

## Reviews

# Practical Aspects of Carbon–Carbon Cross-Coupling Reactions Using Heteroarenes

Vincent F. Slagt,<sup>†</sup> André H. M. de Vries,<sup>\*,‡</sup> Johannes G. de Vries,<sup>‡</sup> and Richard M. Kellogg<sup>\*,†</sup>

Syncom BV, Kadijk 3, 9747 AT Groningen, The Netherlands, DSM Pharmaceutical Products - Innovative Synthesis and Catalysis, P.O. Box 18, 6160 MD Geleen, The Netherlands

### Abstract:

The use of cross-coupling reactions for the preparation of alkylated and arylated heteroaromatic compounds has increased tremendously over the past two decades. This has been driven on the one hand by the increasingly complex structures of new drugs, most of which contain one or more heterocyclic motifs. On the other hand, the development of new catalysts and reaction conditions for these reactions has rendered even the most unreactive of heteroarenes amenable to cross-coupling chemistry. Not only have new bulky electron-donating ligands been created that allow the coupling of aryl chlorides under mild conditions, but also the use of ligand-free palladium, in particular at very low doses, sometimes called homeopathic palladium, has served to bring down the cost of these reactions. More recent and enabling developments are the use of catalysts based on cheap metals such as nickel, copper, and iron. Scale-up issues are availability and cost of starting materials, cost of the catalysts (related to cost of the metal and the ligand, intrinsic activity and stability of the catalyst), solvent choice, and removal of the metal to <10 ppm from the final product. This latter point is aggravated with heteroaromatics as they tend to be good ligands for the transition metal. For the same reason substrate and product inhibition are quite common.

### 1. Introduction

On the basis of our own experience, we estimate that at least one-third of the organic compounds that need to be prepared as part of drug development programs contains a heteroaromatic fragment.<sup>1</sup> It is therefore little wonder that organic chemists make such extensive efforts to develop new and efficient synthetic transformations to prepare a wide variety of heteroaromatics.<sup>2</sup> Among the novel synthetic transformations, transition metal catalyzed reactions provide some of the most attractive methodologies for the synthesis and substitution of these

heterocyclic structures. In particular, the use of transition metal catalyzed cross-coupling reactions has increased tremendously during the past two decades. In industry, these transformations play an important role in discovery chemistry where fast and easy access to small focused libraries is mandatory, and where also the preparation of large batches for clinical trials as well as for manufacturing is flourishing.<sup>3</sup> Arguably the most important remaining challenge is the development of a universal method for cross-coupling substrates that includes nitrogen heterocycles.<sup>4</sup> The presence of such moieties, which are particularly pervasive in medicinal chemistry, too often leads to low reactivity in coupling reactions. This is often caused by binding of the heteroatom in the substrate and product to the metal complex.<sup>5</sup> Although binding is reversible, the large excess of substrate can lead to a strong inhibitory effect.

Many types of cross-coupling reactions have been known for several decades, and advances in recent years have greatly increased their scope and practicality. This has had a significant impact on research and its employment in a variety of synthetic venues. Progress has been greatly facilitated by an increased understanding of the mechanism by which these and related reactions proceed. Furthermore, a tremendous upsurge in the development of new ligands has contributed substantially to recent advances. Cross-coupling reactions have become a standard tool for the synthetic chemist. These processes make use of carbon-based nucleophiles such as aryl, vinyl, or alkyl derivatives of magnesium (Kumada, Corriu),<sup>6</sup> boron (Suzuki, Miyaura),<sup>7</sup> tin (Stille–Migita),<sup>8</sup> zinc (Negishi),<sup>9</sup> or silicon

\* Authors to whom correspondence may be sent. E-mail: r.m.kellogg@syncom.nl; Hans-J.G.Vries-de@dsm.com.

<sup>†</sup> Syncom BV.

<sup>‡</sup> DSM Pharmaceutical Products.

- (1) Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*, 2337–2347.
- (2) (a) Li, J. J.; Gribble, G. W. *Palladium in Heterocyclic Chemistry*; Pergamon: Amsterdam, The Netherlands, 2000. (b) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 4th ed.; Blackwell Science: Cambridge, MA, 2000. (c) Eicher, T.; Hauptmann, S. *The Chemistry of Heterocycles*, Wiley-VCH, New York, 2003.

- (3) King, A. O.; Yasuda, N. *Top. Organomet. Chem.* **2004**, *6*, 205–245.
- (4) For a discussion of the widespread occurrence of nitrogen heterocycles, in pharmaceutically active compounds, see: (a) Bonnet, V.; Mongin, F.; Trecourt, F.; Breton, G.; Marsais, F.; Knochel, P.; Quéguiner, G. *Synlett* **2002**, 1008–1010. (b) Pozharskii, A. F.; Sodartenko, A. T.; Katritzky, A. *Heterocycles in Life and Society*; Wiley: New York, 1997.
- (5) Billingsley, K.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3358–3366.
- (6) (a) Tamao, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 4374–4376. (b) Corriu, R. J. P.; Massé, J. P. *J. Chem. Soc., Chem. Commun.* **1972**, 144–145.
- (7) (a) Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, *19*, 3437–3440. (b) Miyaura, N.; Suzuki, A. *J. Chem. Soc., Chem. Commun.* **1979**, 866–867.
- (8) (a) Kosugi, M.; Sasazawa, K.; Shimizu, Y.; Migita, T. *Chem. Lett.* **1977**, 301–302. (b) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1978**, *100*, 3636–3638.
- (9) King, A. O.; Okukado, N.; Negishi, E. *J. Chem. Soc., Chem. Commun.* **1977**, 683–684.

(Hiyama).<sup>10</sup> In most cases the catalysts are palladium-based, although various nickel (Kumada, Negishi)<sup>11</sup> and more recently iron-based catalysts (Kumada) have been reported.<sup>12</sup>

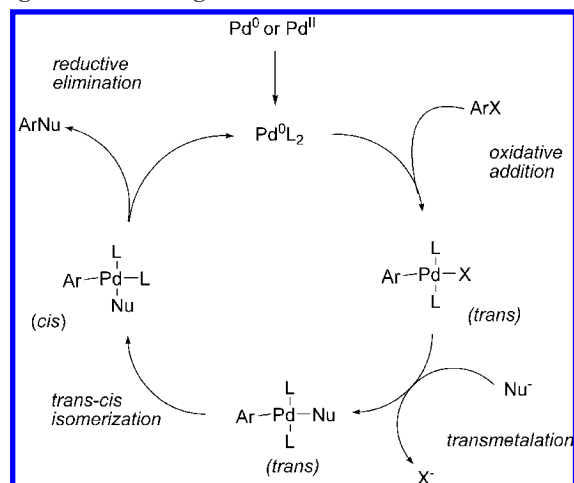
In this review we will focus on the practical aspects of these reactions with the main focus on C–C coupling using heteroaromatic substrates. Viewed from the synthetic angle, the main considerations in this field are high yields and selectivities and the availability of the starting materials. For large-scale production a number of other considerations are important as well: (i) the cost of the production process, (ii) the toxicity of the reagents and catalysts, and (iii) the freedom to use those ligands, catalysts, or specific transformations at scale. These points will be discussed in more detail at the end of the manuscript.

## 2. Choice of Catalyst and Mechanistic Considerations

An impressive array of cross-couplings with structurally simple organometallic compounds and substrates has succeeded using nickel and palladium complexes as catalysts.<sup>2</sup> In general, nickel catalysts are more reactive and therefore more sensitive than palladium-based systems. For example, a nitro group is not compatible with nickel phosphine catalysts owing to redox reactions, whereas under the influence of palladium catalysts in many cases good results are obtained. For example, Negishi et al. isolated the expected product from the palladium-catalyzed reaction of *o*-tolylzinc chloride and *p*-bromonitrobenzene in good yield.<sup>13</sup> Under similar conditions, the reaction in the presence of the analogous nickel catalyst did not give any cross-coupling product. It was also observed that nickel catalysts led to more homocoupling than palladium catalysts, particularly with aryl bromides and iodides.<sup>14,15</sup> For these reasons palladium is often more convenient and more often applied as catalyst compared with nickel-based systems. However, for the activation of aryl chlorides nickel is often a better choice in view of the lower reactivity of the carbon–chlorine bond.<sup>14</sup> With these substrates little homocoupling is found.

The development of even better catalysts for cross-coupling reactions has expanded the scope of this reaction enormously. Nickel and palladium catalysts with tailored phosphine ligands have been applied successfully. More recently, carbene ligands have also been introduced as ligands in active catalysts. The influence of the ligand used is very large, and not yet fully understood. It exerts influence on the metal center and thereby affects the course of the catalytic reaction in three ways: by change of the steric bulk around the metal center, influence on the electronic properties of the metal, and change of the bite angle preferred by the ligand (for bidentate ligands).<sup>16</sup> The

### Scheme 1. General mechanism for cross-coupling reactions using monodentate ligands



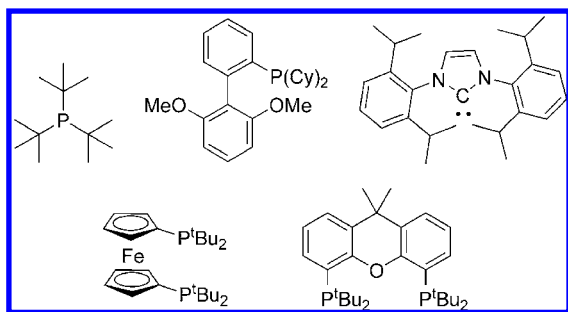
generally accepted mechanism of the catalytic cycle consists of several consecutive elementary steps: oxidative addition, transmetalation, trans–cis isomerization (only with monodentate ligands), and reductive elimination (Scheme 1, shown here and discussed for palladium catalysis).

Each step will be influenced by ligand modification differently, and therefore ligand effects in catalysis are not always straightforward. In recent years, however, much knowledge has been acquired on the individual reaction steps. Although the knowledge obtained from isolated stoichiometric reactions cannot always be extrapolated to the catalytic system,<sup>17</sup> it has led to more rational catalyst design. The mechanism of the oxidative addition of aryl iodides to zerovalent palladium was investigated by Fauvarque et al.<sup>18</sup> On the basis of kinetics and observation of a linear Hammett relationship, they concluded that the mechanism could be best described as an aromatic nucleophilic substitution by the reactive bis-ligated PdL<sub>2</sub>. The reaction is assisted by halide coordination; in addition, it was shown that for monodentate phosphines the presence of labile ligands (such as dibenzylidene acetone (dba),<sup>19</sup> halide,<sup>20</sup> and acetate<sup>21</sup>) can change the kinetics of the reaction by coordination to the low valent palladium intermediates. Rate enhancement by electron-withdrawing substituents on oxidative addition to aryl triflates was also found by Jutand<sup>22</sup> and for aryl chlorides by Milstein.<sup>23</sup> As expected, electron-withdrawing substituents on the aryl chloride and a more basic phosphine led to a faster oxidative addition. In most cases the oxidative addition is the rate-determining step if palladium is used as catalyst. Thus, ligands that donate electrons to the metal centre should be able to accelerate this step.

This understanding led to development of a new class of ligands as illustrated in Figure 1. Several groups have estab-

- (10) Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1988**, *53*, 918–920.  
 (11) Terao, J.; Kambe, N. *Acc. Chem. Res.* **2008**, *41*, 1545–1554.  
 (12) Sherry, B. D.; Fürstner, A. *Acc. Chem. Res.* **2008**, *41*, 1500–1511.  
 (13) Negishi, E.; Takahashi, T.; King, A. O. *Org. Synth. Coll. Vol 8* **1993**, 430.  
 (14) (a) Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340–348. (b) Negishi, E. *Pure Appl. Chem.* **1981**, *53*, 2333–2356.  
 (15) (a) Minato, A.; Tamao, K.; Suzuki, K.; Kumada, M. *Tetrahedron* **1980**, 4017–4020. (b) Fiandanese, V.; Marchese, G.; Ronzini, N. F. *J. Chem. Soc. Chem. Commun.* **1982**, 647–649.  
 (16) (a) Kamer, P. C. J.; Reek, J. N. H.; van Leeuwen, P. W. N. M. *CHEMTECH* **1998**, *28*, 27–33. (b) Dierkes, P.; van Leeuwen, P. W. N. M. *J. Chem. Soc., Dalton Trans.* **1999**, 1519–1530. (c) Casey, C. P.; Whiteker, G. T. *Isr. J. Chem.* **1990**, *30*, 299–304.

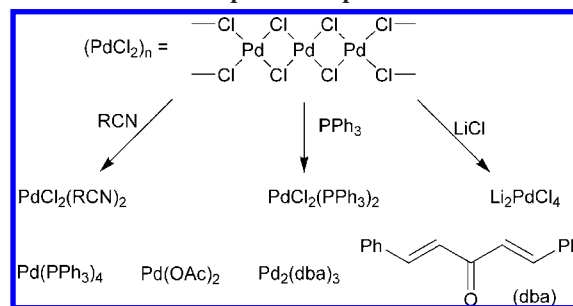
- (17) Amatore, C.; Jutand, A. *J. Organomet. Chem.* **1999**, *576*, 254–278.  
 (18) Fauvarque, J.-F.; Pflueger, F.; Troupel, M. *J. Organomet. Chem.* **1981**, *208*, 419–427.  
 (19) Amatore, C.; Broecker, G.; Jutand, A.; Khalil, F. *J. Am. Chem. Soc.* **1997**, *119*, 5176–5185.  
 (20) Amatore, C.; Jutand, A.; Khalil, F.; M'Barki, M. A.; Mottier, L. *Organometallics* **1993**, *12*, 3168–3178.  
 (21) Amatore, C.; Jutand, A.; Suarez, A. *J. Am. Chem. Soc.* **1993**, *115*, 9531–9541.  
 (22) Jutand, A.; Moshleh, A. *Organometallics* **1995**, *14*, 1810–1817.  
 (23) (a) Portnoy, M.; Milstein, D. *Organometallics* **1993**, *12*, 1655–1664. (b) Portnoy, M.; Milstein, D. *Organometallics* **1993**, *12*, 1665–1673.



**Figure 1.** Strong  $\sigma$ -donating bulky ligands.

lished that the combination of bulky and electron-rich phosphines or carbenes with different sources of palladium generate species that show high catalytic activity for a wide range of cross-coupling reactions.<sup>24</sup> These catalysts are particularly preferred for less reactive substrates, such as aryl chlorides or aryl halides containing one or two ortho substituents. The experimental observations also indicated that the source of the palladium and the palladium/ligand ratio employed have a great impact on the catalytic activity of the corresponding system. Detailed mechanistic studies revealed that the monoligated palladium complexes play an important role in the cross-coupling reactions. The generation of the catalytically active species from the corresponding palladium precursor needs to be considered; this step has been demonstrated to be rate limiting in some cases. Interestingly, it was shown that the optimal ligand/palladium ratio for high catalytic activity was between 1 and 1.5. It was observed that Pd(P<sup>t</sup>Bu<sub>3</sub>)<sub>2</sub> was a very poor catalyst in the Suzuki reaction, whereas the addition of Pd<sub>2</sub>(dba)<sub>3</sub> to Pd(P<sup>t</sup>Bu<sub>3</sub>)<sub>2</sub> led to an increase in activity.<sup>25</sup> These studies were followed by various reports in which it was shown that other types of cross-coupling reactions occur readily in the presence of a range of palladium sources and bulky phosphine ligands.<sup>26</sup> It was found that the rate of reductive elimination is usually increased by the coordination of bulky ligands to the palladium center. In addition, the bulkiness of the phosphine group not only controls the catalytic activity but also the rate of activation of the catalyst.<sup>27</sup> Sterically demanding ligands have the ability to stabilize low-coordinating palladium complexes, in particular monoligated species which, owing to their low electron count, are more reactive. Low-ligated palladium(0) complexes are generally very prone to formation of nanoparticles and, worse still, palladium black. The presence of the bulky ligand presumably prevents the formation of a dimeric species and thus suppresses catalyst deactivation. On the other hand electron-donating ligands generate an electron-rich metal

**Scheme 2.** Convenient palladium precursors



complex which undergoes fast oxidative addition.<sup>28</sup> Palladium complexes with a P<sup>t</sup>Bu<sub>3</sub> ligand showed high activity and selectivity in oxidative addition to substituted aromatics in the order of I > Br > Cl ≫ OTf, whereas PCy<sub>3</sub> proved to be a good ligand for efficient oxidative addition with vinyl and aryl triflates.<sup>24</sup>

The source of the palladium catalyst can play an important role in the efficiency of the cross-coupling reactions. Some convenient palladium precursors are depicted in Scheme 2. Although several of these palladium catalysts are commercially available, one may prefer to make them if larger quantities are needed. Activation of the palladium(II) precursors by reduction to Pd(0) can be carried out by the addition of DIBAL-H, Grignard reagents or may occur *in situ* via the oxidation of ligand, substrate, solvent, and/or transmetalating agent present in the reaction mixture.<sup>29,30</sup> In a study of comparative reactivity of palladium(0) as a function of precursors in oxidative addition to phenyl iodide, it was found that additives could have a major impact on the activation of the catalyst. The addition of LiCl or ZnCl<sub>2</sub> to PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> led to a 3-fold increase in the often rate-determining oxidative addition step. As discussed above, the palladium precursor itself also affects the rate {Pd(OAc)<sub>2</sub> + 3 PPh<sub>3</sub>} > {Pd(PPh<sub>3</sub>)<sub>4</sub>} > {Pd(dba)<sub>2</sub> + 2 PPh<sub>3</sub>} > {Pd(dba)<sub>2</sub> + 4 PPh<sub>3</sub>}, as does the amount of ligand present in the reaction mixture.<sup>31</sup> The use of bidentate ligands retards the oxidative addition step compared to monodentate ligands and proceeds in the order of {Pd<sup>0</sup>(dba)<sub>2</sub> + 2 PPh<sub>3</sub>} ≫ {Pd<sup>0</sup>(dba)<sub>2</sub> + 1 DIOP} > {Pd<sup>0</sup>(dba)<sub>2</sub> + 1 dppf} > {Pd<sup>0</sup>(dba)<sub>2</sub> + 1 BINAP}. The type of bidentate ligand used plays an important role.

