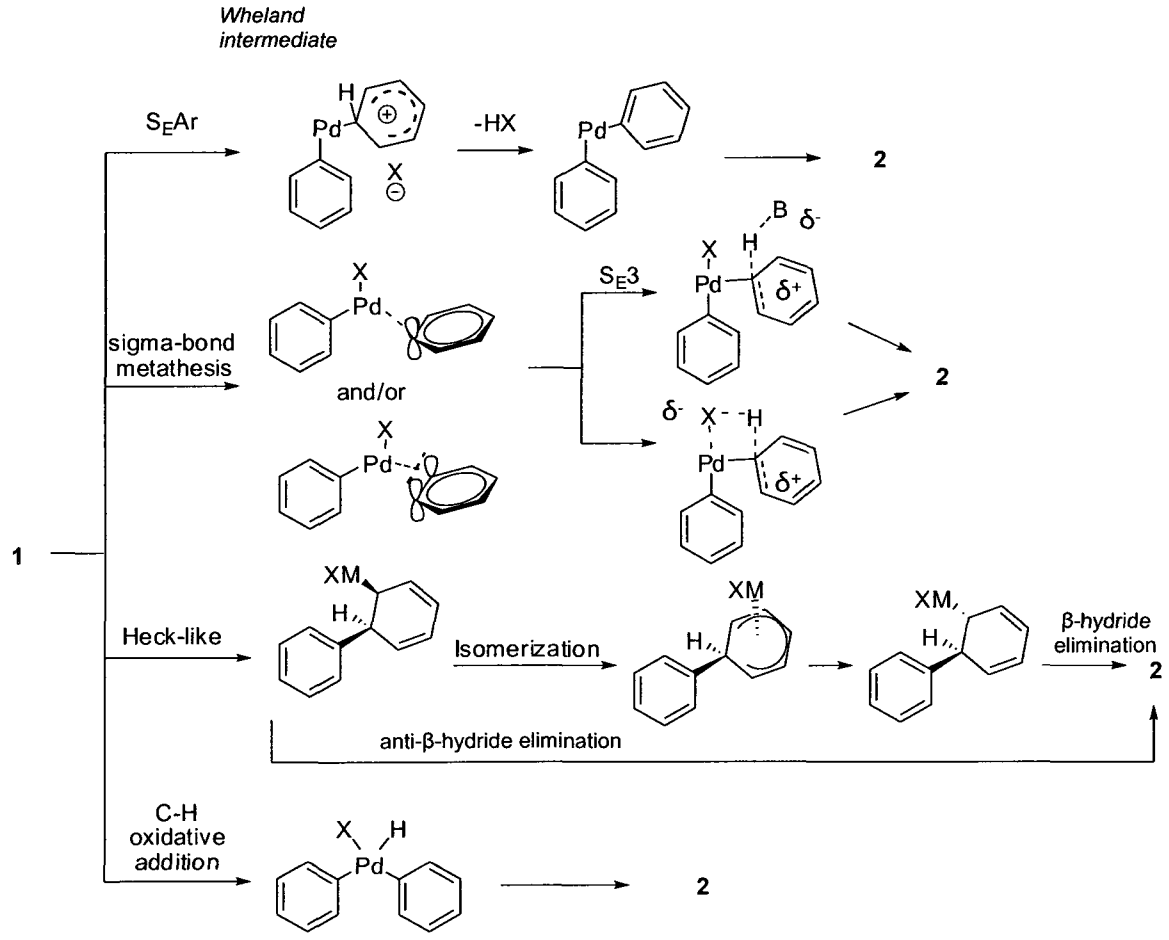


Figure 3-2: Different reaction pathways proposed for direct arylation

Fagnou, Echavarren and Maseras provided mechanistic support for a concerted metalation and proton abstraction to a base, which accounts for the arylation of electron-deficient and electron-neutral arenes.[49,51,56] The proposed pathway is a concerted metalation-deprotonation (CMD) process which would be favoured by electron-poor arenes such as perfluorobezene. For a S_EAr pathway, the formation of the Wheland intermediate is described as the rate determining step, which is followed by a rapid deprotonation to regain aromaticity. However, studies show that for the proposed CMD pathway, the deprotonation step has a kinetic isotope effect greater than one, demonstrating that the C-H bond cleaving step is a kinetically significant catalytic event.[51,54a] This difference in reactivity is evidence that a S_EAr pathway is not probable for these types of arenes.

Fagnou and co-workers propose a CMD catalytic manifold with two possible pathways for the arylation of perfluorobenzene (Figure 3-3).[51] Proof is still lacking to differentiate between the two pathways. Pathway **A** involves a concerted metalation and loss of HBr to afford the diarylpalladium intermediate. The alternate pathway suggests exchange of the bromide ligand for the carbonate anion and allows for a related palladation- deprotonation process through transition state ***C***. Pathway **B** is the more plausible mechanism, since it has calculated and experimental results that are in strong agreement.[57] However, the near-insolubility of K_2CO_3 makes pathway **A** plausible even though the calculated results are favourable to pathway **B**.

[56] Garcia-Cuadrado, D.; Braga, A. A, C.; Maseras, F.; Echavarren, A. *J. Am. Chem. Soc.* **2006**, *128*, 1066.
[57] Values are available in the supporting info of ref. 52.

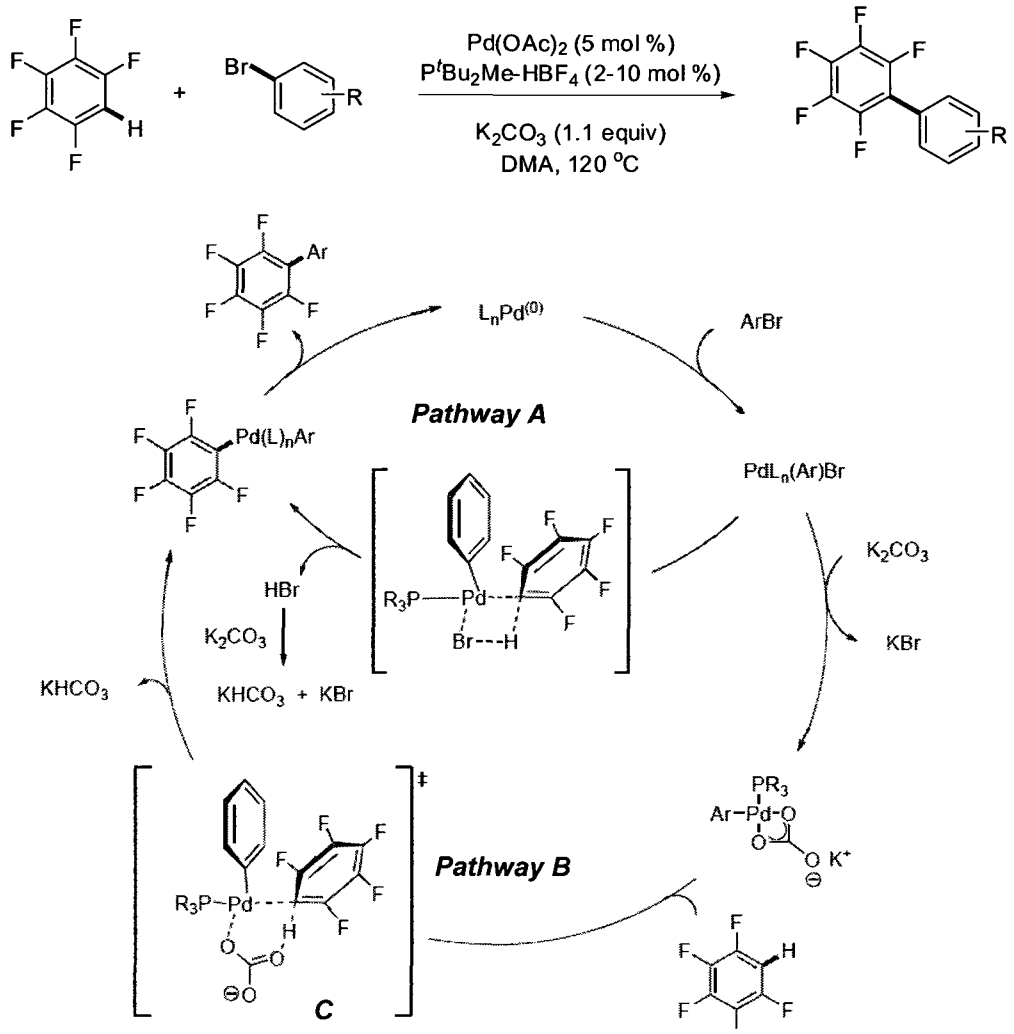


Figure 3-3: Catalytic cycle for the direct arylation of perfluorobenzene

When the authors looked at the reactivity of perfluorobenzene, they found two trends. First, reactivity seems to parallel relative C-H bond acidity. Second, when multiple bonds are available for arylation, the most acidic C-H bond reacts preferentially. This discovery promotes the idea that C-H bond acidity is a factor in determining regioselectivity. Experimentally, arylation occurs *ortho* to the fluorine atom and computational studies supports that C-H acidity corresponds to the observed selectivity; which is in disagreement with previously believed concept that nucleophilicity is responsible for regioselectivity.

An interesting result was found for fluorobenzene (Figure 3-4). Direct arylation was only observed in 8 % yield. There seems to be a trend between the number of fluorine atoms and the observed yield of arylation. The reaction works well with very acidic protons (perfluorobenzene) and reactivity diminishes as we approach neutral arenes (fluorobenzene).

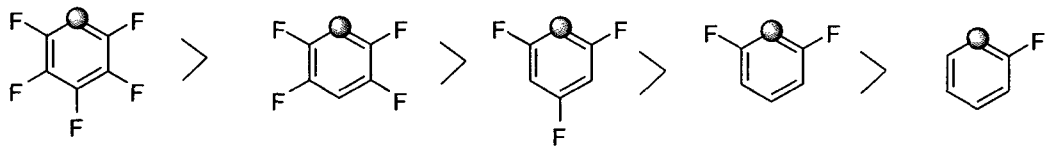
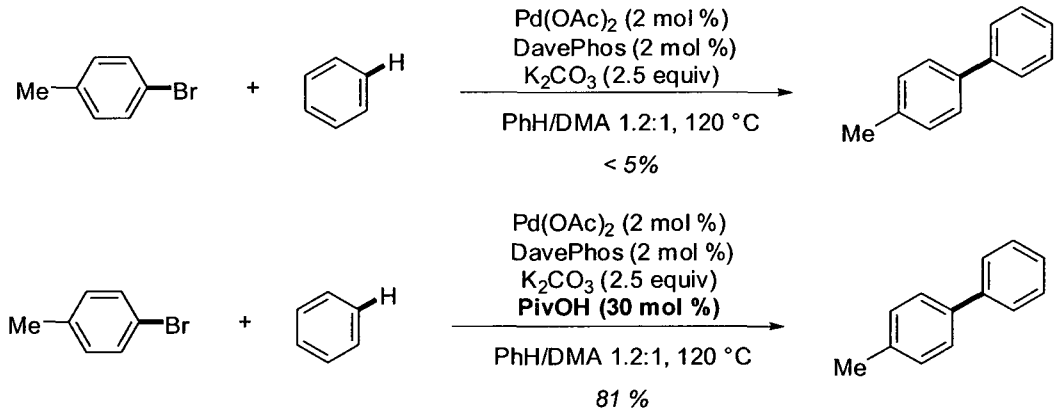


Figure 3-4: The correlation between decrease in reactivity and the presence in electron-withdrawing groups

When the authors applied similar reaction conditions to electron-neutral benzene, lower then 5% arylation was observed.[58] However, arylation is possible with the addition of 30 mol % of PivOH (Scheme 3-3).[51]



Scheme 3-3: Influence of PivOH on the direct arylation of benzene

The authors propose a new catalytic manifold to account for this radical change in reactivity with the addition of PivOH. Experimental and computational evidence is in agreement with a CMD pathway and with the implication of the pivalate anion in the C-H bond cleaving step. A new catalytic cycle is therefore proposed to include the additive

[58] Determined by CG-MS

(Figure 3-5). This new catalytic pathway suggests the exchange of the bromide ligand for the pivalate anion and allows for a related palladation- deprotonation process. K_2CO_3 regenerates the pivalate anion.

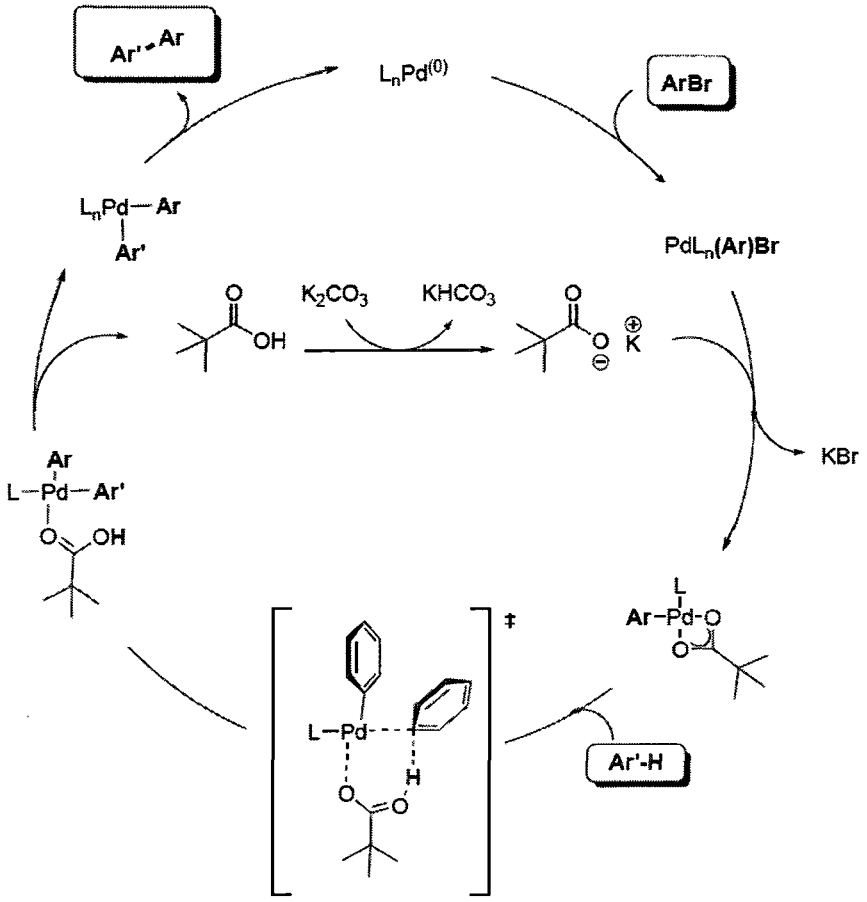


Figure 3-5: Catalytic cycle of the arylation of benzene and the role of PiVOH

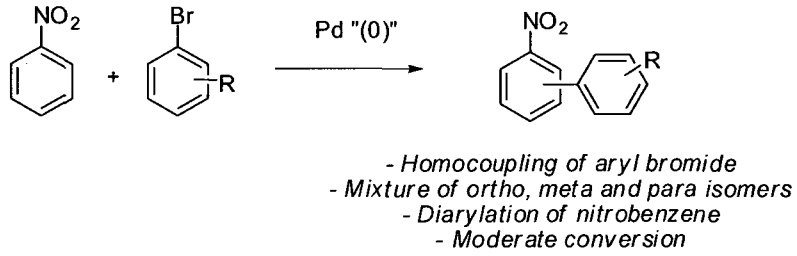
In spite of these new developments, when the CMD reaction pathway was introduced, it was believed that only electron-poor and electron-neutral arenes could follow the proposed reaction pathway, and that electron-rich, π-nucleophilic arenes were most likely reacting through an S_EAr pathway. In 2008, Fagnou and co-workers demonstrated that the CMD pathway could actually predict reactivity for not only neutral- and electron-deficient arenes, but for all substrates ongoing direct arylation.[59] Through experimental and computational mechanistic studies, they were able to correlate the observed experimental outcomes of direct arylation for all arenes, including π-

[59] Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 10848 and references therein.

nucleophilic arenes, to the outcomes predicted by the CMD reaction pathway. These observations are discussed in chapter 5.

3.2 Objective

Following the immediate success of azine/diazine *N*-oxides and perfluorobenzene, other π-deficient aromatics rings were screened, in the hopes that the previously observed reactivity could be recreated. When the developed direct arylation conditions were tested on various electron-poor substrates, it was found that nitrobenzene cross-coupled with aryl bromides in moderate yield (Scheme 3-4.) Although other coupling products were observed, the most reactive site was the *ortho* position.



Scheme 3-4: First attempts at the direct arylation of nitrobenzene

This reactivity had in fact been predicted for nitrobenzene. This anticipated reactivity was two-fold.

- First, the nitro functional group could mimic the electron-withdrawing (EWD) activity of the N-oxide. The nitro group is known as a strong EWD group and renders the C-H bond *ortho* to the nitro group much more acidic than the *meta* and *para* C-H bonds due to an inductive effect (Figure 3-6). Fu, Guo and co-workers have calculated the pK_a of the three different C-H bonds on nitrobenzene.[60] The *ortho* proton has a calculated pK_a of 36.2, which more acidic then the *meta* proton whose calculated pK_a is 39.9. The pK_a of the *para* proton is close to that of the *meta* proton, equal to 40.1. As seen with

[60] Shen, K.; Fu, Y.; Li, J.-N.; Liu, L.; Guo, Q.-X. *Tetrahedron* **2007**, *63*, 1568.

perfluorobenzene arylation, it is believed that increased acidity favours the functionalization of C-H bonds, favouring the *ortho* arylation of nitroarenes.

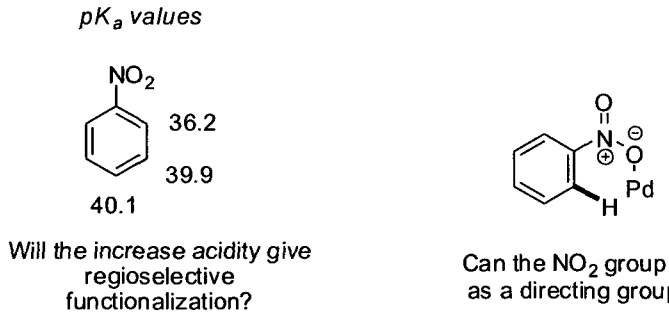


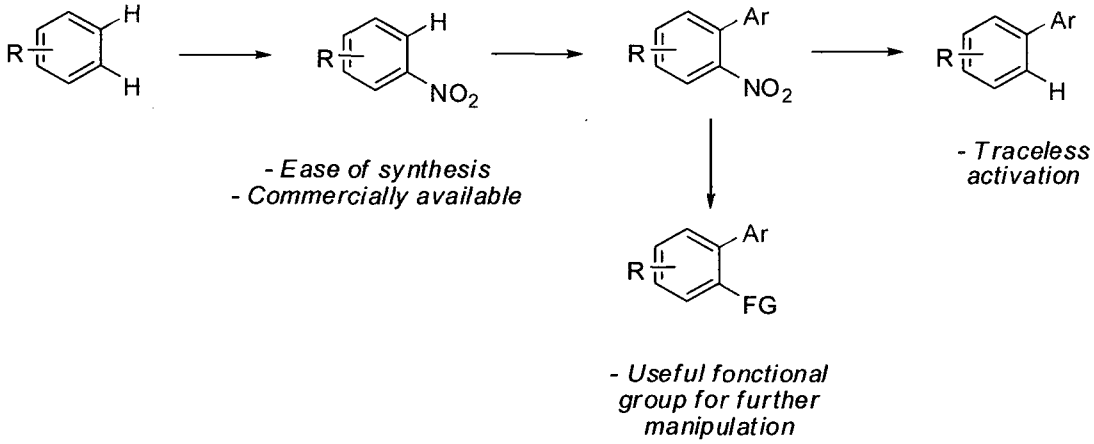
Figure 3-6: The possibilities of nitrobenzene in direct arylation

- Second, the nitro group could be involved in binding to the metal catalyst (Figure 3-6). This binding would bring the metal catalyst into close proximity to the reaction site and therefore could favour reactivity as well as regioselectivity. Although formation of a metallacycle using a directing group has never been described with a nitro functional group, the use of electron rich heteroatoms, like nitrogen and oxygen, is common.

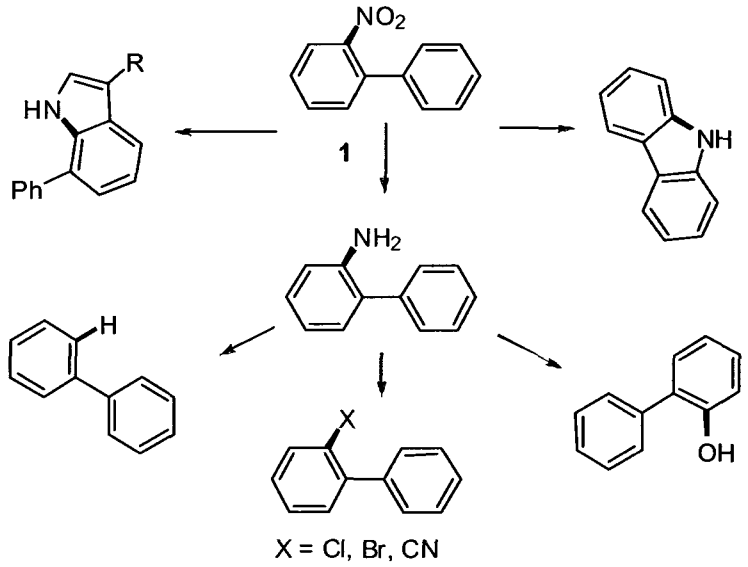
Other than its proposed reactivity in direct arylation, nitrobenzene was a choice substrate from a synthetic point of view. For example, the nitro functional group could be used as a synthetic lever, as it is easily transformable (Scheme 3-5). Complete removal of the nitro group presents a form of traceless activation. Removal of the starting directing group opens up a bigger field of applicability for the reaction. The transformation of the nitro group into other useful functional groups as well as its complete removal is well documented and easily achievable (Scheme 3-6).[61]

[61] For selected examples of the transformation of nitrobiphenyl into indole, see: (a) Ragaini, F.; Rapetti, A.; Visentin, E.; Monzani, M.; Caselli, A.; Cenini, S. *J. Org. Chem.* **2006**, *71*, 3748. (b) Bartoli, G.; Palmieri, G. *Tetrahedron Lett.* **1989**, *30*, 2129. For selected examples of the transformation of nitrobiphenyl into carbazole, see: (c) Sanz, R.; Escribano, J.; Pedrosa, M. R.; Aguado, R.; Arnáiz, F. J. *Adv. Synth. Catal.* **2007**, *349*, 713. (d) Smitrovich, J. H.; Davies, I. W. *Org. Lett.* **2004**, *6*, 533. For selected examples of the transformation of nitrobiphenyl to 2-hyrdoxybiphenyl, see: (e) Boldt, P.; Bruhnke, D.; Gerson, F.; Scholz, M.; Jones, J. G.; Bär, F. *Helv. Chim. Acta* **1993**, *76*, 1739. For selected examples of the transformation of nitrobiphenyl into 2-aminobiphenyl, see: (f) Tafesh, A. M.; Weiguny, J. *Chem. Rev.* **1996**, *96*, 2035. (g) McLaughlin, M. A.; Barnes. D. M. *Tetrahedron Lett.* **2006**, *47*, 9095. (h) Liu, Y.; Lu, Y.; Prashad, M.; Repič, O.; Blacklock, T. J. *Adv. Synth. Catal.* **2005**, *347*, 217. (i) Hanaya, K.; Muramatsu, T.; Kudo, H.; Chow, Y. L. *J. Chem. Soc., Perkin Trans. 1* **1979**, *10*, 2409. (j) Vass, A.; Dudas, J.; Toth, J.; Varma, R. S. *Tetrahedron Lett.* **2001**, *42*, 5347. (k) Huber, D.; Andermann, G.; Leclerc, G. *Tetrahedron Lett.* **1988**, *29*,

Furthermore, nitroarenes are easily accessible due to their low cost and ease of synthesis.



Scheme 3-5: The versitality of nitrobenzene



Scheme 3-6: Possible transformations of nitrobenzene

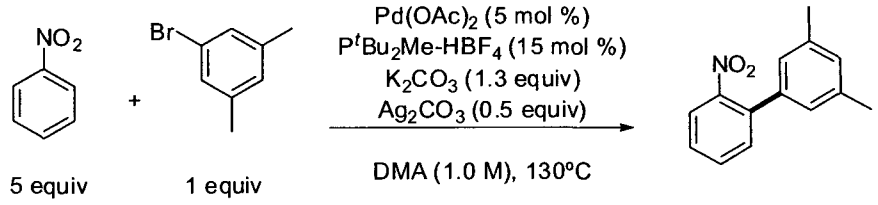
Although the potential for arylation of nitro-substituted aromatics was previously demonstrated in our group, reactivity and regioselectivity needed to be improved. There

635. For selected examples of the transformation of nitrobiphenyl into 2-cyanobiphenyl, 2-chlorobiphenyl and 2-bromobiphenyl, see: (l) Suzuki, N.; Azuma, T.; Kaneko, Y.; Izawa, Y.; Tomioka, H.; Nomoto, T. *J. Chem. Soc., Perkin Trans. 1* **1987**, *3*, 645. (m) Lee, J. G.; Cha, H. T. *Tetrahedron Lett.* **1992**, *33*, 3167. (n) Doyle, M. P.; Siegried, B.; Dellaria Jr., J. F. *J. Org. Chem.* **1977**, *42*, 2426. For selected examples of the transformation of nitrobiphenyl into biphenyl, see: Wang, Y.; (o) Guziec Jr., F. S. *J. Org. Chem.* **2001**, *66*, 8293. (p) Roe, A.; Graham, J. R. *J. Am. Chem. Soc.* **1952**, *74*, 6297.

were also a few problems that were immediately apparent and that need to be addressed. Homocoupling of the aryl bromide as well as diarylation of nitrobenzene have to be reduced to a minimum. In addition, good isolated yields are needed to make the reaction a viable route to access biaryl molecules. It is also crucial to develop mild reaction conditions that can be applied on a large scale, giving great economical and environmental value to the reaction.

3.3 Optimization

A previous graduate student, Louis-Charles Campeau, started the project using the reaction conditions in Equation 3-2.



Equation 3-2: Initial conditions for the arylation of nitrobenzene

The best conversion obtained was 85% and the selectivity was approximately 7 to 1 in favour of arylation at the *ortho* position (versus arylation in the *meta* and *para* position combined). Although these results were encouraging, improvement of the yield of the *ortho* isomer was an important objective. Each of the reagents used could have an impact on reactivity and selectivity of the system and further optimization is required. Also, the replacement of silver, a toxic metal, by a non-metallic substitute is an important part of achieving mild reaction conditions.

Other parameters that can possibly impact our system:

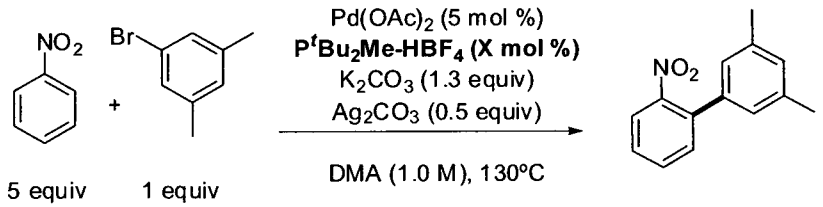
- Ligand/ metal ratio
- Solvent concentration

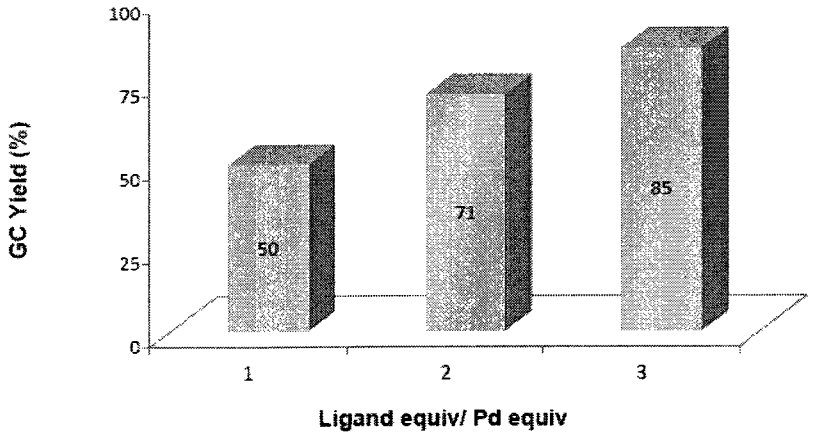
- Nitrobenzene/ aryl bromide equivalents ratio
- Reaction temperature
- Reaction vessel
- Reaction stoichiometry

All of these possible issues are addressed in our optimization strategy for the direct arylation nitro-substituted aromatics.

3.3.1 Ligand/ Metal Ratio

The ligand/ metal ratio was optimized first. The best conversion into biaryl (mixture of the three isomers) is obtained with a 3 to 1 ligand to metal ratio (Graph 3-1).[62] Diarylation is observed when the lower ratios are used, reducing the yield of *ortho* arylation.



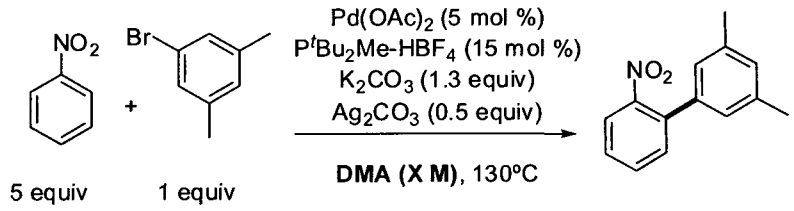


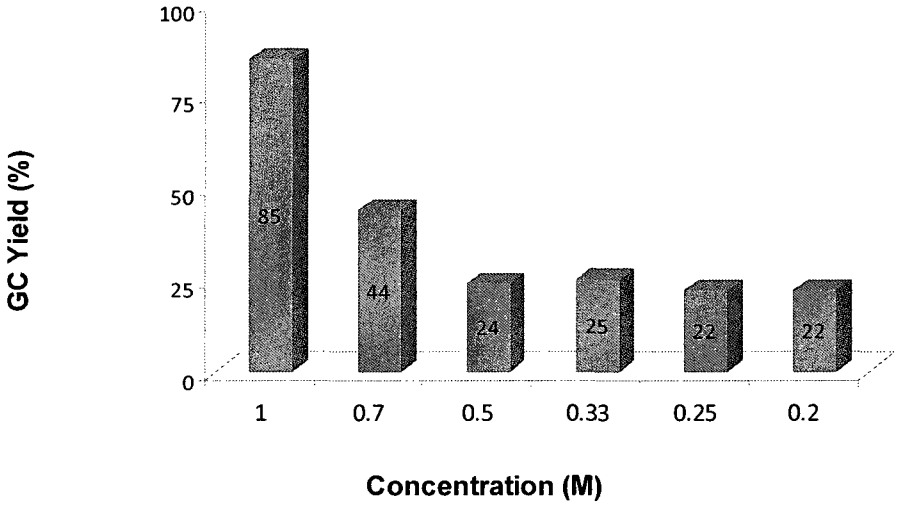
Graph 3-1: The influence of ligand/palladium ratio on conversion

[62] All conversionsi this chapter are obtained by analysis of GC-MS trace.

3.3.2 Solvent Concentration

The solvent concentration was varied from of 1.0 M to 0.2 M. The most concentrated solution, 1.0 M, gives the best conversion (Graph 3-2).



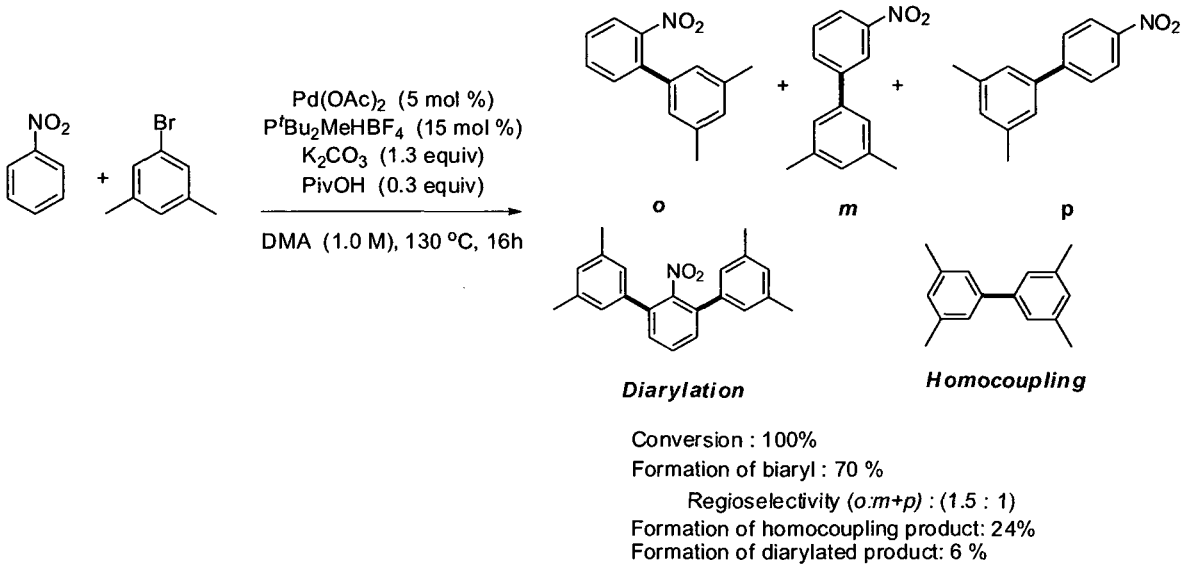


Graph 3-2: Influence of the concentration of DMA on conversion

3.3.3 Additive

An important objective is to eliminate the use of silver in our system. Fagnou and co-workers have reported the use of PivOH as an additive for the direct arylation of benzene in good yields and this additive seemed like a valid substitution option.[51] Furthermore, PivOH is cheap, non-toxic and soluble in most organic solvents, making it a mild and viable alternative to silver salts.

When Ag_2CO_3 is replaced with PivOH, complete conversion is observed (Scheme 3-7). Unfortunately, of that 100% conversion, only 70% is the desired mixture of biaryl isomers. The isomers are obtained in poor regioselectivity: 1.5 to 1 for *ortho* product versus the mixture of *meta* and *para*. This resulted in about a 42% yield of the desired *ortho* product.[63] Homocoupling and diarylation were present in 24 and 6% respectively.



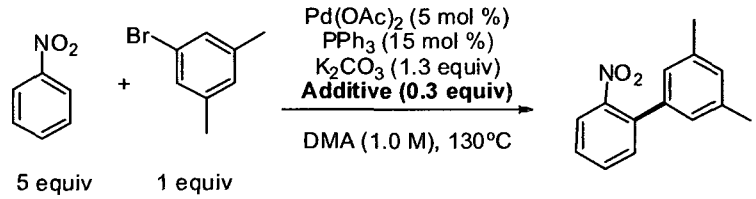
Scheme 3-7: Products formed from the direct arylation of nitrobenzene

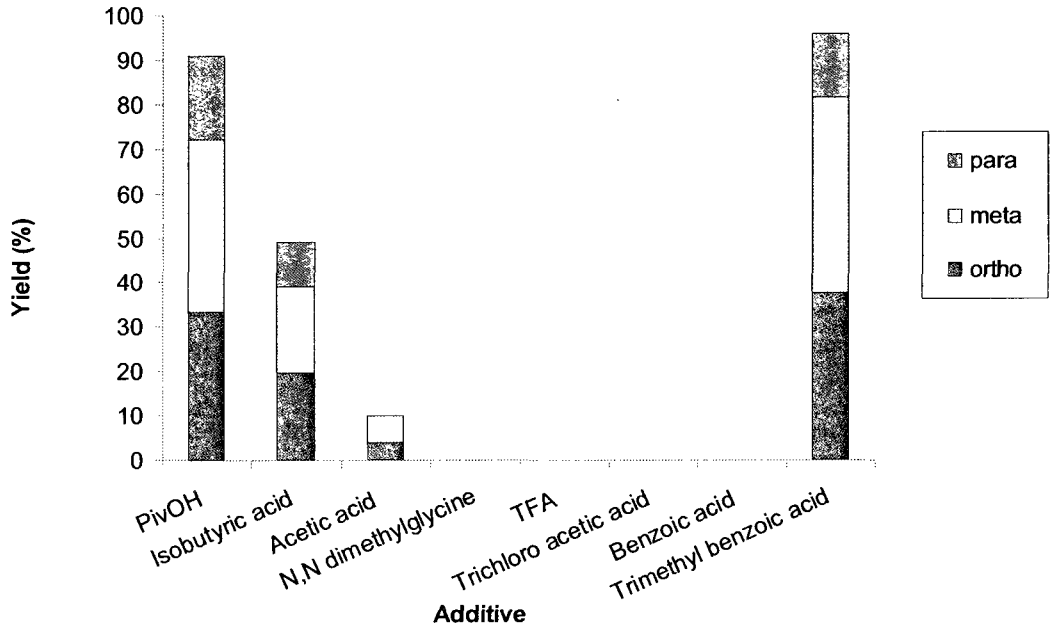
The loss of selectivity using PivOH, from 7:1 to 1.5:1, was an important setback. However, there was a gain in conversion of biaryl product, going from 85 to 100%. Because of the implication of PivOH in the catalytic cycle, the *t*-butyl moiety of PivOH could have an impact on reactivity, or on any part of the catalytic cycle. The use of other functional groups then *t*-butyl could adjust reactivity and selectivity. Seven other carboxylic acids were tested using the same ratio (Graph 3-3). The functional groups were varied from smaller aliphatic groups to bigger aromatic groups.[64] 2,4,6-Trimethylbenzoic acid gives good results, with slightly better conversion then PivOH. However, the regioselectivity did not improve and because the cost of 2,4,6-

[63] To correlate the observed GC-MS yields with the isolated yields, a reaction mixture is purified and isomers are isolated. The isomers are then submitted to GC-MS analysis to compare isomers with retention time and verify regioselectivity ratios.

[64] PPh_3 was used as a ligand.

trimethylbenzoic acid[65] is greater then the cost of PivOH, no substitution is made in the reaction conditions.



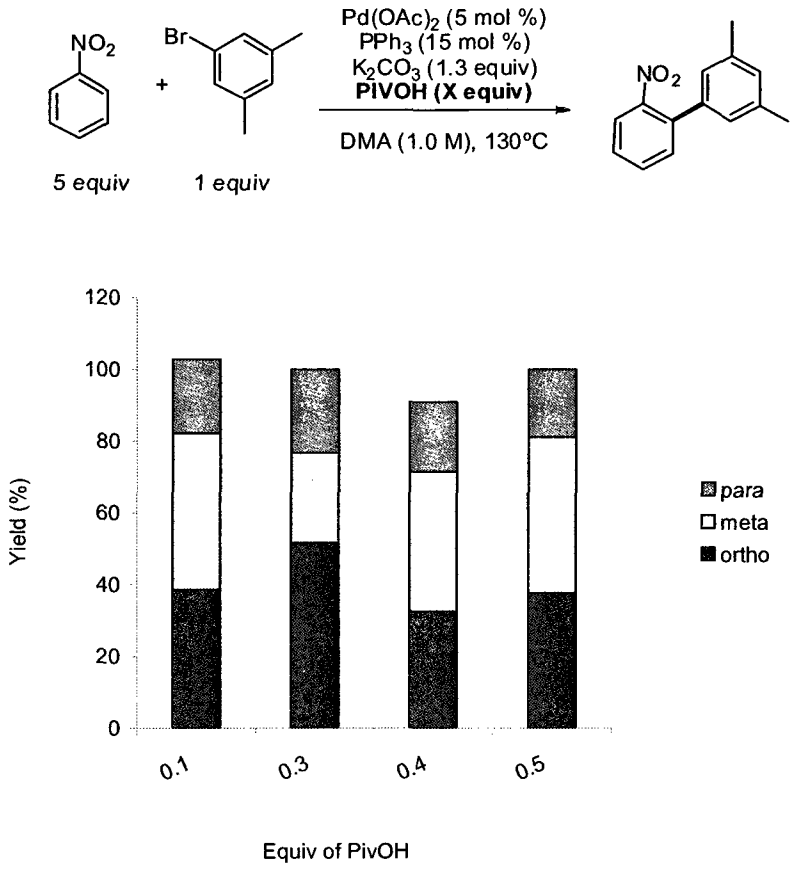


Graph 3-3: Influence of acid additive on conversion and regioselectivity

Choosing to optimize the PivOH conditions, the stoichiometry of PivOH was varied from 0.1 equivalents to 0.5 (Graph 3-4).[66] 0.3 equivalents gives the best regioselectivity, providing the most conversion into *ortho* biaryl product. Because 0.3 equivalents was the starting amount, no gain in regioselectivity or conversion was observed. However, 0.3 equivalents of PivOH could be confirmed as the optimal quantity for our system.

[65] 2,4,6-Trimethylbenzoic acid : 10g for 88.50 $ while PivOH :100ml for 27.80$ (Pricing obtained from Sigma-Aldrich Canada

[66] PPh_3 was used as the ligand.



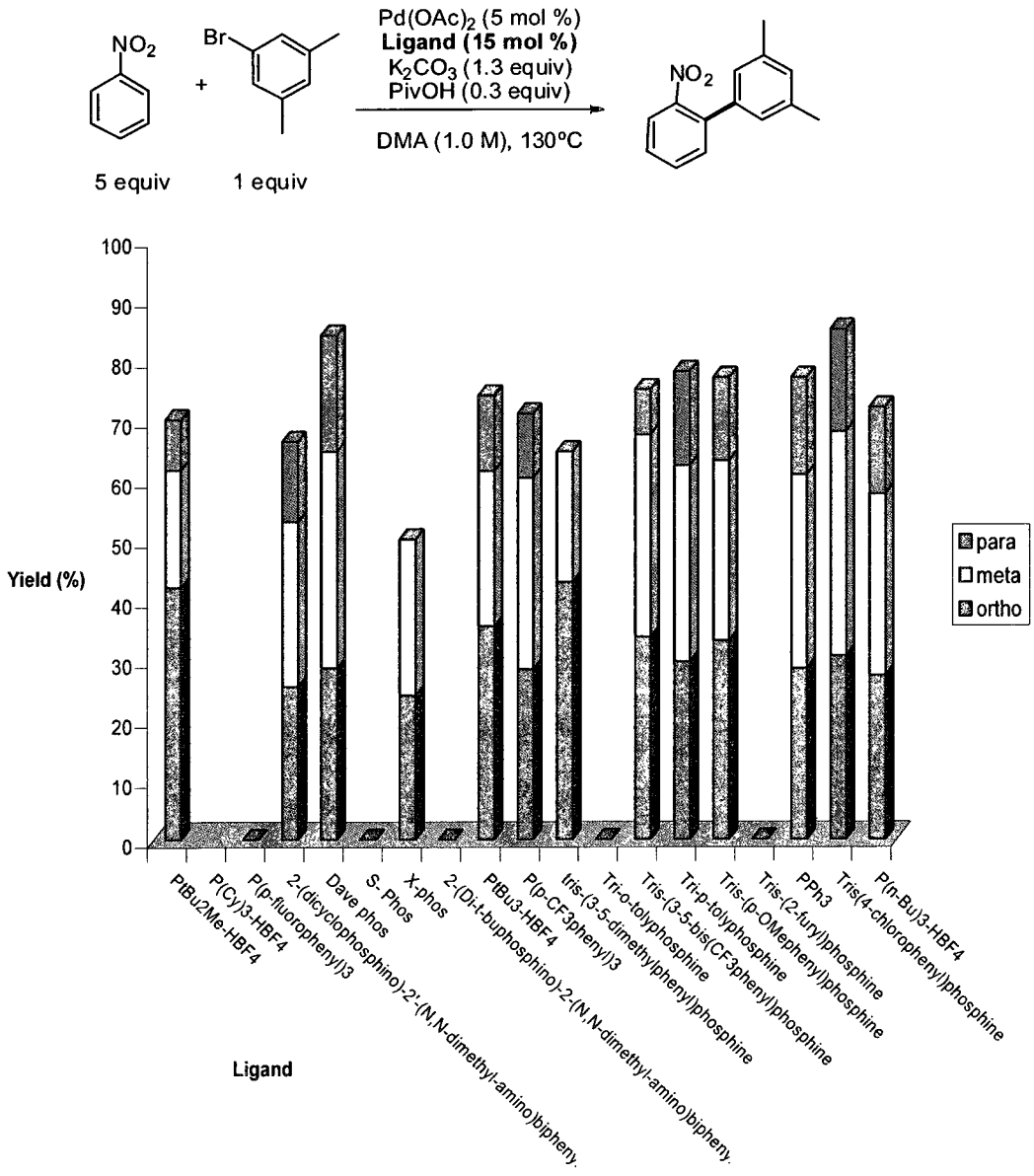
Graph 3-4: Influence of the quantity of PivOH on conversion and regioselectivity

At this point, PivOH gave disappointing regioselectivity but a 100% conversion while Ag_2CO_3 gave good regioselectivity without complete conversion. The balance between these two conditions still needed to be established.

3.3.4 Ligand

A variety of ligands are commonly used in direct arylation and no ultimate ligand has been found to work for all of the different direct arylation reactions. Therefore, an extensive ligand screen was performed to find the ligand that will give optimal selectivity and conversion for our system. Small alkyl, aromatic and biphenyl phosphines were tested to evaluate their effect on regioselectivity and conversion.

Two sets of base/additive conditions were tested: the combination of $PivOH/K_2CO_3$ as well as the combination of Ag_2CO_3/K_2CO_3. The first combination tried was $PivOH/K_2CO_3$ (Graph 3-5.). $P^tBu_2Me\text{-}HBF_4$ and $P^tBu_3\text{-}HBF_4$ gave the best selectivity of all the ligands tested, but the selectivity was still not synthetically useful. Consequently, $P^tBu_2Me\text{-}HBF_4$ was maintained as the ligand of choice.

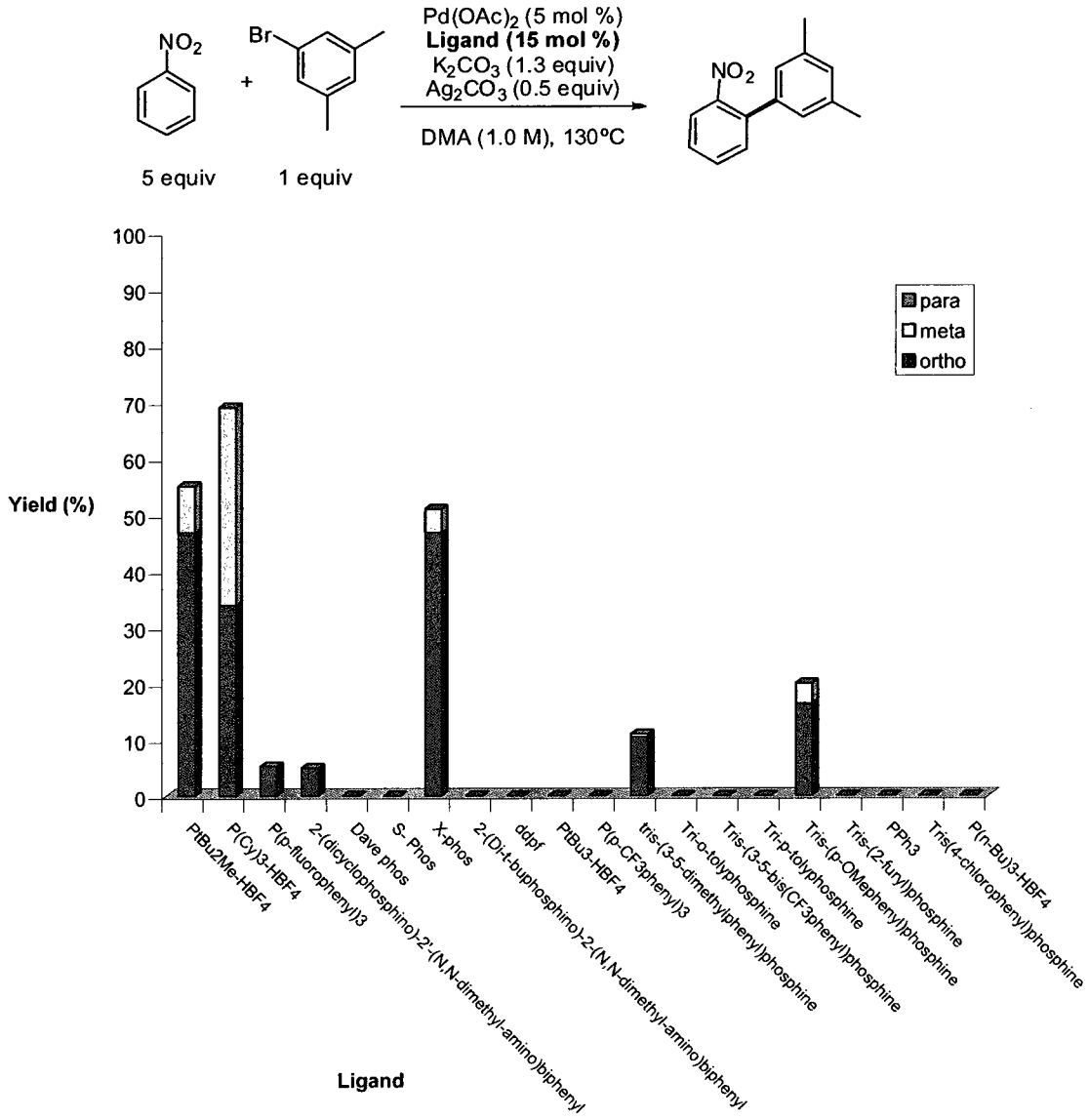


Graph 3-5: Influence of ligand on conversion and regioselectivity for the $K_2CO_3/PiVOH$ conditions

The K_2CO_3/Ag_2CO_3 conditions were tested against a similar ligand scope (Graph 3-6). However, many of the ligands tried had a negative impact on the system and shutdown reactivity. X-Phos[67] exhibited good regioselectivity but moderate conversion. In fact, an 11 to 1 ratio was obtained for arylation at the *ortho* position versus the *meta* position, with the *para* isomer only visible in trace amounts. This was the highest regioselectivity observed for the direct arylation of nitrobenzene. The yield of the mixture of products was 51%.

For further optimization, X-Phos was not carried on since conversion never surpassed the 50% mark. $P^tBu_2Me\text{-}HBF_4$, the original ligand, was carried forth for use in the K_2CO_3/Ag_2CO_3 conditions as well as the K_2CO_3/PivOH conditions.

[67]Buchwald phosphine ligand: 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl.

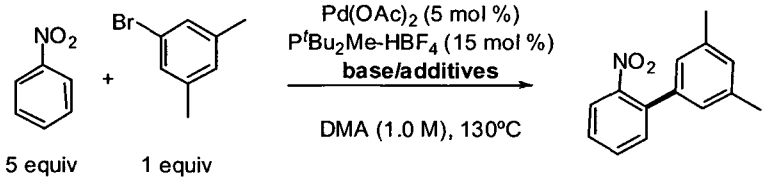


Graph 3-6: Influence of ligand on conversion and regioselectivity for the K_2CO_3/Ag_2CO_3 conditions

3.3.5 Silver

At this time, regioselectivity was deemed more important then conversion and our efforts were oriented towards the improvement of the conditions that employ silver.

To try and improve regioselectivity and conversion, variation of the silver conditions were tested (Equation 3-3):



Equation 3-3: Influence of the variation of base/additive on direct arylation

1. Ag_2CO_3 (0.5 equiv), PivOH (0.3 equiv) and K_2CO_3 (1.3 equiv) were employed together in the same reaction. The regioselectivity obtained was lower then silver alone, only around 3 to 1 for *ortho* isomer versus the *meta* and *para* isomers. There was also a slight decrease in yield compared to the PivOH/ K_2CO_3 conditions. The equivalents of Ag_2CO_3 and PivOH were varied one at a time in the system, but no increase in yield or selectivity was observed.

2. 2,4,6-Trimethylbenzoic acid, which had previously shown equivalent regioselectivity as PivOH (Graph 3-3) was added to K_2CO_3 (1.3 equiv) and Ag_2CO_3 (0.5 equiv). A significantly lower yield was obtained.

3. Ag_2CO_3 was reacted without any base, giving 0% percent conversion. Addition of 0.2 equivalents of PivOH gave 0 % conversion.

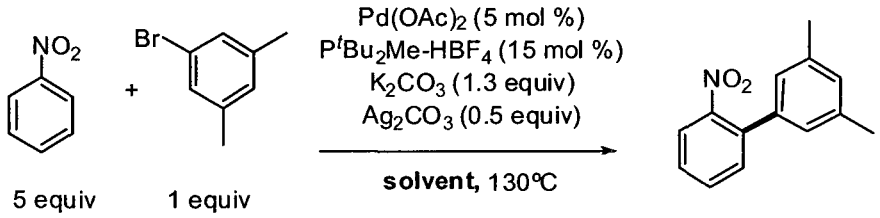
4. The silver source was modified, replacing Ag_2CO_3 for silver triflate (AgOTf). Using 1.3 equivalents of K_2CO_3, no conversion was achieved. When PivOH (0.3 equiv) was added, 14% conversion was achieved.

5. The effect of silver concentration was also evaluated. Using 1.3 equivalents of K_2CO_3, and varying the equivalents of silver from 0.5 to 1.0, no change conversion or selectivity was observed.

All of these variations did not improve the direct arylation conditions. The best regioselectivity was still obtained using 0.5 equivalents of Ag_2CO_3 and 1.3 equivalents of K_2CO_3.

3.3.6 Solvent

Using 0.5 equivalents of Ag_2CO_3 and 1.3 equivalents of K_2CO_3, the effect of the reaction solvent was evaluated (Equation 3-4). The temperature was varied according to the boiling points of the solvent used. The starting solvent was DMA, a polar aprotic solvent. Moving in a different direction, apolar solvents were tested.



