TRANSITION METAL CATALYSIS FOR ORGANIC SYNTHESIS

BY

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ABSTRACT OF THE THESIS
TRANSITION METAL CATALYSIS FOR ORGANIC SYNTHESIS

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Thesis Director:
Dr. Xumu Zhang

Transition metal-catalyzed reactions are one of the most powerful and direct approaches for the synthesis of organic molecules. During the past several decades, phosphorus containing ligands have been extensively used in transition metal catalyzed C-C and C-H bond forming reactions. Development of new phosphine ligands for palladium cross coupling and also methodology for C-H activation strategies will be the focus of this dissertation. A variety of triazole containing monophosphine ligands have been prepared via efficient 1,3-dipolar cycloaddition of readily available azides and acetylenes. Their palladium complexes provided excellent yields in the amination reactions (up to 98% yield) and Suzuki-Miyaura coupling reactions (up to 99% yield) of unactivated aryl chlorides. A CAChe model for one of the Pd-complexes shows that the likelihood of a Pd-arene interaction might be a rationale for its high catalytic reactivity. A main goal for Organic chemists is to develop and utilize efficient and atom-economical methods for the elaboration of

complex structures from simple and readily available starting materials. C-H bonds are the most fundamental linkage in organic chemistry and recently tremendous strides have been have been made in the functionalization of C-H bonds. A central goal in the development of any new methodology is synthetic utility, which has been difficult to achieve with C-H activation strategies because of the inherent stability of C-H bond. Aryl carboxylic acid derivatives are very prevalent in industrial and pharmaceuticals and thus a direct C-H activation approach would be very desirable. A general protocol for the rhodium-catalyzed oxidative carbonylation of arenes to form esters has been developed. A broad substrate scope has been demonstrated allowing carbonylation of electron rich, electron-poor, and heterocyclic arenes, and the reaction shows wide functional group tolerance and excellent regioselectivities. Up to 96% yield of *ortho*-substituted aryl or heteroaryl carboxylic esters were obtained with this methodology. The possible mechanism for the rhodium-catalyzed oxidative carbonylation reaction was proposed in this article. Studies show that Oxone play an important role in the transformation. We have developed a new C_2-symmetric monophosphine ligand based upon a C_3* tunephos backbone. The ligand was available in several steps from commercially available starting materials. In future studies this ligand was be tested for its use in chiral cross coupling reactions.

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Triazole-Based Monophosphine Ligands for Palladium Catalyzed Coupling Reactions of Aryl Chlorides

1.1 Introduction and Background

Transition metal catalyzed cross-coupling reactions to form C-C, C-N, C-O and C-S bonds are among the most powerful organometallic transformations in organic chemistry. [1] In the past few decades, there has been remarkable progress in the cross coupling reactions of organometallic reagents containing various nucelophiles such as B, Mg, Li, Sn, Al, Zn with unsaturated electrophiles containing alkenyl, aryl, allyl, alkynyl groups. The general catalytic cycle involves an oxidative addition of the organic electrophile to a coordinatively unsaturated metal complex, followed by transmetallation from the nucleophile to the intermediate species formed in the first step. Reductive elimination affords the coupling products with regeneration of the

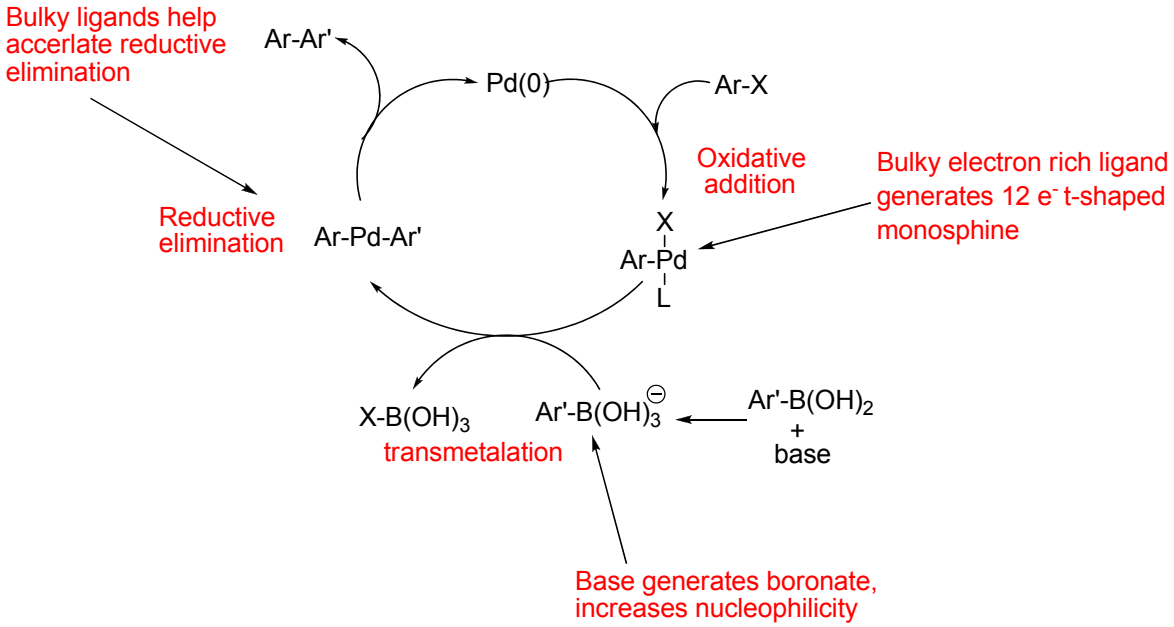


Figure **1-1**: General Mechanism for Transition Metal Catalyzed Cross-coupling Reactions.

catalyst (Figure 1-1). Palladium catalyst is one of the most commonly used transition metal catalysts due to its low toxicity and ease of handling. Pd-catalyzed cross-coupling reaction, Heck reaction, Sonogashira reaction and Buchwald-Hartwig amination reaction have been employed extensively in the synthesis of nature products and drug molecules (Figure 1-2). It has been well-recognized that structural and conformational information imparted through metal bound ligands have significant impacts on the reactivity and stereochemical outcomes of these processes.[2] Designing ligands that can activate the transition metal, stabilize the intermediates in each elemental step, and also direct the selectivity to the desired transformations, is

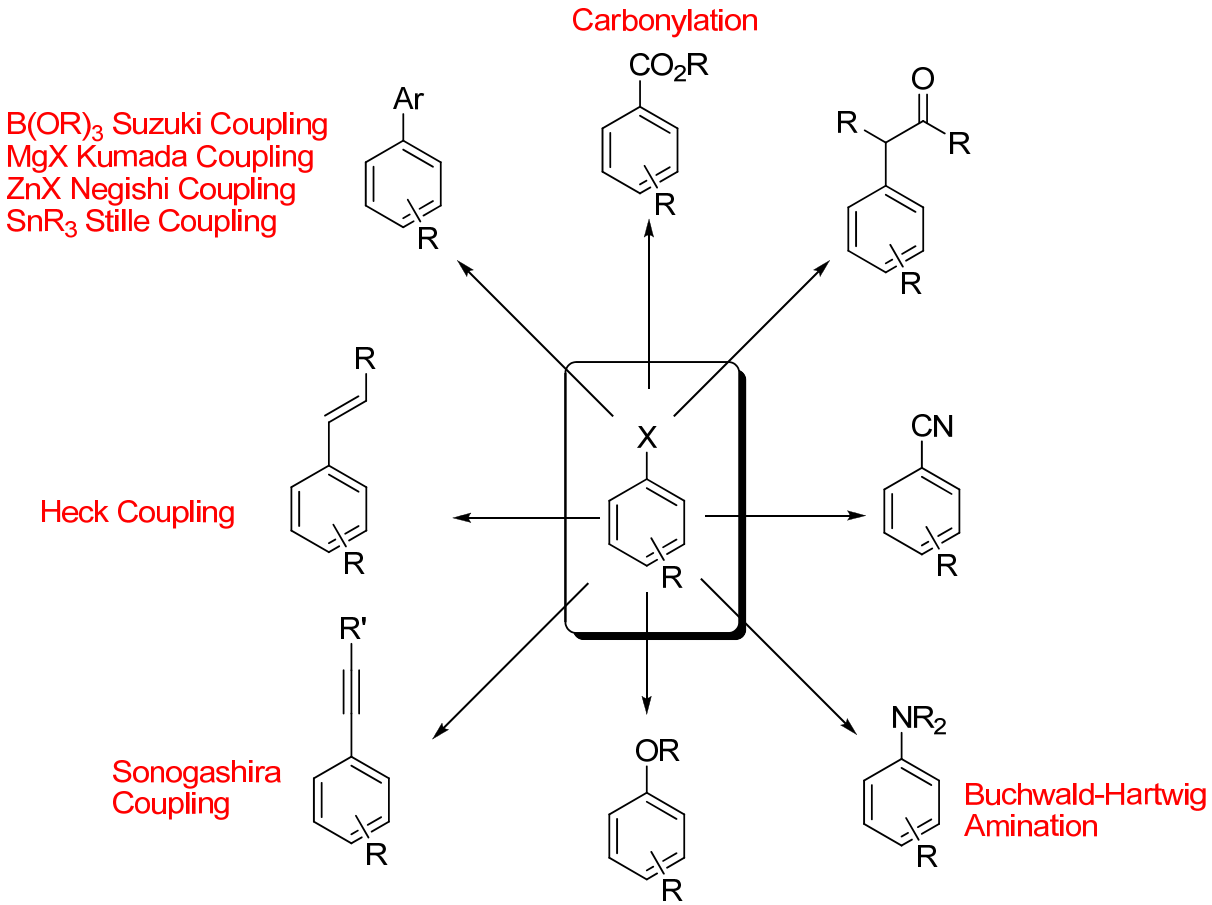
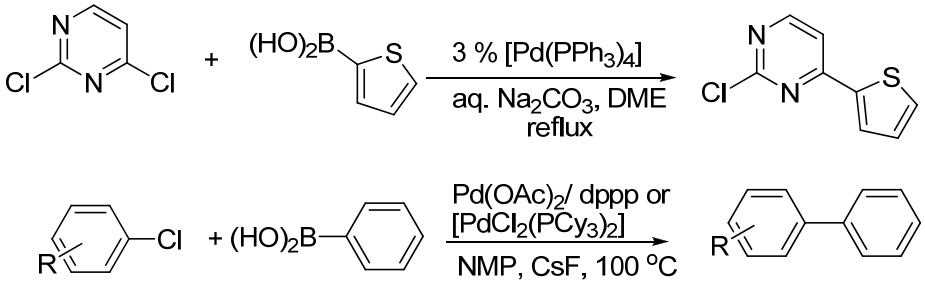


Figure **1-2**: Palladium Catalyzed C-X Coupling Reactions

crucial for solving the challenging problems in this area.

1.1.1 Palladium Catalyzed Suzuki-Miyaura Coupling Reactions

Among the various palladium catalyzed cross-coupling reactions, the Suzuki-Miyaura reaction using aryl halides/triflates with boronic acids as the coupling partners is one of the most attractive methods for the preparation of substituted biaryl compounds.[3] Several factors can be attributed to the popularity of this reaction, which include but are not limited to the wide functional group tolerance as compared to Kumada and Negishi couplings, the availability of a large number of commercial available boronic acids or easily prepared from a simple synthesis, and as well that they are highly stabile and nontoxic as compared to toxic tin reagants. [3] In the early years of development, most reports involved the usage of aryl bromides, aryl iodides, and electron-deficient aryl chlorides (Figure 1-3). [4] A very wide range of Pd(0) catalysts or precursors have been developed for Suzuki coupling reactions. Pd(PPh3)4 is most commonly used, PdCl2(PPh3)2 and Pd(OAc)2/PPh3 are also efficient as they are readily reduced to the active Pd(0) complex. Prior to 1998, there was no report of an effective catalyst system for palladium catalyzed Suzuki-Miyaura reactions of electro-neutral or electron-rich aryl chlorides.



Scheme **1-1**: Some Examples of Pd-Catalyzed Suzuki Reaction of Activated Aryl Chlorides

Recent progress with this reaction has focused on the use of inactivated aryl chlorides as coupling partners in view of their low cost and readily available diversity. [5] A number of reports have shown that Pd complexes derived from sterically hindered and electron-rich phosphines are effective catalysts for this transformation (Figure 1-3).

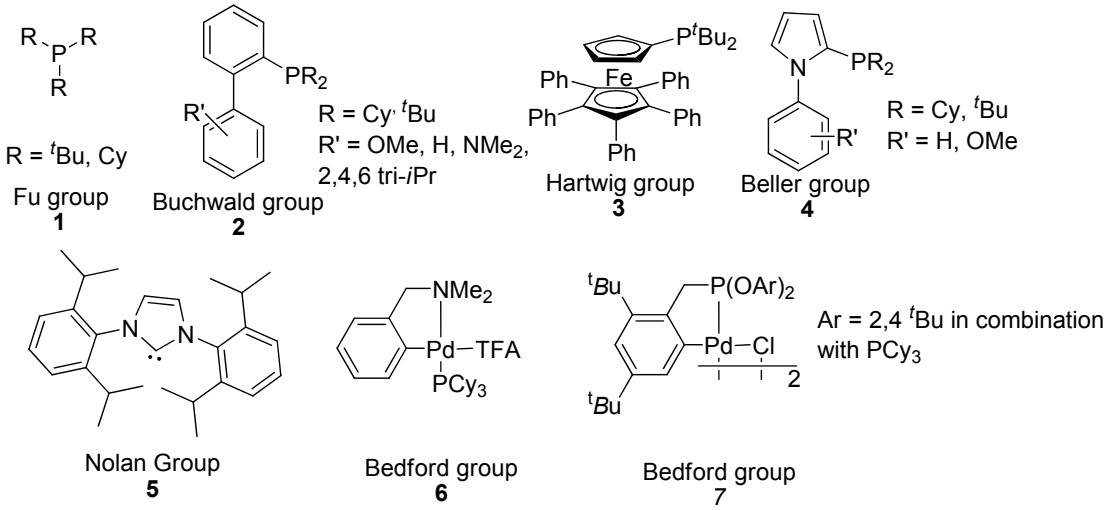


Figure **1-3**: Some Representative Ligands for Pd-Catalyzed Suzuki-Miyaura Reactions

Some notable examples include the use of bulky trialkylphosphines **1** (P^tBu_3 or PCy_3) by Fu, [6] dialkyl biphenylphosphines **2** by Buchwald, [7] ferrocenyl dialkylphosphines **3** by Hartwig, [8] and heteroaromatic phosphine ligands **4** by Beller. [9] Using sterically hindered *N*-heterocyclic carbenes (NHCs, i.e. **5**) as ligands by Herrmann et. al.,[10] and using palladacycles (i.e.**6 and 7**) as the precatalysts by Bedford et al. and Nolan et al.,[11] also led to efficient catalytic systems for the coupling of aryl chlorides (Figure 1-3). Recently, microwave irradiation has been found to be capable of activating aryl chlorides for Suzuki-Miyaura coupling. [12]

In this chapter, the synthetic background for the development of new

monophosphine ligands will be introduced. The application of these ligands in the Pd catalyzed Suzuki coupling reactions will be discussed in detail. Finally, a CaChe model of a Pd/ligand complex based on MM2 calculations will be provided to rationalize the superior catalytic reactivity of this ligand.

1.2 Results and Discussion

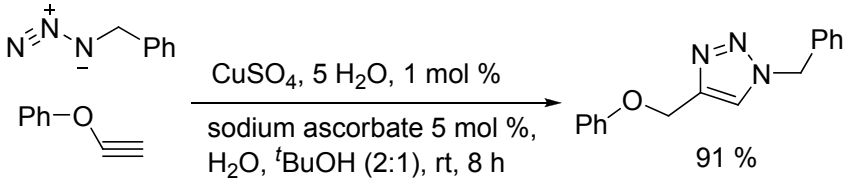
1.2.1 Ligand Design and Synthesis

The fast development of the fine chemical and pharmaceutical industry urges the introduction of economically attractive yet powerful ligands for use in the palladium catalyzed coupling reactions. As it is well known, there is no universally effective phosphine ligand. Also, most of the ligands which can achieve very high yields for specific coupling reactions are highly substrate-dependent. It would be desirable to design a series of ligands with facile synthesis and easy diversification for various types of coupling reactions. Recently, Sharpless and coworkers have reported elegant chemistry for the formations of 1,4 and 1,5-disubstituted triazole compounds, which they termed “click chemistry”.[13] The unique properties such as modularity, wide reaction scope, mild reaction conditions, high yields and regioselectivity, are the key criteria of click chemistry.[13]

One interesting example of click chemistry is represented in hetero-cycloaddition reactions, most notably 1,3-dipolar cycloaddions.[14] Huisgen 1,3-cycloaddition of

azides and alkynes is a classic method for the formation of 1,2,3-triazoles.[13] The original synthetic method for the transformation required elevated temperature and usually resulted in a mixture of 1,4 and 1,5 regioisomers. Due to the unique structure and chemical properties, it may have useful application in organic and medicinal chemistry. However, little attention has been paid to the application of this reaction likely due to the safety concerns associated with azides.

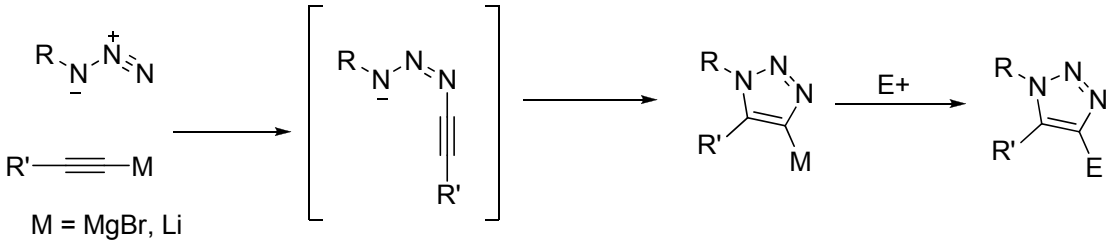
A copper(I) catalyzed regioselective Huisgen cycloaddition was recently reported by Rostovtsev and Sharpless et. al. (Scheme 1-2).[13b] Using *in situ* prepared Cu(I) catalyst, the reaction was completed in 8 h at room temperature with a high yield (91%) of 1,4-disubstituted product and 100% regioselectivity.



Scheme **1-2**: revisited synthesis of 1,5-disubstituted triazoles

On the basis of earlier published results, a revisited synthesis of 1,5-disubstituted triazoles was reported recently.[13c] The scope of this reaction was first investigated by Akimova et. al. in the late 1960s but no further use of this one-step reaction has yet to be reported likely due to the poor yield. Bromomagnesium acetylide was generated *in situ* by the reaction of a terminal alkyne with Grignard reagents. By addition of bromomagnesium acetylides to azides, a wide array of triazoles was obtained with improved yields. Additionally, the intermediates of this reaction can be quenched with various electrophiles to form 1,4,5-trisubstitued triazoles. A possible mechanism has

been proposed (Scheme 1-3).[13c] Nucleophilic attack of acetylide on the terminal nitrogen atom of the azide followed by ring closure affords 4-metalotriazole species. After hydrolysis, preferentially 1,5-disubstituted triazoles are obtained. Different types of electrophiles have been used to quench the reaction with good yields.



Scheme **1-3**: Proposed mechanism for the synthesis of 1,5 substituted triazoles

Following the general procedure reported by Sharpless, a straightforward two step synthesis of ClickPhos has been developed (Scheme 1-2). 1,5-Disubstituted triazoles **8a-8e** were obtained in good yields from phenyl azide and various aryl acetylenes, which can be easily prepared from Corey-Fuchs reaction of the analogous aldehydes.30 Treatment of **8a-8e** with LDA followed by addition of various chlorophosphines furnished ligands **9a-j** in good to excellent yields as shown in figure **1-4.**.