Special mention should be made of the use of ligand-free palladium catalysts. Using Pd(OAc)<sub>2</sub> as catalyst, immediate reduction to Pd(0) occurs in all coupling reactions. Initially this will be in the form of palladium clusters that are stabilized to some extent by the anions present in solution. If the oxidative addition reaction is slow, the clusters may undergo Ostwald ripening to form larger crystals that precipitate as palladium black. To prevent this it may be better to *increase* the substrate/catalyst ratio (S/C). Thus, it is possible to perform Suzuki reactions at S/C ratios between 0.005–0.1 mol % at 140 °C,

(24) (a) Christmann, U.; Vilar, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 366–374. (b) Yamamoto, T.; Nishiyama, M.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 2367–2370. (c) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3387–3388.

(25) (a) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020–4028. (b) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176–4211. (c) Altenhoff, G.; Goddard, R.; Lehmann, C. W.; Glorius, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 3690–3693.

(26) (a) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1999**, *38*, 2411–2113. (b) Littke, A. F.; Fu, G. C. *J. Org. Chem.* **1999**, *64*, 10–11. (c) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473–1478. (d) Zapf, A.; Ehrentraut, A.; Beller, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4153–5155.

(27) Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 13978–13980.

(28) Galardon, E.; Ramdeehul, S.; Brown, A. M.; Cowley, A. A.; Hii, K. K.; Jutand, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1760–1763.

(29) Baba, S.; Negishi, E. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1958–1969.

(30) (a) Millard, A. A.; Rathke, M. W. *J. Am. Chem. Soc.* **1977**, *99*, 6730–6739. (b) Albaugh-Roberson, P.; Katzenellenbogen, J. A. *Tetrahedron Lett.* **1982**, *23*, 723–726.

(31) Negishi, E., Ed. *Handbook of Organopalladium Chemistry for Organic Synthesis*; Wiley: New York, 2002; p 946.

or at even lower ratios if the temperature is further increased.<sup>32</sup> This phenomenon has been dubbed “homeopathic palladium”. It is also possible to use preformed palladium nanoparticles as catalyst, but this does not offer any advantage over the use of Pd(OAc)<sub>2</sub>.<sup>33</sup> In large-scale production, use of ligand-free palladium is preferred. Not only does it save the cost of the ligand, it also simplifies the purification if no ligands are present. In addition, most if not all, palladium will precipitate as palladium black at the end of the reaction and can be simply removed by filtration.

It has now been generally recognized that most palladium catalyst precursors will form palladium nanoparticles in high-temperature (>120 °C) coupling reactions.<sup>34</sup> This is true not only for Pd(OAc)<sub>2</sub> but also for palladacycles, catalysts based on the so-called pincer ligands, and palladium triarylphosphine complexes. The use of Pd(PPh<sub>3</sub>)<sub>4</sub> in coupling reactions is never the best option for that reason. Even at room temperature, it forms nanoparticles that are particularly unreactive in view of the presence of the large excess of PPh<sub>3</sub>.<sup>35</sup> Heterogeneous palladium catalysts also function as homogeneous catalysts via a similar mechanism.<sup>36</sup> The situation is most likely different for catalysts derived from electron-rich phosphines, also because high temperatures are often not required due to the high activity.

The concentration of the reaction can be used as a parameter to control the reaction rate: in most cases the reaction goes faster upon using less solvent. In general a concentration of 1 mol/L is convenient. However, at higher substrate concentration substrate and product inhibition may become more prominent, especially if heteroarenes are involved.

The various cross-coupling reactions show different functional group compatibilities (Figure 2). The Grignard reagents as used in the Kumada coupling only tolerate a limited number of functionalities, whereas in Suzuki and Stille cross-couplings most functional groups are tolerated. However, in all cases beware of free amines and/or alcohols, which often poison the metal catalyst via inter/intra molecular ligation or act as a nucleophile and need to be protected (tosyl, Boc, benzyl, acetate). Upon using bidentate ligands more robust catalytic systems are formed, which are less prone to catalyst poisoning by free amines and/or alcohols.<sup>37</sup>

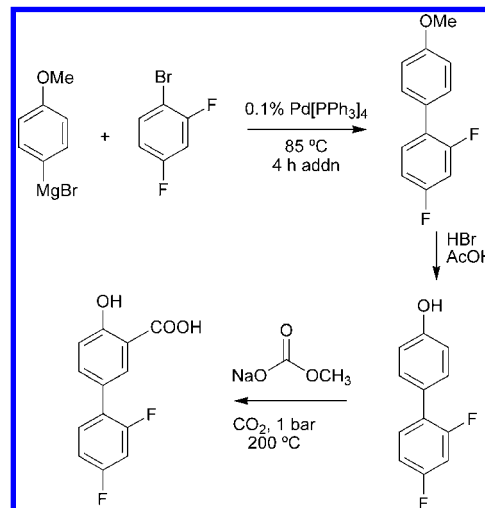
### 3. Kumada–Corriu Reaction

The nickel-catalyzed coupling of ethyl magnesium bromide with chlorobenzene published in 1972 was a major breakthrough

Kumada (MgX):	R, OR, H, F (sometimes COOR, NR <sub>2</sub> )
Negishi (Zn):	R, OR, COOR, NO <sub>2</sub> , NR <sub>2</sub> , H, F, CO, COH
Suzuki (B):	Most functional groups (problematic COOH, OH)
Stille (Sn):	Most functional groups (problematic COOH)

**Figure 2.** Functional group compatibility of various cross-coupling reactions.

**Scheme 3.** Zambon route to diflunisal



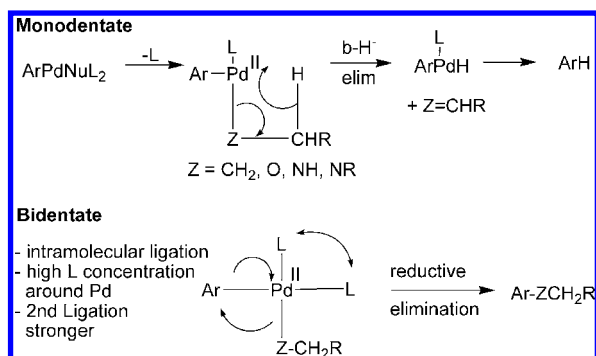
in cross-coupling chemistry.<sup>6</sup> This nickel-catalyzed coupling of Grignard reagents with alkyl, vinyl, or aryl halides provides an economical transformation, but the reaction is limited to halide partners that do not contain functional groups that can react with organomagnesium compounds. One example is in the industrial-scale production of styrene derivatives. The Kumada cross-coupling is the method of choice for the low-cost synthesis of unsymmetrical biaryls.<sup>38</sup> An example of this is the industrial production of flunisal by Zambon (Scheme 3).<sup>39</sup>

The advantage of this reaction is that Grignard reagents are used directly, which avoids additional reaction steps such as the conversion to zinc compounds for the starting materials required in Negishi coupling.

Nearly all of the nickel and palladium precatalysts used for the Kumada cross-coupling are ligated by mono- or bidentate phosphines. Beletskaya compared PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> with the “ligandless” PdCl<sub>2</sub>(CH<sub>3</sub>CN)<sub>2</sub> in the reactions of arylmagnesium bromides with *p*-iodoanisole and found the latter complex much less selective.<sup>40</sup> For the Kumada coupling the monodentate ligand triphenylphosphine appears to be effective,<sup>41</sup> although in many cases the use of bidentate phosphine ligands results in superior selectivity compared with monodentate. Upon use of bidentate ligands less homocoupling, less isomerization and less β-H elimination (Figure 3) were observed with both nickel and palladium catalysts. Bidentate ligands with nickel catalysts lead to faster reactions compared to monodentate nickel catalysts. The reason for this is that the organic groups introduced by

- (32) Alimardanov, A.; Schmieder-van de Vondervoort, L.; de Vries, A. H. M.; de Vries, J. G. *Adv. Synth. Catal.* **2004**, *346*, 1812–1817.
- (33) (a) Reetz, M. T.; Breinbauer, R.; Wanninger, K. *Tetrahedron Lett.* **1996**, *37*, 4499–4502. (b) Li, Y.; Hong, X. M.; Collard, D. M.; El-Sayed, M. A. *Org. Lett.* **2000**, *2*, 2385–2388.
- (34) (a) Phan, N. T. S.; Van Der Sluys, M.; Jones, C. W. *Adv. Synth. Catal.* **2006**, *348*, 609–679. (b) Djakovitch, L.; Köhler, K.; de Vries, J. G. In *Nanoparticles and Catalysis*; Astruc, D., Ed.; Wiley-VCH: New York, 2008; pp 303–348.
- (35) Ye, E.; Tan, H.; Li, S.; Fan, W. Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 1120–1123.
- (36) Conlon, D. A.; Pipik, B.; Ferdinand, S.; LeBlond, C. R.; Sowa, J. R., Jr.; Izzo, B.; Collins, P.; Ho, G.-J.; Williams, M.; Shi, Y.-J.; Sun, Y. *Adv. Synth. Catal.* **2003**, *345*, 931–935.
- (37) Negishi, E., Ed. *Handbook of Organopalladium Chemistry for Organic Synthesis*; Wiley: New York, 2002.

- (38) (a) Katayama, T.; Umeno, M. *Chem. Lett.* **1991**, *20*, 2073–2076. (b) Jeong, N.; Lee, S. J.; Choi, K. H.; Chung, S. *Bull. Korean Chem. Soc.* **2000**, *21*, 165–166.
- (39) (a) Giordano, C.; Coppi, L.; Minisci, F. (Zambon Group S.p.A.). U.S. Patent 5,312,975, 1994. (b) de Vries, J. G. In *Encyclopedia of Catalysis*; Horváth, I. T., Ed.; John Wiley & Sons: New York, 2003; Vol. 3, pp 295–347.
- (40) Bumagin, N. A.; Ponomaryov, A. B.; Beletskaya, I. P. *J. Organomet. Chem.* **1985**, *291*, 129–132.
- (41) Kumada, M. *Pure Appl. Chem.* **1980**, *52*, 669–679.



**Figure 3.**  $\beta$ -H elimination.

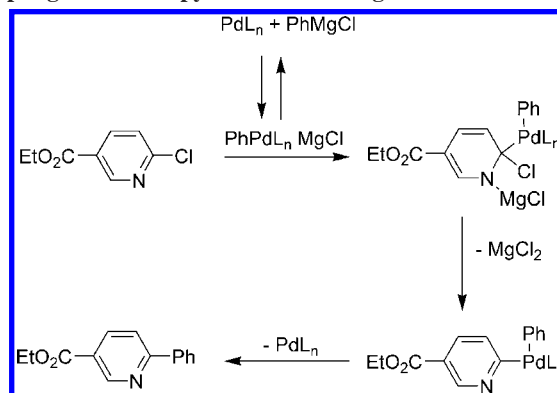
oxidative addition and transmetalation have to be in the cis-position for an easy reductive elimination. This condition is automatically met in the case of a bidentate phosphine ligand. In contrast, monodentate ligands with palladium catalysts give faster cross-coupling reactions compared to bidentate palladium catalysts, which can be explained by the fact that with palladium the oxidative addition is often the rate-limiting step.<sup>24b</sup>

The most commonly used leaving groups in cross-coupling reactions are in the order of decreasing reactivity I, OTf, Br, and Cl. Other leaving groups such as SR, SOR,  $\text{SO}_2\text{R}$ ,  $\text{SCONR}_2$ ,  $\text{OP(O)(OEt)}_2$ ,  $\text{OCONR}_2$ , OMe, OSiMe<sub>3</sub> have also been applied, but in combination with nickel or iron catalysts.<sup>12,42</sup> As mentioned before, the Kumada coupling is somewhat limited because of the incompatibility of Grignard reagents with certain functional groups.<sup>43</sup>

However, these issues with functional group compatibility encouraged the development of alternative protocols with less nucleophilic coupling reagents.<sup>44</sup> Knochel has pioneered the development of methods for the preparation of functionalized Grignard reagents.<sup>45</sup> In most cases, however, these compounds cannot be used directly in cross-coupling procedures because of their instability at the temperatures required for these reactions.<sup>46</sup> Nevertheless, a few examples with heteroarenes have been reported.<sup>47</sup>

For example, certain 2-chloropyridine derivatives react with functionalized aryl Grignard reagents under very mild conditions (Scheme 4).<sup>48</sup> The use of low-temperature conditions means that the presence of normally incompatible esters is tolerated. The facility of this process suggests operation of an

**Scheme 4.** Possible mechanism for Pd<sup>0</sup>-catalyzed Kumada coupling of 2-chloropyridine and PhMgCl



addition–elimination mechanism. Nucleophilic addition of a palladium “ate” complex, formed from the reaction between PdL<sub>n</sub> and PhMgCl, to the highly electrophilic 2-chloropyridine yields a stabilized magnesium amide which, after loss of MgCl<sub>2</sub> and reductive elimination, furnishes the coupled product. Recently, studies on the development of a Pd-catalyzed Kumada–Corriu cross-coupling process<sup>49</sup> showed that the couplings can be conducted at temperatures ranging from –20 to –65 °C, that the reaction can be extended to heteroarenes other than pyridine, and that the presence of a wide variety of functional groups in either coupling partner is tolerated (Table 1).<sup>50</sup>

In addition to the common aryl halides and sulfonates, aryl nitriles have also been found to participate in cross-coupling reactions via nickel-catalyzed activation of the C–CN bond. With the development of these synthetically useful transformations, heteroaryl nitriles can now be considered along with heteroaryl halides and sulfonates as viable substrates for these types of reactions.<sup>51</sup> The scope of this novel cross-coupling reaction is rather large, and a wide variety of both benzonitrile and aryl Grignard substrates is tolerated (Scheme 5). It is particularly noteworthy that all three cyanopyridines participate well in this biaryl-forming reaction. Relative to the 2-, 3-, or 4-halopyridines, the corresponding cyanopyridines are considerably less expensive and are commercially available in their free base form (4-halopyridines may only be purchased as their respective hydrohalide salts). This fact can make cyanopyridines (vs halopyridines) the preferred substrates for preparation of pyridine-containing biaryls in pharmaceutical, fine chemical, or liquid crystal applications.<sup>52</sup>

Recently, dinickel complexes of bis-*N*-heterocyclic carbene ligands have been shown to be highly active catalysts for the

(42) Brandsma, L.; Vasilevsky, S. F.; Verkrujisse, H. D. *Application of Transition Metal Catalysts in Organic Synthesis*; Springer: New York, 1998; pp 231–235.