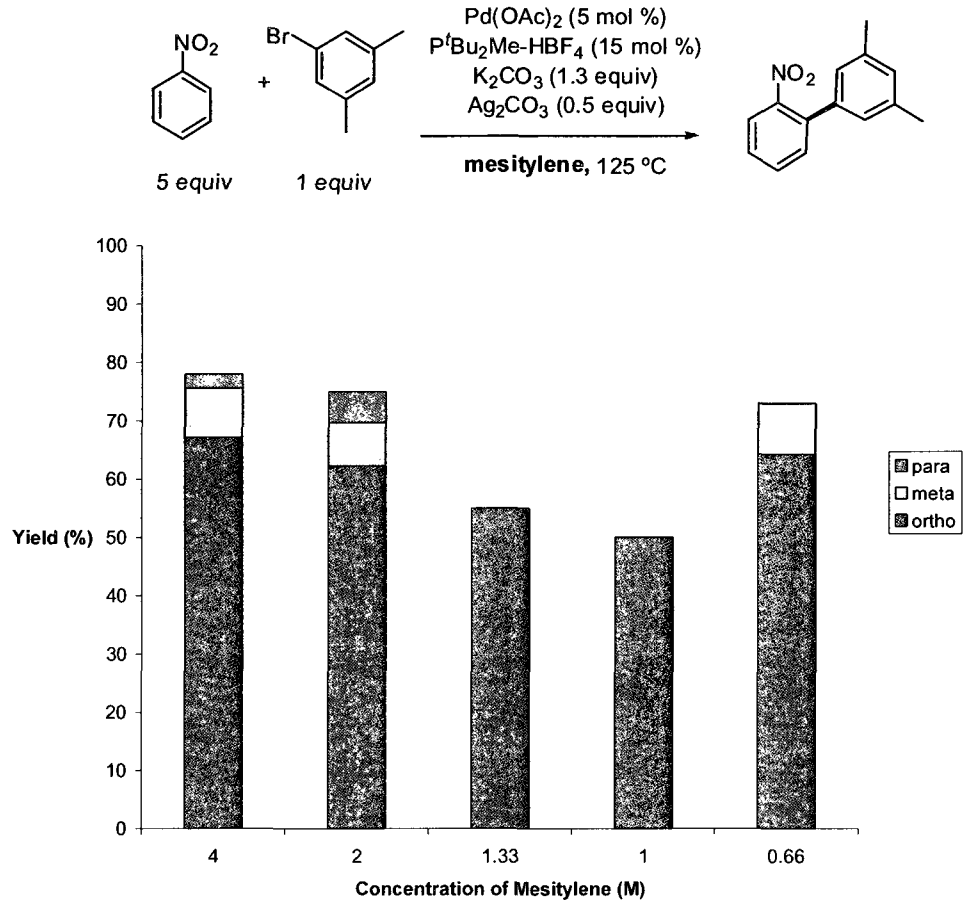
Equation 3-4: Influence of solvent on direct arylation

Toluene was first tested. The low toxicity and ease of removal of the solvent dictates the choice of this solvent. The reaction temperature was lowered from 130 °C to 100 °C to accommodate the low boiling point of toluene (bp = 110 °C). Moderate reactivity was obtained in toluene, giving 33% to 32% conversion for concentrations of 4.0, 2.0, 1.33 and 1.0 M. Even if these yields are low, GC-MS analysis showed no homocoupling of the aryl bromide. To try and increase the conversion, the polarity of the solvents was lowered again.

Xylene, used as an isomeric mixture, was the second solvent evaluated. The trials were performed at two different concentrations and at a temperature of 125 °C. The yields of the monoarylated biaryl product obtained at 2.0 and 1.0 M were 77% and 51% respectively with an isomeric ratio similar to the one obtained with DMA. The decrease in polarity of the solvent has a positive effect on our system and more concentrated reactions give enhanced conversion.

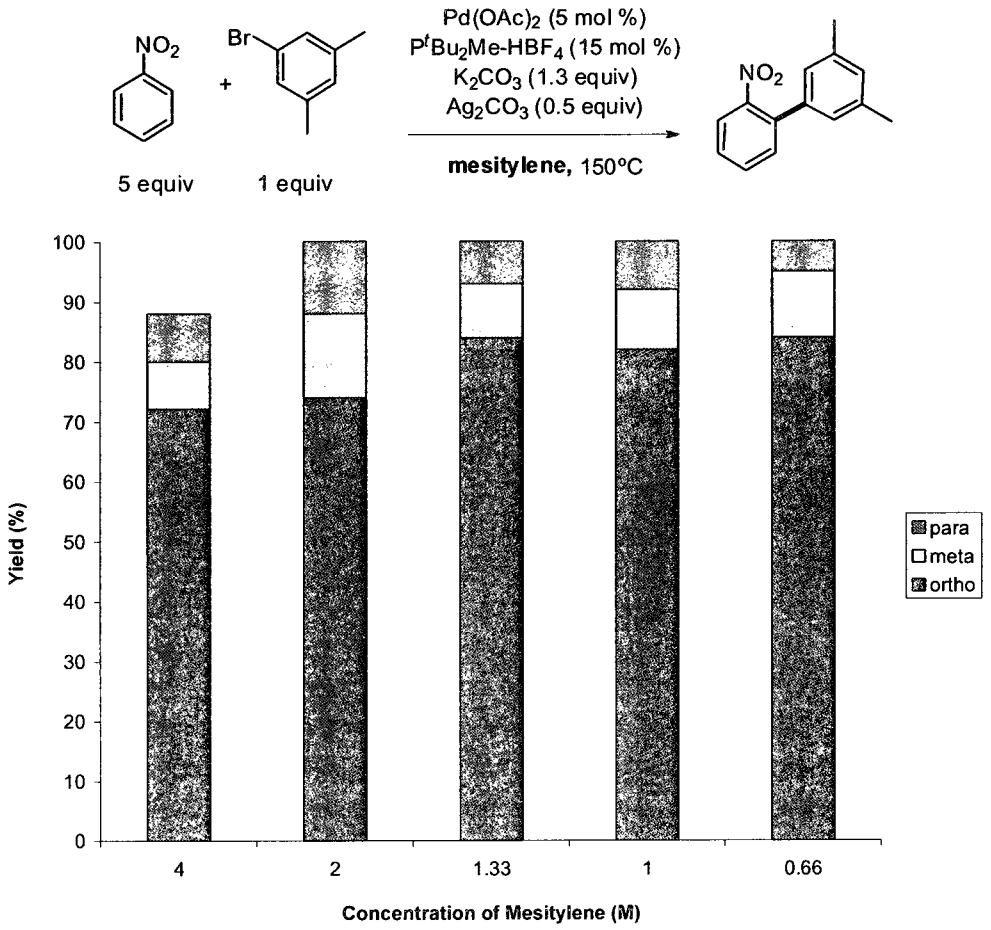
Next, the reaction was set up neat (without solvent). The tests were performed with 5.0 and 10 equivalents of nitrobenzene at a temperature of 125 °C. The conversions were of 62 and 100% respectively and this was the first time that complete conversion was achieved using Ag_2CO_3/K_2CO_3 combination. The reaction could now generate moderate to good regioselectivity as well as complete conversion. The latter reaction was purified by flash chromatography and a 47% isolated yield was obtained indicating that, although consumption of the limiting reagent was complete, the formation of the *ortho*-arylated compound was not sufficient for the envisioned reaction development. The evaluation of the solvent effect was pursued to increase *ortho* arylation of nitrobenzene. Although 10 equivalents of nitrobenzene gave better conversion, 5 equivalents were used for optimization to reduce the waste generated by the reaction.

The various concentrations of mesitylene were evaluated at a temperature of 125 °C. Graph 3-7 depicts the regioselectivity and the yields that were obtained. Overall, good regioselectivity is obtained for 4.0, 2.0, 1.33, 1.0 and 0.66 M solvent concentration and conversion is between 50% and 78%. At concentrations of 1.33 and 1.0 M, the *meta* and *para* isomers are only present in trace amounts and are not detectable for integration by GC-MS. Mesitylene is the best solvent evaluated so far in terms of regioselectivity over a wide range of concentrations.



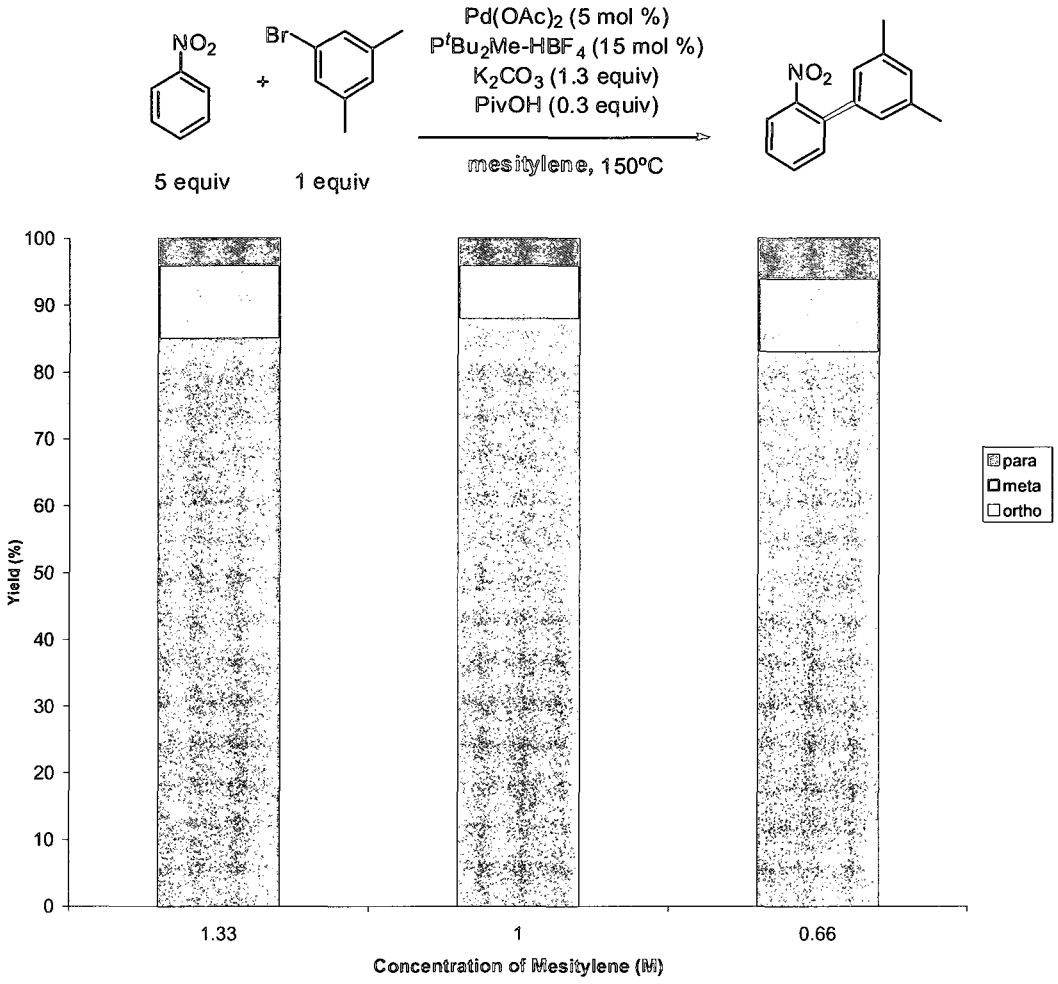
Graph 3-7: Influence of the concentration of mesitylene on conversion and regioselectivity for the K_2CO_3/Ag_2CO_3 conditions

The reaction temperature was raised from 125 °C to 150 °C to try and attain complete conversion (boiling point of mesitylene is 160 °C). The five concentrations are performed in mesitylene and a 100% conversion is achieved for all the reactions except for 4.0 M due to some homocoupling of the aryl bromide (Graph 3-8). Complete conversion and high regioselectivity for the *ortho* biaryl product is obtained. The 1.33 M solution gives the highest regioselectivity.



Graph 3-8: Influence of concentration on conversion and regioselectivity for the K_2CO_3/Ag_2CO_3 conditions at 150 °C

With these results, the combination of K_2CO_3/PivOH was reinvestigated (Graph 3-9). Substitution of Ag_2CO_3 with PivOH results in complete conversion and satisfactory regioselectivity for concentrations of 1.33, 1.0 and 0.66 M. The concentration of 1.33 M was used in further experiments to reduce waste and contribute to the overall atom economy of the methodology.

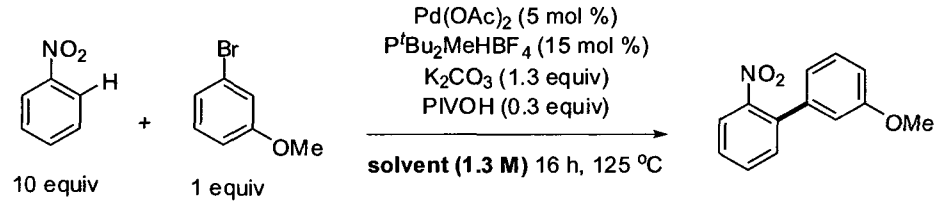


Graph 3-9 Influence of concentration on conversion and regioselectivity for the K_2CO_3/PivOH conditions

There is a trend towards better conversion in apolar solvents. The solvent effect was evaluated with long chain alkanes and bulky aromatics solvents. Decane was the first solvent tried (Table 3-2. entry 6). Surprisingly, a 100% conversion was achieved and the observed regioselectivity is similar to the values obtained in mesitylene.

The effect of tetradecane, octane and *t*-butylbenzene was also evaluated (Table 3-2, entries 7, 8, 9). All three solvents gave similar conversion and regioselectivity. No radical change in regioselectivity is observed; strongly suggesting that regioselectivity of nitrobenzene has peaked under the proposed reaction conditions.

Table 3-2 outlines the influences of the solvent choice on the reaction, focusing on isolated yields. The conditions were modified to include ten equivalents of nitrobenzene and a reaction temperature of 125 °C. Mesitylene and xylene give similar results and although xylene gives the highest yield for this aryl bromide, the yields using other aryl halides are lower than the reactions performed in mesitylene.



entry	solvent	conversion[a]	yield
1	DMA	100%	67%
2	Toluene	94%	45%
3	p-Xylene	100%	79%
4	Nitrobenzene	100%	64%
5	Mesitylene	100%	77%
6	Decane	100%	70%
7	Tetradecane	100%	66%
8	t-Butylbenzene	100%	63%
9	Octane	100%	71%
10[b]	Octane	100%	70%

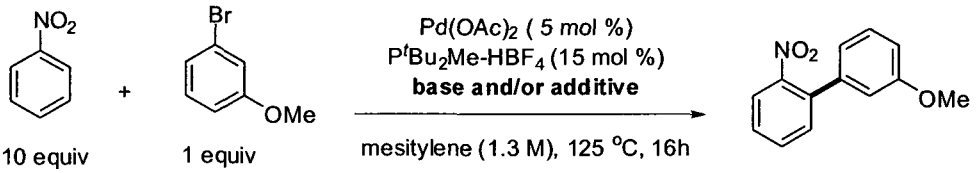
a: Dertemined by GC-MS, b: 0.9 M was used

Table 3-2: Effects of solvent on conversion and isolated yield

3.3.7 Base

The effect of various bases was also evaluated. The first trials were performed without PivOH to maximize the impact of the change in base on conversion and

regioselectivity (Table 3-3). Bases previously reported for direct arylation were chosen.[22d,54c,68,69,70] While the use of K_3PO_4 (Table 3-3, Entry 2) does not induce reaction, bases such as Cs_2CO_3 and K_2CO_3, lead to partial conversion (Table 3-3, Entry 1,3). The use of stoichiometric pivalate bases provides low conversion and isolated yields (Table 3-3, Entries 4, 5). The highest regioselectivity is achieved using the carbonate bases.



10 equiv 1 equiv

entry	base (1.3 equiv)	conversion[a]	yield	regioselectivity (*o*: *m*+ *p*)[a]
1	Cs_2CO_3	52%	28%	27: 1
2	K_3PO_4	0	0	0
3	K_2CO_3	73%	43%	5.1: 1
4	CsOPIV	22%	10%	1.7: 1
5	KOPIV	19%	7.2%	1.8: 1

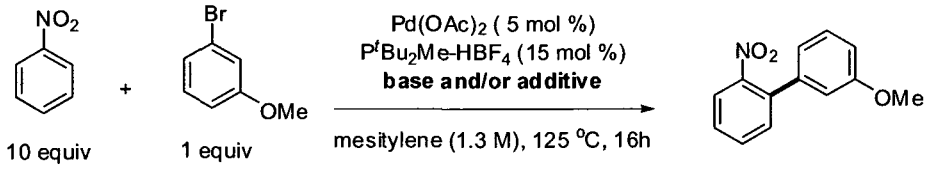
[a] Values obtained from the GC-MS trace.

Table 3-3: Influence of base on conversion

In contrast, the combined use of a carbonate base and pivalic acid provides 100% conversion and a synthetically useful isolated yield of the *ortho*-arylated biaryl compound (Table 3-4, Entries 2, 3). While Cs_2CO_3 gives slightly better regioselectivity (36: 1) than its potassium equivalent (34: 1), the isolated yield was 8% lower. Interestingly, the "ortho: *meta* + *para*" selectivity is also strongly influenced by the base and pivalic acid combination.[71] While relatively poor regioselectivity is obtained with either K_2CO_3 (5.1: 1) or KOPiv (1.8: 1) (Table 3-3, Entries 3 and 5), when K_2CO_3 is combined with a sub-stoichiometric quantity of KOPiv, excellent regioselectivity is obtained (32: 1) (Table 3-4, Entry 4). The reasons for this change in selectivity are a

[68] For selected examples using Cs_2CO_3, see: (a) Denmark, S. E.; Ober, M. H. *Adv. Synth. Catal.* **2004**, *346*, 1703. (b) Lafrance, M.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 14570.
[69] For selected examples using K_3PO_4, see: Miguez, J. M. A.; Adrio, L. A.; Sousa-Pedrares, V. J. M.; Hii, K. K. *J. Org. Chem.* **2007**, *72*, 7771.
[70] For selected example using K_2CO_3, see: 35c.
[71] *Meta* to *para* ratio was around 2:1, but was combined because of overlapping peaks on the GC-MS trace.

focus of ongoing study. Our attempts at improving selectivity by changing the base parameter did not increase the isolated yields of the desire regioisomer.



10 equiv 1 equiv

entry	base (1.3 equiv)	additive	conversion[a]	yield	regioselectivity (*o*: *m*+ *p*)[a]
1	K_3PO_4	PivOH (0.3 equiv)	65%	29%	6: 1
2	Cs_2CO_3	PivOH (0.3 equiv)	100%	69%	36: 1
3	K_2CO_3	PivOH (0.3 equiv)	100%	77%	34: 1
4	K_2CO_3	PivOK (0.5 equiv)	100%	-	32 :1

[a] Values obtained from the GC-MS trace.

Table 3-4: Influence of base and aditive on conversion

3.3.8 Reaction Vessel

During the course of optimization, various reaction vessels were evaluated. The optimization started using 2 mL screw cap vials with Teflon septa, but unfortunately, these vials did not give reproducible results. The vials were small and the resulting reaction pressure often produced leaks through the septa. Radley's Green House Reactor, a sealed stir-plate apparatus accommodating up to 20 experiments, was used for setting up numerous reactions. Disappointingly, these results were not reproducible.

The next vessel used was a 5 mL flask equipped with a reflux condenser. The results were reproducible in these types of vessels, and scale up was easier. Because there was a risk of having product adhere to the walls of the condenser, 10 mL test tubes were also evaluated and gave excellent results. The test tube was sealed with a rubber septa using electrical tape. The walls of the test tube are cold enough, at room temperature, to cool the hot vapours created in the vessel.

3.3.9 Influence of Functional Groups on Ease of Purification by Silica Gel Chromatography

Using the described conditions, a rapid examination of various aryl bromides and nitro-substituted aromatics was conducted to establish functional group tolerance and perfect the purification techniques. The reaction conditions tolerated most functional groups that did not have acidic protons. However, the purification of the various biaryls was difficult.

Even though the *para* and *meta* isomers are observed to form in minor quantities, they often have the same R_f on silica gel as the major isomer. Thus, achieving good isolated yields of *ortho* biaryl compound, through the common method of flash chromatography, was difficult. Moreover, the use of aryl bromides with a non polar alkyl substituent (an electron-neutral substituent), did not induce differences in polarity between the starting nitro-substituted aromatic ring and the final biaryl products. Nitro-substituted aromatics were observed to have low polarity which did not give much leeway for purification.

These factors made isolation difficult and after trying many different purification techniques, the isolated yields of *ortho* arylated products were only moderate to good, with many interesting motifs in the 30% yield range. The combination of functional groups on both coupling partners can be decisive in the ease of separation of products. Reaction design should be used to obtain biaryls that are separable from the other reagents and side-products.

3.4 Scope of Biaryls

3.4.1 Scope of Aryl Halides

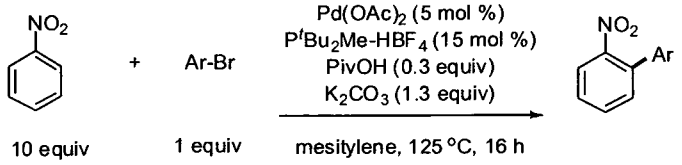
Using the established conditions, nitrobenzene is coupled with aryl halides having a wide range of functional groups.[72] Most cross-coupling pairs attain a 100%

[72] These results have been published: Caron, L.; Campeau, L.-C.; Fagnou, K. *Org. Lett.* **2008**, *10*, 4533.

conversion and provide moderate to good isolated yields of pure *ortho*-arylated compound. As previously mentioned, the isolated yield is largely influenced by the ease or difficulty with which the major isomer can be separated from the minor isomers. 10 equivalents of nitrobenzene are used.

A wide range of functional groups are tolerated on the aryl halide including electron-poor (Table 3-5, Entries 5, 6, 8, 9) and electron-rich (Entries 2, 4, 7) groups. The use of an aryl iodide (Entry 2) is tolerated only when half an equivalent of silver carbonate is used.[73] Aryl chlorides (Entry 2) may also be employed, but lower yields are obtained compared to the use of aryl bromides.

[73] For precedent on the use of silver to sequester iodide, see: 39, 54b.



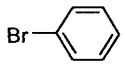
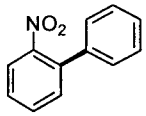
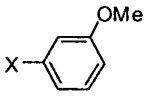
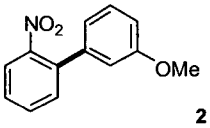
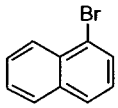
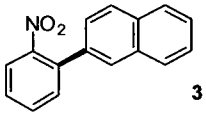
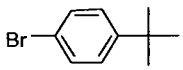
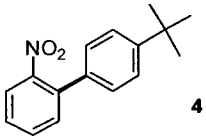
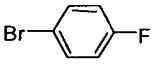
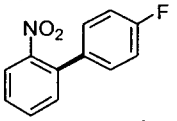
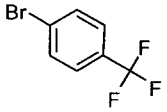
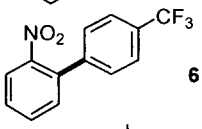
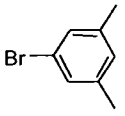
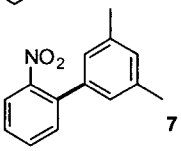
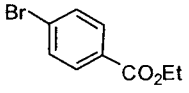
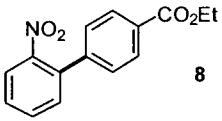
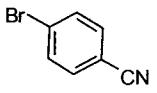
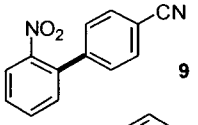
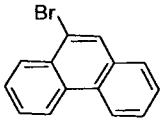
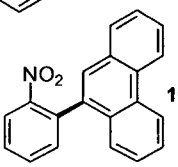
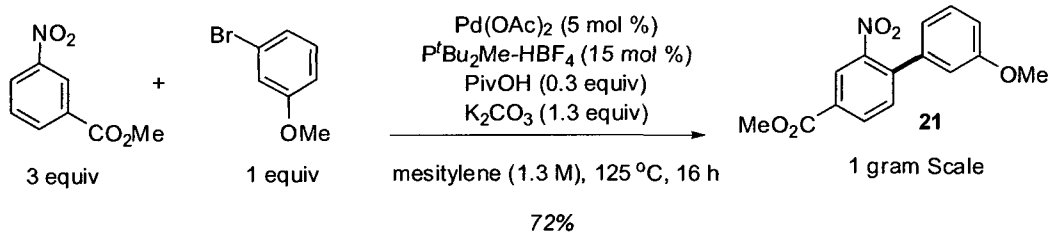
entry	Ar-Br	product	yield
1		 **1**	62%
2	 X= Br X= Cl X= I	 **2**	77% 42% 42%
3		 **3**	62%
4		 **4**	54%
5		 **5**	68%
6		 **6**	60%
7		 **7**	76%
8		 **8**	73%
9		 **9**	54%
10		 **10**	56%

Table 3-5: Scope of direct arylation using aryl halides and nitrobenzene

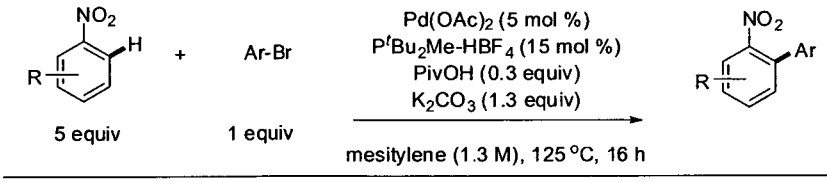
3.4.2 Scope of Nitro-Substituted Aromatics

Reactions with substituted nitrobenzenes were performed with 5 equivalents of the nitroarene. Because the arenes are mainly solids, the excess reagent has to be separated from the biaryl compounds by flash chromatography or recrystallization. However, it was determined that as few as three equivalents of the nitroarene can be employed while maintaining good yields. For example, treatment of 1.0 gram of 3-bromoanisole (1.0 equiv) with three equivalents of 3-methylnitrobenzoate under the standard reaction conditions produces the *ortho* arylated product in good isolated yield (Equation 3-5). The successful realization of a gram scale process with only 3 equivalents of nitro-substituted aromatic under operationally simple conditions, may bode well for a larger scale application of this chemistry.



Equation 3-5: Scale up and reduction of equivalents of nitro-substituted aromatics

The effect of substitution on the nitroarene is also examined and in many cases, very high levels of regioselectivity are obtained (Table 3-6). When a substituent is situated *ortho* to the nitro functionality, 1,2,3-trisubstituted arenes are generated in moderate to good yields, (Entries 1, 2, 3, 5, 7). Similarly, a *para*-substituent may also be tolerated (Entry 10). When *meta*-functionalized nitroarenes are employed, the regioselectivity is governed by both substituents. In each instance, arylation occurs adjacent to the nitro group. When a *meta* methyl or methyl ester group is present, arylation occurs at the more sterically accessible position (Entries 4, 6, 9). On the contrary, when a *meta* nitrile functionality is present, arylation occurs between the two substituents (Entry 8) indicating that other directing group influences are at play.



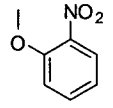
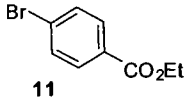
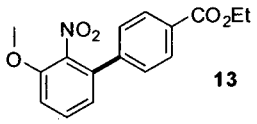
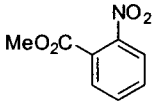
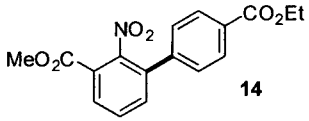
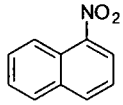
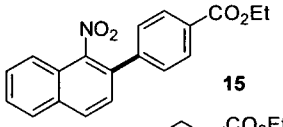
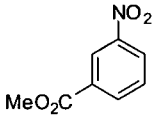
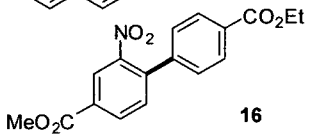
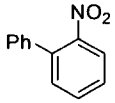
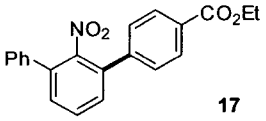
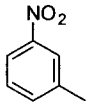
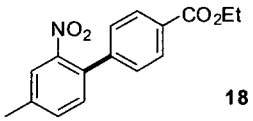
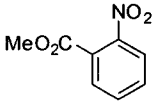
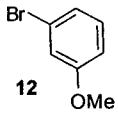
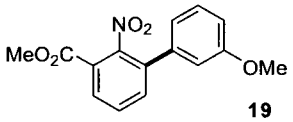
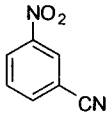
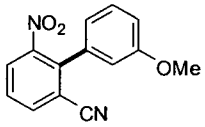
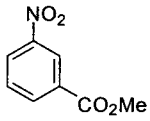
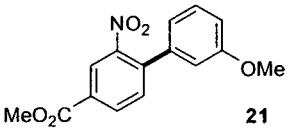
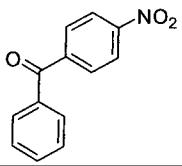
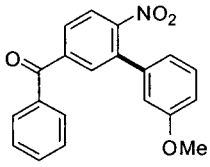
entry	nitrobenzene	aryl bromide	product	yield
1		 **11**	 **13**	61%
2		**11**	 **14**	45%
3		**11**	 **15**	60%
4		**11**	 **16**	65%
5		**11**	 **17**	43%
6		**11**	 **18**	59%
7		 **12**	 **19**	40%
8		**12**	 **20**	63%
9		**12**	 **21**	72%
10		**12**	 **22**	50%

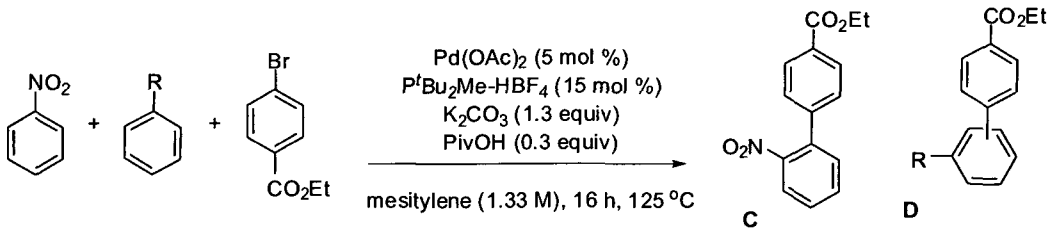
Table 3-6: Scope of substituted nitroarenes

3.5 Reactivity

Early on, it was hypothesized that the nitro functionality could have two distinct roles in direct aylation. The first was associated with C-H bond acidity imparted by the electron-withdrawing force of the nitro group, while the second hypothesis focused more on the possible binding of the metal catalyst to the nitro group. Although a mechanism has not been elucidated, interesting results were obtained while trying to probe the reactivity.

3.5.1 Competition Reactions

Two types of competition reactions were conducted to compare the reactivity of nitrobenzene with that of methylbenzoate and anisole using 4-bromomethylbenzoate (Table 3-7). First, it is hypothesized that if the nitro functionality was only acting as an EWG, other electron-poor cycles should be as equally reactive as nitrobenzene to the developed direct arylation conditions. Experimentally, the arylation of nitrobenzene is highly favored over electron-poor methylbenzoate. It was also observed that when methylbenzoate is reacted alone with the aryl bromide (i.e. not in competition reaction with nitrobenzene), arylation occurred only in low yield (Table 3-7, Entry 2). These results suggest that the activation imparted by the nitro substituent cannot be simply attributed to simple resonance withdrawing/donating patterns and that it is more complex.



entry	R	equiv. nitrobenzene	equiv methyl benzoate	GCMS conversion	
				C	D
1	CO_2Me	5	5	97%	3%
2	"	0	10	0	11%
3	OMe	5	5	99.3%	0.7%
4	"	0	10	0	8.6%

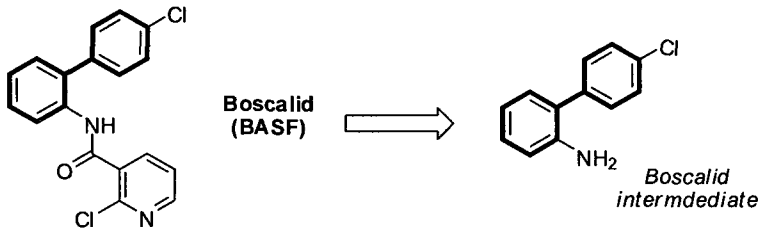
Table 3-7: Competition experiments

Second, we tested nitrobenzene against an electron rich-cycle to verify that the mechanism could not be an S_EAr. Anisole is an electron rich ring and it should be more reactive in that type of mechanism. Our results show that anisole is not more reactive then nitrobenzene and that it is hardly reactive at all in our reaction conditions (Table 3-7, Entries 3, 4). These results suggest that the activation imparted by the nitro substituent cannot be simply attributed to simple resonance withdrawing/donating patterns and is more complex.

3.6 Application of Methodology in the Synthesis of an Agrochemical

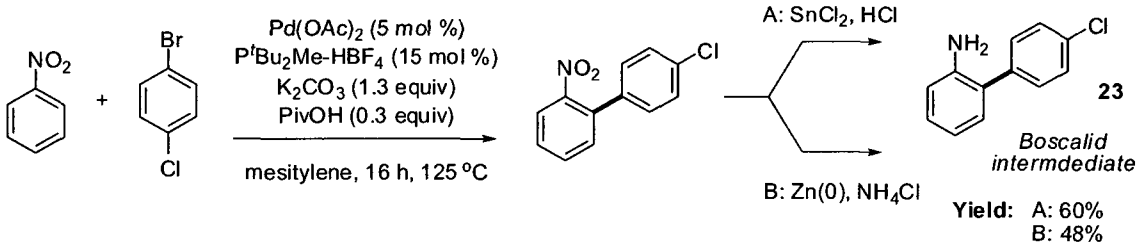
As mentioned in the introduction, many biaryl compounds have strong economic value. The synthesis of these products in a limited number of steps and by using mild reaction conditions that can be easily scaled up is very important and can have an economic impact. To demonstrate that the methodology described above does in fact possess those requirements and that it is an easy and convenient way to access these important molecules, a known chemical product is synthesized. We investigated its use in the rapid preparation of a key intermediate in the synthesis of an agrochemical

We focused our efforts on the agrochemical Boscalid®, produced by BASF.[74,75] Boscalid is an agricultural fungicide used for specialty crops. The synthesis of this molecule is well known and other groups have published partial and total syntheses.[34c,76] The synthesis was limited to the biaryl core intermediate as the last step is a typical peptide coupling between an amine and an ester using a coupling agent (Scheme 3-8).



Scheme 3-8: Retrosynthesis of Boscalid demonstrating the key intermediate

The yield of the first step is low due to poor separation of the *ortho*-arylated product from a mixture of other products (Scheme 3-9). To overcome this problem, the crude mixture was directly carried forth to the reduction of the nitro group into a primary amine. Two different methods were found in the literature for the reduction of nitro-substituted biaryls,[7776b] and even if good yields were reported for both methods, the reduction using tin (pathway A) always gave better results. The use of zinc (pathway B) is a much greener method but unfortunately, only low yields were achieved. Boscalid intermediate **23** was prepared in rapid fashion in moderate to good yield.



Scheme 3-9: Two step synthesis of the Boscalid intermediate

[74] http://www.corporate.basf.com/en/?id=1umAdCh_Rbcp.K9
[75] Ehrenfreund, J.; Lamberth, C.; Tobler, H.; Walter, H. WO pat. **2004**, 058723
[76] Spivey, A. C.; Tseng, C.-C.; Hannah, J. P.; Gripton, C. J. G.; de Fraine, P.; Parr, N. J.; Scicinski, J. J. *Chem. Commun.* **2007**, 2926.
[77] For pathway B, see: Tsukinoki, T.; Tsuzuki, H. *Green Chem.* **2001**, *3*, 37.

3.7 Conclusion

In conclusion, the combination of PivOH and K_2CO_3 as well as the choice of solvent proved to be important in reaching selective arylation of diverse arenes. Electron-poor and electron-rich substrates can be used in combination to obtain good to moderate yields. This method can serve as a viable alternative to the traditional cross coupling to obtain a diverse range of biaryls. Furthermore, the conditions can easily be converted to gram scale and can be used to improve existing synthetic routes of diverse molecules, as illustrated by the rapid synthesis of Boscalid.

Although a detailed discussion on the mechanism is not explored, the role of PivOH is evident. The low conversion into biaryl in the absence of PivOH situates the electronic property of nitrobenzene as being somewhere between those of perfluorobenzene and those of benzene.

Chapter 4: Direct Arylation of Heterocycles

4.1 Introduction

Many heterocycles are present in pharmaceuticals and natural products. Heterocycles are an integral part of nature, and two primary natural amino acids are in fact heteroarenes: tryptophan and histidine (Figure 4-1).

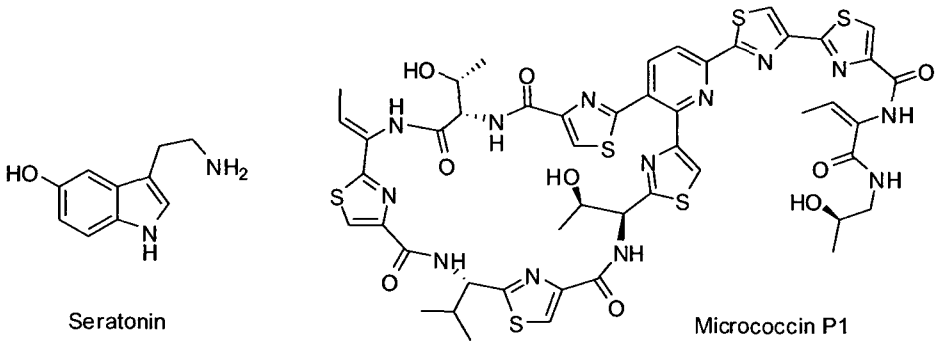


Figure 4-1: Heterocycles in natural products

Direct arylation of heterocycles has appeared in the last 30 years. Often, the desired substitution patterns on the heterocycles can be obtained in the same step as

the formation of the heterocycle. Many methods are known.[78] Common examples include the Paal-Knorr furan and pyrrole syntheses[79], Bartoli[80] or Fischer[81] indole syntheses, and the Robinson-Gabriel oxazole synthesis[82] (Figure 4-2).

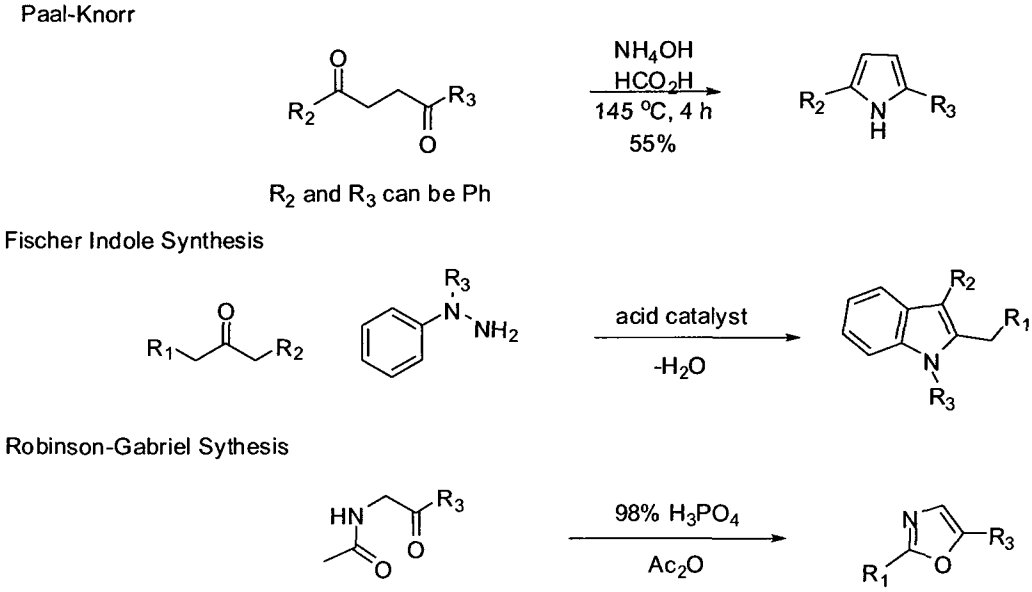


Figure 4-2: Formation of heterocycles through traditional methods

Although substituted heterocycles can be obtained through these various methods, direct arylation presents a few advantages.[21c,d] A common starting material can be used to make a variety of biaryl motifs, while condensation methods often require complicated synthesis of the starting linear product. By using different catalyst systems and additives, different substitution patterns can be achieved from one simple starting material. This presents a great advantage for the construction of molecular libraries and the rapid screening of potential drug candidates.

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[78] *Name Reactions in Heterocyclic Chemistry*; Li, J.-J.; Corey, E. J.; John Wiley & Sons: Hoboken, NJ, 2005.

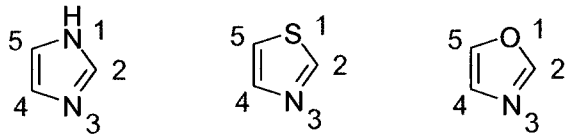
[79] (a) Fu, L.; Gribble, G. W. *Tetrahedron Lett.* **2008**, *49*, 3545. (b) Banik, B. K.; Banik, I.; Renteria, M.; Dasgupta, S. K. *Tetrahedron Lett.* **2005**, *46*, 2643. (c) Amarnath, V.; Amarnath, K. *J. Org. Chem.* **1995**, *60*, 301. (c) Zhu, L.; Shen, D. *Synthesis* **1987**, 1019.

[80] Bartoli, G.; Palmieri, G. *Tetrahedron Lett.* **1989**, *30*, 2129.

[81] (a) Christoffers, J. *Synlett*, **2006**, *2*, 318. (b) Simoneau, C. A.; Ganem, B. *Tetrahedron* **2005**, *61*, 11374. (c) Robinson, B. *Chem. Rev.* **1969**, *69*, 227.

[82] (a) Wasserman, H. H.; Vinivk, F.; *J. Org. Chem.* **1973**, *38*, 2407. (b) Kerr, V. H.; Hayes, F. N.; Ott, D. G.; Lier, R.; Hansbury, E. *J. Org. Chem.* **1959**, *24*, 1864.

In addition to imidazoles, thiazoles and oxazoles, which are the focus of this thesis (Figure 4-3), several other heterocyclic arenes have found application in direct arylation including indoles,[83,22b] indolizines and pyrimidines,[84,55c,d] pyrroles,[85,] triazoles,[22a,32c] furans,[86] thiophenes[87] and their benzo derivatives.[88]



Imidazole Thiazole Oxazole

Figure 4-3: Azole classification

Miura and co-workers were the first to observe that the choice in reagents can have a dramatic impact on regioselectivity.[89] It was found that Pd-catalysis favoured arylation at the C5 position for *N*-methylimidazole and thiazole. However, when Cu is used either as an additive or as the sole metal reagent, there is a clear inversion of regioselectivity. Typically, Pd-catalyzed reactions favour C5 arylation, followed by arylation at C2 and C4. However, when Cu is present in the reaction medium, it can exchange with the most acidic proton, that proton being at the C2 position, to form an organocopper intermediate. This metallic species can then undergo a cross-coupling reaction with an aryl halide and form the C-C bond at C2. The authors demonstrate through reaction development that the order of reactivity can easily be manipulated by either exploiting π-nucleophilicity for C5 arylation or exploiting acidity for C2 functionalization (Figure 4-4). It is not always easy to differentiate between the two reactive positions and C5/C2 double arylation is often present.

---

[83] For selected examples, see: (a) Bellina, F.; Benelli, F.; Rossi, R. *J. Org. Chem.* **2008**, *73*, 5529. (b) Lane, B. S.; Sames, D. *Org. Lett.* **2004**, *6*, 2897. (c) Touré, B. B.; Lane, B. S.; Sames, D. *Org. Lett.* **2006**, *8*, 1979.

[84] For selected examples, see: (a) 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.

[85] Deprez, N. R.; Kalyani, D.; Krause, A.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 4972.

[86] For selected examples, see: (a) Glover, B.; Harvey, K. A.; Liu, B.; Sharp, M. J.; Tymoschenko, M. F. *Org. Lett.* **2003**, *5*, 301.

[87] For selected examples, see: (a) Okazawa, T.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2002**, *124*, 5286. (b) Kobayashi, K.; Sugie, A.; Takahashi, M.; Masui, K.; Mori, A. *Org. Lett.* **2005**, *7*, 5083. (c) Arai, N.; Miyaoku, T.; Teruya, S.; Mori, A. *Tetrahedron Lett.* **2008**, *49*, 1000. (d) Nakano, M.; Tsurugi, H.; Satoh, T.; Miura, M. *Org. Lett.* **2008**, *10*, 1851.

[88] For selected examples, see: (a) Gottumukkala, A. L.; Derridj, F.; Djebbar, S.; Doucet, H.; *Tetrahedron Lett.* **2008**, *49*, 2926. (b) Alagille, D.; Baldwin, R. M.; Tamagnan, G. D. *Tetrahedron Lett.* **2005**, *46*, 1349. (c) Chabert, J.; Joucla, L.; David, E.; Lemaire, M. *Tetrahedron* **2004**, *60*, 3221.

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

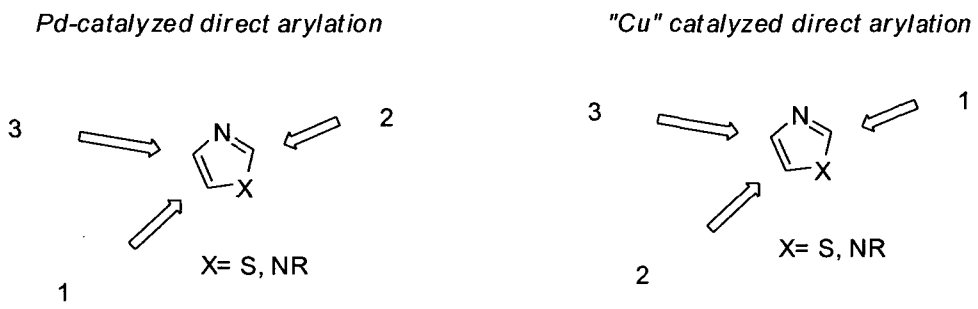
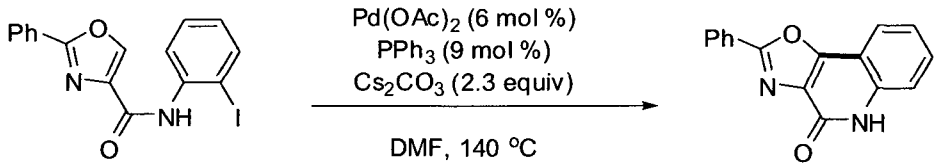


Figure 4-4: Order of reactivity of azoles under Pd and Cu conditions

4.2 Intramolecular Direct Arylation of Azoles

Intramolecular reactions that use imidazole, thiazole or oxazole are rare and are of limited scope.[90] One relevant example is based on research done at Neurogen. Researchers developed an efficient synthesis of molecules having a high affinity for a GABA receptor using an intramolecular direct arylation strategy.[91] By reacting tethered oxazole compound with $Pd(OAc)_2$, PPh_3 and Cs_2CO_3 in DMF at 140 °C, cyclised product is achieved in 63% isolated yield (Equation 4-1).

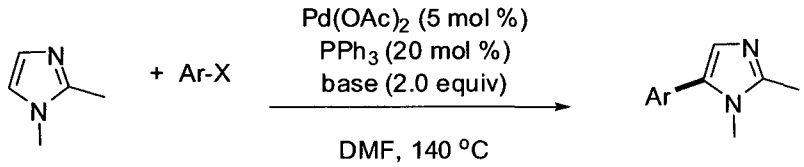


Equation 4-1: Intramolecular direct arylation

[90] Arai, N.; Takahashi, M.; Mitani, M.; Mori, A. *Synlett* **2006**, *18,* 3170.
[91] Hodgetts, K. J.; Kershaw, M. T. *Org. Lett.* **2003**, *5*, 2911.

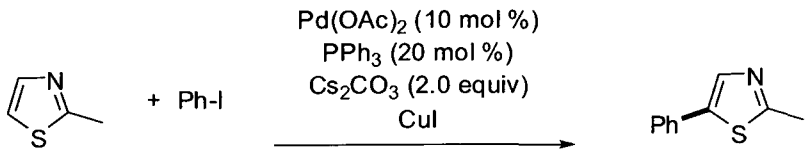
4.3 Intermolecular Direct Arylation of Azoles

Miura and co-workers have studied Pd-catalyzed direct arylation on a wide array of azoles.[89] 1,2-Dimethylimidazoles are found to undergo arylation using $Pd(OAc)_2$, PPh_3 and carbonate bases in DMF at 140 °C (Table 4-1). The authors found that Cs_2CO_3 gave best results with aryl iodides and that K_2CO_3 worked better with aryl bromides to give heterobiaryl compounds in good yields. The authors were the first to report that Cu, as the additive or as the catalyst, is particularly reactive towards thiazoles (Table 4-2).



X	Ar	base	yield
I	C_6H_5	Cs_2CO_3	83%
I	4-$MeOC_6H_4$	Cs_2CO_3	80%
I	4-ClC_6H_4	Cs_2CO_3	84%
I	1-naphthyl	Cs_2CO_3	68%
Br	C_6H_5	K_2CO_3	82%

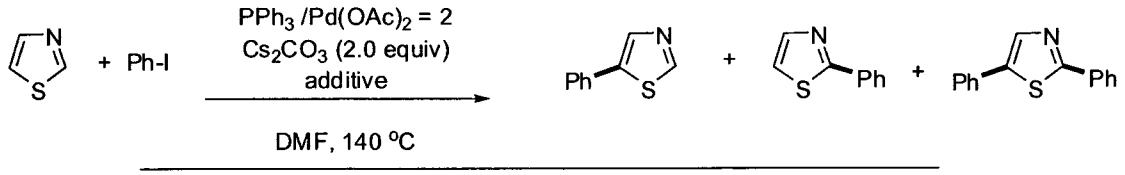
Table 4-1: Arylation of 1,2-dimethylimidazoles using Miura and co-workers' conditions



CuI (equiv)	yield (GLC)
-	43%
2.0	68%

Table 4-2: Effect of Cu on conversion for the arylation of 2-methylthiazole

When thiazole is arylated, a mixture of C2/C5 isomers as well as diarylation is obtained. When Pd and Cu are used, a mixture of monoarylated and diarylated products is obtained, and when CuI is used as the metal reagent, exclusive C2 product is obtained (*Table 4-3*).



		yield (GLC)		
$Pd(OAc)_2$ (equiv)	CuI (equiv)	*C5*	*C2*	*Di*
0.10	-	17%	-	35%
0.10	2.0	-	-	66%
-	2.0	-	15%	-

Table 4-3: Effect of Cu on conversion for the arylation of thiazole

A few years later, the authors presented another methodology for the arylation of thiazole.[92] This method is not selective for mono-arylation and the diarylated product is obtained in good yield (Figure 4-5). Selective arylation of the C5 position is only possible using thiazoles which are substituted at C2.

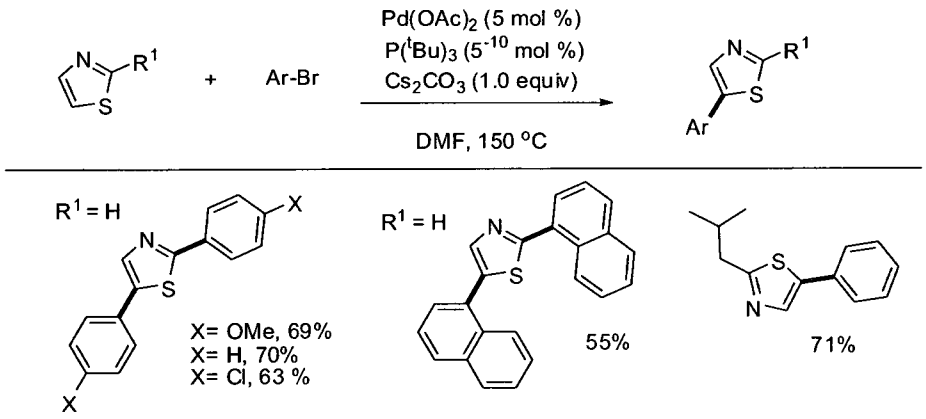


Figure 4-5: Arylation of 2-substituted thiazoles

[92] Yokooji, A.; Okazawa, T.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron* **2003**, *59*, 5685.

By changing the ligand and using a carbamoyl directing group, the elusive C4 arylation is possible (Figure 4-6). After the C4 arylation, the carbamoyl group is cleaved and the free C5 position is arylated to give the corresponding diarylated product.

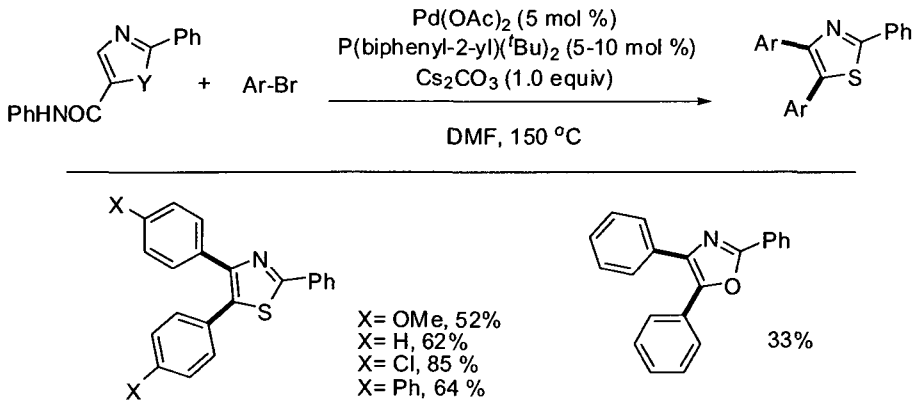
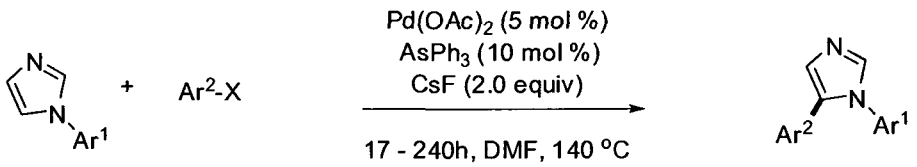


Figure 4-6: Arylation using a carbamoyl directing group

For most arylation reactions of imidazole, the free secondary nitrogen must be protected. A wide array of protecting groups is known in the literature and most often, either aryl or alkyl groups are used. Sames and co-workers reported the C5 arylation of N-protected imidazole.[83] Rossi and co-workers have successfully arylated imidazoles bearing a wide range or aryl and alkyl protecting groups. They have also demonstrated that various reagents or additives can have a completely different impact on regioselectivity. Using a catalyst precursor consisting of $Pd(OAc)_2$ and $AsPh_3$, CsF as base in DMF at 140 °C, C5 arylation of 1-aryl-1*H*-imidazoles is achievable in low to moderate yields (Table 4-4).[93] This protocol is plagued by extremely long reaction time ranging from 17 to 240 hours, however.

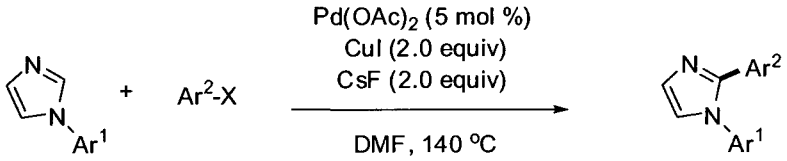
[93] Bellina, F.; Cauteruccio, S.; Mannina, L.; Rossi, R.; Viels, S. *J. Org. Chem.* **2005**, *70*, 3997.



Ar^1	Ar^2	X	yield
Ph	4-$MeOC_6H_4$	I	49%
Ph	4-$MeOC_6H_4$	Br	43%
Ph	4-$CF_3C_6H_4$	I	38%
Ph	4-$CF_3C_6H_4$	Br	59%
4-$MeOC_6H_4$	4-$MeOC_6H_4$	I	36%
4-$MeOC_6H_4$	4-$MeOC_6H_4$	Br	22%

Table 4-4: C5 arylation of imidazole using Rossi and co-workers' conditions

Rossi and co-workers can change selectivity by removing $AsPh_3$ and replacing it with a copper additive (Table 4-5).[94] Cu can insert into the C2 C-H bond and after transmetallation, the Pd catalyst is transferred to the C2 position were the C-C bond will be formed. Because of the reactivity of Cu, diarylation is often observed as a side product in the reaction.



