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Cross-Coupling Catalysts

The Development of Bulky Palladium NHC Complexes for the Most-Challenging Cross-Coupling Reactions

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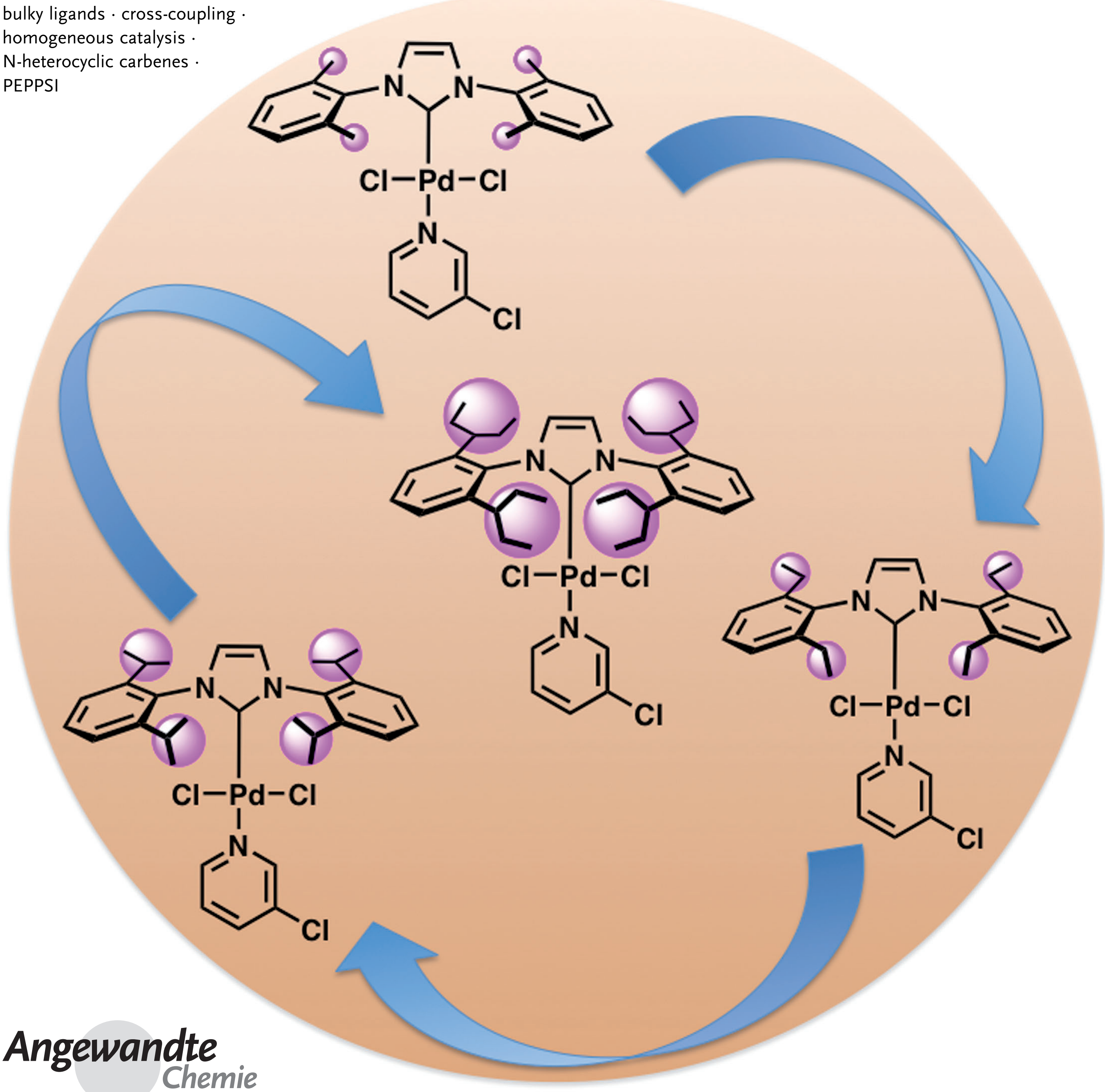
Keywords:
bulky ligands · cross-coupling · homogeneous catalysis · N-heterocyclic carbenes · PEPPSI



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Palladium-catalyzed cross-coupling reactions enable organic chemists to form C–C bonds in targeted positions and under mild conditions. Although phosphine ligands have been intensively researched, in the search for even better cross-coupling catalysts attention has recently turned to the use of N-heterocyclic carbene (NHC) ligands, which form a strong bond to the palladium center. PEPPSI (pyridine-enhanced precatalyst preparation, stabilization, and initiation) palladium precatalysts with bulky NHC ligands have established themselves as successful alternatives to palladium phosphine complexes. This Review shows the success of these species in Suzuki–Miyaura, Negishi, and Stille–Migita cross-couplings as well as in amination and sulfination reactions.

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1. Introduction

The 2010 Nobel Prize in Chemistry was awarded jointly to Richard F. Heck, Ei-ichi Negishi, and Akira Suzuki "for palladium-catalyzed cross-couplings in organic synthesis".[1] This chemical tool has improved the capabilities of the organic chemist to form C–C bonds with precision under mild reaction conditions,[2] and has benefited greatly of late with advancements in ligand design. Although phosphine-based ligands have been investigated most intensively so as to improve the catalytic proficiency in cross-coupling reactions, recently N-heterocyclic carbene (NHC) ligands have generated attention in light of many favorable attributes, including the relatively high thermal stability of the Pd–NHC bond.[3,4] The strong binding of the electron-rich carbene to the metal center helps the palladium retain its ligand, the consequence of which is longer catalyst lifetime and a consistent reactivity throughout the course of the transformation. A number of monoligated palladium NHC complexes have been prepared and demonstrated to have high levels of reactivity as reported notably by Caddick and Cloke,[5] Bellemin-Laponnaz and Gade,[6] Nolan,[7,8] Beller,[9] Herrmann,[10] and Organ[11] (Figure 1). The activities of complexes **1**–**14** have been correlated with the steric environment around Pd; in general, the bulkier the NHC (typically IPr had ideal structural and electronic properties for general use), the higher the catalytic activity.[12,13] Based on empirical data, Espinet and co-workers previously suggested that bulky ligands tend to promote a tri-coordinated palladium intermediate thereby lowering the overall activation energy in cross-coupling reactions.[14] In a recent computational study of the alkyl–alkyl Negishi reaction,[13,15] the Organ group demonstrated that an increase in steric bulk close to the metal center can play a role in promoting more than one step of the catalytic cycle, but that the largest effect is seen in transmetalation, which is viewed to be rate-limiting for at least that particular coupling.

Over the course of the last five years, Organ and co-workers developed a family of air-stable, user-friendly palladium NHC pre-catalysts and systematically varied the electronic and steric properties about the metal center to independently fine-tune the propensity for palladium to oxidatively insert and reductively eliminate with comparable efficiency.[16–18] The first-generation pre-catalysts (**12**–**14**) in the Pd-PEPPSI series (PEPPSI is an acronym for pyridine-enhanced precatalyst preparation, stabilization, and initiation) are prepared in air by heating their precursor azolium salts with $PdCl_2$ and K_2CO_3 in neat 3-chloropyridine to provide near quantitative yields of the corresponding Pd-PEPPSI complexes (Scheme 1).[11–13]

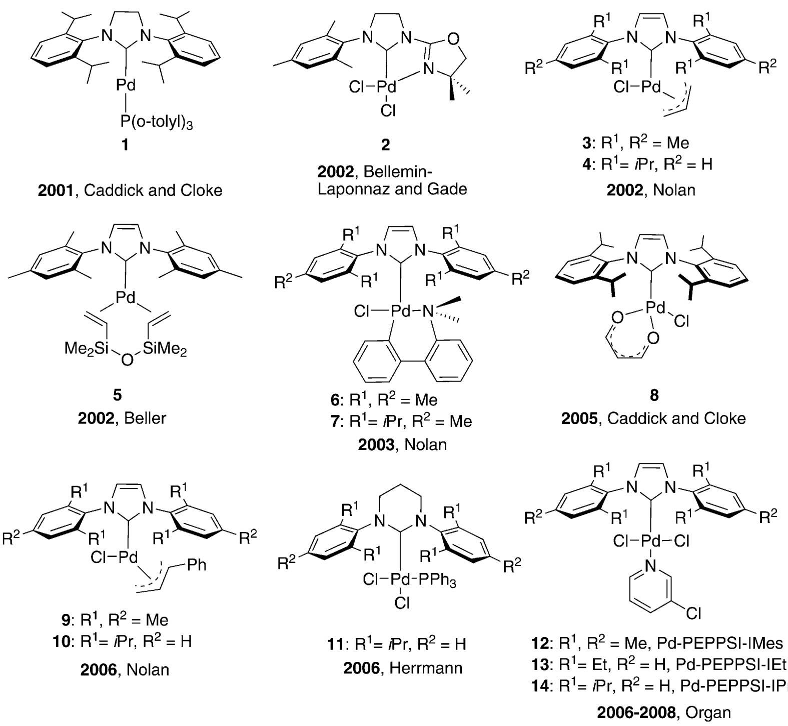

Figure 1. A selection of monoligated palladium NHC complexes used in palladium-catalyzed cross-coupling reactions.