(43) Bonnet, V.; Mongin, F.; Trécourt, F.; Quéguiner, G.; Knochel, P. *Tetrahedron Lett.* **2001**, *42*, 5717–5719.

(44) (a) Diederich, F.; Stang, P. J., Eds. *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH: Weinheim, Germany, 2004. (b) Lau, S. Y. W.; Hughes, G.; O’Shea, P. D.; Davies, I. W. *Org. Lett.* **2007**, *9*, 2239–2242.

(45) For recent reviews, see: (a) Hiriyakkanavar, I.; Baron, O.; Wagner, A. J.; Knochel, P. *Chem. Commun.* **2006**, 583–593. (b) Knochel, P.; Dohle, W.; Gommersmann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4302–4320.

(46) For some exceptions, see: (a) Bonnet, V.; Mongin, F.; Trécourt, F.; Quéguiner, G.; Knochel, P. *Tetrahedron* **2002**, *58*, 4429–4438. (b) Bonnet, V.; Mongin, F.; Trécourt, F.; Breton, G.; Marsais, F.; Knochel, P.; Quéguiner, G. *Synlett* **2002**, 1008–1010.

(47) (a) Isobe, K.; Kawaguchi, S. *Heterocycles* **1981**, *16*, 1603–1612. (b) Minato, A.; Suzuki, K.; Tamao, K.; Kumada, M. *J. Chem. Soc., Chem. Commun.* **1984**, 511–513.

(48) Bonnet, V.; Mongin, F.; Trécourt, F.; Quéguiner, G.; Knochel, P. *Tetrahedron Lett.* **2001**, *42*, 5717–5719.

(49) (a) Organ, M. G.; Abdel-Hadi, M.; Avola, S.; Hadei, N.; Nasielski, J.; O’Brien, C. J.; Valente, C. *Chem.–Eur. J.* **2007**, *13*, 150–157.

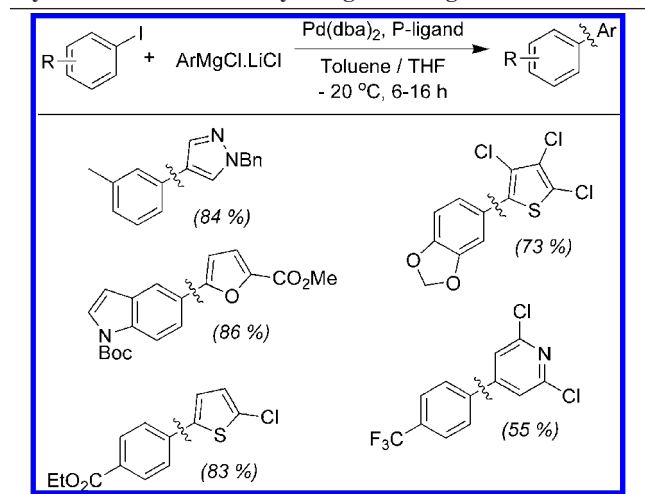
(b) Limmert, M. E.; Roy, A. H.; Hartwig, J. F. *J. Org. Chem.* **2005**, *70*, 9364–9370. (c) Ackermann, L.; Born, R.; Spatz, J. H.; Meyer, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 7216–7219. (d) Huang, J.; Nolan, S. P. *J. Am. Chem. Soc.* **1999**, *121*, 9889–9890.

(50) Martin, R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3844–3845.

(51) Miller, A.; Dankwardt, J. W.; Penney, J. M. *Synthesis* **2003**, 1643–1648.

(52) For a review of biaryl syntheses, see: Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263–303.

**Table 1.** Palladium-catalyzed Kumada–Corriu reactions of aryl iodides with heteroaryl Grignard reagents



coupling of aryl Grignard reagents with aryl chlorides, including heteroaromatic ones.<sup>53</sup>

Noteworthy also is the iron-catalyzed cross-coupling reaction. Originally thought to be essentially limited to the reaction of alkenyl halides with unfunctionalized Grignard reagents, iron-catalyzed methods have shown a significant growth in the past years.<sup>12</sup> Substantial advancements have been made to increase the range of nucleophilic and electrophilic partners amenable to such transformations (Table 2).<sup>54</sup>

The reducing ability of Grignard reagents is one of the major limiting factors in “standard” cross-coupling reactions of these nucleophiles in the presence of palladium complexes as catalysts, causing the precipitation of palladium black and, hence, the arrest of the catalytic turnover. In sharp contrast, this propensity is possibly the key to success for the iron-catalyzed processes described herein. The mechanism of these reactions, though, is still a matter of controversy: Fe(0) nanoparticles have been shown to be present in the coupling of alkyl halides with aryl Grignard reagents; they may be the actual catalyst in an Fe(0)/Fe(II) cycle.<sup>55</sup> On the other hand, Fürstner and co-workers proposed the intermediacy of iron in the –2 oxidation state.<sup>56</sup> Recently, Norrby and co-workers proposed an Fe(I)/Fe(III) cycle, based on DFT calculations.<sup>57</sup> The fact that aryl chlorides, triflates, and tosylates are inherently better substrates than the corresponding bromides or iodides represents a major advantage in practical terms. The favorable profile of this new method is further increased by the low cost as well as the toxicologically and environmentally benign character of the iron salts used as precatalysts. Although one may object that the high reactivity of the C–MgX bond restricts the scope of the iron-catalyzed cross-coupling methodology, the rapidly growing number of functionalized Grignard reagents

indicates that this is not a fatal drawback and that the scope of this methodology can be increased.<sup>58,59</sup>

#### 4. Negishi Coupling

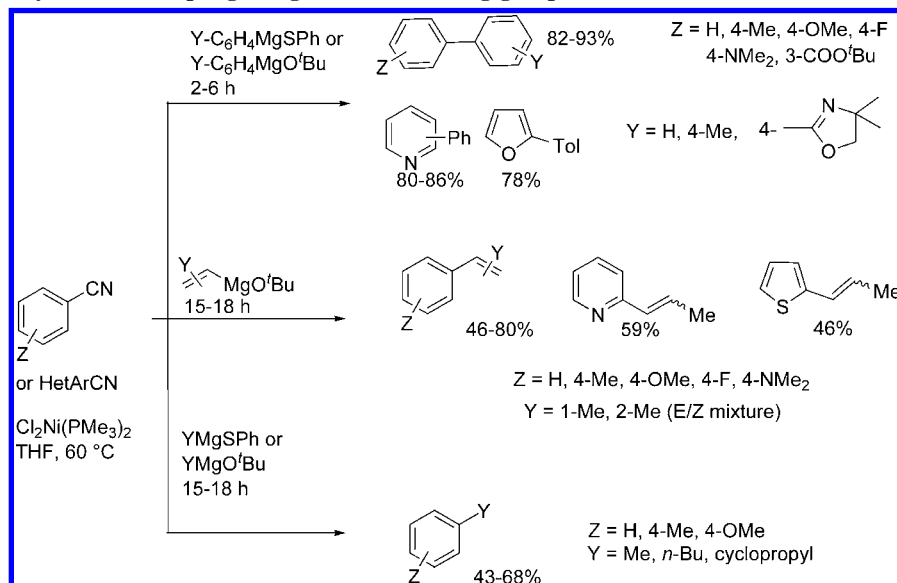
The Negishi coupling, published in 1977,<sup>9</sup> was the first reaction that allowed the preparation of unsymmetrical biaryls in good yields. This versatile nickel- or palladium-catalyzed coupling of organozinc compounds with various halides (aryl, vinyl, benzyl, or allyl) has broad scope and is not restricted to the formation of biaryl systems.<sup>14,37</sup> There are quite a few examples of heterocyclic substrates known, mainly nitrogen-containing, that participate in the Negishi reaction. Thus, chloropyridines (Scheme 6),<sup>60</sup> triazines,<sup>61</sup> pyrazines,<sup>62</sup> and pyrimidines<sup>63</sup> are suitable substrates, as are fused heterocycles such as chloroquinolines,<sup>64</sup> quinazolines,<sup>65</sup> and purines.<sup>66</sup>

The cross-coupling under palladium-catalyzed conditions has the following order of reactivity: zinc > magnesium ≫ lithium. The high potency of the zinc reagents is especially striking. Note that compared to zinc, magnesium and lithium reagents are highly nucleophilic. In general, Negishi couplings are fast and proceed under relatively mild reaction conditions. Moreover, the functional group compatibility of zinc reagents is much broader than that of Grignard reagents.<sup>67</sup> Functional groups such as NO<sub>2</sub>, CN, OR, NR<sub>2</sub>, CO, COOR, COH, SCN are in general applicable. In general alcohols and acids should be protected. As in the Kumada-type coupling, both nickel- and palladium-catalyzed Negishi reactions are possible. Similar to findings using Grignard reagents, the palladium-catalyzed reactions in the Negishi coupling are more stereospecific and give less homocoupling and isomerization than nickel-catalyzed ones. With palladium catalysis, aryl, vinyl, and alkyl groups couple fairly well in the Negishi cross-coupling reaction, whereas allyl, benzyl, and propargyl groups are difficult to use. The most

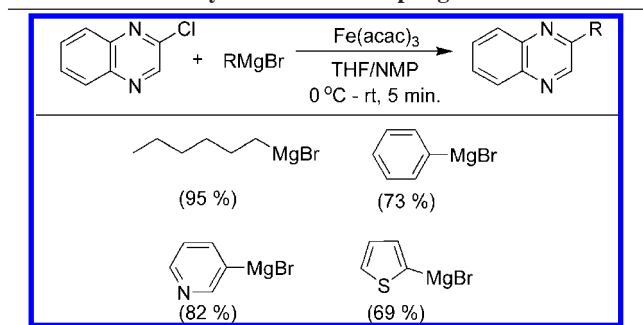
- (53) Zhou, Y.; Xi, Z.; Chen, W.; Wang, D. *Organometallics* **2008**, *27*, 5911–5920.
- (54) Ila, H.; Baron, O.; Wagner, A. J.; Knochel, P. *Chem. Commun.* **2006**, 583–593.
- (55) Bedford, R. B.; Betham, M.; Bruce, D. W.; Davis, S. A.; Frost, R. M.; Hird, M. *Chem. Commun.* **2006**, 1398–1400.
- (56) Fürstner, A.; Martin, R.; Krause, H.; Seidel, G.; Goddard, R.; Lehmann, C. W. *J. Am. Chem. Soc.* **2008**, *130*, 8773–8787.
- (57) Kleimark, J.; Hedström, A.; Larsson, P.-F.; Johansson, C.; Norrby, P.-O. *Chem. Cat. Chem.* **2009**, *1*, 152–161.

- (58) (a) Hatakeyama, T.; Nakamura, M. *J. Am. Chem. Soc.* **2007**, *129*, 9844–9845. (b) Fürstner, A.; Leitner, A.; Méndez, M.; Krause, H. *J. Am. Chem. Soc.* **2002**, *124*, 13856–13863. (c) Frisch, A. C.; Shaikh, N.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 609–612.
- (59) For recent reviews on iron-catalyzed reactions see: (a) Bolm, C.; Legros, J.; Le Pailh, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217–6254. (b) Fürstner, A.; Martin, R. *Chem. Lett.* **2005**, *34*, 624–629. (c) Correa, A.; Mancheno, O. G.; Bolm, C. *Chem. Soc. Rev.* **2008**, *37*, 1108–1117. (d) Farrell, D.; Majetich, S. A.; Wilcoxon, J. P. *J. Phys. Chem. B* **2003**, *107*, 11022–11030.
- (60) (a) Minato, Q.; Tamao, K.; Hayashi, T.; Suzuki, K.; Kumada, M. *Tetrahedron Lett.* **1980**, *21*, 845–848. (b) Hall, J. H.; Chien, J. Y.; Kaufmann, J. M.; Litak, P. T.; Adams, J. K. R. A.; Henry, R. A.; Hollins, R. A. *J. Heterocycl. Chem.* **1992**, *29*, 1245–1273.
- (61) Sonoda, M.; Inaba, A.; Itahashi, K.; Tobe, Y. *Org. Lett.* **2001**, *3*, 2419–2421.
- (62) Amat, M.; Hadida, S.; Pshenichnyi, G.; Bosch, J. *J. Org. Chem.* **1997**, *62*, 3158–3175.
- (63) (a) Sakamoto, T.; Nishimura, S.; Kondo, Y.; Yamanaka, H. *Synthesis* **1988**, 485–486. (b) Sandosham, J.; Undheim, K.; Rise, F. *Heterocycles* **1993**, *35*, 235–244. (c) Angioletti, M. E.; Casalnuovo, A. L.; Selby, T. P. *Synlett* **2000**, 905–907.
- (64) (a) Bracher, F.; Hildebrand, D. *Tetrahedron Lett.* **1994**, *50*, 12329–12336. (b) Murata, N.; Sugihara, T.; Kondo, Y.; Sakamoto, T. *Synlett* **1997**, 298–300.
- (65) Chapriot, B.; Brun, J.; Donze, I.; Naef, R.; Stefani, M.; Mueller, T. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2891–2896.
- (66) (a) Gundersen, L.-L.; Bakkestuen, A. K.; Aasen, A. J.; Overas, H.; Rise, F. *Tetrahedron* **1994**, *50*, 9743–9756. (b) Hocek, M.; Holy, A.; Votruba, I.; Dvorakova, H. *Collect. Czech. Chem. Commun.* **2001**, *66*, 483–499.
- (67) (a) Boudier, A.; Bromm, L. O.; Lotz, M.; Knochel, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 4415–4435. (b) Knochel, P.; Millot, N.; Rodriguez, A. L.; Tucker, C. A. In *Organic Reactions*; Overman, L. E., Ed.; Wiley & Sons Ltd.: New York, 2001; Vol. 58, p 417.

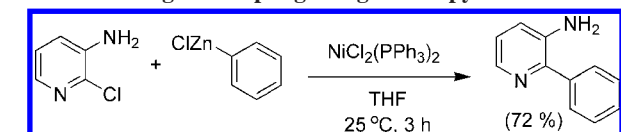
**Scheme 5. Nickel-catalyzed cross-coupling using nitriles as leaving groups**



**Table 2. Iron-catalyzed Kumada coupling reactions**



**Scheme 6. Negishi coupling using amino pyridine chlorides**

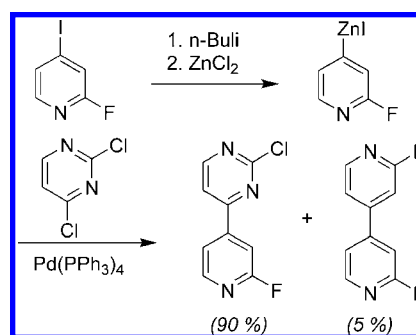


challenging part of the Negishi cross-coupling is generally not the cross-coupling itself, but the preparation of organozinc derivatives. The latter is often the determining factor when choosing this type of cross-coupling reaction.

One of the most straightforward procedures to prepare heteroarylzinc halides is via the direct lithiation of halo heteroarenes.<sup>68</sup> For example, 2-fluoro-4-iodopyridine is lithiated via lithium–halogen exchange with *n*-butyllithium at the 4-position and, following addition of thoroughly dried ZnCl<sub>2</sub>, yields the zincate.<sup>69</sup> The subsequent regioselective Negishi coupling with 2,4-dichloropyrimidine affords the desired pyridinylpyrimidine in a reasonable yield in a one-pot reaction.

Note that in the initial experiment equimolar amounts of *n*-butyllithium and iodide were used and the product was accompanied by the formation of a significant amount of bipyridyl (14%). This problem was solved by using a slight

**Scheme 7. Preparation of arylzinc halides via direct lithiation**



excess of the lithium reagent (1.05 equiv); the yield increased to 90% with only traces of the homocoupled product (Scheme 7).

Alternatively, arylzinc halides can be prepared via magnesium reagents.<sup>70</sup> It was shown that a halogen–magnesium exchange<sup>71</sup> allows the preparation of arylmagnesium halides bearing sensitive functional groups such as an ester,<sup>72</sup> nitrile, or imine<sup>73</sup> function. These unsaturated organometallic reagents combine a good functional group tolerance with an intrinsic high reactivity. By performing various stoichiometric or catalytic transmetalations, this reactivity can be fine-tuned, allowing optimum reaction conditions with numerous classes of electrophiles. The mild conditions required for performing the iodine– or bromine–magnesium exchange<sup>74</sup> are compatible

(68) Milne, J. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 13028–13032.