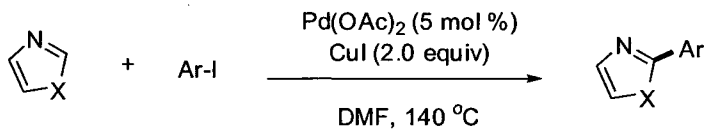
Ar^1	Ar^2	X	yield
Ph	C_6H_5	I	55%
Ph	4-$CF_3C_6H_4$	I	64%
4-$MeSO_2C_6H_4$	3.4,5-$(MeO)_3C_6H_4$	I	79%
4-$MeSO_2C_6H_4$	4-$MeOC_6H_4$	I	94%

Table 4-5: C2 arylation of imidazole

The described methodology can be employed to arylate at the C2 position of other five-membered heterocycles like thiazole and oxazole as well as unprotected

[94] Bellina, F.; Cauteruccio, S.; Mannina, L.; Rossi, R.; Viel, S. *Eur. J. Org. Chem.* **2006**, 693.

imidazoles (Table 4-6).[95] By simply removing the CsF, good to excellent yields are obtained. In 2007, the authors demonstrated that aryl bromides can be used, albeit slightly lower yields, by replacing DMF with DMA and heating 20 °C higher at 160 °C.[96]

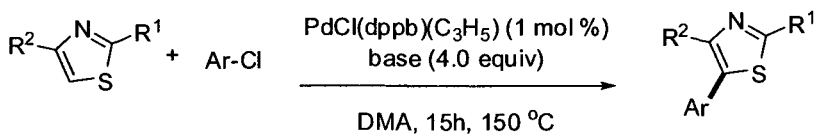


X	Ar	yield
4-$SO_2MeC_6H_4$	4-$MeOC_6H_4$	84%
NH	C_6H_5	89%
S	4-$MeOC_6H_4$	84%
O	4-$MeOC_6H_4$	23%

Table 4-6: C2 arylation of azoles

Aryl chlorides present various advantages, such as their availability in great diversity, but are also known for lower reactivity than other aryl halides. Doucet and co-workers have found that using PdCl(dppb)(C_3H_5), AcOK or AcONa in DMA at 150 °C, moderate to good yields are obtained with ArCl (Table 4-7).[97]. For aryl chlorides, electron-withdrawing groups in the *para*-position are favored but electron-donating groups are not tolerated.

[95] (a) Bellina, F.; Cauteruccio, S.; Rossi, R. *Eur. J. Org. Chem.* **2006**, 1379. (b) Bellina, F.; Calandri, C.; Cauteruccio, S.; Rossi, R. *Tetrahedron* **2007**, *63*, 1970.
[96] Bellina, F.; Cauteruccio, S.; Rossi, R. *J. Org. Chem.* **2007**, *72*, 8543.
[97] Gottumukkala, A. L.; Doucet, H. *Eur. J. Inorg. Chem.* **2007**, 3629.



R^1	R^2	Ar	base	yield
n-propyl	H	4-$COHC_6H_4$	AcOK	74%
n-propyl	H	4-$COHC_6H_4$	AcONa	63%
n-propyl	H	4-$MeCO_2C_6H_5$	AcOK	72%
n-propyl	H	4-CNC_6H_4	AcOK	75%
ethyl	methyl	4-CNC_6H_4	AcOK	71%

Table 4-7: C5 arylation of thiazoles with ArCl using Doucet and co-workers' conditions

Using the same conditions, but with 5 mol % catalyst, substituted bromothiophenes and bromofurans can be used as efficient coupling partners for thiazole, giving access to a biaryl motif compromised of two heterocycles (Figure 4-7).[22e]

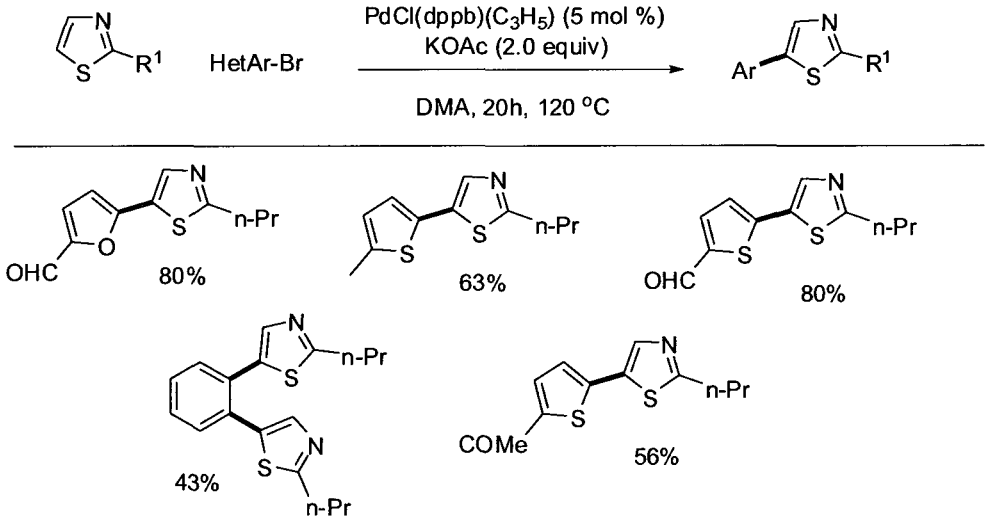
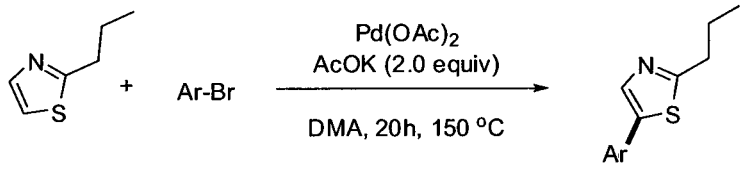


Figure 4-7: Cross-coupling of two heterocycles

Higher yields are obtained when the aryl chloride is replaced by its bromide counterpart and when the Pd source is switched from PdCl(dppb)(C_3H_5) to $Pd(OAc)_2$ (Table 4-8).[98] No ligand is needed and the catalyst loading can be lowered to 0.01%

[98] Požgan, F.; Roger, J.; Doucet, H. *ChemSusChem*, **2008**, *1*, 404.

while maintaining excellent isolated yield. Electron-donating and electron-withdrawing groups can be used successfully.



Ar	sbstrate/ catalyst	yield
4-$COMeC_6H_4$	10 000	94%
4-CNC_6H_4	10 000	89%
4-FC_6H_4	10 000	90%
4-$OMeC_6H_5$	1000	79%
4-$NMe_2C_6H_4$	1000	44%

Table 4-8 :C5 arylation of n-propylthiazole

The authors are able to switch from aryl chlorides to aryl triflates and obtain moderate to good yields for arylation of the C5 position.[99] Other heterocycles can be arylated with triflates, like furan, thiophene and the corresponding benzyl derivatives. Electron-withdrawing functionalities are not tolerated on the aryl halide.

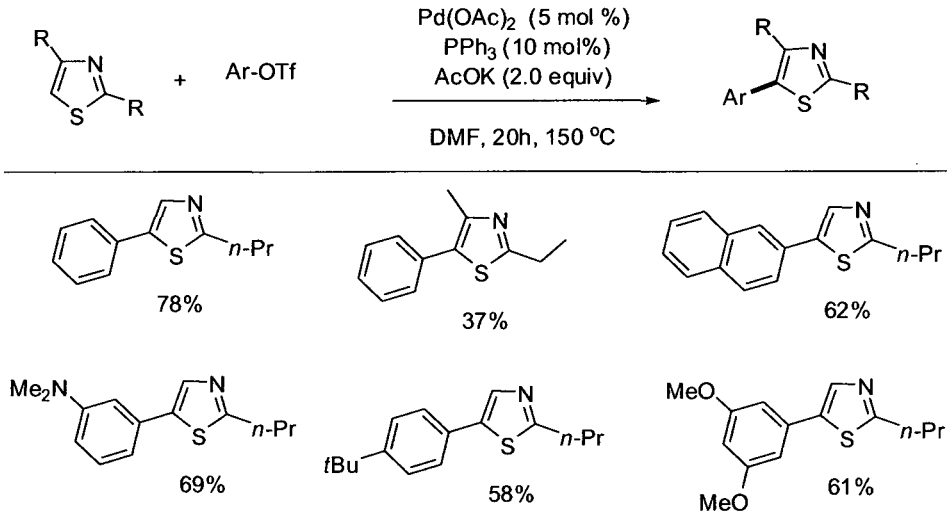
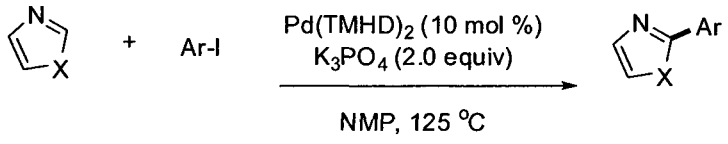


Figure 4-8: C5 arylation of substituted thiazoles using aryl triflates

[99] Roger, J.; Doucet, H. *Org. Biomol. Chem.* **2008**, *6*, 169.

Bhanage and co-workers report the use of a new type of catalyst, palladium bis(2,2,6,6-tetramethyl-3,5-heptanedionate) ($Pd(THMD)_2$), to obtain selective C2 arylation of thiazole, oxazole and there benzyl derivatives (Table 4-9).[100] Aryl iodides are used and moderate to good yields are realized.

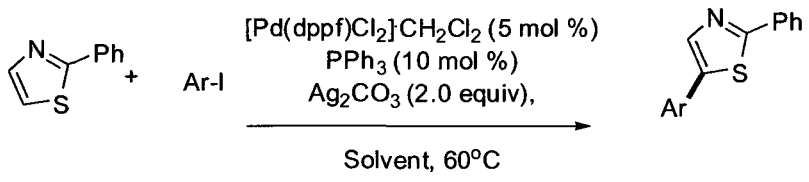


X	Ar	yield
S	4-$MeOC_6H_4$	40%
S	C_6H_5	67%
O	C_6H_5	62%
O	4-$MeOC_6H_4$	63%

Table 4-9: C2 arylation of azole using a new Pd source

Greaney and co-workers follow a different approach for the direct arylation of thiazole.[101] They replace high boiling solvents, like DMA or DMF, with water as the reaction solvent. The authors initially performed the reaction in acetonitrile over 3 days at 60 °C. When conditions were optimized to achieve shorter reaction times, it was found that water reduced the reaction time by 12 hours with increased isolated yields for most arylated products (Table 4-10). Because the organic reagents are not soluble in the aqueous media, the reaction is designated as being "on water".

[100] Nandurkar, N. S.; Bhanushali, M. J.; Bhor, M. D.; Bhanage, B. M. *Tetrahedron Lett.* **2008**, *49*, 1045.
[101] Turner, G. L.; Morris, J. A.; Greaney, M. F. *Angew. Chem. Int. Ed.* **2007**, *46*, 7996.



Ar	yield in MeCN	yield in H_2O
4-MeC_6H_4	74%	90%
4-$MeOC_6H_4$	78%	>99%
4-$CF_3C_6H_4$	62%	>99%
3-FC_6H_4	65%	>99%
3-pyridine	36%	>99%

Table 4-10 : Arylation of thiazole "on water" and in MeCN

The reaction can also be expanded to arylate different substitution patterns on thiazole as well as other heterocycles such as oxazole, thiophene and benzo derivatives (Figure 4-9).

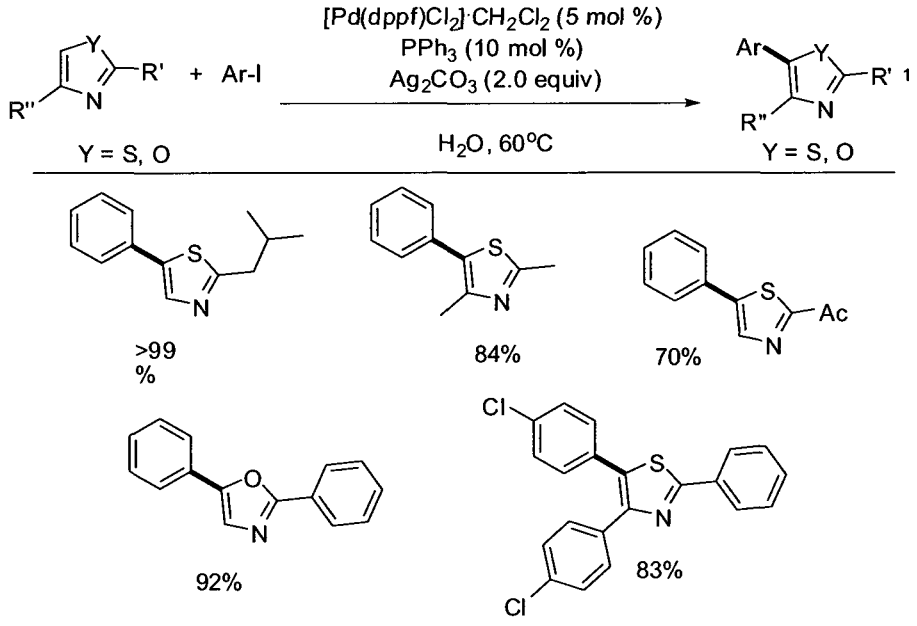
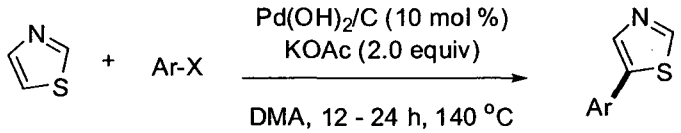


Figure 4-9: Arylation of azoles "on water"

Fagnou and co-workers have shown that arylation is possible using Pearlman's catalyst.[102] The solid-supported catalyst efficiently catalyzes direct arylation of thiazole using aryl iodides and bromides (Table 4-11).



X	Ar	yield
Br	C_6H_5	82%
I	4-$MeOC_6H_4$	73%
I	4-MeC_6H_4	71%

Table 4-11: Arylation using Pearlman's catalyst

Fagnou and co-workers achieved arylation of the *N*-oxide version of thiazole (Table 4-10).[22d] They observed selective sequential arylation of the three available positions on the thiazole core, by first oxidizing the nitrogen into its *N*-oxide form. The oxygenated derivative has a reliable C2>C5>C4 reactivity profile. Mild conditions can be used for all three arylations and the oxygenation/deoxygenation methodology is rapid and can tolerate various functional groups.

[102] Parisien, M.; Valette, D.; Fagnou, K. *J. Org. Chem.* **2005**, *70*, 7578.

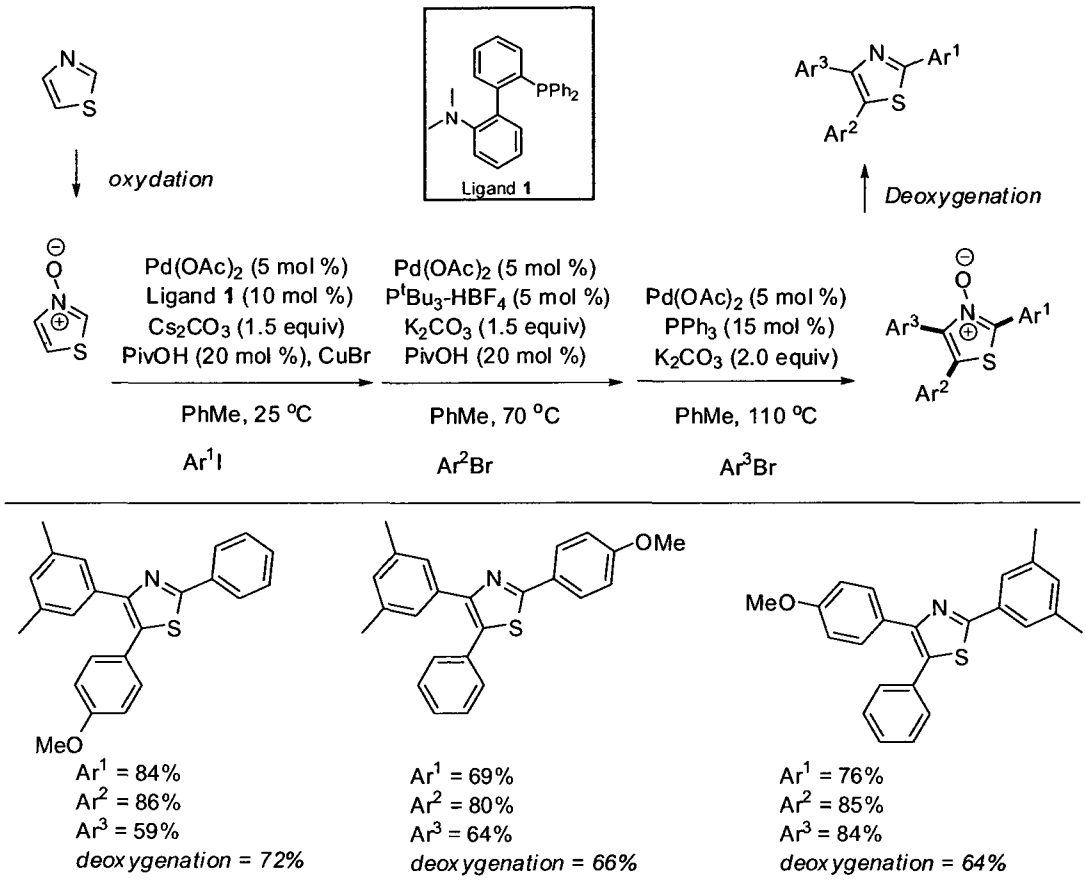
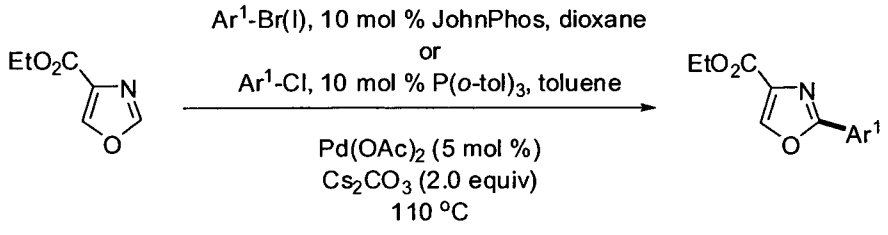


Figure 4-10: Arylation of thiazole N-oxide

Hoarau and co-workers are able to obtain C2, C5 sequential arylation of C4 substituted oxazoles.[103] The first arylation takes place at C2 and various aryl halides can be used (Table 4-12). The choice of aryl halides dictates the conditions that one must use. Aryl iodides and bromides work well with JohnPhos[104] in dioxane while aryl chlorides undergo arylation with P(*o*-tol)$_3$ in toluene. Furthermore, raising the ratio of heteroaryl to aryl halide from 1 to 2 significantly increases yields.

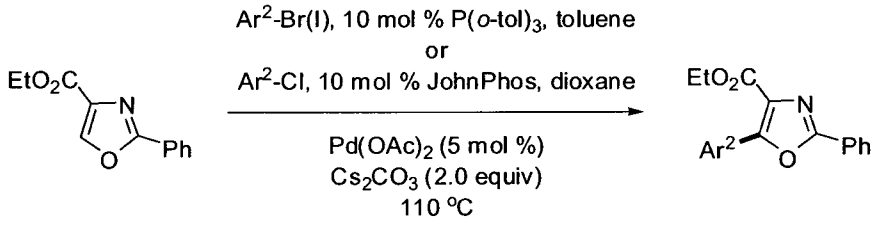
[103] Verrier, C.; Martin, T.; Hoarau, C.; Marsais, F. *J. Org. Chem.* **2008**, *73*, 7383.
[104] Buchwald's JohnPhos ligand: 2-(dicyclohexyl-phoshino)biphenyl.



Ar^1 (2.0 equiv)	X	yield
4-CNC_6H_4	I	91%
4-$CHOC_6H_4$	Br	60%
4-$OMeC_6H_4$	I	77%
4-$OMeC_6H_4$	Cl	68%
2-pyridine	I	98%
3-pyridine	Br	98%
2-thiazole	Cl	73%

Table 4-12: C2 arylation of oxazole using Hoarau and co-workers' conditions

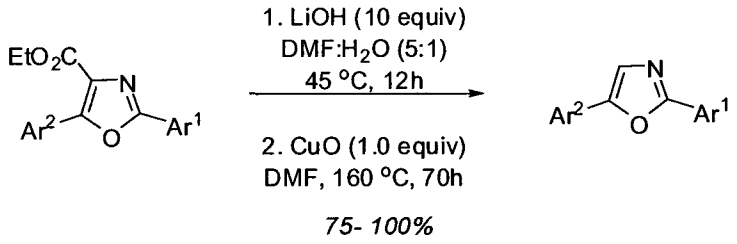
The second arylation occurs at C5 in good to excellent yields (Table 4-13). The second arylation can tolerate various functional groups on both aryl rings.



Ar^2 (1.0 equiv)	X	yield
2-$NO_2C_6H_4$	I	84%
3,4-$OMeC_6H_4$	Br	84%
2-pyridine	I	95%
2-pyridine	Br	72%
2-pyridine	Cl	55%
2-thiophene	I	89%

Table 4-13: C5 arylation of oxazole

The authors show that removal of the ethyl ester at C4 is possible, although the molecule must be submitted to harsh conditions, which include high heat (160 °C) and long reaction times (70 hours) (Equation 4-2).



Equation 4-2: Removal of the ethyl ester from oxazole

Chapter 5 : Direct Arylation of Azoles

5.1 Introduction

Nearly all direct arylation reactions require harsh conditions such as high temperatures reached by the use of high boiling solvents like DMF, DMA and NMP. While this is not a problem for medicinal chemists who are trying by any means to make small molecules, these rigorous reaction conditions do have an impact on the construction of complex natural products. Severe conditions can be hazardous in the last few steps of a long total synthesis. A direct arylation strategy is indeed favourable for functionalization, but milder conditions are indispensable. As seen in chapter 4, mild conditions are sometimes available but the lack of viable and reproducible reactions conditions for all type of heterocycles is lacking.

5.2 Mechanisms

When direct arylation is considered, the main concern is regioselectivity. Although regioselectivity is still an issue in the case of heteroarenes, there is strong electronic bias for these types of molecules. Regioselectivity is made possible with heteroarenes because of the presence of the heteroatoms that favour reactivity at one site. Fagnou and co-workers have calculated and demonstrated that the regioselectivity of direct arylation can be predicted for heteroarenes by the CMD pathway.[59] The preferential reaction sites are illustrated in Figure 5-1.

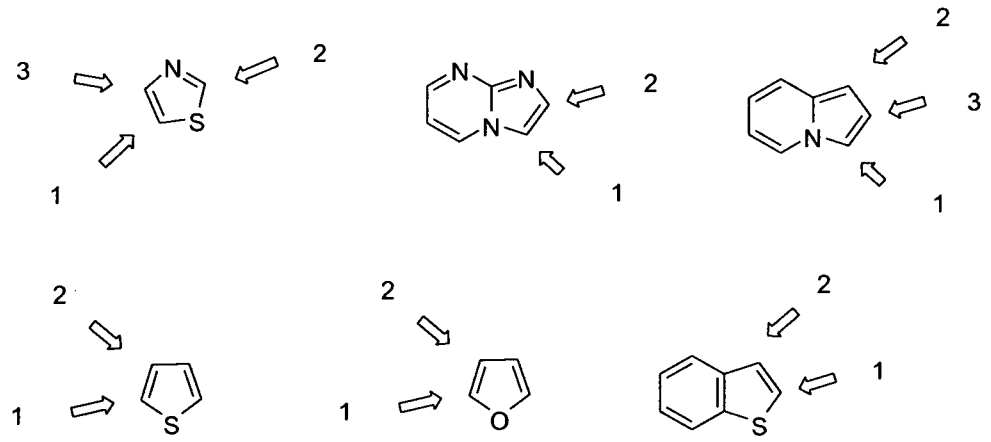
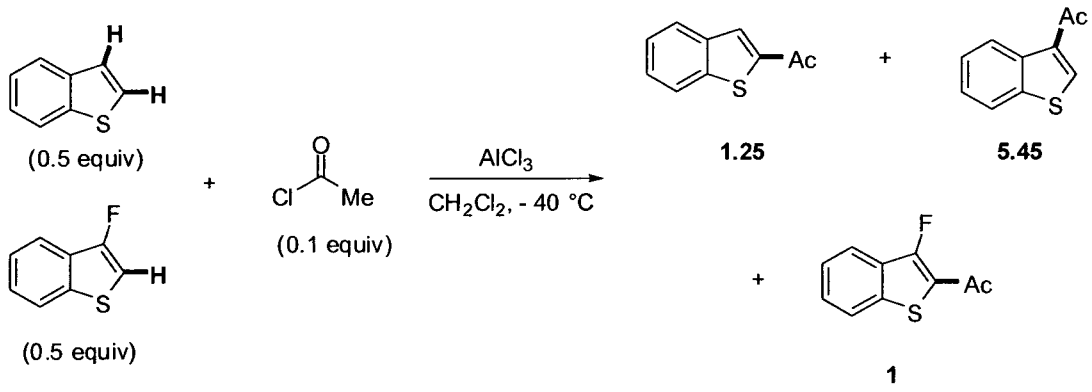


Figure 5-1: Order of reactivity of heterocycle as predicted by the CMD pathway

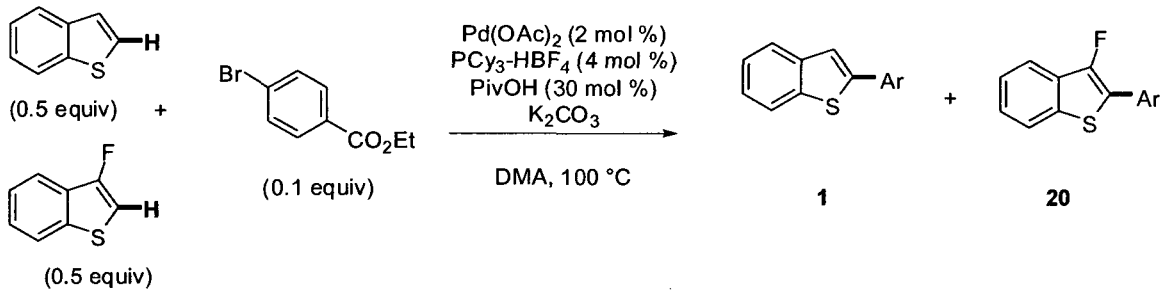
Experimentally, the authors observed that π-rich benzothiophene reacted preferentially over the less π-rich 3-fluorobenzothiophene under Friedel-Crafts acylation conditions (Scheme 5-1). The more nucleophilic benzothiophene gave a higher conversion. The fluorine is clearly deactivating under these types of conditions and this follows the established reactivity for S_EAr reactions.



Scheme 5-1: Competition reaction under Friedel-Crafts acylation conditions

In a different experiment, Fagnou and co-workers observed that 3-fluorobenzothiophene reacted preferentially over the more nucleophilic benzothiophene using direct arylation conditions (Scheme 5-2). The S_EAr pathway predicts that the more electron-rich substrate should react preferentially. The observed outcome is incompatible with this hypothesis since 3-fluorobenzothiophene is preferentially arylated. In this scenario, the electron-withdrawing group is activating (these results were

observed with the arylation of fluorinated benzene). This result promotes the possibility that all heterocycles may follow the CMD pathway in the presence of PivOH as a co-catalyst, just like electron neutral arenes such as benzene.



Scheme 5-2: Competition experiment under direct arylation conditions

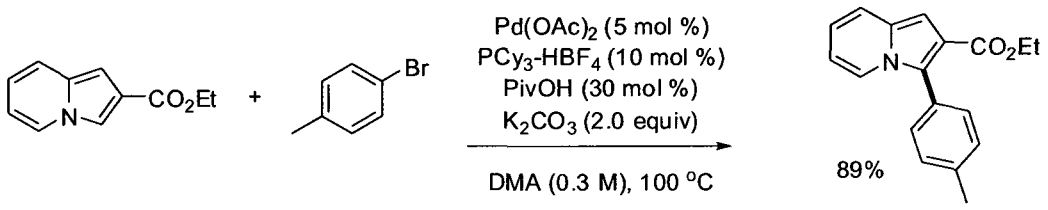
5.3 Objectives

It is essential to establish one set of reaction conditions that can work with all types of heterocycles without any regioselectivity issues. It would also be essential that this methodology be applied to all sorts of electrophiles: iodides, bromides, chlorides and triflates.

Because different reports show the arylation of different heterocycles and pseudo-halides, an easy to follow, widely applicable methodology is greatly lacking in the field. Oxazoles, imidazoles and thiazoles are the focus of this thesis and are part of a project to create broadly applicable direct arylation conditions for all heterocycles. Low catalyst loading, short reaction time, efficacy and environmentally friendly conditions are indispensable in this reaction development.

5.4 Direct Arylation

Building on our knowledge of the CMD pathway and the previously described observation and application of the PivOH/Pd catalyst system,[72,51,59] a model substrate, indolizine, was employed in initial reaction optimization efforts.[105] Once viable conditions could be achieved, the objective was to apply the conditions to a wide spectrum of heterocycles and aryl halides. These studies lead to the finding that 5 mol % $Pd(OAc)_2$, 10 mol % PCy_3-HBF_4, 30 mol % PivOH, 2.0 equiv of K_2CO_3 in DMA at a 100 °C efficiently induce direct arylation with this substrate (Equation 5-1). The reaction is complete in about 3 hours.

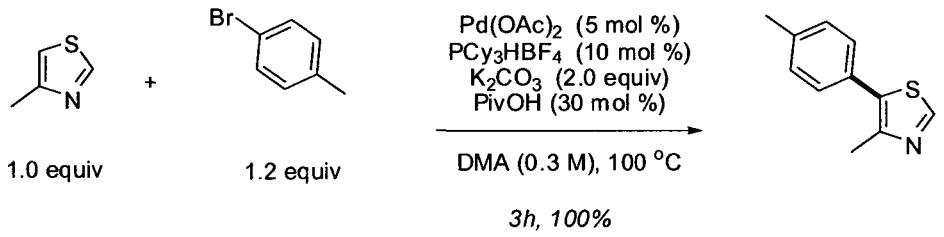


Equation 5-1: Optimized conditions for the arylation of indolizine

5.4.1 Arylation of Thiazole

The optimized conditions for indolizine were first used to arylate 4-methylthiazole. When 4-methylthiazole was submitted to the previous conditions for 3 hours, a 100% conversion was achieved (Equation 5-2).

[105] Work done by David Lapointe



Equation 5-2: Application of developed conditions to the arylation of thiazole

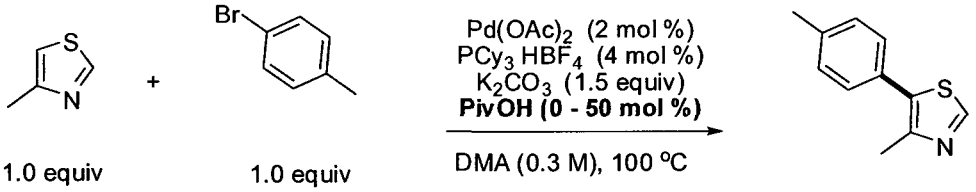
Preliminary tests show that the reaction actually reaches complete conversion within 35 minutes. When no PivOH is added, the reaction still reaches a 100% conversion but the reaction time is longer, taking over 3 hours to complete.

5.4.1.1 Timed Experiments

Following the successful arylation of 4-methylthiazole, the conditions were partially re-optimized. The amount $Pd(OAc)_2$ and PCy_3HBF_4 was reduced to 2 mol % and 4 mol % respectively. The quantity of base was lowered to 1.5 equiv and the heteroarene/aryl bromide ratio was lowered from 1:1.2 to 1:1. Detailed experiments that follow conversion through time were compiled to find the best concentration of PivOH and measure the possible influence of the co-catalyst.

Four reactions were set up having different amounts of PivOH and were followed over time to measure the conversion into C5 arylated thiazole (Figure 5-2). The decrease in catalyst and base loading increases the reaction time from 35 minutes to 55 minutes. Most importantly, the variation of PivOH loading has a substantial impact on reactivity. The experimental results show that 30 mol % of PivOH is the optimal percentage. Increasing the amount to 50 mol % reduces conversion and elongates reaction time. When the amount of PivOH is lowered to 10 mol %, conversion is again lower and the reaction time is prolonged. Complete removal of the PivOH significantly slows down the reaction and lowers conversion to around 50%. The activation period is short when 30 mol % is used and any change in the amount of PivOH lengthens the activation period. The formation of the active catalyst is still difficult to understand and

these experimental results seem to indicate that the presence of the co-catalyst influences the formation of the active species.



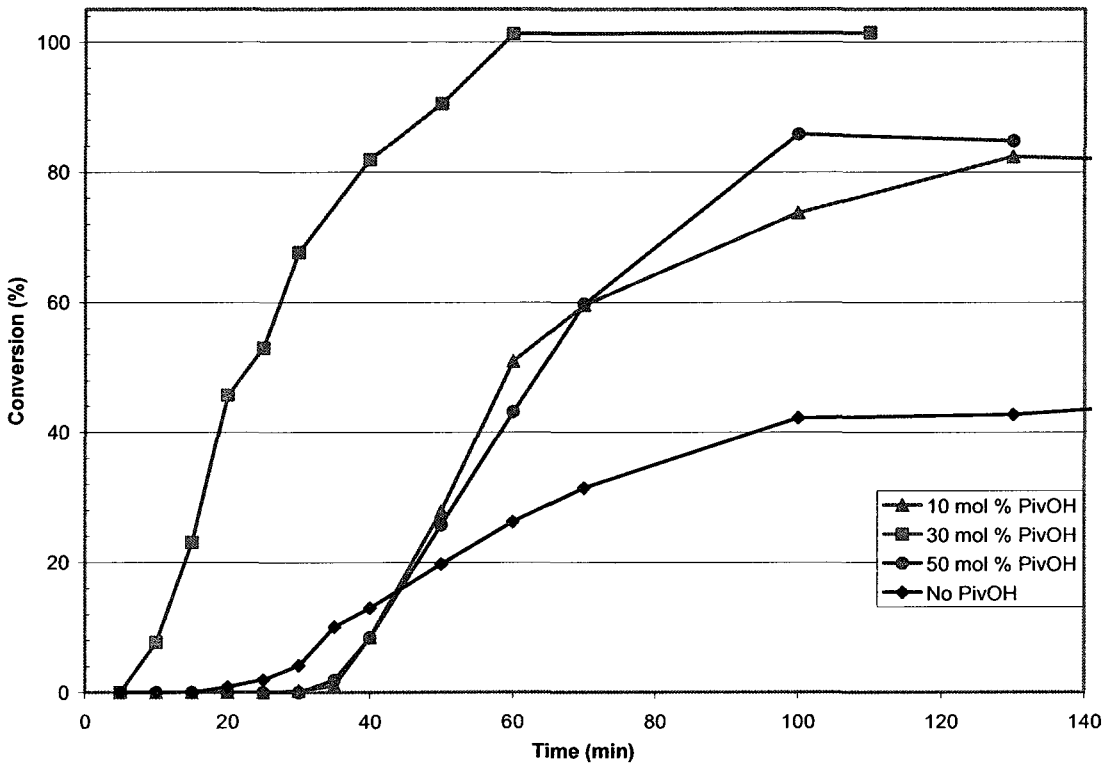


Figure 5-2: Conversion versus time for the arylation of 4-methylthiazole

To validate these findings, the curves were compared to the curves obtained from the arylation of other heterocycles.[106] The trends vary. First, benzothiophene was submitted to the same conditions as described above (Figure 5-2). For this heterocycle, the different amounts of PivOH (10, 30, 50 mol %) give similar results. 30 mol % gives the highest conversion. When 10 mol % of PivOH is used, conversion is lowered by about 15%. 50 mol % gives very similar conversion to 30 mol %. The absence of PivOH significantly lowers conversion and the importance of the additive is evident. The

[106] The graphs shown were done by Benoît Liégault and David Lapointe rescpectively.

activation period for this system is very similar for all reactions and the amount of PivOH does not seem to have an impact on this parameter.

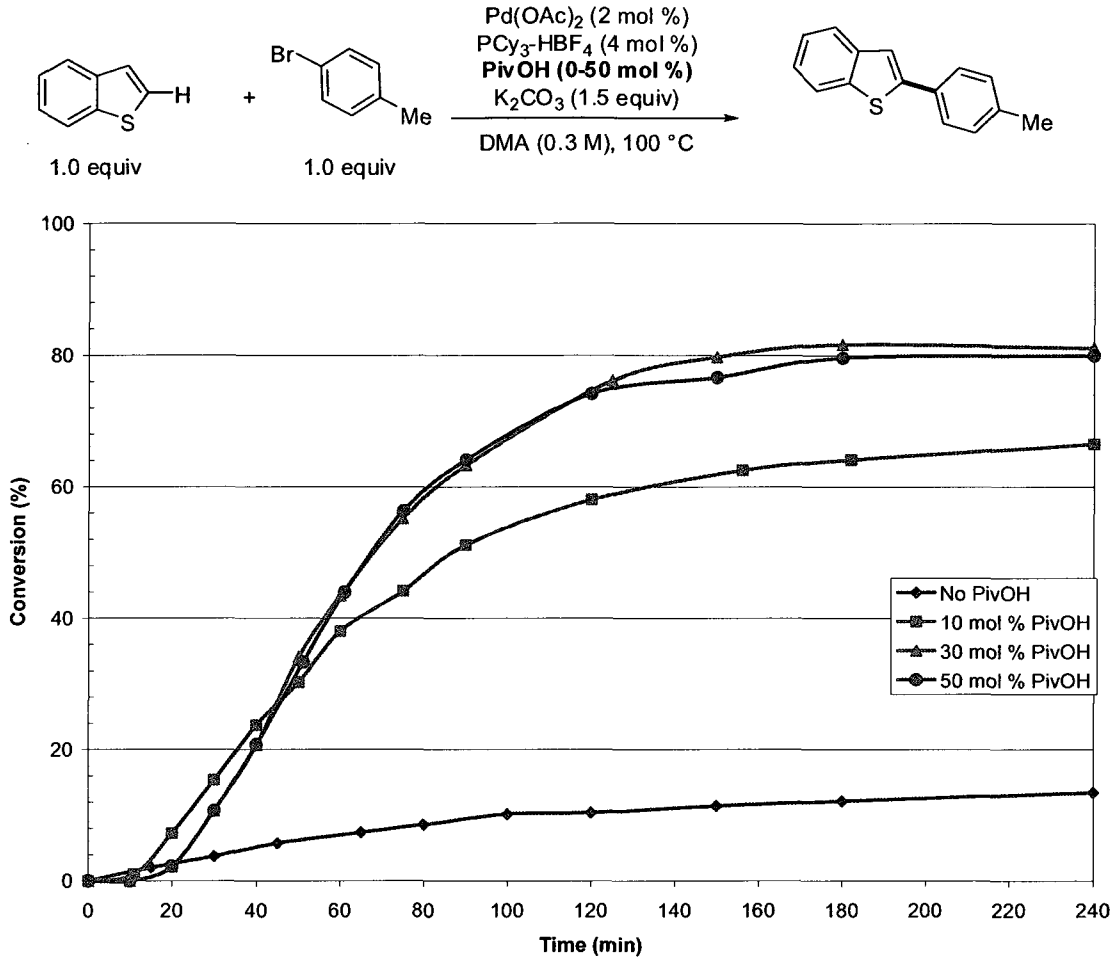
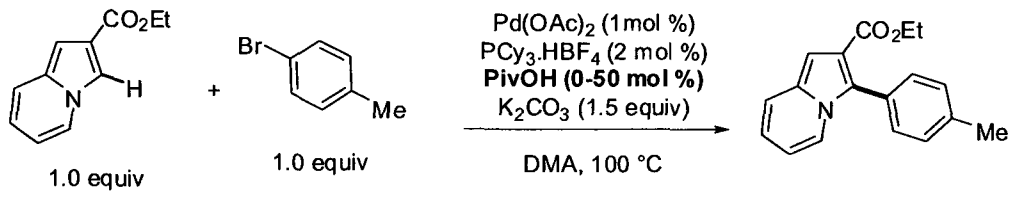


Figure 5-3: Conversion versus time for the arylation of thiophene

Indolizine was also submitted to the same conditions and a different outcome was observed (Figure 5-4). For this heterocycle, the amount of PivOH does not greatly influence reactivity. There is only a difference of 10% conversion between the reaction without PivOH and the one with 30 mol %. Conversion obtained with 10 and 50 mol % is situated between the two curves. This substrate seems to be more reactive then the other two, since the presence of the co-catalyst is not necessary to induce reactivity.



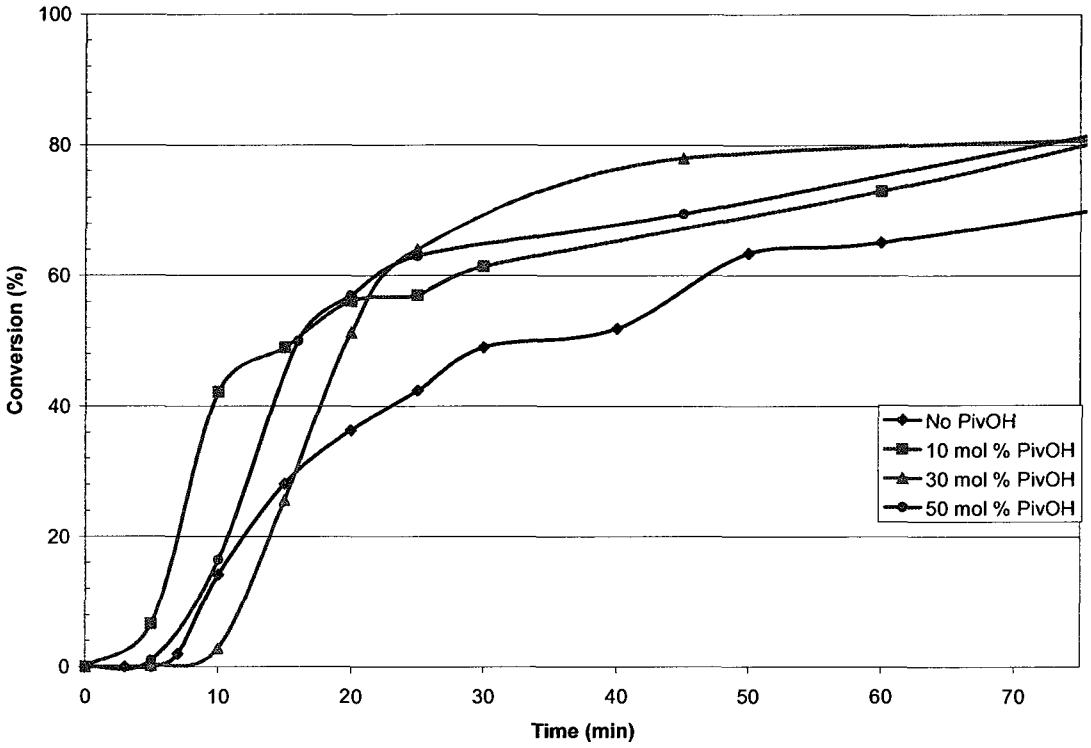


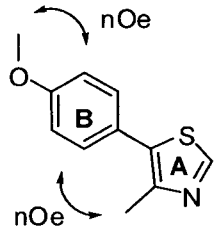
Figure 5-4: Conversion versus time of azaindole

Not all heterocycles have the same reaction profile, but for benzothiophene and 4-methylthiazole, the use of PivOH as a co-catalyst is mandatory to achieve good conversion and rapid reaction times. Having optimized conditions that meet the set objectives, a scope of aryl halides and thiazoles is undertaken.

5.4.1.2 Scope

To assure the wide applicability of the method, thiazoles were chosen according to their commercial availability and cost.[107] Most thiazoles were reactive under the described conditions and gave the C5 arylated product in good to excellent yields (Table 5-1). Reaction times vary from 1h30 to 25h. Electron-withdrawing and electron-donating groups are reactive as well as sterically hindered substrates such as phenanthrene. Aryl chlorides are tolerated but produce lower yields then their bromide counterpart.

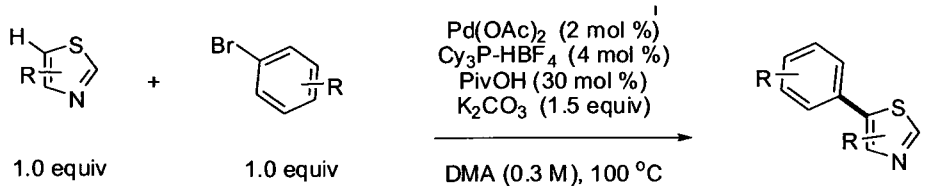
Regioselectivity was demonstrated through 2-D experiment for compound **33**. The NOESY experiment provides evidence of the long range interaction between the C-H bonds on ring **B** to the methoxy and the long range interaction between C-H bonds on ring **B** and the methyl on ring **A**.



33

*Figure 5-5: Representation of the long range interactions for compound **33***

1. [107] These results have been published: Lapointe, D.; Liégault, B.; Caron, L.; Vlassova, A., Fagnou, K.. *J. Org. Chem.* **2009**, *74*, 1826.



1.0 equiv 1.0 equiv

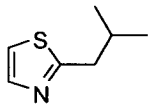
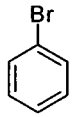
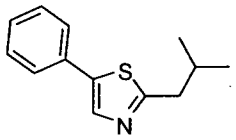
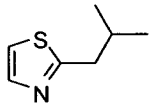
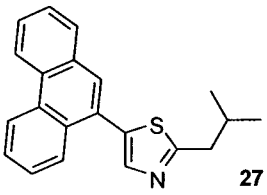
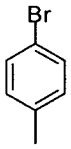
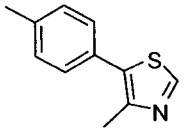
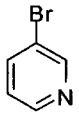
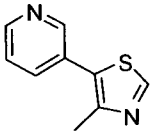
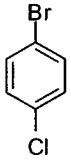
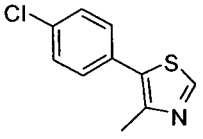
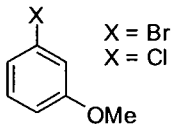
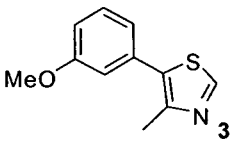
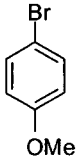
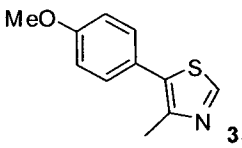
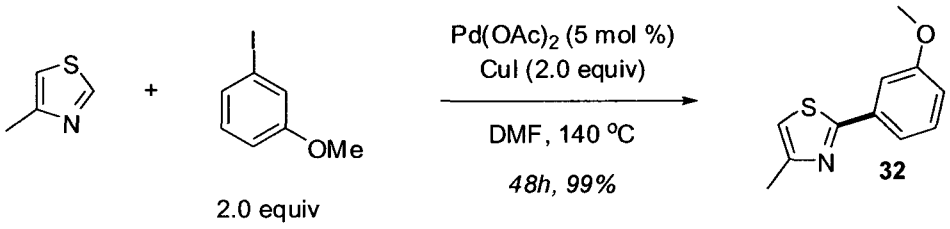
entry	thiazole	Ar-Br	product	reaction time	yield
1			 **26**	3h15	89%
2			 **27**	3h15	88%
3			 **28**	1h30	78%
4			 **29**	25h	56%
5			 **30**	4h	66%
6		 X = Br X = Cl	 **31**	1h30 2h	74% 16%
7			 **33**	2h30	65%

Table 5-1: Scope of various thiazoles

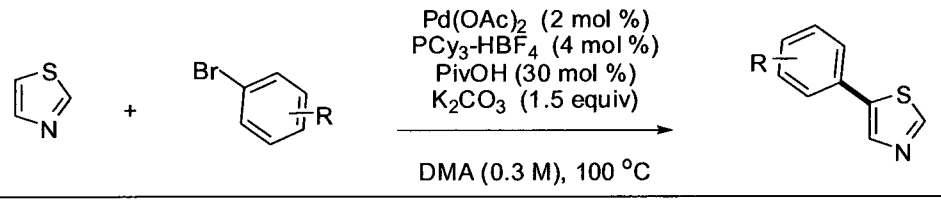
To further investigate the regioselectivity of our developed conditions, 4-methylthiazole and 3-bromoanisole were arylated using conditions developed by Rossi and co-workers (Equation 5-3).[95a] Copper is used in these conditions and, although the authors did not prepare this specific substrate, all of their coupling reactions that used thiazoles produced the C2 product. The NMR data obtained for product **32** does not correspond to the data obtained for compound **31** and suggests that the C2 isomer is compound **32** because the chemical shift of the C-H heterocyclic bond corresponds closely to the value of the C5 C-H bond.[108] Although C5 regioselectivity can not be definitely assigned to compound **31**, this provides good evidence that our conditions are not selective for C2 arylation when the C5 and C2 positions are available.



Equation 5-3: Direct arylation using Rossi and co-workers' conditions

For unsubstituted thiazole, the equivalents ratio between the starting materials was modified to produce moderate to good isolated yields of the monoarylated product (Table 5-2). For 4-bromoanisole, 1.4 to 1 ratio gives a 62% isolated yield (Entry 1).[109] For 9-bromophenanthrene (Entry 2), mono- and diarylated product is isolated in low to moderate yields. Increasing the amount of thiazole from 1.0 equivalent to 1.5 equivalents gives a better isolated yield of monoarylated product and a decrease in diarylated product. The choice in heterocycle quantity can be varied according to the required results and cost of the heterocycle.

[108] For calculated and observed chemical shifts for thiazole C-H bonds, see: Abraham, R. J.; Reid, M. *J. Chem. Soc., Perkin Trans.* **2002**, *2*, *1081*.
[109] No diarylation product was observed.



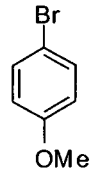
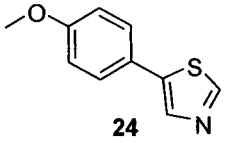
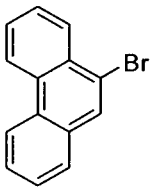
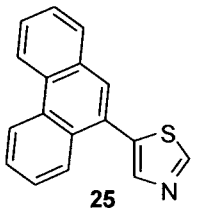
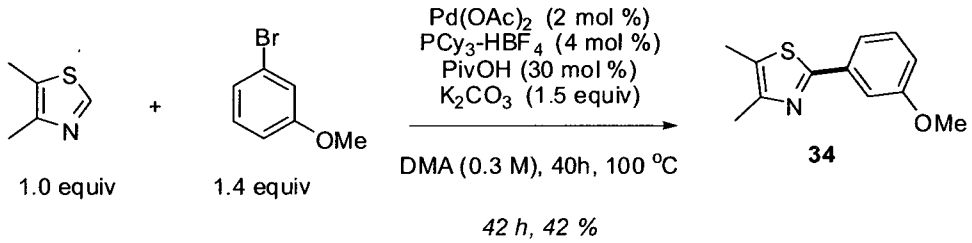
entry	Ar-Br	product	thiazole: ArBr	reaction time	yield (mono/diarylation)
1		 **24**	1.4:1	19h	62%
2		 **25**	1:1 1.5:1	18h 18h	60%/27% 80%/17%

Table 5-2 : Scope of thiazole with varying ratios of reactants

The reactivity of our reaction conditions was tested and C2 arylation was attempted with the C4 and C5 position blocked by substitution. C2 is known to be reactive to direct arylation in the presence of copper.[110] C2 arylation was possible, and only one product was obtained in low yields. 4,5-Dimethylthiazole is arylated in 42% yield using the same catalyst previously described (Equation 5-4).

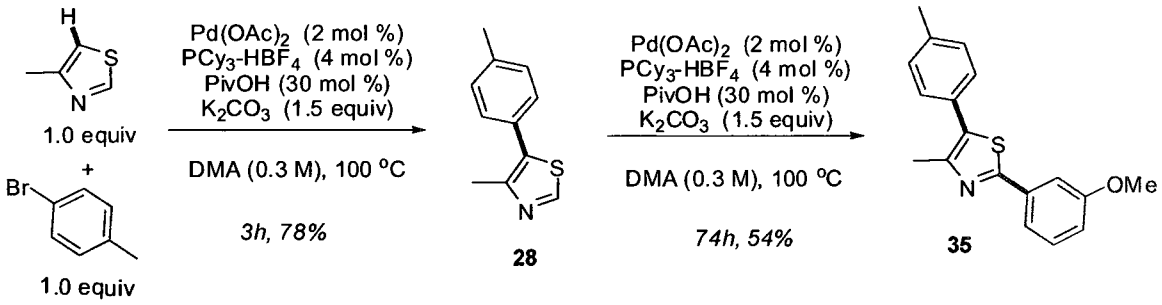


Equation 5-4: C2 arylation of thiazole

To further probe the reactivity of the C2 position and to attempt sequential arylation, the electronics of the C5 positions were varied. Compound **28** was submitted

[110] See figure 4.4

to the optimized arylation conditions and C2 arylation is achieved in 54% isolated yield (Scheme 5-3).



Scheme 5-3: Sequential arylation of 4-methylthiazole

Attempts to arylate the C2 position using 5-methylthiazole failed as well as the arylation of benzothiazole (Figure 5-6). In addition, thiazoles which were substituted with NH were completely unreactive and gave no conversion.

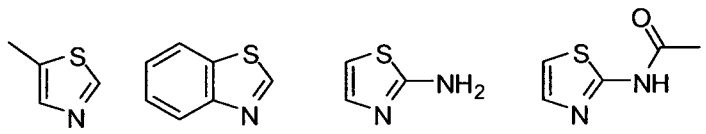


Figure 5-6: Thiazole derivatives that were unreactive towards the developed methodology

5.4.2 Arylation of Imidazole

Imidazole substrates are difficult to arylate. Indeed, they're known to bind to metal and the results are reflected in our experiments. Free N-H imidazoles resulted in no reaction with the optimized conditions (Figure 5-7). 1-Benzy-2-methyllimidazole, which has no free N-H, gave only trace conversion.

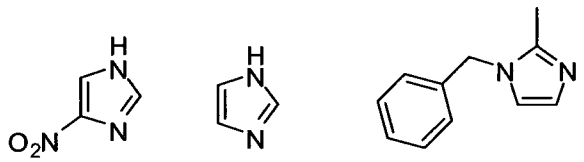
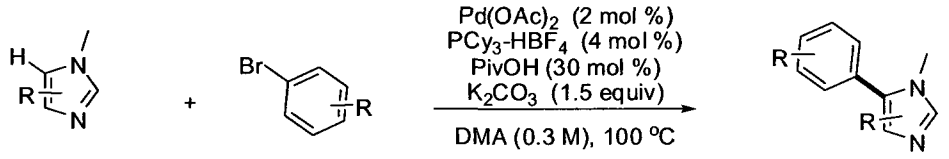


Figure 5-7 : Imidazoles that were not arylated under the standard conditions

N-Methylimidazoles were more reactive but gave arylated products in low yields over long reaction time (Table 5-3). 1-Methylimidazole and 1,2-dimethylimidazole are reactive under the optimized reaction conditions and couple with electron-rich aryl bromides.



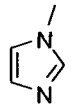
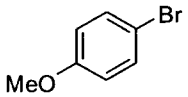
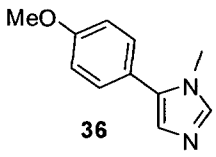
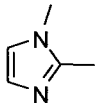
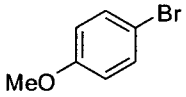
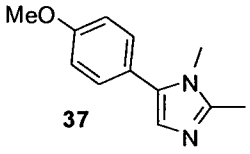
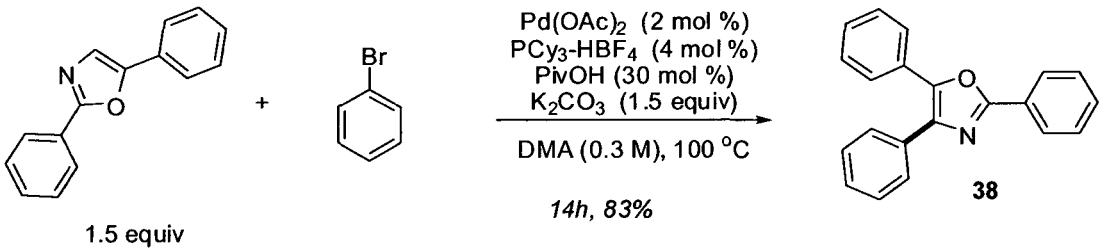
entry	thiazole	Ar-Br	product	reaction time	yield
1			 **36**	25h	34%
2			 **37**	23h	32%

Table 5-3: Scope of imidazole

5.4.3 Arylation of Oxazoles

2,5-Diphenyloxazole is arylated in excellent yield using the optimized conditions over a period of 14 hours (Equation 5-5). No other oxazoles were tried due to limitations in time and substrates. However, isoxazole was tried but no arylated product was recuperated.