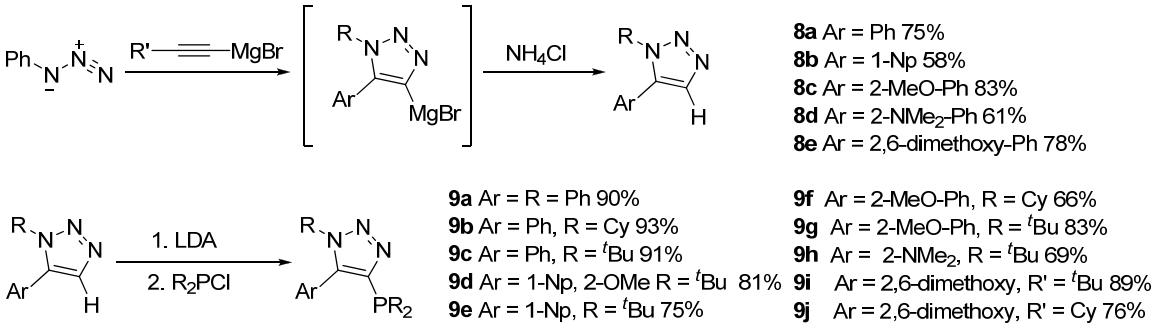


Figure 1-4: Synthesis of ClickPhos ligands

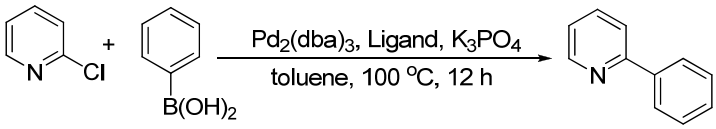
1.2.2 Pd-Catalyzed Suzuki-Miyaura Coupling Reactions of Heteroaromatic

Chlorides

Recently, we have shown that triazole-based monophosphines (ClickPhos, **9a-j**) are highly active ligands for the Suzuki cross-coupling reactions of aryl chlorides, [15] and they could be easily and quickly derivatized into a series of ligands for different purposes. Herein, we present our contribution in Pd-catalyzed Suzuki cross-coupling between heteroaromatic chlorides and arylboronic acids using the highly electron-donating ClickPhos as the ligand. High yields were generally observed for a series of substrates including substituted pyridines and thiophenes.

Functionalized heteroaromatics are prevalent in natural products, pharmaceuticals and functional materials with pyridine and thiophene moieties being exceptionally common. Direct cross-coupling of pyridyl halides and boronic acids represents one of the most convenient approaches of their synthesis. Previously 2-chloro and 3-chloropyridine as well as pyridine boronic acids have been reported as coupling substrates by Fu, Buchwald and others. [16] However, the scope of these methods still needs to be explored. One of the major concerns of these particular important substrates is that pyridine has a tendency to coordinate to metal centers and impede the catalytic cycle. We anticipated that our electron rich ligands could help to negate pyridine coordination and result in high reaction rates and product yields. Challenging substrates such as dichloro and trichloro pyridines were examined, which are challenging because of the steric hindrance of the second and third Suzuki coupling. Some notable examples are that highly hindered substrates such as 2,3-dichloropyridine and 2,3,5-trichloropyridine can be coupled with good yields.

Chlorothiophenes can also be coupled under the reaction conditions resulting in good yields. The high activities of the Pd/ClickPhos catalysts Suzuki Coupling reactions of aryl chlorides led us to further explore their applications in Suzuki-Miyaura coupling reactions of heteroaromatic chlorides. The reaction between 2-chloropyridine and phenylboronic acid was first tested with ligands **9a-h** (Table 1-3, entries 1-8). The reactions were performed in the presence of the catalysts derived from 1 mol% of Pd(dba)2 and 2 mol% of ligands. While very low yield (<5%) of the coupling product was observed with diphenyl phosphine ligand **16a**, good to excellent yields were achieved with dialkyl phosphine ligands **9f** and **9i** (86% and 9g%, respectively). These results are consistent with the general trend of the ligand efficiency observed in coupling reactions with other structurally related ligand sets.23 In general, sterically hindered and electron-rich ligands are more efficient for coupling reactions.

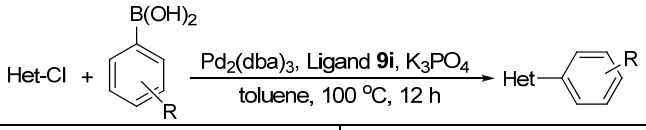


Entry	Ligand	Base	Yield (%)
1	9a	K_3PO4	<5
2	9b	K_3PO4	<7
3	9c	K_3PO4	<10
4	9d	K_3PO4	80
5	9e	K_3PO4	82
6	9f	K_3PO4	86
7	9g	K_3PO4	68
8	9h	K_3PO4	43
9	9i	K_3PO4	96
10	9i	KF	84
11	9i	CsF	57
12	9i	Cs_2CO_3	61

Table 1-1: Screeing of ligands for Suzuki Coupling of 2-chloro pyridine

Using the best ligand **9i**, a variety of bases, such as K_3PO4, KF, and CsF, were examined. K_3PO_4 was found to be the base of choice for the Pd/**9i** catalytic system (Table 1-2, entries 3, 9 and 10).

With the optimized reaction conditions, the coupling reactions between a range of heteroaromatic chlorides and various aryl boronic acids were carried out to explore the general effectiveness of the Pd/**9i** catalytic system (Table 1-4). Excellent yields were obtained with 0.1 mol% of the catalyst in the reactions between various electron-deficient heteroaromatic chlorides and various boronic acid (Table 1-2, entries 5-12). Under the reaction conditions, 2-phenylpyridine and 2-(*p*-toyl*)*-pyridine



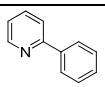
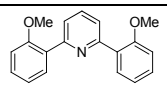
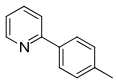
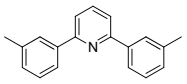
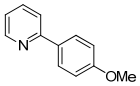
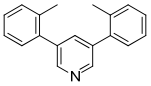
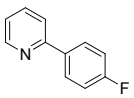
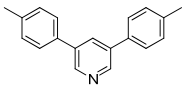
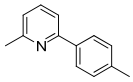
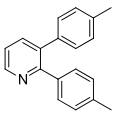
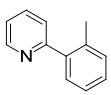
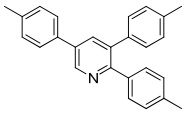
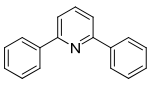
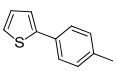
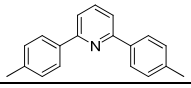
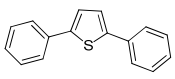
Entry	Product	Yield	Entry	Product	Yield
1		96	9		86
2		97	10		82
3		84	11		80
4		81	12		85
5		88	13		81
6		85	14		77
7		91	15		88
8		88	16		90

Table 1-2 Pd/ClickPhos Suzuki Coupling of heteroaromatic chlorides

can be achieved in almost quantitative yields (entries 1 and 2). Very electron rich boronic acids can also give high reactivity, as in the reaction of *p*-methoxy benzeneboronic acid with 2-chloropyridine (entry 3, 84%). Sterically hindered 2-chloropyridines were examined, coupling of 2-chloro-6-methylpyridine with *p*-toylboronic acid resulted in 88% yield, despite the steric hindrance of the methyl group (entry 5). *Ortho*-substituted boronic acids can also be tolerated leading to 85% yield of the desired product (entry 6).

Based on the coupling of 2-chloro-6-methylpyridine, we explored the effect of steric hindrance on the second and third sequential cross-couplings of dichloro and trichloro heteroaromatics, as this could lead to highly functionalized hindered pyridines in a single step. Generally, reactions of 2,6-dichloropyridines resulted in good yields (entries 7-10, 82-91%). To explore the effect of steric hindrance on the second Suzuki coupling we first examined the reaction of 2,6-dichloropyridine with phenylboronic acid, which gave high yield of the desired product (entry 7, 91%). To evaluate the effects of steric hindrance on the first and second Suzuki couplings, we examined the coupling of *o*-methoxybenzene bornic acid with 2,6-dichloropyridine, which gave a 86% yield of the hindered product (entry 9). 3,5-Dichloropyridines were next explored to expand the versatility of the catalytic system, and good results were obtained (entries 11 and 12).

Reactions of challenging hindered dichloro and trichloropyridines were explored as a means to test our catalytic system. Coupling of 2,3-dichloropyridine with

p-toylboronic acid gave 81% yield of the highly hindered product (entry 13). Reaction of the highly hindered 2,3,5-trichloropyridine with *p*-toylboronic acid resulted in the desired product in 77% yield (entry 14). This method could lead to the efficient synthesis of a vast construction of highly hindered pyridine derivatives.

The reaction of thiophene chlorides was explored under the same reaction conditions and our Pd/ClickPhos system represents a good approach to synthesizing these derivatives. We first conducted the reaction of 2-chlorothiophene with *p*-toylboronic acid, 88% yield of the desired product was achieved (entry 15). The coupling of 2,5-dichlorothiophene with phenylboronic acid was explored, and 90% yield of the product was achieved (entry 16). In order to further understand the special activity of ligand **9i,** a CAChe model of Pd/**9i** complex based on the MM2 calculation was obtained (Figure 1-6). The key feature of the complex structure is the orientation of the arene group on the 5-position of the triazole ring. The distance between the palladium and the *sp*2-carbon on the 2,6- dimethoxybenzene moiety (as indicated by the arrow in Figure 1-6) is around 2.245Å based on the MM2 calculation, which is appreciably shorter than the sum of the van der Waals radii for Pd and C, 3.33 Å (Pd = 1.63 Å, C = 1.70 Å). This interaction leads us to believe the likelihood of a metal-arene interaction, which might stabilize the palladium complex in the catalytic cycle and therefore enhance the catalyst reactivity. Similar observations have previously been reported by Buchwald,23c and Fink.32

1.3 Conclusion

In conclusion, we have developed a new series of monophosphine ligands **9** (ClickPhos) bearing a triazole heterocycle in the backbone. These ligands are readily accessible and can be easily diversified via efficient 1,3-dipolar cycloadditions of various azides and acetylenes. With the Pd complex derived from ligand **9i**, up to 97% yield was achieved in the Suzuki-Miyaura coupling of heteroaromatic chlorides with excellent yields and TONs. Among the ClickPhos series, ligand **9i**, which has a 2,6-dimethoxybenzene moiety on the triazole ring, was particularly effective in the Pd-catalyzed Suzuki-Miyaura coupling to various substituted biaryl compounds (up to 96% yield). A CAChe model for the Pd/**9i** complex shows that the likelihood of a Pd-arene interaction might be a rationale for its high catalytic reactivity.

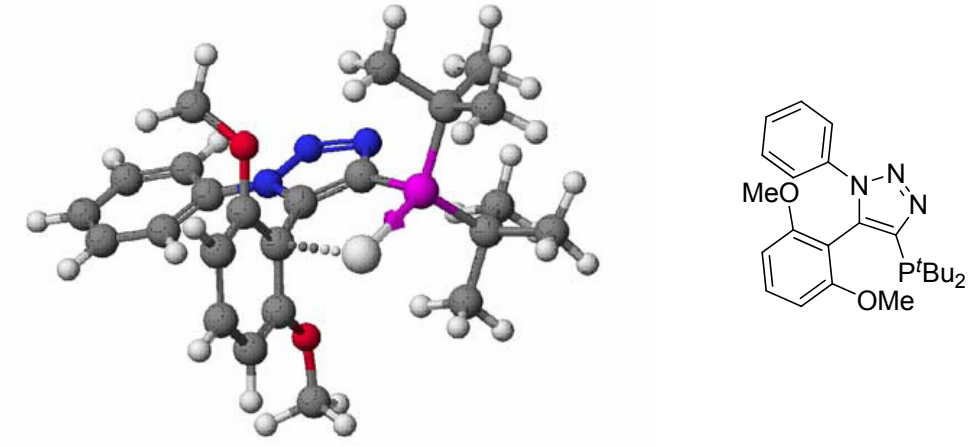


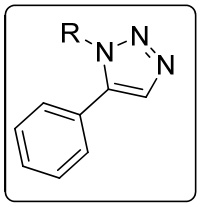
Figure **1-5**: MM2 Calculations of Pd/**16i** Complex Based on the CAChe Program

Experimental Section

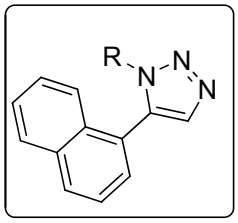
General information:

Column chromatography was carried out on silica gel. 1H NMR spectra were recorded on 500 MHz or 400 MHz in CDCl3 and 13C NMR spectra were recorded on 125 MHz or 100 MHz in CDCl3. All new products were further characterized by HRMS. Unless otherwise stated, all arenes and solvents were purchased from commercial suppliers and used without further purification.

General Procedure for Suzuki Coupling of heteroaromatic Chlorides. To a Schlenk tube, which was flame-dried under vacuum and backfilled with nitrogen, was charged with heteroaromatic chloride (0.5 mmol), boronic acid (1.3 eqv. per halide) and K3PO4 (2 eqv. Per halide). The flask was evacuated and backfilled with nitrogen three times. In a dry box, toluene (3 mL), a stock solution of ligand **5g** in toluene (0.002 mmol), a stock solution of Pd2(dba)3 (0.001 mmol) in toluene were subsequently added. The flask was sealed and the reaction mixture was heated to 100 °C with vigorous stirring for 12 h. After cooling the mixture to rt, 15 mL of EtOAc was added and the mixture was washed with 5 mL of brine. The organic layer was dried over Na2SO4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel.

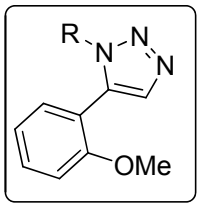


1,5-Diphenyl-1*H*-[1,2,3]triazole (8a). To a solution of EtMgBr in THF (1.0 M, 11.9 mL) was added phenylacetylene (1.3 mL, 11.9 mmol) at rt. The reaction mixture was heated to 50 ^{o}C for 15 min. After cooling the mixture to rt, a solution of phenylazide (1.41 g, 11.9 mmol) in THF (4 mL) was added. The resulting solution was stirred at rt for 30 min, and then heated to 50 ^{o}C for 1 h before quenching with saturated NH4Cl (10 mL). The layers were separated, and the aqueous layer was extracted with CH2Cl2 (10 mL × 3). The combined organic layers were dried over Na2SO4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford **8a** as a white solid (1.98 g, 75%). 1H NMR (CDCl3, 300 MHz) δ 7.86 (s, 1H), 7.44-7.30 (m, 8H), 7.23-7.20 (m, 2H); 13C NMR (CDCl3, 75 MHz) δ 137.6, 136.5, 133.4, 129.3, 129.2, 128.8, 128.5, 126.7, 125.1.

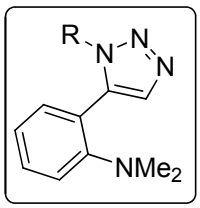


1-Phenyl-5-(1-naphthyl)-1*H*-[1,2,3]triazole (8b). To a solution of EtMgBr in THF (3.0 M, 2.5 mL) was added 1-naphthlyne (1.12 g, 7.36 mmol) at rt. The reaction mixture was heated to 50 oC for 15 min. After cooling the mixture to rt, a solution of phenylazide (0.88 g, 7.36 mmol) in THF (4 mL) was added. The resulting solution was stirred at rt for 30 min, and then heated to 50 ^{o}C for 1 h before quenching with saturated NH4Cl (10 mL). The layers were separated, and the aqueous layer was extracted with CH2Cl2 (10 mL × 3). The combined organic layers were dried over

Na2SO4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford **8b** as a white solid (1.16 g, 58%). 1H NMR (CDCl3, 360 MHz) δ 7.98 (s, 1H), 7.94 (t, *J* = 9.2 Hz, 3H), 7.67 (d, *J* = 8.3 Hz, 1H), 7.56 – 30 7.46 (m, 3H), 7.35-7.24 (m, 6H); 13C NMR (CDCl3, 90 MHz) δ 136.6, 135.7, 135.4, 133.6, 131.7, 130.2, 129.2, 129.0, 128.8, 128.6, 127.2, 126.6, 125.1, 124.8, 124.6, 124.1;
HRMS (ESI+) calcd. for C18H14N3 (MH+) 272.1188, found 272.1182.

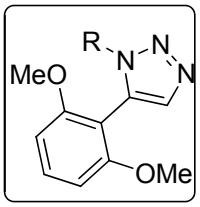


1-Phenyl-5-(2-methoxyphenyl)-1*H*-[1,2,3]triazole (8c). To a solution of EtMgBr in THF (3.0 M, 2.3 mL) was added 2-methoxyphenylacetylene (0.92 g, 6.96 mmol) at rt. The reaction mixture was heated to 50 ^{o}C for 15 min. After cooling the mixture to rt, a solution of phenylazide (0.83 g, 6.96 mmol) in THF (4 mL) was added. The resulting solution was stirred at rt for 30 min, and then heated to 50 oC for 1 h before quenching with saturated NH4Cl (10 mL). The layers were separated, and the aqueous layer was extracted with CH2Cl2 (10 mL × 3). The combined organic layers were dried over Na2SO4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford **8c** as a white solid (1.45 g, 83%). 1H NMR (CDCl3, 300 MHz) δ 7.85 (s, 1H), 7.44-7.33 (m, 6H), 7.01(t, *J* = 7.5 Hz, 1H), 6.87 (d, *J* = 8.3 Hz, 1H) 3.44 (s, 3H); 13C NMR (CDCl3, 75 MHz) δ 156.9, 138.1, 135.1, 134.9, 131.7, 131.4, 129.4, 129.0, 124.2, 121.2, 116.6, 111.8, 55.3; HRMS (ESI+) calcd. for C15H14N3O (MH+) 252.1137, found 252.1127.

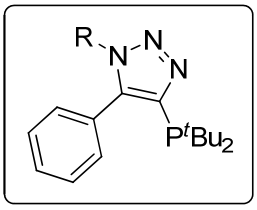


1-Phenyl-5-(2-*N,N*-dimethylphenyl)-1*H*-[1,2,3]triazole (8d). To a solution of EtMgBr in THF (3.0 M, 2.3 mL) was added 2-*N,N*-dimethylphenylacetylene (1.01 g, 6.96 mmol) at rt. The reaction mixture was heated to 50 oC for 15 min. After cooling the mixture to rt, a solution of phenylazide (0.83 g, 6.96 mmol) in THF (4 mL) was added. The resulting solution was stirred at rt for 30 min, and then heated to 50 oC for 1 h before quenching with saturated NH4Cl (10 mL). The layers were separated, and the aqueous layer was extracted with CH2Cl2 (10 mL × 3). The combined organic layers were dried over Na2SO4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford **8d** as a yellow solid (1.12 g, 61%).1H NMR (300 MHz, CDCl3) δ 7.87 (s, 1H), 7.25-7.35 (m, 7H),

7.02-7.05 (m, 1H), 6.88 (d, J = 8.2 Hz, 1H), 2.19 (s, 6H); 13C NMR (75 MHz, CDCl3) δ 151.5, 137.8, 137.1, 133.6, 131.4, 130.6, 128.6, 128.2, 122.7, 119.8, 118.8, 41.9; HRMS (ESI+) calcd. for C16H17N4 (MH+) 265.1453, found 265.1444.

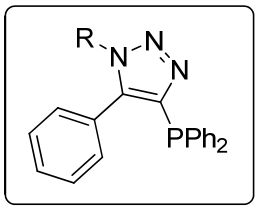


1-Phenyl-5-(2,6-dimethoxy-phenyl)-1*H*-[1,2,3]triazole (8e). To a solution of EtMgBr in THF (3.0 M, 2.3 mL) was added 2,6dimethoxyphenylacetylene (0.95 g, 6.96 mmol) at rt. The reaction mixture was heated to 50 oC for 15 min. After cooling the mixture to rt, a solution of phenylazide (0.83 g, 6.96 mmol) in THF (4 mL) was added. The resulting solution was stirred at rt for 30 min, and then heated to 50 oC for 1 h before quenching with saturated NH4Cl (10 mL). The layers were separated, and the aqueous layer was extracted with CH2Cl2 (10 mL × 3). The combined organic layers were dried over Na2SO4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford **8e** as a white solid (1.39 g, 78%). 1H NMR (300 MHz, CDCl3) δ 7.76 (s, 1H), 7.27-7.33 (m, 6H), 6.49 (d, *J* = 8.4 Hz, 2H), 3.51 (s, 6H); 13C NMR (75 MHz, CDCl3) δ 158.0, 137.7, 135.5, 131.5, 130.3, 128.6, 128.3, 123.3, 104.6, 103.7, 55.4; HRMS (ESI+) calcd. for C16H15N3O2Na (M + Na+) 304.1062,found 304.1063.