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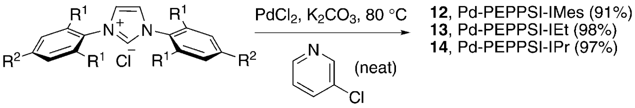
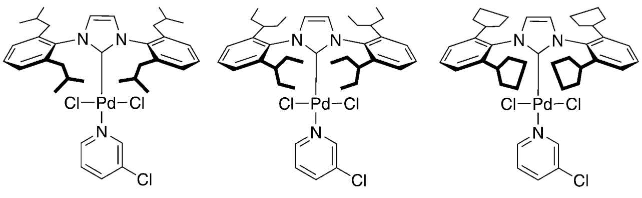


Scheme 1.

In particular, the effects that the carbene ligand has on catalyst performance in Negishi,[19] Suzuki–Miyaura,[11] and Kumada–Tamao–Corriu[20] cross-coupling reactions as well as Buchwald–Hartwig–Yagupol'skii[21] amination have been investigated.[22] Consistent with catalyst steric bulk being important, yields obtained using Pd-PEPPSI-IPr (**14**) were much greater than those obtained when using the less bulky Pd-PEPPSI-IEt (**13**) or Pd-PEPPSI-IMes (**12**) pre-catalysts. The role that steric effects play in the activity of Pd-PEPPSI-IPr (**14**) has been investigated using a variety of techniques, including computation[13,15,17] and NMR spectroscopy.[23] Since the σ-donor abilities of IMes, IEt, and IPr carbenes are similar,[15] steric factors are likely at work in the improved performance of **14**.

More recently, attention has been put on further increasing the steric bulk at the *ortho* positions of the N-phenyl moieties of the NHCs as this might continue the trend and lead to further increases in catalyst reactivity. On the basis of this hypothesis, second-generation Pd-PEPPSI complexes, namely Pd-PEPPSI-IBu (**15**), Pd-PEPPSI-IPent (**16**), and Pd-PEPPSI-cPent (**17**) were synthesized (Figure 2).[18]



Pd-PEPPSI-IBu (**15**) Pd-PEPPSI-IPent (**16**) Pd-PEPPSI-cPent (**17**)

Figure 2. Second-generation Pd-PEPPSI complexes with increased steric bulk on the NHC.

2. Applications of Pd-PEPPSI Catalysts in Cross-Coupling Reactions

It has been repeatedly shown that Pd-PEPPSI-IPr (**14**) is an efficient and versatile catalyst in cross-coupling reactions.[12,13,24,25] However, limitations remain in a handful of difficult but useful cross-coupling reactions. Based on literature reports and unpublished results, attention was focused on what are generally regarded to be some of the most challenging cross-coupling and amination reactions in order to evaluate and compare catalysts **14**–**17**. These include 1) Suzuki–Miyaura and 2) Negishi cross-couplings reactions to produce tetra-*ortho* substituted (hetero)biaryl compounds, 3) Negishi cross-coupling reactions of secondary alkylzinc halides with aryl halides, 4) Stille–Migita cross-couplings of heteroaryl stannanes with aryl halides, 5) Buchwald–Hartwig–Yagupol'skii aminations under mildly basic conditions,

Cory Valente obtained a HBSc in biological chemistry from York University in 2003 before pursuing a Ph.D. in organic chemistry with Professor Michael G. Organ at the same institution (NSERC scholarship). His PhD work on the total synthesis of neodolabellane-type diterpenoids and Pd-catalyzed cross-coupling reactions was awarded the 2009 Governor Generals Gold Medal. As a postdoc at Northwestern University with Sir Fraser Stoddart, he worked on the synthesis of new carbon allotropes, conformational control in polyrotaxanes, and on novel applications of metal–organic frameworks. He is currently a Senior Chemist in the Advanced Materials Division of The Dow Chemical Company.

Debasis Mallik has a BSc in Chemistry from Presidency College, Kolkata, India and an MSc from the Indian Institute of Technology, Kanpur, India. For his PhD he moved to York University in Toronto (Canada) under the supervision of Professor Michael G. Organ where he studied the silicon-mediated [2+2] photocyclization reaction and its use in total synthesis. In 2003 he joined Total Synthesis Ltd. in Toronto (Canada) where he led several industrial and academic projects including the development of the Pd-PEPPSI-IPent precatalyst. Currently, he is working with Professor Organ toward the automation of the microwave-assisted continuous-flow organic synthesis (MACOS) system for commercial applications.

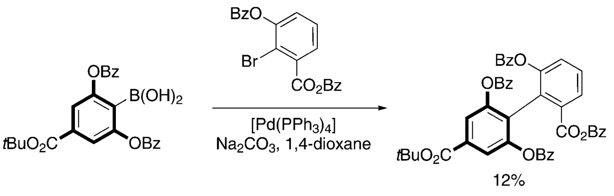
Selçuk Calimsiz studied chemistry at the Ankara University, Faculty of Sciences. In 2003, he completed his MSc in Professor George M. Bodner's Group at Purdue University, with a scholarship from the Republic of Turkey, Ministry of Education. He completed his PhD with Professor Mark A. Lipton at Purdue University on the total synthesis of Callipetins and Papuamides. In 2007, he joined Professor Michael G. Organ's group. His work focused on the development of Pd-PEPPSI-IPent precatalyst and its applications in various cross-coupling reactions. Currently, he is working as a Research Scientist at Gilead in Alberta, Canada.

Ka Hou Hoi was born in China in 1985. In 2007, he obtained a BSc in biological chemistry from York University in Toronto (Canada). He is currently pursuing a PhD in organic chemistry under the supervision of Professor Michael G. Organ at the same institution. His main research interests include transition-metal-catalyzed cross-coupling reactions, in particular the Pd NHC catalyzed C–N bond formation and elucidation of its mechanism.

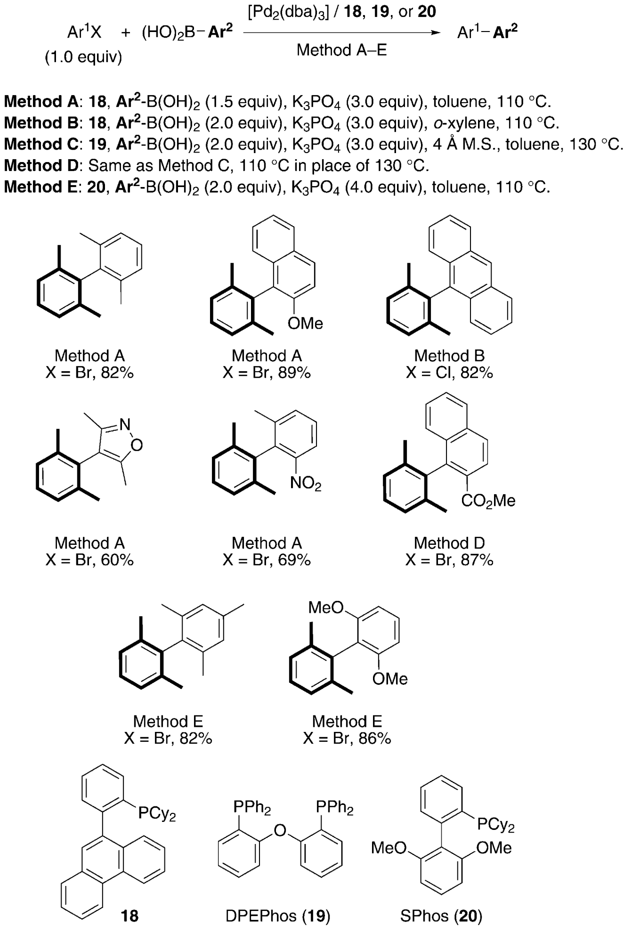
and 6) sulfination reactions of electronically and sterically deactivated aryl and heteroaryl halides and sulfides. In this Review, state-of-the-art palladium-catalyzed methods for these cross-coupling reactions will be summarized, and then head-to-head comparison experiments of Pd-PEPPSI complexes (and when relevant other ligand systems) will be presented along with a general survey of the most active catalyst in this series to date, Pd-PEPPSI-IPent (**16**).