Equation 5-5: Arylation of oxazole

5.5 Conclusion

A simple set of reaction conditions was used to arylate various azoles. The reaction time and the reactant ratio were the only variations of the method. The primordial use of PivOH as an additive for azoles is in accordance with the previously described CMD pathway. Imidazoles are difficult to arylate and more work is necessary to develop a high yielding methodology for this class of substrates.

Chapter 6: Supporting Information for Palladium-Catalyzed Direct Arylation of Nitro-Substituted Aromatics with Aryl Halides

6.1 General Methods

All experiments were carried out under an atmosphere of argon. ^{1}H and ^{13}C NMR spectra were recorded in acetone-d_6 solutions using a Bruker AVANCE 400 spectrometer. High-resolution mass spectra were obtained on a Kratos Concept IIH. Infra-Red analysis was performed with a Bruker EQUINOX 55. 98% purity mesitylene was employed and was degassed with argon before every use. ACS grade nitrobenzene was degassed with argon before every use. Phosphonium salts were purchased from Strem, stored in a dessicator and used without further purification. Palladium sources were purchased from Pressure Chemicals and stored in a dessicator. Phosphonium salts and palladium sources were weighed out to air. All other reagents and solvents were used without further purification from commercial sources.

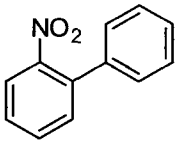
6.2 General Procedure

$(CH_3)_3CCO_2H$ (0.3 equiv), K_2CO_3 (1.3 equiv), di-t-butylmethylphosphonium tetrafluoroborate (0.15 equiv) and $Pd(OAc)_2$ (0.05 equiv) were weighed to air and placed in a test tube (10 mL), equipped with a magnetic stir bar and capped with a rubber septum and sealed with electrical tape. The reaction vessel was evacuated and

backfilled with argon (x3). The aryl bromide (1.0 equiv) is added via a gastight syringe. Nitrobenzene (10 equiv) and mesitylene (1.3 M) were then added via syringe and the reaction was heated to 125°C for 16 hours. Upon completion, the reaction is cooled to room temperature and diluted in ethyl acetate. Water is added to the solution and the two phases are separated. The aqueous phase was extracted (x3) with ethyl acetate and the organic phases were combined, washed with brine and dried using anhydrous Na_2SO_4 or $MgSO_4$. The resulting solution was filtered and evaporated. The crude mixture was purified by loading onto a silica gel packed flash chromatography column typically using petroleum ether\ethyl acetate mixtures or petroleum ether\toluene mixtures as the eluent (see below for exact eluent compositions).

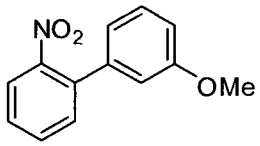
6.3 Characterization of Nitro-Substituted Biaryls

2-Nitrobiphenyl (1)



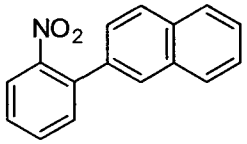
The compound was prepared according to the general procedure in 62% yield. This product is commercially available from Aldrich (CAS [86-00-0]). R_f = 0.2 (SiO_2, toluene: petroleum ether 30:70). IR (ν_{max}/cm^{-1}): 2922, 2861, 1527, 1350. ^{1}H NMR (400 MHz, Acetone-d_6, 293K): 7.93 (dd, J = 8.0, 1.1 Hz, 1H), 7.75 (ddd, J = 7.6, 7.6, 1.3 Hz, 1H), 7.62 (ddd, J = 8.0, 7.6, 1.4 Hz, 1 H), 7.55 (dd, J = 7.7, 1.3 Hz, 1H), 7.42-7.48 (m, 3H), 7.35-7.37 (m, 2H). ^{13}C NMR (100 MHz, Acetone-d_6, 293K): 151.4, 139.4, 137.6, 134.3, 133.7, 129.7, 130.5, 130.5, 130.0, 125.8. HRMS calcd for $C_{12}H_9NO_2$ (M+) 199.0633; found: 199.0636.

3'-methoxy-2-nitrobiphenyl (2)



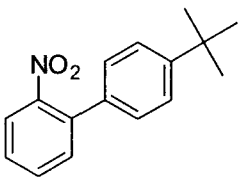
The compound was prepared according to to the general procedure in 77% yield. mp 58-60 °C. R_f = 0.2 (SiO_2, ethyl acetate: petroleum ether 5:95). IR (ν_{max}/cm^{-1}): 3070, 2943, 2842, 1601, 1525, 1357. ^{1}H NMR (400 MHz, Acetone-d_6, 293K): 7.91 (dd, J = 8.0, 1.0 Hz, 1H), 7.74 (ddd, J = 7.6, 7.6, 1.3 Hz, 1H), 7.62 (ddd, J = 7.8, 7.6, 1.4 Hz, 1H), 7.56 (dd, J = 7.7, 1.2 Hz, 1H), 7.36 (dd, J = 7.9, 7.9 Hz, 1H), 6.99 (ddd, J = 0.8, 2.5, 8.3 Hz, 1 H), 6.94-6.90 (m, 2H), 3.83 (s, 3H). ^{13}C NMR (100 MHz, Acetone-d_6, 293K): 161.8, 151.5, 140.6, 137.4, 134.2, 133.6, 131.6, 130.5, 125.6, 121.9, 115.4, 115.4, 56.6. HRMS calcd for $C_{13}H_{11}NO_3$ (M+) 229.0739; found: 229.0761.

2-(2-nitrophenyl)naphthalene (3)



The compound was prepared according to the general procedure in 60% yield. mp 70-73°C. R_f = 0.2 (SiO_2, toluene: petroleum ether 30:70). IR (ν_{max}/cm^{-1}): 3066, 2922, 2850, 1525, 1347. ^{1}H NMR (400 MHz, Acetone-d_6, 293K): 8.14 (dd, J = 8.1, 1.1 Hz, 1H), 8.00-7.97 (m, 2H), 7.86 (ddd, J= 7.5, 7.5, 1.3 Hz, 1H), 7.76 (ddd, J = 8.1, 7.5, 1.5 Hz, 1H), 7.59-7.51 (m, 3H), 7.46-7.44 (m, 2H), 7.40 (dd, J = 7.0, 1.2 Hz, 1H). ^{13}C NMR (100 MHz, Acetone-d_6, 293K): 151.9, 137.5, 136.5, 135.5, 134.9, 134.7, 133.4, 131.0, 130.3, 128.4, 128.0, 127.9, 127.2, 126.6; 126.0. HRMS calcd for $C_{16}H_{11}NO_2$ (M+) 249.0790; found: 249.0769.

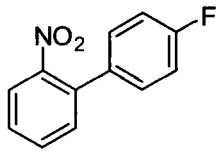
4'-tert-butyl-2-nitrobiphenyl (4)



The compound was prepared according to the general procedure in 54% yield. R_f = 0.4 (SiO_2, ethyl acetate: petroleum ether 5:95). IR (ν_{max}/cm^{-1}): 3066, 2964, 2868, 1528,

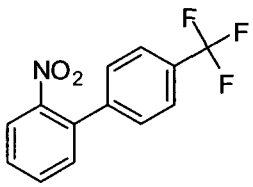
1360. ^{1}H NMR (400 MHz, Acetone-d_6, 293K): 7.90 (dd, J = 8.0, 1.1 Hz, 1H), 7.76 (ddd, J = 7.6, 7.6, 1.3 Hz, 1H), 7.64 (ddd, J = 8.0, 7.6, 1.4 Hz, 1 H), 7.55 (dd, J = 7.7, 1.2 Hz, 1H), 7.51 (br d, J = 8.6 Hz, 2H), 7.30 (br d, J= 8.6 Hz, 2H), 1.34 (s, 9H). ^{13}C NMR (100 MHz, Acetone-d_6, 293K): 152.9, 151.6, 137.3, 136.3, 134.2, 133.7, 130.2, 129.4, 127.5, 125.7, 36.1, 32.5. HRMS calcd for $C_{16}H_{17}NO_2$ (M+) 255.1259; found: 255.1251.

4'-fluoro-2-nitrobiphenyl (5)



The compound was prepared according to the general procedure in 68% yield. R_f = 0.3 (SiO_2, ethyl acetate: petroleum ether 4:96). IR (ν_{max}/cm^{-1}): 3071, 1526, 1355, 1226. ^{1}H NMR (400 MHz, Acetone-d_6, 293K): 7.95 (dd, J = 8.1, 1.1 Hz, 1H), 7.74 (ddd, J = 7.6, 7.6, 1.3 Hz, 1H), 7.61 (ddd, J = 9.0, 5.8, 1.4 Hz, 1 H), 7.55 (dd, J = 7.7, 1.2 Hz, 1H), 7.43-7.38 (m, 2H), 7.26-7.20 (m, 2H). ^{13}C NMR (100 MHz, Acetone-d_6, 293K): 164.6 (d, J_F = 245.8 Hz), 151.4, 136.6, 135.7 (d, J_F = 3.4 Hz), 134.5, 133.8, 131.9 (d, J_F = 8.4 Hz), 130.7, 125.9, 117.4 (d, J_F = 22.0 Hz). HRMS calcd for $C_{12}H_8FNO_2$ (M+) 217.0539; found: 217.0539.

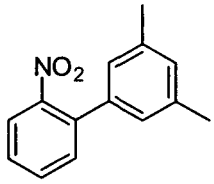
2-nitro-4'-(trifluoromethyl)biphenyl (6)



The compound was prepared according to the general procedure in 60% yield. R_f = 0.3 (SiO_2, ethyl acetate: petroleum ether 10:90). IR (ν_{max}/cm^{-1}): 2927, 1529, 1326. ^{1}H NMR (400 MHz, Acetone-d_6, 293K): 8.05 (dd, J = 8.1, 1.2 Hz, 1H), 7.85-7.81 (m, 3H), 7.72 (ddd, J = 8.1, 7.6, 1.5 Hz, 1H), 7.62-7.60 (m, 3H). ^{13}C NMR (100 MHz, Acetone-d_6, 293K): 151.0, 143.9, 136.5, 134.9, 133.9, 131.5 (q, J_F = 32 Hz), 131.3, 130.7, 127.4 (q,

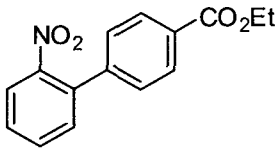
J_F = 3.8 Hz), 126.3 (q, J_F = 271.3 Hz), 126.2. HRMS calcd for $C_{13}H_8F_3NO_2$ (M+) 267.0507; found: 267.0506.

3',5'-dimethyl-2-nitrobiphenyl (7)



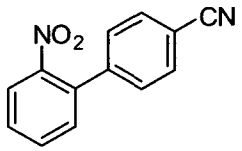
The compound was prepared according to the general procedure in 76% yield. R_f = 0.4 (SiO_2, ethyl acetate: petroleum ether 5:95). IR (ν_{max}/cm^{-1}): 3036, 2919, 2863, 1602, 1527, 1358. ^{1}H NMR (400 MHz, Acetone-d_6, 293K): 7.89 (dd, J = 8.0, 1.0 Hz, 1H), 7.72 (ddd, J = 7.6, 7.6, 1.3 Hz, 1H), 7.60 (ddd, J = 8.0, 7.5, 1.5 Hz, 1H), 7.50 (dd, J = 7.7, 1.1 Hz, 1H), 7.06-7.05 (m, 1H), 6.96-6.96 (m, 2H), 2.32 (s, 3H), 2.32 (s, 3H). ^{13}C NMR (100 MHz, Acetone-d_6, 293K): 151.5, 140.0, 139.3, 137.7, 134.1, 133.7, 131.5, 130.2, 127.4, 125.6, 22.2. HRMS calcd for $C_{14}H_{13}NO_2$ (M+) 227.0946; found: 227.0924

Ethyl 2'-nitrobiphenyl-4-carboxylate (8)



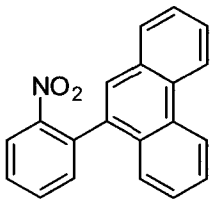
The compound was prepared according to the general procedure in 73% yield. mp 63-65°C. R_f = 0.2 (SiO_2, ethyl acetate: petroleum ether 10:90). IR (ν_{max}/cm^{-1}): 2980, 1714, 1527, 1277. ^{1}H NMR (400 MHz, Acetone-d_6, 293K): 8.09 (br d, J = 8.8 Hz, 2H), 8.01 (dd, J = 8.1, 1.2 Hz, 1H), 7.80 (ddd, J = 7.6, 7.6, 1.3 Hz, 1 H), 7.68 (ddd, J = 7.6, 7.6, 1.3 Hz, 1H), 7.58 (dd, J = 7.6, 1.4 Hz, 1H), 7.50 (br d, J = 8.8 Hz, 2H), 4.38 (q, J = 7.1 Hz, 2H), 1.38 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, Acetone-d_6, 293K): 167.3, 151.0, 144.2, 136.9, 134.7, 133.7, 132.1, 131.4, 131.1, 130.0, 126.1, 62.6, 15.6. HRMS calcd for $C_{15}H_{13}NO_4$ (M+) 271.0845; found: 271.0867.

2'-nitrobiphenyl-4-nitrile (9)



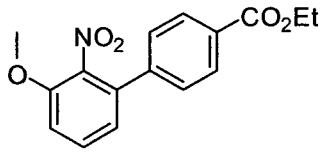
The compound was prepared according to the general procedure in 54% yield. mp 140-142°C. R_f = 0.3 (SiO_2, ethyl acetate: petroleum ether 20:80). IR (ν_{max}/cm^{-1}): 2927, 2853, 2233, 1531, 1348. ^{1}H NMR (400 MHz, Acetone-d_6, 293K): 8.06 (dd, J = 8.1, 1.2 Hz, 1H), 7.89 (br d, J = 8.5 Hz, 2H), 7.84 (ddd, J = 7.6, 7.6, 1.3 Hz, 1 H), 7.73 (ddd, J = 8.0, 7.6, 1.4 Hz, 1H), 7.61-7.59 (m, 3H). ^{13}C NMR (100 MHz, Acetone-d_6, 293K): 150.7, 144.5, 136.4, 135.0, 134.3, 133.7, 131.5, 130.9, 126.4, 120.0, 113.8. HRMS calcd for $C_{13}H_8N_2O_2$ (M+) 224.0586; found: 224.0574.

9-(2-nitrophenyl)phenanthrene (10)



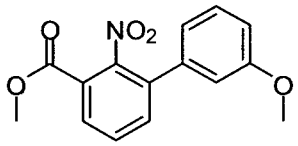
The compound was prepared according to the general procedure in 56% yield. mp 126-128°C. R_f = 0.3 (SiO_2, ethyl acetate: petroleum ether 10:90). IR (ν_{max}/cm^{-1}): 3070, 1529, 1346. ^{1}H NMR (400 MHz, Acetone-d_6, 293K): 8.90 (br d, J = 8.4 Hz, 1H), 8.85 (br d, J = 8.3 Hz, 1H), 8.20 (dd, J = 8.1, 1.3 Hz, 1H), 7.98 (dd, J = 7.8, 1.4 Hz, 1 H), 7.87 (ddd. J = 7.5, 7.5, 1.1 Hz, 1H), 7.79 (dd, J = 7.9, 7.5, 1.5 Hz, 1H), 7.76-7.63 (m, 5H), 7.55 (ddd, J = 8.2, 6.8, 1.2 Hz, 1H), 7.49 (dd, J = 8.2, 1.0 Hz, 1H). ^{13}C NMR (100 MHz, Acetone-d_6, 293K): 151.8, 136.7, 136.6, 135.0, 134.9, 133.2, 132.6, 132.2, 132.1, 131.2, 130.6, 129.1, 129.0, 128.9, 128.8, 128.6, 127.6, 126.1, 125.1, 124.6. HRMS calcd for $C_{20}H_{13}NO_2$ (M+) 299.0946; found: 299.0937.

Ethyl 3'-methoxy-2'-nitrobiphenyl-4-carboxylate (13)



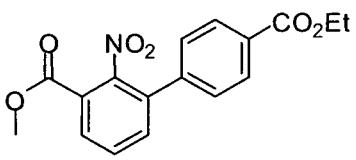
The compound was prepared according to the general procedure in 61% yield. mp 105-107°C. R_f = 0.1 (SiO_2, ethyl acetate: petroleum ether 10:90). IR (ν_{max}/cm^{-1}): 2982, 2942, 2847, 1717, 1533, 1277. ^{1}H NMR (400 MHz, Acetone-d_6, 293K): 8.08 (br d, J = 8.6 Hz, 2H), 7.64 (dd, J = 8.5, 7.8 Hz, 1H), 7.52 (br d, J = 8.6 Hz, 2 H), 7.38 (dd, J = 8.5, 0.9 Hz, 1H), 7.12 (dd, J = 7.8, 1.0 Hz, 1H), 4.37 (q, J = 7.1 Hz, 2H), 3.99 (s, 3H), 1.38 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, Acetone-d_6, 293K): 167.2, 152.7, 142.5, 135.8, 133.3, 132.6, 131.5, 130.1, 123.8, 114.7, 62.7, 58.2, 15.5. HRMS calcd for $C_{16}H_{15}NO_5$ (M+) 301.0950; found: 301.0945.

Methyl 3'-methoxy-2-nitrobiphenyl-3-carboxylate (19)



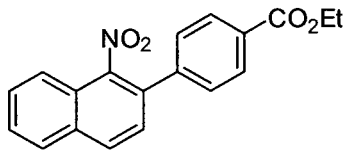
The compound was prepared according to the general procedure in 40% yield. mp 84-86 °C. R_f = 0.2 (SiO_2, ethyl acetate: petroleum ether 10:90). IR (ν_{max}/cm^{-1}): 3015, 2956, 2845, 1733, 1544, 1286. ^{1}H NMR (400 MHz, Acetone-d_6, 293K): 8.07 (dd, J = 6.0, 3.2 Hz, 1H), 7.82-7.78 (m, 2H), 7.38 (dd, J = 8.3, 8.1 Hz, 1H), 7.03 (ddd, J = 8.4, 2.4, 1.0 Hz, 1H), 6.93-6.91 (m, 2H), 3.90 (s, 3H), 3.83 (s, 3H). ^{13}C NMR (100 MHz, Acetone-d_6, 293K): 163.6, 159.9, 149.3, 137.0, 135.6, 134.8, 130.6, 130.1, 129.9, 123.4, 120.3, 114.3, 113.9, 54.8, 52.5. HRMS calcd for $C_{15}H_{13}NO_5$ (M+) 287.0794; found: 287.0776.

4'-ethyl 3-methyl 2-nitrobiphenyl-3,4'-dicarboxylate (14)



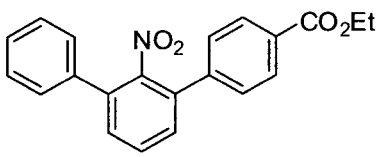
The compound was prepared according to recrystallization in ethyl acetate and petroleum ether in 45% yield. mp 98-100 °C. R_f = 0.1 (SiO_2, ethyl acetate: petroleum ether 10:90). IR (ν_{max}/cm^{-1}): 2983, 2957, 1733, 1714, 1544, 1279. ^{1}H NMR (400 MHz, Acetone-d_6, 293K): 8.13-8.09 (m, 3H), 7.88-7.81 (m, 2H), 7.53 (br d, J = 8.5 Hz, 2 H), 4.38 (q, J= 7.12 Hz, 2H), 3.91 (s, 3H), 1.38 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, Acetone-d_6, 293K): 167.2, 165.4, 151.0, 142.0, 137.2, 135.9, 132.9, 132.8, 132.5, 131.5, 130.4, 125.5, 62.7, 54.5, 15.5. HRMS calcd for $C_{17}H_{15}NO_6$ (M+) 329.0899; found: 329.0897.

Ethyl 4-(1-nitronaphthalen-2-yl)benzoate (15)



The compound was prepared by recrystallization in ethyl acetate and petroleum ether in 60% yield. Decomposition at 132 °C. R_f = 0.1 (SiO_2, ethyl acetate: petroleum ether 10:90). IR (ν_{max}/cm^{-1}): 3070, 2985, 2906, 1716, 1528, 1281. ^{1}H NMR (400 MHz, Acetone-d_6, 293K): 8.30 (br d, J = 8.5 Hz, 1H), 8.19-8.14 (m, 3H), 7.82-7.75 (m, 3H), 7.70 (br d, J = 8.5 Hz, 1H), 7.65 (br d, J = 8.6 Hz, 2H), 4.40 (q, J = 7.1, 2H), 1.40 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, Acetone-d_6, 293K): 167.2, 143.0, 135.6, 133.2, 132.8, 132.2, 131.7, 131.3, 130.4, 130.3, 129.9, 129.0, 126.0, 123.2, 62.7, 15.6. HRMS calcd for $C_{19}H_{15}NO_4$ (M+) 321.1001; found: 321.1006.

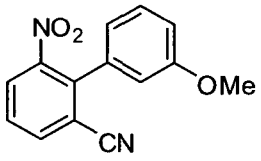
2-Nitrobiphenyl-3-benzoate (17)



The compound was prepared according to recrystallization in ethyl acetate and petroleum ether in 45% yield. mp 121-123 °C. R_f = 0.3 (SiO_2, ethyl acetate: petroleum

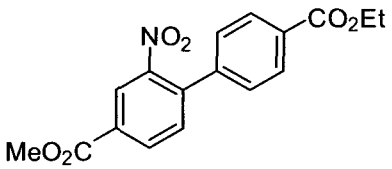
ether 10:90). IR (ν_{max}/cm^{-1}): 2996, 2932, 1717, 1533, 1275. ^{1}H NMR (400 MHz, Acetone-d_6, 293K): 8.10 (br d, J = 8.4 Hz, 2H), 7.79 (dd, J = 7.7, 7.7 Hz, 1H), 7.62-7.60 (m, 2H), 7.56 (br d, J = 8.4 Hz, 2H), 7.49-7.41 (m, 5H), 4.38 (q. J = 7.1 Hz. 2H), 1.38 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, Acetone-d_6, 293K): 167.2, 151.3, 142.9, 138.3, 136.3, 135.2, 132.9, 132.6, 132.6, 132.1, 131.5, 130.7, 130.5, 130.3, 129.9, 62.7, 15.5. HRMS calcd for $C_{21}H_{17}NO_4$ (M+) 347.1159; found: 347.1158.

3'-methoxy-6-nitrobiphenyl-2-carbonitrile (20)



The compound was prepared according to the general procedure in 49% yield. mp 124-127 °C. R_f = 0.2 (SiO_2, ethyl acetate: petroleum ether 15:85). IR (ν_{max}/cm^{-1}): 3087, 2941, 2842, 2232, 1533, 1362. ^{1}H NMR (400 MHz, Acetone-d_6, 293K): 8.27 (dd, J = 8.2, 1.2 Hz, 1H), 8.21 (dd, J = 7.8, 1.2 Hz, 1H), 7.88 (dd, J = 8.0, 8.0 Hz, 1H), 7.45 (dd, J = 8.0, 8.0 Hz, 1H), 7.09 (ddd, J = 8.4, 5.6, 0.9 Hz, 1H), 7.05-7.04 (m, 1H), 6.99 (ddd, J = 7.6, 1.6, 0.9 Hz, 1H), 3.84 (s, 3H). ^{13}C NMR (100 MHz, Acetone-d_6, 293K): 161.7, 152.1, 140.5, 138.7, 136.8, 131.8, 131.8, 129.7, 122.5, 118.0, 117.4, 116.7, 116.1, 56.7. HRMS calcd for $C_{14}H_{10}N_2O_3$ (M+) 254.0691; found: 254.0692.

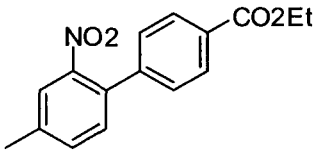
4'-ethyl 4-methyl 2-nitrobiphenyl-4,4'-dicarboxylate (16)



The compound was prepared according to the general procedure in 65% yield. mp 80-83 °C. R_f = 0.2 (SiO_2, ethyl acetate: petroleum ether 10:90). IR (ν_{max}/cm^{-1}): 3088, 2987, 2960, 2850, 1717, 1535, 1278. ^{1}H NMR (400 MHz, Acetone-d_6, 293K): 8.53 (br d, J = 1.4 Hz, 1H), 8.36 (dd, J = 7.1, 1.4 Hz, 1H), 8.12 (br d, J = 7.1 Hz, 2H), 7.77 (dd, J = 8.2, 4.0 Hz, 1H), 7.56 (br d, J = 8.6 Hz, 2H), 4.39 (q, J = 7.1 Hz, 2 H), 3.99 (s, 3H), 1.40 (t, J

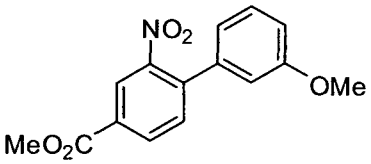
= 7.1 Hz, 3H). ^{13}C NMR (100 MHz, Acetone-d_6, 293K): 167.2, 166.3, 151.0, 143.2, 141.0, 134.9, 134.4, 133.1, 132.7, 131.5, 130.0, 126.9, 62.7, 54.1, 15.6. HRMS calcd for $C_{17}H_{15}NO_6$ (M+) 329.0899; found: 329.0907.

Ethyl 4'-methyl-2'-nitrobiphenyl-4-carboxylate (18)



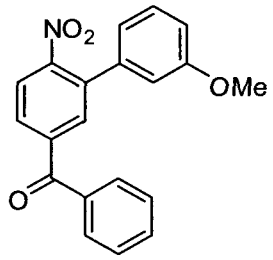
The compound was prepared according to the general procedure in 59% yield. R_f = 0.5 (SiO_2, ethyl acetate: petroleum ether 15:85). IR (ν_{max}/cm^{-1}): 2986, 2929, 2850, 1716, 1531, 1275. ^1H NMR (400 MHz, Acetone-d_6, 293K): 8.08 (br d, J = 8.2 Hz, 2H), 7.82 (br s, 1H), 7.61 (br d, J = 7.8 Hz, 1H), 7.48-7.45 (m, 3H), 4.38 (q, J = 7.1 Hz, 2H), 2.51 (s, 3H), 1.38 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, Acetone-d_6, 293K): 167.3, 150.9, 144.2, 141.8, 135.3, 134.0, 133.4, 132.0, 131.4, 130.0, 126.3, 62.6, 21.8, 15.6. HRMS calcd for $C_{16}H_{15}NO_4$ (M+) 285.1001; found: 285.1005.

Methyl 3'-methoxy-2-nitrobiphenyl-4-carboxylate (21)



The compound was prepared according to the general procedure in 72% yield. mp 65-67°C. R_f = 0.3 (SiO_2, ethyl acetate: petroleum ether 15:85). IR (ν_{max}/cm^{-1}): 3002, 2957, 2919, 2837, 1728, 1534, 1289. ^1H NMR (400 MHz, Acetone-d_6, 293K): 8.43 (d, J = 1.5 Hz, 1H), 8.29 (dd, J = 8.0, 1.7 Hz, 1H), 7.72 (d, J = 8.2 Hz, 1H), 7.39 (dd, J = 8.0, 8.0 Hz, 1H), 7.03 (ddd, J = 8.4, 5.6, 0.9 Hz, 1H), 6.97-6.93 (m, 2H), 3.97 (s, 3H), 3.84 (s, 3H). ^{13}C NMR (100 MHz, Acetone-d_6, 293K): 166.3, 161.9, 151.4, 141.5, 139.7, 134.5, 134.3, 132.5, 131.8, 126.5, 121.8, 116.1, 115.3, 56.7, 54.1. HRMS calcd for $C_{15}H_{13}NO_5$ (M+) 287.0794; found: 287.0789.

(3'-methoxy-6-nitrobiphenyl-3-yl)benzophenone (22)



The compound was prepared according to the general procedure in 50% yield. R_f = 0.4 (SiO_2, ethyl acetate: petroleum ether 15:85). IR (ν_{max}/cm^{-1}): 3069, 2939, 2836, 1665, 1529, 1290. ^{1}H NMR (400 MHz, Acetone-d_6, 293K): 8.07 (d, J = 8.3 Hz, 1H), 7.96 (dd, J = 8.3, 1.8 Hz, 1H), 7.90-7.88 (m, 3 H), 7.72-7.68 (m, 1H), 7.61-7.56 (m, 2H), 7.40-7.36 (m, 1H), 7.03-6.96 (m, 3H), 3.82 (s, 3H). ^{13}C NMR (100 MHz, Acetone-d_6, 293K): 195.9, 161.9, 153.2, 142.7, 139.7, 138.4, 137.3, 135.1, 134.6, 131.8, 131.5, 130.5, 125.9, 121.9, 115.9, 115.5, 56.6. HRMS calcd for $C_{20}H_{15}NO_4$ (M+) 333.1001; found: 333.1001.

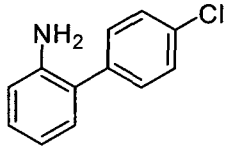
6.4 Synthesis of Boscalid® Intermediate

$(CH_3)_3CCO_2H$ (0.3 equiv), K_2CO_3 (1.3 equiv), di-t-butylmethylphosphonium tetrafluoroborate (0.15 equiv), $Pd(OAc)_2$ (0.05 equiv) and 4-bromochlorobenzene (1.0 equiv) were weighed to air and placed in a test tube (10 mL), equipped with a magnetic stir bar and capped with a rubber septum and sealed with electrical tape. The reaction vessel was evacuated and backfilled with argon (x3). Nitrobenzene (10 equiv) and mesitylene (1.3 M) were then added via syringe and the reaction was heated to 125 °C for 5 hours. Upon completion, the reaction was cooled to room temperature and diluted in ethyl acetate. Water was added to the solution and the two phases are separated. The aqueous phase was extracted (x2) with ethyl acetate and the organic phases were combined, washed with brine, dried over anhydrous Na_2SO_4 or $MgSO_4$ and concentrated. Excess nitrobenzene was removed from the crude reaction mixture by distillation using the Kugelrhor apparatus. The crude mixture was diluted in a 130 mL of a 1:1 mixture of THF and ethanol. $SnCl_2$ (12 equiv) and 13 mL of conc. HCL were added to the solution. The mixture was stirred for 14 hours at room temperature. A saturated solution of K_2CO_3 was added and the reaction mixture was partitioned between Et_2O and

water. The phases were separated; the aqueous phase was extracted with CH_2Cl_2 (x2) and the combined organic extracts were dried over anhydrous $MgSO_4$. The crude mixture was purified by loading onto a silica gel packed flash chromatography column using petroleum ether\toluene mixtures (30\70).

6.5 Characterization of Boscalid® Intermediate

4'-Chloro-2-aminobiphenyl (23)



The compound was obtained in 60% yield. The ^{1}H and ^{13}C spectra of this compound were consistent with those reported (Spivey, A. C.; Tseng, C.-C.; Hannah, J. P.; Gripton, C. J. G.; de Fraine, P.; Parr, N. J., Scicinski, J. J. *Chem. Commun.* **2007**, 2926).

Chapter 7: Supporting Information for Direct Arylation of Azoles

7.1 General Methods:

All experiments were carried out under an atmosphere of argon. ^{1}H and ^{13}C NMR spectra were recorded in acetone-d_6 and $CDCl_3$ solutions using a Bruker AVANCE 400 spectrometer. High-resolution mass spectra were obtained on a Kratos Concept IIH. Infra-Red analysis was performed with a Bruker EQUINOX 55. 98% purity mesitylene was employed and was degassed with argon before every use. Phosphonium salts were purchased from Strem, stored in a dessicator and used without further purification. Palladium sources were purchased from Pressure Chemicals and stored in a dessicator. Phosphonium salts and palladium sources were weighed out to air. All other reagents and solvents were used without further purification from commercial sources.

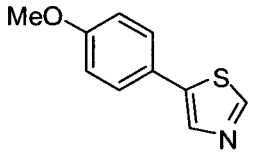
7.2 General procedure

$(CH_3)_3CCO_2H$ (0.3 equiv), K_2CO_3 (1.5 equiv), $Pd(OAc)_2$ (0.02 equiv), tricyclohexylphosphonium tetrafluoroborate (0.04 equiv) and any solid aryl halide (1.0 equiv) are weighed to air and placed in a 4 mL screw cap vial equipped with a Teflon septum. A balloon filled with argon, equipped with a needle, is added to the septum and an out needle is added. The system is purged for around 10 minutes. The out needle is removed and the aryl bromide (if liquid) is added via syringe. The heterocyclic compound (1.0 equiv) is added via syringe and DMA (0.3 M) is added via syringe. The argon filled balloon is removed and the vial is added to a metal stir plate block, preheated at 100 °C, and allowed to go to full completion. The advancement of the reaction is followed by GC-MS analysis. Upon completion, the reaction is cooled to

room temperature and diluted in ethyl acetate. Water is added to the solution and the two phases are separated. The aqueous phase is extracted (x2) with ethyl acetate and the organic phases are combined, washed with brine and dried using anhydrous Na_2SO_4 or $MgSO_4$. The resulting solution is filtered and evaporated. The crude mixture is purified by loading onto a silica gel packed flash chromatography column (see below for exact eluent compositions).

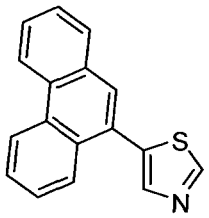
7.3 Characterization of Heterobiaryls

5-(4-methoxyphenyl)thiazole (24)



The compound was prepared using a 0.35 M of DMA and a yellow oil was obtained in 62% yield. R_f = 0.4 (SiO_2, ethyl acetate: toluene 4:96). The ^1H and ^{13}C spectra of this compound were consistent with those reported (Sheldrake, P. W.; Matteucci, M.; McDonald, E. *Synlett*, **2006**, *3*, 460).

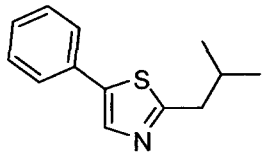
5-(phenanthren-9-yl)thiazole (25)



The compound was prepared according to the general procedure and was obtained in 80% yield. Yellow solid; mp 93-95 °C. R_f = 0.2 (SiO_2, ethyl acetate: petroleum ether 8:92). IR (ν_{max}/cm^{-1}): 3080, 3059, 3008, 1462, 1447. ^1H NMR (400 MHz, $CDCl_3$, 293K): 8.93 (s, 1H), 8.72 (d, J = 8.7 Hz, 1H), 8.66 (d, J = 8.2 Hz, 1H), 8.07-8.05 (m, 2H), 7.85 (d, J = 7.8 Hz, 1H), 7.80 (s, 1H), 7.69-7.64 (m, 2H), 7.61-7.56 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, 293K): 153.2, 142.7, 136.2, 130.9, 130.8, 130.5, 130.4, 130.0, 128.8,

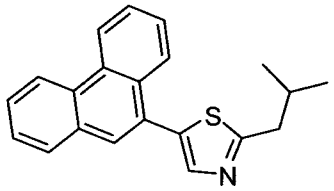
127.4, 127.1, 127.0, 126.9, 126.8, 126.0, 123.0, 122.5. HRMS calcd for $C_{17}H_{11}NS$ (M+) 261.0612; found: 261.0597.

2-isobutyl-5-phenylthiazole (26)



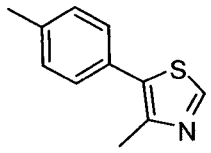
The compound was prepared according to the general procedure and yellow oil was obtained in 89% yield. R_f = 0.4 (SiO_2, ethyl acetate: petroleum ether 5:95). The ^1H and ^{13}C spectra of this compound were consistent with those reported (Yokooji, A.; Okazawa, T.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron*, **2003**, *59*, 5685).

2-isobutyl-5-(phenanthren-9-yl)thiazole (27)



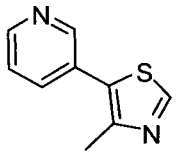
The compound was prepared according to the general procedure and a yellow oil was obtained in 88% yield. R_f = 0.3 (SiO_2, ethyl acetate: petroleum ether 5:95). IR (ν_{max}/cm^{-1}): 3054, 2957, 2866, 1152. ^1H NMR (400 MHz, $CDCl_3$, 293K): 8.73 (d, J = 8.2 Hz, 1H), 8.67 (d, J = 8.6 Hz, 1H), 8.15 (dd, J = 8.1, 1.0 Hz, 1H), 7.86 (dd, J = 7.8, 1.4 Hz, 1H), 7.81-7.80 (m, 2H), 7.70-7.64 (m, 2H), 7.62-7.58 (m, 2H), 2.97 (d, J = 7.2 Hz, 2H), 2.21 (m, 1H), 1.09 (d, J = 6.6 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, 293K): 170.7, 141.3, 135.3, 131.0, 130.9, 130.5, 130.3, 129.6, 128.7, 127.5, 127.2, 127.0, 126.9, 126.8, 126.1, 122.9, 122.5, 42.4, 29.8, 22.4. HRMS calcd for $C_{21}H_{19}NS$ (M+) 317.1232; found: 317.1247.

4-methyl-5-p-tolylthiazole (28)



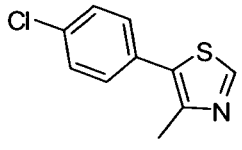
The compound was prepared according to the general procedure and a yellow oil was obtained in 78% yield. R_f = 0.3 (SiO_2, ethyl acetate: petroleum ether 8:92). IR (ν_{max}/cm^{-1}): 3024, 2923, 2852, 1414. ^{1}H NMR (400 MHz, Acetone-d_6, 293K): 8.82 (s, 1H), 7.38 (bd, J = 8.2 Hz, 2 H), 7.27 (bd, J = 8.2 Hz, 2H), 2.47 (s, 3H), 2.36 (s, 3H). ^{13}C NMR (100 MHz, Acetone-d_6, 293K): 152.0, 149.9, 139.6, 133.4, 131.3, 131.0, 130.8, 22.1, 17.3. HRMS calcd for $C_{11}H_{11}NS$ (M+) 189.0612; found: 189.0611.

4-methyl-5-(pyridin-3-yl)thiazole (29)



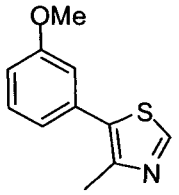
The compound was prepared according to the general procedure and a yellow oil was obtained in 56% yield. R_f = 0.2 (SiO_2, ethyl acetate: petroleum ether 45:55). IR (ν_{max}/cm^{-1}): 3412, 2922, 1528, 1417. ^{1}H NMR (300 MHz, $CDCl_3$, 293K): 8.77 (s, 1H), 8.73 (bs, 1H), 8.61 (bd, J = 3.9 Hz, 1H), 7.77 (ddd, J = 7.9, 2.3, 1.7 Hz, 1H), 7.38 (ddd, J = 7.9, 4.8, 0.7 Hz, 1H), 2.56 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, 293K): 151.2, 149.8, 149.8, 149.0, 136.4, 128.2, 128.1, 123.4, 16.0. HRMS calcd for $C_9H_8N_2S$ (M+) 176.0408; found: 176.0402.

5-(4-chlorophenyl)-4-methylthiazole (30)



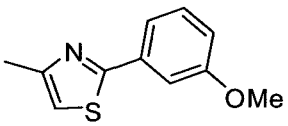
The compound was prepared according to the general procedure and a yellow oil was obtained in 66% yield. R_f = 0.2 (SiO_2, ethyl acetate: petroleum ether 7:93). IR (ν_{max}/cm^{-1}): 3071, 2953, 1474, 1394, 1084. ^{1}H NMR (400 MHz, $CDCl_3$, 293K): 8.69 (s, 1H), 7.40 (bd, J = 8.8 Hz, 2H), 7.36 (bd, J = 8.8 Hz, 2H), 2.52 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, 293K): 150.4, 148.8, 133.9, 130.6, 130.4, 130.4, 128.9, 16.0. HRMS calcd for $C_{10}H_8NSCl$ (M+) 209.0066; found: 209.0044

5-(3-methoxyphenyl)-4-methylthiazole (31)



The compound was prepared according to the general procedure and a yellow oil was obtained in 74% yield. R_f = 0.2 (SiO_2, ethyl acetate: petroleum ether 8:92). IR (ν_{max}/cm^{-1}): 3081, 3003, 2949, 2834, 1599, 1479, 1286, 1168, 1051. ^{1}H NMR (400 MHz, $CDCl_3$, 293K): 8.67 (s, 1H), 7.33 (dd, J = 8.0, 7.9 Hz, 1H), 7.04-7.01 (m, 1H), 6.98-6.97 (m, 1H), 6.91-6.88 (m, 1H), 3.83 (s, 3H), 2.55 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, 293K): 159.6, 150.2, 148.5, 133.1, 131.7, 129.6, 121.7, 115.0, 113.2, 55.2, 16.1. HRMS calcd for $C_{11}H_{11}NOS$ (M+) 205.0561; found: 205.0548.

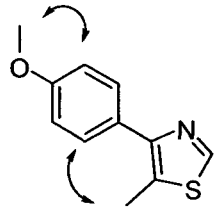
2-(3-methoxyphenyl)-4-methylthiazole (32)



The compound was prepared according to a literature procedure (Bellina, F.; Cauteruccio, S.; Rossi, R. *Eur. J. Org. Chem.* **2006**, 1379) and was obtained in 99% yield. R_f = 0.4 (SiO_2, ethyl acetate: petroleum ether 8:92). IR (ν_{max}/cm^{-1}): 3002, 2958, 2921, 1594, 1524, 1469, 1437, 1271. ^{1}H NMR (400 MHz, $CDCl_3$, 293K): 7.51-7.47 (m, 2H), 7.30 (dd, J = 8.1, 8.1 Hz, 1H), 6.93 (ddd, J = 8.3, 2.5, 1.0 Hz, 1H), 6.85-6.84 (m, 1H), 3.85 (s, 3H), 2.49 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, 293K): 167.3, 159.9, 153.6,

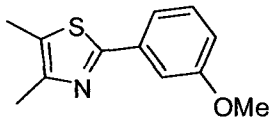
135.0, 129.8, 119.0, 115.9, 113.4, 111.1, 55.3, 17.2. HRMS calcd for $C_{11}H_{11}NOS$ (M+) 205.0561; found: 205.0542.

4-(4-methoxyphenyl)-5-methylthiazole (33)



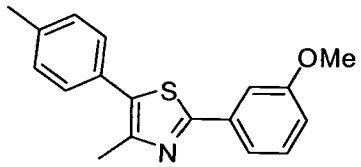
The compound was prepared according to the general procedure and a yellow oil was obtained in 65% yield. R_f = 0.3 (SiO_2, ethyl acetate: petroleum ether 8:92). IR (ν_{max}/cm^{-1}): 3077, 2961, 2840, 1606, 1506, 1287, 1259, 1178. ^{1}H NMR (400 MHz, $CDCl_3$, 293K): 8.64 (s, 1H), 7.36 (bd, J = 8.9 Hz, 2H), 6.95 (bd, J = 8.8 Hz, 2H), 3.84 (s, 3H), 2.51 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, 293K): 159.3, 149.6, 147.9, 131.7, 130.5, 124.1, 114.1, 55.3, 15.9. HRMS calcd for $C_{11}H_{11}NOS$ (M+) 205.0561; found: 205.0557.

2-(3-methoxyphenyl)-4,5-dimethylthiazole (34)



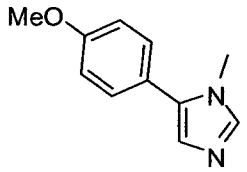
The compound was prepared according to the general procedure and a white solid was obtained in 42% yield. White solid; mp 55-56 °C. R_f = 0.3 (SiO_2, ethyl acetate: petroleum ether 5:95). IR (ν_{max}/cm^{-1}): 3004, 2948, 2921, 2834, 1598, 1548, 1469, 1271. ^{1}H NMR (400 MHz, $CDCl_3$, 293K): 7.44-7.40 (m, 2H), 7.30 (dd, J = 8.1, 7.4 Hz, 1H), 6.93-6.90 (m, 1H), 3.86 (s, 3H), 2.38 (bs, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, 293K): 163.1, 159.9, 149.2, 135.2, 129.8, 126.6, 118.7, 115.6, 110.7, 55.4, 14.8, 11.4. HRMS calcd for $C_{12}H_{13}NOS$ (M+) 219.0718; found: 219.0711.

2-(3-methoxyphenyl)-4-methyl-5-p-tolylthiazole (35)



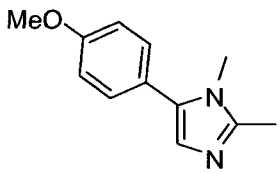
The compound was prepared according to the general procedure and was obtained in 54% yield. R_f = 0.2 (SiO_2, ethyl acetate: petroleum ether 5:95). IR (ν_{max}/cm^{-1}): 3024, 2964, 2925, 2832, 1601, 1492, 1438, 1267. ^{1}H NMR (400 MHz, $CDCl_3$, 293K): 7.51-7.47 (m, 2H), 7.38-7.29 (m, 3H), 7.24-7.22 (m, 2H), 6.97-6.93 (m, 1H), 3.88 (s, 3H), 2.55 (s, 3H), 2.40 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, 293K): 164.5, 159.9, 148.4, 137.7, 135.0, 132.4, 129.9, 129.4, 129.2, 129.0, 118.9, 116.0, 110.8, 55.4, 21.2, 16.3. HRMS calcd for $C_{18}H_{17}NOS$ (M+) 295.1031; found: 295.1043.

1-Methyl-5-(4-methoxyphenyl)-1*H*-imidazole (36)



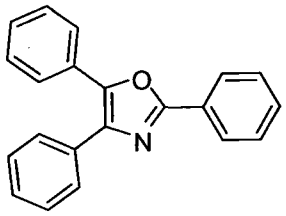
The compound was prepared according to the general procedure and was obtained in 34% yield. White solid; mp 123-125 °C. R_f = 0.1 (SiO_2, ethyl acetate: MeOH 97:3). IR (ν_{max}/cm^{-1}): 3089, 2948, 2933, 2838, 1549, 1251. ^{1}H NMR (400 MHz, $CDCl_3$, 293K): 7.49 (s, 1H), 7.31 (bd, J = 8.8 Hz, 2H), 7.03 (s, 1H), 6.97 (bd, J = 8.8 Hz, 2H), 3.85 (s, 3H), 3.63 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, 293K): 159.4, 138.6, 133.2, 129.9, 127.6, 122.2, 114.1, 55.3, 32.3. HRMS calcd for $C_{11}H_{12}N_2O$ (M+) 188.0950; found: 188.0927.

5-(4-methoxyphenyl)-1,2-dimethyl-1*H*-imidazole (37)



The compound was prepared according to the general procedure and was obtained in 32% yield. R_f = 0.3 (SiO_2, ethyl acetate: MeOH 95:5). The ^1H spectrum of this compound is consistent with those reported (Pivsa-Art, S.; Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 467). ^{13}C NMR (100 MHz, $CDCl_3$, 293K): 159.2, 145.4, 133.2, 130.0, 125.3, 123.0, 114.0, 55.3, 31.1, 13.7. HRMS calcd for $C_{12}H_{14}N_2O$ (M+) 202.1106; found: 202.1104.

2,4,5- Triphenyloxazole (38)



The compound was prepared according to the general procedure, 1.5 equivalents of heterocycle and was obtained in 83% yield. R_f = 0.5 (SiO_2, ethyl acetate: petroleum ether 3:97). The ^1H and ^{13}C spectra of this compound are consistent with those reported (Prager, R. H.; Smith, J. A.; Weber, B.; Williams, C. M. *J. Chem. Soc., Perkin Trans.* **1997**, *1*, 2665).

Claims to Original Research

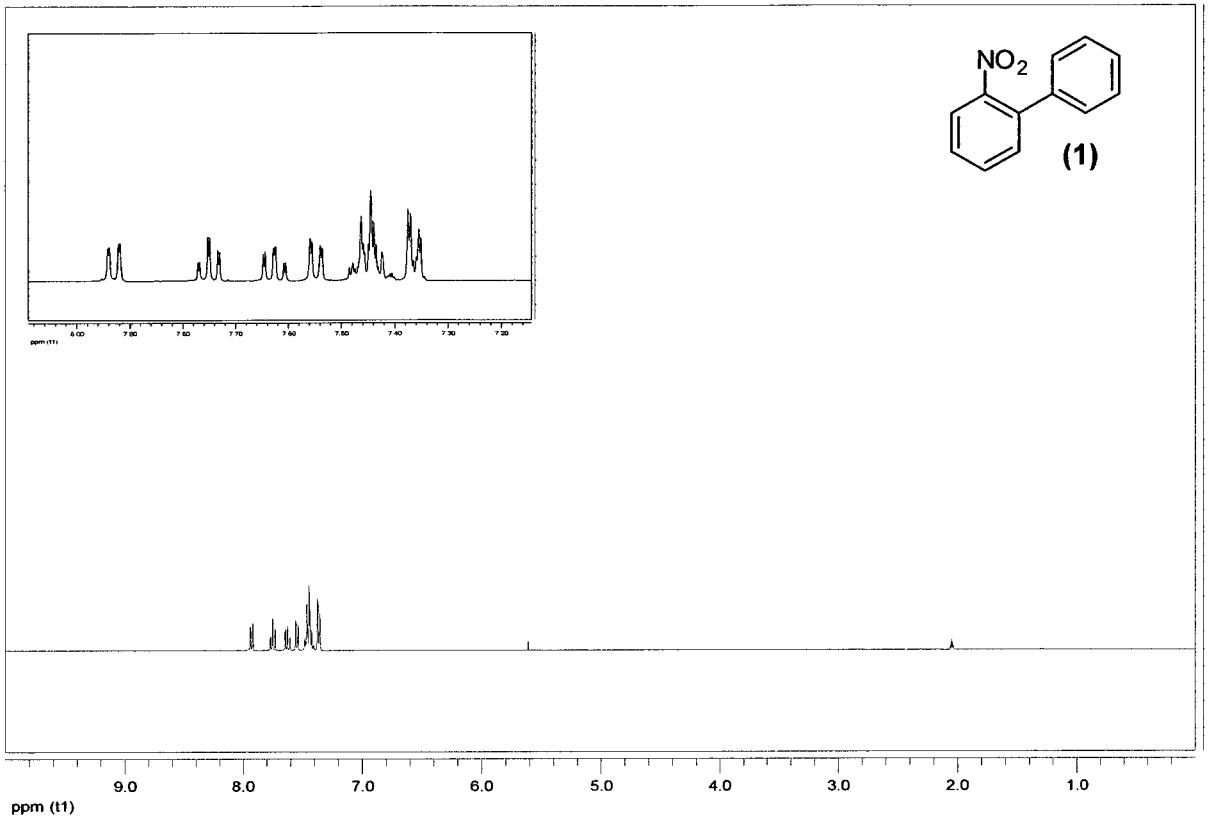
1. Developed new conditions for the intermolecular direct arylation of aryl bromides with nitrobenzene to form biaryl compounds. This methodology was also applied to the synthesis of an agrochemical: Boscalid.

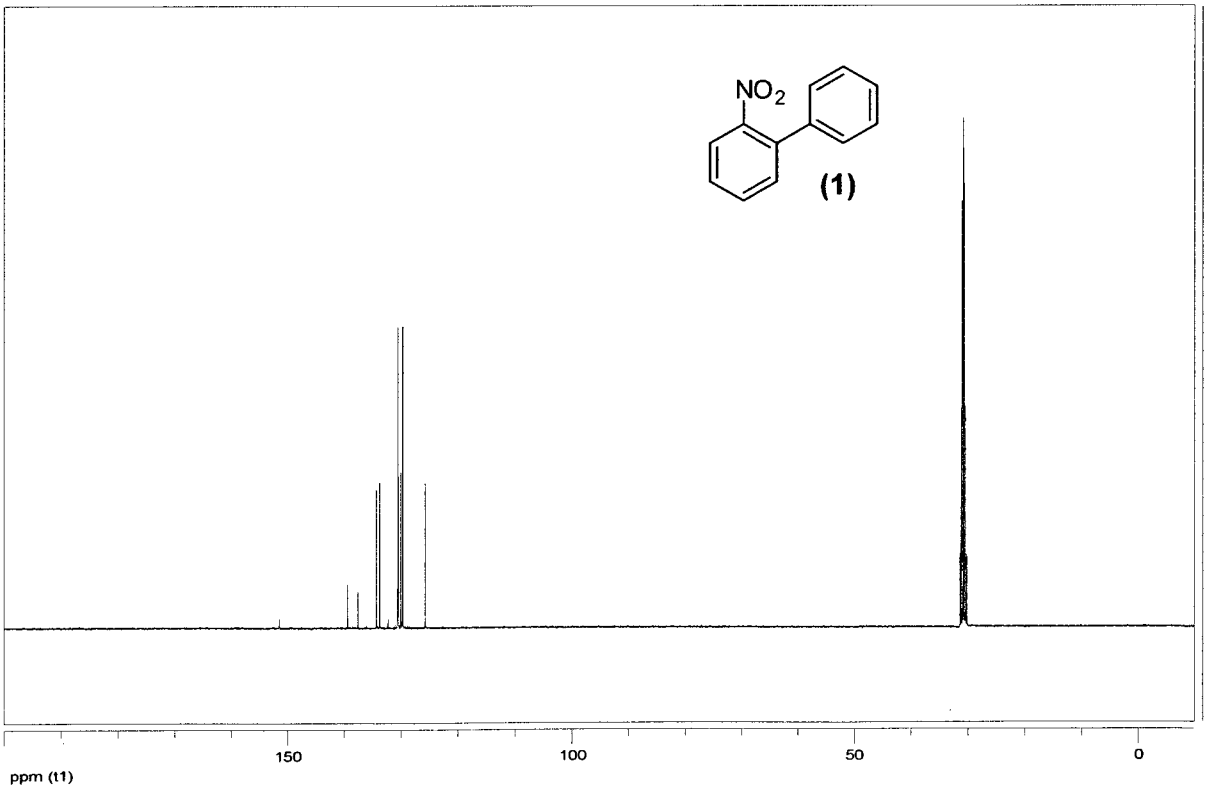
2. Developed new conditions for the intermolecular direct arylation of azoles with aryl bromides and aryl chlorides to form heterobiaryl compounds.