(69) (a) Stanetty, P.; Schnuerch, M.; Mihovilovic, M. D. *Synlett* **2003**, *12*, 1862–1864. (b) Stanetty, P.; Hattinger, G.; Schnuerch, M.; Mihovilovic, M. D. *J. Org. Chem.* **2005**, *70*, 5215–5220.

(70) Jensen, A. G.; Dohle, W.; Sapountzis, I.; Lindsay, D. M.; Vu, V. A.; Knochel, P. *Synthesis* **2002**, 565–569.

(71) (a) Villieras, J. *Bull. Soc. Chim. Fr.* **1967**, 1520–1532. (b) Paradies, H. H.; Goerbing, M. *Angew. Chem., Int. Ed.* **1969**, *8*, 279. (c) Furukawa, N.; Shibutani, T.; Fujihara, H. *Tetrahedron Lett.* **1987**, *28*, 5845–5848. (d) Nishiyama, H.; Isaka, K.; Itoh, K.; Ohno, K.; Nagase, H.; Matsumoto, K.; Yoshiwara, H. *J. Org. Chem.* **1992**, *57*, 407–411. (e) Bolm, C.; Pupowicz, D. *Tetrahedron Lett.* **1997**, *38*, 7349–7352.

(72) (a) Boymond, L.; Rottländer, M.; Cahiez, G.; Knochel, P. *Angew. Chem., Int. Ed.* **1998**, *37*, 1701–1703. (b) Rottländer, M.; Boymond, L.; Bérillon, L.; Leprêtre, A.; Varchi, G.; Avolio, S.; Laaziri, H.; Quéguiner, G.; Ricci, A.; Cahiez, G.; Knochel, P. *Chem.–Eur. J.* **2000**, *6*, 767–770.

(73) Varchi, G.; Jensen, A. E.; Dohle, W.; Ricci, A.; Cahiez, G.; Knochel, P. *Synlett* **2001**, 477–480.

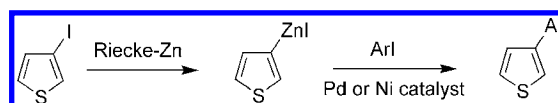
with sensitive functionalities on the aryl halide. Thus, an ester or nitrile group is compatible with the generation of an arylmagnesium reagent via an iodine–magnesium exchange, which is complete at  $-20\text{ }^{\circ}\text{C}$  within a few hours. Under these mild conditions, no attack on the ester or nitrile group occurs. The rate of the iodine–magnesium exchange is significantly slower than the iodine–lithium exchange,<sup>75</sup> and it is observed that the nature of the aromatic or heteroaromatic ring strongly influences the rate of the exchange. The more electron-poor the aromatic ring, the faster the exchange reaction. Also, the presence of chelating groups ortho to the carbon–halogen bond strongly accelerates the exchange and allows the bromine–magnesium exchange to take place under milder conditions than usual. Note that bromine–magnesium exchanges under mild conditions in the absence of ortho-chelating groups have also been reported.<sup>76</sup> In general, iodine–magnesium exchange reactions are considerably faster than the corresponding bromine–magnesium exchange reactions.

Other approaches to arylzinc halides proceed via the use of Rieke zinc, which is prepared through the reduction of  $\text{ZnCl}_2$  by Li in THF using naphthalene as an electron carrier.<sup>77</sup> The active metals can be washed using THF to remove both the electron carrier and the lithium chloride formed. These Rieke metals readily undergo oxidative addition to 3-iodothiophene to form 3-thienyl organometallic reagents, which react with electrophiles in THF at room temperature (Scheme 8). The preparation of the active metals and the reactions of the organometallics are conducted under an inert atmosphere.

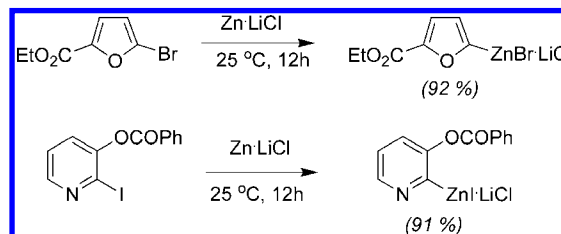
An effective procedure to prepare organozinc halides in good yields, using a LiCl-mediated insertion of zinc dust into alkyl, aryl, and heteroaryl iodides (Scheme 9), was published.<sup>78</sup> All of these reactions proceed within a practical temperature range ( $25\text{--}50\text{ }^{\circ}\text{C}$ ) and can be extended to large-scale preparation. Additives such as lithium acetylacetonate can also be very useful for the preparation of zinc reagents (Scheme 10). The latter ensured high functional-group compatibility with, for example, ester, ketone, cyano, aldehyde, or isothiocyanate groups as substituents.<sup>79</sup> Alternative approaches to organozinc reagents are via zinc/TMS-Cl/1,2-dibromoethane,<sup>80</sup>  $\text{R}_3\text{Al}/\text{ZnCl}_2$ <sup>81</sup> and  $\text{Zn}(\text{Cu})$ .<sup>82</sup>

The Negishi cross-coupling reaction is a good method to prepare functionalized bipyridines. Both 2-bromopyridines and 2-chloropyridines (with electron-withdrawing groups) are suit-

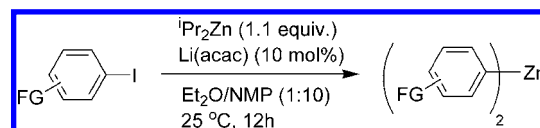
#### Scheme 8. Preparation of 3-thienylzinc iodide using Rieke zinc



#### Scheme 9. Lithium-mediated zinc insertion into heteroaryl bromides



#### Scheme 10. Preparation of diarylzinc using lithium acetyl acetonate as additive



able substrates for this reaction. Subsequent work has revealed the limitations of bipyridine synthesis starting from bromopyridines, and introduced pyridyl triflates as higher-yielding substrates for 2-pyridylzinc chloride.<sup>83</sup> It was demonstrated that commercially available halopyridines are indeed more general substrates for 2-pyridylzinc bromides than previously thought (Table 3).

An even more efficient Negishi strategy for preparation of substituted bipyridines using tetrakis(triphenylphosphine)palladium(0) as a simple, commercially available, and relatively inexpensive catalyst for both 2-bromo- and 2-chloropyridines (Scheme 11) has been published.<sup>84</sup>

Buchwald et al. examined the catalyst derived from a biarylphosphorus ligand (RuPhos) and Pd(0) for Negishi coupling reactions involving heteroaromatic substrates.<sup>68</sup> As shown in Table 4, the cross-coupling of a variety of heteroaromatic chlorides and bromides was accomplished in good to excellent yields using Pd/RuPhos catalyst system, including quinoxalines, benzothiazoles, pyrimidines, pyrazines, quinolines, tetrazoles, and pyrazoles as well as substituted pyridines.

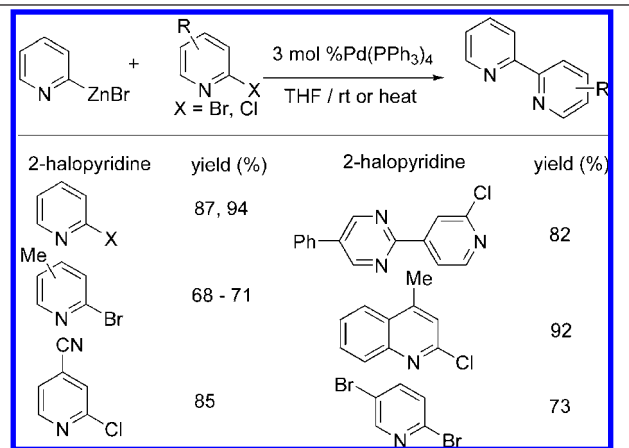
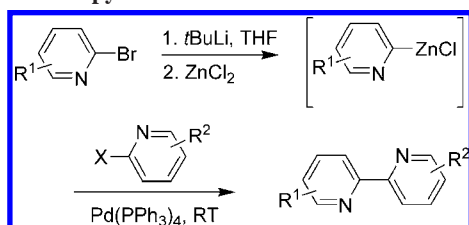
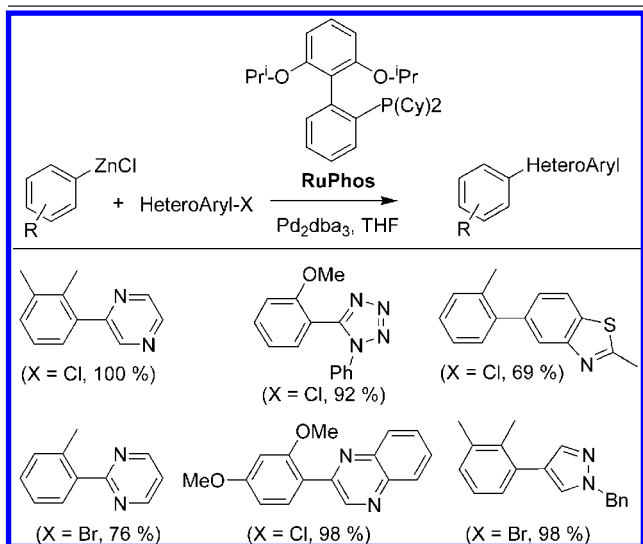
An impressive enantioselective palladium-catalyzed Negishi cross-coupling relies on Beak's sparteine-mediated enantioselective deprotonation of *N*-Boc-pyrrolidine with butyllithium. The lithiated species is quenched using zinc chloride, and the resultant chiral organozinc chloride is allowed to react in the presence of (hetero)aryl halides to yield a broad range of 2-aryl-*N*-Boc-pyrrolidines in high enantiomeric ratio (Scheme 12).<sup>85</sup>

Studies have shown that the choice of ligand on palladium is crucial in many transformations.<sup>25b,86</sup> Pioneering work by Dai and Fu afforded the first general protocol for performing Negishi

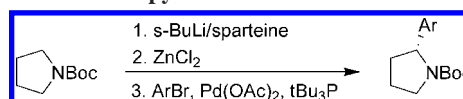
- (74) (a) Abarbri, M.; Thibonnet, J.; Bérillon, L.; Dehmel, F.; Rottländer, M.; Knochel, P. *J. Org. Chem.* **2000**, *65*, 4618–463. For alternative preparations of functionalized arylmagnesium reagents: (b) Lee, J.; Velarde-Ortiz, R.; Guijairo, A.; Wurst, J. R.; Rieke, R. D. *J. Org. Chem.* **2000**, *65*, 5428–5430. (c) Kitagawa, K.; Inoue, A.; Shinokubo, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 2481–2483.
- (75) Bailey, W. F.; Punzalan, E. R. *J. Org. Chem.* **1990**, *55*, 5404–5406, and references cited therein.
- (76) Krasovskiy, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3333–3336.
- (77) Wu, X.; Rieke, R. D. *J. Org. Chem.* **1995**, *60*, 6658–6659.
- (78) Krasovskiy, A.; Malakhov, V.; Gavryushin, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 6040–6044.
- (79) Kneisel, F. F.; Dochnahl, M.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 1017–1021.
- (80) Corley, E. G.; Conrad, K.; Murry, J. A.; Savarin, C.; Holko, J.; Boice, G. *J. Org. Chem.* **2004**, *69*, 5120–5123.
- (81) Negishi, E.-I.; Takahashi, T.; Baba, S. *Org. Synth.* **1993**, *8*, 295.
- (82) Tamaru, Y.; Ochiai, H.; Nakamura, T.; Yoshida, Z. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1157–1158.

- (83) Savage, S. A.; Smith, A. P.; Fraser, C. L. *J. Org. Chem.* **1998**, *63*, 10048–10051.
- (84) Kiehne, U.; Bunzen, J.; Staats, H.; Lützen, A. *Synthesis* **2007**, 1061–1069.
- (85) Campos, K. R.; Klapars, A.; Waldman, J. H.; Dormer, P. G.; Chen, C.-Y. *J. Am. Chem. Soc.* **2006**, *128*, 3538–3539.
- (86) van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Reek, J. N. H.; Dierkes, P. *Chem. Rev.* **2000**, *100*, 2741–2769.



**Table 3.** Negishi cross-coupling for preparing bipyridines**Scheme 11.** Negishi cross-coupling protocol for preparation of substituted bipyridines**Table 4.** Negishi cross-coupling of heteroaryl halides using RuPhos

cross-coupling reactions of unactivated and deactivated aryl chlorides, in which the electron-rich complex Pd[P<sup>t</sup>Bu<sub>3</sub>]<sub>2</sub> was used as the precatalyst.<sup>87</sup> Using a standard set of conditions (2% Pd[P<sup>t</sup>Bu<sub>3</sub>]<sub>2</sub>, THF/NMP, 100 °C), the synthesis of quite hindered biaryls was accomplished in excellent yield. In the Negishi cross-coupling reaction strongly  $\sigma$ -donating ligands with steric bulk, such as P<sup>t</sup>Bu<sub>3</sub> and S-Phos, are the best performing monodentate ligands, especially for bulky substrates and unactivated aryl chlorides. Other Negishi cross-coupling procedures have been reviewed.<sup>88</sup>

(87) Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 2719–2724.(88) Negishi, E.; Hu, Q.; Huang, Z.; Qian, M.; Wang, G. *Aldrichimica Acta* **2005**, *38*, 71–88.**Scheme 12.** Enantioselective, palladium-catalyzed  $\alpha$ -arylation of *N*-Boc-pyrrolidine

Recently, mono- and dinickel complexes of bis-*N*-heterocyclic carbene ligands have been shown to be highly active catalysts in the Negishi coupling reactions of aryl chlorides, including several heteroaryl ones.<sup>89</sup> Yields are in general above 90%, even at 0.1 mol % catalyst loading, so this system looks to be a valuable alternative to the palladium catalysts described above.

An additional consideration when applying Negishi reactions on large scale is the zinc waste. In most countries there is a limit on the amount of zinc in the wastewater. Thus, it will be necessary to treat the wastewater stream with NaOH to precipitate the zinc as its hydroxide. After filtration, this material is either returned to the producer or landfilled. In view of the costs associated with this process, reduction of the amount of zinc is highly desirable. Catalytica Pharmaceuticals developed an interesting “double catalytic” Negishi reaction in which catalytic amounts of ZnCl<sub>2</sub> and a cost-effective nickel–phosphite complex was used.<sup>90</sup> This process has been used for the ton-scale production of *o*-tolylbenzotrile, an intermediate for the Sartan class of blood pressure-lowering agents.<sup>91</sup> There are generally no limitations on the presence of borate in wastewater. For this reason a Suzuki reaction may be the preferred option if a Kumada reaction is not possible.

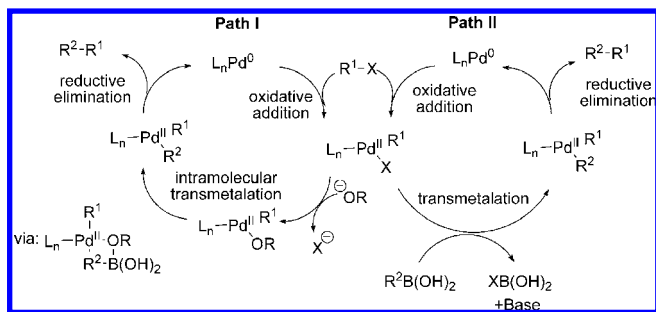
## 5. Suzuki–Miyaura Reaction

The Suzuki reaction has become one of the most efficient methods for the construction of substituted heteroaromatic compounds.<sup>92,93</sup> The key advantage of the Suzuki reaction is the observed high tolerance to most functional groups, the mild conditions under which the reaction is conducted, the relative stability of boronic acids/esters to heat, oxygen, and water, the ease of handling and separation of boron-containing byproducts, and their abundant commercial availability. These are all desirable features for the construction of diverse aryl and heteroaryl species needed in medicinal chemistry.