2.1. *Suzuki–Miyaura Cross-Coupling Reactions for the Formation of Tetra-*ortho*-Substituted (Hetero)biaryl Compounds*

The cross-coupling of organoboron reagents with organic electrophiles is generally accepted as the most widely used coupling method in light of the commercial availability of a wide selection of air- and moisture-stable boronic acids, the limited toxicity of these reagents and their by-products, and the mild reaction conditions that can be employed which tolerate a variety of functional groups. One of the most challenging couplings remains the formation of tetra-*ortho*-substituted biaryl compounds, especially under mild reaction conditions. In 1997, Johnson and Foglesong reported the preparation of an unsymmetrical tetra-*ortho*-substituted biaryl in 12% overall yield using [Pd(PPh$_3$)$_4$] and Na$_2$CO$_3$ as the base (Scheme 2, no temperature was given).[26] More recently, Buchwald and co-workers reported Suzuki–Miyaura reactions for the synthesis of tetra-*ortho*-substituted biaryl compounds from aryl bromides using hindered biarylphosphine ligands **18**, **19**, and **20** in conjunction with [Pd$_2$(dba)$_3$] (dba = dibenzylideneacetone) at 110 °C (Scheme 3).[27] In 2004, a similar series of biaryl compounds were prepared by Glorius and co-workers in which they coupled substituted aryl chlorides and boronic acids using their bioxazoline-derived ligand IBiox12·HOTf (**21**) with Pd(OAc)$_2$ at 110 °C (Scheme 4).[28] In 2008, Hoshi, Hagiwara, and co-workers reported the use of ruthenocenylphosphine RPhos (**22**) with [Pd$_2$(dba)$_3$] to provide three tetra-*ortho*-substituted biaryl compounds from aryl chlorides and boronic acids at 100 °C (Scheme 5).[29] The requirement for high reaction temperatures places limitations on this methodology. Thus, the development of a catalyst that could perform such conversions at a relatively low reaction temperature would be a



Scheme 2. Bz = benzoyl.

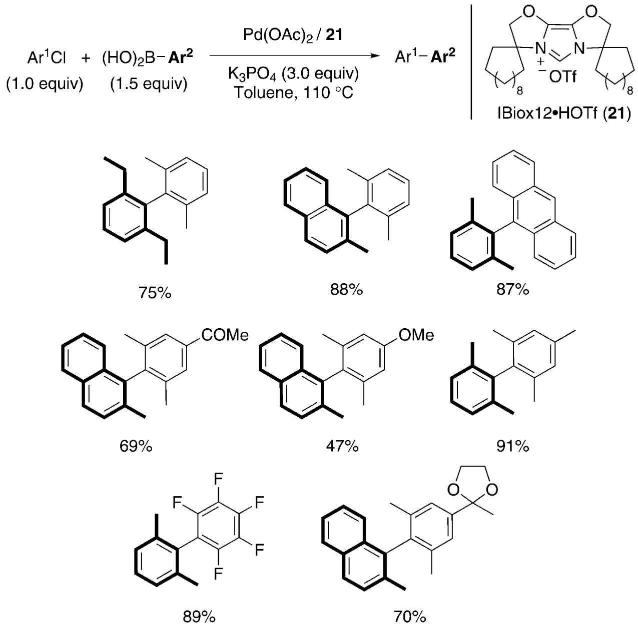


Method A: **18**, **Ar^2**-B(OH)$_2$ (1.5 equiv), K$_3$PO$_4$ (3.0 equiv), toluene, 110 °C.
Method B: **18**, **Ar^2**-B(OH)$_2$ (2.0 equiv), K$_3$PO$_4$ (3.0 equiv), *o*-xylene, 110 °C.
Method C: **19**, **Ar^2**-B(OH)$_2$ (2.0 equiv), K$_3$PO$_4$ (3.0 equiv), 4 Å M.S., toluene, 130 °C.
Method D: Same as Method C, 110 °C in place of 130 °C.
Method E: **20**, **Ar^2**-B(OH)$_2$ (2.0 equiv), K$_3$PO$_4$ (4.0 equiv), toluene, 110 °C.

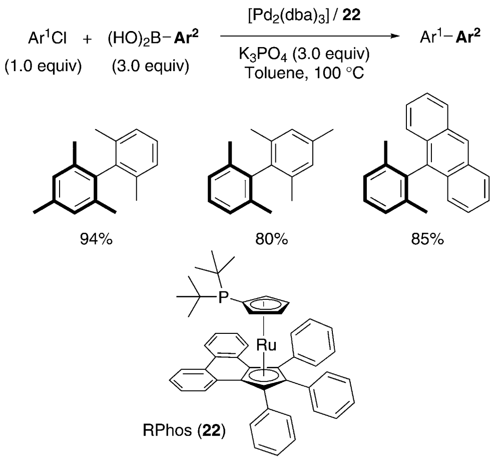
Scheme 3. Cy = cyclohexyl.

Mahmoud Sayah completed his undergraduate and masters studies in 2006 at the Department of Organic Chemistry, Stockholm University (Sweden). In 2007 he joined the group of Professor Michael G. Organ at York University, Toronto (Canada) as a PhD student. His research focus is on the synthesis and catalytic applications of organometallic reagents. He has made contributed to the development of the Pd-PEPPSI-IPent precatalyst and its use in the formation of C–C and C–S bonds.

Michael G. Organ is professor for organic chemistry at York University in Toronto (Canada). His research focuses on synthetic efficiency and its application to catalysis, natural products synthesis, and flow chemistry. His group has pioneered the development of a new, highly efficient Pd catalyst system based on the N-heterocyclic carbene ligand system. Pd-PEPPSI-IPr, launched in 2006, and Pd-PEPPSI-IPent, introduced in 2009, are the two primary members of this catalyst family. He has also developed the concept of microwave-assisted, continuous-flow organic synthesis.

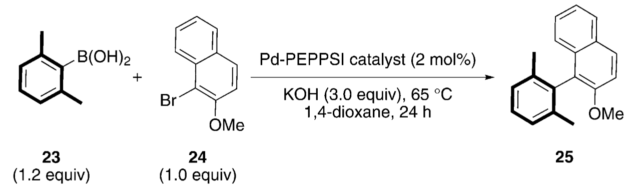


Scheme 4. Tf = trifluoromethanesulfonyl.



Scheme 5.

Table 1: Evaluation of Pd-PEPPSI complexes **14–17** in the Suzuki–Miyaura coupling to provide tetra-*ortho*-substituted biaryl compounds.



Entry	Pd-PEPPSI-Catalyst	Conversion [%][a]
1	Pd-PEPPSI-IPr (**14**)	41
2	Pd-PEPPSI-IPent (**16**)	91
3	Pd-PEPPSI-IBu (**15**)	4
4	Pd-PEPPSI-cPent (**17**)	9

[a] Percent conversion was assessed by GC analysis using undecane as a calibrated internal standard; reactions were performed in duplicate.

considerable advancement in the production of sterically congested and functionalized biaryls.

Pd-PEPPSI complexes were evaluated in a model reaction, the coupling of 2,6-dimethylphenylboronic acid (**23**) and 1-bromo-2-methoxynaphthalene (**24**; Table 1). Initial studies were conducted on two base/solvent systems: KOH/dioxane and KO*t*Bu/*t*BuOH. The KOH/dioxane system at 65 °C with a slight excess of arylboronic acid (1.2 equiv) and 2 mol % Pd-PEPPSI-IPr (**14**) delivered the desired product (**25**) in 41 % yield (Table 1, entry 1). Under the same reaction conditions, Pd-PEPPSI-IPent (**16**) led to 91 % yield of **25** (Table 1, entry 2), while the subtly less-hindered derivatives Pd-PEPPSI-IBu (**15**) and Pd-PEPPSI-cPent (**17**) provided 4 and 9 % yields, respectively (Table 1, entries 3 and 4).