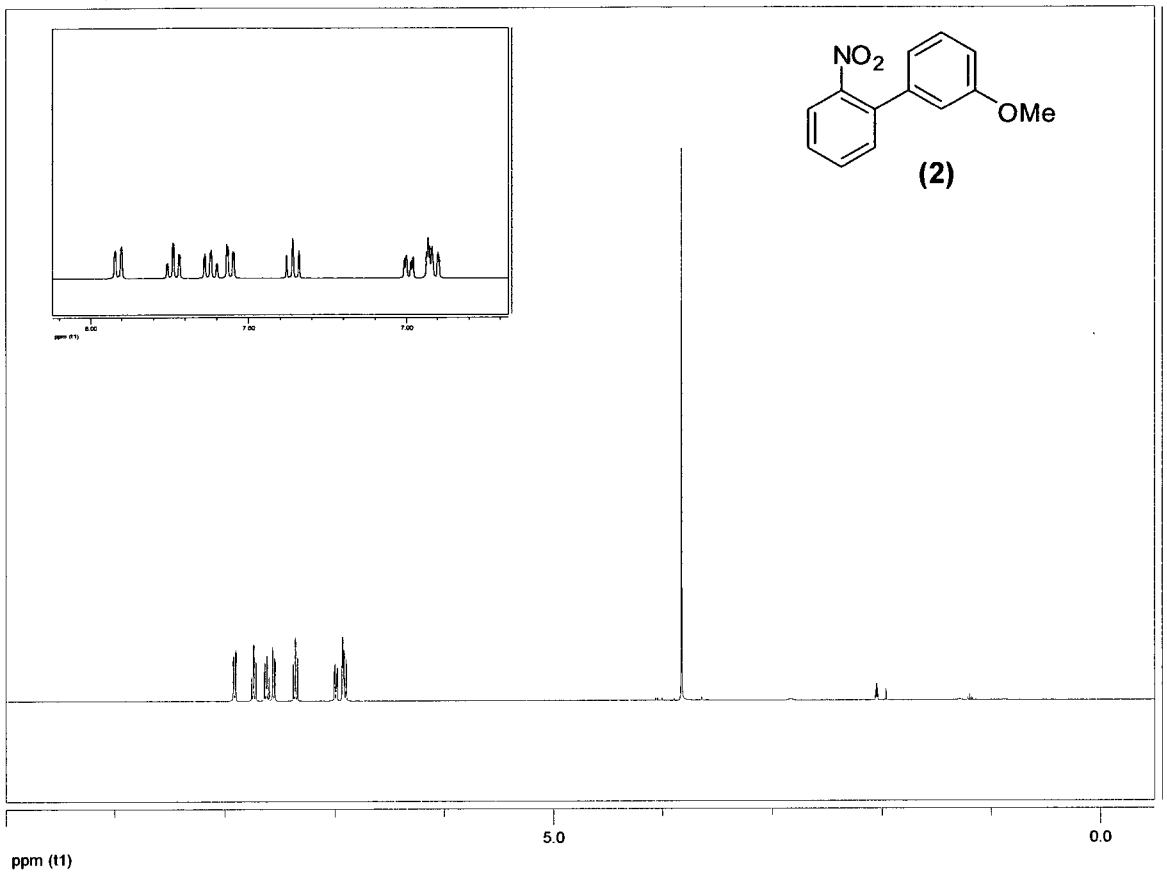
3. Publications: i) Caron, L.; Campeau, L.-C.; Fagnou, K. **Palladium-Catalyzed Direct Arylation of Nitro-Substituted Aromatics with Aryl Halides**, *Org. Lett.* **2008**, *10*, 4533. ii) Lapointe, D.; Liégault, B.; Caron, L.; Vlassova, A., Fagnou, K. **Palladium-Catalyzed Direct Arylation of Heterocycles**, *J. Org. Chem.* **2009**, *74*, 1826.

4. Poster presentations: i) Caron, L.; Campeau, L. C.; Fagnou, K. **Traceless/Versatile Activation of Simples Arenes: Direct Arylation of Nitroarenes,** Quebec-Ontario Mini Symposium of Bioorganic and Organic Chemistry, Université de Montreal, November 9th to 11th **2007**. ii) Caron, L.; Campeau, L. C.; Fagnou, K. **Traceless/Versatile Activation of Simples Arenes: Direct Arylation of Nitroarenes,** 37th Spring Organic Synthesis Symposium, University of Ottawa, June 18th **2007**

Spectra


NO2
(1)
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)