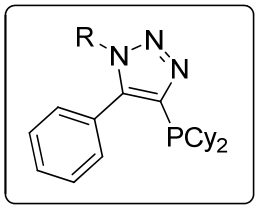


4-Di-*tert*-butylphosphanyl-1,5-diphenyl-1*H*-[1,2,3]triazole (16c). To a solution of 1,5-Diphenyl-1*H*-[1,2,3]triazole (**8a**) (0.520 g, 2.35 mmol) in THF (20 mL) was added LDA (2.35 mmol) at 0 oC. The reaction mixture was stirred at 0 oC for 1.5 h followed by addition of P*t*Bu2Cl (0.446 mL, 2.35 mmol). The resulting mixture was slowly warmed to rt and stirred overnight. TLC showed the reaction was essentially complete after 16 h. The solvent was removed under vacuum. A degassed mixture of brine/H2O (1:1) was added, and the resulting mixture was extracted with degassed ether (15 mL × 3). The combined organic layers were dried over Na2SO4 and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel under nitrogen (hexanes:ether, 80:20) to afford **9c** as a sticky solid (0.78 g, 91%). 1H NMR (CD2Cl2, 360 MHz) δ 7.41-7.23 (m, 10H), 1.27 (d, *J* = 12.1 Hz, 18H); 13C NMR (CDCl3, 90 MHz) δ 145.2 (d, *J* = 39.0 Hz), 142.2 (d, *J* = 27.9 Hz), 137.2, 131.1 (d, *J* = 2.5 Hz), 129.4, 129.3, 129.0, 128.6, 128.5, 125.2,

33.1 (d, *J* = 17.0 Hz), 30.6 (d, *J* = 14.4 Hz); 31P NMR (CD2Cl2, 145 MHz) δ 3.51; HRMS (ESI+) calcd. for C22H29N3P (MH+) 366.2084, found 366.2099.

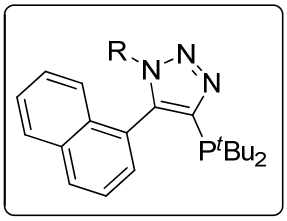


4-Diphenylphosphanyl-1,5-diphenyl-1*H*-[1,2,3]triazole (16a). To a solution of 1,5-Diphenyl-1*H*-[1,2,3]triazole (**8a**) (0.26 g, 1.18 mmol) in THF (20 mL) was added LDA (1.18 mmol) at 0 oC. The reaction mixture was stirred at 0 oC for 1.5 h followed by addition of PPh2Cl (0.242 mL, 1.24 mmol). The resulting mixture was slowly warmed to rt and stirred overnight. TLC showed the reaction was essentially complete after 12 h. The solvent was removed under vacuum. A degassed mixture of brine/H2O (1:1) was added, and the resulting mixture was extracted with degassed ether (15 mL × 3). The combined organic layers were dried over Na2SO4 and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel under nitrogen (hexanes:ether, 80:20) to afford **9a** as a sticky solid (0.43 g, 90%). 1H NMR (CDCl3, 360 MHz) δ 7.73-7.69 (m, 4H), 7.44-7.36 (m, 14H), 7.26 (d, *J* = 7.3 Hz, 2H); 13C NMR (CDCl3, 90 MHz) δ 143.3 (d, *J* = 39.5 Hz), 141.1 (d, *J* = 14.2 Hz), 136.40, 136.38 (d, *J* = 15.4 Hz), 133.8, 133.5, 130.1 (d, *J* = 3.5 Hz), 129.2, 129.0, 128.8, 128.6, 128.35, 128.28, 128.2, 126.5, 124.8; 31P NMR (CDCl3, 145 MHz) δ −35.85; HRMS (ESI+) calcd. for C26H21N3P (MH+) 406.1475, found 406.1473.

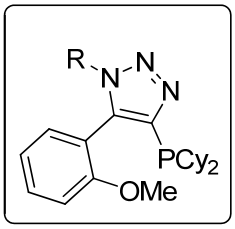


4-Dicyclohexylphosphanyl-1,5-diphenyl-1*H*-[1,2,3]triazole(9b). To a solution of **15a** (0.500g, 2.26 mmol) in THF (20 mL) at 0 oC was added LDA (2.26 mmol) at 0 ^{o}C. The reaction mixture was stirred at 0 ^{o}C for 1.5 h followed by addition of PCy2Cl (0.500 mL, 2.26 mmol). The resulting mixture was slowly warmed to rt and stirred for 4 h. TLC showed the reaction was essentially complete. The organic solution was washed with brine (10 mL), dried over Na2SO4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel under nitrogen (hexanes:ether, 80:20) to afford **9b** as a white solid (0.88 g, 93%). 1H NMR (CD2Cl2, 360 MHz) δ 7.41 - 7.23 (m, 10H), 2.28-2.21 (m, 2H), 1.87-1.67 (m, 10H), 1.38-1.09 (m, 10H); 13C NMR (CDCl3, 90 MHz) δ 144.7 (d, *J* = 34.8 Hz), 141.2 (d, *J* = 24.6 Hz), 137.2, 130.9 (d, *J* = 2.9 Hz), 129.4, 129.3, 129.1, 128.6, 128.0, 125.3, 33.5 (d, *J* = 8.4 Hz), 30.8 (d, *J* = 16.3 Hz), 29.8 (d, *J* = 7.5 Hz), 27.5 (d, *J* = 18.5 Hz), 27.4 (d, *J* = 1.6 Hz), 26.8; 31P NMR (CD2Cl2, 145 MHz) δ −27.76; HRMS

(ESI+) calcd. for C26H33N3P (MH+) 418.2419, found 418.2412.

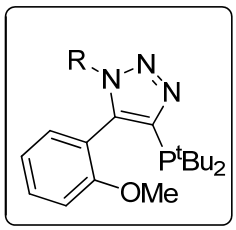


4-Di-*tert*-butylphosphanyl-1-phenyl-5-(1-naphthyl)-1*H*-[1,2,3]triazole(9e). To a solution of 1-Phenyl-5-(1-naphthyl)-1*H*-[1,2,3]triazole (**8b**) (0.544 g, 2.0 mmol) in THF (20 mL) was added LDA (2.0 mmol) at 0 oC. The reaction mixture was stirred at 0 ^{o}C for 1.5 h followed by addition of P*t*Bu2Cl (0.38 mL, 2.0 mmol). The resulting mixture was slowly warmed to rt and stirred overnight. TLC showed the reaction was essentially complete after 16 h. The solvent was removed under vacuum. A degassed mixture of brine/H2O (1:1) was added, and the resulting mixture was extracted with degassed ether (15 mL × 3). The combined organic layers were dried over Na2SO4 and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel under nitrogen (hexanes:ether, 80:20) to afford **16e** as a white solid (0.67 g, 75%). 1H NMR (CD2Cl2, 300 MHz) δ 7.98-7.88 (m, 2H), 7.55-7.21 (m, 10H), 1.34-1.24 (m, 18H); 13C NMR (CDCl3, 75 MHz) δ 144.1 (d, *J* = 14.9 Hz), 143.7 (d, *J* = 28.6 Hz), 137.3, 133.7, 132.4, 130.6, 130.3, 129.3, 129.0, 128.8, 127.0, 126.6, 126.1, 125.6, 125.3, 124.2, 32.9 (dd, *J* = 17.0, 21.7 Hz), 30.8 (dd, *J* = 10.3, 14.3 Hz); 31P NMR (CD2Cl2, 145 MHz) δ3.63; HRMS (ESI+) calcd. for C26H31N3P (MH+) 416.2256, found 416.2252.

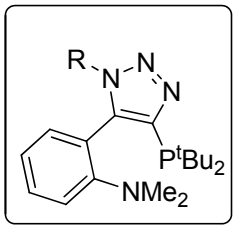


4-Dicyclohexylphosphanyl-1-phenyl-5-(2-methoxyphenyl)-1*H*-[1,2,3]triazole (9f). To a solution of 1-Phenyl-5-(2-methoxyphenyl)-1*H*-[1,2,3]triazole (**8c**) (0.504 g, 2.0 mmol) in THF (20 mL) was added LDA (2.0 mmol) at 0 ^{o}C. The reaction mixture was stirred at 0 ^{o}C for 1.5 h followed by addition of PCy2Cl (0.442 mL, 2.0 mmol). The resulting mixture was slowly warmed to rt and stirred overnight. TLC showed the reaction was essentially complete after 16 h. The solvent was removed under vacuum. A degassed mixture of brine/H2O (1:1) was added, and the resulting mixture was extracted with degassed ether (15 mL × 3). The combined organic layers were dried over Na2SO4 and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel under nitrogen (hexanes:ether, 80:20) to afford **9f** as a white solid (0.574 g, 64%). 1H NMR (360 MHz, CD2Cl2) δ 7.36-7.42 (m, 6H), 7.30 (dd, *J* = 1.3, 7.5 Hz, 1H), 7.05-7.09 (m, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 3.47 (s,

3H), 2.10-2.33 (m, 2H), 1.61-2.05 (m, 10H), 0.98-1.52 (m, 10H); 13C NMR (90 MHz, CD2Cl2) δ 157.2, 141.8 (d, *J* = 27.4 Hz), 141.5 (d, *J* = 15.3 Hz), 137.6, 132.4, 131.1, 128.8, 128.4, 123.8, 120.3, 117.1, 111.1, 55.0, 33.0 (d, *J* = 42.4 Hz), 30.3, 29.4 (d, *J* = 30.8 Hz), 27.2 (d, *J* = 19.5 Hz), 27.1, 26.6; 31P NMR (145 MHz, CD2Cl2) δ -27.99; HRMS (ESI+) calcd. for C27H35N3OP (MH+) 448.2518, found 448.2510.

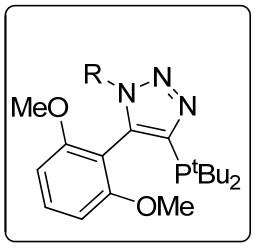


4-Di-*tert*-butylphosphanyl-1-phenyl-5-(2-methoxyphenyl)-1*H*-[1,2,3]triazole (9g) To a solution of 1-Phenyl-5-(2-methoxyphenyl)-1*H*-[1,2,3]triazole (**8c**) (0.504 g, 2.0 mmol) in THF (20 mL) was added LDA (2.0 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1.5 h followed by addition of P*t*Bu2Cl (0.38 mL, 2.0 mmol). The resulting mixture was slowly warmed to rt and stirred overnight. TLC showed the reaction was essentially complete after 16 h. The solvent was removed under vacuum. A degassed mixture of brine/H2O (1:1) was added, and the resulting mixture was extracted with degassed ether (15 mL × 3). The combined organic layers were dried over Na2SO4 and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel under nitrogen (hexanes:ether, 80:20) to afford **9g** as a white solid (0.602 g, 76%). 1H NMR (CD2Cl2, 360 MHz) δ 7.47-7.32 (m, 7H), 7.09 (t, *J* = 7.2 Hz, 1H), 6.90 (d, *J* = 8.2 Hz, 1H), 3.48 (s, 3H), 1.41 (d, *J* = 11.8 Hz, 9H), 1.24 (d, *J* = 11.8 Hz, 9H); 13C NMR (CDCl3, 90 MHz) δ 157.3, 142.5 (d, *J* = 9.3 Hz), 142.2 (d, *J* = 24.5 Hz), 137.6, 132.6 (d, *J* = 2.6 Hz), 131.1, 128.8, 128.5, 123.9, 120.3, 117.4, 111.0, 54.9, 32.5 (dd, *J* = 10.3, 17.0 Hz), 30.2 (dd, *J* = 14.1, 44.1 Hz); 31P NMR (CD2Cl2, 145 MHz) δ 3.47; HRMS (ESI+) calcd. for C23H31N3OP (MH+) 396.2205, found 396.2202.

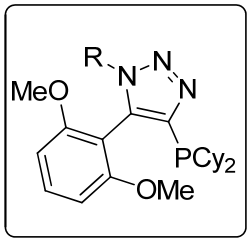


4-Di-*tert*-butylphosphanyl-1-phenyl-5-(2-*N,N*-dimethylphenyl)-1*H*-[1,2,3]-triazole(9h). To a solution of 1-Phenyl-5-(2-*N,N*-dimethylphenyl)-1*H*-[1,2,3]triazole (**8d**) (0.53 g, 2.0 mmol) in THF (20 mL) was added LDA (2.0 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1.5 h followed by addition of P*t*Bu2Cl (0.38 mL, 2.0 mmol). The resulting mixture was slowly warmed to rt and stirred overnight. TLC showed the reaction was essentially complete after 16 h. The solvent was removed under vacuum. A degassed mixture of brine/H2O (1:1) was added, and the resulting mixture was extracted with degassed ether (15 mL × 3). The combined

organic layers were dried over Na2SO4 and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel under nitrogen (hexanes:ether, 80:20) to afford **9h** as a white solid (0.565 g, 69%). 1H NMR (360 MHz, CD2Cl2) δ 7.53 (d, *J* = 7.6 Hz, 1H), 7.35-7.40 (m, 4H), 7.26-7.29 (m, 2H), 7.05-7.10 (m, 1H), 6.88 (d, *J* = 8.2 Hz, 1H), 2.16 (s, 6H), 1.38 (d, *J* = 11.8 Hz, 9H), 1.30 (d, *J* = 12.1 Hz, 9H); 13C NMR (90 MHz, CD2Cl2) δ 151.8, 143.9 (d, *J* = 38.2 Hz), 141.5 (d, *J* = 28.6 Hz), 138.2, 133.5 (d, *J* = 5.0 Hz), 130.4, 128.6, 128.1, 122.8, 120.7, 120.1, 118.8, 41.8, 33.1 (dd, *J* = 17.1, 22.3 Hz), 30.6 (dd, *J* = 8.7, 14.4 Hz); 31P NMR (145 MHz, CD2Cl2) δ 2.72; HRMS (ESI+) calcd. for C24H34N4P (MH+) 409.2521, found 409.2537.

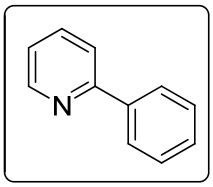


4-Di-*tert*-butylphosphanyl-1-phenyl-5-(2,6-dimethoxyphenyl)-1*H*-[1,2,3]- triazole (9i). To a solution of 1-Phenyl-5-(2,6-dimethoxy-phenyl)-1*H*-[1,2,3]triazole (**8e**) (0.562 g, 2.0 mmol) in THF (20 mL) was added LDA (2.0 mmol) at 0 oC. The reaction mixture was stirred at 0 ^{o}C for 1.5 h followed by addition of P*t*Bu2Cl (0.38 mL, 2.0 mmol). The resulting mixture was slowly warmed to rt and stirred overnight. TLC showed the reaction was essentially complete after 16 h. The solvent was removed under vacuum. A degassed mixture of brine/H2O (1:1) was added, and the resulting mixture was extracted with degassed ether (15 mL × 3). The combined organic layers were dried over Na2SO4 and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel under nitrogen (hexanes:ether, 80:20) to afford **9i** as a white solid (0.673 g, 79%). 1H NMR (360 MHz, CD2Cl2) δ 7.37-7.42 (m, 6H), 6.58 (d, *J* = 8.4 Hz, 2H), 3.63 (s, 6H), 1.28 (d, *J* = 12.0 Hz, 18 H); 13C NMR (90 MHz, CD2Cl2) δ 158.5, 143.0, 139.5, 137.4, 131.5, 128.7, 128.5, 124.1, 105.7, 103.3, 55.2, 32.3 (d, *J* = 16.2 Hz), 30.2 (d, *J* = 14.4 Hz); 31P NMR (145 MHz, CD2Cl2) δ 4.73; HRMS (ESI+) calcd. for C24H33N3O2P (MH+) 426.2310, found 426.2307.

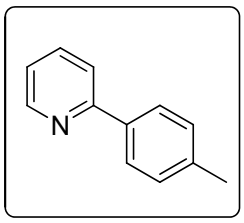


4-Dicyclohexylphosphanyl-1-phenyl-5-(2,6-dimethoxyphenyl)-1*H*-[1,2,3]- triazole (9j). To a solution of 1-Phenyl-5-(2,6-dimethoxy-phenyl)-1*H*-[1,2,3]triazole (**ee**) (0.562 g, 2.0 mmol) in THF (20 mL) was added LDA (2.0 mmol) at 0 ^{o}C. The reaction mixture was stirred at 0 ^{o}C for 1.5 h followed by addition of PCy2Cl (0.442

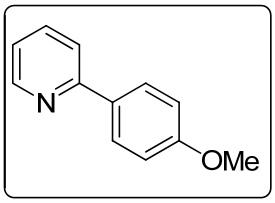
mL, 2.0 mmol). The resulting mixture was slowly warmed to rt and stirred overnight. TLC showed the reaction was essentially complete after 16 h. The solvent was removed under vacuum. A degassed mixture of brine/H2O (1:1) was added, and the resulting mixture was extracted with degassed ether (15 mL × 3). The combined organic layers were dried over Na2SO4 and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel under nitrogen (hexanes:ether, 80:20) to afford **9j** as a white solid (0.727 g, 76%). 1H NMR (360 MHz, CD2Cl2) δ 7.38-7.42 (m, 6H), 6.59 (d, *J* = 8.4 Hz, 2H), 3.65 (s, 6H), 2.16-2.22 (m, 2H), 1.69-1.77 (m, 10H), 1.13-1.39 (m, 10H); 13C NMR (90 MHz, CD2Cl2) δ 158.9, 142.6 (d, *J* = 20.4 Hz), 139.0 (d, *J* = 40.6 Hz), 137.7, 131.9, 129.1, 128.8, 124.2, 105.9, 103.8, 55.7, 33.2 (d, *J* = 7.8 Hz), 30.5 (d, *J* = 16.3 Hz), 29.7 (d, *J* = 7.9 Hz), 27.5 (d, *J* = 10.5 Hz), 27.4 (d, *J* = 6.0 Hz), 26.9; 31P NMR (145 MHz, CD2Cl2) δ -27.36; HRMS (ESI+) calcd. for C28H37N3O2P (MH+) 478.2623, found 478.2599.