The catalytic cycle of the palladium-catalyzed Suzuki reaction is thought to proceed via the same sequence as in other cross-coupling reactions. The process begins with oxidative addition of an aryl halide to a Pd(0) complex to form an arylpalladium(II) halide intermediate. The transmetalation with a boronic acid and the reductive elimination complete the catalytic cycle (see Figure 4).<sup>34a</sup>

The selection of a base is, however, still empirical, and no general rule has been established. The role of the base in these reactions is to facilitate the transmetalation of the boronic acid

(89) Xi, Z.; Zhou, Y.; Chen, W. *J. Org. Chem.* **2008**, *73*, 8497–5801.(90) Miller, J. A.; Farrell, R. P. *Tetrahedron Lett.* **1998**, *39*, 7275–7278.(91) Meudt, A.; Nerdinger, S.; Lehnemann, B. *Chim. Oggi* **2004**, *22* (8), 6–9.(92) (a) Billingsley, K.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3358–3366. (b) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685–4696. (c) Barder, T. E.; Buchwald, S. L. *Org. Lett.* **2004**, *6*, 2649–2652.(93) Kotha, S.; Lahiri, K.; Kashinanth, D. *Tetrahedron* **2002**, *58*, 9633–9695.



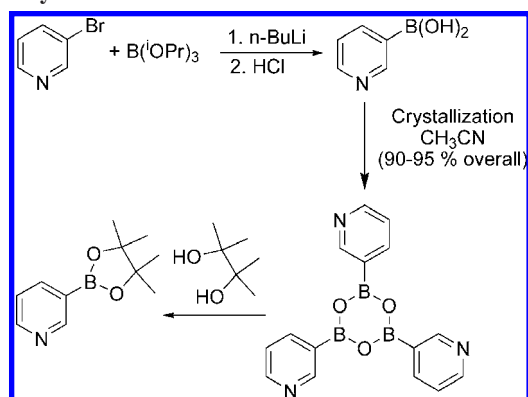
**Figure 4.** Proposed mechanisms for the palladium-catalyzed Suzuki reactions.

by forming a more reactive boronate species. Although not proven, this is likely because boronates are known to be formed at pH 11–12. Two catalytic cycles have been proposed. In the first one, the base replaces the halide on the palladium complex and facilitates the intramolecular transmetalation (path I).<sup>94</sup> Alternatively, the boronate interacts with the metal center and transmetalates in an intramolecular fashion (path II).<sup>95</sup>

The selective functionalization of aryl and heteroaryl compounds with boron species is an important synthetic task, and the efficiency of this step plays an important role in the decision making for the use of the Suzuki–Miyaura coupling. A typical preparation of arylboronic acids involves a reaction between an organoborate and an organometallic (Li or Mg) species, usually prepared by magnesium insertion or lithium–halogen exchange of the corresponding aryl halides.<sup>96</sup> However, this method has its limitations. First, it is difficult to apply this method to substrates bearing functional groups not compatible with organolithium reagents, such as esters and nitriles. Second, some aryllithium intermediates are intrinsically unstable, as in the case of many aromatic heterocycles.<sup>97</sup> Reider reported an improved protocol for the preparation of some heteroaryl boronic acids/esters.<sup>98</sup> In this approach *n*-butyllithium was added to a solution of 3-bromopyridine and triisopropyl borate followed by an acid quench (Scheme 13). As it turned out, this sequence of addition was superior to those previously described. Not only did it consistently afford good yields, but it also proved to be temperature tolerant, giving the best yields (90–95%) at –40 °C and a respectable 80% yield even at 0 °C. The optimized procedure was easily scaled up to produce 1 kg of crystalline boroxin, which functioned very well in a palladium-catalyzed cross-coupling reaction with aryl halides.

Senanayake showed that the presence of bis[2-(*N,N*-dimethylamino)ethyl] ether allows a selective halide–magnesium exchange of iodo- and bromoaromatics bearing sensitive carboxylic ester and cyano groups with isopropylmagnesium chloride. A subsequent reaction with trimethylborate as elec-

**Scheme 13.** Improved protocol for the preparation of some heteroaryl boronic acids/esters



trophile afforded arylboronic acids in good to excellent yields.<sup>99</sup> Other examples have also been reported.<sup>100</sup>

Knochel published an effective method to prepare iodoheteroaryl boronic esters from heterocyclic diiodides by an I/Mg exchange followed by treatment with a dioxaborolane (Scheme 14).<sup>101</sup> These reagents provided access to a broad array of polyfunctional boronic esters, which underwent smooth Suzuki cross-coupling reactions. The use of these boronic esters is advisable when reactive functional groups are present, and in this respect the choice of base is also essential. Moreover, in the case of sensitive or unreactive organoboron compounds it is wise to use the boronic ester instead of the boronic acid.

Alternatively, arylboronic esters can be prepared from aryl halides or aryl triflates via a palladium-catalyzed cross-coupling reaction with tetraalkoxydiboron or dialkoxyhydroborane.<sup>102</sup> The so-called Miyaura borylation reaction enables the synthesis of boronates by cross-coupling of bis(pinacolato)diboron ( $B_2pin_2$ ) with aryl halides and vinyl halides (Scheme 15). Borylated products derived from  $B_2pin_2$  survive normal work up including chromatographic purification and are stable towards air. Pinacol esters are difficult to hydrolyze, but they may serve as coupling partners in the Suzuki coupling and similar reactions without prior hydrolysis. Crucial for the success of the borylation reaction is the choice of an appropriate base, as strong activation of the product enables the competing Suzuki coupling. The use of KOAc and KOPh is actually the result of a screening of different reaction conditions by the Miyaura group.<sup>103</sup> The starting material bis(pinacolato)diboron is a poor Lewis acid and <sup>11</sup>B-NMR of KOAc and  $B_2bin_2$  in DMSO-*d*<sub>6</sub> shows no evidence for the coordination of the acetoxy anion to a boron

(94) Braga, A. A. C.; Morgon, N. H.; Ujaque, G.; Maseras, F. *J. Am. Chem. Soc.* **2005**, *127*, 9298–9307.

(95) Miyaura, N. *J. Organomet. Chem.* **2002**, *653*, 54–57.

(96) (a) Gerrard, W. *The Chemistry of Boron*; Academic: New York, 1961. (b) Brown, H. C.; Cole, T. E. *Organometallics* **1983**, *2*, 1316–1319. (c) Brown, H. C.; Bhat, N. G.; Srebnik, M. *Tetrahedron Lett.* **1988**, *29*, 2631–2634.

(97) Gilman, H.; Spatz, S. M. *J. Org. Chem.* **1951**, *16*, 1485–1494.

(98) Li, W.; Nelson, D. P.; Jensen, M. S.; Hoerner, R. S.; Cai, D.; Larsen, R. D.; Reider, P. J. *J. Org. Chem.* **2002**, *67*, 5394–5397.

(99) Wang, X.-J.; Sun, X.; Zhang, L.; Xu, Y.; Krishnamurthy, D.; Senanayake, C. H. *Org. Lett.* **2006**, *8*, 305–307.

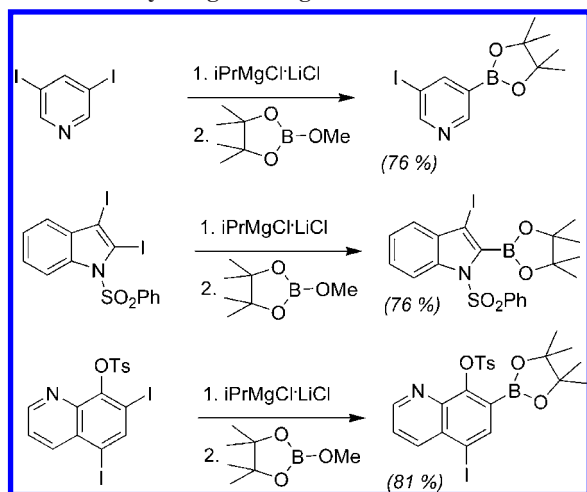
(100) (a) Jiang, Q.; Ryan, M.; Zhichkin, M. *J. Org. Chem.* **2007**, *72*, 6618–6620. (b) Hawkins, V. F.; Wilkinson, M. C.; Whiting, M. *Org. Process Res. Dev.* **2008**, *12*, 1265–1268.

(101) Baron, O.; Knochel, P. *Angew. Chem., Int. Ed.* **2005**, *44*, 3133–3135.

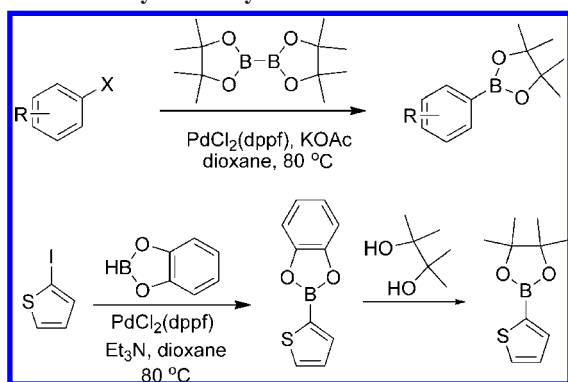
(102) (a) Takagi, J.; Kamon, A.; Ishiyama, T.; Miyaura, N. *Synlett* **2002**, 1880–1882. (b) Ishiyama, T.; Itoh, Y.; Kitano, T.; Miyaura, N. *Tetrahedron Lett.* **1997**, *38*, 3447–3450. (c) Murata, M.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* **1997**, *62*, 6458–6459. (d) Murata, M.; Oyama, T.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* **2000**, *65*, 164–168. (e) Baudoin, O.; Gue'nard, D.; Gue'ritte, F. *J. Org. Chem.* **2000**, *65*, 9268–9271. (f) Thompson, A. L. S.; Kabalka, G. W.; Akula, M. R.; Huffman, J. W. *Synthesis* **2005**, 547–550. (g) Wolan, A.; Zaidlewicz, M. *Org. Biomol. Chem.* **2003**, *1*, 3724–3726.

(103) (a) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508–7510. (b) Takagi, J.; Kou Takahashi, K.; Ishiyama, T.; Miyaura, N. *J. Am. Chem. Soc.* **2002**, *124*, 8001.

**Scheme 14. Synthesis of iodo-substituted heterocyclic boronic esters by I/Mg exchange**



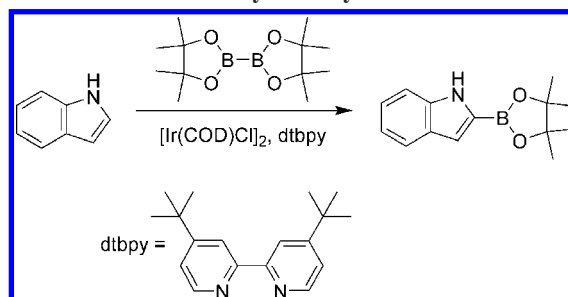
**Scheme 15. Miyaura borylation**



atom leading to a tetrahedral activated species (compared to Suzuki coupling). However, the formation of an (acetato)palladium(II) complex after the oxidative addition of the halide influences the reaction rate of the transmetalation step. The Pd–O bond, which consists of a hard Lewis base with a soft Lewis acid, is more reactive than a Pd–X (X = Br, I) bond. In addition, the high oxophilicity of boron has to be considered as a driving force for the transmetalation step, which involves an acetate ligand. The mild reaction conditions allow the preparation of boronates which are not accessible via lithium or Grignard intermediates. The use of HBPin instead of B<sub>2</sub>Pin<sub>2</sub> allows similar reactions in large-scale synthesis and also permits use of various reducible functional groups, although side products may arise due to dehalogenation of the aryl halide.<sup>103</sup> An efficient catalyst system for the cross-coupling of pinacolborane with aryl bromides is the combination of Pd(dba)<sub>2</sub> and bis(2-di-*tert*-butyl-phosphinophenyl)ether. This system enables the synthesis of ortho-, meta-, and para-substituted electron-rich and -deficient arylboronates.<sup>104</sup> These methods tolerate a wide range of functional groups. Buchwald et al. reported a one-pot procedure for the synthesis of biaryls from different aryl or heteroaryl chlorides. In this process, the substrates were subjected to the standard Pd-catalyzed borylation condition with subsequent addition of the second aryl chloride and aqueous K<sub>3</sub>PO<sub>4</sub>, resulting in the formation of the desired

(104) Murata, M.; Sambommatsu, T.; Watanabe, S.; Masuda, Y. *Synlett* **2006**, *12*, 1867–1870.

**Scheme 16. Iridium-catalyzed borylation**



products.<sup>105</sup> Other palladium-catalyzed methods have also been reported.<sup>104,106</sup>

A more recent *halogen-free* strategy to arylboronic acids/esters and trifluoroborates is the iridium-catalyzed borylation of (hetero)arenes (Scheme 16).<sup>107</sup> This one-pot approach to boronic esters and subsequently to boronic acids (by oxidative cleavage of the pinacol boronates with NaIO<sub>4</sub>) and aryltrifluoroborate (displacement of pinacol by KHF<sub>2</sub>) proceeds at room temperature. One factor that clearly distinguishes the C–H activation of arenes by these complexes is the subsequent formation of functionalized product. This functionalization by the formation of arylboronate esters results from the strong thermodynamic driving force for B–C bond formation and the overall favorable thermodynamics for the reaction of B<sub>2</sub>pin<sub>2</sub> with arenes to form ArBpin and HBpin.<sup>108</sup> These favorable thermodynamics create a catalytic process that allows the direct generation of arylboronate esters without the intermediacy of halogenated reagents, Grignard reagent, or a hydrolytic workup characteristic of the conventional synthesis of arylboronate esters.<sup>107d</sup> In addition, the iridium-catalyzed selective ortho borylation of arenes using a conceptually novel approach based on hydrosilanes as directing groups was reported. This concept has been applied to the development of regioselective functionalization of benzylic silanes, phenols, and anilines.<sup>109</sup> Other approaches to prepare boronates from acetals,<sup>110</sup> alkenes,<sup>111</sup>

(105) Billingsley, K.; Barder, T. E.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 5359–5363.

(106) Ishiyama, T.; Ishida, K.; Miyaura, N. *Tetrahedron* **2001**, *49*, 9813–9816.

(107) (a) Tse, M. K.; Cho, J.-Y.; Smith, M. R. *Org. Lett.* **2001**, *3*, 2831–2833. (b) Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N. *J. Am. Chem. Soc.* **2002**, *124*, 390–391. (c) Ishiyama, T.; Nobuta, Y.; Hartwig, J. F.; Miyaura, N. *Chem. Commun.* **2003**, 2924–2924. (d) Boller, T. M.; Murphy, J. M.; Hapke, M.; Ishiyama, T.; Miyaura, N.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 14263–14278. (e) Takagi, J.; Sato, K.; Hartwig, J. F.; Ishiyama, T.; Miyaura, N. *Tetrahedron Lett.* **2002**, *43*, 5649–5651.

(108) (a) Rablen, P. R.; Hartwig, J. F.; Nolan, S. P. *J. Am. Chem. Soc.* **1994**, *116*, 4121–4122. (b) Rablen, P.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 4648–4653.

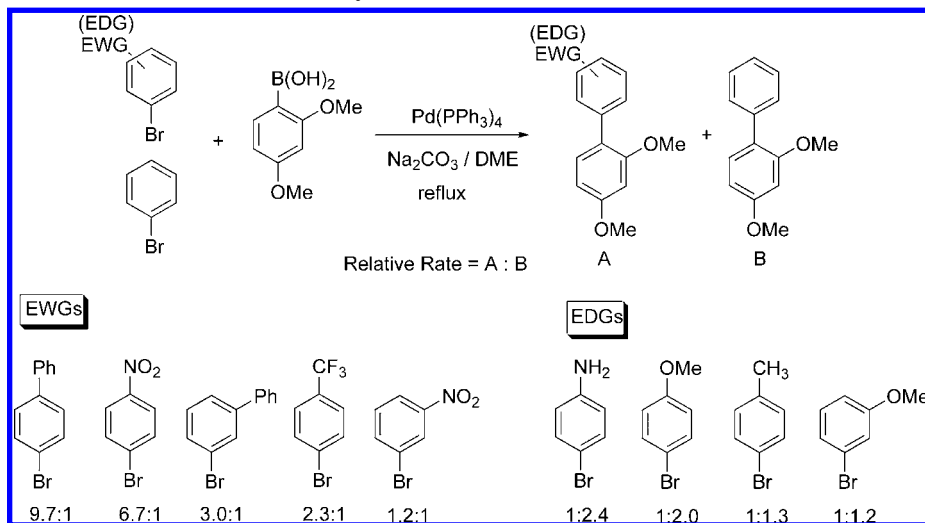
(109) Boebel, T. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 7534–7535.