NO2
(1)
150
100
50
0
ppm (t1)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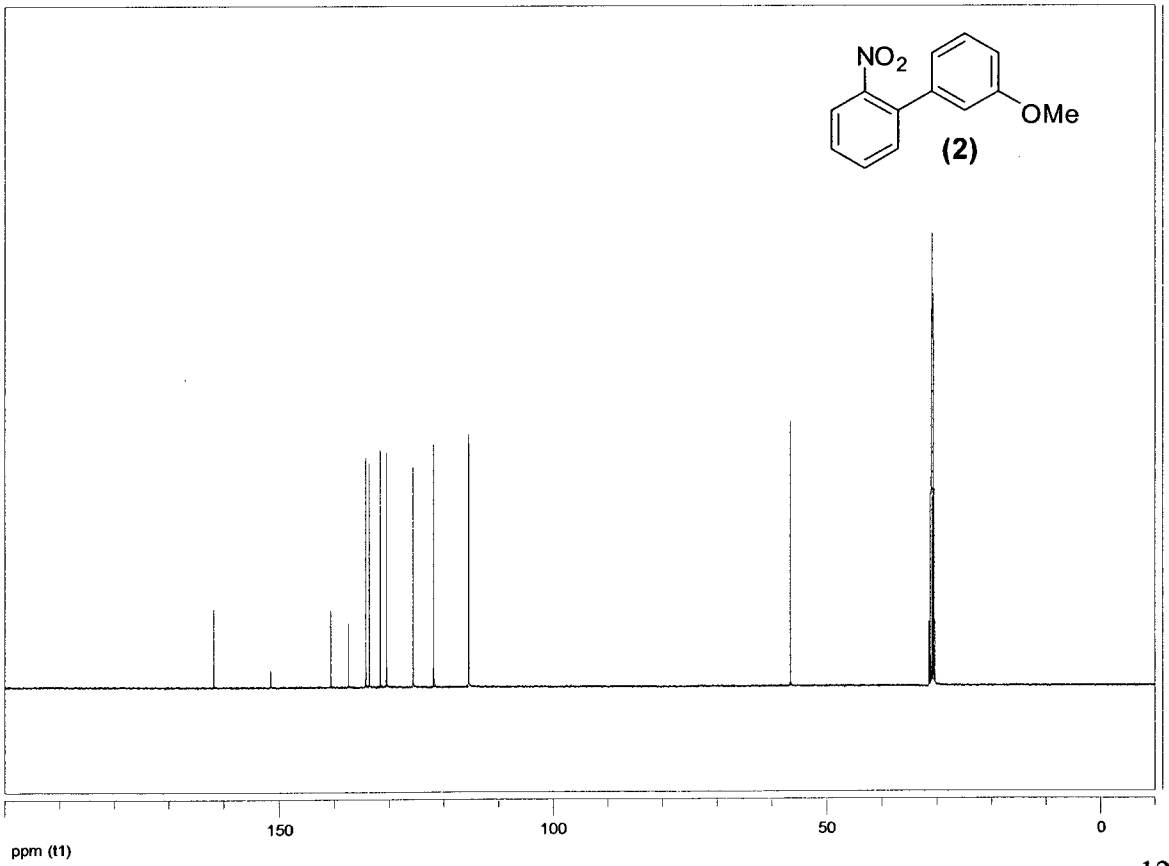
ppm (t1)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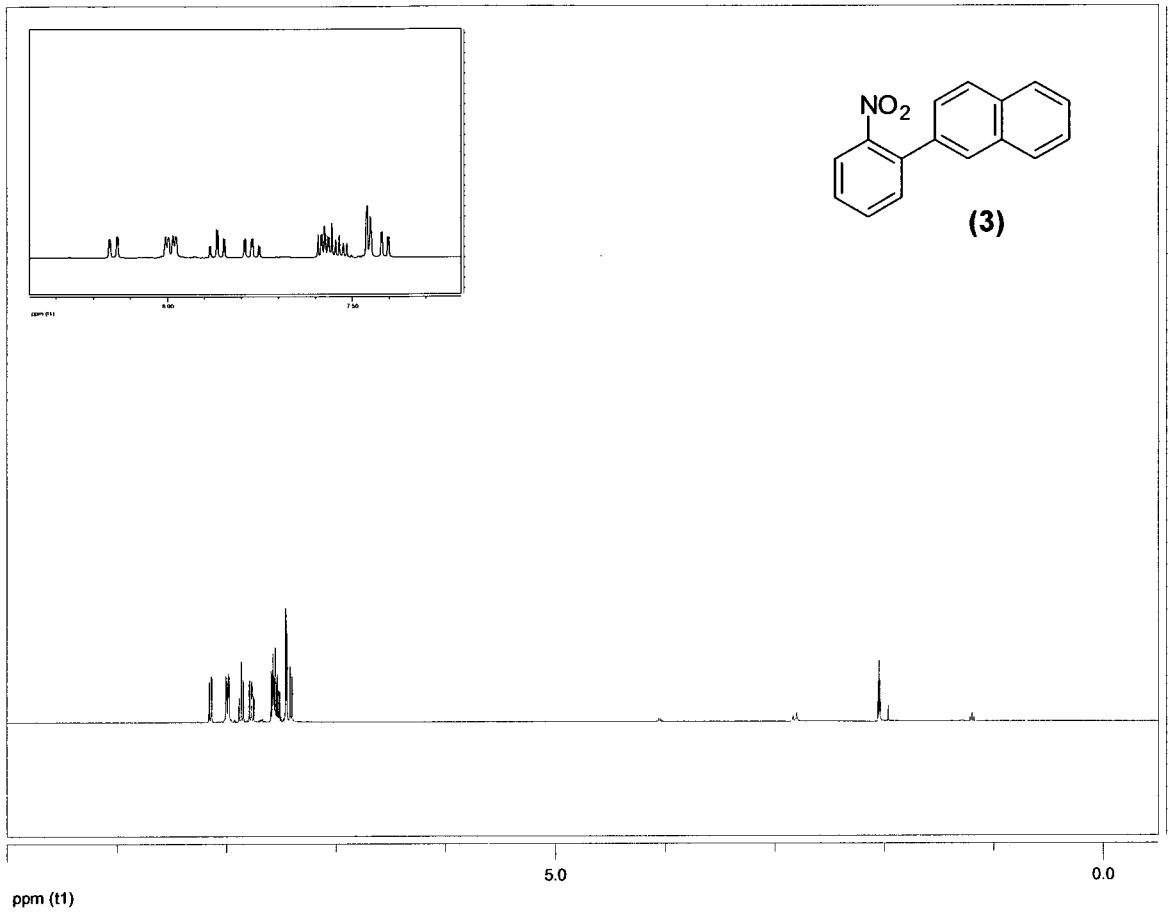
ppm (t1)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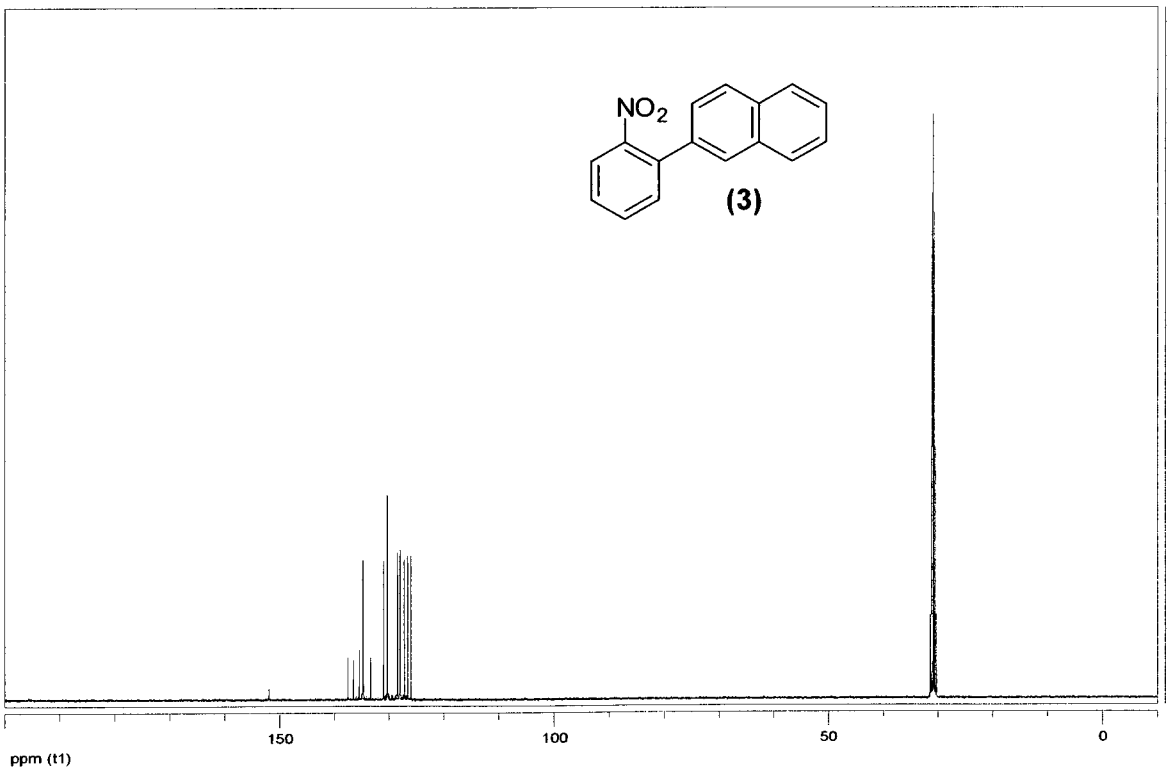
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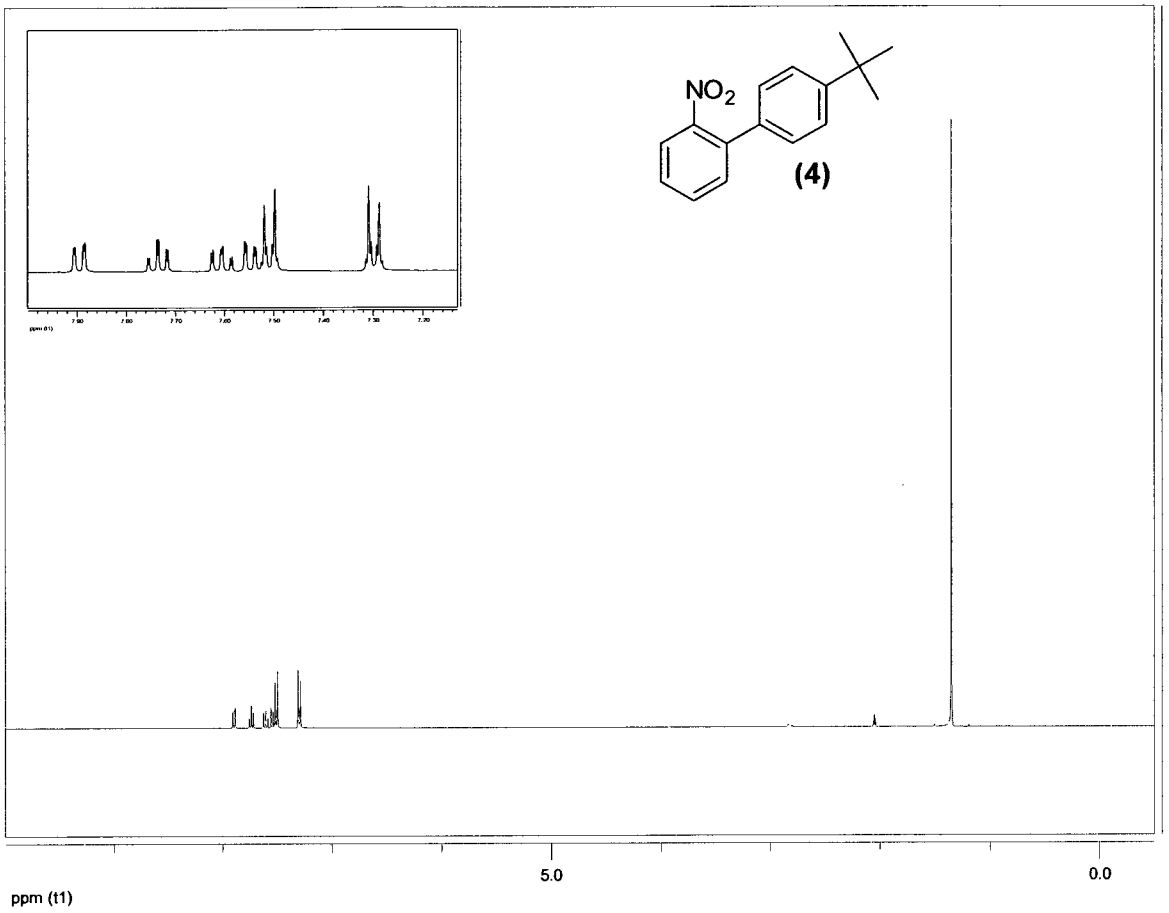
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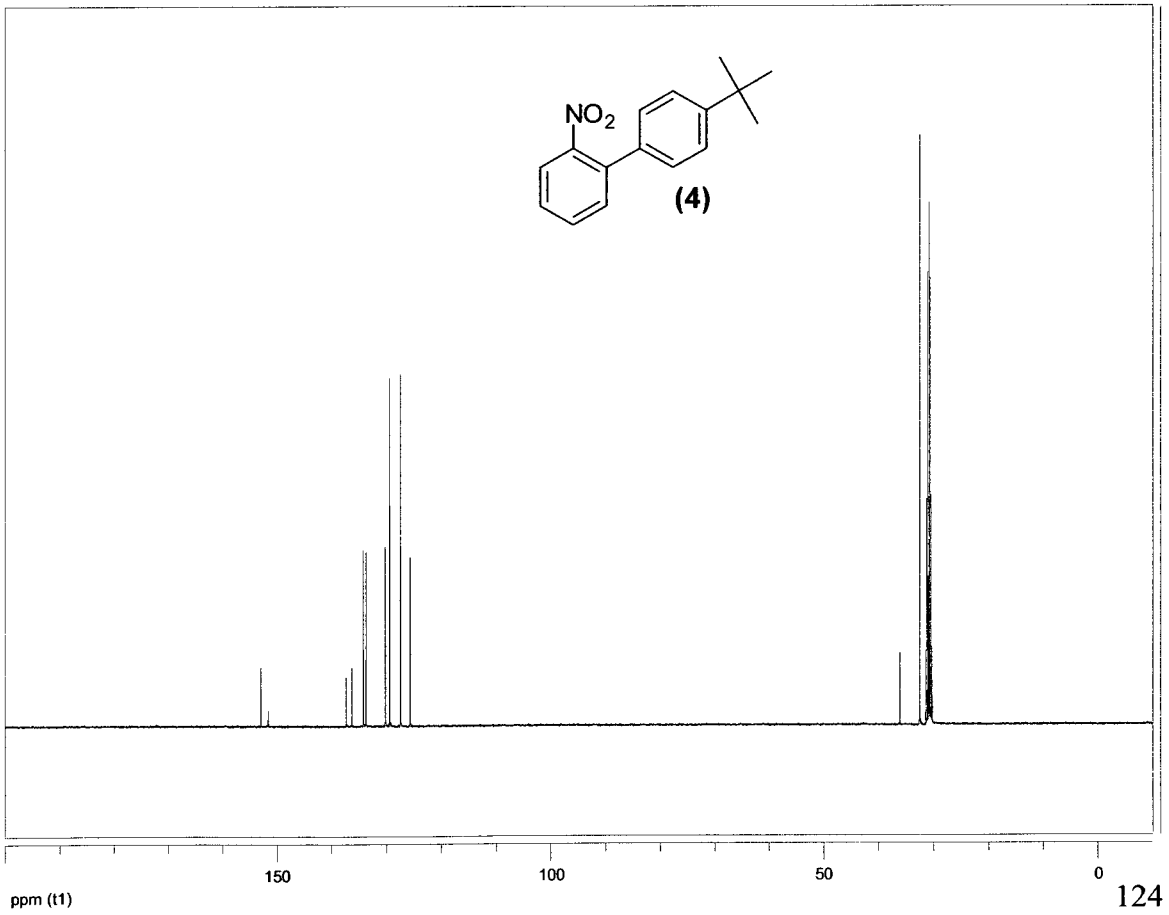
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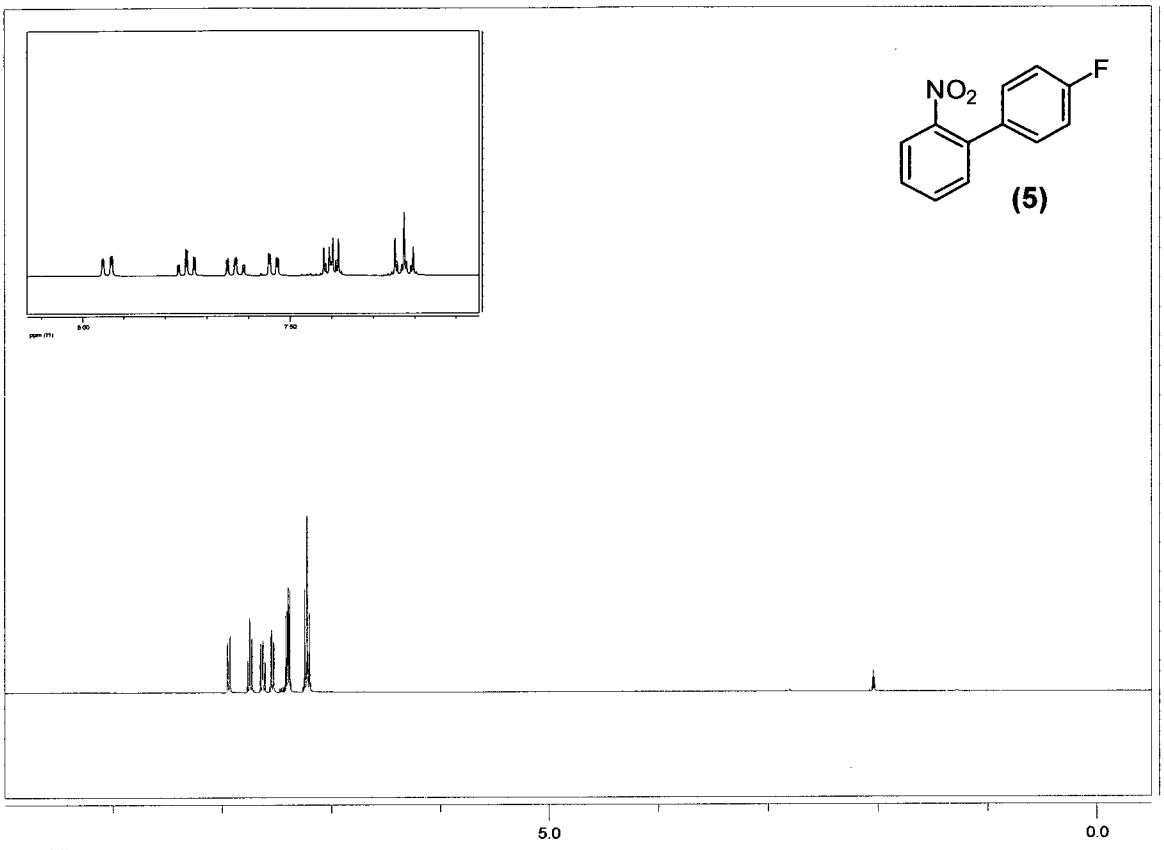
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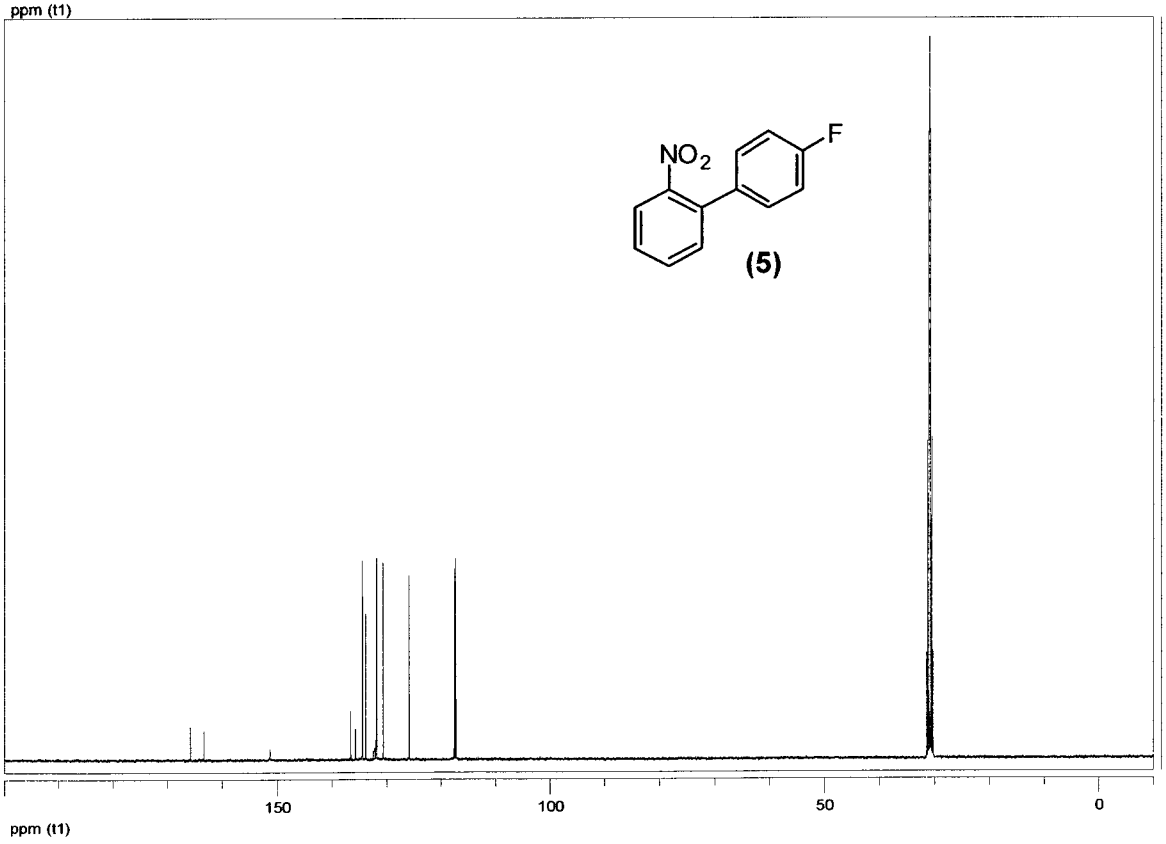
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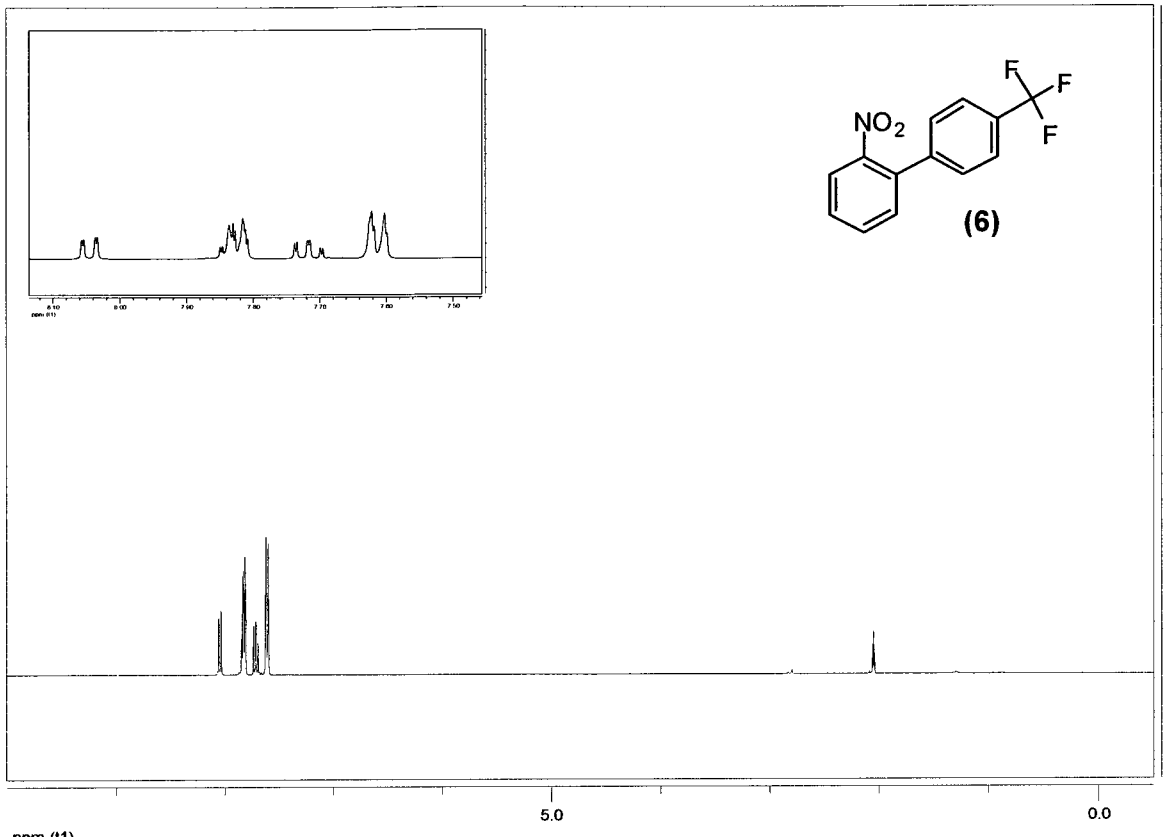
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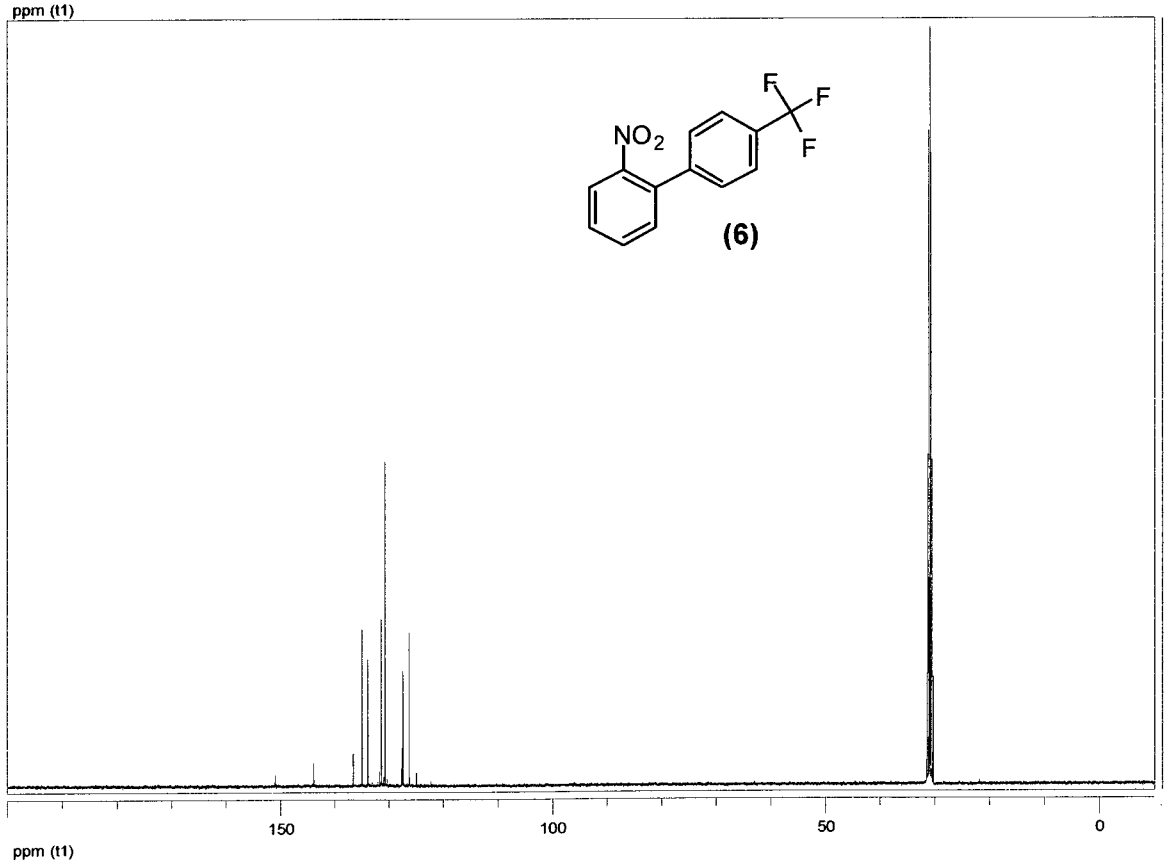
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F
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(6)
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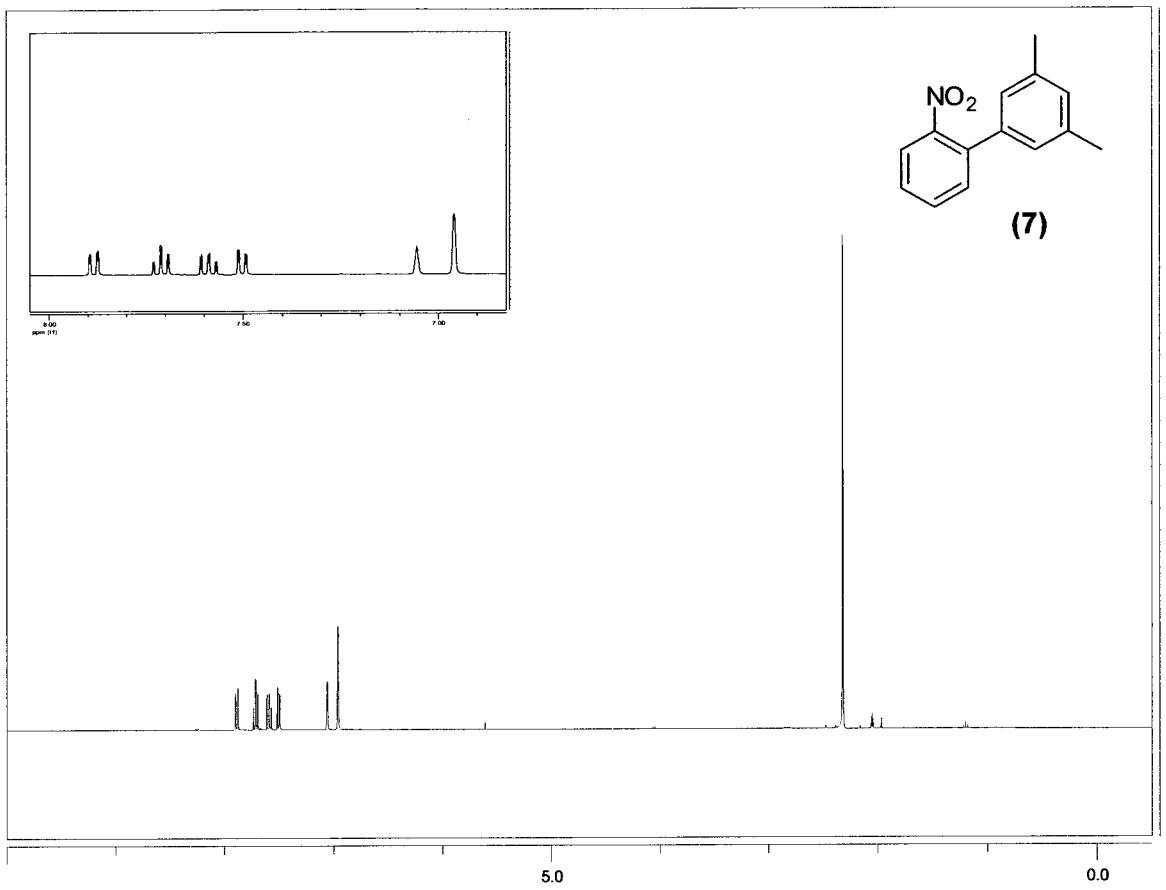
ppm (t1)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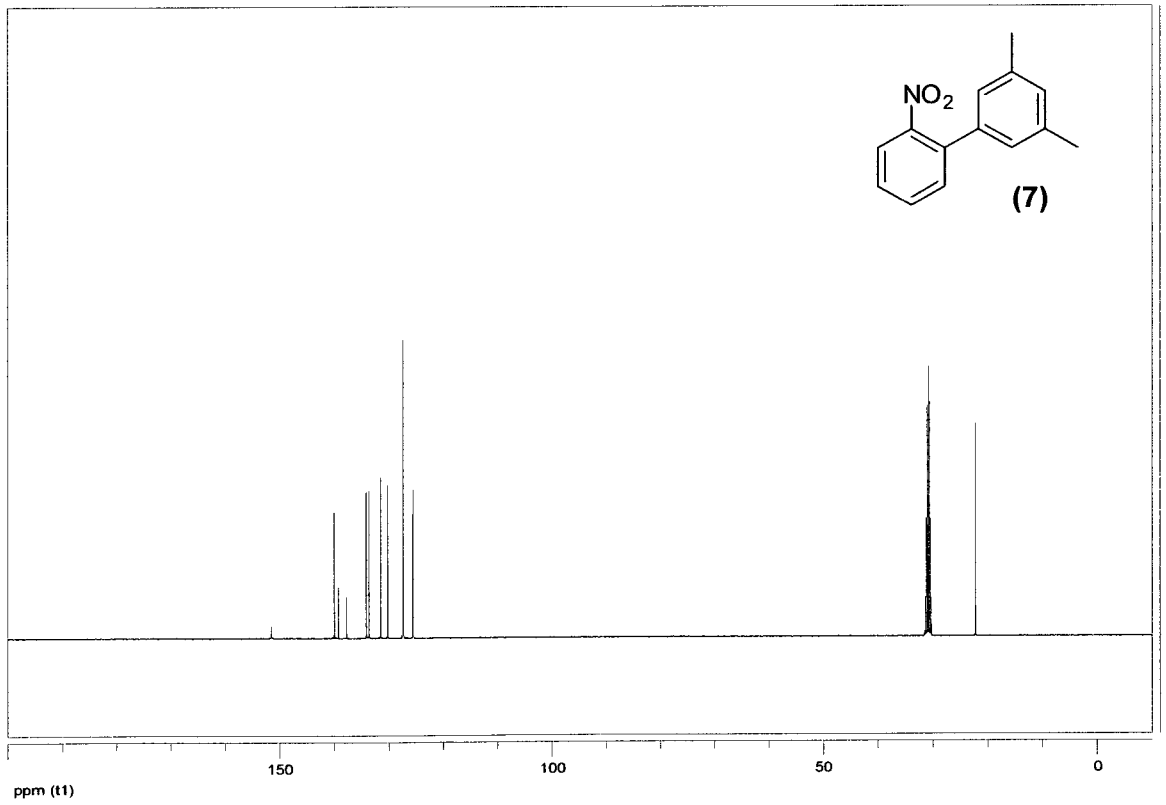
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(7)
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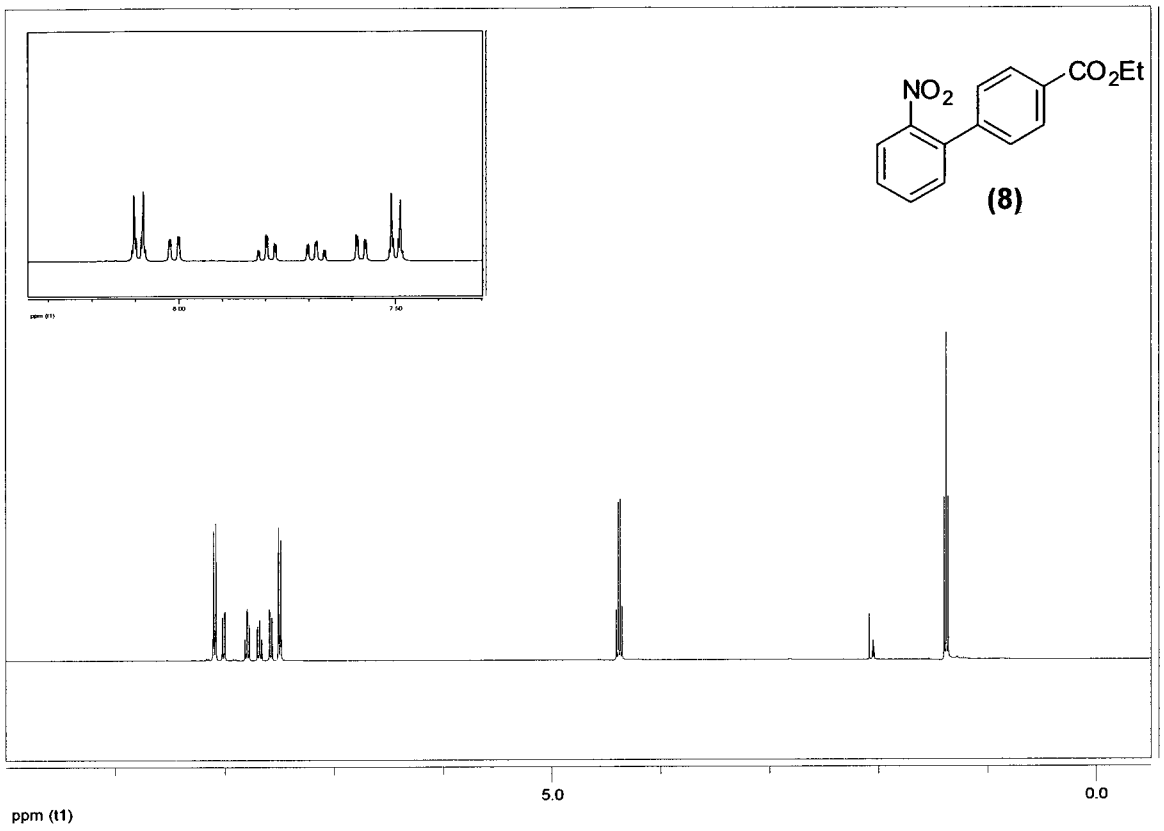
ppm (t1)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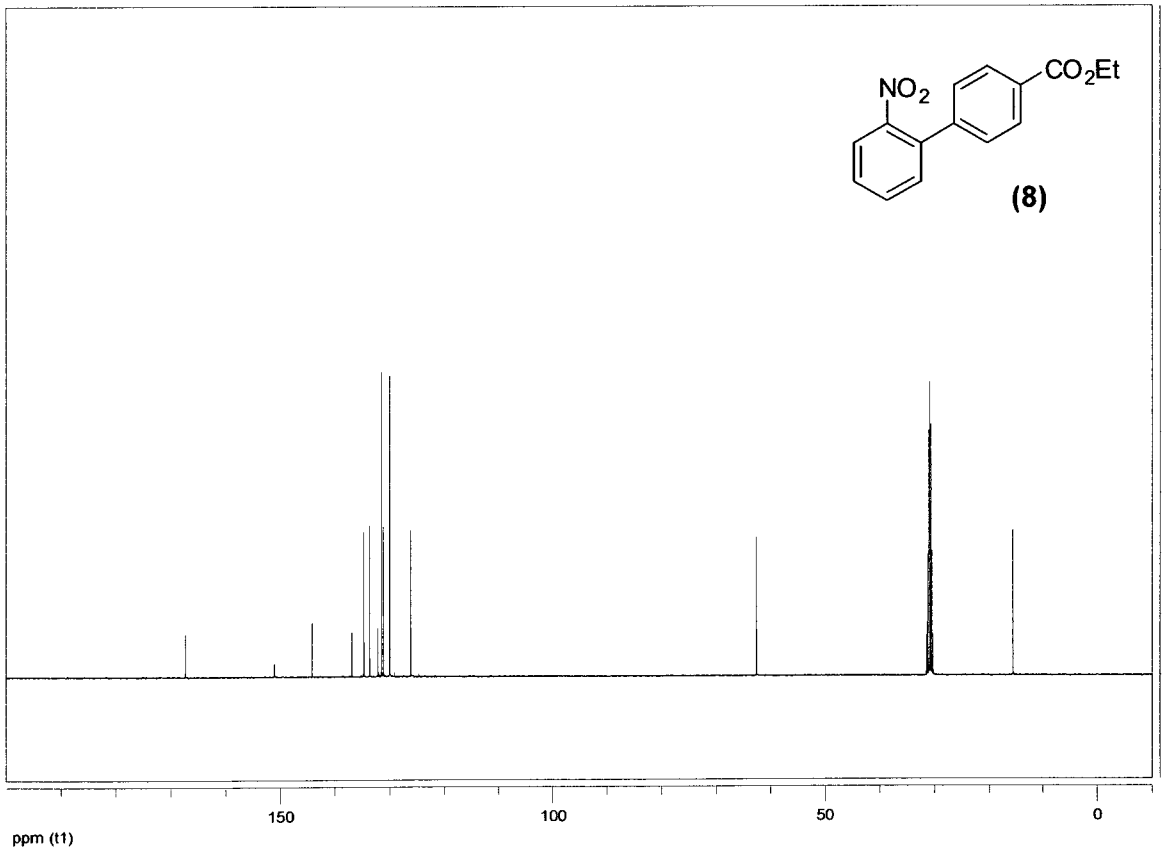
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(8)
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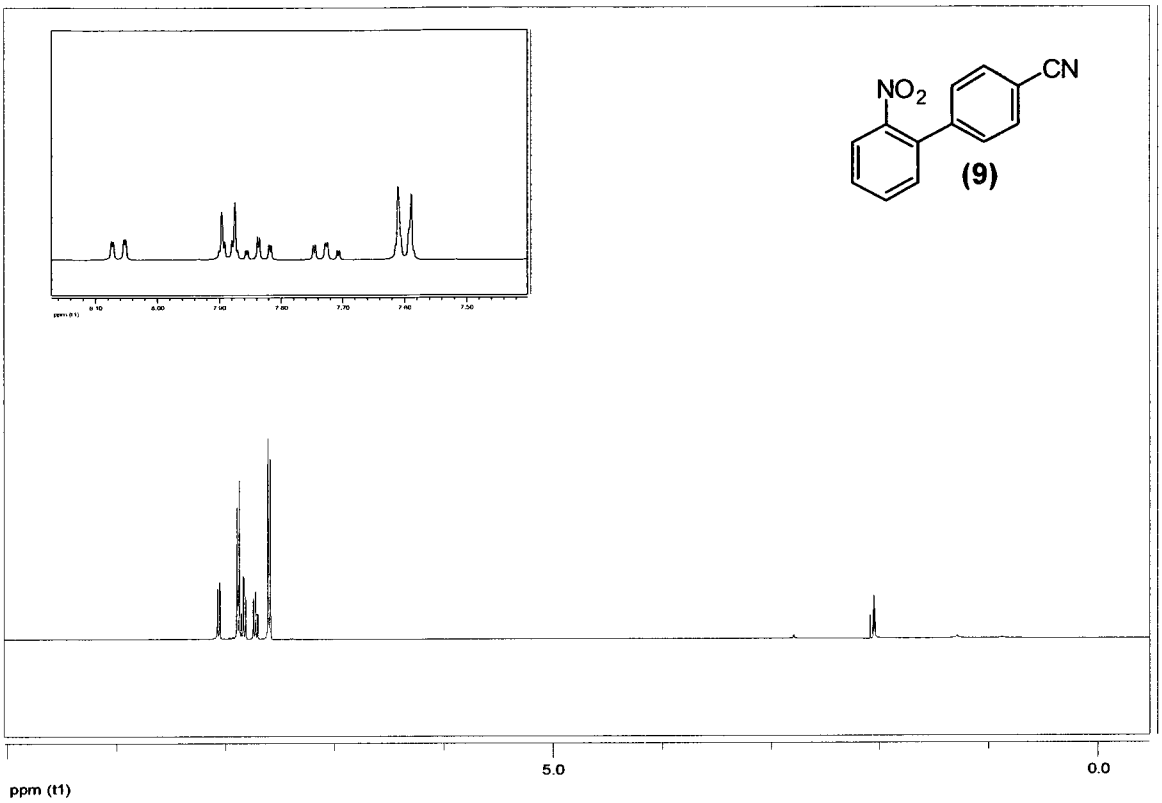
ppm (t1)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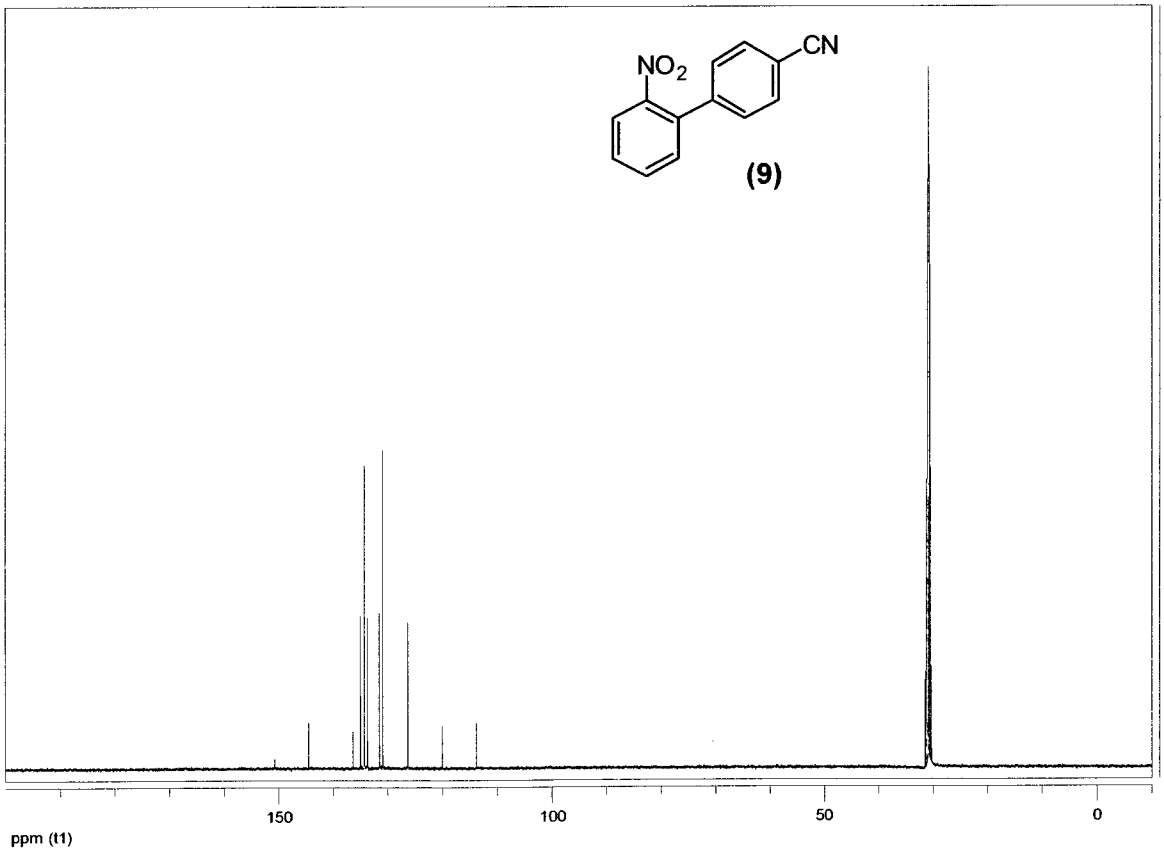
ppm (t1)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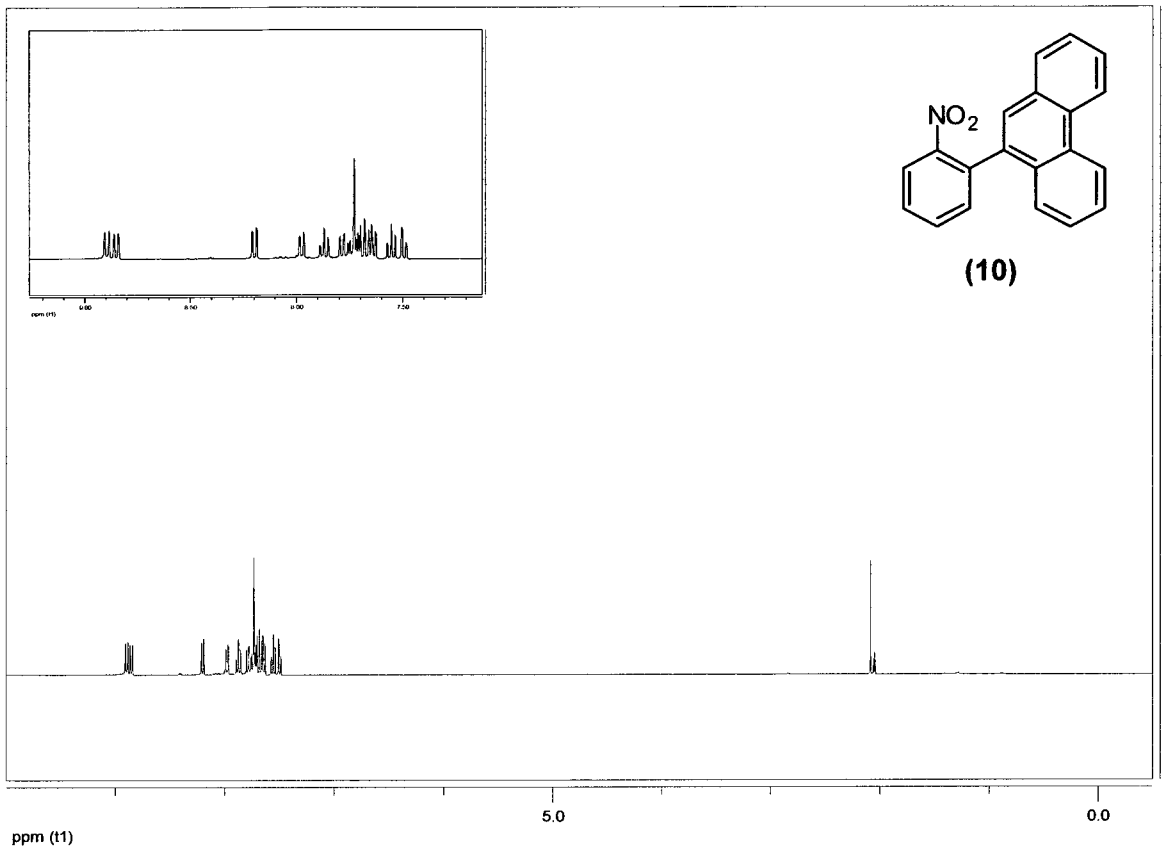
ppm (t1)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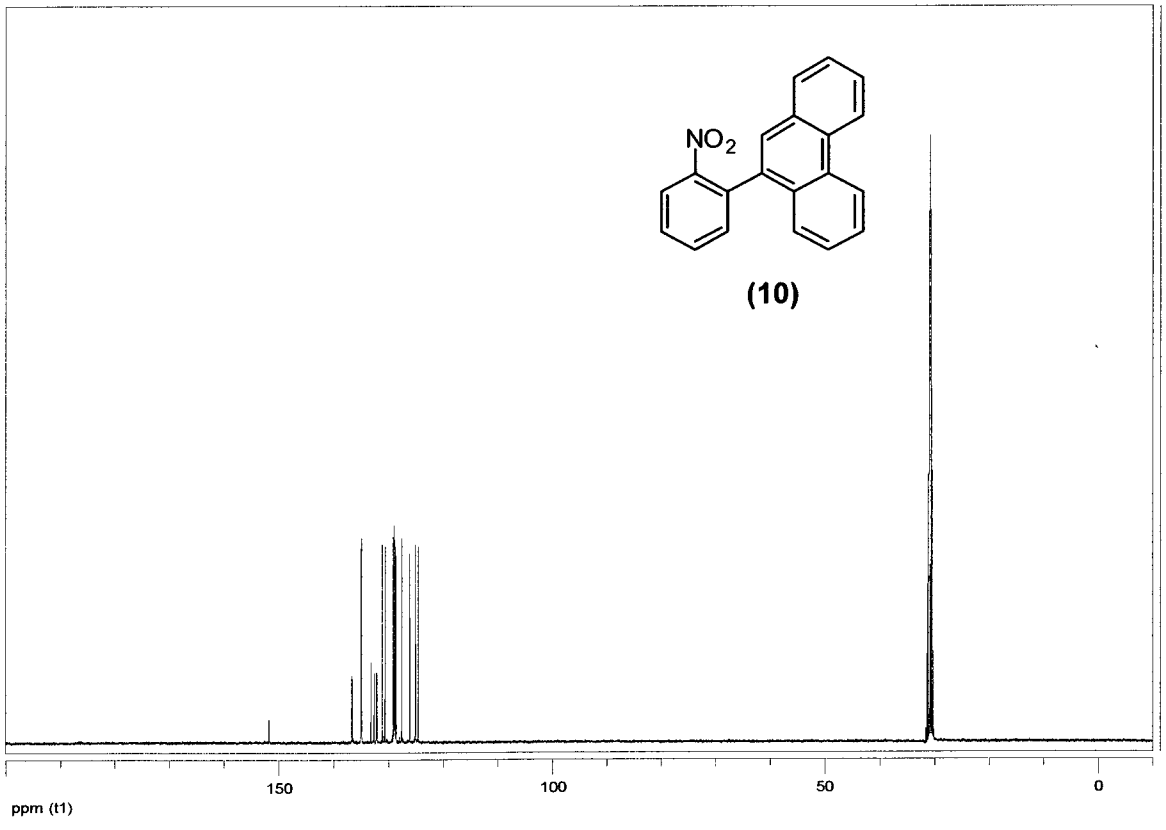
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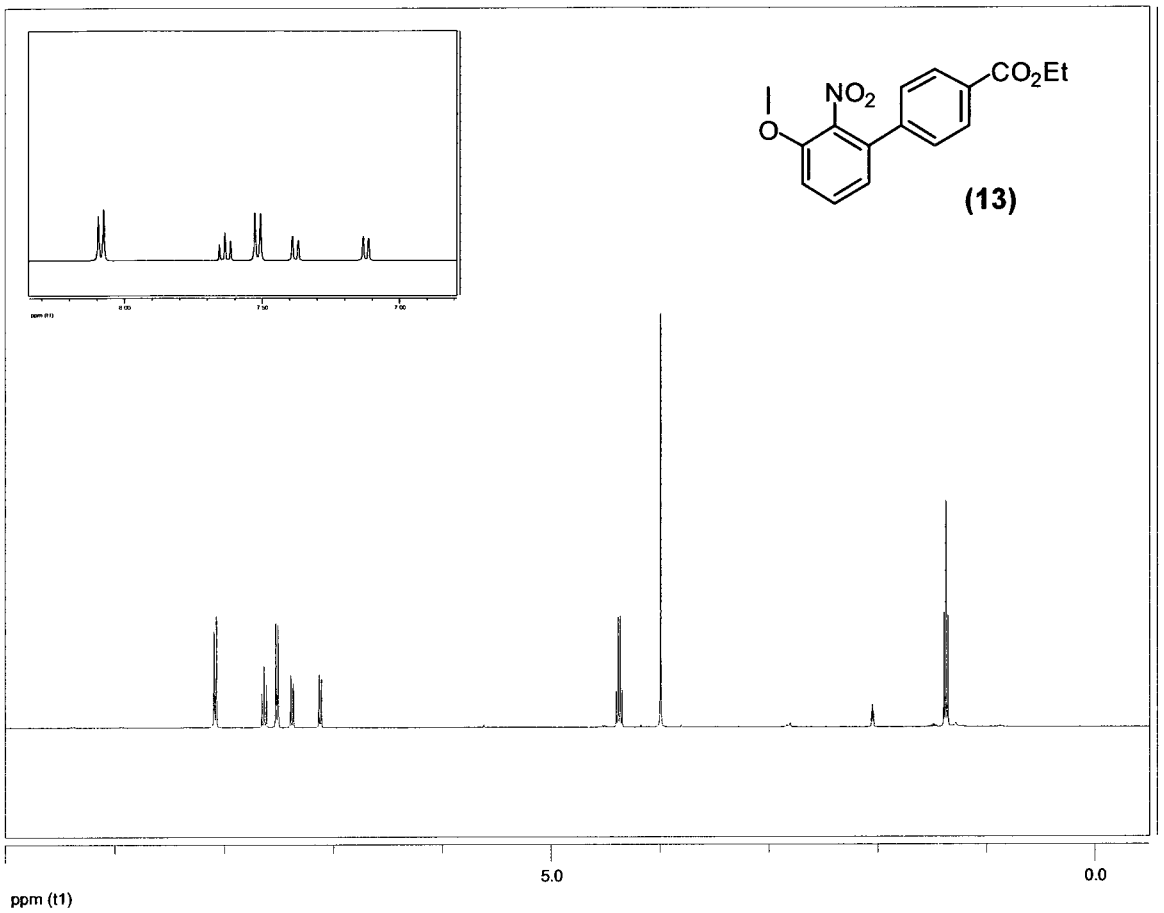
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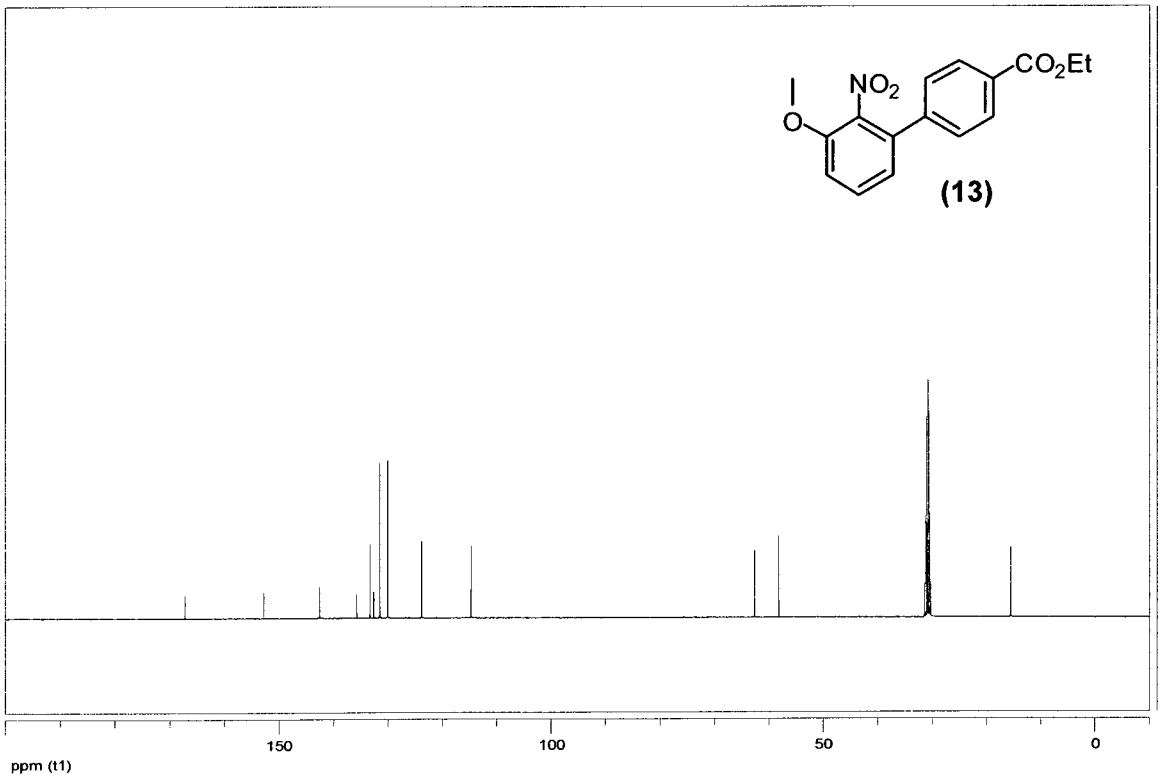
ppm (t1)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(13)
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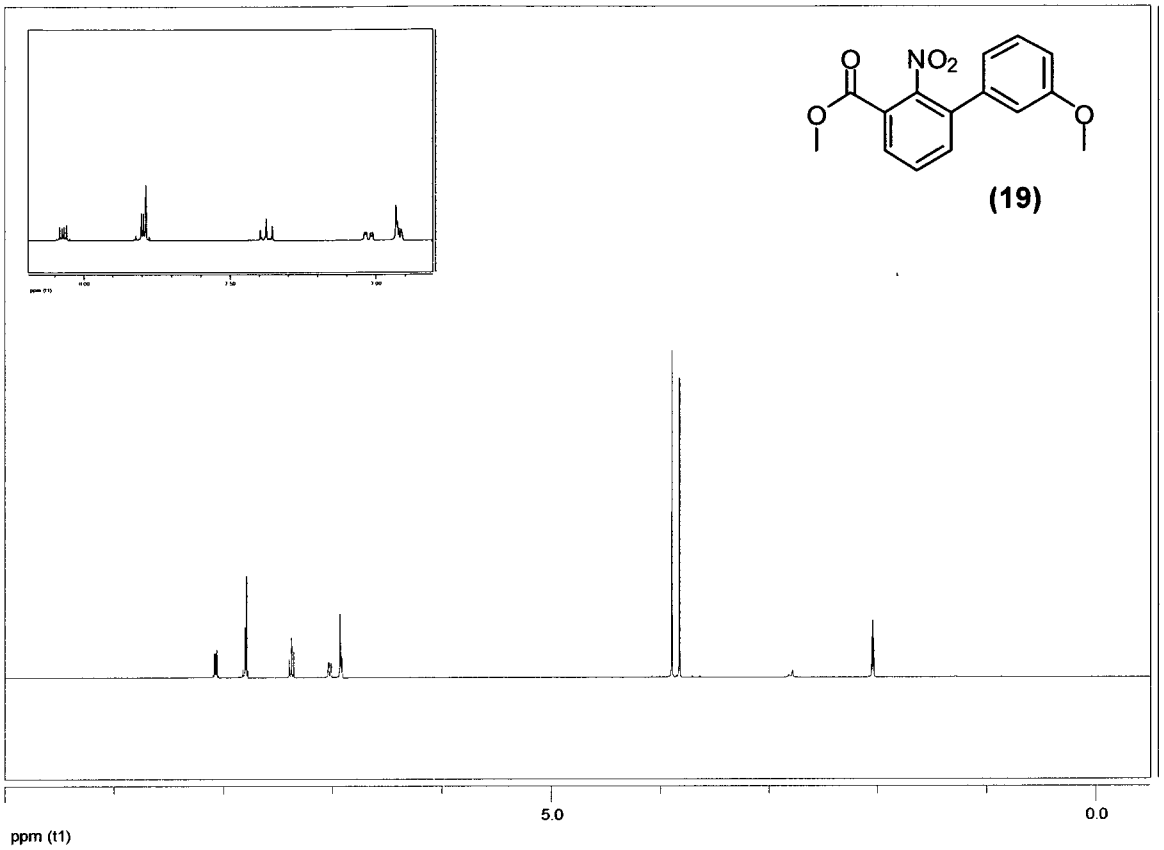
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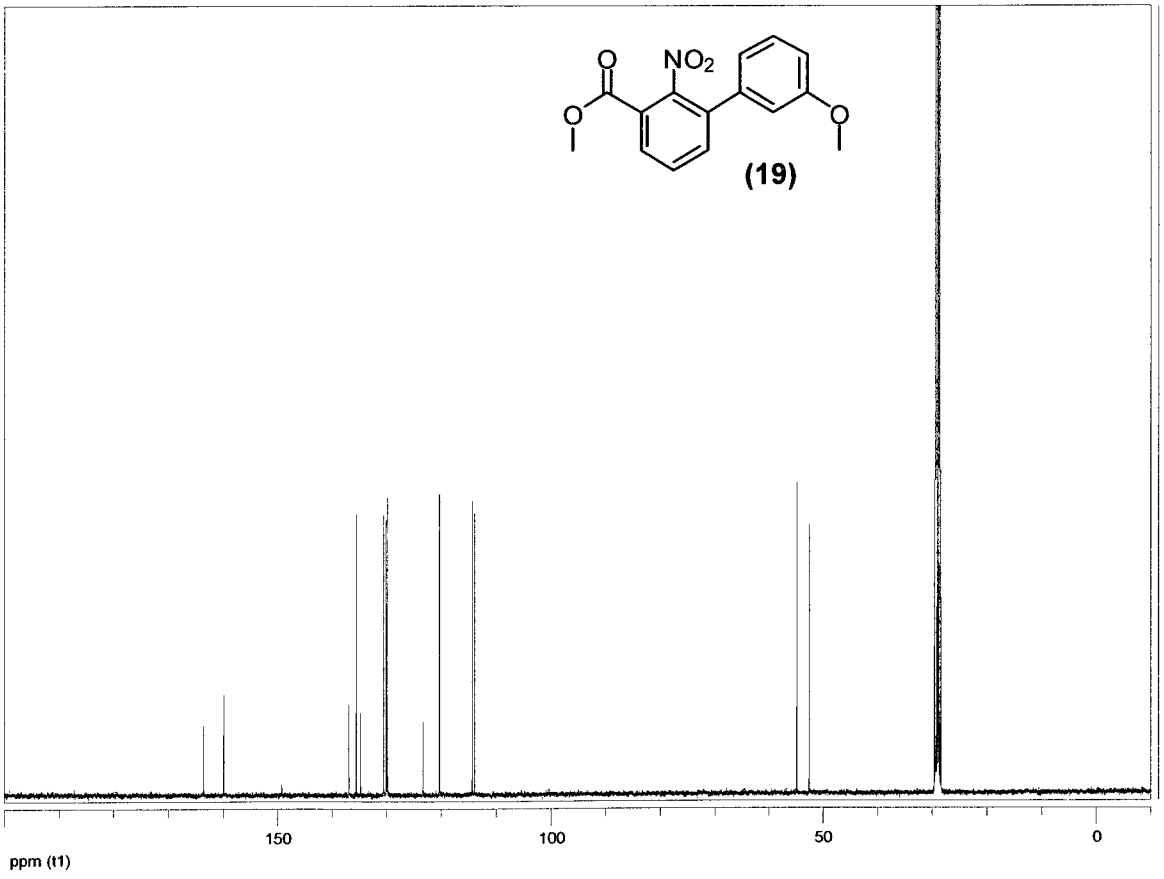
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(19)
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100
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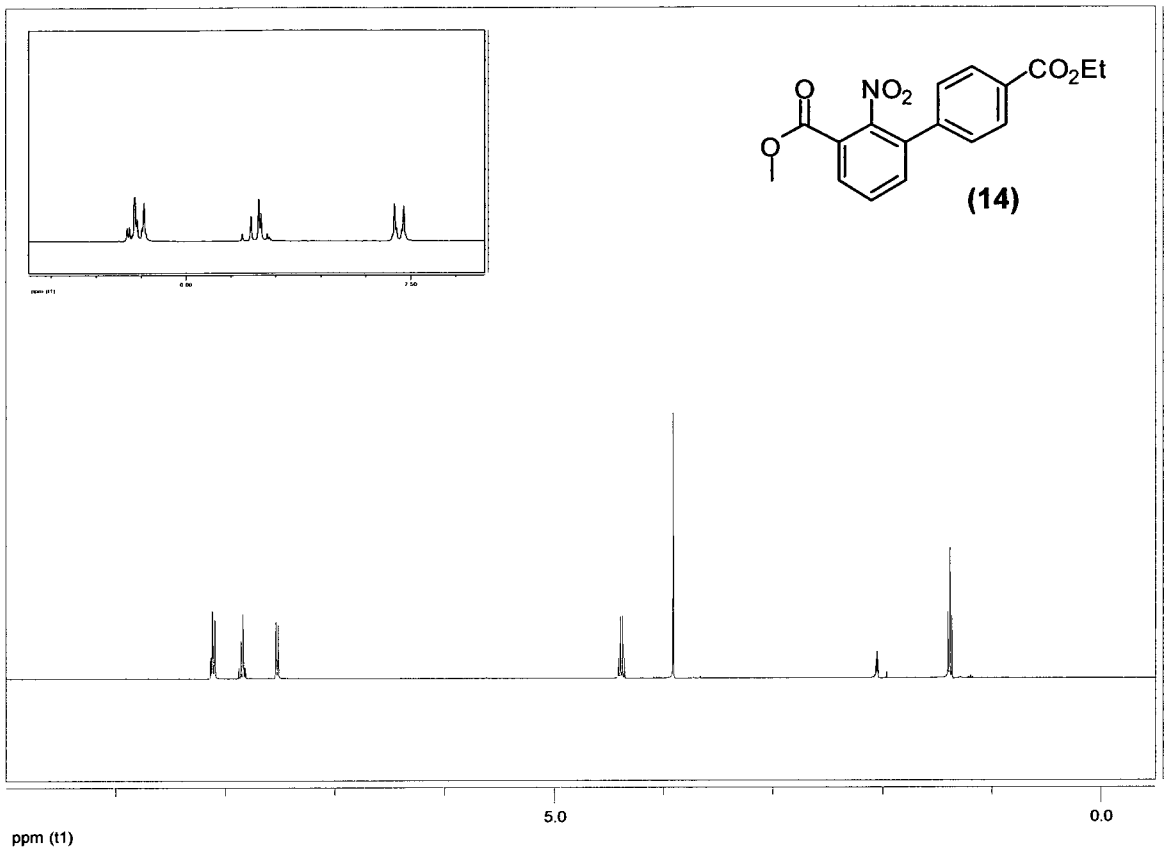
ppm (t1)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CO2Et
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(14)
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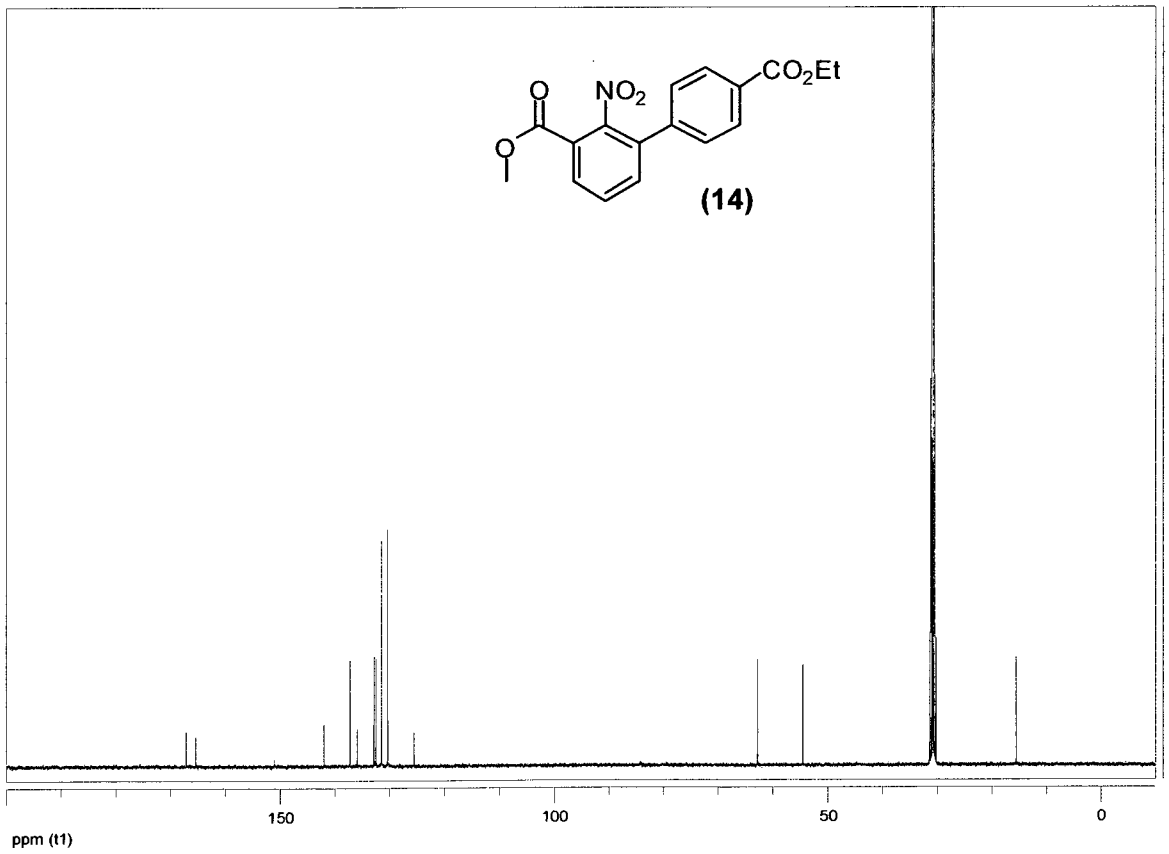
ppm (t1)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NO2
CO2Et
O
(14)
150
100
50
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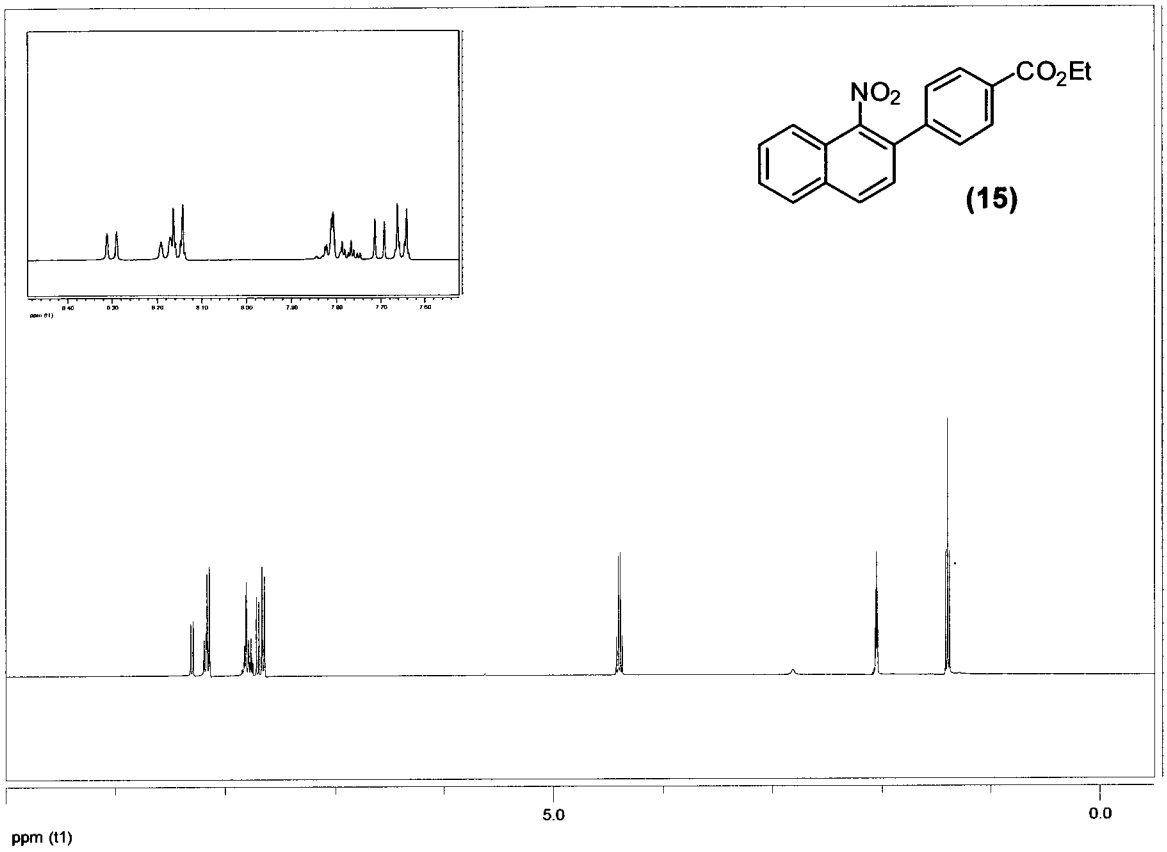
ppm (t1)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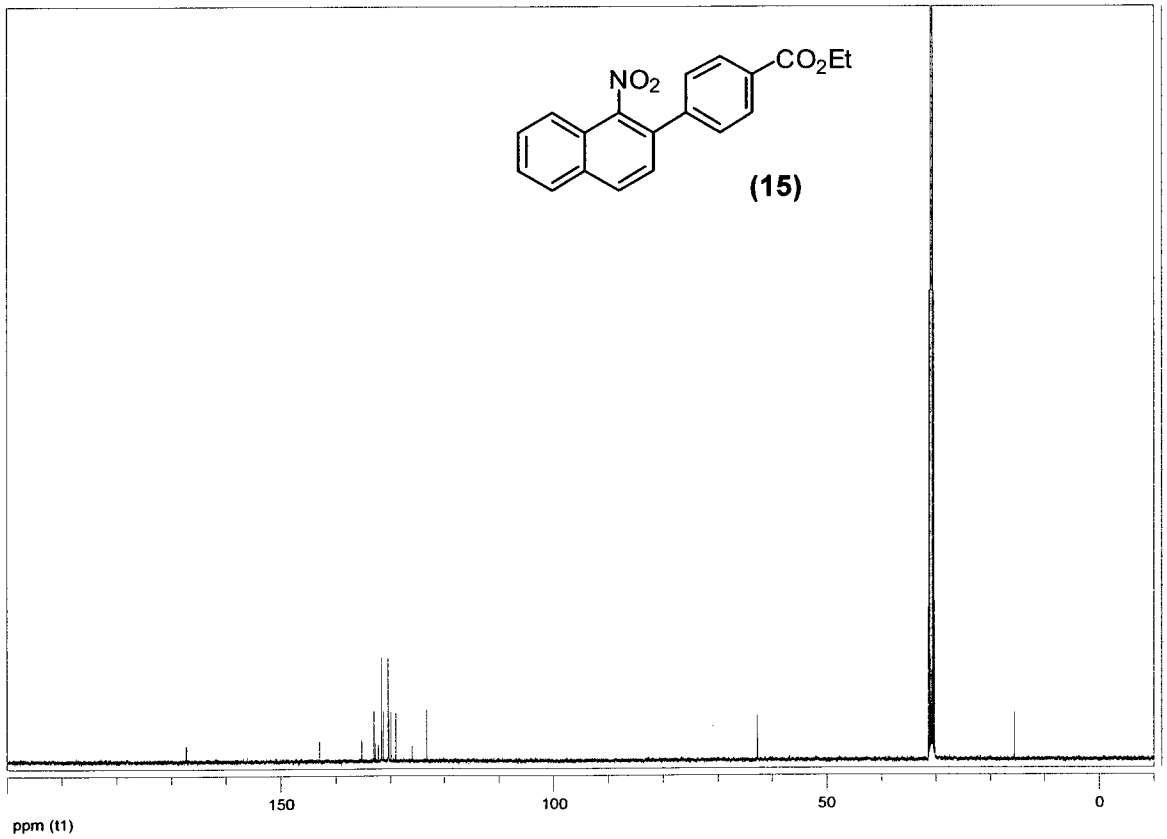
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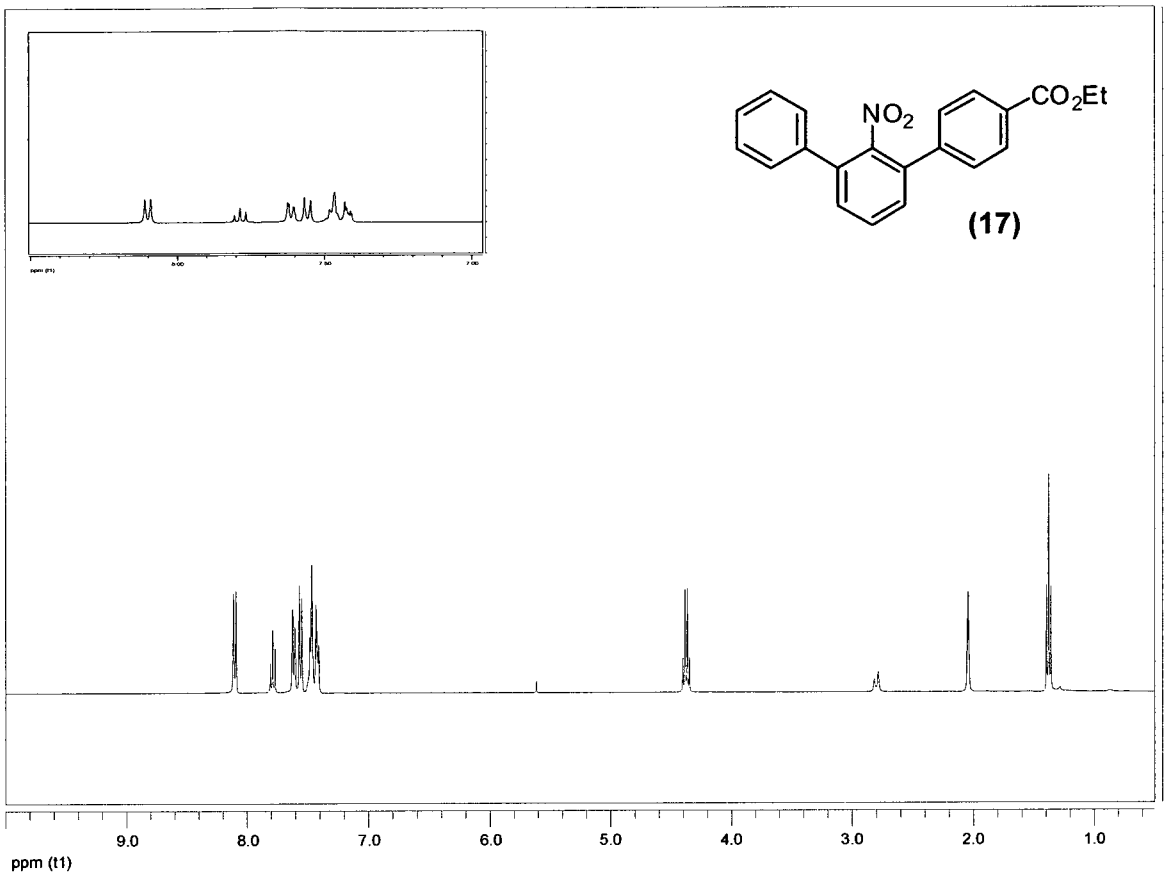
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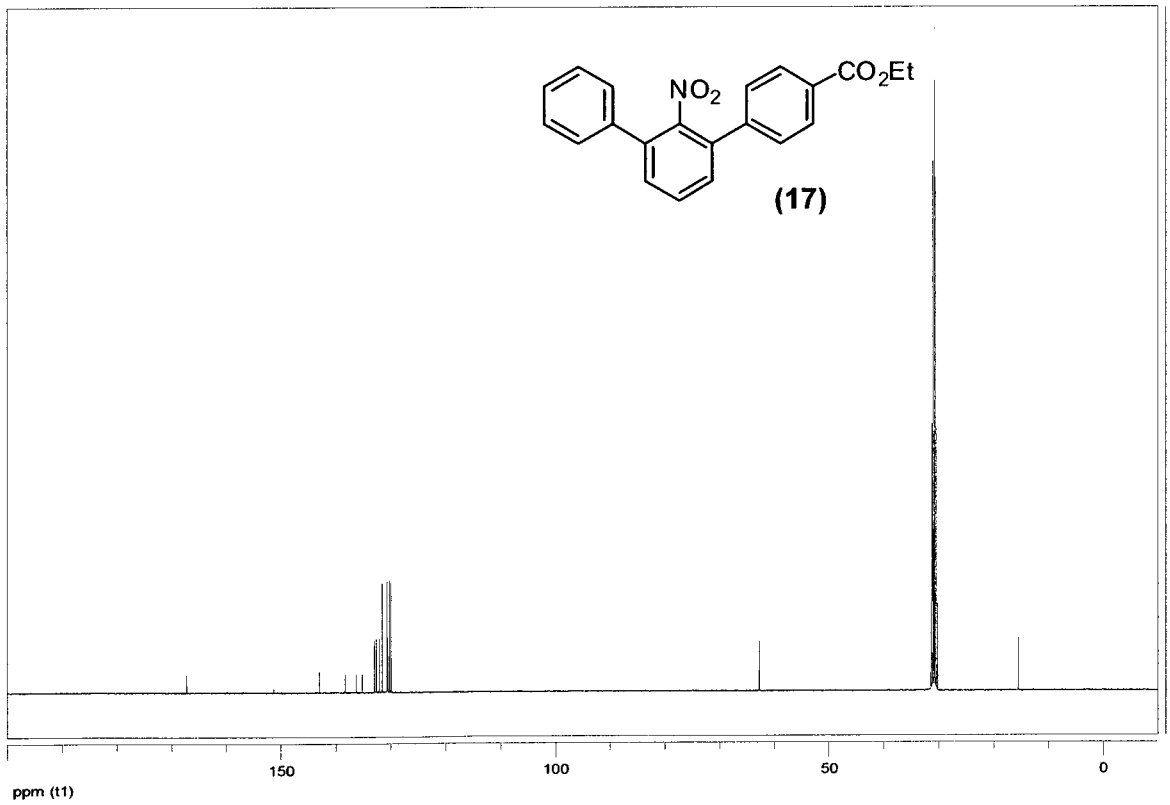
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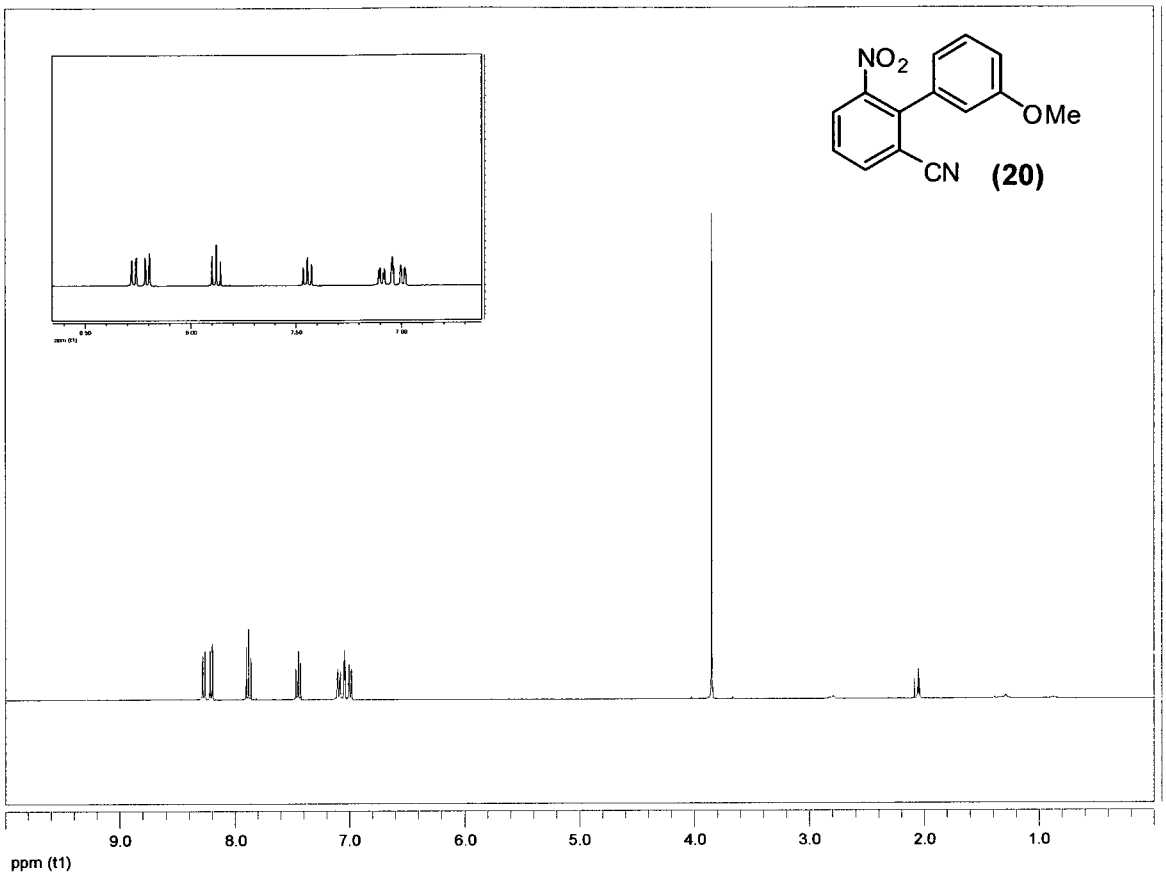
ppm (t1)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OMe
CN
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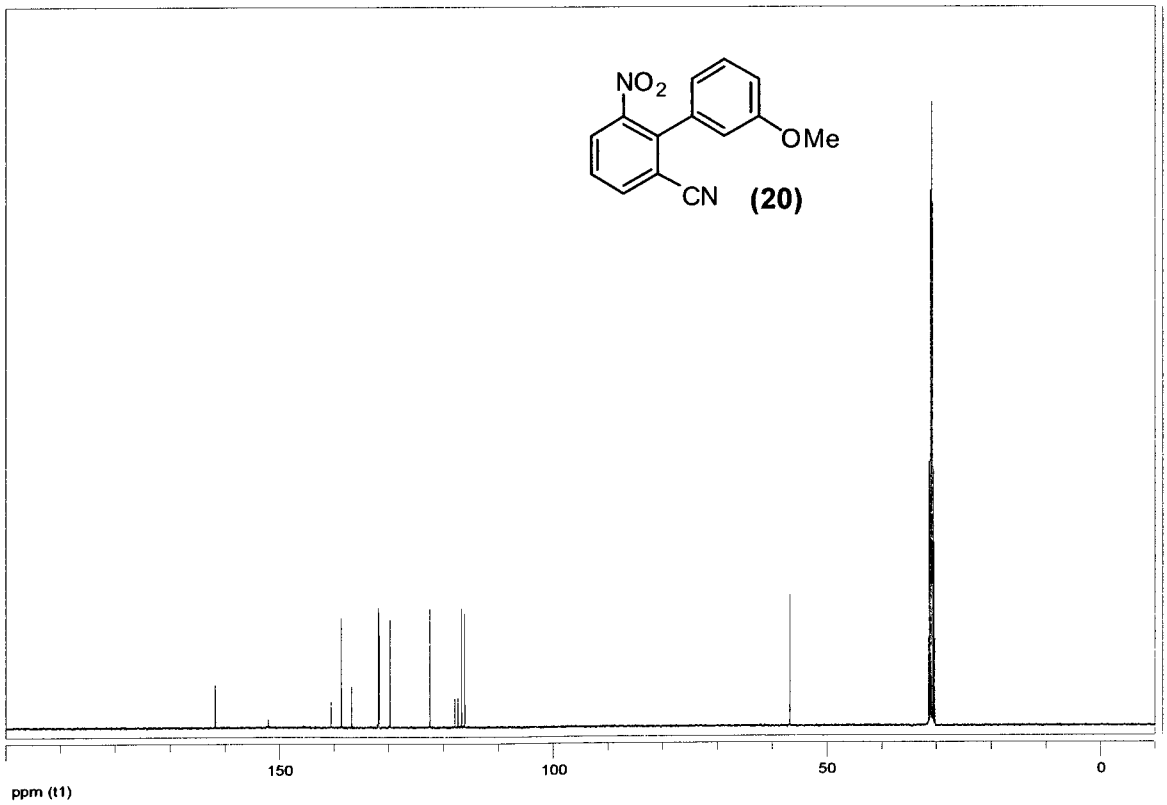
ppm (t1)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CN
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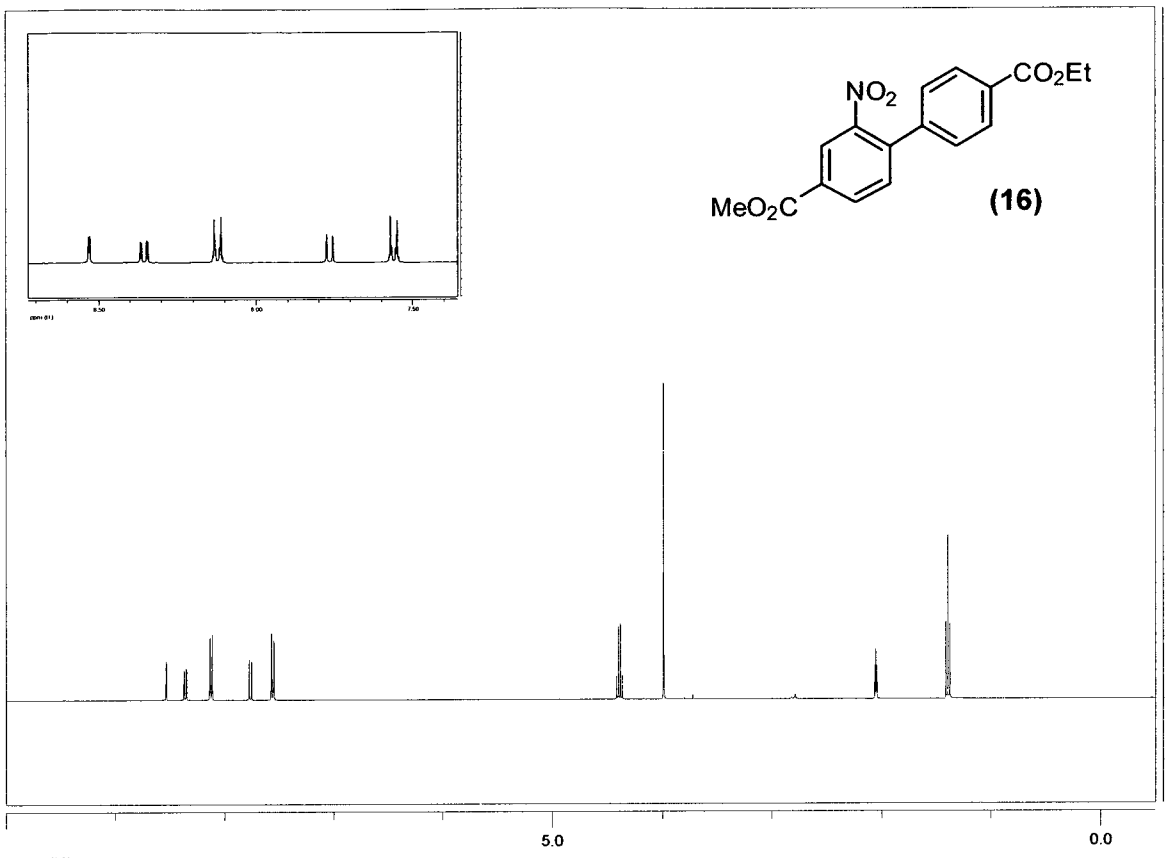
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(16)
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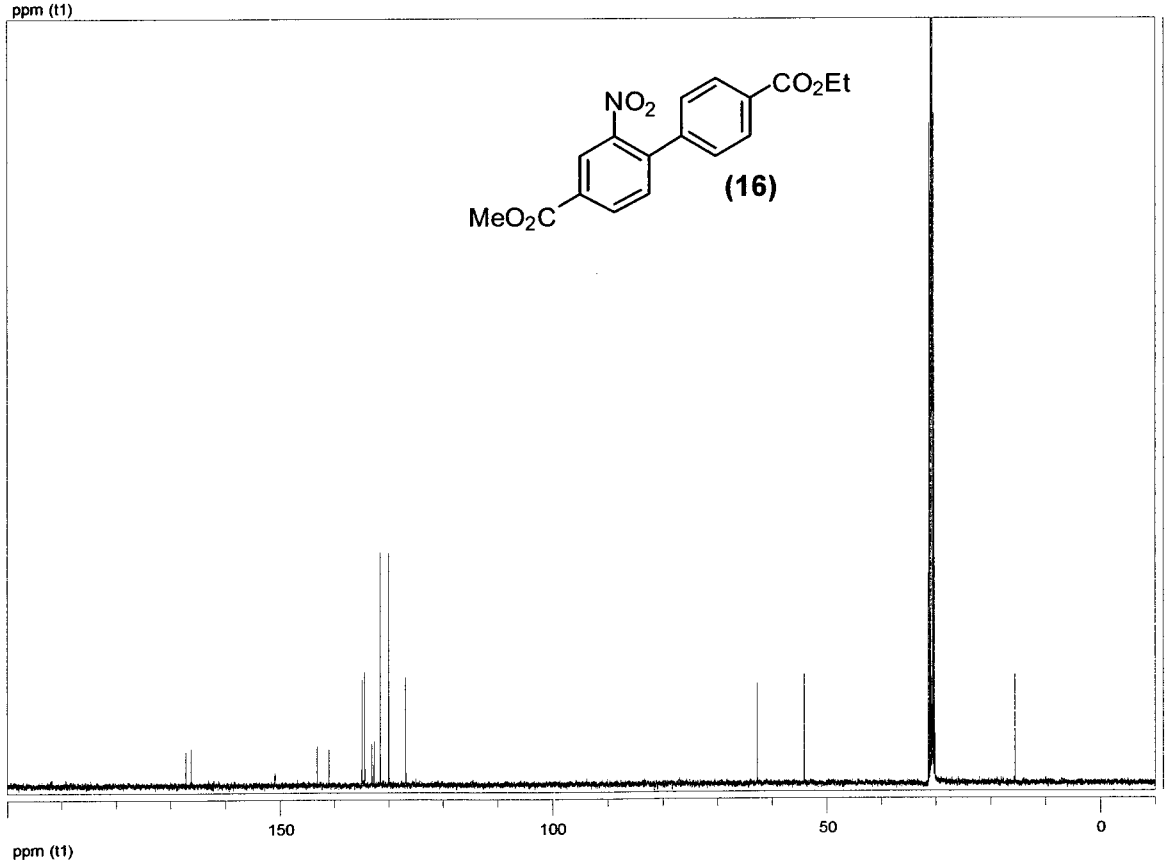
ppm (t1)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CO2Et
MeO2C
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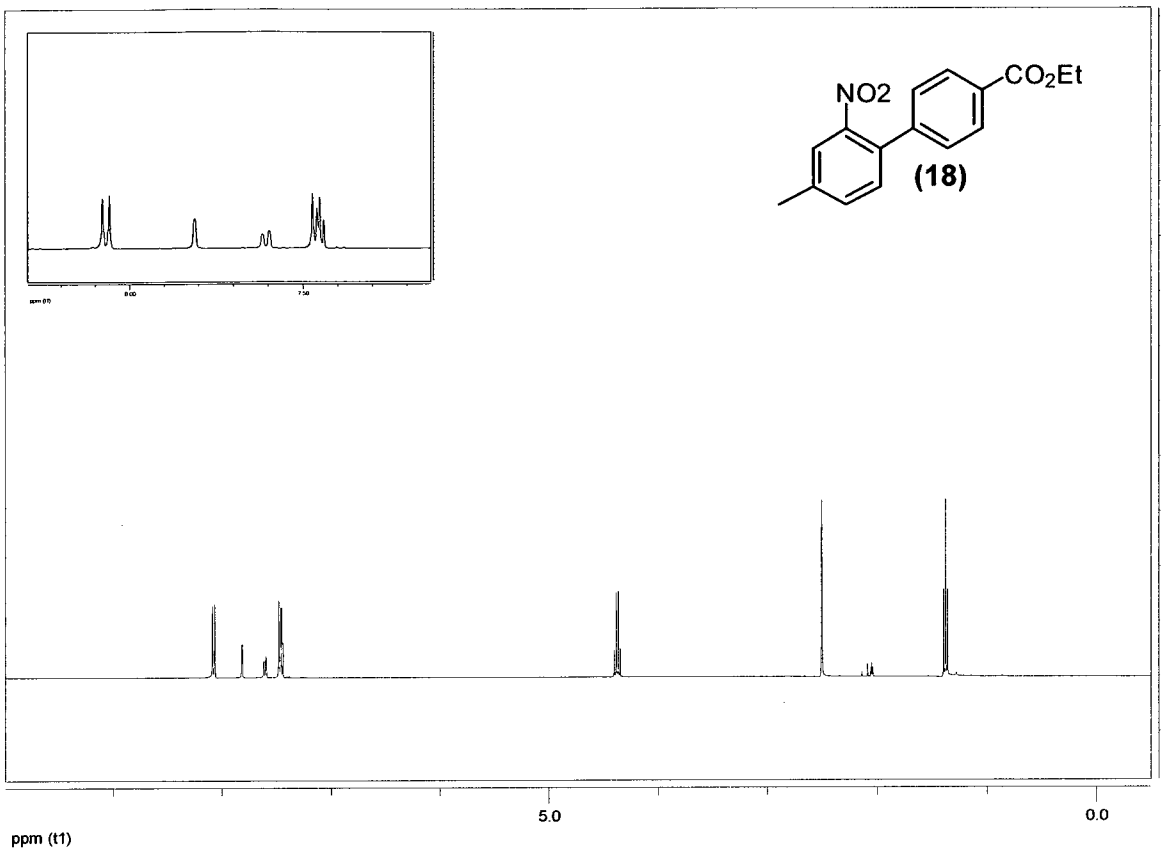
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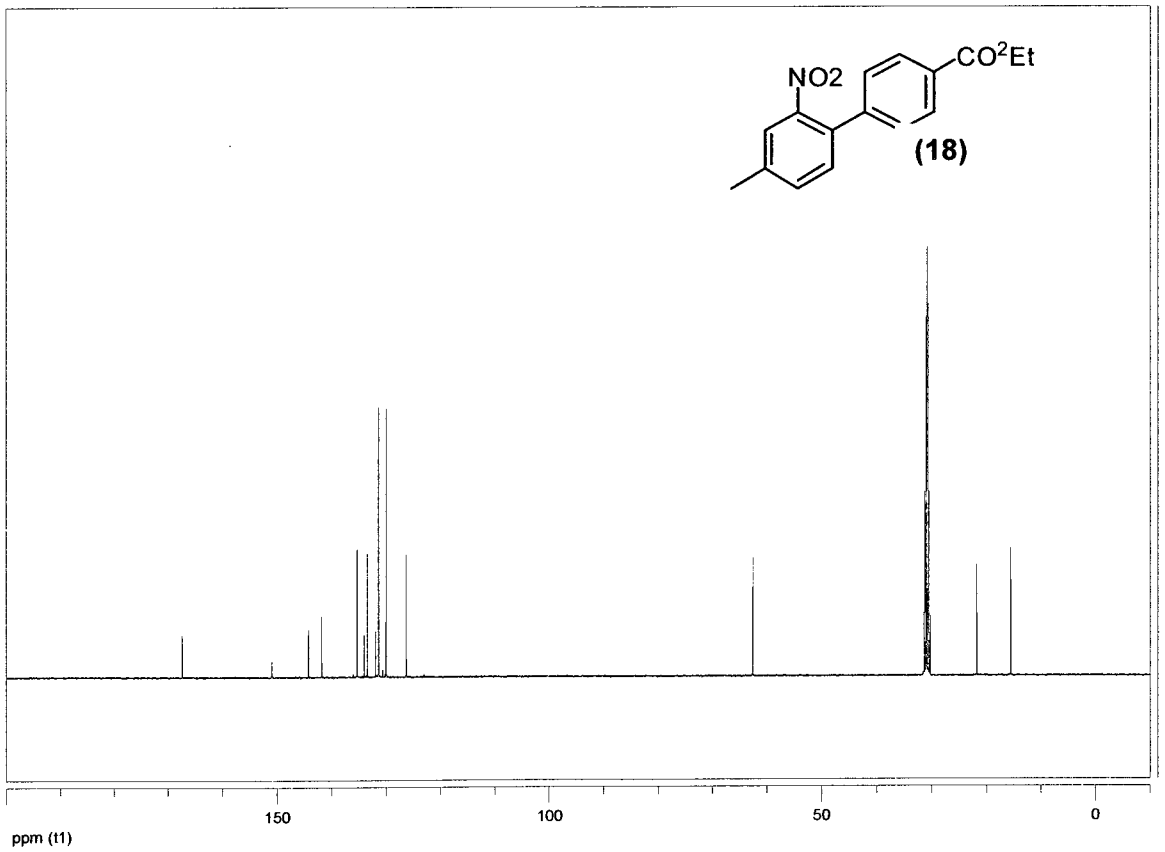
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CO2Et
(18)
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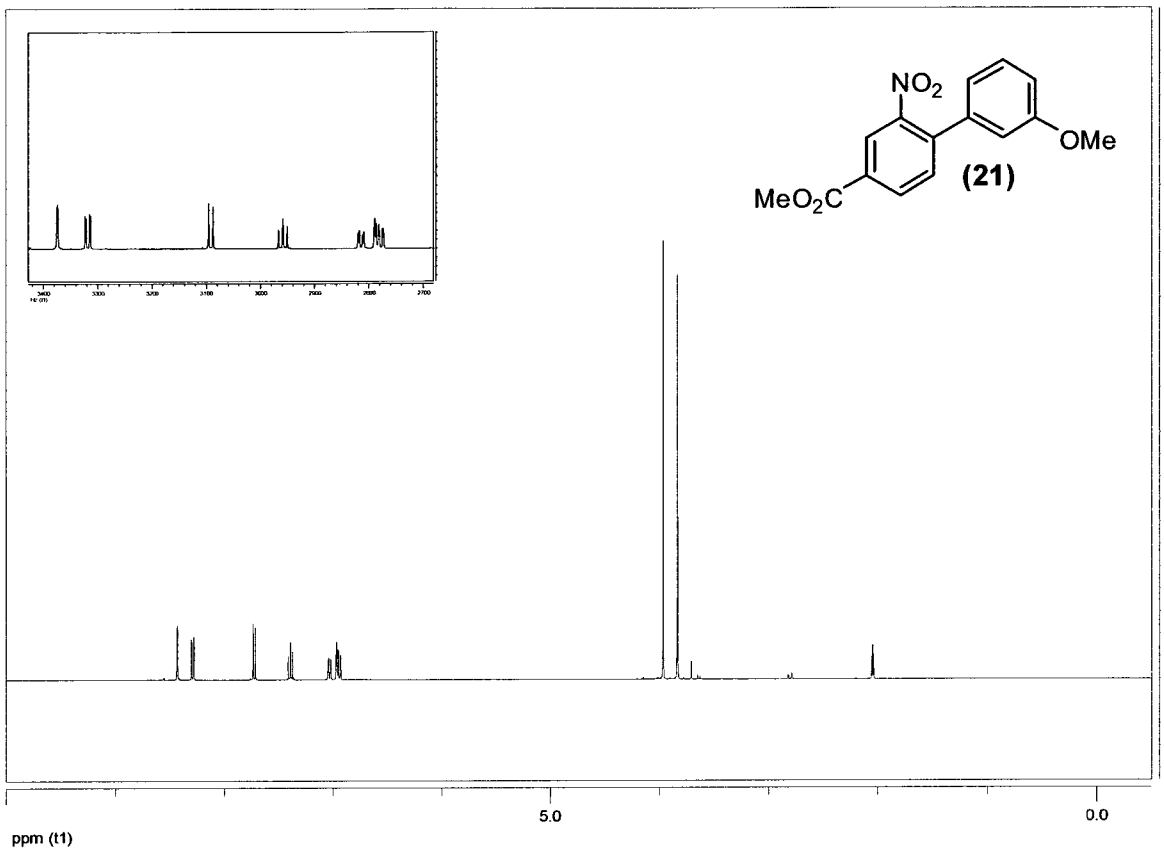
ppm (t1)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MeO2C
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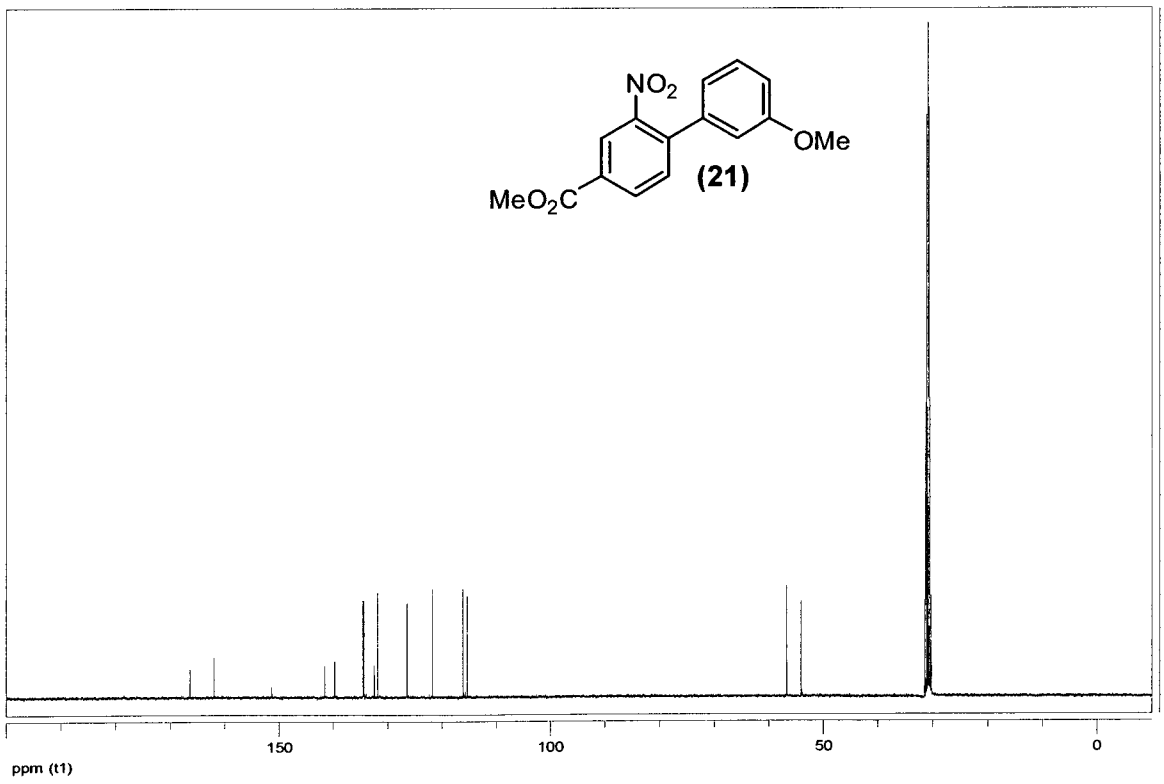
ppm (t1)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OMe
MeO2C
(21)
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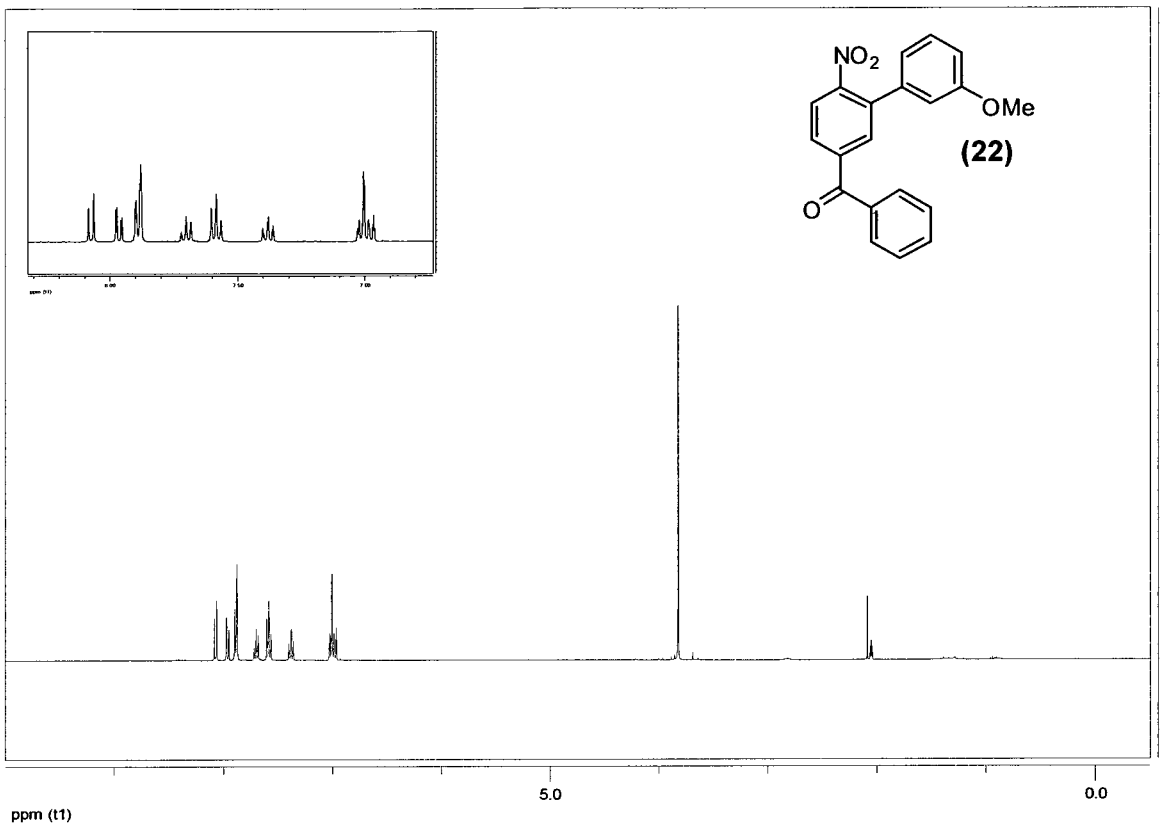
ppm (t1)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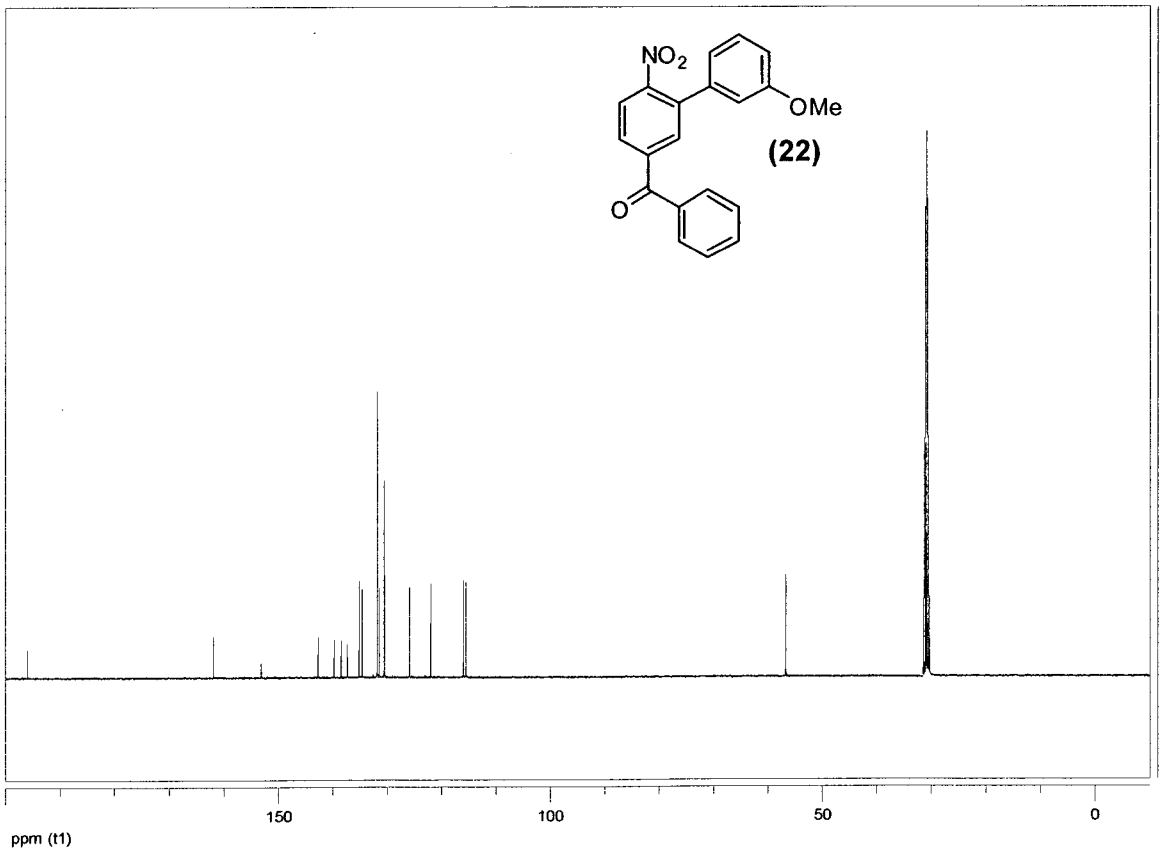
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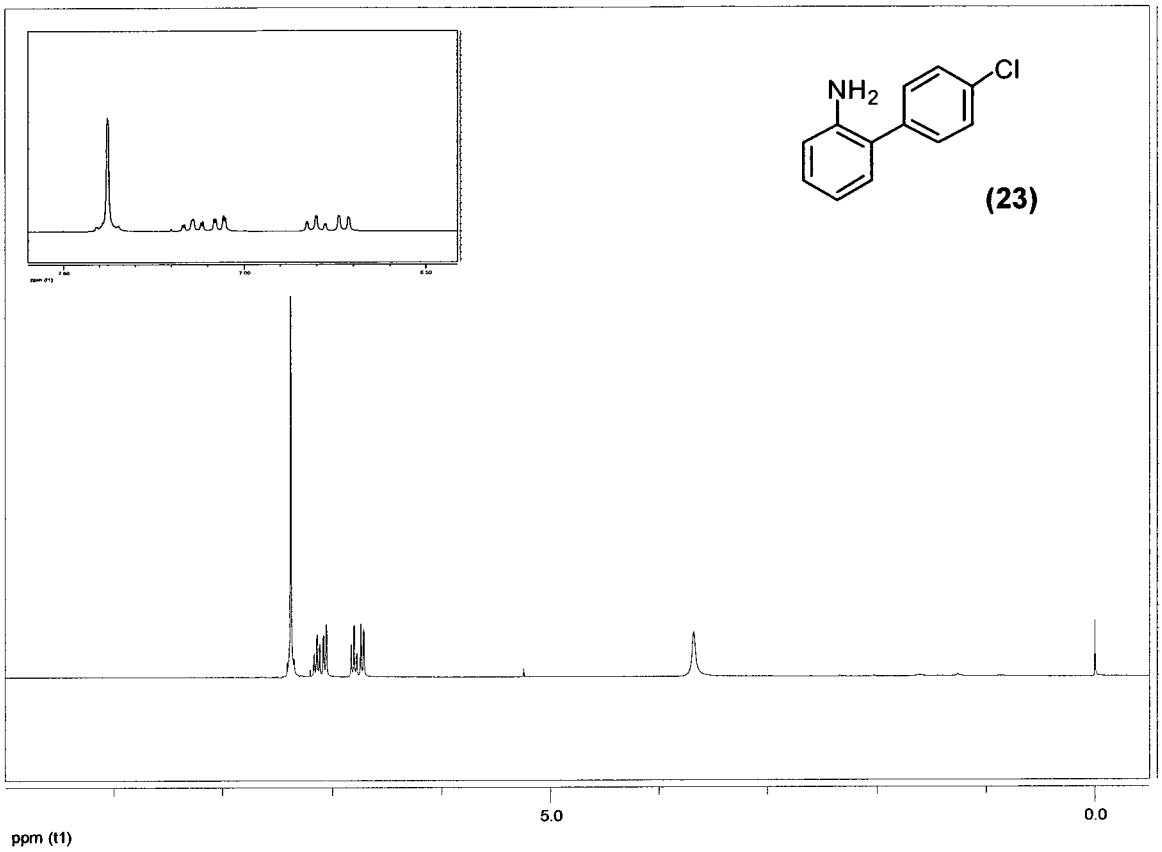
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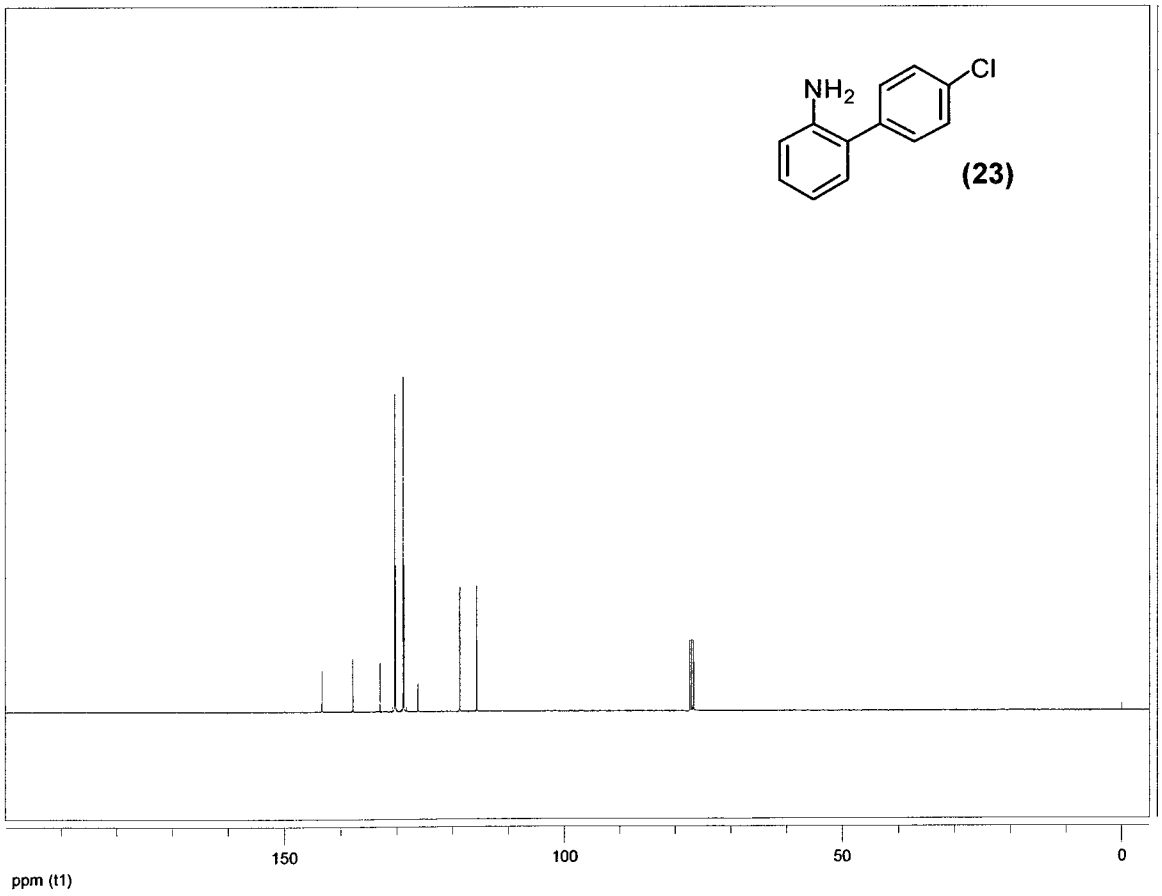
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Cl
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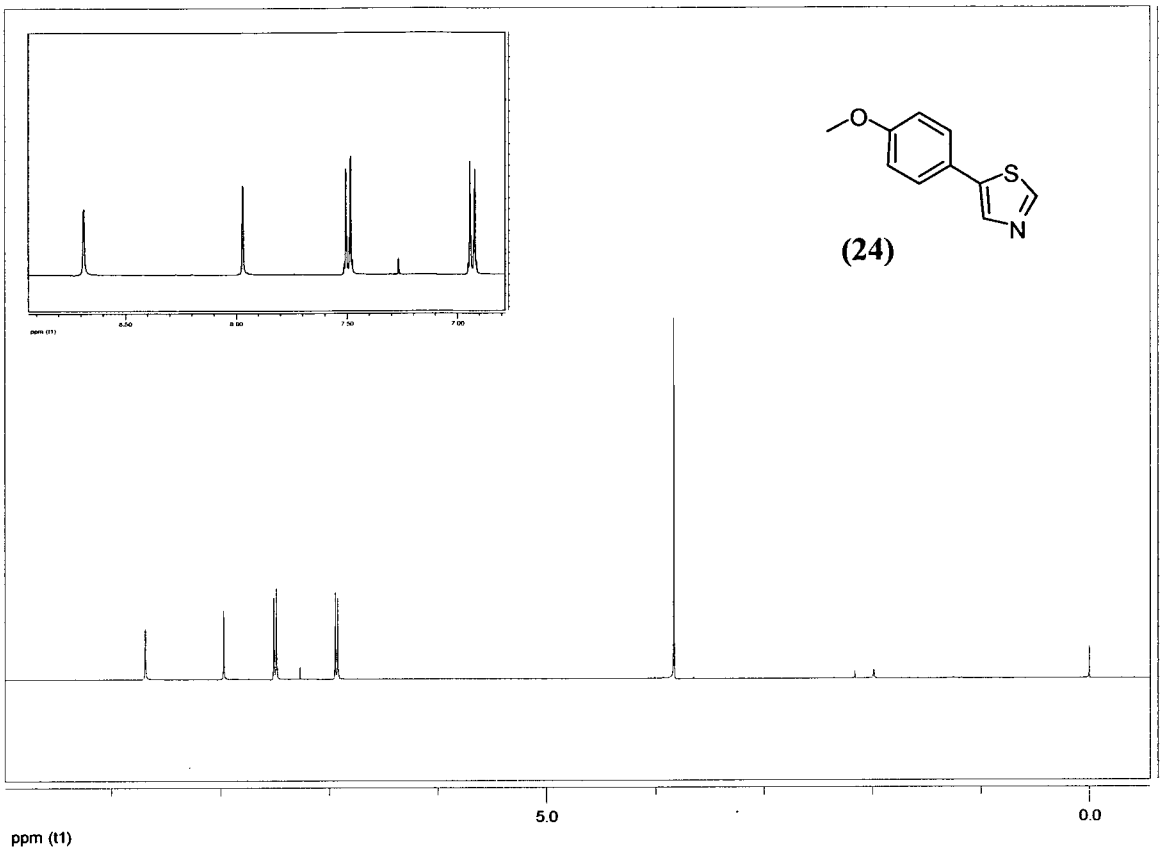
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S
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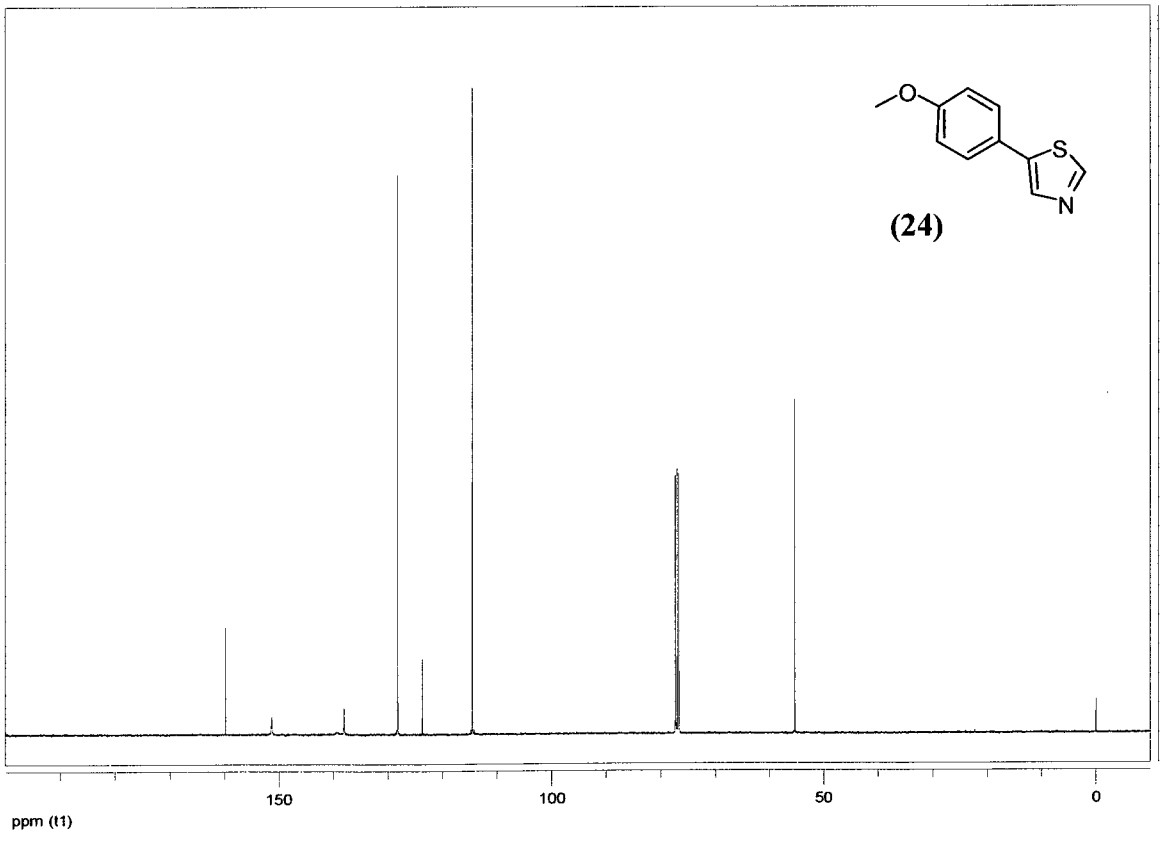
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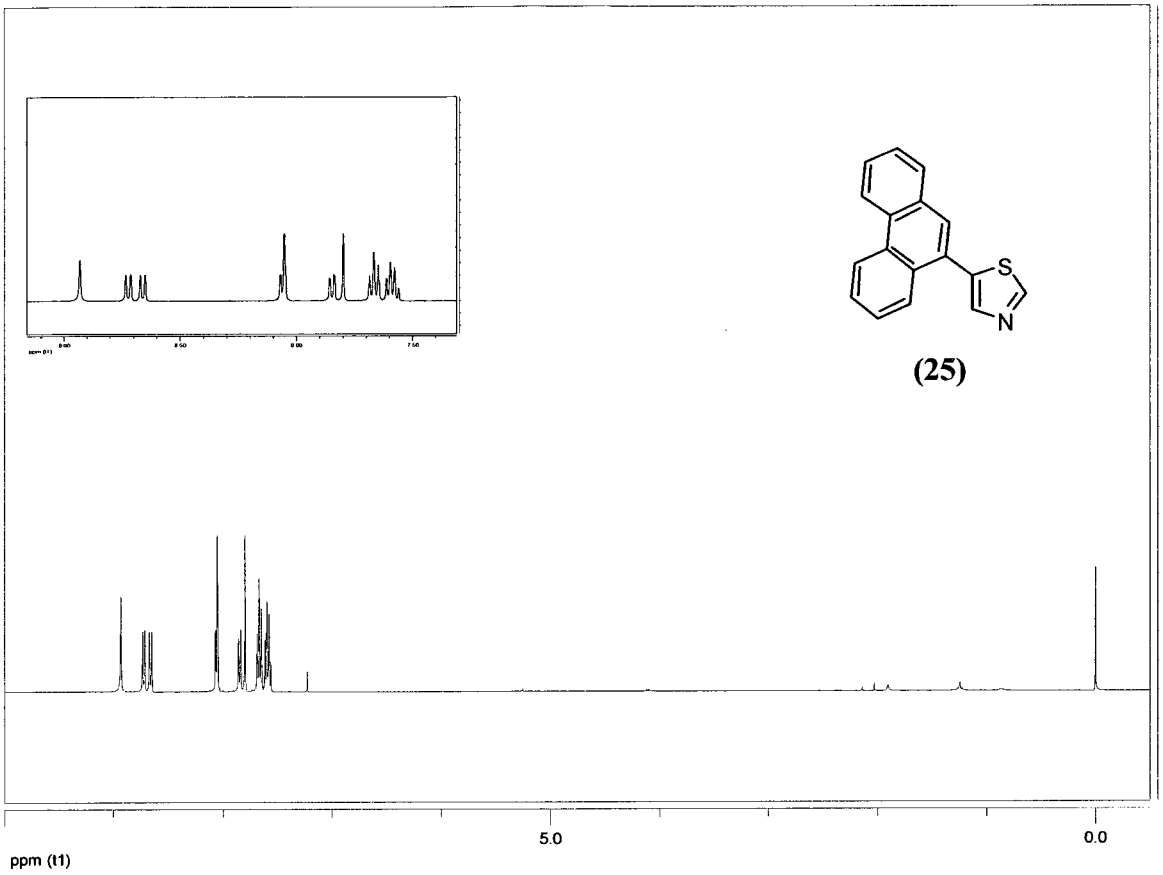
ppm (t1)