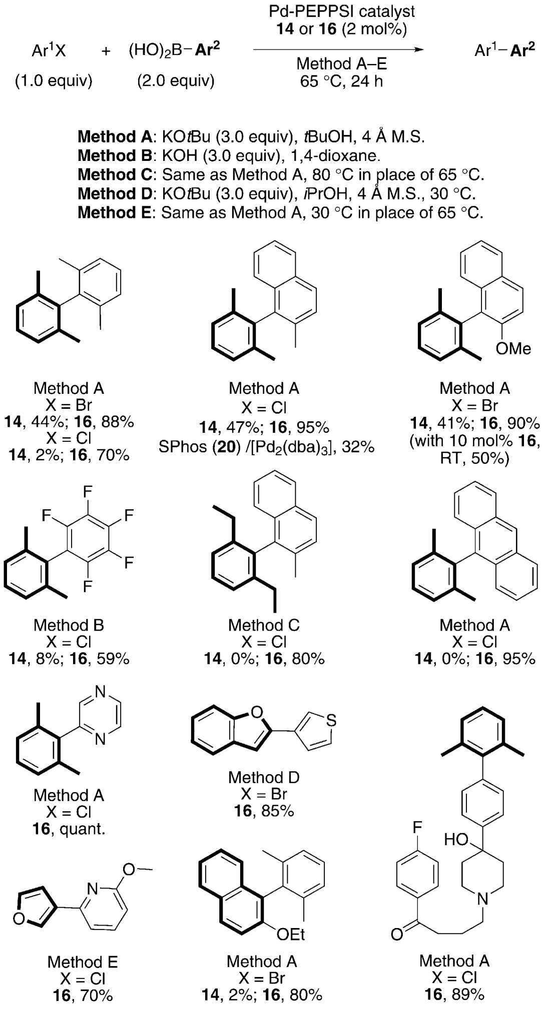
These initial results are consistent with previous findings that the steric topography around the palladium atom is crucial. It has been recognized that the bulk around the metal must be "fluid" or "conformationally flexible" to exert a positive influence on the cross-coupling process.[13,15–18,28,30] A systematic series of investigations has revealed the following factors that are essential for useful catalyst turnover of Pd-NHC complexes:

1) branching at the benzylic carbon of the *ortho*-alkyl substituent is necessary (compare IMes (as in **12**) versus IPr (in **14**) and IBu (in **15**) versus IPent (in **16**))
2) increasing the steric bulk, provided Point 1 is satisfied, improves catalyst performance (compare IPr (in **14**) versus IPent (in **16**))
3) flexible steric bulk in the alkyl substituent is essential, (compare IPent (in **16**) versus cPent (in **17**)).

Pd-PEPPSI-IPr (**14**) and Pd-PEPPSI-IPent (**16**) were next evaluated in a head-to-head comparison study for the coupling of a variety of hindered aryl bromides and aryl chlorides with hindered arylboronic acids using KO*t*Bu in *t*BuOH in the presence of 4 Å molecular sieves (Scheme 6).[31] Pd-PEPPSI-IPent (**16**) proved to be an excellent catalyst for these demanding cross-coupling reactions to form tetra-*ortho*-substituted biaryls in good yields under relatively mild reaction conditions. Substituents in the *ortho* position, such as methyl, primary alkyl, phenyl, fluorine, and alkoxy groups were accommodated. With few exceptions, Pd-PEPPSI-IPr (**14**) provided considerably lower product yields under identical reaction conditions. In certain cases, Pd-PEPPSI-IPent (**16**) is active enough to provide useful turnover at room temperature to give tetra-*ortho*-substituted biaryl products (Scheme 6).[18]

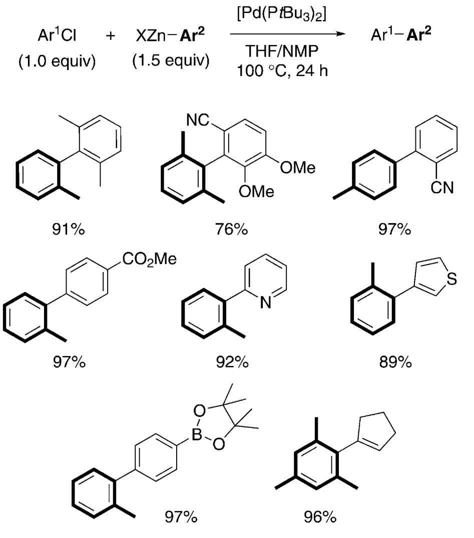
2.2. Negishi Cross-Coupling Reactions for the Formation of Tetra-ortho-Substituted (Hetero)biaryl Compounds

Mild and efficient preparative routes for organozinc reagents, their superb functional group tolerance, and mild reaction conditions makes the Negishi cross-coupling reaction an attractive alternative and viable method to prepare the biaryl motif.[32] In 2001, Dai and Fu reported the first general method for palladium-catalyzed Negishi couplings between arylzinc reagents and (hetero)aryl chlorides that provided

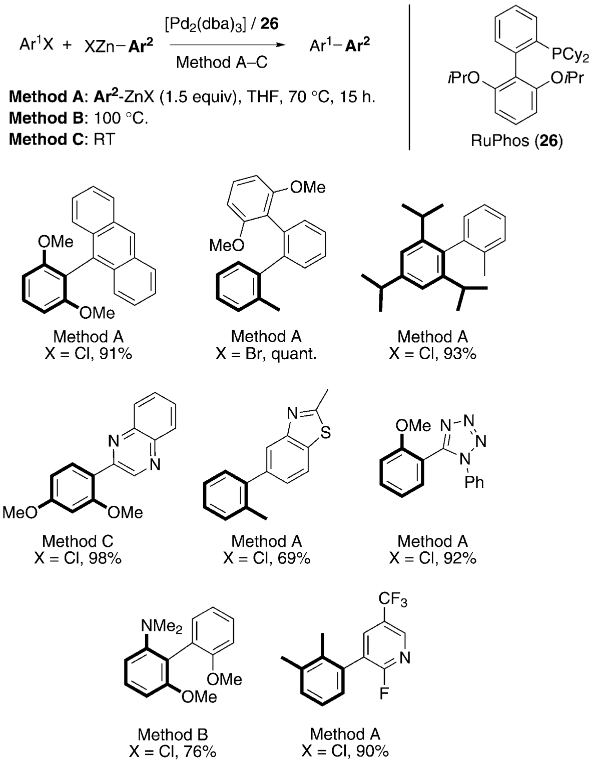


Scheme 6.

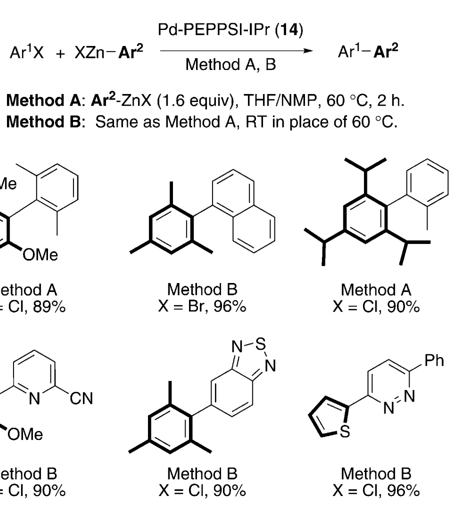
good yields in the presence of [Pd(PtBu$_3$)$_2$] in THF/NMP at 100 °C (Scheme 7).[33] In 2004, Milne and Buchwald prepared a variety of sterically bulky biaryl compounds that contained functional heterocycles by coupling (hetero)aryl halides with arylzinc reagents that were prepared in situ using the hindered RuPhos ligand (**26**) in conjunction with [Pd$_2$(dba)$_3$] at 70 °C (Scheme 8).[34] In 2006, Organ and co-workers developed a user-friendly Negishi method capable of cross-coupling arylzinc halides with aryl bromides and chlorides in excellent yields using Pd-PEPPSI-IPr (**14**) under mild reaction conditions (Scheme 9).[19] Similarly, in 2008, Knochel and co-workers reported a one-pot method employing Pd-PEPPSI-IPr (**14**) to form (hetero)biaryl compounds from in situ generated (hetero)arylzinc reagents and aryl bromides,



Scheme 7. NMP = N-methylpyrrolidone.