(110) Tivola, P. B.; Deagostino, A.; Prandi, C.; Venturello, P. *Org. Lett.* **2002**, *4*, 1275–1277.

(111) (a) Yamamoto, Y.; Fujikawa, R.; Umemoto, T.; Miyaura, N. *Tetrahedron* **2004**, *60*, 10695–10700. (b) Rubina, M.; Rubina, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2003**, *125*, 7198–7199. (c) Varala, R.; Nuvula, S.; Adapa, S. R. *J. Org. Chem.* **2006**, *71*, 8283–8286. (112) (a) Fang, G.-H.; Yan, Z.-J.; Deng, M.-Z. *Synthesis* **2006**, 1148–1154. (b) Shirakawa, K.; Arase, A.; Hoshi, M. *Synthesis* **2004**, 1814–1820. (c) PraveenGanesh, N.; d'Hondt, S.; Chavant, P. Y. *J. Org. Chem.* **2007**, *72*, 4510–4514. (d) Sugimoto, M.; Shirakura, M.; Yamamoto, A. *J. Am. Chem. Soc.* **2006**, *128*, 14438–14439.

(113) Ito, H.; Kawakami, C.; Sawamura, M. *J. Am. Chem. Soc.* **2005**, *127*, 16034–16035.

**Scheme 17. EWG/EDG substituent effects on the aryl bromide**



alkenyls,<sup>112</sup> allylic carbonates,<sup>113</sup> allyls,<sup>114</sup> and allenyls<sup>115</sup> have been described.

In large-scale productions the availability of the boronic acid may be an issue. If not available at reasonable cost, it is usually made from the Grignard reagent via reaction with  $\text{B}(\text{OMe})_3$  followed by hydrolysis. If possible, the crude boronic acid solution in THF is then used as such in the next coupling step as solvent switches are quite cumbersome in production. An example of large-scale use of the Suzuki reaction is for the production of *o*-tolyl-benzonitrile, an intermediate for the Sartans<sup>91</sup> and Boscalid agrochemicals from BASF.<sup>116</sup>

Substituent effects on the (hetero)aryls have great impact on the reactivity of the Suzuki reaction. In general, electron-withdrawing groups (EWG) such as phenyl, nitro, and trifluoromethyl enhance the oxidative addition in comparison with electron-donating groups (EDG) such as amine, methoxy, and methyl (Scheme 17).<sup>117</sup> The choice of base also plays an important part in the Suzuki reaction, although it is still empirical, and no general rule for selection has been established. The role of base is to facilitate the otherwise slow transmetalation of the boronic acid. In general, inorganic bases work better, and the reactivity is in the order  $\text{Cs}_2\text{CO}_3 > \text{CsF} > \text{K}_2\text{CO}_3 > \text{KOAc} > \text{Na}_2\text{CO}_3 > \text{Et}_3\text{N}$ .<sup>118</sup> In the case of sterically hindered boronic acids or esters, a mild base should be used to avoid elimination of the boronic acid/ester group. The use of milder bases such as  $\text{Na}_2\text{CO}_3$  or  $\text{K}_3\text{PO}_4$  is also advisable if unprotected

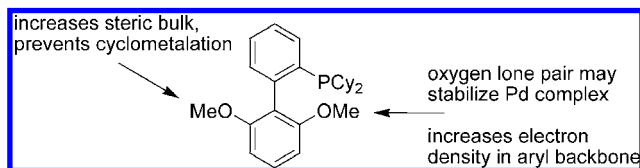
phenols or acids are present.<sup>119</sup> For performance of a Suzuki coupling at scale, cesium bases may be less attractive owing to their cost.

Suzuki cross-coupling of heteroaryl halides using S-Phos was shown to be very effective.<sup>120</sup> Pyrazoles, indoles, pyridines, tetrazoles, and quinolines could be coupled to aryl halides in high yield and low catalyst loading. The structural features of these types of dialkylbiarylphosphines contribute to the efficiency of the catalytic system (Figure 5). The bulky and electron-donating character is important for the stabilization of the monoligated Pd-species and ensures a fast oxidative addition. The molecular framework of these systems can be easily varied in order to fine-tune the ligand properties.<sup>121</sup> It was shown that the catalysts based on S-Phos were not inhibited in the presence of aminopyridines and aminopyrimidines,<sup>122</sup> as found with earlier ligand systems.<sup>123</sup> Various heterocycles including pyrroles, thiophenes, pyrazines, pyridines, quinoxalines, indoles, and quinolines have been successfully employed using these systems.<sup>121</sup>

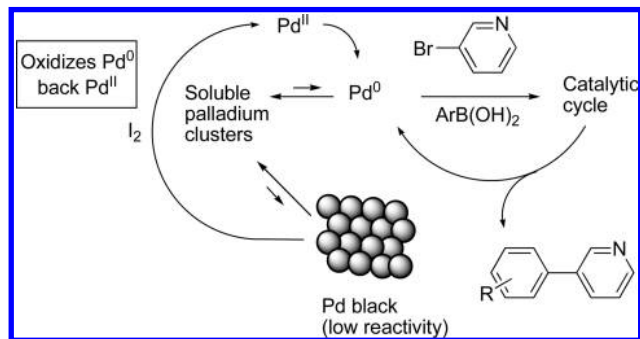
A versatile method for Suzuki cross-coupling reactions of nitrogen heteroaromatics was reported by Fu.<sup>124</sup> An array of nitrogen-containing boronic acids and (hetero)aryl halides was coupled using  $\text{Pd}/\text{PCy}_3/\text{K}_3\text{PO}_4/\text{dioxane}/\text{H}_2\text{O}$ -based method. The wide ranging study provided a protocol effective for cross-couplings of not only boronic acids, but also heteroaryl boronic esters and trifluoroborates. The attractive feature of this method is the single procedure that can be employed, which is very

- (114) Sebelius, S.; Olsson, V. J.; Wallner, O. A.; Szabó, K. J. *J. Am. Chem. Soc.* **2006**, *128*, 8150–8151.
- (115) (a) Yang, F.-Y.; Shanmugasundaram, M.; Chuang, S.-Y.; Ku, P.-J.; Wu, M.-Y.; Cheng, C.-H. *J. Am. Chem. Soc.* **2003**, *125*, 12576–12583. (b) Burks, H. E.; Liu, S.; Morken, J. P. *J. Am. Chem. Soc.* **2007**, *129*, 8766–8773. (c) Pelz, N. F.; Woodward, A. R.; Burks, H. E.; Sieber, J. D.; Morken, J. P. *J. Am. Chem. Soc.* **2004**, *126*, 16328–16329.
- (116) Rouhi, A. M. *Chem. Eng. News* **2004**, *82* (36), 49–58.
- (117) Campbell, M. G. Ph.D. Thesis, University of Waterloo, Canada, 1996.
- (118) (a) Zhang, C.; Huang, J.; Trudell, M. L.; Nolan, S. P. *J. Org. Chem.* **1999**, *64*, 3804–380. (b) Bei, X.; Crevier, T.; Guram, A. S.; Jandeleit, B.; Powers, T. S.; Turner, H. W.; Uno, T.; Weinberg, W. H. *Tetrahedron Lett.* **1999**, 3855–3858.

- (119) (a) Sakurai, H.; Tsukuda, T.; Hirao, T. *J. Org. Chem.* **2002**, *67*, 2721–2722. (b) Houpiis, I. N.; Shields, D.; Nettekoven, U.; Schnyder, A.; Bappert, E.; Weerts, K.; Canters, M.; Vermeulen, W. *Org. Process Res. Dev.* **2009**, *13*, 598–606.
- (120) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871–1876.
- (121) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461–1473.
- (122) Billingley, K.; Anderson, K. W.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 3484–3488.
- (123) Itoh, T.; Mate, T. *Tetrahedron Lett.* **2005**, *46*, 3573–3577.
- (124) Kudo, N.; Perseghini, M.; Fu, G. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 1282–1284.
- (125) Guram, A. S.; King, A. O.; Allen, J. G.; Wang, X.; Schenkel, L. B.; Chan, J.; Bunel, E. E.; Faul, M. M.; Larsen, R. D.; Martinelli, M. J.; Reider, P. *J. Org. Lett.* **2006**, *8*, 1787–1789.



**Figure 5.** Structural features of dialkylbiarylphosphines.



**Figure 6.** Representation of the use of homeopathic palladium in the Suzuki reaction.

useful in library synthesis. Other effective catalysts for the Suzuki reaction of heteroaryl chlorides have also been reported.<sup>125</sup>

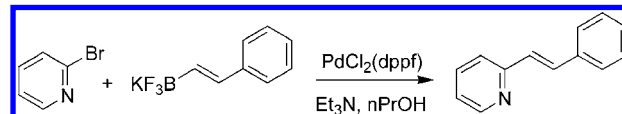
An intriguing example of ligand free Suzuki reactions is the use of homeopathic amounts of palladium. It was shown that the use of 0.01–0.05% of palladium acetate works very well with aryl iodides and bromides, and with some activated aryl chlorides (Figure 6). The turnover frequencies are up to 30,000 and the product can be isolated in high yield. The palladium precipitates as palladium black at the end of the reaction. The precipitated catalyst may be recycled by reoxidation with I<sub>2</sub>.<sup>126</sup> Both the reactivation protocol with iodine, and the homeopathic loading protocol are cost-effective. The elegance of this approach is that the undesirable formation of inactive palladium black is overcome simply by using less palladium, which means that lower palladium concentrations give rise to the reaction. The reaction rates of these ligand-free methods are in the same order as for the well-known Herrmann-Beller catalyst and it is anticipated that the same active ligand-free palladium species is involved. In production these ligand-free methods are preferred, thanks to easier workup. An alternative to this strategy is the use of homeopathic palladium in the presence of DABCO.<sup>127</sup> Very high turnover numbers (up to 950,000) are obtained in coupling aryl iodides with boronic acids (0.0001% palladium acetate). Earlier claims of Suzuki reactions using microwave conditions giving high yields without the use of palladium were withdrawn, since closer analysis showed that the reaction is catalyzed very efficiently by ppb amounts of palladium present as an impurity in the Na<sub>2</sub>CO<sub>3</sub>.<sup>128</sup> Pd/C and Pearlman's catalyst (Pd(OH)<sub>2</sub>) have also been used with

(126) (a) de Vries, A. H. M.; Parlevliet, F. J.; Schmieder-van de Vondervoort, L.; Mommers, J. H. M.; Henderickx, H. J. W.; Walet, M. A. M.; de Vries, J. G. *Adv. Synth. Catal.* **2002**, *9*, 996–1002. (b) Parlevliet, F. J.; de Vries, A. H. M.; de Vries, J. G. Process for Regenerating Palladium Catalysts. (DSM n.v.). WO/2002/00340 A1, 2002.

(127) Li, J.-H.; Liu, W.-J. *Org. Lett.* **2004**, *6*, 2809–2811.

(128) (a) Leadbeater, N. E.; Marco, M. *Angew. Chem., Int. Ed.* **2003**, *12*, 1407–1409. (b) Arvela, R. K.; Leadbeater, N. E.; Sangi, M. S.; Williams, V. A.; Granados, P.; Singer, R. D. *J. Org. Chem.* **2005**, *1*, 161–168.

### Scheme 18. Suzuki cross-coupling using fluoroborate salts



success—the active palladium catalyst is of homogeneous nature.<sup>33,119,129</sup>

Beside boronic acids and esters the use of fluoroborate salts as cross-coupling reagents has become more general in recent years (Scheme 18).<sup>130,131</sup> Compared to boronic acids (esters), these fluoroborate salts are more robust, easier to purify, often easier to handle, and in general more reactive under standard conditions. The advantage of trifluoroborates is that the reactions can be carried out in air with no attenuation in the yields. These systems also tolerate many reactive functional groups: NO<sub>2</sub>, CN, OR, NR<sub>2</sub>, CO, COOR, COH, and even OH and COOH. Note that the higher electron-withdrawing strength of the trifluoroborate group and the preformed “ate”-complex can lead to facile protodeboration.<sup>132</sup> The fluoroborate salts can be prepared from their boronic acid or ester analogues simply by displacement with KHF<sub>2</sub>.<sup>133</sup> A more recent synthetic method for the preparation of potassium organotrifluoroborates proceeds through nucleophilic substitution of potassium bromo- and iodomethyltrifluoroborates. Potassium halomethyltrifluoroborates have been prepared via in situ reaction of *n*-BuLi with dibromo- and diiodomethane, respectively, in the presence of trialkyl borates, followed by treatment with KHF<sub>2</sub>.<sup>134</sup>

Deboronation followed by protonation is a frequently occurring side reaction in Suzuki reactions with boronic acids. The reaction is both acid and base catalyzed; it may also be catalyzed by metals. For small-scale reactions this is easily countered by using an excess of the boronic acid. In large-scale production this can be an important issue, and careful tuning of the reaction conditions may be necessary to suppress this side reaction.

## 6. Stille Reactions

The palladium-catalyzed Stille cross-coupling of aryl and vinyl halides/triflates with organostannanes is a powerful and widely used method for the formation of carbon–carbon bonds.<sup>8,135</sup> The Stille reaction has proven to be an especially popular tool in complex natural product synthesis, in part as a result of the air- and moisture-stability of organotin reagents and the excellent functional group compatibility of the process. Thus the Stille cross-coupling has played a pivotal role in a

(129) Keen, S. P.; Cowden, C. J.; Bishop, B. C.; Brands, K. M. J.; Davies, A. J.; Dolling, U. H.; Lieberman, D. R.; Stewart, G. W. *J. Org. Chem.* **2005**, *70*, 1771–1779.

(130) (a) Molander, G. A. *Org. Lett.* **2002**, *107*. (b) Molander, G. A.; Bernardi, C. R. *J. Org. Chem.* **2002**, *67*, 8424–8429.

(131) A review of recent advances in organotrifluoroborates including the Suzuki reaction, see: Stefani, H. A.; Cella, R.; Vieira, A. S. *Tetrahedron* **2007**, *63*, 3623–3658.

(132) Molander, G. A.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 4302.

(133) (a) Molander, G. A.; Katona, B. W.; Machrouhi, F. *J. Org. Chem.* **2002**, *67*, 8416–8423. (b) Murphy, J. M.; Tzschucke, C. C.; Hartwig, J. F. *Org. Lett.* **2007**, *9*, 757–760. (c) Kabalka, G. W.; Venkataiah, B.; Dong, G. *J. Org. Chem.* **2004**, *69*, 5807–5809.

(134) Molander, G. A.; Ham, J. *Org. Lett.* **2006**, *8*, 2031–2034.

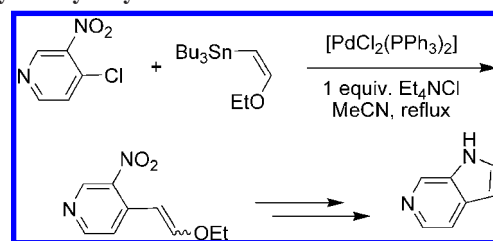
(135) For general reviews of the Stille reactions, see: (a) Mitchell, T. N. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998. (b) Farina, G.; Krishnamurthy, V.; Scott, W. *J. Org. Reactions* **1997**, *50*, 1–652. (c) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508–524.

number of total syntheses, such as those of rapamycin<sup>136</sup> and dynemicin.<sup>137</sup> The Stille reaction is robust and versatile for C–C bond-forming reaction between stannanes and halides or pseudohalides with well-elaborated methods that allow the preparation of different products. The main drawbacks are the toxicity of the tin compounds and their low polarity, which makes them poorly soluble in water. As a result, the reaction products are usually purified by column chromatography to remove the lipophilic tin residue. Both issues preclude the use of the Stille reaction on large scale. Although stannanes are stable, boronic acids and their derivatives undergo much the same chemistry. The current improvements in the Suzuki coupling may soon lead to the same versatility without the drawbacks of using tin compounds.