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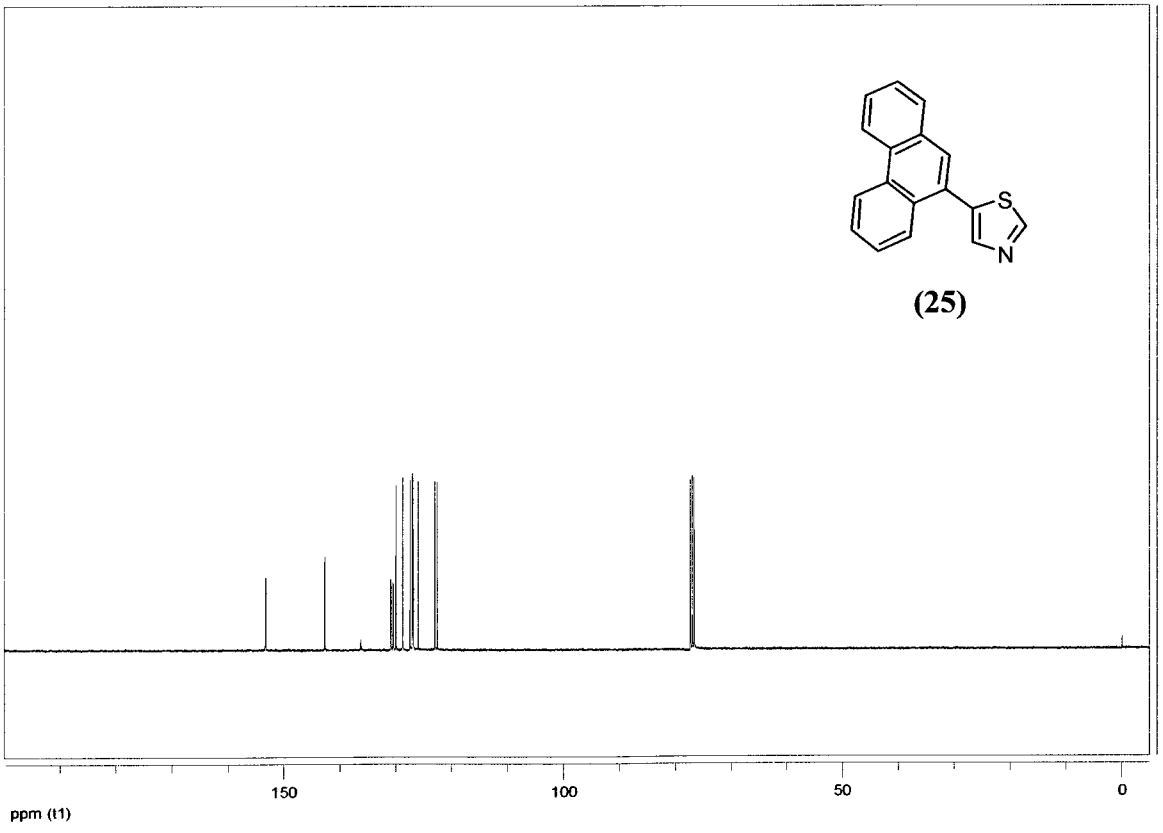

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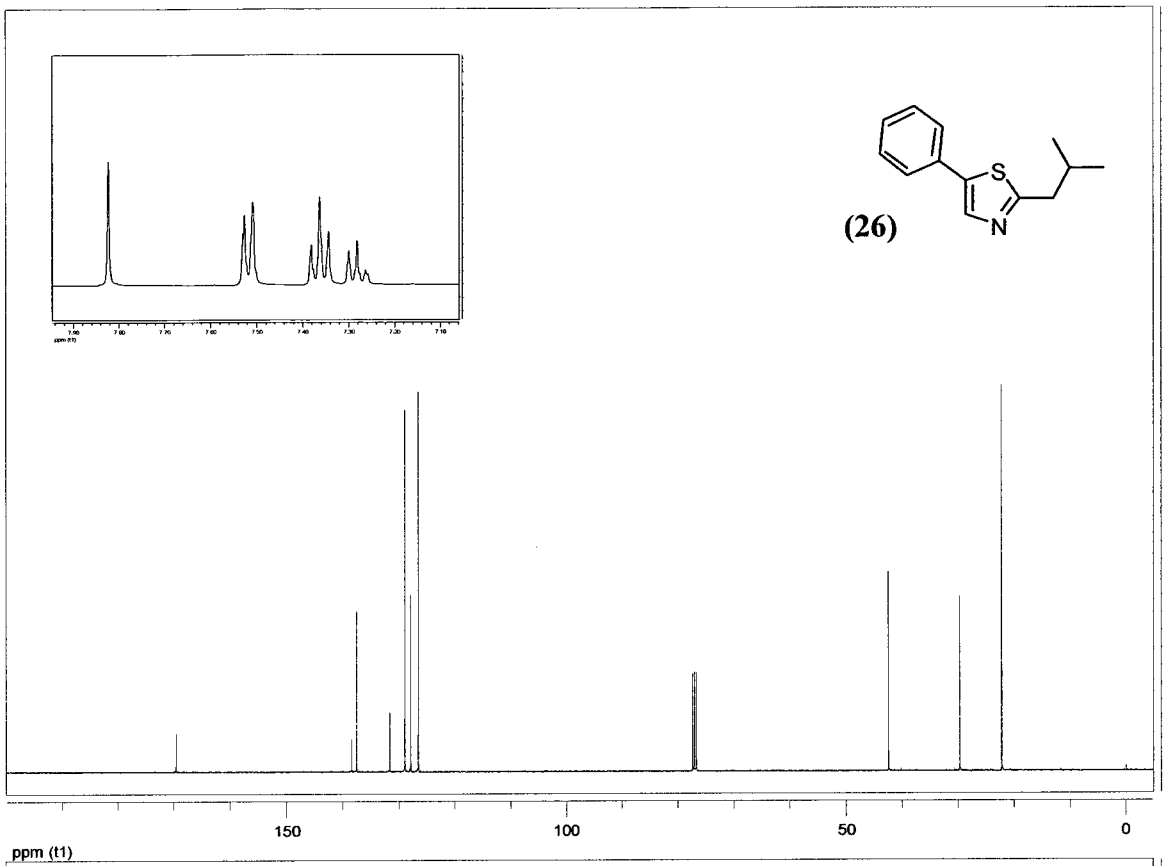
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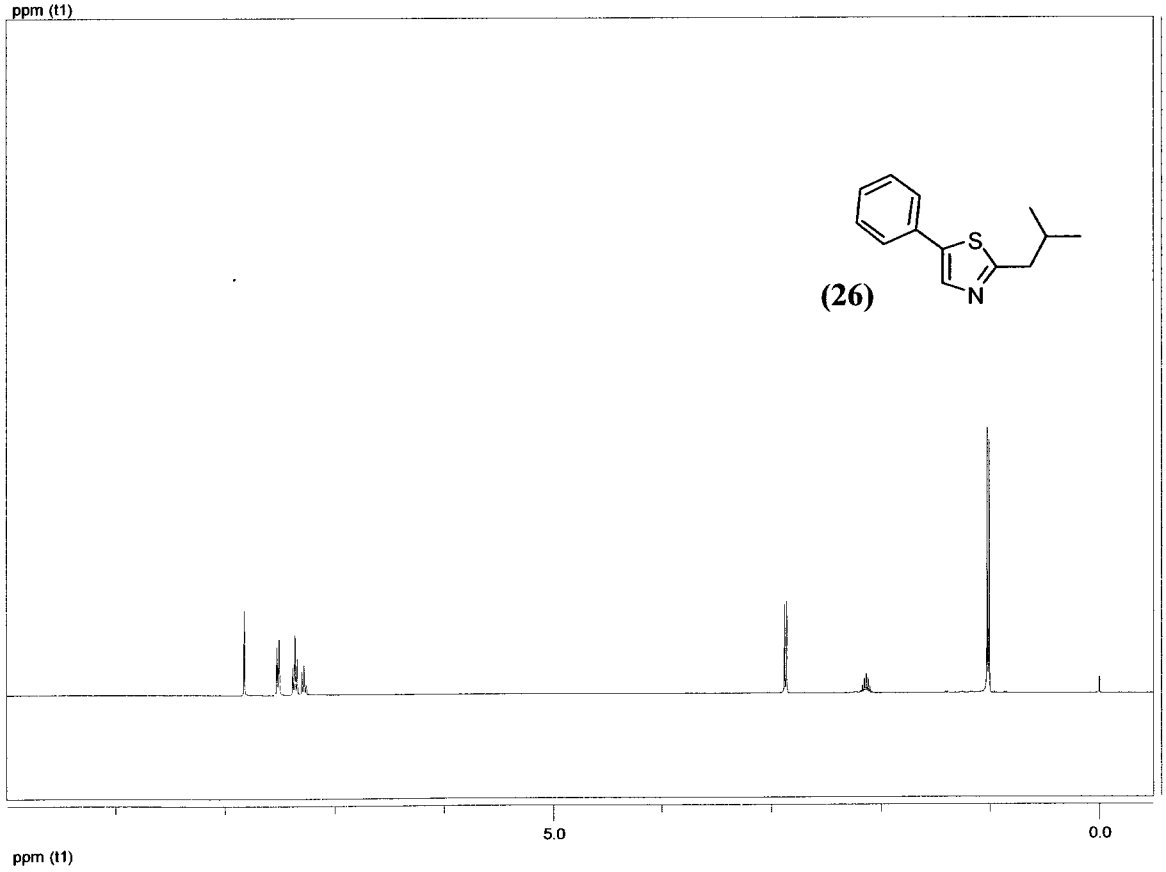
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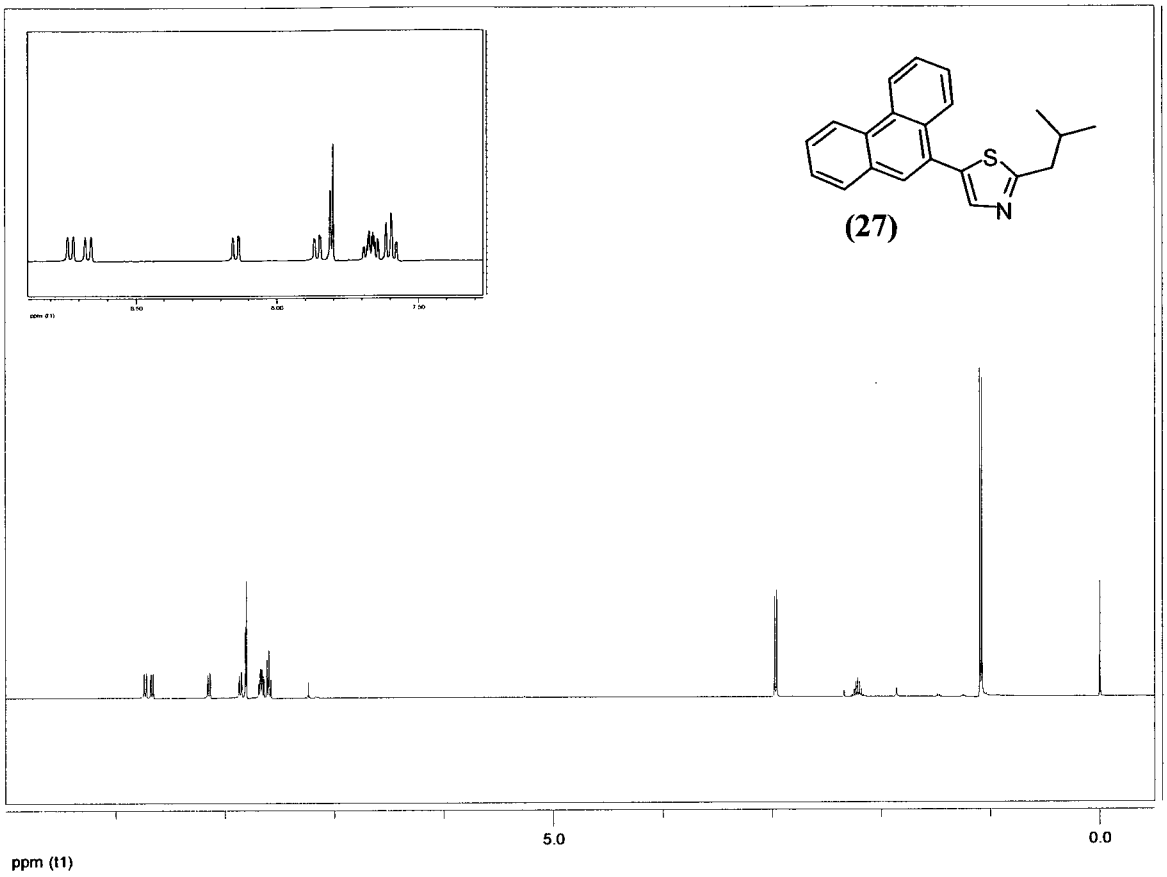
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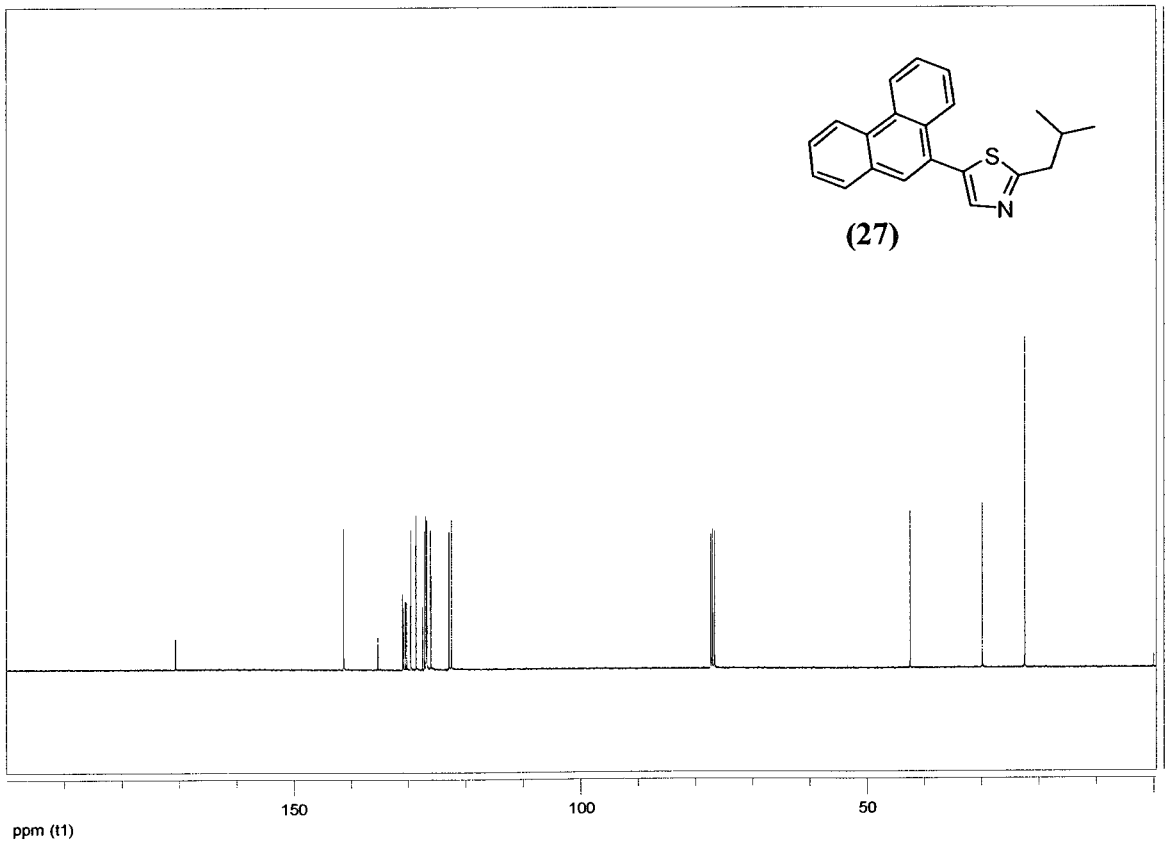
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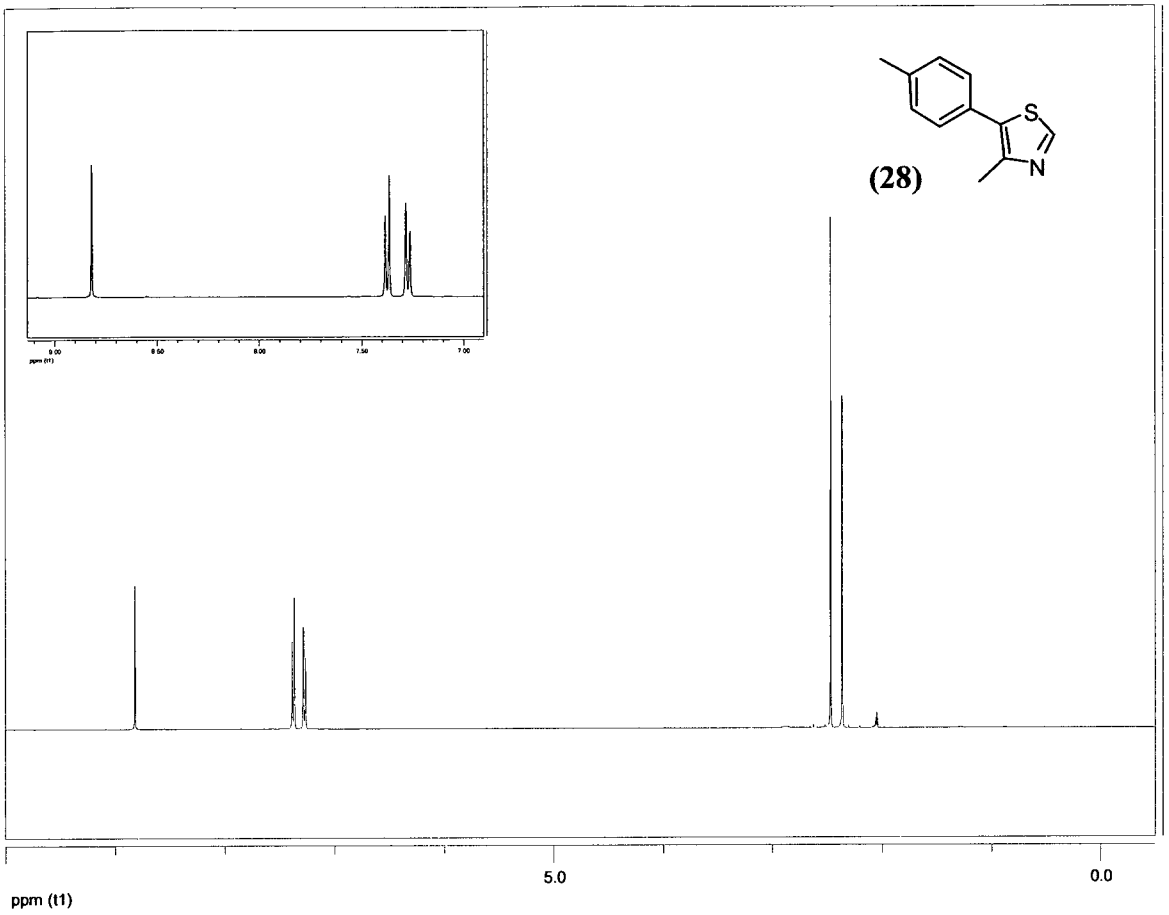
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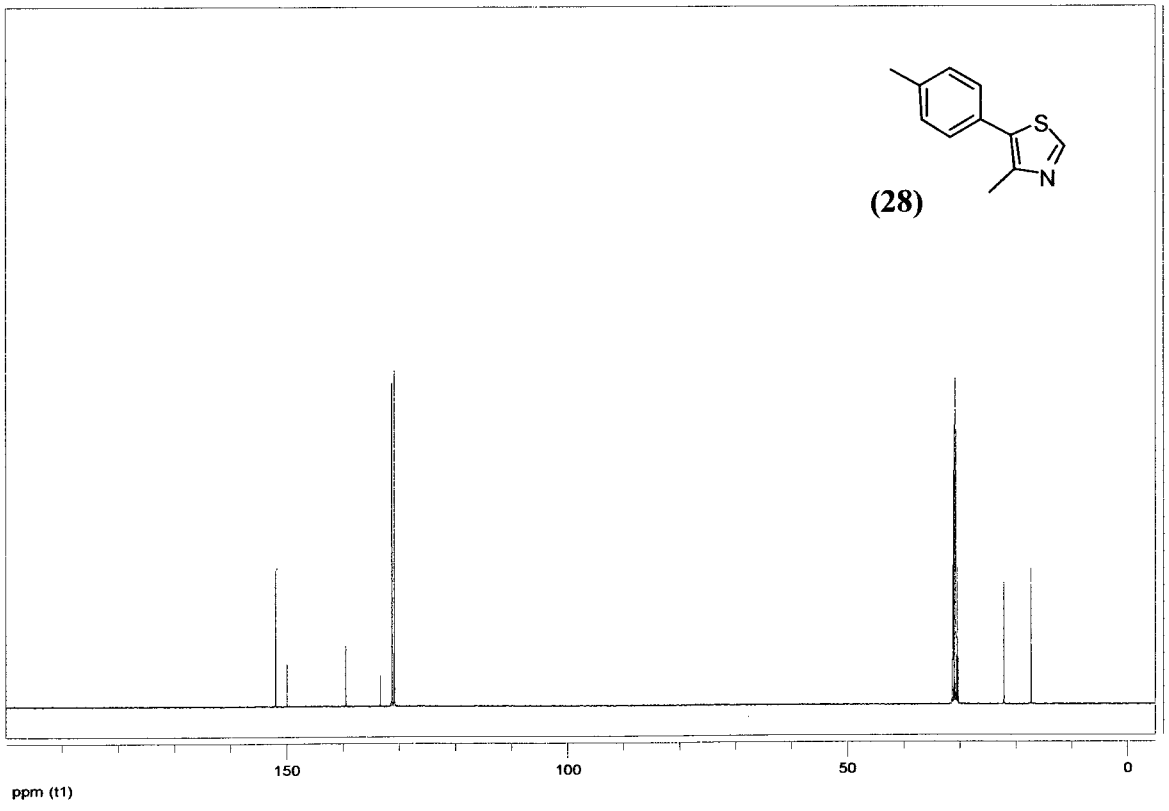
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(28)
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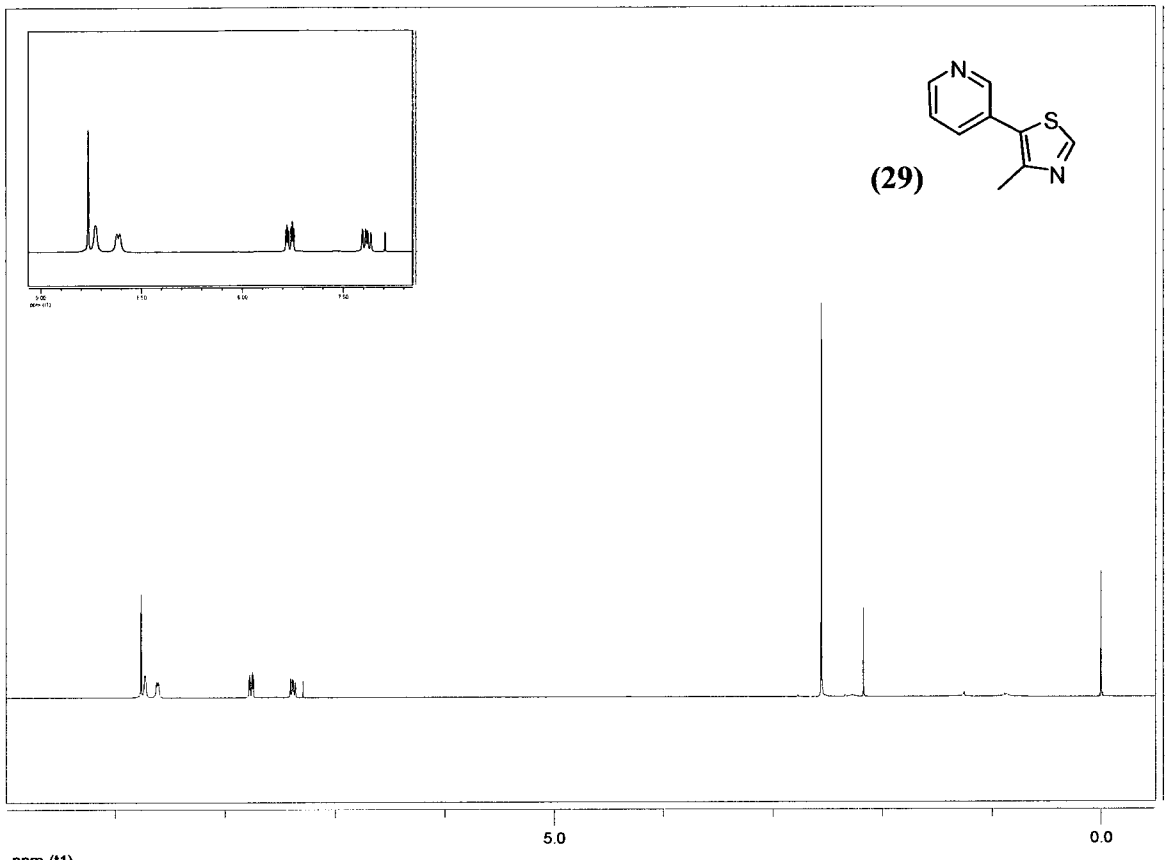
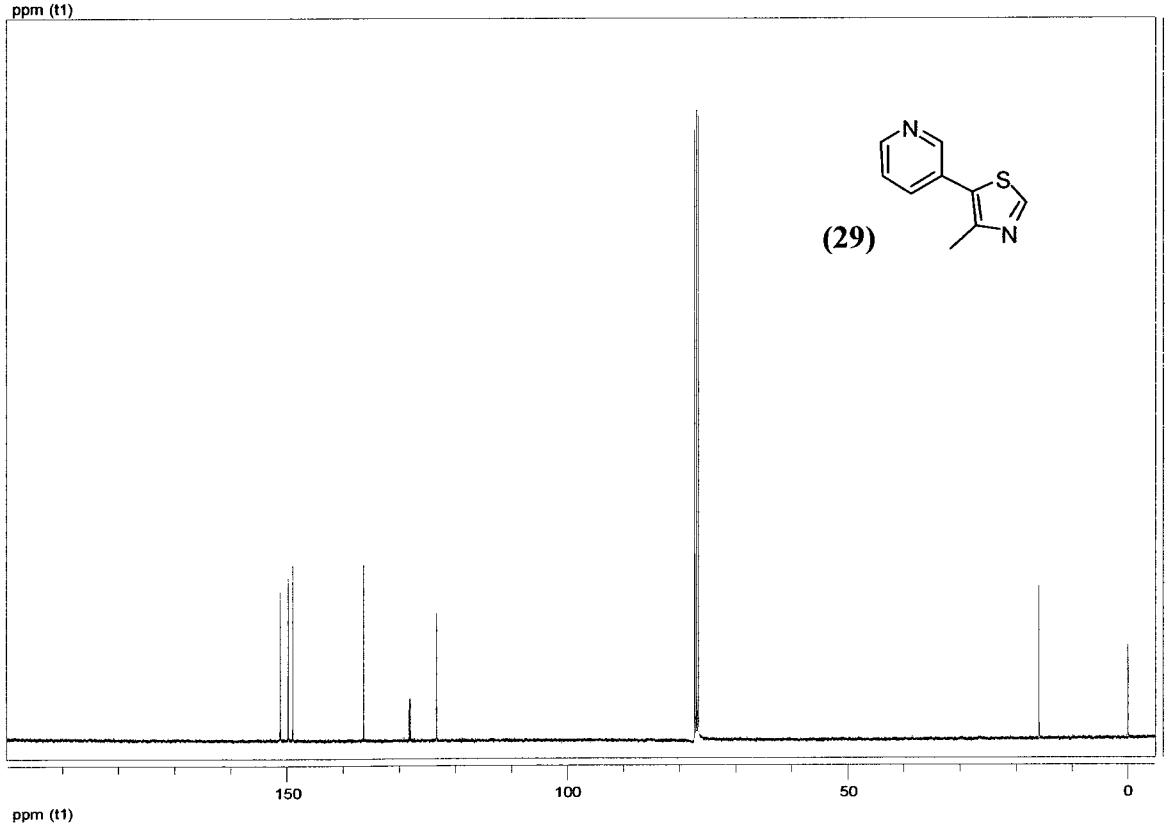
ppm (t1)


(29)
5.0
0.0
ppm (t1)