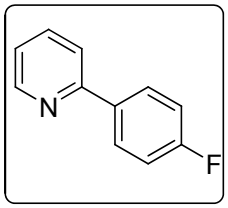
2-phenylpyridine (Table 1-2, entry 1)**:** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.69 (m, 1H) 8.00(d, *J*=7 Hz, 2H) 7.67 (d, *J*=5.5 Hz, 2H) 7.464 (m, 2H) 7.39 (m, 1H) d 7.16 (m, 1H) ^{13}C NMR ($CDCl_3$, 125 MHz) δ 157.5, 149.9, 139.6, 136.9, 129.2, 129.0, 127.1, 122.3, 120.7



2-(*p*-tolyl)pyridine : ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.69 (m, 1H) 8.00(d, *J*=7 Hz, 2H) 7.67 (d, *J*=5.5 Hz, 2H) 7.464 (m, 2H) 7.39 (m, 1H) d 7.16 (m, 1H) ^{13}C NMR ($CDCl_3$, 125 MHz) δ 157.5, 149.9, 139.6, 136.9, 129.2, 129.0, 127.1, 122.3, 120.7

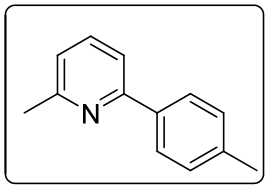


2-(*p*-methoxyphenyl)pyridine (Table 1-2, entry 3) ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.66 (m, 1H) 7.97 (m, 2H) 7.32 (m, 1H) 7.69 (d, 1H) 7.18 (m, 1H) 6.99 (m, 2H) 3.87 (s, 3H) ^{13}C NMR ($CDCl_3$, 125 MHz) δ 160.6, 157.3, 149.7,136.8, 128.3, 121.6, 120.0, 114.3, 55.5

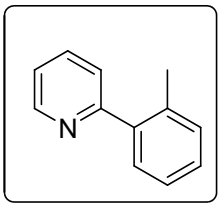


2-(*p*-fluorophenyl)pyridine(Table 1-2, entry 4): δ ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.68 (m,1H) 7.99 (m, 2H) 7.76 (m, 1H) 7.776 (m, 1H) 7.23 (m, 1H) 7.14 (m, 2H) ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.1 1, 149.9, 137.0, 128.6, 128.9, 122.2, 120.4, 115.9

^{19}F NMR (470 MHz, $CDCl_3$) -113.63- 113.59 (m)

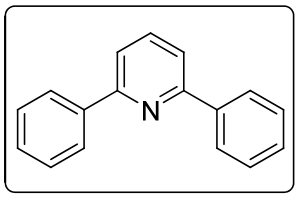


2-methyl-6-(*p*-tolyl)pyridine (Table 1-2, entry 5)**:** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.98 (d, *J*=8.5 Hz, 2H), 7.62 (m, 1 H) 7.50 (d, *J*=8.5 Hz ,1H) 7.27 (d, *J*=7.5 Hz, 2H), 7.075 (d, *J*=7.5 Hz,1H) 2.98 (s, 3H), 2.40 (s, 3H) ^{13}C NMR ($CDCl_3$, 125 MHz) δ 158.5, 157.2,138.8, 137.2, 137.0, 129.6, 127.1,

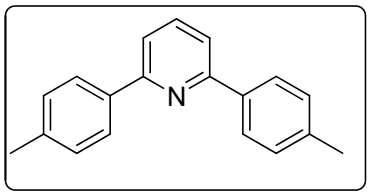


121.5, 117.5, 25.0, 21.5

2-(*o*-tolyl)pyridine (Table 1-2, entry 6): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.17 (m, 1H), 7.76 (m, 1H) 7.41 (m, 2H)7.23 (m, 4H) 2.37(s, 3H) ^{13}C NMR ($CDCl_3$, 125 MHz) δ 160.1, 149.2, 130.3, 136.6, 135.9, 130.9, 129.8, 128.6, 124.4, 121.9, 20.5

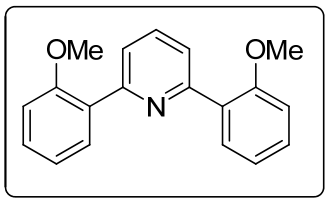


2,6-diphenylpyridine (Table 1-2, entry 7)**:** δ ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.185 (m, 4H) 7.82 (m, 1H) 7.71(d, *J*=7.5 Hz ,2H) 7.58 (m, 4H) 7.44 (m, 2H)^{13}C NMR ($CDCl_3$, 125 MHz) δ 157.1 , 139.7, 137.7, 129.2, 128.9, 127.2, 118.8

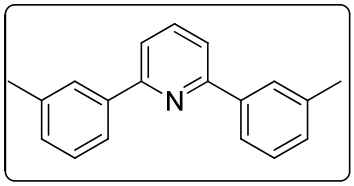


2,6-di(*p*-tolyl)pyridine (Table 1-2, entry 8)**:** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.06 (d, *J*=8,4H), 7.77 (m, 1H), 7.65 (d, *J*=7,5 Hz ,2H) 7.31(d, *J*=7.5 Hz, 4H) 2.43 (s, 6H) ^{13}C

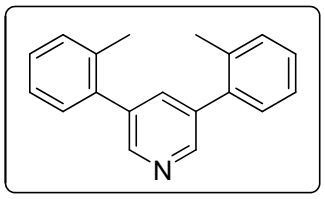
NMR ($CDCl_3$, 125 MHz) δ 156.9, 139.0, 137.5, 137.0, 129.6, 127.0, 118.2, 21.5
HRMS (ESI+) calcd for $C_{19}H_{17}N$ (MH+) 260.1361 found 260.1436



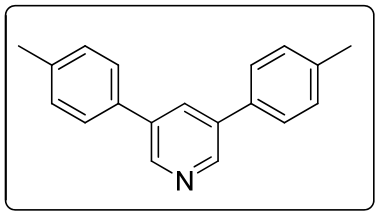
2,6-di(*o*-methoxyphenyl)pyridine (Table 1-2, entry 9)**:** ^{1}H NMR ($CDCl_3$, 400 MHz) 7.93 (d, *J*=2 Hz, 2H) 7.75 (m, 2H) 7.701 (m, 1H) 7.35 (m, 2H) 7.09, (m. 2H) 6.98 (d, 2H)3.87 (s, 6H) ^{13}C NMR ($CDCl_3$, 90MHz) 157.1, 155.4, 135.2, 131.5, 129.7, 129.6, 123.1, 121.1, 111.4, 44.6 HRMS (ESI+) HRMS (ESI+) calcd for $C_{19}H_{17}NO_2$ (MH+) 292.1259 found 292.1335



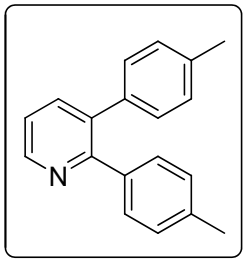
2,6-di(*m*-tolyl)pyridine (Table 1-2, entry 10)**:** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.81 (m, 2H), 8.0 (m, 1H), 7.46 (m, 4H) 7.39 (m, 2H) 7.24 (m, 2H) 2.46 (s, 6H) ^{13}C NMR ($CDCl_3$, 125 MHz) δ147.2, 139.0. 138.0, 136.9, 133.1, 129.2, 129.1, 128.2, 124.7, 21.8
HRMS (ESI+) calcd for $C_{19}H_{17}N$ (MH+) 260.1449 found 260.1439



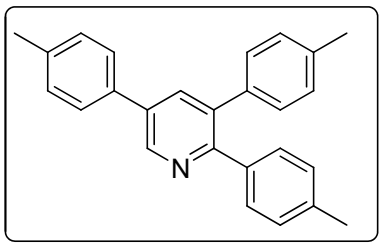
3,5-di(*o*-tolyl*)*pyridine (Table 1-2, entry 12) **:** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.98 (s, 2H) 7.94 (d, *J*=8 Hz,2H) 7.82 (d, *J*=8.5 Hz,1H), 7.68 (d, *J*=8 Hz,2H) 7.399 (m, 2H) d 7.26 (d, *J*=6.5 ,2H) 2.483 (s, 6H) ^{13}C NMR ($CDCl_3$, 125 MHz) δ 157.3, 139.82, 138.5, 137.5, 129.9, 128.8, 127.9, 124.4, 118.9, 21.8



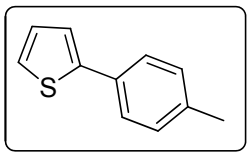
3,5-di(*p*-tolyl) pyridine (Table 1-2, entry 11): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.79 (s, 2H) 8.01(d, *J*=2 1H), 7.55 (d, *J*=8 Hz, 4H), 7.32 (m, 4H), 2.43 (s, 6H) ^{13}C NMR ($CDCl_3$, 125 MHz) δ 146.8, 138.3, 135.2, 132.7, 130.0, 127.3, 21.



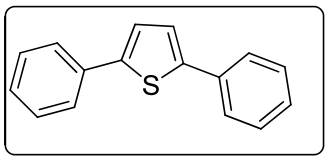
2,3-di(*p*-tolyl)pyridine (Table 1-2, entry 13)**:** ^{1}H NMR($CDCl_3$, 500 MHz) δ 8.65 (m, 1H) 7.68 (m, 1H) 7.26 (m, 3H) 7.03 (m, 6H) 2.33 (d, *J*=14 Hz, 6H) ^{13}C NMR ($CDCl_3$, 125 MHz) δ 148.309, 138.743, 137.6, 137.6, 137.0, 129.9, 129.5, 129.2, 128.8, 122.0, 21.4



2,3,5-(tri-*p*-tolyl)pyridine(Table 1-2, entry 14) δ ^{1}H NMR($CDCl_3$, 400 MHz) 8.88 (s, 1H) 7.87 (d, *J*=2.6, 1H), 7.57 (d, *J* =6 Hz,2H), 7.30 (m, 4H) 7.14 (m, 4H), 7.05 (s, 2H) 2.42 (s, 3H) 2.36 (d, *J*=12.6 Hz, 6H) ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.7, 146.4, 138.2, 137.7, 137.4, 137.2, 136.9, 135.9, 134.8, 130.0, 129.9. 129.6, 129.3, 128.8, 127.1, 21.4



2-(*p*-tolyl)thiophene(Table 1-2, entry 15) : δ ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.52 (m, 2H) 7.30 (m, 2H) 7.20 (m, 2H) 7.08 (m, 1H), 2.42 (d, 3H) ^{13}C NMR ($CDCl_3$, 125 MHz) δ 144.84, 137.5, 131.9, 129.8, 129.6, 128.1, 127.1, 126.1, 124.5, 122.8, 21.2



2,6-diphenylthiophene (Table 1-2, entry 16): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.65(d, *J*=8 Hz, 4H), 7.38(m, 4H), 7.30(m, 4H) ^{13}C NMR ($CDCl_3$, 125 MHz) δ 143.8, 134.5, 129.1, 127.7, 125.8, 124.2

References and Notes

1. (a) Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press: New York, 1985. (b) Collman, J. P., Hegedus, L. S., Norton, J. R., Finke, R. G., Eds.;

Principles and Applications of Organotransition Metal Chemistry; University Science: Mill Valley, CA, 1987. (c) Diederich, F., Stang, P. J., Eds.; *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH: Weinheim, 1998. (d) Diederich, F., Meijere, A. D, Eds.; *Metal-Catalyzed Cross-Coupling Reactions*; 2nd edition, Wiley-VCH: Weinheim, 2004.

2. (a) Christmann, U.; Vilar, R. *Angew. Chem., Int. Ed. Engl.* **2005**, *44*, 366 and references cited therein. (b) Miura, M. *Angew. Chem., Int. Ed. Engl.* **2004**, *43*, 2201.

3. (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Suzuki, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 1998; Chapter 2. (c) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147. (d) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544. (e) Miyaura, N. *Top. Curr. Chem.* **2002**, *219*, 11. (f) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359. (g) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633. (h) Suzuki, A. *In Modern Arene Chemistry*; Astruc, D., Ed.; Wiley-VCH: Weinheim, 2002; pp 53-106. (i) Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, 2419.

4. Gronowitz, S.; Hornfeldt,A. B; Kristjansson,V.; Musil, T. *Chem. Scr*. **1986**, *26*, 305. For more recent examples of this selectivity, see:(a) Cocuzza, A. J.; Hobbs, F. W.; Arnold, C. R.; Chidester, D. R.; Yarem, J. A.; Culp, S.; Fitzgerald, L.; Gilligan, P. J.; *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1057. (b) Jiang, B.; Yang, C.-g *Heterocycles* 50 **2000**, *53*, 1489. (c) Schomaker, J. M.; Delia, T. J. *J. Org. Chem.* **2001**, *66*, 7125. (d) Gong, Y.; Pauls, H. W. *Synlett* **2000**, 829

5. For a review on Pd-catalyzed couplings of aryl chlorides: Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176.

6. (a) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3387. (b) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020. (c) Netherton, M. R.; Dai, C.; Neuschütz, K.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 10099. (d) Kirchhoff, J. H.; Netherton, M. R.; Hills, I. D.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 13662. (e) Kirshhoff, J. H.; Dai, C.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 1945. (f) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 1340.

7. (a) Yin, J.; Rainka, M. P.; Zhang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1162. (b) Barder, T. E.; Buchwald, S. L. *Org. Lett.* **2004**, *6*, 2649. (c) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871. (d) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685

8. (a) Stambuli, J. P.; Kuwano, R.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2002**, *41*, 4746. (b) Kataoka, N.; Shelby, Q.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem*. **2002**,

67, 5553.

8. Zapf, A.; Jackstell, R.; Rataboul, F.; Reirmeier, T.; Monsees, A.; Fuhrmann, C.; Shaikh, N.; Dingerdissen, U.; Beller, M. *Chem. Commun.* **2004**, 38.

9. (a) Zapf, A.; Jackstell, R.; Rataboul, F.; Reirmeier, T.; Monsees, A.; Fuhrmann, C.; Shaikh, N.; Dingerdissen, U.; Beller, M. *Chem. Commun*. **2004**, 38. (b) Harkal, S.; Rataboul, F.; Zapf, A.; Fuhrmann, C.; Reirmeier, T.; Monsees, A.; Beller, M. *Adv. Synth. Catal*. **2004**, *346*, 1742. For a review, see: (c) Zapf, A.; Beller, M. *Chem. Commun*. **2005**, 431.

10. (a) Gstöttmayr, C. W. K.; Böhm, V. P. W.; Herdtweck, E.; Grosche, M.; Herrmann, W. A. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 1363. (b) Grasa, G. A.; Viciu, M. S.; Huang, J.; Zhang, C.; Trudell, M. L.; Nolan, S. P. *Organometallics* **2002**, *21*, 2866. (c) Viciu, M. S.; Germaneau, R. F.; Navarro-Fernandez, O.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2002**, *21*, 5470. (d) Navarro, O.; Kelly, R. A., III; Nolan, S. P. *J. Am. Chem. Soc*. **2003**, *125*, 16194. (e) Navarro, O.; Kaur, H.; Mahjoor, P.; Nolan, S. P. *J. Org. Chem*. **2004**, *69*, 3173. (f) Lebel, H.; Janes, M. K.; Charette, A. B.; Nolan, S. P. *J. Am. Chem. Soc*. **2004**, *126*, 5046.

11. (a) Bedford, R. B.; Cazin, C. S. J.; Hazelwood, S. L. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 4120. (b) Bedford, R. B.; Hazelwood, S. L.; Limmert, M. E. *Chem. Commun.* **2002**, 2610. (c) Bedford, R. B.; Hazelwood, S. L.; Limmert, M. E.; Albisson, D. A.; Draper, S. M.; Scully, P. N.; Coles, S. J.; Hursthouse, M. B. *Chem. Eur. J*. **2003**, *9*, 3216. (d) Bedford, R. B.; Blake, M. E.; Butts, C. P.; Holder, D. *Chem. Commun*. **2003**, 466. (e) Bedford, R. B.; Hazelwood, S. L.; Limmert, M. E. *Organometallics* **2003**, *22*, 1364.

12. (a) Leadbeater, N. E.; Marco, M. *Org. Lett.* **2002**, 4, 2973. (b) Bedford, R. B.; Butts, C. P.; Hurst, T. E.; Lidstrom, P. *Adv. Synth. Catal.* **2004**, *346*, 1627. (c) Miao, G.; Ye, P.; Yu, L.; Baldino, C. M. *J. Org. Chem*. **2005**, *70*, 2332. (d) Arvela, R. K.; Leadbeater, N. E. *Org. Lett.* **2005**, *7*, 2101

13. (a) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew .Chem. Int. Ed.* **2001**, *40*, 2004. (b) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2002**, *41*, 2596. (c) Krasinski, A.; Fokin, V. V.; Sharpless, K. B. *Org. Lett*. **2004**, *6*, 1237. (d) Feldman, A. K.; Colasson, B.; Fokin, V. V. *Org. Lett.* **2004**, *6*, 3897. (e) Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V. V.; Noodleman, L.; Sharpless, K. B.; Fokin, V. V. *J. Am. Chem. Soc*. **2005**, *127*, 210.

14. (a) Huisgen, R. in *1,3-Dipolar Cycloaddition Chemistry* (Ed.: A.Padwa), Wiley, New York, 1984, pp. 1 – 176. (b) Padwa, A. in *Comprehensive Organic Synthesis*, Vol. 4 (Ed.: B. M. Trost), Pergamon, Oxford, 1991, pp. 1069 – 1109

15. Dai, Q.; Gao W.; Liu, D.; Zhang X. *Org. Lett.,* **2005**, *7*, 4907.

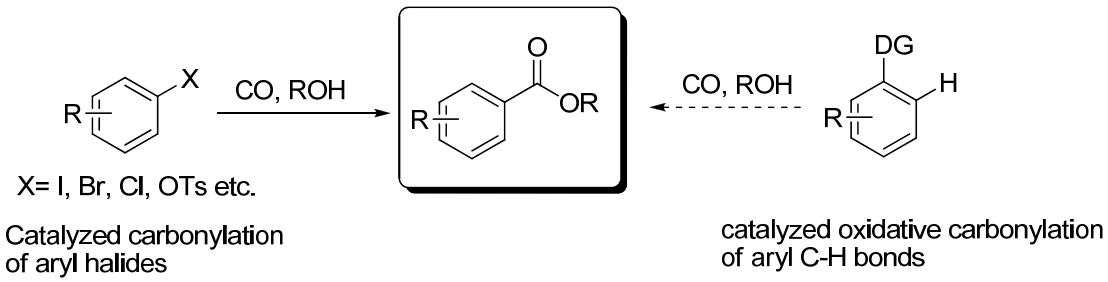
16. (a) Kudo, N.; Perseghini, M.; Fu, G. C. *Angew. Chem., Int. Ed*. **2006**, *45*, 1282. (b) Billingsley, K. L.; Anderson, K. W.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 3484. (c) Guram, A. S.; King, A. O.; Allen, J. G.; Wang, X.; Schenkel, L. B.; Chan, J.; Bunel, E. E.; Faul, M; Larsen, R. D.; Matrinelli, M. J.; Reider, P. J. *Org. Lett*. **2006**, *8*, 1787. (d) Billingsley, K.; Buchwald, S. L., *J. Am. Chem. Soc.*, **2007**, *129*, 3358. (e) Yamamoto, Y.; Takizwa, M; Yu, X. Q., Miyaura, N.; *Angew. Chem., Int. Ed*., **2008**, *47*, 928.

Chapter 2

Rhodium-Catalyzed Direct Oxidative Carbonylation of aromatic C-H bonds with CO and Alcohols

2.1 Oxidative Carbonylation of Aryl C-H Bonds: Introduction and background

Aryl carboxylic acids and derivatives are often present in various valuable commodity chemicals, but so-far the direct synthesis of aryl carboxylic acids has remained elusive. Whereas transition metal-catalyzed carbonylation [17] of aryl iodides, bromides and triflates is a well-known method for the regioselective installation of carbonyl functional groups unto arenes, but this first require the synthesis of aryl halide precursors. [18] Recent advances have allowed the use of the readily available aryl chlorides and aryl tosylates which use cheaper and readily available phenols, [19] but a more ideal and environmentally friendly method to construct aryl carboxylic acids functional groups would be direct carbonylation of aryl C-H bonds in regioselective manner (Scheme 2-1). Previously there has been a few reports of Pd-catalyzed carbonylation of aromatic amines to form benzolactams, however controlling the regiocontrol of the carbonylation reaction remain challenging. [20]



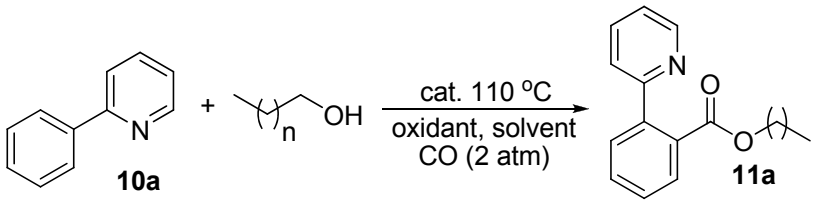
Scheme 2-1: Transition metal carbonylation reactions

Activation[21] and functionalization of C-H bonds is one of the most challenging and important tasks in organic chemistry. [22, 23] Recently, Pd-catalyzed direct functionalizations of aryl C-H to form C-C and C-heteroatom bonds have been investigated intensively by various research groups. [24] While palladium has proved to be one of the most effective catalysts for this transformation, [25-30] however, Pd-catalyzed *ortho*-selective C-H bond carbonylation is exceedingly difficult because the depalladation process is often complicated by the reduction of Pd(II) to Pd(0) under an CO atmosphere which therefore disrupts the catalytic cycle.[31-33] In the past decade, Rh [34] and Ru [35] complexes have emerged as very effective catalysts in the activation and functionalization of C-H bonds. It has been shown before that Rh-CO complexes are the most active species for carbonylation reactions, such as Monsanto acetic acid process [36] and hydroformylation of alkenes. [37] In connection with Rh and Ru catalyzed reductive coupling of aryl C-H bonds with alkenes or CO/alkenes, [38] we envision that it may be possible to conduct direct oxidative carbonylation using a simple Rh-CO catalyst under CO atmosphere.