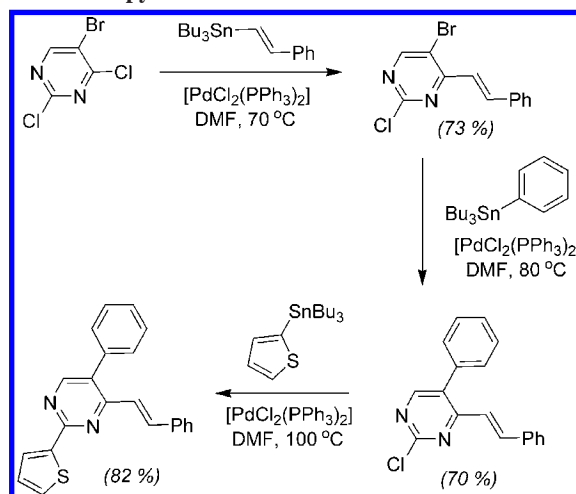
Stille cross-couplings of heteroaryl halides, mainly nitrogen-containing heterocycles, have a rich history. Analogous to Suzuki reactions for this class of substrates, many of these processes have employed traditional palladium/triarylphosphine base catalysts. The traditional four-step mechanism originally proposed by Stille follows the pathway of reaction of a soft nucleophile with a *trans*-palladium complex where the transmetalation is in most cases the rate-determining step.<sup>138</sup>

Many halopyridines participate in Stille couplings.<sup>139</sup> In one of the early examples, Sakamoto demonstrated that 2- and 4-chloro-3-nitropyridines react with a tributylstannylethylene in good yield (Scheme 19). In addition, the products formed can be converted into useful building blocks, namely pyrrolopyridines.<sup>140</sup> Stille cross-couplings of various halogen-substituted pyridazines,<sup>141</sup> pyrimidines,<sup>142</sup> pyrazines,<sup>143</sup> thiadiazoles,<sup>144</sup> and triazines<sup>145</sup> have also been reported. For halopyrimidines, the 4-position is the most activated, followed by the 2-position, and then the 5-position. Therefore, selective coupling can be achieved on the 4-position of 2,4- and 4,5-dichloropyrimidines as well as the 2-position of 2,5-dichloropyrimidines.<sup>146</sup> Interestingly, a 4-chloro group can react more readily than a 5-bromo group, thus allowing the stepwise functionalization of 2,4-dichloro-5-bromopyrimidines (Scheme 20).

### Scheme 19. Stille coupling of halopyridine and tributylstannylethylene



### Scheme 20. Reiterative Stille coupling to form a trisubstituted pyrimidine

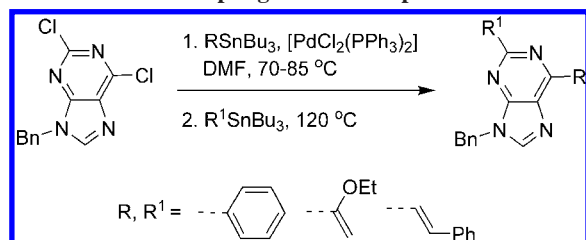


More complex heterocycles, such as quinolines,<sup>147</sup> isoquinolines,<sup>148</sup> quinolones,<sup>149</sup> 1,8-naphthyridines,<sup>150</sup> quinalzoles,<sup>65,151</sup> quinoxalines,<sup>152</sup> benzothiazoles,<sup>153</sup> purines,<sup>66b,154</sup> diazaoxindoles,<sup>155</sup> phenanthrolines,<sup>156</sup> and naphthyridines<sup>157</sup> also undergo

- (136) Nicolaou, K. C.; Chakraborty, T. K.; Piscopio, A. D.; Minowa, N.; Bertinato, P. *Angew. Chem., Int. Ed. Engl.* **1993**, *115*, 4419–4420.  
 (137) Shair, M. D.; Yoon, T. Y.; Mosny, K. K.; Chou, T. C.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1996**, *118*, 9509–9525.  
 (138) (a) Jutand, A. *J. Am. Chem. Soc.* **2003**, *125*, 4212–4222. (b) Casado, A. L.; Espinet, P. *Organometallics* **2003**, *1305*–1309. (c) Espinet, P.; Echvarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4704–4734.  
 (139) (a) Zhang, B.; Breslow, R. *J. Am. Chem. Soc.* **1997**, *109*, 1676–1681. (b) Baxter, P. N. W. *J. Org. Chem.* **2000**, *65*, 1257–1272. (c) Baxter, P. N. W. *J. Org. Chem.* **2001**, *66*, 4170–4179. (d) Crous, R.; Dwyer, C.; Holzapfel, W. W. *Heterocycles* **1999**, *51*, 721–726.  
 (140) Sakamoto, T.; Satoh, C.; Kondo, Y.; Yamanaka, H. *Heterocycles* **1992**, *34*, 2379–2384.  
 (141) Maes, B. U. W.; Lemiere, G. L. F.; Dommissie, R.; Augusyns, K.; Haemers, A. *Tetrahedron* **2000**, *56*, 1777–1781.  
 (142) (a) Sakamoto, T.; Satoh, C.; Kondo, Y.; Yamanaka, H. *Chem. Pharm. Bull.* **1993**, *41*, 81–86. (b) Sandosham, J.; Undheim, K.; Rise, F. *Heterocycles* **1993**, *35*, 235–244. (c) Schubert, U. S.; Eschbaumer, C. *Org. Lett.* **1999**, *1*, 1027–1029.  
 (143) (a) Cuperly, D.; Gros, P.; Fort, Y. *J. Org. Chem.* **2002**, *67*, 238–241. (b) Sato, N.; Narita, N. *Synthesis* **2001**, 1551–1555.  
 (144) Hanasaki, Y. *Heterocycles* **1996**, *43*, 2435–2441.  
 (145) (a) Pchalek, K.; Hay, M. P. *J. Org. Chem.* **2006**, *71*, 6530–6535. (b) Faust, R.; Gobelt, B. *Tetrahedron Lett.* **1997**, *38*, 8017–8020.  
 (146) (a) Solberg, J.; Undheim, K. *Acta Chem. Scand.* **1989**, *43*, 62–68. (b) Benneche, T. *Acta Chem. Scand.* **1990**, *44*, 927–931. (c) Kondo, Y.; Watanabe, R.; Sakamoto, T.; Yamanaka, H. *Chem. Pharm. Bull.* **1989**, *37*, 2814–2816. (d) Majeed, A. J.; Antonsen, O.; Benneche, T.; Undheim, K. *Tetrahedron* **1989**, *45*, 993–1006.

- (147) (a) Dondoni, A.; Fantin, F.; Fofanolo, M.; Medici, A.; Pedrini, P. *Synthesis* **1987**, 693–696. (b) Godard, A.; Fourgez, J. M.; Tamion, R.; Marsais, Queguiner, G. *Synlett* **1994**, 235–23. (c) Hume, W. E.; Nagata, R. *Synlett* **1997**, 473–474. (d) Wolf, C.; Lerebours, R. *J. Org. Chem.* **2003**, *68*, 7077–7084.  
 (148) (a) Ford, A.; Sinn, E.; Woodward, S. *J. Chem. Soc., Perkin Trans. I* **1997**, 927–934. (b) Legros, J.-Y.; Primault, G.; Fiaud, J.-C. *Tetrahedron* **2001**, *57*, 2507–2514.  
 (149) Wentland, M. P.; Perni, R. B.; Dorff, P. H.; Brundage, R. P.; Castaldi, M. J.; Bailey, T. R.; Carabateas, P. M.; Bacon, E. R.; Young, D. C.; Woods, M. G.; Rosi, D.; Drozd, M. L.; Kullnig, R. K.; Dutko, F. J. *J. Med. Chem.* **1993**, *36*, 1580–1596.  
 (150) Laborde, E.; Lesheski, L. E.; Kiely, J. S. *Tetrahedron Lett.* **1990**, *31*, 1837–1840.  
 (151) Laborde, E.; Kiely, J. S.; Schroeder, M. C. *J. Heterocycl. Chem.* **1991**, *28*, 191–198.  
 (152) Kim, K. S.; Qian, L.; Dickinson, K. E. J.; Delaney, C. L.; Bird, J. E.; Waldron, T. L.; Moreland, S. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2667–2670.  
 (153) Kosugu, M.; Koshiba, M.; Atoh, A.; ano, H.; Migita, T. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 677–679.  
 (154) (a) Gundersen, L.-L. *Tetrahedron Lett.* **1994**, *35*, 3155–3158. (b) Gundersen, L.-L.; Bakkestuen, A. K.; Aasen, A. J.; Overas, H.; Rise, F. *Tetrahedron* **1994**, *50*, 9743–9756. (c) Hocek, M.; Masojidkova, M.; Holy, A. *Tetrahedron* **1997**, *53*, 2291–2302. (d) Brathe, A.; Gundersen, L.-L.; Rise, F.; Eriksen, A. B.; Vollsnæs, A. V.; Wang, L. *Tetrahedron* **1999**, *55*, 211–228. (e) Bakkestuen, A. K.; Gundersen, L.-L.; Langli, G.; Liu, F.; Nolsøe, J. M. *J. Bioorg. Med. Chem. Lett.* **2000**, *10*, 1207–1210.  
 (155) Cheung, M.; Harris, P. A.; Lackey, K. E. *Tetrahedron Lett.* **2001**, *42*, 999–1001.  
 (156) Bates, G. B.; Parker, D. *Tetrahedron Lett.* **1996**, *37*, 267–270.  
 (157) (a) Guillier, F.; Nivolières, F.; Cochennecc, C.; Godard, A.; Marsais, F.; Queguiner, G. *Synth. Commun.* **1996**, *26*, 4421–4436. (b) Guillier, F.; Nivolières, F.; Godard, A.; Marsais, F. *J. Heterocycl. Chem.* **1999**, *36*, 1157–1165.

### Scheme 21. Stille coupling for dichloropurine



Stille cross-coupling. For example, good selectivity for coupling of 6,8-chlorosubstituted purines is observed at the more activated 6-position with several stannanes. Only small amounts of disubstituted purines are formed (Scheme 21).<sup>158</sup>

An intriguing example of a complex Stille reaction that highlights its versatility has been reported by Hoveyda.<sup>159</sup> Here, the total synthesis of chloropectin I, an anti-HIV agent, was first achieved stereoselectively through the intermediate II through the use of Pd-mediated cross-coupling, which was a significant breakthrough (Scheme 22).

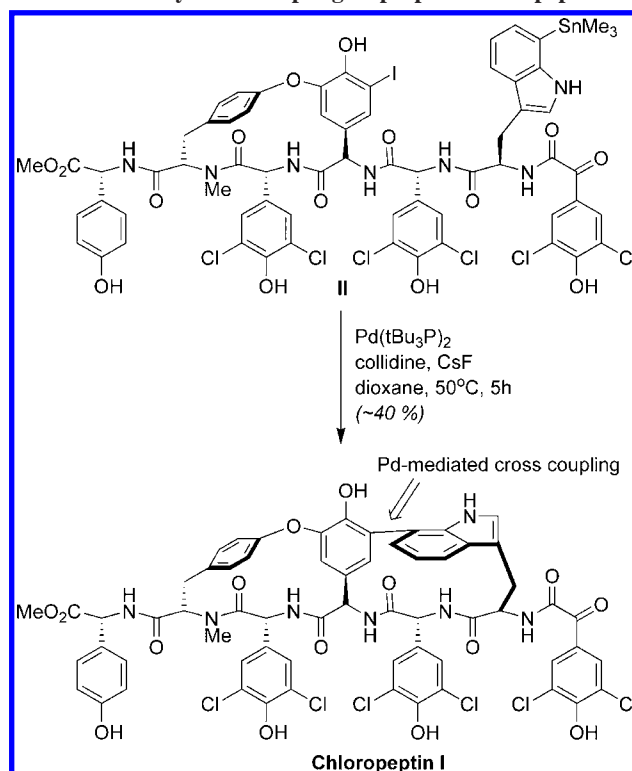
Additives can significantly improve the reaction rate of the Stille reaction. The addition of copper to the reaction medium can accelerate the reaction up to 100-fold. In this copper effect the CuI is a scavenger for free neutral ligand in ethereal solvents (THF, dioxane), which otherwise cause autoretardation of the rate-determining transmetalation step.<sup>160</sup> In highly polar solvents such as NMP and DMF the mechanism proceeds in a different manner; here a more reactive organocopper intermediate is generated, the presence of which determines the reaction rate.<sup>161</sup> The addition of fluoride based salts such as CsF also increases the rate of the Stille coupling (Figure 7), and moreover, the formed tin salts such as Bu<sub>3</sub>SnI (Cl or Br) are transformed into insoluble Bu<sub>3</sub>SnF (polymeric), which can be filtered off easily (Table 5). This allows avoidance of the often tedious workup. In general, CsF and TBAF are good fluoride sources, whereas LiF, NaF, and KF are less effective.

## 7. Hiyama Coupling

Cross-coupling reactions of organosilicon compounds<sup>162</sup> have emerged as viable alternatives to the Suzuki and Stille couplings. Organosilanes have achieved broader utility through the introduction of heteroatoms on the silicon moiety.<sup>163</sup> In particular, chloro- and fluorosilanes are more potent cross-coupling partners. On the other hand these groups are hydrolytically more sensitive and thus harder to handle. Accordingly, heteroatom surrogates such as siletanes, 2-pyridyl-, 2-thienyl-, and benzylsilanes<sup>164</sup> have been introduced that have a greater stability and can be converted to more reactive heterofunctional silanes in the presence of fluoride sources such as tetrabutylammonium fluoride (TBAF).<sup>165</sup>

- (158) Nolsoe, J. M. J.; Gundersen, L.-L.; Rise, F. *Acta Chem. Scand.* **1999**, *53*, 366–372.  
 (159) Deng, H.; Jung, J.; Liu, T.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 9032–9034.  
 (160) Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 5905–5911.  
 (161) Mee, S. P. H.; Lee, V.; Baldwin, J. E. *Angew. Chem., Int. Ed.* **2004**, *43*, 1132–1136.  
 (162) (a) Hiyama, T. In *Organosilicon Compounds in Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-ECH: Weinheim, Germany, 1998; Chapter 10. (b) Spivey, A. C.; Gripton, C. J. G.; Hannah, J. P. *Curr. Org. Synth.* **2004**, *1*, 211–226.

### Scheme 22. Key Stille coupling to prepare chloropectin I



Subsequent studies revealed that silanols and disiloxanes also undergo cross-coupling in comparable yields.<sup>166</sup> From these findings many useful reactions have been developed with good functional group compatibility and with simple removal of byproduct, using siletanes, silanols, silyl hydrides, cyclic silyl ethers, disiloxanes, and oligosiloxanes.<sup>167</sup> The major drawback of this protocol is the need for stoichiometric amounts of fluoride. To achieve the same applicability as that of the Suzuki and Stille reactions, the requirement of fluoride as a means of activation must be bypassed, especially for substrates that bear silyl-protecting groups amenable to large-scale production. Recently, much effort has been put in the development of the fluoride-free Hiyama coupling, and this has stimulated the development of milder and more diverse conditions and reagents for the organosilicon cross-coupling.<sup>168</sup> A Pd(OAc)<sub>2</sub>-catalyzed, mild, fluoride-free cross-coupling between aryl bromides and arylsiloxanes in good to high yields has been achieved in aqueous medium in the presence of poly(ethylene glycol) (PEG) and sodium hydroxide. The product was easily separated with

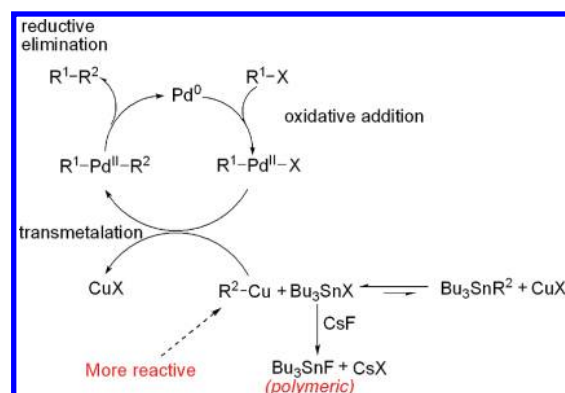



Figure 7. Salt effect in polar solvents in Stille reactions.