(29)
150
100
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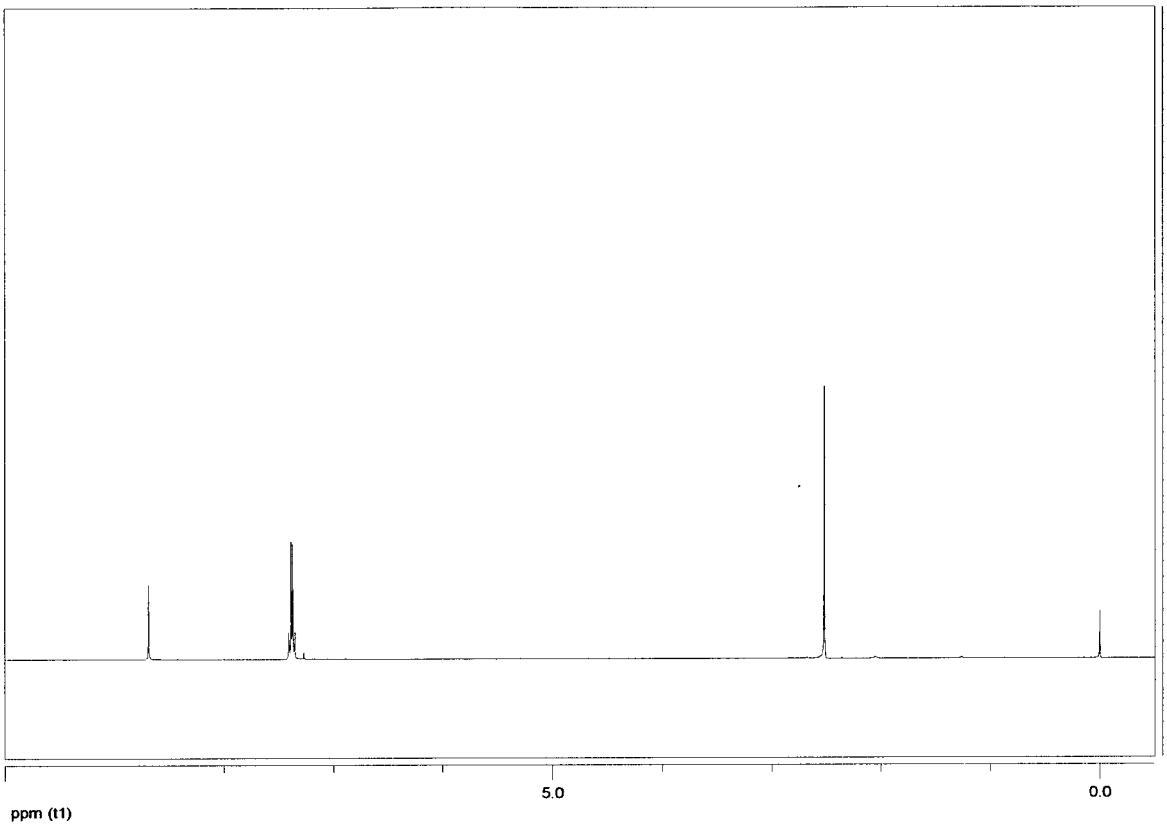
ppm (t1)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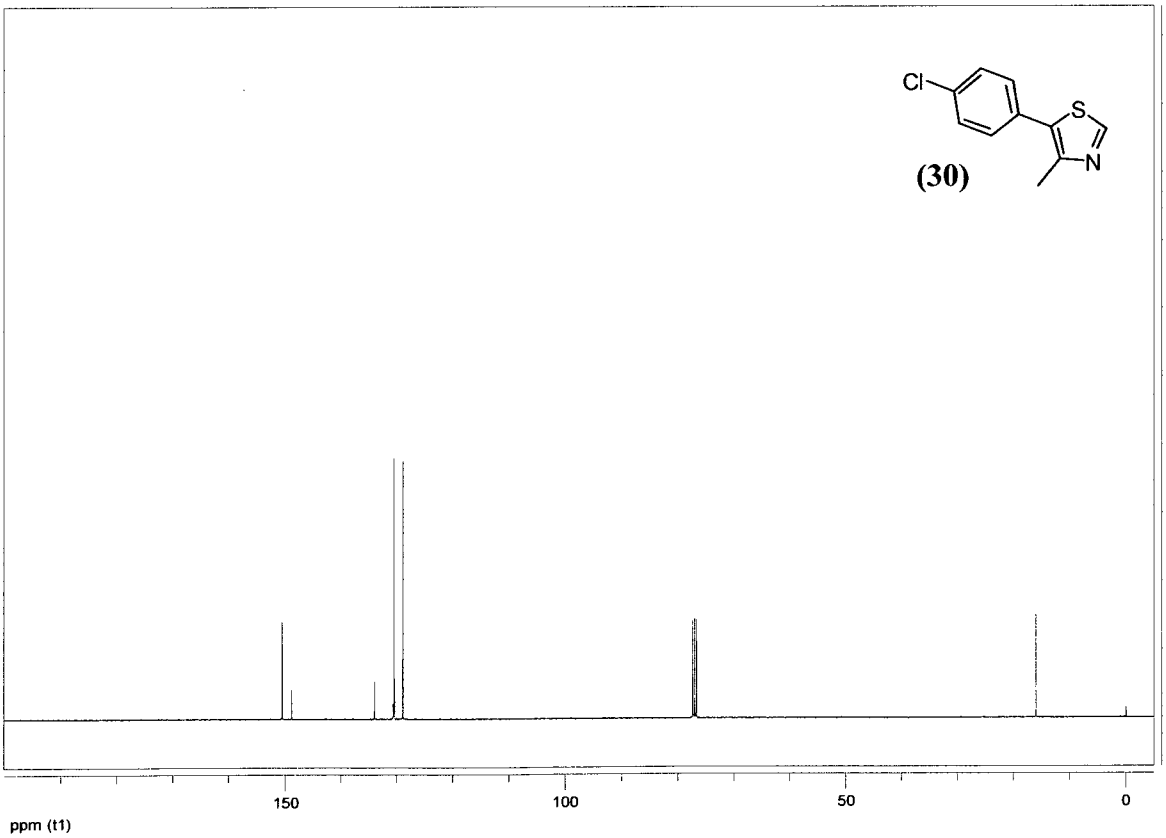
Cl
S
N
(30)
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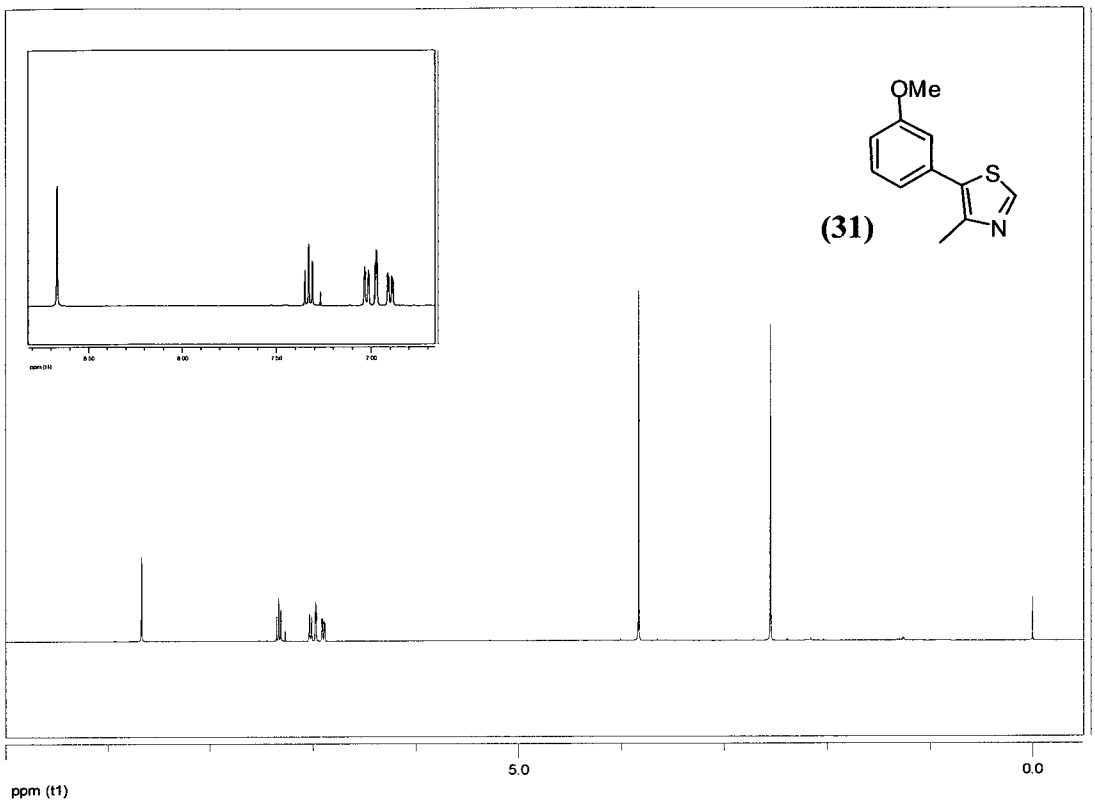
ppm (t1)


OMe
S
N
(31)
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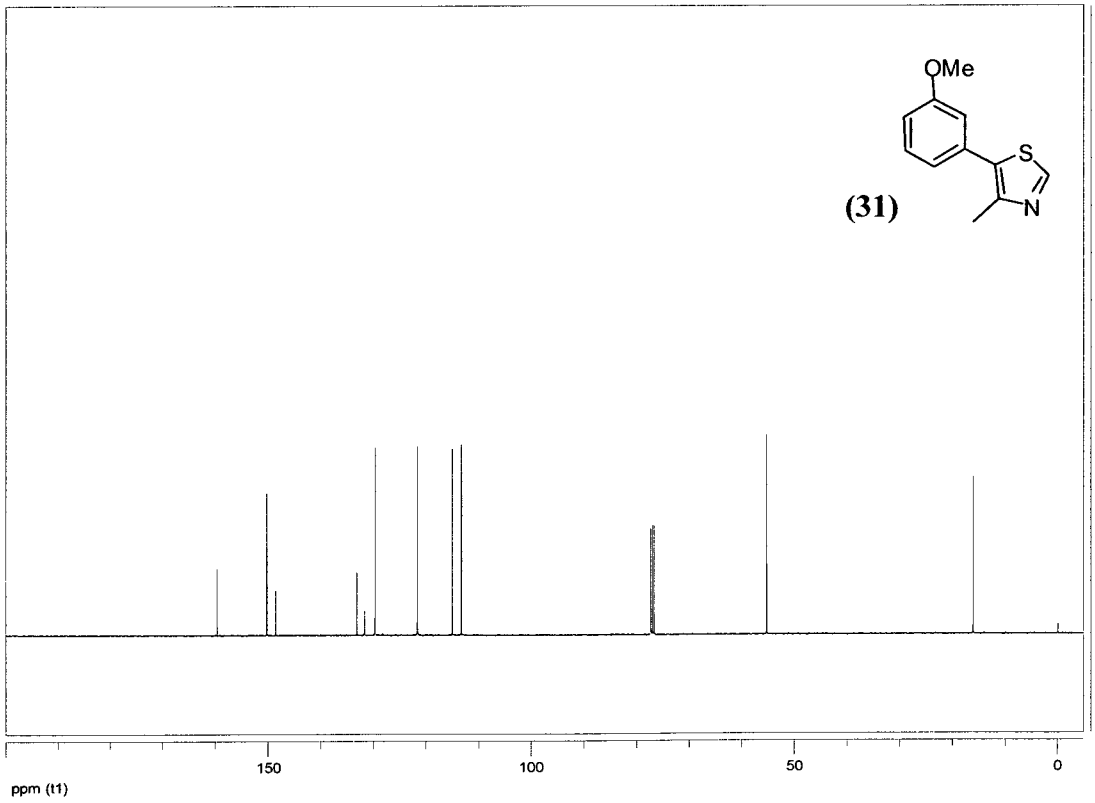
ppm (t1)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(31)
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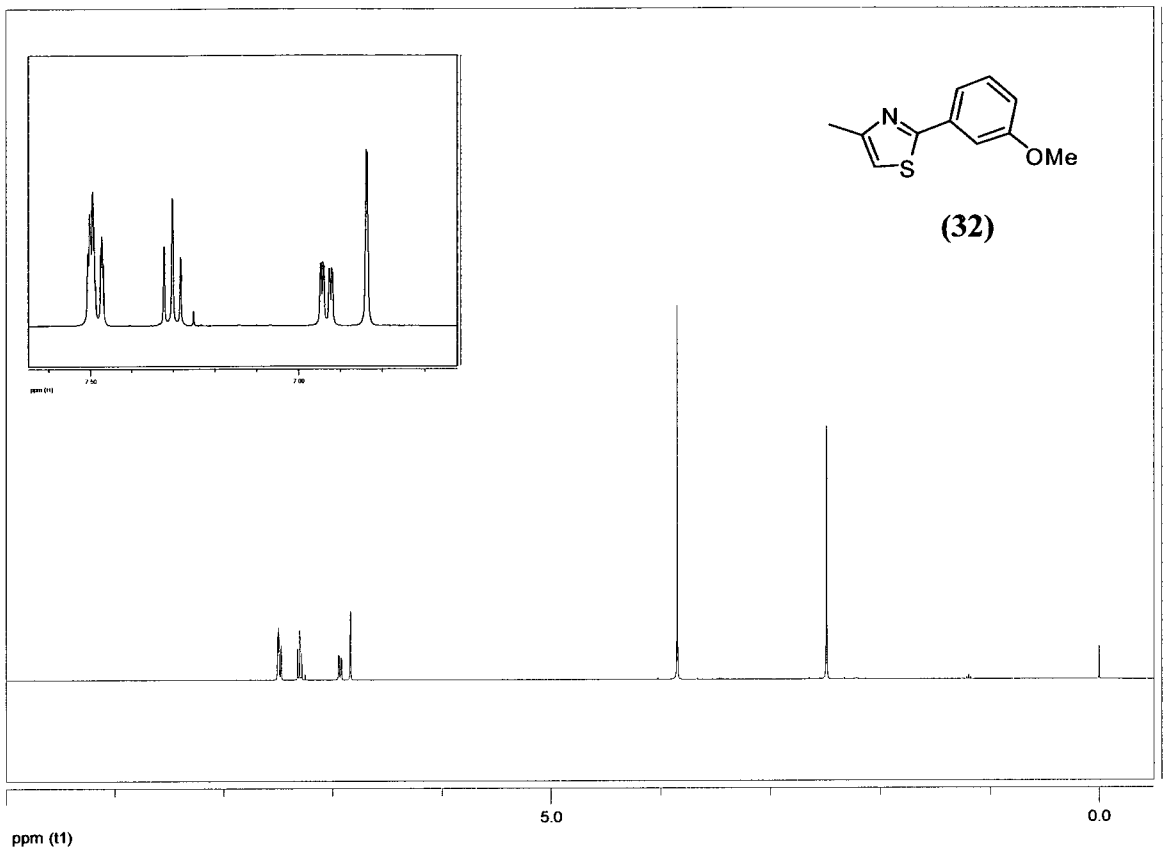
ppm (t1)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S
OMe
(32)
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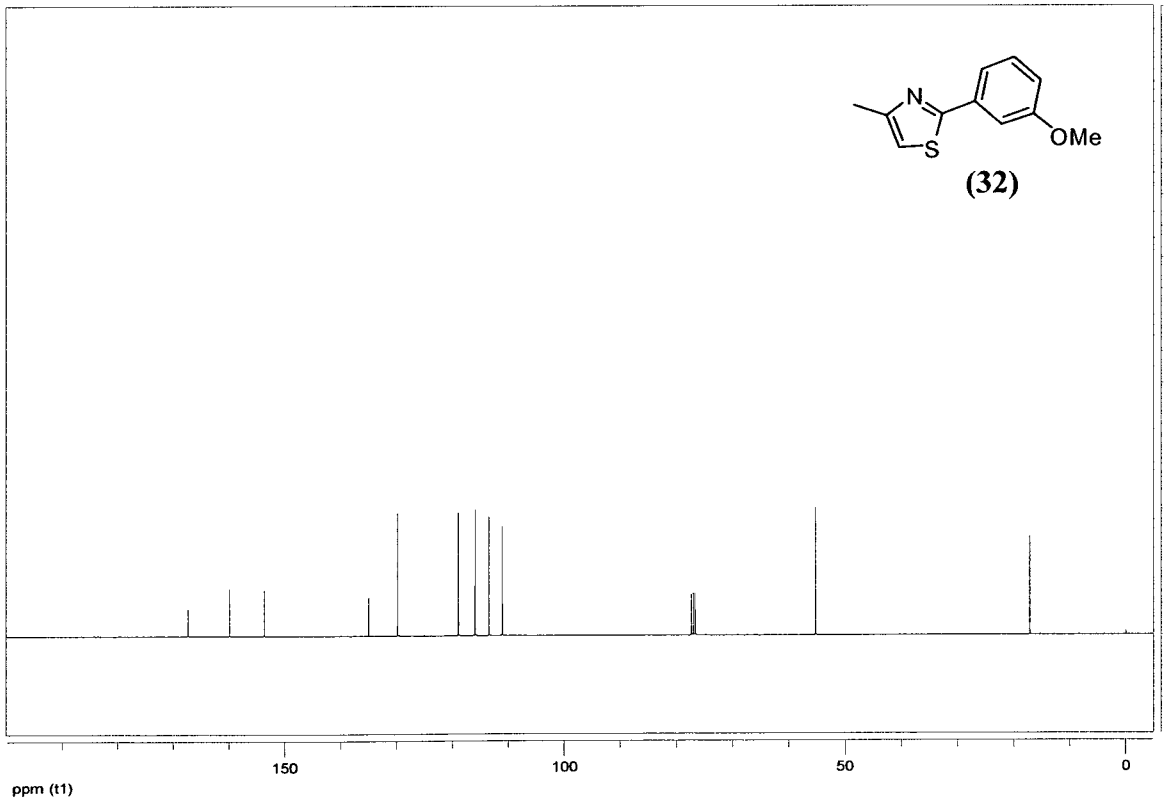
ppm (t1)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OMe
(32)
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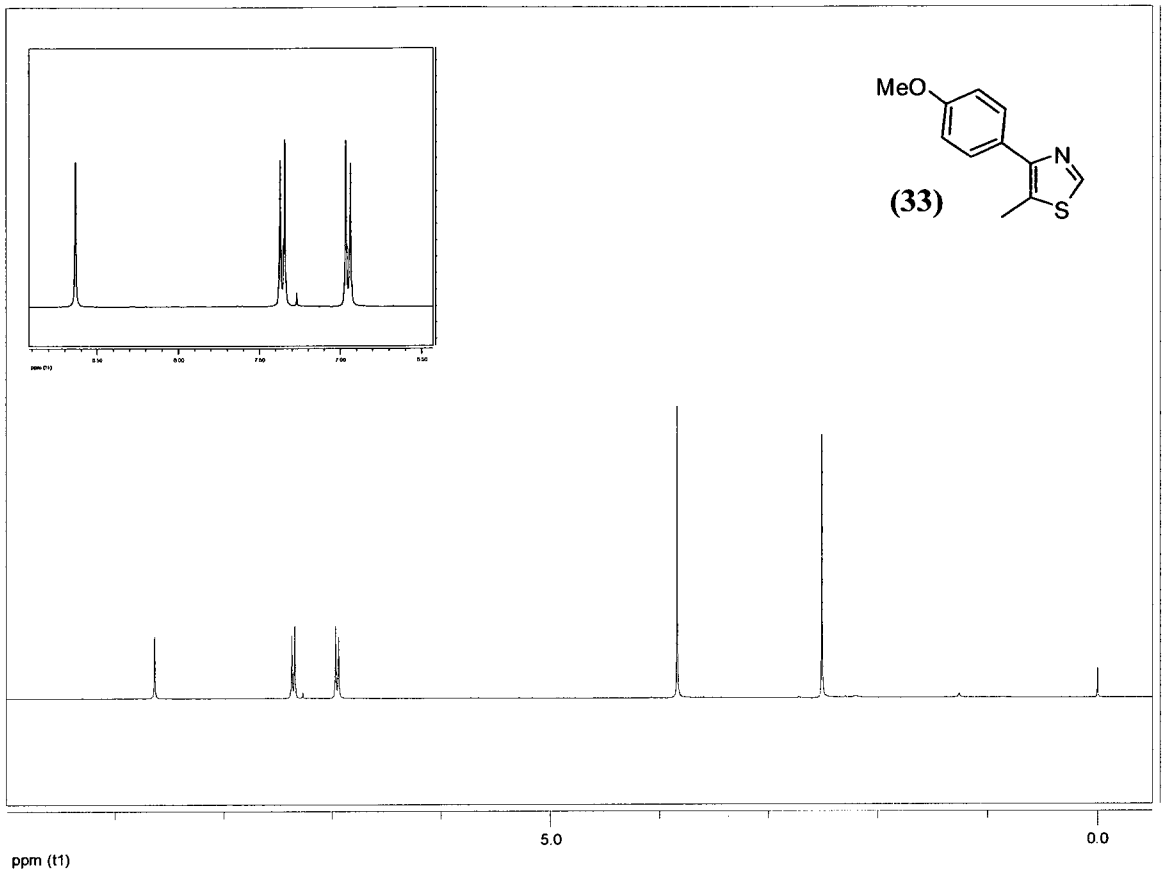
ppm (t1)


MeO
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S
(33)
5.0
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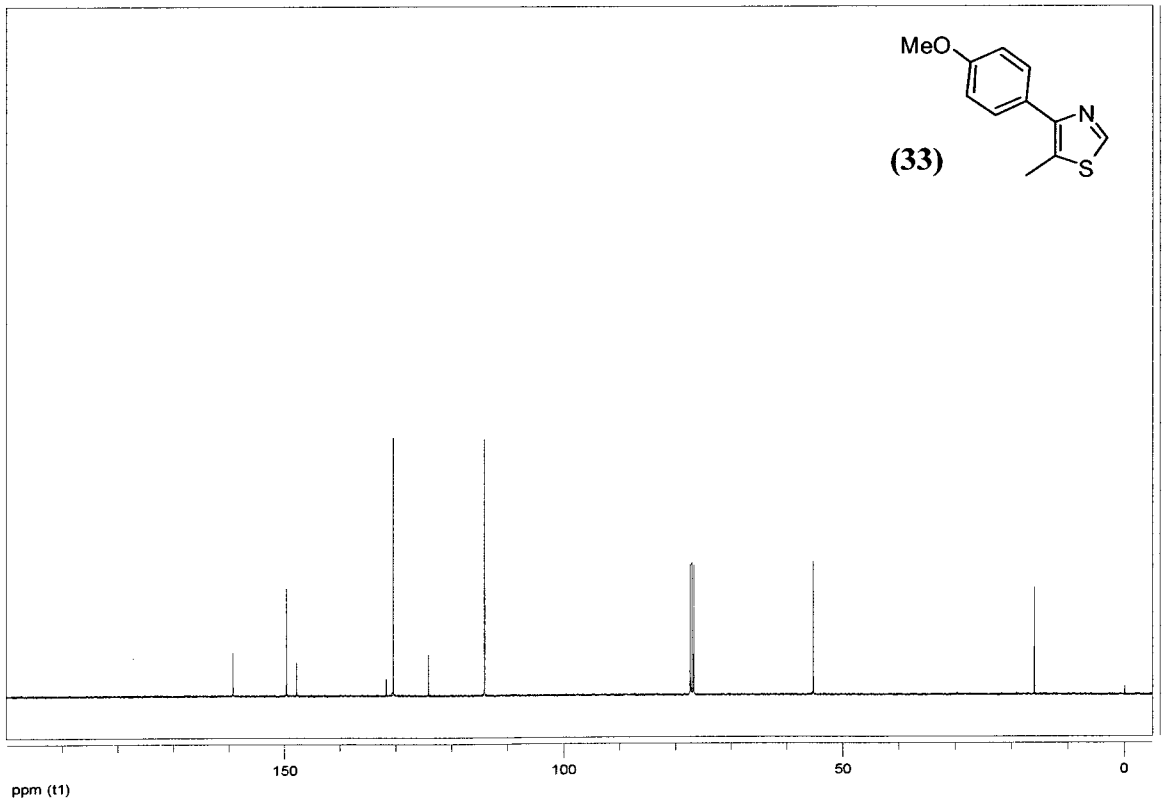
ppm (t1)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(33)
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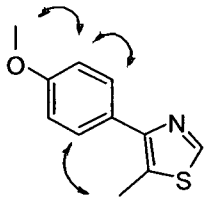
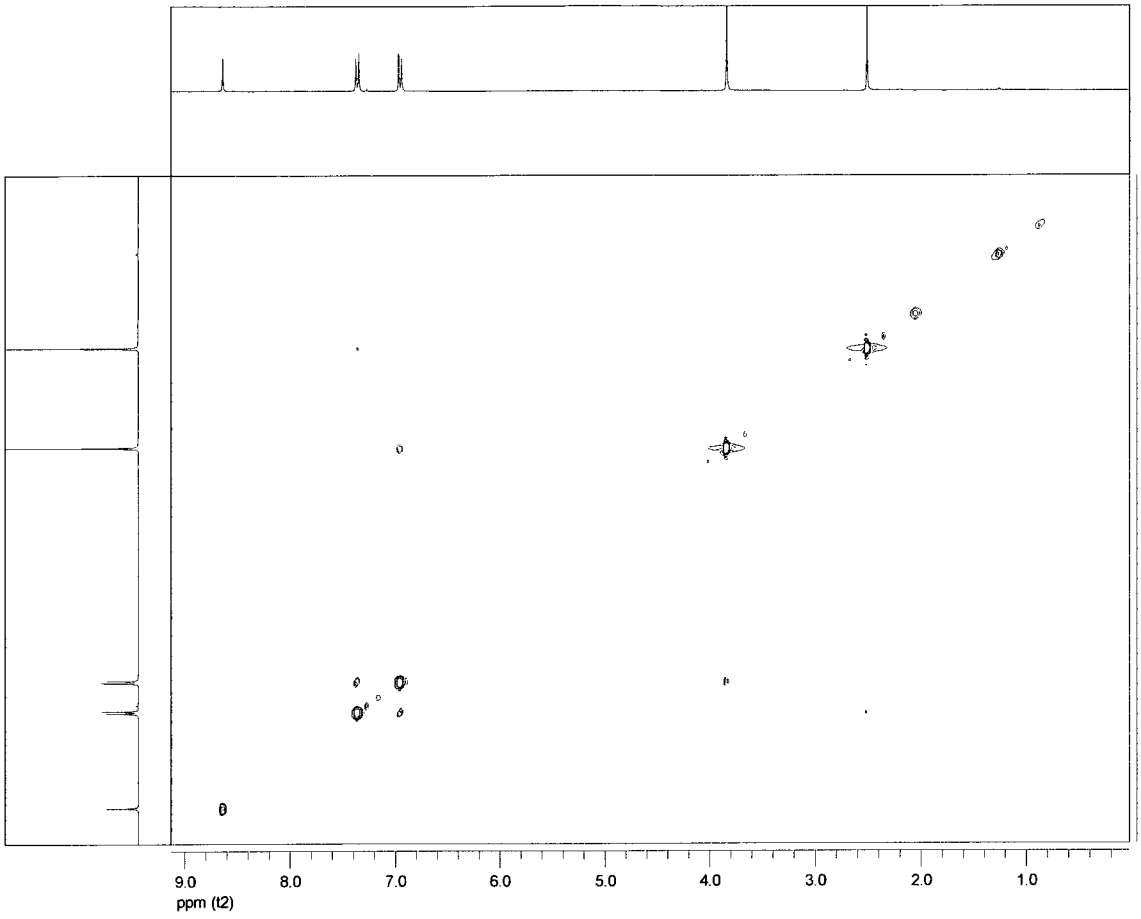
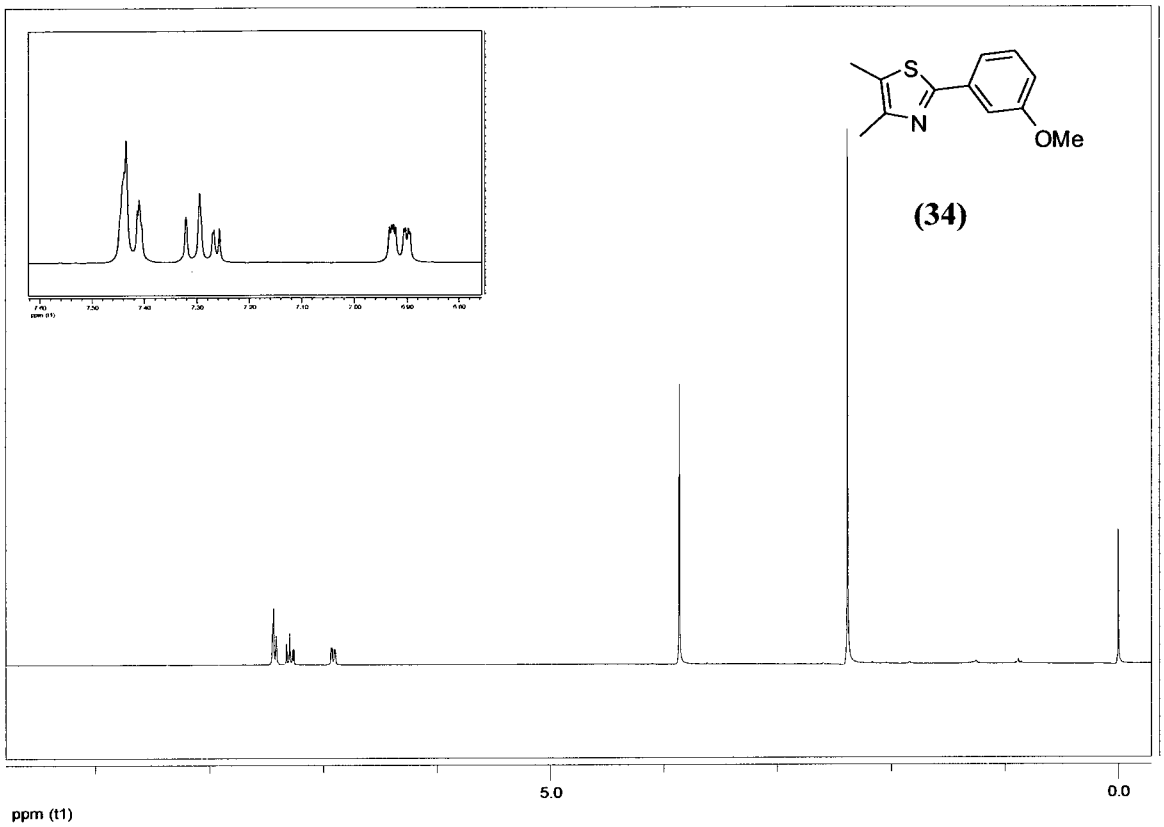
ppm (t1)



(33)

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OMe
(34)
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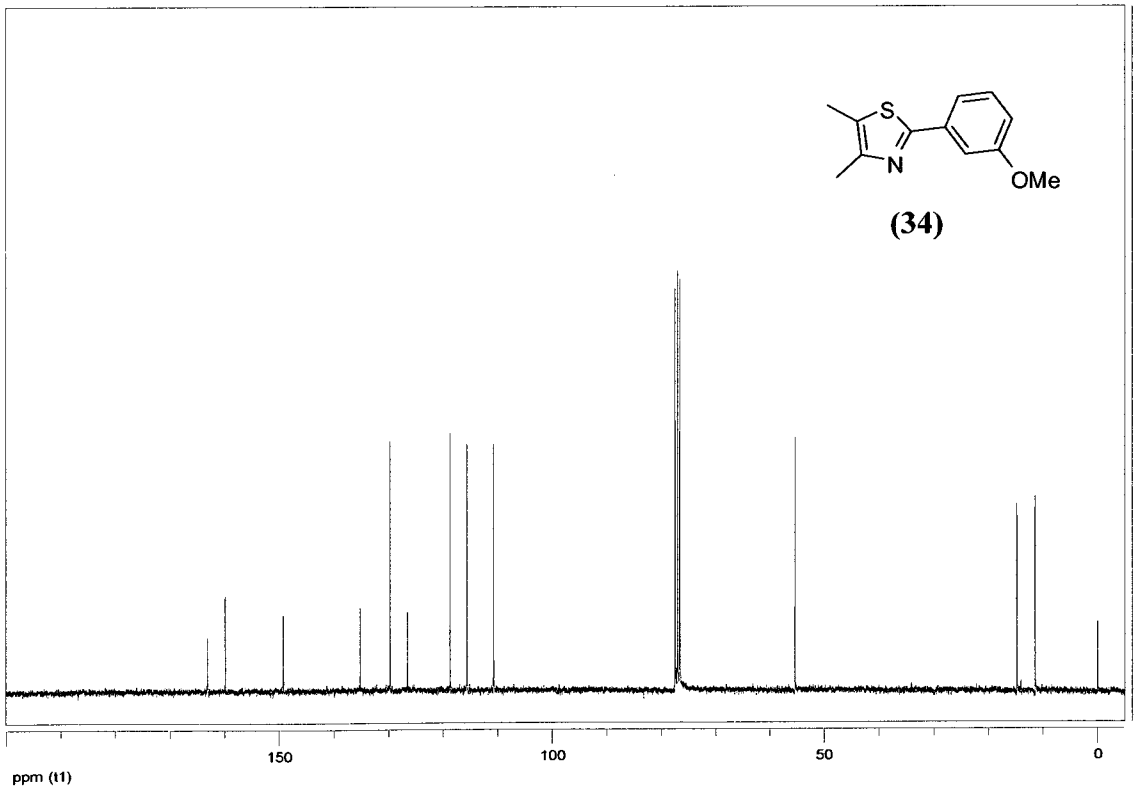
ppm (t1)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OMe
(34)
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100
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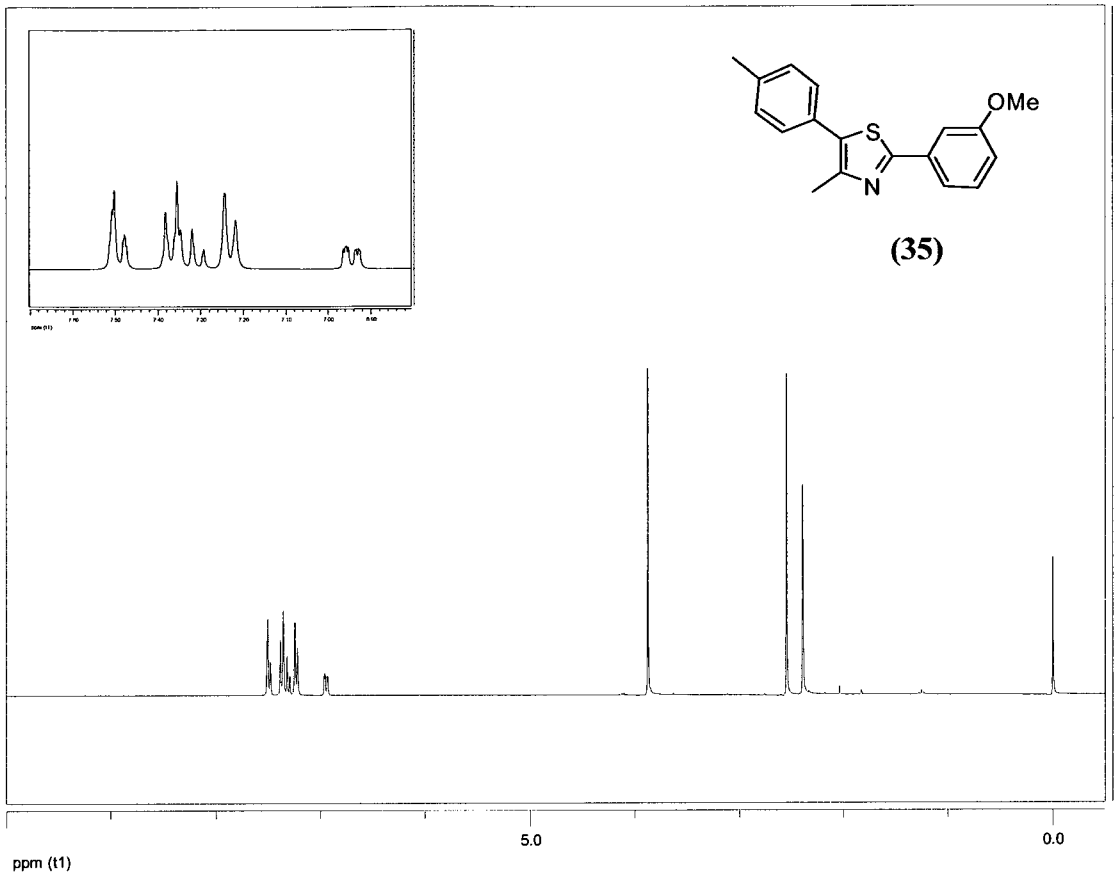
ppm (t1)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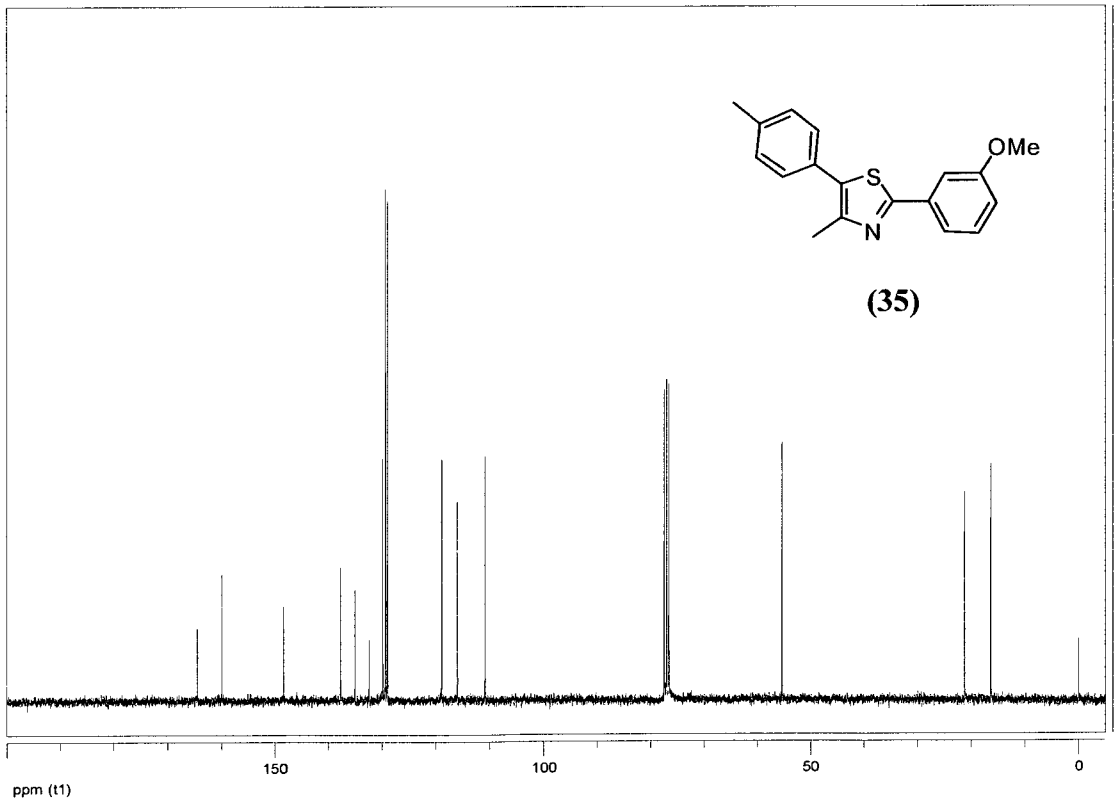
(35)
5.0
0.0
ppm (t1)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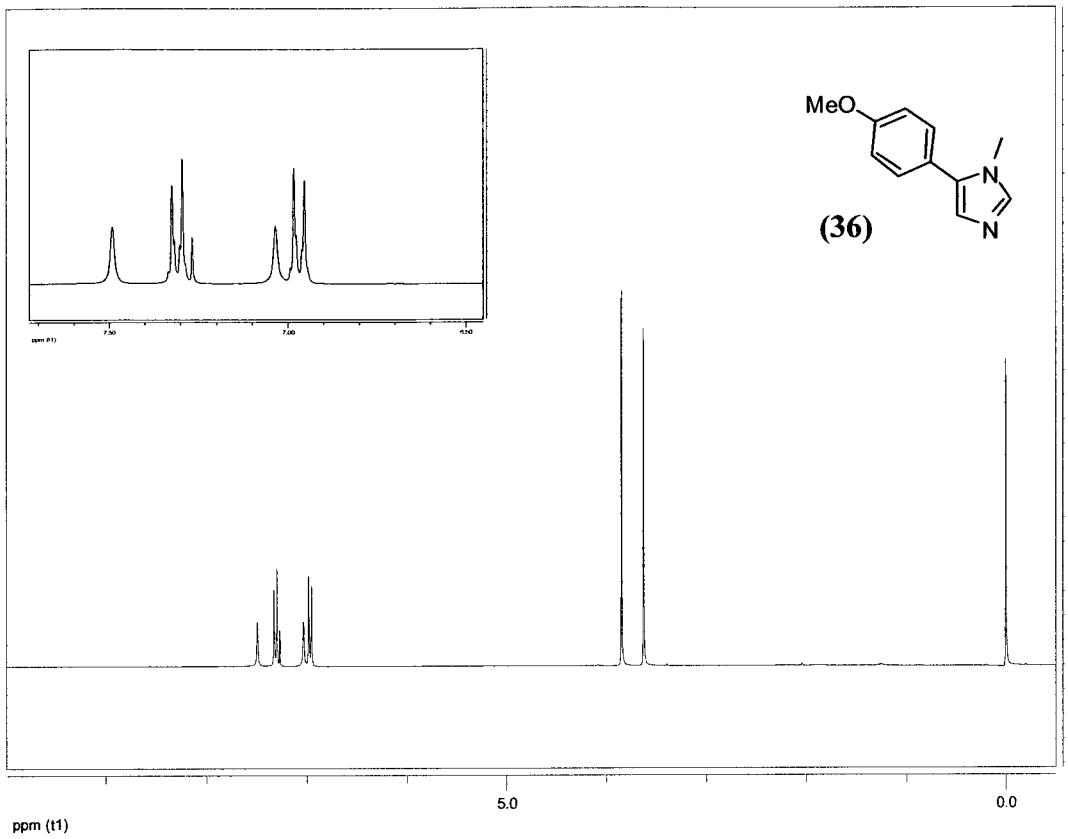
N
(35)
150
100
50
0
ppm (t1)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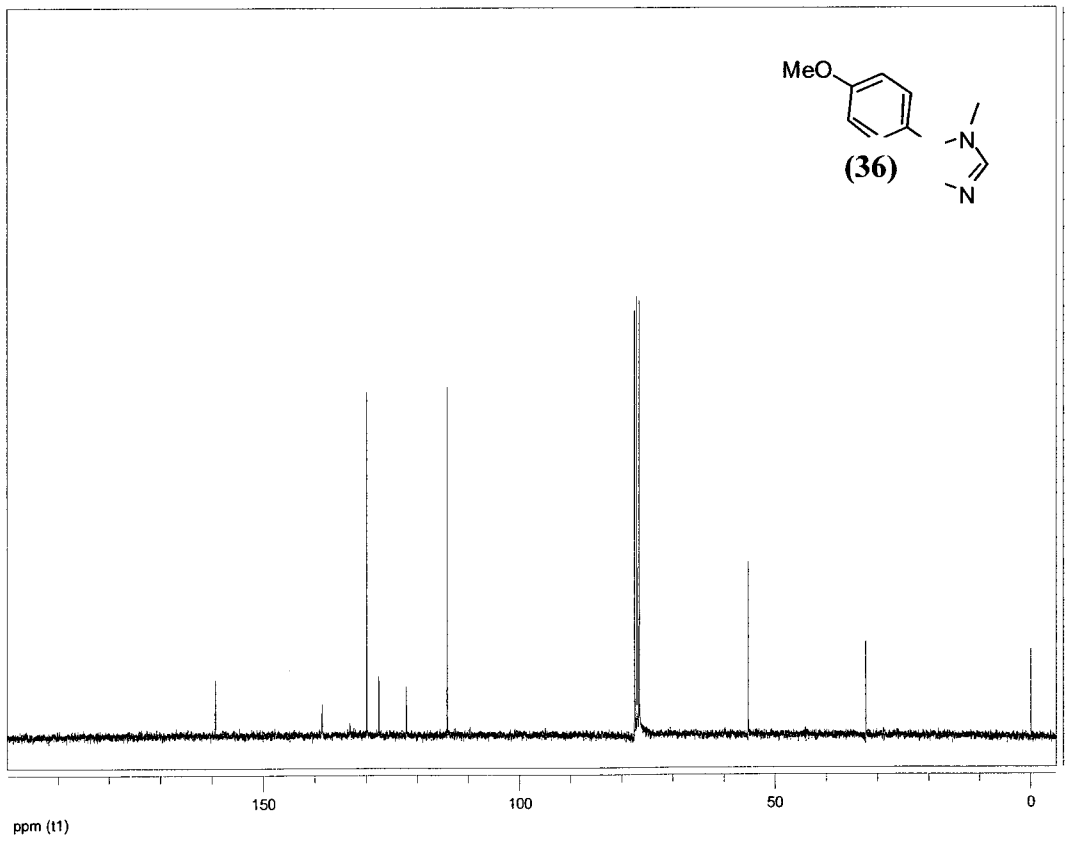
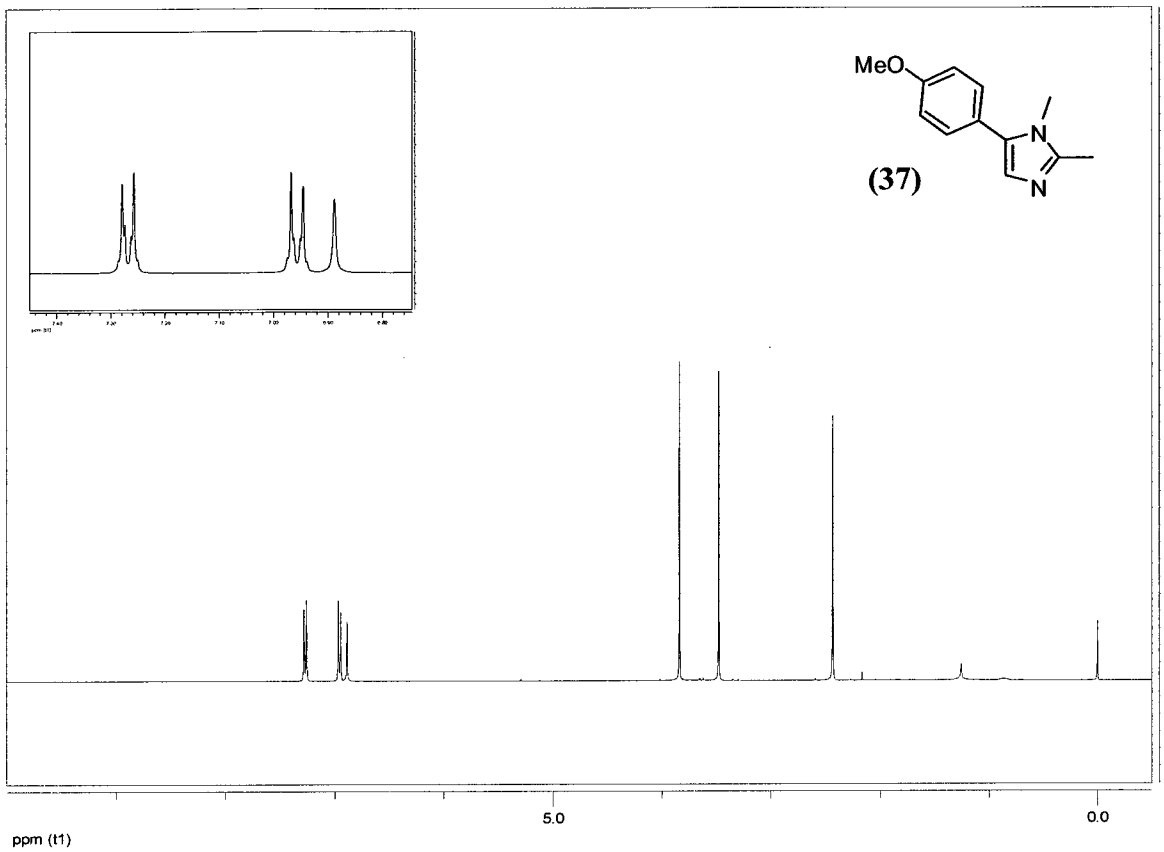
N
(36)
5.0
0.0
ppm (t1)


MeO
N
N
(36)
150
100
50
0
ppm (t1)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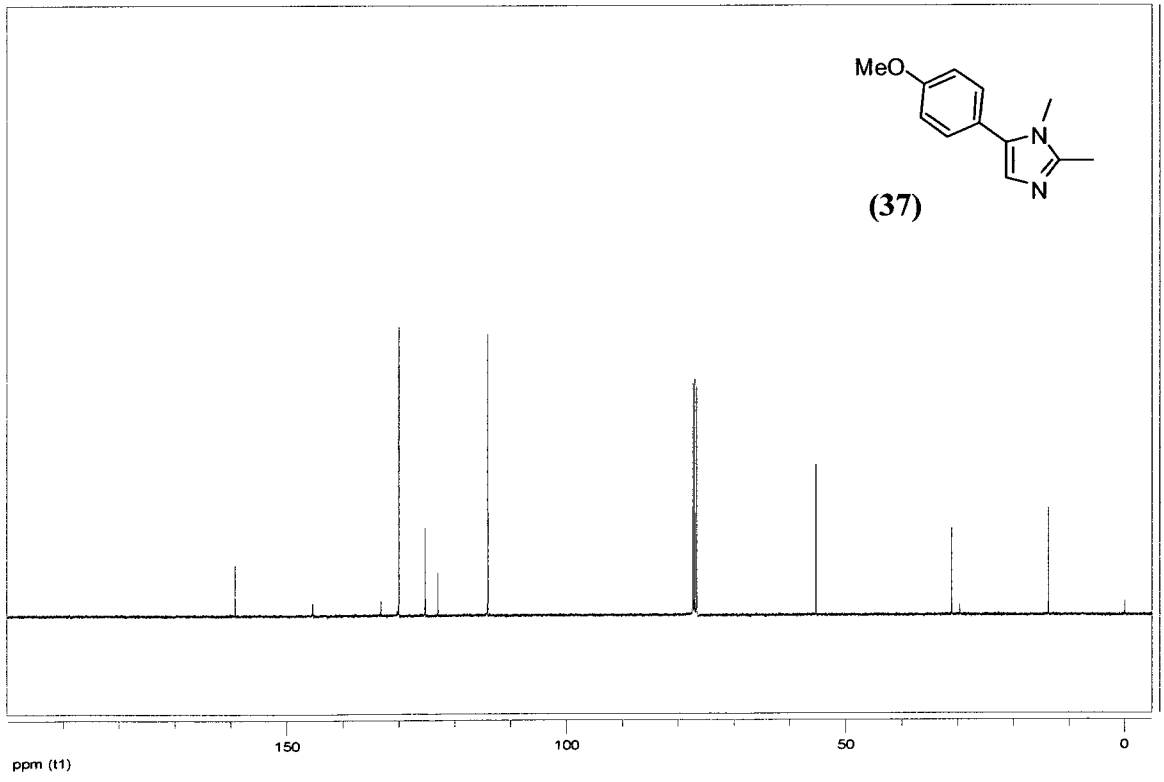
N
N
(37)
5.0
0.0
ppm (t1)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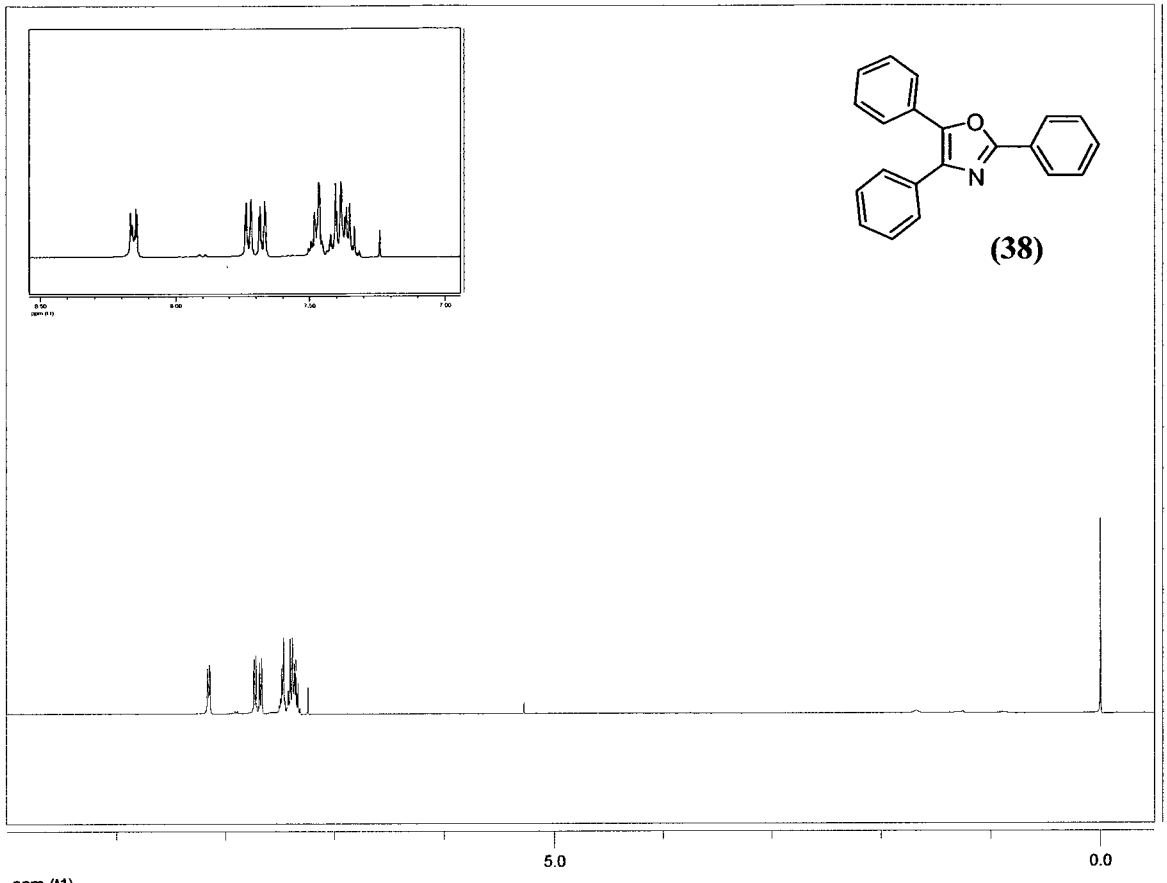
N
N
(37)
150
100
50
0
ppm (t1)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(38)
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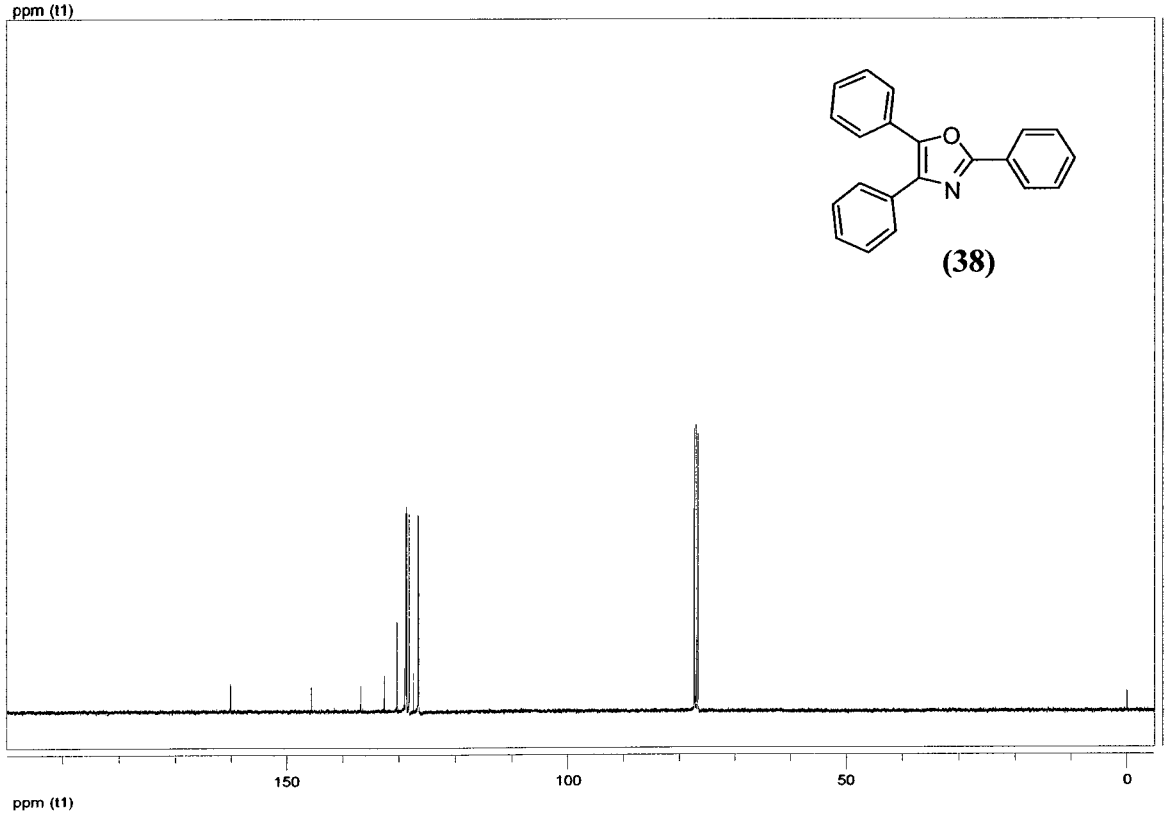
ppm (t1)


O
N
(38)
150
100
50
0
ppm (t1)