2.2 Oxidative Carbonylation of Aryl C-H Bonds: Substrate Scope

Compounds containing heteroatoms are prevalent in nature and natural products and the syntheses of these compounds have attracted much attention in industrial and academic research due to desirable biological and pharmaceutical properties. Our experiment was initially conducted by treating 2-phenylpyridine **10a** with *n*-pentanol (5 equiv), [Rh(COD)Cl]2 (2 mol %), $Cu(OAc)_2$ (3 equiv) in toluene under a CO atmosphere (2 atm) (Table 1, entry 1). We were pleased to find that after 8 h at

110 °C, the reaction resulted in 48% yield of the carbonylation product **11a**. Further experiments showed that Cu(OAc)2 is not a good oxidant for the C-H activation carbonylation. We reasoned that the coordination of Cu(II) to the pyridine moiety might prevent the carbonylation reaction, which is in agreement with the results reported by Yu.[16] Therefore, we screened a variety of other oxidants this transformation. To our delight, Oxone ($2KHSO_5KHSO_4K_2SO_4$) was found to be a particularly effective terminal oxidant in this Rh-catalyzed direct carbonylation reaction. The use of inexpensive, non-toxic, and environmentally benign Oxone also makes this transformation more practical. After treatment of **1a** (0.1 mmol) with *n*-pentanol (5 equiv), Oxone (3 equiv), and [Rh(COD)Cl]2 (2 mol %) in toluene at 110 °C under CO (2 atm) for 8 h, **11a** was obtained in 82% yield (Table 1, entry 5). We also screened other oxidants such as BQ (benzoquinone), CAN (ammonium

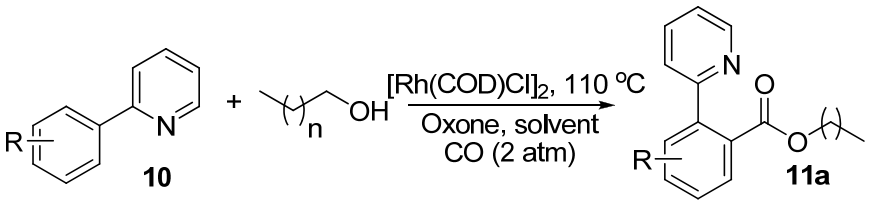


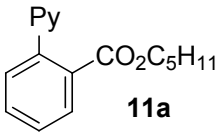
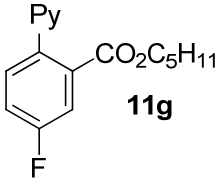
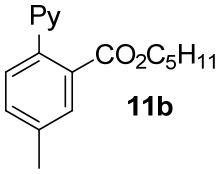
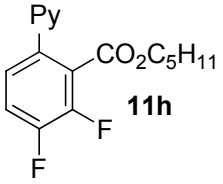
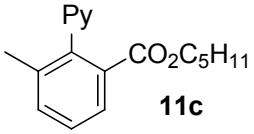
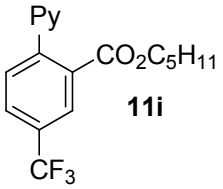
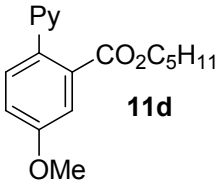
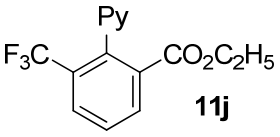
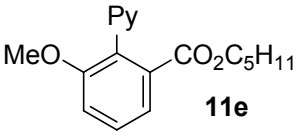
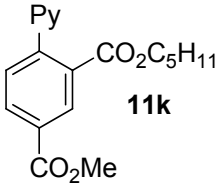
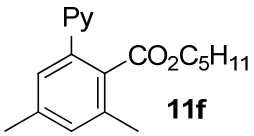
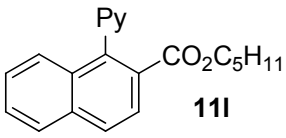
entry	catalyst	oxidant	solvent	yield (%)
1	$[Rh(COD)Cl]_2$	$Cu(OAc)_2$	toluene	48
2	$[Rh(COD)Cl]_2$	BQ	toluene	nd
3	$[Rh(COD)Cl]_2$	CAN	toluene	32
4	$[Rh(COD)Cl]_2$	$K_{2s}S_2O_8$	toluene	75
5	$[Rh(COD)Cl]_2$	Oxone	toluene	82
6	$[Rh(COD)Cl]_2$	Tempo	toluene	Nd
7	$[Rh(COD)Cl]_2$	Oxone	1,4-dioxane	<5
8	$[Rh(COD)Cl]_2$	Oxone	*n*-pentanol	<5
9	$[Rh(COD)Cl]_2$	Oxone	DMF	<5
10	$[Rh(COD)Cl]_2$	Oxone	THF	15
11	$Pd(OAc)_2$	Oxone	toluene	<5
12	$Ru_3(CO)_{12}$	Oxone	toluene	<5

Table 2-1: Optimization of Direct Oxidative Carbonylation of Arene

cerium (IV) nitrate), $K_2S_2O_8$, and TEMPO (2, 2, 6, 6-tetramethylpiperidine-*N*-oxyl radical) are all less effective for this Rh-catalyzed reaction (Table 1, entries 2-4, 6).

After having screened the effect of oxidants and various catalysts, we further screened



Entry	Product	yield	entry	product	yield
1	 **11a**	82	7	 **11g**	75
2	 **11b**	88	8	 **11h**	90
3	 **11c**	86	9	 **11i**	80
4	 **11d**	63	10	 **11j**	38
5	 **11e**	61	11	 **11k**	83
6	 **11f**	70	12	 **11l**	78

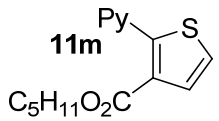
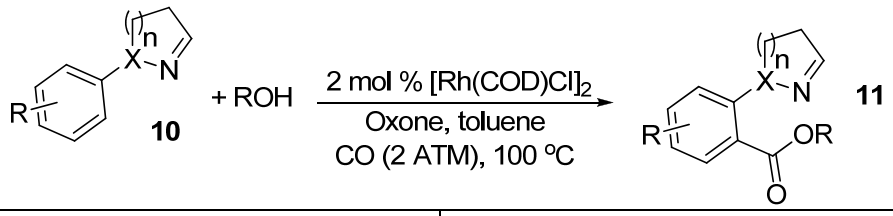
13		96	

Table 2-2: Rh-Catalayzed Carbonlayation of Aromatic C-H bonds

the effect of solvents on this transformation; toluene was found to be most effective (Table 2-1, entries 7-10). Rhodium was found to be the metal of choice for this reaction, as low conversion was observed when $Pd(OAc)_2$ or $Ru_3(CO)_{12}$ was

employed as the catalyst in the oxidative carbonylation reaction (Table 2-1, entries 11-12). Under the optimized conditions, for this direct carbonylation process, we have explored the substrate scope (Table 2-2). This new carbonylation procedure displayed good functional group tolerance. Arenes with ester, trifluoromethyl, and ether groups all gave high yields of corresponding esters (Table 2-2, entries 4, 5, 9-11). Aryl fluoride containing molecules are prevalent in important drug molecules, and using our system, an aryl C-F bond was tolerated under the reaction conditions; **2g** and **2h** were obtained in high yields and without any products of C-F bond carbonylation (Table 2, entries 7, 8). To examine the electronic effects of this transformation, we found that electron-rich arenes show more reactivity and gave slightly higher yields than electron-deficient arenes (Table 2-2, entries 2, 3, 7, 9, and 11). Whereas relatively slightly lower yields were achieved for the carbonylation reaction of 2-(4-methoxyphenyl)pyridine **1d** and 2-(2-methoxyphenyl)pyridine **1e** due to partial decomposition of the substrates during the course carbonylation reaction (Table 2-2, entries 4, 5). Hetero arenes exhibit higher reactivity than arenes. The carbonylation product **2m** was obtained in excellent yield from 2-(thiophen-2-yl)pyridine **1m** (Table



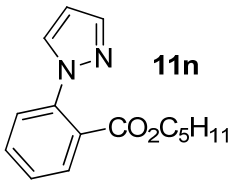
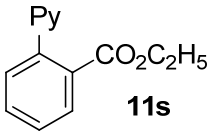
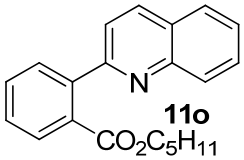
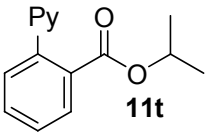
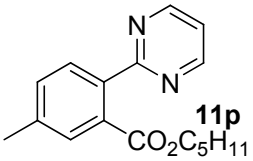
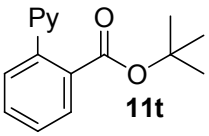
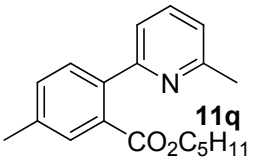
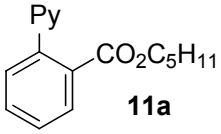
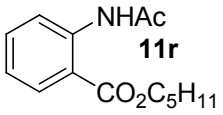
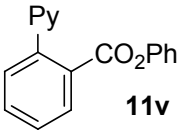
entry	product	yield (%)	entry	product	yield (%)
1	 **11n**	66	6	 **11s**	40
2	 **11o**	52	7	 **11t**	35
3	 **11p**	80	8	 **11t**	<5
4	 **11q**	45	9	 **11a**	82
5	 **11r**	<5	10	 **11v**	<5

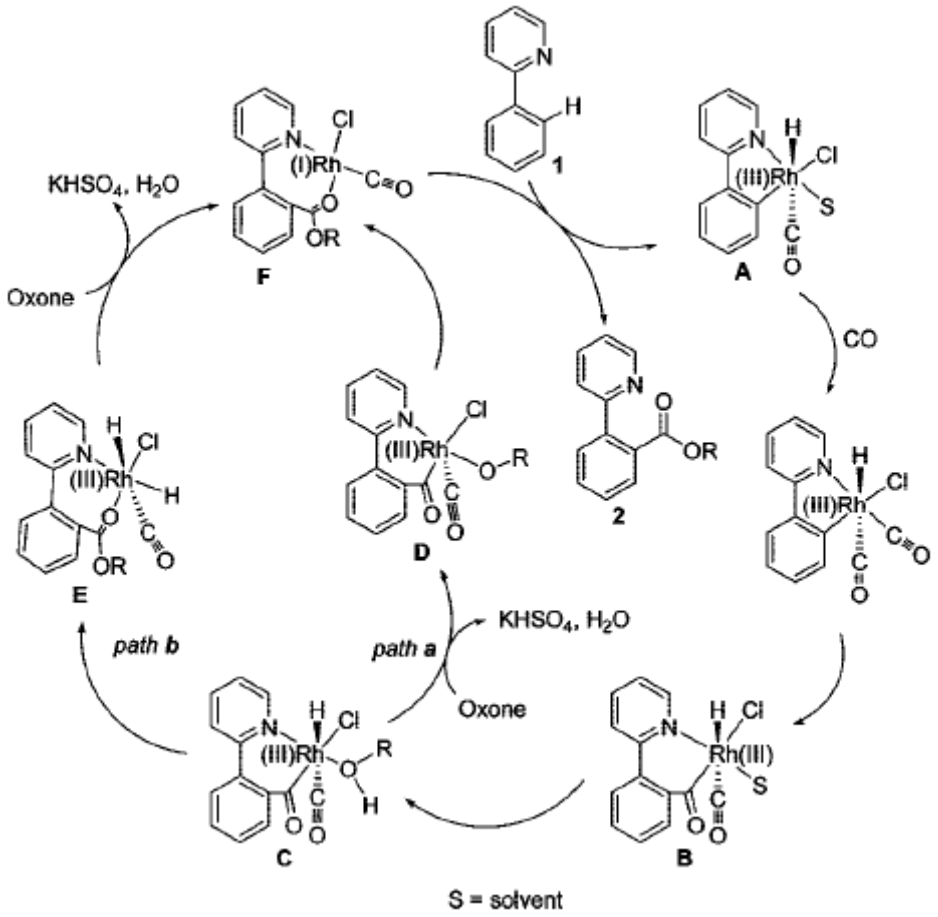
Table 2-3: Effect of directing groups and alcohols on Carbonylation of aromatic C-H bonds

2, entry 13). In addition, the synthesis of esters derived from low molecular weight alcohol was also achieved, albeit the yield was limited by the boiling point of the alcohol.3a Ethyl 2-(pyridin-2-yl)-3-(trifluoromethyl) benzoate **2j** was obtained in moderate yield with 56% of the starting material **10j** recovered (Table 2-2, entry 10).

Furthermore, different directing groups and different alcohols were tested for this

oxidative carbonylation reaction (Table 3). Nitrogen heterocycles, such as pyrazole and quinoline, can serve as efficient directing groups and generate the carbonylation products in moderate to good yields under the optimal conditions (Table 2-3, entries 1, 2). It is important to note that the monocarbonylation products were obtained in all cases from the corresponding substrates. Even with pyrimidine which possibly contains two nitrogen directing groups, the monocarbonylation product **11p** was formed exclusively from 2-*p*-tolylpyrimidine **11p** (Table 2-3, entry 3). The steric hindrance of a directing group played an important role in the transformation. The carbonylation product **11q** was achieved in only 45% yield when 6-methylpyridyl group was used as the directing group (Table 2-3, entry 4) and even when the catalyst loading was doubled, the yield did not improve. It has been recently reported that acetanilide shows a good reactivity in Pd-catalyzed C-H activation.[26b,28a] However, only very low conversion was observed when acetanilide was employed as the substrate in this Rh-catalyzed oxidative carbonylation reaction (Table 2-3, entry 5) due to their relatively low boiling points. An extensive investigation of the reaction shows that both steric hindrance and boiling point of the alcohol played the important role in the transformation. Ethanol and 2-propanol gave lower yields of the carbonylation products (Table 2-3, entries 6, 7) due to the volatility of the alcohol. Only very low conversion was observed when *t*-BuOH was employed (Table 3, entry 8). Additionally, phenol exhibited no reactivity under the carbonylation reaction conditions (Table 3, entry 10), possibly due to the increased strength of the phenol bond.

Although the exact mechanism of the reaction remains unclear, two mechanisms were proposed on the basis of our own observations and other related studies [22a,d,34a] for this oxidative carbonylation reaction (Scheme 2). In one case, first, coordination of the *ortho*-directing group and oxidative addition of an aromatic C-H bond to Rh(I) gives a Rh(III) complex **A**.[39] Next, insertion of CO in the resulting C-Rh bond to form an acylrhodacycle intermediate **B**, followed by coordination of alcohol to form intermediate **C**. The acylrhodacycle intermediate **C** is assumed to be oxidized by Oxone to give the Rh(III) complex **D** (path a) and undergoes a subsequent reductive elimination to afford the active catalyst species Rh(I) **F** and the carbonylation product **2**. An alternative mechanism (path **b**) is alcoholysis24 of acylrhodium species **C** to give the Rh-H species **E**. The latter is assumed to be oxidized by Oxone to afford the active catalyst species Rh(I) **F**.[34f,41] If the reaction is proceeded though path **b**, we will expect to observe the reaction when a stoichiometric $[Rh(COD)Cl]_2$ is used. Therefore, a study was carried out to establish the fundamental steps of this catalytic cycle and the role of Oxone therein. Indeed, this reaction does not occur at all in the absence of Oxone even when the stoichiometric $[Rh(COD)Cl]_2$ was used, which indicates that the path **b** is less likely.



Scheme 2-1: Mechanism of Rh-Catalyzed oxidative carbonylation

2.3 Conclusion

In summary, we have developed a mild and general procedure for the Rh-catalyzed oxidative carbonylation of arenes and heteroarenes with carbon monoxide and alcohols. This Rh catalyzed oxidative carbonylation reaction shows high regioselectivity and good functional group tolerance. Up to 96% yield of *ortho*-substituted aryl or heteroaryl carboxylic esters were obtained with this methodology. The use of Oxone as an inexpensive and environmentally benign terminal oxidant makes his unprecedented transformation attractive in organic synthesis. A possible mechanism was proposed in this article, and the study rovides a new avenue for the direct carbonylation of aryl C-H onds. Current research is focused

on extending the scope and aining more detailed information on the exact mechanism of this reaction.

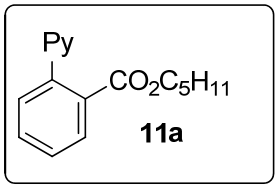
Experimental Section

General information:

Column chromatography was carried out on silica gel. 1H NMR spectra were recorded on 500 MHz or 400 MHz in CDCl3 and 13C NMR spectra were recorded on 125 MHz or 100 MHz in CDCl3.

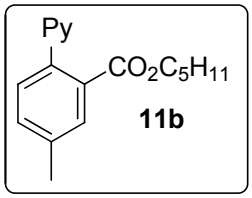
Typical procedure for carbonylation of 1 with CO and Alcohol

A vial (5 mL) charged with arene **10** (0.1 mmol), *n*-pentanol (0.5 mmol), Oxone (185 mg, 0.3 mmol), $[Rh(cod)Cl]_2$ (2 mol %) and toluene (2.0 mL) was stirred in a steel autoclave under CO (2 atm). After stirring at 110 °C for 8 h, the CO was released carefully and the solution was subjected to a short column of silica gel to remove the solid and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to afford corresponding products **11**



11a

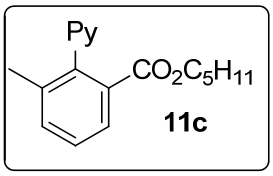
11a: oil. 1H NMR (500 MHz, CDCl3) δ 8.65-8.64 (d, *J* = 4.0 Hz, 1H), 7.85-7.83 (d, *J* = 7.5 Hz, 1H), 7.76-7.73 (t, *J* = 7.5 Hz, 1H), 7.55 (m, 2H), 7.49-7.46 (t, *J* = 7.5 Hz, 2H), 7.26-7.24 (d, *J* = 7.5 Hz, 1H), 4.09-4.06 (t, *J* = 6.5 Hz, 2H), 1.44-1.40 (m, 2H), 1.24-1.21 (m, 2H), 1.13-1.08 (m, 2H), 0.86-0.83 (t, *J* = 7.5 Hz, 3H). 13C NMR (125 MHz, CDCl3) δ 168.9, 158.9, 149.1, 140.9, 136.1, 131.9, 131.0, 129.8, 129.7, 128.3, 122.8, 122.0, 65.2, 28.0, 27.9, 22.3, 13.9.
HRMS (ESI) Calcd for C17H20NO2 (MH+): 270.1489, found (MH+): 270.1483.