**Table 5.** Comparison of yields of Stille coupling using CuI and/or CsF<sup>a</sup>



reagent	yield [%]
[Pd(PPh <sub>3</sub> ) <sub>4</sub> ]	2
[Pd(PPh <sub>3</sub> ) <sub>4</sub> ], CsF	8
[Pd(PPh <sub>3</sub> ) <sub>4</sub> ], CuI	46
[Pd(PPh <sub>3</sub> ) <sub>4</sub> ], CsF, CuI	98
CuI, CsF	0

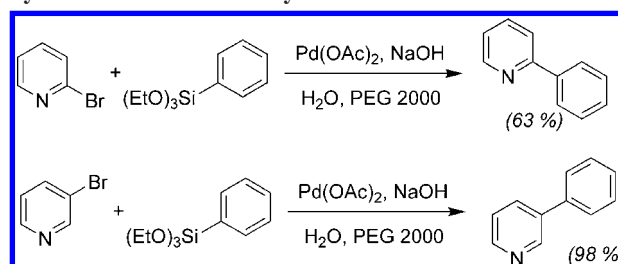
<sup>a</sup> Conditions: 10 mol %, [Pd(PPh<sub>3</sub>)<sub>4</sub>], 20 mol % CuI, 2.0 equiv CsF.

ethyl ether extraction, and the catalytic system can be reused eight times with high efficiency (Scheme 23).<sup>169</sup>

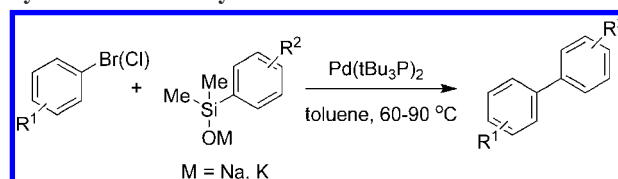
Denmark et. al published a broadly applicable protocol for the cross-coupling of alkali metal aryl- and heteroarylsilanolates with aromatic bromides and chlorides.<sup>170</sup> By means of catalysis with Pd(P<sup>t</sup>Bu<sub>3</sub>)<sub>2</sub>, a wide range of electron-rich, electron-poor, and sterically hindered aryl dimethylsilanolates underwent smooth coupling with a wide range of aryl halides (Scheme 24). The advantages of using the preformed silanolate salts include their ease of synthesis from inexpensive precursors, stability to storage, resistance to disiloxane formation, and self-activating properties. The broad substrate scope, functional group compatibility, and anhydrous conditions for cross-coupling bode well for the adoption of this method, particularly in cases where the use of traditional boron- or tin-based reagents is problematic.

Organosilanes are stable and easily prepared compounds with low toxicity. With the many improvements in the reaction conditions that have been reported, the Hiyama coupling has become an interesting alternative to the Suzuki coupling and offers a comparable scope of conversions. On the other hand, the broad commercial availability of boronic acids and boronates currently makes the Suzuki coupling the more convenient choice.

**Scheme 23.** Fluoride-free cross-coupling reactions of arylsiloxanes with heteroaryl bromides



**Scheme 24.** Fluoride-free cross-coupling reactions of arylsiloxanes with aryl bromides



## 9. Arylation of Heteroaromatic Compounds via C–H Activation

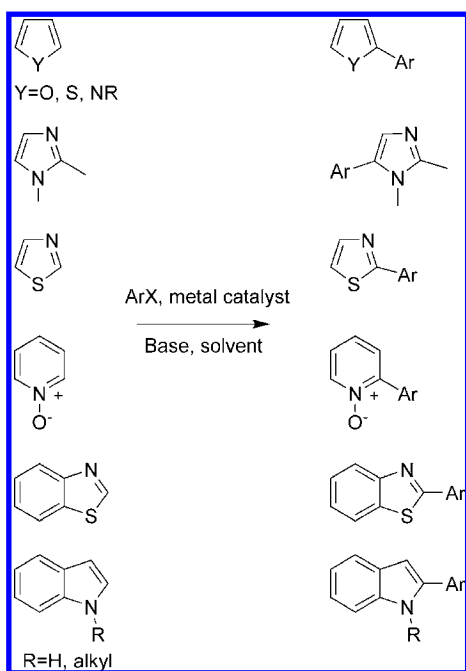
In recent years, cross-coupling reactions of aryl halides to unfunctionalized heteroaromatic compounds via C–H activation of the heteroaromatic has become a viable route.<sup>171</sup> Although not the focus of this review, we mention briefly the many possibilities that currently exist to achieve this type of coupling reaction, which may be considered one of the most environmentally benign options as only one equivalent of a halide salt is produced as side product. Two versions exist: In the first version the heterocycle functions as an ortho-directing group for the functionalisation of an aromatic ring, as in the ortho arylation of 2-phenyl-pyridine. In the second version the heterocyclic compound itself is arylated directly. This latter reaction has been shown to be possible on (benzo)furans, (benzo)thiophenes, pyrroles, (benz)oxazoles, (benz)isoxazoles, (benz)imidazoles, (benz)thiazoles, triazoles, indoles, indolizines, purines, pyrazines, quinolines, pyridine-*N*-oxides, and *N*-oxides of other heterocycles (see Scheme 25 for some selected examples). Most work has been performed using palladium catalysts and aryl iodides and aryl bromides as the arylating agents. More recently, other catalysts such as iridium,<sup>172</sup> rhodium,<sup>173</sup> ruthenium,<sup>174</sup> nickel,<sup>175</sup> and copper<sup>176</sup> have been used. Although most early versions require relatively large amounts of palladium catalysts, Doucet and co-workers recently

- (163) (a) Handy, C. J.; Mansoso, A. S.; McElroy, W. T.; Seganiash, W. M.; DeShong, P. *Tetrahedron* **2005**, *61*, 12201–12225. (b) Lee, H. M.; Nolan, S. P. *Org. Lett.* **2000**, *2*, 2053–2055. (c) Shibata, K.; Miyazawa, K.; Goto, Y. *Chem. Commun.* **1997**, 1309–1310. (d) Hirabayashi, K.; Kondo, T.; Toriyama, F.; Nishihara, Y.; Mori, A. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 749–750.
- (164) (a) Itami, K.; Nokami, T.; Yoshida, J. *J. Am. Chem. Soc.* **2001**, *123*, 5600–5601. (b) Hosoi, K.; Nozaki, T.; Hiyama, T. *Chem. Lett.* **2002**, 138–139. (c) Trost, B. M.; Machanek, M. R.; Ball, Z. T. *Org. Lett.* **2003**, *5*, 1895–1898.
- (165) (a) Denmark, S. E.; Choi, J. Y. *J. Am. Chem. Soc.* **1999**, *121*, 5821–5822. (b) Li, J.-H.; Deng, C.-L.; Liu, W.-J.; Xie, Y.-X. *Synthesis* **2005**, 3039–3044. (c) Denmark, S. E.; Tymonko, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 8004–8005. (d) Powell, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 7788–7789. (e) Lee, J.-Y.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 5616–5617.
- (166) Denmark, S. E.; Choi, J. Y. *Org. Lett.* **2000**, *2*, 2491–2494.
- (167) (a) Denmark, S. E.; Sweis, R. F. *Chem. Pharm. Bull.* **2000**, *50*, 1531–1541. (b) Denmark, S. E.; Sweis, R. F. *Acc. Chem. Res.* **2002**, *35*, 835–846. (c) Denmark, S. E.; Baird, J. D. *Chem. Eur. J.* **2006**, *12*, 4954–4963.
- (168) (a) Srirami, D.; Sawoo, S.; Sarkar, A. *Org. Lett.* **2007**, *9*, 3639–3642. (b) Murata, M.; Shimazaki, R.; Watanabe, S.; Masuda, Y. *Synthesis* **2001**, 2231–2233. (c) Gordillo, I.; de Jesús, E.; López-Mardomingo, C. *Org. Lett.* **2006**, *8*, 3517–3520. (d) So, C. M.; Lee, H. W.; Lau, C. P.; Kwong, F. Y. *Org. Lett.* **2009**, *11*, 317–320.
- (169) Shi, S.; Zhang, Y. *J. Org. Chem.* **2007**, *72*, 5927–5930.
- (170) Denmark, S. E.; Smith, R. L. C.; Chang, W.-T. T.; Muhuhi, J. M. *J. Am. Chem. Soc.* **2009**, *131*, 3104–3118.

- (171) For reviews see: (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174–238. (b) Campeau, L.-C.; Stuart, D. R.; Fagnou, K. *Aldrichimica Acta* **2007**, *40* (2), 35–41. (c) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173–1193. (d) Liégault, B.; Lapointe, D.; Caron, L.; Vlasosva, A.; Fagnou, K. *J. Org. Chem.* **2009**, *74*, 1826–1834.
- (172) Join, B.; Yamamoto, T.; Itami, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 3644–3647.
- (173) Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2008**, *41*, 1013–1025.
- (174) Ackermann, L.; Mulzer, M. *Org. Lett.* **2008**, *10*, 5043–5045.
- (175) Hachiya, H.; Hirano, K.; Sato, T.; Miura, M. *Org. Lett.* **2009**, *11*, 1737–1740.
- (176) (a) Zhao, D.; Wang, W.; Yang, F.; Lan, J.; Yang, L.; Gao, G.; You, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 3296–3300. (b) Yoshizumi, T.; Satoh, T.; Hirano, K.; Matsuo, D.; Orita, A.; Otera, J.; Miura, M. *Tetrahedron Lett.* **2009**, *50*, 3273–3276. (c) Do, H. Q.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 12404–12405.



**Scheme 25.** Selected examples of arylation of heteroaromatics via C–H activation



reported the use of “homeopathic palladium” for the arylation of thiophenes<sup>177</sup> and thiazoles.<sup>178</sup>

In rare cases, the direct cross-coupling of two nonfunctionalized arenes (double C–H activation) is possible under oxidative conditions. Fagnou et al. described the phenylation of *N*-acylated indole, catalysed by Pd(OTf)<sub>2</sub> in the presence of 3 equiv of Cu(OAc)<sub>2</sub>, 3-nitro-pyridine (10 mol %), and cesium pivalate (40 mol %).<sup>179</sup>

## 10. Scale-Up Issues

As mentioned in the introduction, additional issues are very important for large-scale production: (i) the cost of the production process, (ii) toxicity of the reagents and catalysts, and (iii) freedom to operate with ligands, catalysts, or specific transformations at scale.

(i) Cost of the production process. In general the cost of the starting materials increases going through the range ArCl < ArBr < ArI. Thus there is an incentive to use the chlorides where possible. Because aryl chlorides are less reactive, more active catalysts need to be used. These active catalysts are often based on palladium - most expensive metal for these C–C couplings - with relatively expensive electron-rich ligands. In addition, the amount of palladium used in most publications is often in the order of 1 mol %. This would have a serious cost impact on industrial scale, and this can be a very valid reason to turn to homeopathic palladium loadings for aryl bromides, or to nickel- or even iron-based catalysts. The cost of the nucleophile also varies enormously. Grignard reagents and alkylaluminum compounds tend to be inexpensive, whereas the boronic acids and ArZnX compounds usually are made from the Grignard reagents, and as a result are more expensive. Even the costs of

the base may be a consideration. Cesium carbonate is often mentioned as a base that performs well in many of these reactions. However, in general its use is prohibited by its high cost.

(ii) A second aspect is the toxicity of the reagents and the catalysts. Whereas use of tin reagents on small scale is perfectly acceptable, on production scale it is not and will not be considered. All toxic heavy metals will have to be removed from the final product. As a rule of thumb, the level of a toxic metal in a drug should be less than 10 ppm. In an earlier intermediate this level could be somewhat higher. Attainment of such low levels can be quite problematic. An obvious first choice is filtration over silica or aluminum oxide which is expected to work well with ligand-free palladium. Surprisingly, in many cases this reduces the level only a limited extent, particularly in cases where phosphine ligands have been used. Specialized resins containing amines, phosphines, or sulfur compounds are often necessary to remove the remaining traces of metal. It has been observed that this process is more efficient and takes less time at higher temperatures.<sup>180</sup> As the cost of these resins is relatively high, Livingstone and co-workers developed a method in which the palladium nanoparticles were first removed using ultrafiltration, followed by treatment of the filtrate with a resin. Thus, with 10 times less resin they achieved an 8.5 times better reduction of the palladium levels.<sup>181</sup> Extraction with 20% NaHSO<sub>3</sub> at 60 °C during 1 h has been shown to be capable of bringing down the palladium concentration from 8000 ppm to 36 ppm from a Suzuki product where Pd(OAc)<sub>2</sub>/dppf was used as the catalyst.<sup>182</sup> Especially for this review, it is interesting to note that basic heterocyclic Suzuki products have been freed from palladium by simple extraction of an acidic solution with organic solvents, most likely the method of choice from the cost point of view. This led to reduction of the Pd level from 8000 to <50 ppm.<sup>183</sup>

(iii) Last but not least, when considering the use of one of the coupling technologies on industrial scale, one has to be aware of the rather complicated “freedom to operate situation”.<sup>184</sup> Many ligands, catalysts, and specific applications of those catalysts are patent protected by companies or academia. Fortunately, several companies specializing in catalysts supply them at the market with the license fee included in the price/kg. In this case one immediately knows the cost for the specific transformation. If time-consuming negotiations are needed, for example with academia, about license fees based on amount of sold product, other possibly less active catalysts will be immediately considered for production.

(177) Roger, J.; Požgan, F.; Doucet, H. *Green Chem.* **2009**, *11*, 425–432.

(178) Roger, J.; Požgan, F.; Doucet, H. *J. Org. Chem.* **2009**, *74*, 1179–1186.

(179) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172–1175.

(180) Allgeier, A. M.; Bunel, E. M.; Correll, T.; Dilmeghani, M.; Faul, M.; Milne, J.; Murry, J.; Payack, J. F.; Scardino, C.; Shaw, B. J.; Wang, X. In *Catalysis of Organic Reactions*; Prunier, M. L., Ed.; Chemical Industries, 123; CRC Press: Boca Raton, FL, 2009; pp 51–59.

(181) Pink, C. J.; Wong, H.; Ferreira, F. C.; Livingstone, A. G. *Org. Process Res. Dev.* **2008**, *12*, 589–595.

(182) Bullock, K. M.; Mitchell, M. B.; F. Toczko, J. F. *Org. Process Res. Dev.* **2008**, *12*, 896–899.

(183) Chen, C.-Y.; Dagneau, P.; Grabowski, E. J. J.; Oballa, R.; O’Shea, P.; Prasit, P.; Robichaud, J.; Tillyer, R.; Wang, X. *J. Org. Chem.* **2003**, *68*, 2633–2638.

(184) For a discussion on this subject in relation with asymmetric catalysis, see: Hawkins, J. M.; Watson, T. J. N. *Angew. Chem., Int. Ed.* **2004**, *43*, 3224–3228.

## Conclusions

In summary, the selection of the optimal conditions for the C–C coupling reaction is crucial for its success, and the following points should be considered:<sup>37,42</sup> (1) Analysis of the substrates: (non)activated system towards oxidative addition (electron-donating and/or electron-withdrawing groups, steric bulk, leaving group, functional groups such as OMe, NO<sub>2</sub>, CO<sub>2</sub>R, CHO, NH, OH, use of protecting groups, sensitivity to β-H elimination). (2) Selection of reaction type including Kumada (Mg), Negishi (Zn), Suzuki (B), Stille (Sn), Hiyama (Si). (3) Catalyst: palladium (Pd(OAc)<sub>2</sub>, PdCl<sub>2</sub>(CH<sub>3</sub>CN)<sub>2</sub>, Pd(dba)<sub>2</sub>, Pd(PPh<sub>3</sub>)<sub>4</sub>), Ni, Fe. (4) Ligands: free, monodentate (PPh<sub>3</sub>, P<sup>t</sup>Bu<sub>3</sub>), bidentate (dppf, binap). (5) Base: strong/weak base, organic or inorganic base. (6) Solvent: solubility, solvent effects (stability, reactivity). (7) Additives (cocat.): salt-effects (LiCl, ZnCl<sub>2</sub>, CuI). (8) Reaction conditions: inert atmosphere, temperature. (9) Workup (purification of the product, catalyst recycling, waste disposal).

In conclusion, during the past decade very important advances have taken place in the development of highly active

catalysts to carry out cross-coupling reactions with (un)reactive and sterically hindered (hetero)aryl substrates. The bulky electron-rich ligands that have been developed have contributed greatly to the diversity and utility of cross-coupling chemistry. Various protocols have been developed that are of practical use to the organic chemist. The majority of functional groups can be tolerated, which certainly simplifies the construction of complex heterocyclic structures. The success of the described systems provides a good basis for a more rational approach to the design and development of new catalytic systems for cross-coupling reactions. Important structure–activity relationships have been established that open possibilities for even more active and general catalytic systems that are becoming an increasingly more powerful tool in synthetic heterocyclic chemistry.

Received for review August 20, 2009.

OP900221V