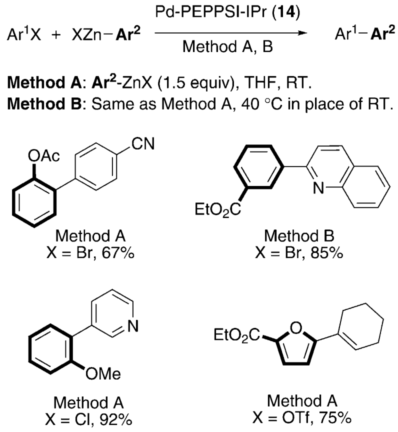


Scheme 8.

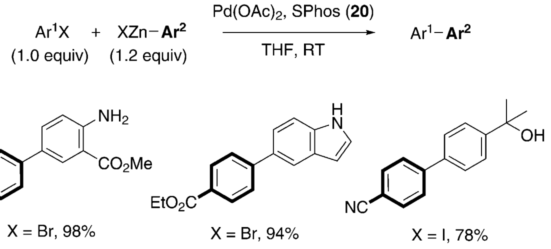


Scheme 9.

chlorides, and triflates under relatively mild reaction conditions (Scheme 10).[25] In a series of publications, Knochel and co-workers also reported Negishi reaction conditions for coupling organozinc reagents with aryl halides bearing relatively acidic protons using $Pd(OAc)_2$ in conjunction with Buchwald's SPhos ligand (**20**) (Scheme 11).[35]



Scheme 10.



Scheme 11.

A comparative study of Pd-PEPPSI-IPent (**16**), Pd-PEPPSI-IPr (**14**), and the well-tailored dialkylbiaryl phosphine ligands **20** and **27** [Pd source = $Pd_2(dba)_3$] in the coupling of 2-mesitylzinc halide with 1,3-dimethyl-2-bromobenzene was conducted (Figure 3).[36] In this study, each reaction was prematurely terminated at 2.5 h to give a snapshot of the species present and to allow room for a temperature study. At room temperature, only the NHC-based catalysts were active under these mild reaction conditions, with Pd-PEPPSI-IPent (**16**) outperforming Pd-PEPPSI-IPr (**14**). Turnover by all catalysts was achieved by heating the reaction mixture to 70 °C in a THF/NMP co-solvent system, wherein **14**, **20**, and **27** provided comparable results (i.e., 45–55 % desired product and a significant quantity of homocoupling of the aryl bromide).[37] Omitting NMP had a detrimental effect on this cross-coupling reaction for all the catalyst systems evaluated.

Pd-PEPPSI-IPent (**16**) and Pd-PEPPSI-IPr (**14**) were next evaluated in a scope study of arylzinc reagents (prepared in situ by transmetalation of organomagnesium bromides with $ZnCl_2$) with oxidative-addition partners bearing considerable steric bulk and/or various functional groups at room temperature or under mild heating (Scheme 12). Relatively

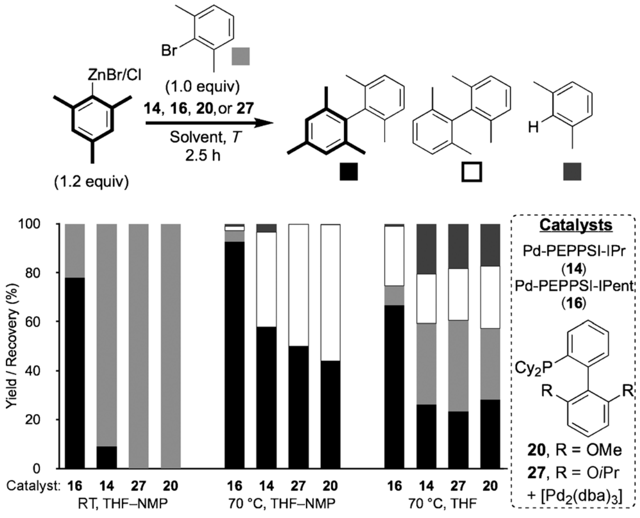
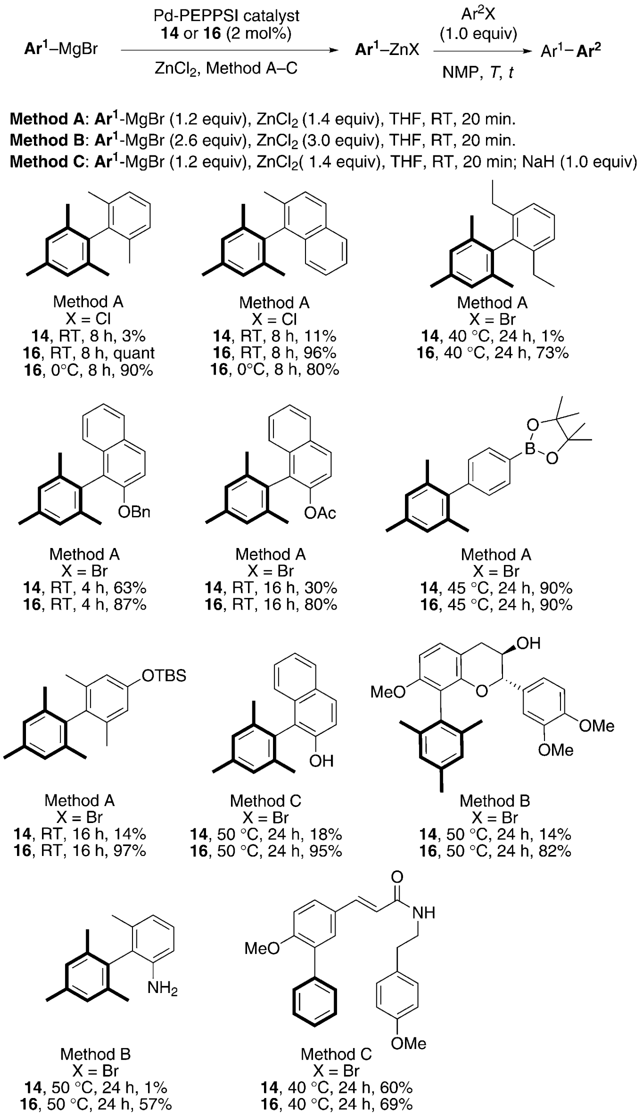


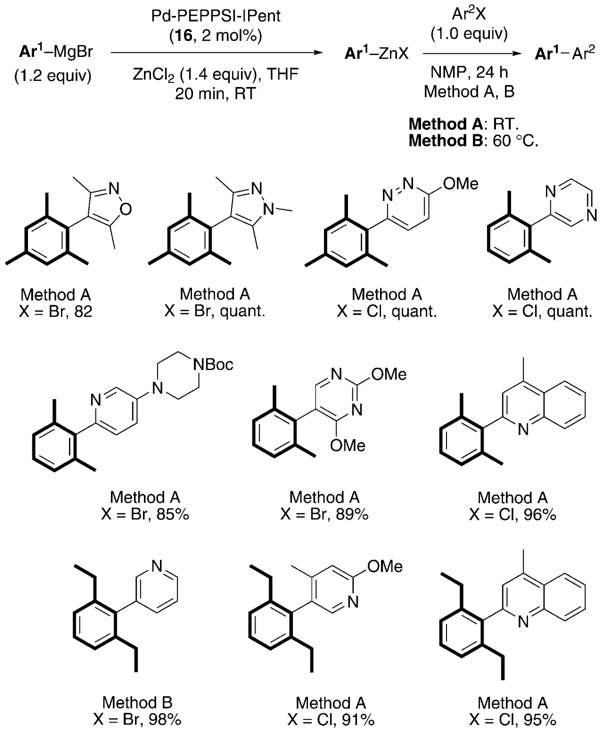
Figure 3. Comparison of catalysts **14** and **16** and ligands **20** and **27**/$[Pd_2(dba)_3]$ under various Negishi reaction conditions in the cross-couplings leading to tetra-*ortho*-substituted biaryl compounds.