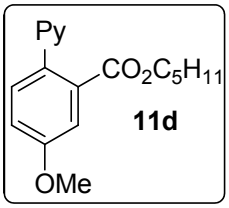
11b

11b: oil. 1H NMR (500 MHz, CDCl3) δ 8.64-8.63 (m, 1H), 7.73-7.70 (m, 1H), 7.63 (s, 1H), 7.46-7.43 (m, 2H), 7.37-7.35 (m, 1H), 7.24-7.21 (m, 1H), 4.08-4.05 (t, *J* = 6.5

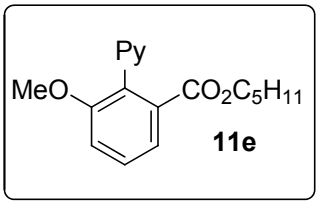
Hz, 2H), 2.44 (s, 1H), 1.44-1.38 (m, 2H), 1.26-1.19 (m, 2H), 1.11-1.07 (m, 2H), 0.85-0.82 (t, *J* = 7.5 Hz, 3H). 13C NMR (125 MHz, CDCl3) δ 169.2, 158.9, 149.0, 138.3, 138.1, 136.0, 131.8, 131.6, 130.2, 129.7, 122.7, 121.8, 65.2, 28.0, 27.9, 22.3, 21.0, 13.9.
HRMS (ESI) Calcd for C18H22NO2 (MH+): 284.1645, found (MH+): 284.1638.



11c: oil. 1H NMR (500 MHz, CDCl3) δ 8.68-8.67 (m, 1H), 7.83-7.81 (m, 1H), 7.63 (d, *J* = 7.5 Hz, 1H), 7.75-7.71 (m, 1H), 7.44-7.42 (m, 1H), 7.38-7.35 (t, *J* = 7.5 Hz, 1H), 7.28-7.25 (m, 1H), 3.98-3.95 (t, *J* = 6.5 Hz, 2H), 2.12 (s, 1H), 1.37-1.33 (m, 2H), 1.27-1.23 (m, 2H), 1.19-1.14 (m, 2H), 0.88-0.85 (m, 3H). 13C NMR (100 MHz, CDCl3) δ 167.7, 159.4, 149.1, 140.9, 137.1, 135.7, 133.7, 131.0, 127.9, 127.8, 124.0, 121.7, 65.0, 28.0, 27.9, 22.3, 20.1, 13.9.
HRMS (ESI) Calcd for C18H22NO2 (MH+): 284.1645, found (MH+): 284.1643.

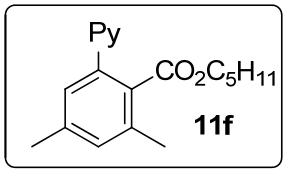


11d: oil. 1H NMR (500 MHz, CDCl3) δ 8.61-8.60 (m, 1H), 7.72-7.69 (m, 1H), 7.52-7.48 (m, 1H), 7.43-7.42 (m, 1H), 7.33-7.32 (m, 1H), 7.22-7.20 (m, 1H), 7.09-7.06 (m, 1H), 4.09-4.06 (t, *J* = 6.5 Hz, 2H), 3.91-3.88 (m, 3H), 1.43-1.39 (m, 2H), 1.26-1.20 (m, 2H), 1.11-1.07 (m, 2H), 0.86-0.82 (m, 3H). 13C NMR (125 MHz, CDCl3) δ 169.0, 159.5, 158.5, 149.0, 136.1, 133.4, 133.2, 131.1, 122.6, 121.6, 116.9, 114.6, 65.3, 55.6, 28.0, 27.9, 22.2, 13.9. HRMS (ESI) Calcd for C18H22NO3 (MH+): 300.1594, found (MH+):
300.1588.

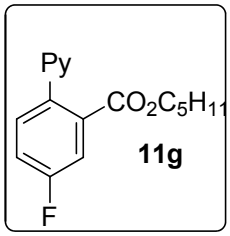


11e: oil. 1H NMR (500 MHz, CDCl3) δ 8.64-8.63 (d, *J* = 4.0 Hz, 1H), 7.72-7.69 (m, 1H), 7.51-7.50 (d, *J* = 3.0 Hz, 1H), 7.45-7.39 (m, 2H), 7.24-7.21 (m, 1H), 7.13-7.11 (d, *J* = 8.0 Hz, 1H), 3.99-3.96 (t, *J* = 6.5 Hz, 2H), 3.75 (s, 3H), 1.37-1.32 (m, 2H), 1.26-1.20 (m, 2H), 1.15-1.10 (m, 2H), 0.89-0.84 (m, 3H). 13C NMR (125 MHz, CDCl3) δ 167.9, 157.0, 156.0, 148.9, 135.3, 133.3, 130.3, 129.2, 125.1, 122.0, 121.7,

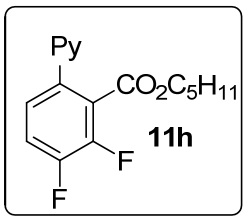
114.2, 65.0, 56.1,28.0, 27.9, 22.2, 13.9.
HRMS (ESI) Calcd for C18H22NO3 (MH+): 300.1594, found (MH+): 300.1585.



11f: oil. 1H NMR (500 MHz, CDCl3) δ 8.62-8.61 (m, 1H), 7.72-7.69 (m, 1H), 7.53-7.51(dd, *J1* = 8.0 Hz, *J2* = 1.0 Hz, 1H), 7.26 (s, 1H), 7.22-7.19 (m, 1H), 7.09 (s, 1H),4.07-4.04 (t, *J* = 6.5 Hz, 2H), 2.41 (s, 3H), 2.38 (s, 3H), 1.43-1.40 (m, 2H), 1.23-1.18(m, 2H), 1.08-1.05 (m, 2H), 0.84-0.81 (m, 3H). 13C NMR (125 MHz, CDCl3) δ 170.1,158.4, 149.1, 139.3, 139.0, 136.3, 136.3, 131.3, 130.4, 127.3, 122.3, 121.9, 65.0, 27.9,27.9, 22.3, 21.2, 19.7, 13.9.
HRMS (ESI) Calcd for C19H24NO2 (MH+): 298.1802, found (MH+): 298.1796.

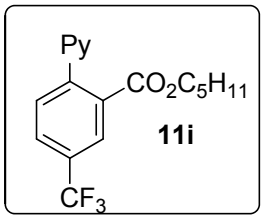


11g: oil. 1H NMR (500 MHz, CDCl3) δ 8.63-8.62 (m, 1H), 7.75-7.71 (m, 1H), 7.54-7.51(m, 2H), 7.44-7.42 (dd, *J1* = 8.0 Hz, *J2* = 1.0 Hz, 1H), 7.26-7.24 (m, 2H), 4.09-4.07 (m, 2H), 1.45-1.41 (m, 2H), 1.27-1.21 (m, 2H), 1.13-1.08 (m, 2H), 0.87-0.82 (m, 3H). 13C NMR (125 MHz, CDCl3) δ 167.6 (d, *J* = 2.3 Hz), 162.2 (d, *JCF* = 248.1 Hz), 157.8,149.0, 137.0 (d, *JCF* = 3.8 Hz), 136.2, 133.7 (d, *JCF* = 7.4 Hz), 131.7 (d, *JCF* = 7.9 Hz),
122.7, 122.0, 117.9 (d, *JCF* = 21.3 Hz), 116.8 (d, *JCF* = 23.6 Hz), 65.5, 27.9, 27.8, 22.2,13.8. 19F NMR (470 MHz, CDCl3): δ –113.32 - –113.37 (m). HRMS (ESI) Calcd for C17H19FNO2 (MH+): 288.1394, found (MH+): 288.1388.

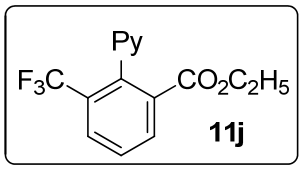


11h: oil. 1H NMR (500 MHz, CDCl3) δ 8.68-8.67 (dd, *J1* = 4.5 Hz, *J2* = 1.0 Hz, 1H), 7.80-7.77 (m, 1H), 7.74-7.71 (m, 1H), 7.48-7.47 (d, *J* = 8.0 Hz, 1H), 7.33-7.26 (m, 2H),4.02-3.99 (t, *J* = 6.5 Hz, 2H), 1.39-1.33 (m, 2H), 1.25-1.21 (m, 2H), 1.13-1.09 (m, 2H),0.86-0.83 (t, *J* = 7.5 Hz, 3H). 13C NMR (125 MHz, CDCl3) δ 166.2 (d, *J* = 2.3 Hz),152.6 (dd, *JCF1* = 254.0 Hz, *JCF2* = 13.9 Hz), 152.3 (d, *JCF1* = 2.8 Hz), 149.4,

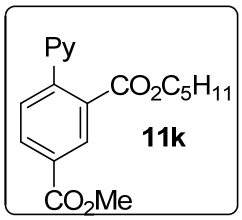
148.2 (dd, *JCF1* = 248.5 Hz, *JCF2* = 13.5 Hz), 136.0, 131.6 (d, *JCF* = 12.9 Hz), 128.6 (d, *JCF* = 3.6
Hz), 126.4 (m), 124.7 (d, *JCF* = 2.8 Hz), 122.8, 116.7 (d, *JCF* = 17.5 Hz), 65.5, 27.9, 27.9, 22.2, 13.8. 19F NMR (470 MHz, CDCl3): δ –131.82 - –131.90 (m, 1F), –140.56 -–140.62 (m, 1F).
HRMS (ESI) Calcd for C17H18F2NO2 (MH+): 306.1300, found (MH+):306.1292.



11i: oil. 1H NMR (500 MHz, CDCl3) δ 8.66-8.65 (m, 1H), 8.08 (s, 1H), 7.81-7.76 (m,2H), 7.69-7.67 (d, *J* = 8.5 Hz, 1H), 7.50-7.48 (m, 1H), 7.32-7.29 (m, 1H), 4.12-4.09(m, 2H), 1.45-1.40 (m, 2H), 1.25-1.21 (m, 2H), 1.12-1.08 (m, 2H), 0.87-0.82 (m, 3H). 13C NMR (125 MHz, CDCl3) δ 167.7, 157.4, 149.3, 144.1, 136.4, 132.7, 130.4 (d, *J* = 36.5 Hz), 127.6 (q, *J* = 4 Hz), 126.8 (q, *J* = 4 Hz), 122.8, 124.4 (q, *J* = 270 Hz), 122.8,
122.6, 65.7, 27.9, 27.8, 22.2, 13.8. 19F NMR (470 MHz, CDCl3): δ –63.15 (s).
HRMS(ESI) Calcd for C18H19F3NO2 (MH+): 338.1362, found (MH+): 338.1355.

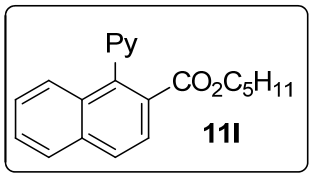


11j: oil. 1H NMR (500 MHz, CDCl3) δ 8.64-8.63 (m, 1H), 8.13-8.12 (d, *J* = 8.0 Hz, 1H) 7.92-7.91 (d, *J* = 8.0 Hz, 1H), 7.76-7.73 (m, 1H), 7.62-7.59 (t, *J* = 8.0 Hz, 1H), 7.40-7.38 (d, *J* = 7.5 Hz, 1H), 7.33-7.31 (m, 1H), 4.05-4.00 (q, *J* = 7.0 Hz, 2H),1.01-0.98 (t, *J* = 7.0 Hz, 3H). 13C NMR (125 MHz, CDCl3) δ 166.5, 156.2, 148.6,140.1, 135.3, 133.6 (d, *J* = 32 Hz), 129.5, 129.1 (q, *J* = 4 Hz), 128.3, 124.8 (q, *J* = 272 Hz,), 124.5, 122.5, 122.2, 61.2, 13.7. 19F NMR (470 MHz, CDCl3): δ –57.25 (s).
HRMS (ESI) Calcd for C15H13F3NO2 (MH+): 296.0893, found (MH+): 296.0886.

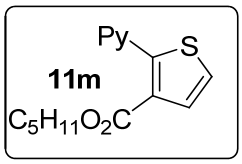


11k: oil. 1H NMR (500 MHz, CDCl3) δ 8.66-8.65 (m, 1H), 8.47-8.47 (d, *J* = 1.5 Hz, 1H), 8.21-8.19 (dd, *J1* = 8.0 Hz, *J2* = 1.5 Hz, 1H), 7.78-7.75 (m, 1H), 7.64-7.63 (d, *J*

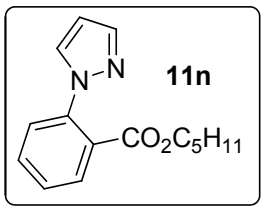
= 8.0 Hz, 1H), 7.50-7.49 (d, *J* = 8.0 Hz, 1H), 7.30-7.26 (m, 1H), 4.11-4.09 (t, *J* = 6.5 Hz, 2H), 3.96 (s, 3H), 1.47-1.43 (m, 2H), 1.26-1.21 (m, 2H), 1.14-1.09 (m, 2H), 0.87-0.82 (m, 3H). 13C NMR (125 MHz, CDCl3) δ 168.1, 166.0, 157.7, 149.2, 144.8, 136.3, 132.3, 131.8, 130.9, 130.1, 130.0, 122.8, 122.5, 65.5, 52.4, 28.0, 27.9, 22.2, 13.9. HRMS (ESI)
Calcd for C19H22NO4 (MH+): 328.1543, found (MH+): 328.1534.



11l: oil. 1H NMR (500 MHz, CDCl3) δ 8.78-8.77 (dd, *J1* = 5.0 Hz, *J2* = 1.0 Hz, 1H) 8.06 8.05 (d, *J* = 8.5 Hz, 1H), 7.97-7.95 (d, *J* = 8.5 Hz, 1H), 7.93-7.91 (d, *J* = 8.0 Hz, 1H), 7.84-7.81 (m, 1H), 7.57-7.54 (m, 1H), 7.47-7.37 (m, 4H), 4.06-4.03 (t, *J* = 6.5 Hz, 2H), 1.43-1.38 (m, 2H), 1.30-1.24 (m, 2H), 1.23-1.18 (m, 2H), 0.93-0.85 (m, 3H). 13C NMR (100 MHz, CDCl3) δ 167.7, 158.5, 149.3, 140.4, 135.7, 135.0, 132.1, 128.5, 127.9, 127.7, 127.6, 127.1, 126.8, 125.8, 125.1, 122.1, 65.2, 28.0, 28.0, 22.3, 13.9.
HRMS (ESI) Calcd for C21H22NO2 (MH+): 320.1645, found (MH+): 320.1638.

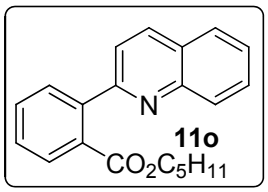


11m: oil. 1H NMR (500 MHz, $CDCl_3$) δ 8.64-8.62 (m, 1H), 7.86-7.84 (m, 1H), 7.73-7.70 (m, 1H), 7.51-7.50 (m, 1H), 7.34-7.33 (m, 1H), 7.27-7.24 (m,1H), 4.23-4.20 (m, 2H), 1.65-1.61 (m, 2H), 1.33-1.26 (m, 4H), 0.89-0.87 (m, 3H). 13C NMR (125 MHz, $CDCl_3$) δ 163.6, 151.8, 149.8, 149.1, 135.9, 130.2, 129.1, 125.9, 124.4, 122.9, 65.0, 28.2, 28.1, 22.3, 13.9.
HRMS (ESI) Calcd for $C_{15}H_{18}NO_2S$ (MH^+): 276.1053, found (MH^+): 276.1045.

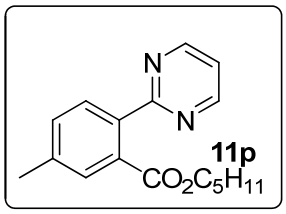


11n: oil. 1H NMR (500 MHz, CDCl3) δ 7.82-7.80 (d, *J* = 8.0 Hz, 1H), 7.69-7.68 (m, 2H),7.58-7.54 (m, 1H), 7.48-7.42 (m, 2H), 6.43-6.43 (d, *J* = 1.5 Hz, 1H), 4.13-4.11 (t, *J* = 6.5 Hz, 2H), 1.52-1.48 (m, 2H), 1.30-1.18 (m, 4H), 0.88-0.85 (m, 3H). 13C NMR (125 MHz, CDCl3) δ 166.9, 140.8, 139.3, 131.8, 130.4, 129.9, 128.0, 127.7, 125.3, 106.9, 65.6, 27.9, 27.9, 22.2, 13.8. HRMS (ESI) Calcd for C15H19N2O2 (MH+):

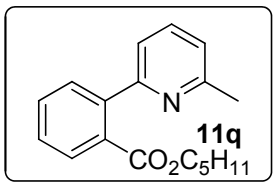
259.1441,found (MH+): 259.1433.



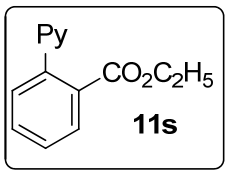
11o: oil. 1H NMR (500 MHz, CDCl3) δ 8.20-8.18 (d, *J* = 8.5 Hz, 1H), 8.13-8.11 (d, *J* = 8.5 Hz, 1H), 7.92-7.90 (d, *J* = 8.0 Hz, 1H), 7.85-7.84 (d, *J* = 8.0 Hz, 1H), 7.73-7.70 (m,1H), 7.67-7.66 (d, *J* = 7.5 Hz, 1H), 7.61-7.49 (m, 4H), 4.03-4.00 (m, 2H), 1.26-1.19(m, 2H), 1.01-0.97 (m, 2H), 0.86-0.81 (m, 2H), 0.67-0.64 (m, 3H). 13C NMR (125 MHz, CDCl3) δ 168.8, 158.9, 147.8, 141.3, 135.9, 131.9, 131.2, 130.0, 129.9, 129.6, 129.5, 128.5, 127.4, 126.9, 126.4, 121.2, 65.2, 27.9, 27.8, 22.1, 13.7.
HRMS (ESI)
Calcd for C21H22NO2 (MH+): 320.1645, found (MH+): 320.1633.



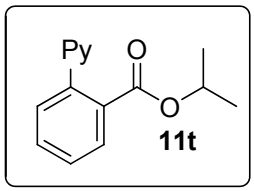
11p: oil. 1H NMR (500 MHz, CDCl3) δ 8.78-8.77 (m, 2H), 7.92-7.91 (d, *J* = 7.5 Hz, 1H),7.52 (s, 1H), 7.39-7.37 (m, 1H), 7.21-7.19 (t, *J* = 5.0 Hz, 1H), 4.17-4.14 (t, *J* = 6.5 Hz,2H), 2.43 (s, 3H), 1.53-1.48 (m, 2H), 1.28-1.22 (m, 2H), 1.19-1.14 (m, 2H), 0.88-0.83(m, 3H). 13C NMR (125 MHz, CDCl3) δ 169.8, 165.8, 156.8, 139.9, 133.2, 131.3,129.9, 129.5, 118.8, 65.3, 28.1, 28.0, 22.3, 21.2, 13.9.
HRMS (ESI) Calcd for C17H21N2O2 (MH+): 285.1598, found (MH+): 285.1590.



11q: oil. 1H NMR (500 MHz, CDCl3) δ 7.61-7.58 (m, 2H), 7.44-7.43 (d, *J* = 7.5 Hz, 1H), 7.34-7.33 (m, 1H), 7.26-7.24 (m, 1H), 7.09-7.08 (d, *J* = 8.0 Hz, 1H), 4.07-4.04 (m, 2H), 2.57 (s, 3H), 2.42 (s, 3H), 1.42-1.39 (m, 2H), 1.26-1.20 (m, 2H), 1.09-1.06 (m, 2H), 0.85-0.82 (m, 3H). 13C NMR (125 MHz, CDCl3) δ 169.4, 158.1, 157.6, 138.2, 138.1,136.3, 131.9, 131.5, 130.1, 129.6, 121.3, 119.5, 65.1, 28.0, 27.9, 24.5, 22.3, 21.0, 13.9.
HRMS (ESI) Calcd for C19H24NO2 (MH+): 298.1802, found (MH+): 298.1797.



2s: oil. 1H NMR (500 MHz, CDCl3) δ 8.65-8.64 (m, 1H), 7.85-7.84 (m, 1H), 7.75-7.74 (m, 1H), 7.56-7.55 (m, 2H), 7.48-7.45 (m, 2H), 7.28-7.26 (m, 1H), 4.16-4.12 (m, 2H), 1.08-1.04 (m, 3H). 13C NMR (125 MHz, CDCl3) δ 168.7, 158.9, 148.9, 141.0, 136.1, 131.8, 131.1, 129.8, 129.8, 128.3, 122.9, 122.0, 60.9, 13.8.



11t: oil. 1H NMR (500 MHz, CDCl3) δ 8.65-8.63 (m, 1H), 7.84-7.82 (m, 1H), 7.75-7.72 (m, 1H), 7.55-7.52 (m, 2H), 7.48-7.45 (m, 2H), 7.27-7.25 (m, 1H), 5.06-5.01 (m, 1H), 1.09 (s, 3H), 1.08 (s, 3H). 13C NMR (125 MHz, CDCl3) δ 168.2, 159.0, 149.0, 140.9, 136.1, 132.2, 130.9, 129.8, 129.7, 128.2, 122.9, 121.9, 68.5, 21.5.

Notes and References:

17. (a) Schoenberg, A.; Bartoletti, I.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3318. (b) Schoenberg, A.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3327.
18. For general reviews, see: (a) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., de Meijere, A., Eds.; Wiley: New York, 2002; Vol. 2, p 2309. (b) Skoda-Foldes, R.; Kollar, L. *Curr. Org. Chem.* **2002**, *6*, 1097–1119. (c) Beller, M.; Cornils, B.; Frohning, C. D.; Kohlpaintner, C. W. *J. Mol. Catal. A* **1995**, *104*, 17–85. (d) Tsuji, J. *Palladium Reagents and Catalysis: Innovation in Organic synthesis*; John Wiley & Sons: Chichester, U.K., 1995. (e) Colquhoun, H. M.; Thompson, D. J.; Twigg, M. V. *Carbonylation, Direct Synthesis of Carbonyl Compounds*; Plenum Press: New York, 1991.
19. For recent examples, see: (a) Munday, R. H.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 2754. (b) Martinelli, J. R.; Clark, T. P.; Watson, D. A.; Munday, R. H.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 8460. (c) Cai, C.; Rivera, N. R.; Balsells, J.; Sidler, R. R.; McWilliams, J. C.; Shultz, C. S.; Sun, Y. *Org. Lett.* **2006**, *8*, 5161. (d) Ben-David, Y.; Portnoy, M.; Milstein, D. *J. Am. Chem. Soc.* **1989**, *111*, 8742.
20. (a) Orito, K.; Horibata, A.; Nakamura, T.; Ushito, H.; Nagasaki, H.; Yuguchi, M.; Yamashita, S.; Tokuda, M. *J. Am. Chem. Soc.* **2004**, *126*, 14342. (b) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633. (c) Fujiwara, Y.; Takaki, K.; Taniguchi, Y. *Synlett* **1996**, 591.
21. (a) Lersch, M.; Tilset, M. *Chem. Re*V. **2005**, *105*, 2471. (b) Go¨ttker- Schnetmann, I.; White, P.; Brookhart, M. *J. Am. Chem. Soc.* **2004**, *126*, 1804. (c) Labinger, J.

A.; Bercaw, J. E. *Nature* **2002**, *417*, 507. (d) Arndsten, B. A.; Bergman, R. G.; Mobley, T. A.; Peterson, T. H. *Acc. Chem. Res.* **1995**, *28*, 154. (e) Bergman, R. G. *Science* **1984**, *223*, 902. (f) Janowicz, A. H.; Bergman, R. G. *J. Am. Chem. Soc.* **1982**, *104*, 352.

22. (a) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Re*V. **2002**, *102*, 1731. (b) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826. (c) Dyker,G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1698. (d) Shilov, A. E.; Shul'pin, G. B. *Chem. Re*V. **1997**, *97*, 2879.
23. (a) Chatani, N. Directed Metallation. In *Topics in Organometallic Chemistry*; Springer: Berlin, 2007. (b) *Handbook of C-H Transformations*; Dyker, G., Ed.; Wiley-VCH: Weinheim, Germany, 2005.
24. Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Re*V. **2007**, *107*, 174.
25. (a) Wang, D.-H.; Wasa, M.; Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 7190. (b) Yang, S.-D.; Sun, C.-L.; Fang, Z.; Li, B.-J.; Li, Y.-Z.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1473. (c) Giri, R.; Maugel, N.; Li, J.-J.; Wang, D.-H.; Breazzano, S. P.; Saunders, L. B.; Yu, J.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 3510. (d) Chen, X.; Goodhue,C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 12634.
26. (a) Yokota, T.; Tani, M.; Sakaguchi, S.; Ishii, Y. *J. Am. Chem. Soc.* **2003**, *125*, 1476. (b) Boele, M. D. K.; van Strijdonck, G. P. F.; de Vries, A. H. M.; Kamer, P. C. J.; de Vries, J. G.; van Leeuwen, P. W. N. M. *J. Am. Chem. Soc.* **2002**, *124*, 1586.
27. (a) Kawai, H.; Kobayashi, Y.; Qi, S.; Inoue, Y. *Chem. Commun.* **2008**, 1464. (b) Chen, X.; Li, J.-J.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 78.
28. (a) Yang, S.; Li, B.; Wan, X.; Shi, Z. *J. Am. Chem. Soc.* **2007**, *129*, 6066. (b) Giri, R.; Chen, X.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2005**, *44*, 2112.
29. (a) Chiong, H. A.; Pham, Q.-N.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 9879. (b) Campeau, L. C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581. (c) Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 8754. (d) Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496. (e) Ren, H.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 3462. (f) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**,*127*, 13154. (g) Daugulis, O.; Zaitsev, V. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4046.
30. (a) Zhang, Y.; Feng, J.; Li, C.-J. *J. Am. Chem. Soc.* **2008**, *130*, 2900. (b) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172. (c) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 11904. (d) Hull, K. L.; Lanni, E. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 14047. (e) Hull, K. L.; Anani, W. Q.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 7134. (f) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330.
31. (a) Dupont, J.; Consorti, C. S.; Spenser, J. *Chem. Re*V. **2005**, *105*, 2527. (b) Ryabov, A. D. *Synthesis* **1985**, 233.
32. Yu, W. Y.; Sit, W. N.; Lai, K. M.; Zhou, Z.; Chan, A. S. C. *J. Am. Chem. Soc.* **2008**, *130*, 3304.
33. Horino, H.; Inoue, N. *J. Org. Chem.* **1981**, *46*, 4416.
34. (a) Wiedemann, S. H.; Lewis, J. C.; Ellman, J. A.; Bergman, R. G. *J. Am. Chem.*

Soc. **2006**, *128*, 2452, and references therein. (b) Lewis, J. C.; Wu, J. Y.; Bergman, R. G.; Ellman, J. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1589. (c) Shi, L.; Tu, Y.-Q.; Wang, M.; Zhang, F.-M.; Fan, C.-A.; Zhao, Y.-M.; Xia, W.-J. *J. Am. Chem. Soc.* **2005**, *127*, 10836. (d) Ueura, K.; Satoh, T.; Miura, M. *Org. Lett.* **2005**, *7*, 2229. e) Bedford, R. B.; Limmert, M. E. *J. Org. Chem.* **2003**, *68*, 8669. (f) Oi, S.; Fukita, S.; Inoue, Y. *Chem. Commun.* **1998**, 2439.

35. (a) O¨ zdemir, I.; Demir, S.; C¸ etinkaya, B.; Gourlaouen, C.; Maseras, F.; Bruneau, C.; Dixneuf, P. H. *J. Am. Chem. Soc.* **2008**, *130*, 1156.(b) Qi, S.; Sato, H.; Sugawara, S.; Inoue, Y. *Org. Lett.* **2008**, *10*, 1823. (c) Matsuura, Y.; Tamura, M.; Kochi, T.; Sato, M.; Chatani, N.; Kakiuchi, F. *J. Am. Chem. Soc.* **2007**, *129*, 9858. (d) Ackermann, L.; Althammer, A.; Born, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 2619. (e) Kakiuchi, F.; Matsuura, Y.; Kan, S.; Chatani, N. *J. Am. Chem. Soc.* **2005**, *127*, 5936. (f) Kakiuchi, F.; Kan, S.; Igi, K.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* **2003**, *125*, 1698. (g) Oi, S.; Ogino, Y.; Fukita, S.; Inoue, Y. *Org. Lett.* **2002**, *4*, 1783. (h) Oi, S.; Fukita, S.; Hirata, N.; Watanuki, N.; Miyano, S.; Inoue, Y. *Org. Lett.* **2001**, *3*, 2579.
36. Roth, J. F.; Craddock, J. H.; Hershman, A.; Paulik, F. E. *Chem. Tech.* **1971**, *1*, 600.
37. Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987.
38. (a) Matsuura, Y.; Tamura, M.; Kochi, T.; Sato, M.; Chatani, N.; Kakiuchi, F. *J. Am. Chem. Soc.* **2007**, *129*, 9858. (b) Ueno, S.; Mizushima, E.; Chatani, N.; Kakiuchi, F. *J. Am. Chem. Soc.* **2006**, *128*, 16516. (c) Martinez, R.; Chevalier, R.; Darses, S.; Genet, J. P. *Angew. Chem., Int. Ed.* **2006**, *45*, 8232. (d) Asaumi, T.; Matsuo, T.; Fukuyama, T.; Ie, Y.; Kakiuchi, F.; Chatani, N. *J. Org. Chem.* **2004**, *69*, 4433, and references therein. (e) Lenges, C. P.; Brookhart, M. *J. Am. Chem. Soc.* **1999**, *121*, 6616. (f) Chatani, N.; Fukuyama, T.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **1996**, *118*, 493. (g) Moore, E. J.; Pretzer, W. R.; O'Connell, T. J.; Harris, J.; LaBounty, L.; Chou, L.; Grimmer, S. S. *J. Am. Chem. Soc.* **1992**, *114*, 5888.
39. (a) Boyd, S. E.; Field, L. D.; Partridge, M. G. *J. Am. Chem. Soc.* **1994**, *116*, 9492. (b) Rosini, G. P.; Boese, W. T.; Goldman, A. S. *J. Am. Chem. Soc.* **1994**, *116*, 9498.
40. van Leeuwen, P. W. N. M.; Zuideveld, M. A.; Swennenhuis, B. H. G.; Freixa, Z.; Kamer, P. C. J.; Goubitz, K.; Fraanje, J.; Lutz, M.; Spek, A. L. *J. Am. Chem. Soc.* **2003**, *125*, 5523, and references cited therein. (b) Milstein, D. *Acc. Chem. Res.* **1988**, *21*, 428. (c) Ozawa, F.; Kawasaki, N.; Okamoto, H.; Yamamoto, T.; Yamamoto,A. *Organometallics* **1987**, *6*, 1640.
41. (a) Vogler, T.; Studer, A. *Org. Lett.* **2008**, *10*, 129. (b) Ueura, K.; Satoh, T.; Miura, M. *Org. Lett.* **2007**, *9*, 1407.

Chapter 3

Synthesis of axially chiral biaryl monophosphines for asymmetric sp_2-sp_2 cross-couplings: an unresolved problem

3.1 Introduction and Background

Ever since the resolution of tartaric acid by Pasteur in 1848, the steroselective synthesis of compounds has been a very important filed in organic synthesis. There are numerous excellent methods involving diasteroselective and enantioselective variants. But axial chirality, as in the hindered rotation of biaryl compounds has been overlooked mostly. But recently it has been recognized that axial pure compounds are important factors of bioactive compounds [42], in fact in different atropisomers possess different degrees of bioactivity. Axial chirality is also found in important ligands for transition metal catalysis. [43]

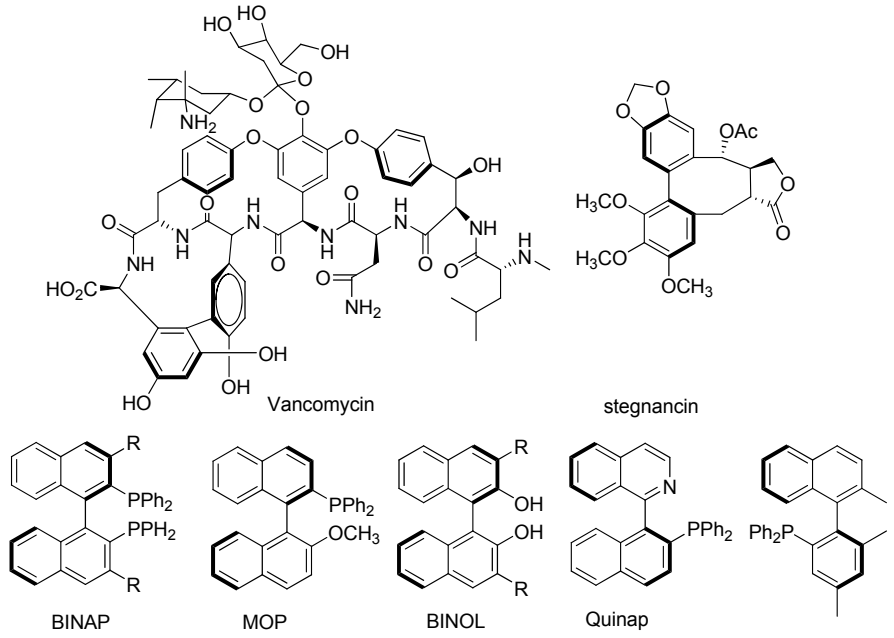


Figure 3-1: Axially chirality in natural products and ligands

Natural products which possess a axially chiral moiety are present in many structurally diverse molecules. One classic example is the antibiotic heptapeptide vancomycin [44] (figure 3-1), which is used to treat many gram positive antibiotic resistant bacteria. Axially chiral biaryls are prevalent in ligand design, starting from the discovery of BINAP. [45] BINOL is another example of a chiral biaryl ligand which has been applied to many transition metal catalyzed reactions [46] ranging from enantioselective epoxidations to Diels-Alder cycloadditions. The isoquinoline-containing phosphine quinap is an example of an axially chiral heteroaromatic biaryl, which has been applied to Pd-catalyzed asymmetric allylic alkylation. [47]

Despite the great implementation of the Suzuki coupling reaction in the construction of biaryl bonds, its application in asymmetric synthesis still remains a challenge due the difficulty in coupling two sterically hindered arenes. There have been historically distinct five approaches to this problem (figure 3-2). The first method was developed by Lipshutz [48] involved the use of chiral tethers to make the intramolecular reaction very favorable. Chiral leaving groups have also been employed in the Sn_{Ar} reaction by D.J. Cram which represents one of the first enantioselective pathways. [49] Diasteroselective intermolecular coupling reactions can also be effected by modifying an arene with an *orthro* chiral auxiliary. [50] Planar chiral induction by using a removable planar-chiral chromium complexes. More recently direct enatioselective complexes have been developed by Hayashi and Buchwald. [51]

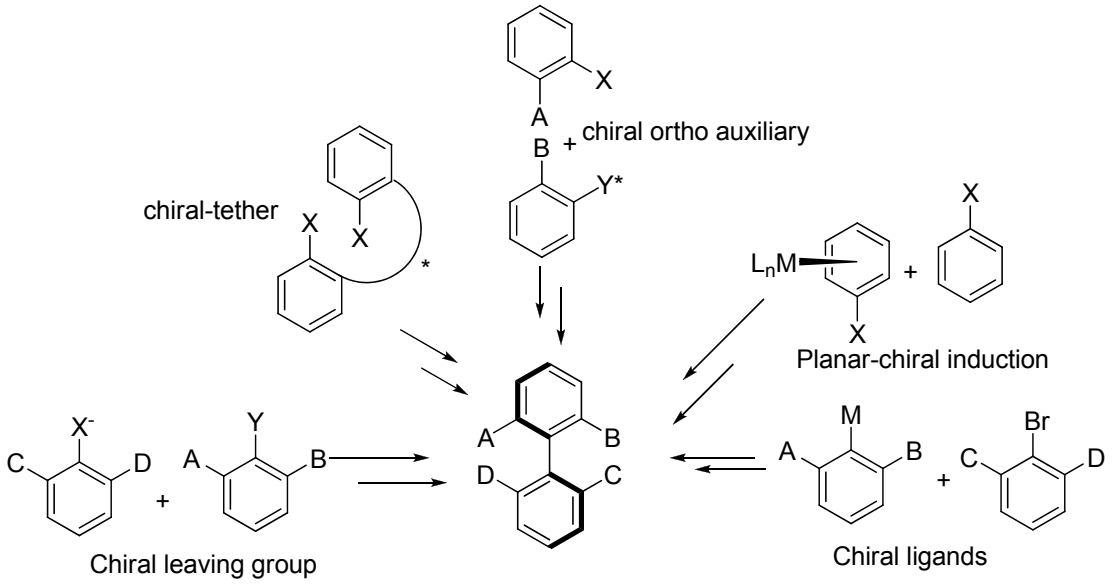


Figure 3-2: Representative approaches to atrposelective construction of biaryl axes

Direct chiral cross-couplings offer several advantages, the first being they can proceed under relatively mild conditions, they are not restricted to a specific substitution patterns and thus can thus reduce the amount of steps required. The first example of chiral cross-coupling was performed by Hayashi on the asymmetric Kuamada coupling [52] which was the first example of direct enatioselective cross-coupling (figure 4-3). In the presence of less than 5 % $NiBr_2$ and chiral Josiphos ligand at low temperature a limited amount of Grinard reagents can be coupled in high yields. The methoxy group was found to be important on the Josiphos ligand, and it was postulated that this side functions as a coordination site for the magnesium

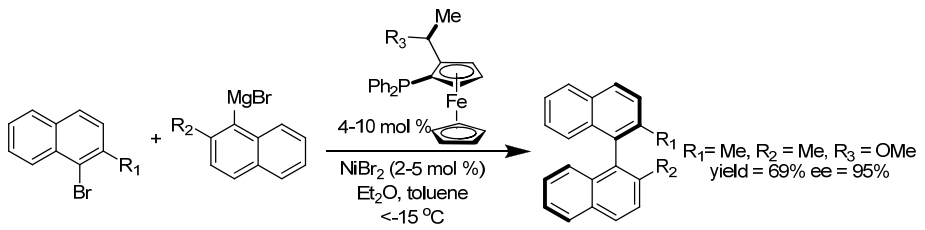


Figure 3-3: Nickel catalyzed asymmetric Kumada coupling

cation. yields. The methoxy group was found to be important on the Josiphos ligand, and it was postulated that this side functions as a coordination site for the magnesium cation. The first example of asymmetric Suzuki coupling was carried out by Cammidge in 2000 (figure 3-4), [53] using 1-iodonaphthalene and 2-methylnapthalene-1-boronic acid as the model substrated with $PdCl_2$ (3 mol %) and

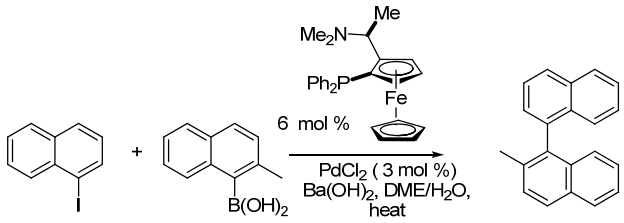


Figure 3-4: Asymmetric Suzuki Coupling using a ferrocenyl phosphine ligand

a modified Josiphos derivative. Over long reaction times (6 days) and high temperature yielded only 63 % ee and 44% yield. More recently Buchwald reported the Combination of $Pd_2(dba)_3$ and the MOP ligand to catalyze the enatioselective cross- coupling of various naphthyl phosphonates and phenyl boronic acids with excellent enatioselectivity (figure 3-5). The phosphonate could later be converted into a PPh_2 group allowing the synthesis of various monodentate ligands. Though many

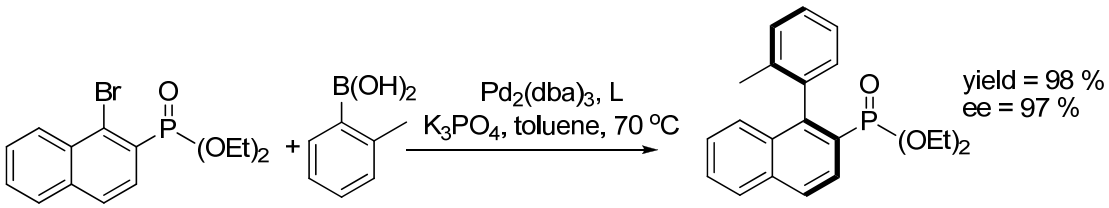


Figure 3-5: Asymmetric Suzuki coupling with Pd/MOP system

aryl bromides can be coupled in very high yields and enatioselectivity, the substrate scope remains narrow as 2,6-disubstituents and heteroaromatic substrates are not included. Also high temperatures and long reaction times were necessary for high

yield. There are few applications of the asymmetric Suzuki cross –coupling in natural product synthesis. A notable exception is in the synthesis of the A-B ring of vancomycin. The Pd-catalyzed reaction of cyclic boronic acid and an aryl iodide was performed with BINAP and up to 3.5:1 selectivity was obtained as seen in figure 3-6.