Scheme 12. TBS = *tert*-butyldimethylsilyl.

acidic species including anilines, phenols, alkyl alcohols, and amides were well-tolerated. With few exceptions, **14** provided considerably lower yields of cross-coupled products relative to **16**, which was also found to be active at 0°C in representative couplings.[36]

Using Pd-PEPPSI-IPent (**16**), the coupling between heteroaryl halides and hindered arylzinc reagents was examined (Scheme 13). A variety of heterocyclic chlorides and bromides were coupled in excellent yields; these included pyrazine, quinoline, sterically bulky isoxazoles and pyrazoles, as well as substituted pyrimidine, pyridazine, and pyridines.[36]

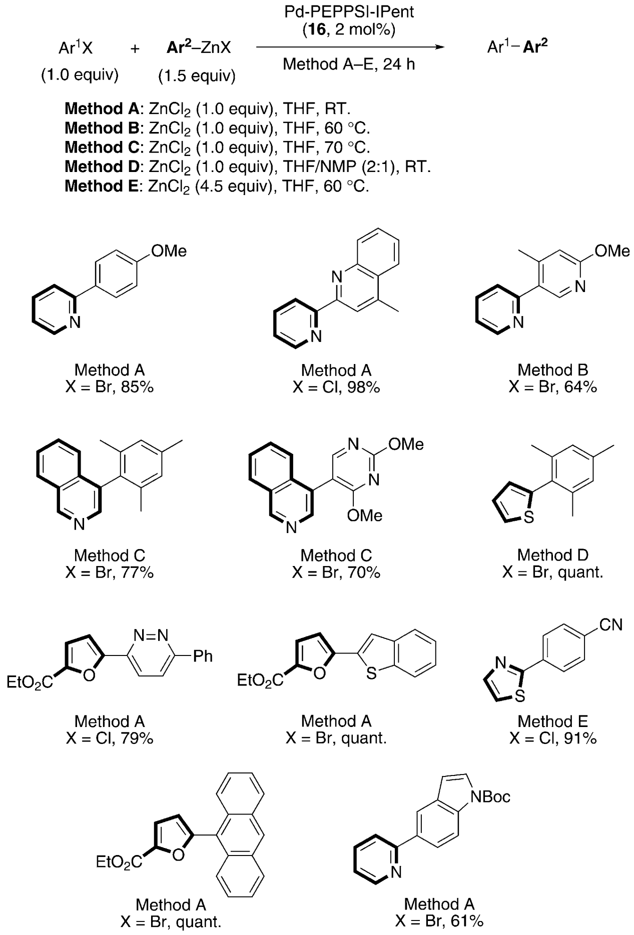


Scheme 13.

A variety of heteroarylzinc reagents, including 2-pyridyl, 4-isoquinolinyl, 2-thiophenyl, 2-thiazolyl, and 5-ethoxycarbonyl-2-furyl, were also effectively coupled with (hetero)aryl bromides/chlorides at room temperature or under mild heating (Scheme 14).[36]

2.3. *Negishi Cross-Couplings of Secondary Alkylzinc Halides with Aryl Halides*

The cross-coupling between C_{sp^2} and secondary C_{sp^3} centers remains a challenge. During the last decade, a number of groups have developed catalyst systems that are uniquely suited for the coupling of secondary alkyl halides with sp^2-hybridized aryl/alkenyl nucleophiles.[38] On the other hand, only a handful of studies have been published relating to the equally useful cross-coupling of secondary C_{sp^3}-hybridized organometallic species with aryl halides. One of the major difficulties in this transformation remains β-hydride elimination and migratory insertion (leading to **28a**) that competes with reductive elimination (leading to **28b**) to provide undesired product isomers (Figure 4).



Scheme 14.

From the mechanism, it is clear that changes to the catalyst's structure that speed up the rate of reductive elimination will suppress β-hydride elimination and thus isomerization. Several research groups have addressed this

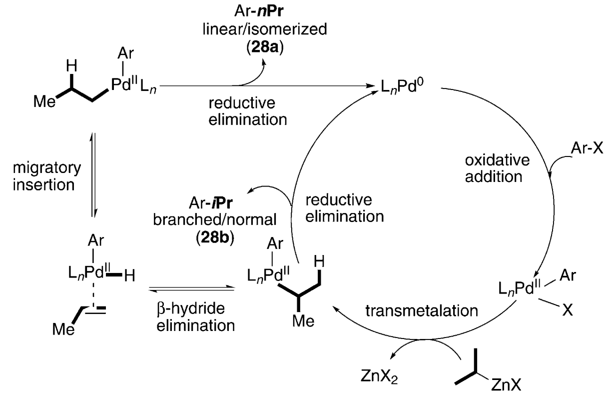
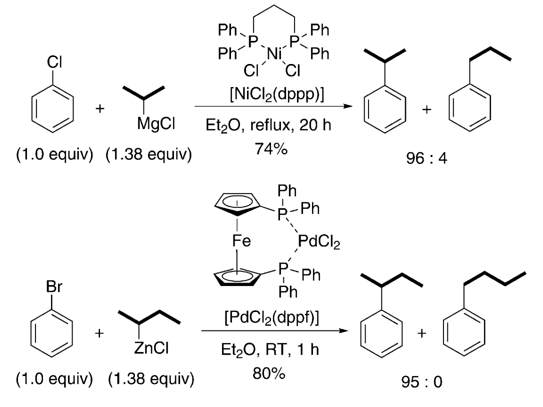


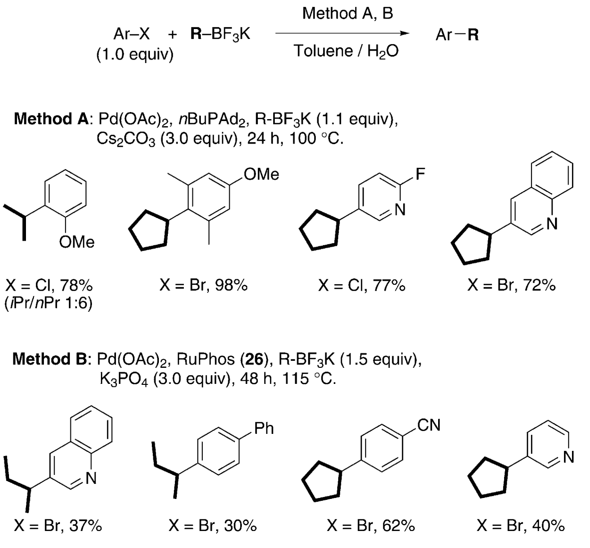
Figure 4. Mechanism for the formation of branched (normal) alkyl-substituted aryl products (**28b**) and linear (isomerized) alkyl-substituted aryl products (**28a**) by the transition-metal-catalyzed Negishi cross-coupling of secondary alkylzinc halides with aryl halides.

issue by employing catalysts containing bulky phosphine ligands that increase the steric topography around Pd that favorably positions the coupling fragments for the reductive elimination. In 1972 and 1984, Kumada/Tamao[39] and Hayashi,[40] respectively, reported that [NiCl$_2$(dppp)] and [PdCl$_2$(dppf)] complexes can couple secondary alkyl Grignard reagents and in situ prepared secondary alkylzinc reagents with a limited array of aryl halides (Scheme 15). In 2008,



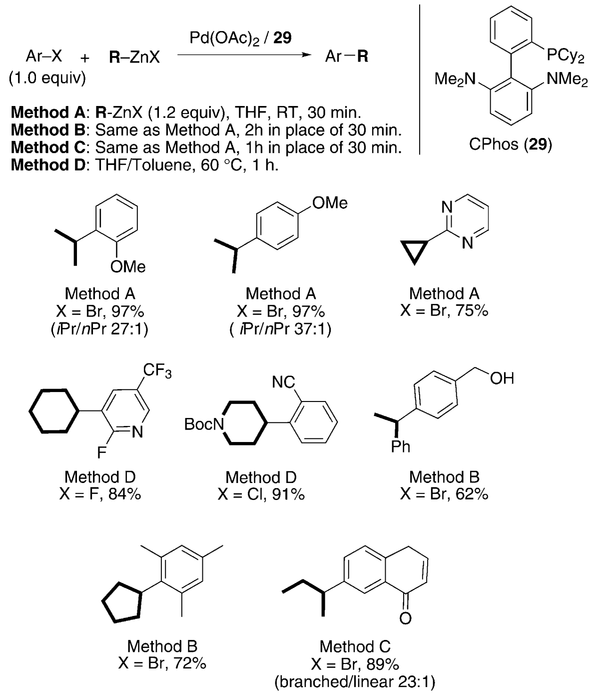
Scheme 15.