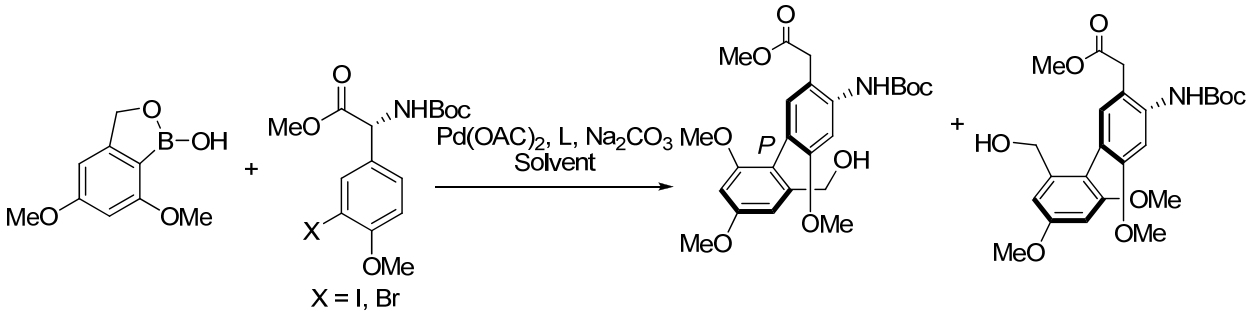


Figure 3-6: Application of the asymmetric Suzuki coupling to the A-B ring of vancomycin

entry	ligand	solvent	time (h)	yield (%)	ratio
1	PPh_3	toluene	2	83	1 : 1
2	(R)-BINAP	THF	2	75	3.5 : 1
3	(S)-BINAP	THF	2	75	1 : 3.5

4.2 Synthesis of chiral biaryl monophosphines for asymmetric sp_2-sp_2 cross-couplings:

Encouraged by the results of Buchwald's chiral MOP ligand, we decided to design rigid, highly tunable monophosphine ligands. We would like to combine the prosperities of the MOP ligand with the rigid backbone from our C_3* tunephos backbone. For the design criteria of our ligand, we have several design criteria: a highly rigid monophosphine is desired, an easy synthesis from readily available precursors, a broad substrate scope, high reactivity and the ability to work at low catalytic levels. We envisioned based upon our previous synthetic route of C_3* tunephos that our desired MOP ligand could be developed in by using an analogues

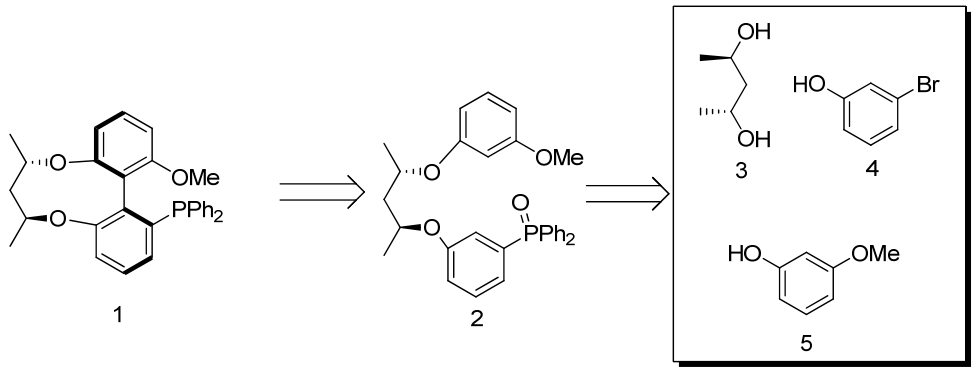


Figure 3-7: Design of a chiral MOP ligand bearing a C_3* tunephos backbone

procedure as seen in figure 3-7. We imagined that our desired monophosphine ligand 1 could come from the chiral iron catalyzed coupling of the lithilated precursor , as we envisioned that both the coordination ability of the phosphine oxide and methoxy group should help with selective lithilation of 2. After coupling, the desired product could be obtained by reducing the phosphine oxide to the corresponding monophosphine. Precursor 2 would be available from commercial precursors 3 ,4 and 5 by two sequential Mitsunobu reactions of 3 with phenols 4 and 5. Starting from commercially available diol 3 and performing a Mitsunobu 5, yielded the mono-substituted ether in almost quantative yields with very small amounts of

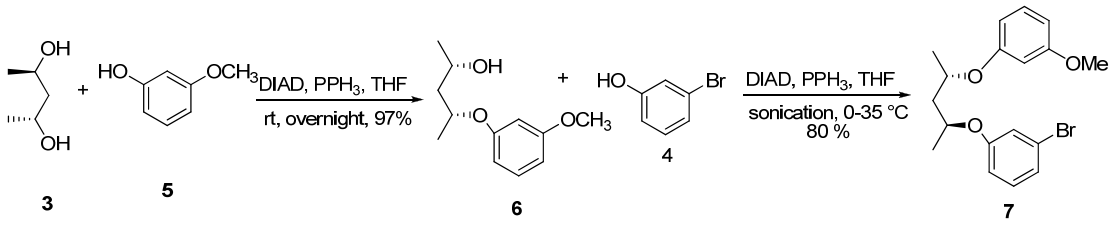


Figure 3-8: Synthesis of precursor 7

di-substituted product. With this product in hand, we performed the second sequential Mitsunobu reaction, which yielded the desired asymmetric ether in hand, we then decided to introduce the phosphine oxide moiety and screen various coupling conditions. By modifying known procedures, by performing the lithilation of 7 at

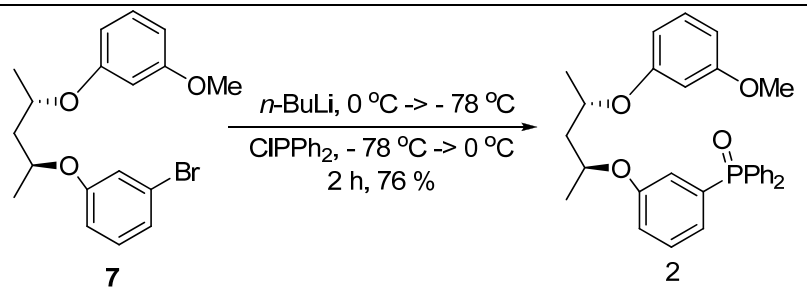
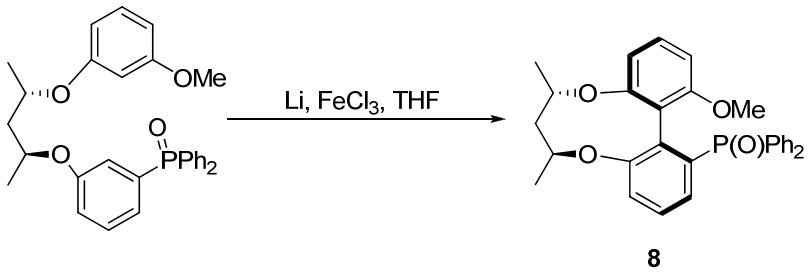


Figure 3-9: Synthesis of coupling precursor 2

0 °C, and then upon cooling to -78 °C and adding the phosphine dropwise yielded the desired product in 76% yield. Next we desired to screen the reaction conditions for the iron catalyzed cross coupling reaction. By screening both the temperature effects and the lithium source, we were able to obtain the coupled product in decent yields.

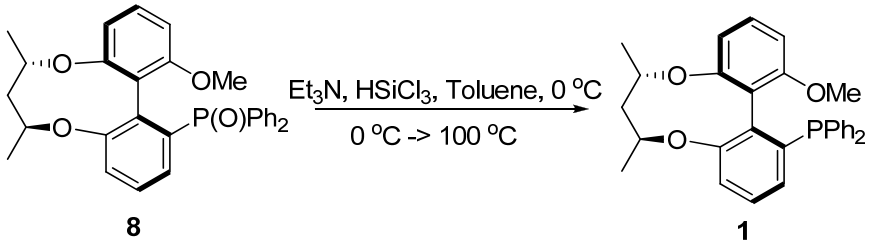


entry	li source	reaction conditions	yield (%)
1	*n*-BuLi	0 °C -> -78 °C -> rt	40
2	*n*-BuLi	0 °C -> rt -> -78 °C -> rt	24
3	*n*-BuLi	-78 °C -> rt	30
4	LDA	0 °C -> -78 °C -> rt	32
5	LDA	-78 °C -> rt	<15
6	*t*-BuLi	-78 °C -> rt	20
7	*t*-BuLi	0 °C -> -78 °C -> rt	28

Table 3-1: Screening the conditions for the iron catalyzed cross coupling

Our first experiment was carried out by performing the lithilation at 0 °C, stirred for 2 hours and then cooled to -78 °C and stirred for another 1 hour before adding $FeCl_3$ batch-wise by the use of a glove under N_2 which yielded the product in 40 % yield (table 4-1, entry 1). We then though perhaps the lithilation was not complete, so after adding *n*-BuLi, we warmed the solution to rt and stirred at rt for 2 hours, the solution turned a deep orange, before lowering the temperature to -78 °C and adding

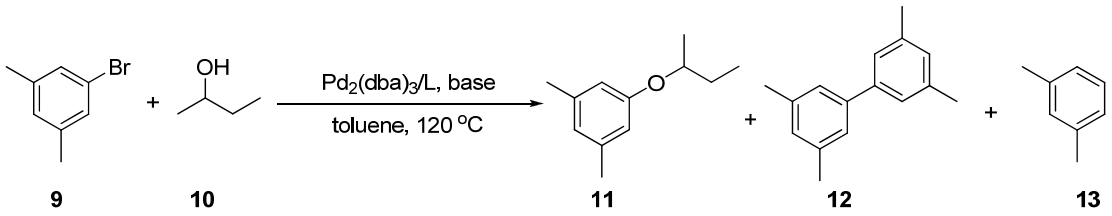
$FeCl_3$ batch-wise, but the yield dropped to 24%. Performing the lithilation at -78 °C, and then adding $FeCl_3$ batch-wise increased the yield to 30%. Based upon previous results in our lab, we decided to investigate the use of other lithium precursors upon



8 1

Figure 3-10: Synthesis of monophosphine 1

this transformation. We investigated the use of LDA, by first performing the lithilation at 0 °C and then cooling to -78 °C, and then adding $FeCl_3$ and the yield was



9 10 11 12 13

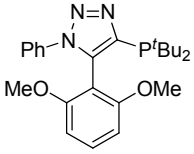
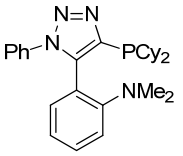
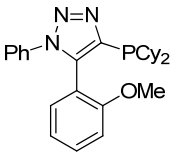
entry	ligand	base	yield
1	1	K_3PO_4	36
2	1	Cs_2CO_3	52
3	1	KF	44
4	 2	Cs_2CO_3	28
5	 3	Cs_2CO_3	<10
6	 4	Cs_2CO_3	15

Table 3-2: Screening reaction conditions for C-O bond formation

found to increase to 32%, but by performing the lithilation at -78 °C, the yield was

found to be less than 15%. We then thought to screen *t*-BuLi but by screening the temperature conditions, no satisfactory yields were obtained. With enough phosphine oxide precursors in hand, we decided to test the reduction step, and to our delight it yielded the monophosphine product in good yields. Next, we decided to test the effect of our newly synthesized monophospine in some challenging reactions. The two reactions we decided our sp2-sp2 reaction as a precursor to asymmetric sp2-sp2 coupling and also C-O bond formation both of which remain challenging problems. Based upon Buchwald's [72] report of using tuneable MOP ligands for C-O bond formation, we decided to screen our new C_3-star ligand for this transformation. We first screened the base effect on this transformation, and found that Cs_2CO_3 yielded the product in 52% yield, but with a lot of biaryl formation and also β-H elimination product. For comparison we also screened our ClickPhos ligands, but relatively low yield of the desired product was found, with most of the product being attributed to β-H elimination.

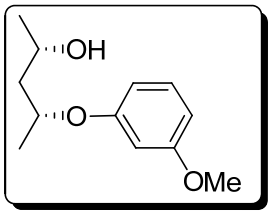
3.3 Conclusion

In conclusion, we have developed a new series of monophosphine ligands **1** a C_3-tunephos backbone. This ligand was easily afforded through a short synthetic sequence, and in the future work will be done to work on derivatives. We tested this on the C-O bond formation, even though good yields were not reported, we will test this ligand for other transformations, and also screen derivatives of this ligand.

Experimental Section

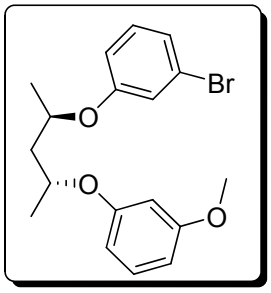
General information:

Column chromatography was carried out on silica gel. 1H NMR spectra were recorded on 500 MHz or 400 MHz in CDCl3 and 13C NMR spectra were recorded on 125 MHz or 100 MHz in CDCl3. All new products were further characterized by HRMS. Unless otherwise stated, all arenes and solvents were purchased from commercial suppliers and used without further purification.



4-(3-methoxyphenoxy)pentan-2-ol

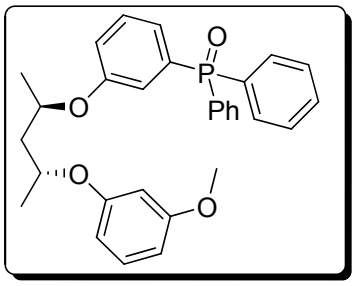
To a solution of 3-methoxy phenol (60 mmol), pentane-2,4-diol (72 mmol) and PPh_3 (72 mmol) in THF (175 mL) was added dropwise DIAD (72 mmol). The reaction was allowed to stir overnight. The solution was evacuated by rota-evaporator. Then cold hexame: EtOAc (4:1), a large amount of $PPh_3(O)$ precipitated from solution and was filtered. The product was then purified by column chromatography to afford a colorless oil, 86 % yield. $_1$H NMR (500 MHz, $CDCl_3$) δ 7.165 (m, 1 H), 6.519-6.483 (m, 3 H), 4.34 (m, 1H), 4.121 (m, 2H), 3.774 (s, 1 H), 1.93 (m, 1H), 1.67 (m, 1H), 1.32-1.32 (m, 3H), 1.21-1.209 (m, 3H) $_{13}$C NMR (125 MHz, $CDCl_3$) δ 160.91, 156.48, 129.94, 108.31, 106.64, 102.65, 73.36, 69.88, 66.53, 45.51, 25.28, 23.78, 21.93, 19.92, 18.34



1-bromo-3-(4-(3-methoxyphenoxy)pentan-2-yloxy)benzene

To a solution of 4-(3-methoxyphenoxy)pentan-2-ol (27.6 mmol), 3-bromo phenol (30.36 mmol) and PPh_3 (30.36 mmol) in THF (30 ml) at 0 ^oC WAS added dropwise DIAD (30.36 mmol). The solution was stirred for 1 h at 0 ^oC before being dropped into a sonicator for 3 hours at 0 ^oC. During the time of the reaction, a lot of solid was formed $PPh_3(O)$, the solid was filtered, and the product was purified by column chromatography to afford a colorless oil in 87 % yield. $_1$H NMR (500 MHz, $CDCl_3$) δ 7.117-7.062 (m. 4H), 6.77 (d, *J* = 2.5, 1 h), 6.452 (m, 2 H), 6.32 (m, 2H), 4.618 (m, 2H), 4.52(s, 3H), 1.99 (m, 2 H), 1.415 (d, *J* = *4*, 6H) $_{13}$C NMR (125 MHz, $CDCl_3$) δ 161.08, 159.50, 159.19, 130.73, 130.09, 124.02, 123.01, 119.73, 115.05, 108.68,

102.73, 71.44, 71.09, 55.38, 45.05, 20.46, 20.28



(3-((2R,4R)-4-(3-methoxyphenoxy)pentan-2-yloxy)phenyl)diphenylphosphine oxide

To a solution of S.M. in THF (150 ml) at -78 ^{o}C was added dropwise *n*-BuLi by syringe. This mixture was stirred for 1 h, then was added Cl-PPh_2 by syringe. The solution was slowly warmed to rt, then stirred for 2.5 h. The solution was cooled to 0 ^{o}C and H_2O_2 was added carefully and stirred overnight. The reaction was dried, and then purified by column chromataogrpahy to give the desired product in 76% yield. $_1$H NMR (500 MHz, $CDCl_3$) δ 7.65 (m, 4H), 7.59 (m, 2H), 7.43 (m, 4H), 7.33 (m, 1H), 7.28 (m, 2H), 7.11(t, *J* = *7*, 1 H), 7.033 (d, *J* = 8.5, 1H), 6.424 (d, *J*= *6.5*, 2H), 4.43 (m, 2H), 3.661 (s, 3H), 1.934(t, *J* = *7*, 2 H), 1.273 (m, 6 H) 31P (125 Mz, $CDCl_3$) -30.152

Notes and References:

42 "Biaryls in nature": Bringmann, G.; Günther, C.; Ochse, M.; Schupp, O.; Tasler, S., In Progress in the Chemistry of Organic Natural Products, Vol. 82, Springer, Vienna, **2001**, pp. 1-249

43 Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103,* 3029.

44 Nicolaou, K.C.; Boddy C.N.; Brase, S.; Winssinger, N. *Angew. Chem. Int. Ed.*, **1999**, *38*, 2096.

45 Noyori, R.; Takaya, T; *Acc. Chem. Res.* **1990**, *23*, 245.

46 Brunel, J. M. *Chem Rev,* **2005**, *105,* 857.

47 Brown, J.M, Hulmes, D.I.; Guiry, P.J; *Tetrahedron*, **1984**, *50*, 4493 (b) Alcock, N.W; Brown, J.M, Hulmes , D.I*, Tetrahedron*, **1993**, *4*, 74

48 Lipshutz, B. H.; Kayser, F.; Lui, Z.-P. *Angew. Chem., Int Ed.* **1994**, *33*, 1842.

49 (a) Wilson, J. A.; Cram, D. J. *J. Am. Chem. Soc*., **1982**, *104*, 881. (b) Wilson, J. A.; Cram, D. J. *J. Org. Chem*., **1984**, *49*, 4930.

50 (a) Broutin, P. E.; Colobert, F. *Org. Lett,* **2003**, 5, 3281. (b) Broutin, P. E.; Colobert, F. *Eur. J. Org. Chem*. **2005**, 1113.

51 (a) Hayashi, T.; Hayashizaki, K.; Kiyoi, T.; Ito, Y. *J. Am. Chem. Soc.* **1988**, *110*, 8153. (b) Buchwald, S. L.; Yin, J. *J. Am. Chem. Soc*. **2000**, *122,* 12051.

52 (21) Hayashi, T.; Hayashizaki, K.; Kiyoi, T.; Ito, Y. *J. Am. Chem. Soc.* **1988**, *110*, 8153.

53 (a) Cammidge, A. N., Crepy, V. L., *Chem. Commun.*, **2000**, 1723 (b) Cammidge, A. N., Crepy, V. L., *Tetrahedron.*, **2004**, *60*, 4377

54 Vorogushin, A ;Huang, X; Buchwald, S. L.; *J. Am. Chem. Soc.*, **2005**, *127*, 8146