Molander[41] and Hoogenband[42] independently reported the Suzuki–Miyaura coupling of secondary alkyltrifluoroborates with aryl halides in the presence of nBuPAd$_2$ and RuPhos (**26**), respectively (Scheme 16). These publications describe primarily the efficient coupling of cyclic alkyltrifluoroborates,



Scheme 16.

which obscures whether isomerization has occurred or not; when linear alkyltrifluoroborates were used the ratio of desired to isomerized product was moderate and functional group incompatibilities surfaced. Recently, Han and Buchwald published a report detailing the palladium-catalyzed coupling of secondary alkylzinc halides with aryl bromides and activated aryl chlorides using the bulky CPhos ligand (**29**).[43] Under their optimal conditions, good ratios of secondary to primary alkyl (isomerized) couplings with several substrates were observed, although the β-hydride elimination pathway was not fully suppressed (Scheme 17).

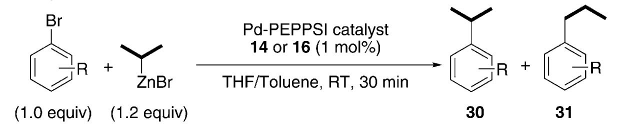


Scheme 17.

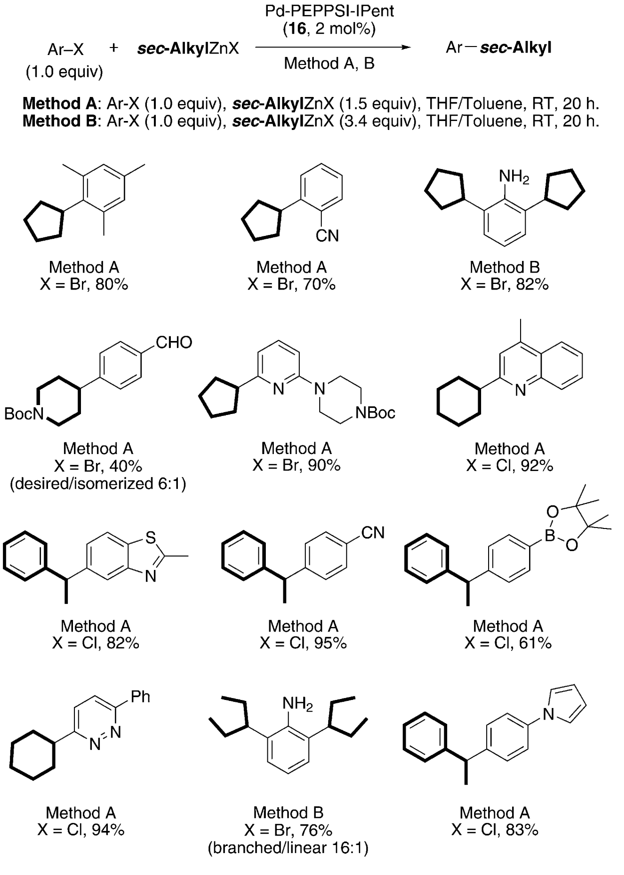
As it is generally true that Group VIII transition-metal complexes containing more-sterically hindered ligands undergo reductive elimination faster than complexes with less-hindered ancillary ligands,[44] Pd-PEPPSI-IPent (**16**) would be anticipated to perform well in the coupling of secondary C$_{sp^3}$-hybridized organometallic complexes with aryl halides. A series of *ortho*-, *meta*-, and *para*-substituted bromobenzene derivatives was coupled with isopropylzinc bromide in the presence of 1 mol% Pd-PEPPSI-IPr (**14**) or Pd-PEPPSI-IPent (**16**) (Table 2). Pd-PEPPSI-IPent (**16**) provided good yields but, more importantly, it exhibited excellent selectivity for the corresponding branched (**30**) over linear (**31**) products. Conversely, while conversions were also high with Pd-PEPPSI-IPr (**14**), the ratios of corresponding branched-to-linear products were notably lower.[45]

Pd-PEPPSI-IPent (**16**) was also evaluated in a more general sense using a variety of cyclic and acyclic secondary alkylzinc reagents with several aryl halides (Scheme 18). Excellent yields were obtained for a range of substrates. Heteroaryl halides including pyridine, quinoline, pyridazine, and benzothiazoles were coupled in high yields and functional groups including aldehydes and nitriles that are susceptible to undergo nucleophilic attack remained intact under these reaction conditions. As in the model study, when acyclic alkylzinc reagents were employed, the ratio of branched to linear products remained good to excellent.[45]

Table 2: Pd-PEPPSI-IPr (**14**) and Pd-PEPPSI-IPent (**16**) catalyzed Negishi cross-coupling of *i*PrZnBr with aryl bromides: selectivity in branched/linear product isomers.



Entry	Ar-Br	Catalyst	Yield [%]	**30/31**
1	R = 4-CN	**14**	85	3:1
		16	92	27:1
2	R = 4-CHO	**14**	64	6:1
		16	78	39:1
3	R = 4-$COCH_3$	**14**	99	6:1
		16	98	30:1
4	R = 4-CO_2CH_3	**14**	83	5:1
		16	99	40:1
5	R = 4-OCH_3	**14**	89	2.5:1
		16	95	33:1
6	R = 3-CN	**14**	77	1:1.4
		16	84	11:1
7	R = 3-CHO	**14**	78	1.6:1
		16	71	22:1
8	R = 3-OCH_3	**14**	31	3.5:1
		16	57	34:1
9	R = 2-CN	**14**	99	1:8
		16	80	2.4:1
10	R = 2-OCH_3	**14**	99	1:9
		16	46	2:1

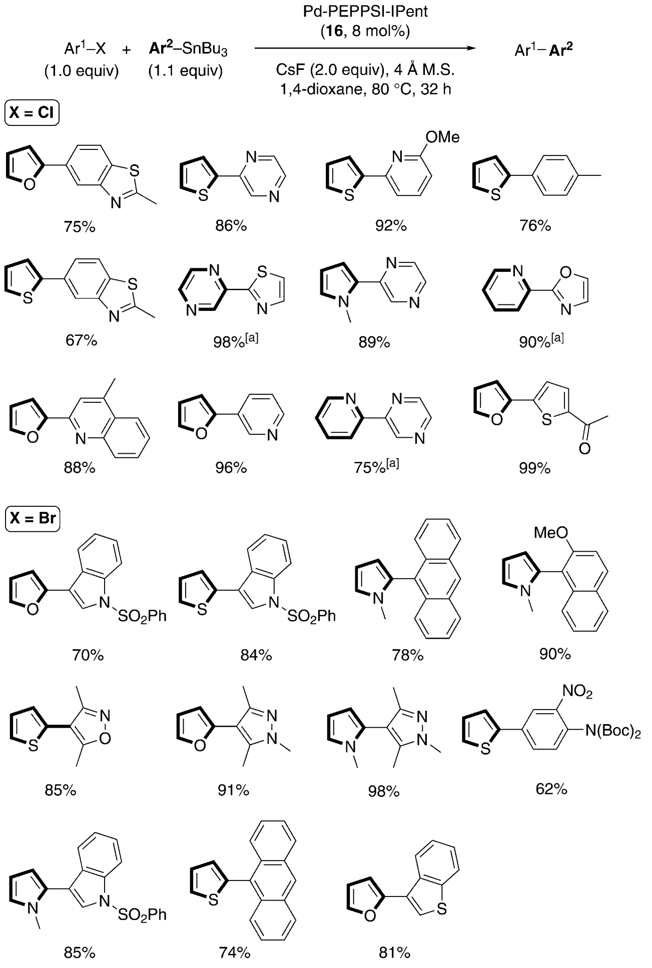


Scheme 18. Boc = *tert*-butyloxycarbonyl.

2.4. Stille–Migita Cross-Coupling Reactions at Low Temperature

The application of organostannanes in natural products synthesis is well established because of their relatively straightforward syntheses and shelf stability.[46] The Stille–Migita cross-coupling reaction has been employed to prepare heterobiaryls, a common structural motif in various pharmaceutical agents,[47] ligand systems for transition-metal catalysis,[48] and functional polymers.[49] However, the stability of the C–Sn bond that makes these reagents so practical to handle renders them less reactive in catalysis, consequently high temperatures (traditionally > 100 °C) are often required for useful levels of conversion to be attained.[50] The PEPPSI-series of catalysts were evaluated with the goal of finding one that is proficient in the Stille–Migita cross-coupling reaction below 100 °C.

In general, Pd-PEPPSI-IPent (**16**) was found to demonstrate high efficiency over a variety of challenging (hetero)-aryl halides with thiophene-, furan-, pyrrole-, piperizine-, oxazole-, and thiazole-based organostannanes (Scheme 19). Suzuki–Miyaura aryl–aryl coupling strategies involving heteroaromatic boronic acids (e.g., 2-thiophene boronic acid) are often plagued with protodeboronation, especially in the



Scheme 19. [a] Reactions performed at 60 °C because of the poor stability of the organostannanes.

presence of a polar protic solvent.[51] For sterically demanding or electron-rich electrophiles, the oxidative-addition step becomes sluggish and side reactions become a greater concern. Drawing on experience with the cross-coupling reactions of hindered boronic acids,[18] it was envisioned that the flexible bulk of the flanking isopentyl groups would impart the steric properties necessary to facilitate reductive elimination. Good-to-excellent yields for all thiophene-based cross-coupling reactions were encountered, even at temperatures as low as 60 °C.[52] These mild reaction conditions facilitated the preparation of other sensitive motifs, such as isooxazoles, benzothiazoles, sulfonamides, and furans. A serious limitation in synthesizing substituted furans is the facile decomposition of furan metalloids (e.g., 2-furanboronic acid and the corresponding trifluoroborate salt) under polar, protic conditions.[53] This phenomenon is the reason why primarily reactive electrophilic partners, such as iodo and bromo-(hetero)aryl systems, have been most commonly reported as coupling partners for these organometallic species. The optimized conditions worked well for the coupling of 2-furyl organostannane reagents with less-reactive aryl bromides and chlorides. In addition, the method was compatible with reactive functional groups, such as sulfonamide and ketone moieties, illustrating the catalytic efficiency and versatility of Pd-PEPPSI-IPent (**16**).

The reactions proceeded equally well to give a variety of pyrrole-based biaryl compounds in excellent yields from a diverse array of oxidative addition partners, including hindered (hetero)aryl bromides. It is noteworthy that poisoning of the Pd catalyst,[54] which is the common cause for the failure of pyrrole-based cross-coupling reactions, was not observed with Pd-PEPPSI-IPent (**16**). The conditions also worked well for substrates containing multiple heteroatoms (e.g., thiazoles, oxazoles, piperizines) that are even more challenging.

The desire to lower the temperature of the Stille–Migita cross-coupling reaction is inspired, in part, by the "thermally delicate" nature of many potentially valuable cross-coupling partners (e.g., thiazoles or oxazoles-based organotin compounds). A thorough screening of various reaction conditions revealed that coupling can occur at as low as 40 °C without any compromise in yield. For example, 2-(tributylstannyl)thiophene was coupled with 2-chloropyrazine quantitatively at 40 °C using Pd-PEPPSI-IPent (**16**). A further reduction in temperature to 30 °C for this coupling was possible using Pd-PEPPSI-SIPr.[55]

2.5. Buchwald–Hartwig–Yagapol'skii Aryl Amination under Mild Reaction Conditions

The palladium-catalyzed aryl amination reaction has become one of the most valuable synthetic tools for the construction of the C–N bond.[56] Since the discovery of the first catalytic aryl amination reaction,[57] extensive efforts have been made towards the development of optimal catalyst/ligand systems to improve reaction efficiency. By far, bulky tertiary phosphines have shown the widest applicability for this transformation.[58] Some remarkable ligands (Figure 5) that are highly active in the amination of aryl halides/pseudo halides include Koie's P*t*Bu$_3$,[59] Beller's monodentate N-substitued heteroarylphosphines,[60] Buchwald's biaryl phosphines,[61] Hartwig's ferrocenyl dialkylphosphines,[62,63] Verkade's and Kwong's amino phosphines,[64] and Stradiotto's phenylene-bridged P,N ligands.[65] Conversely, NHC-type ligands have been much less explored for this transformation.[3,8,21,66,67]

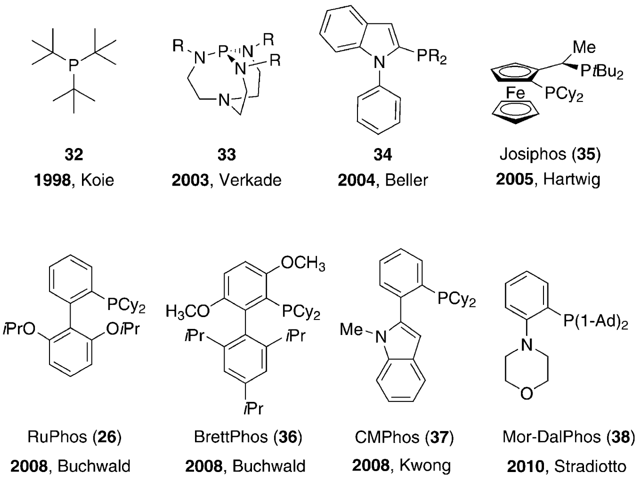


Figure 5. A selection of bulky, highly active phosphine ligands utilized in palladium-catalyzed aryl aminations.

The generally accepted mechanism for this transformation is depicted in Figure 6.[68] Several studies support amine coordination and/or the deprotonation of the subsequent metal ammonium complex as the rate-limiting step in this catalytic cycle.[21,67,69] Hence, strong bases are frequently employed to facilitate the rate-limiting step.[63,70] For example, Hartwig and co-workers succeeded in coupling (hetero)aryl halides with primary amines in the presence of NaO*t*Bu or

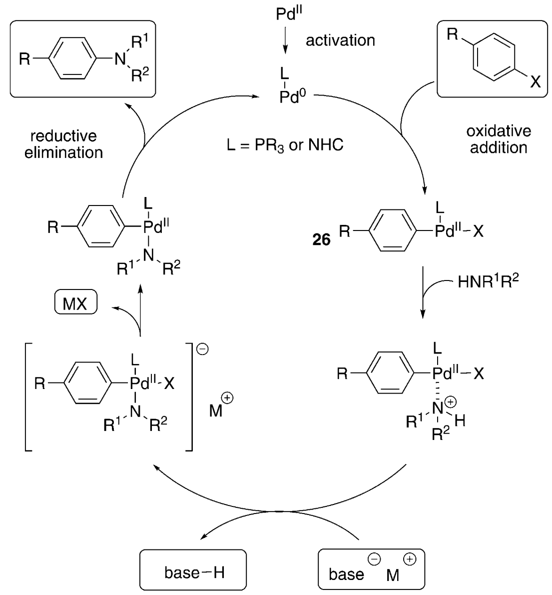
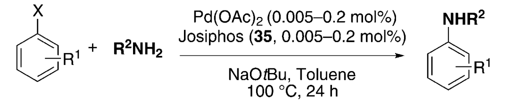


Figure 6. Putative mechanism for the palladium-catalyzed amination reaction.

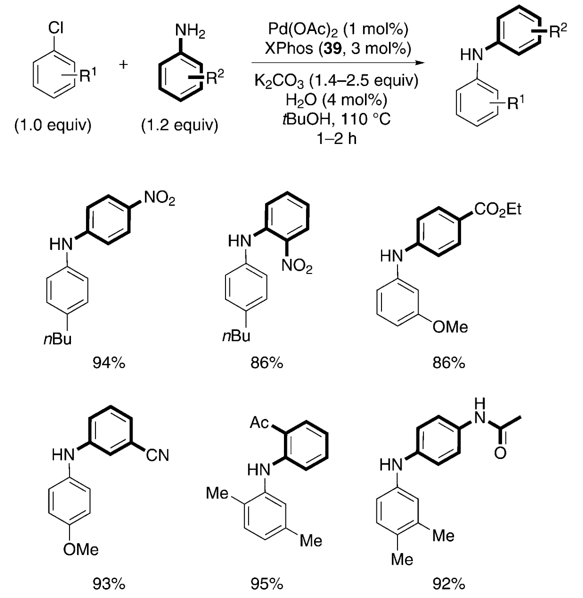
lithium bis(trimethylsilyl)amide with Josiphos (**35**)/Pd(OAc)$_2$ (Table 3).[63] The more challenging reaction involving the coupling of aniline and aminoheterocycles was also achieved under similar strongly basic reaction conditions (Scheme 20).[71] Poor functional-group tolerance was observed, and so the development of mildly basic reaction conditions at low temperature is of interest to broaden the scope of this useful reaction.

Table 3: Cross-coupling of (hetero)aryl halides with primary amines catalyzed by Pd(OAc)$_2$ and Josiphos (**35**) (1:1) in toluene.



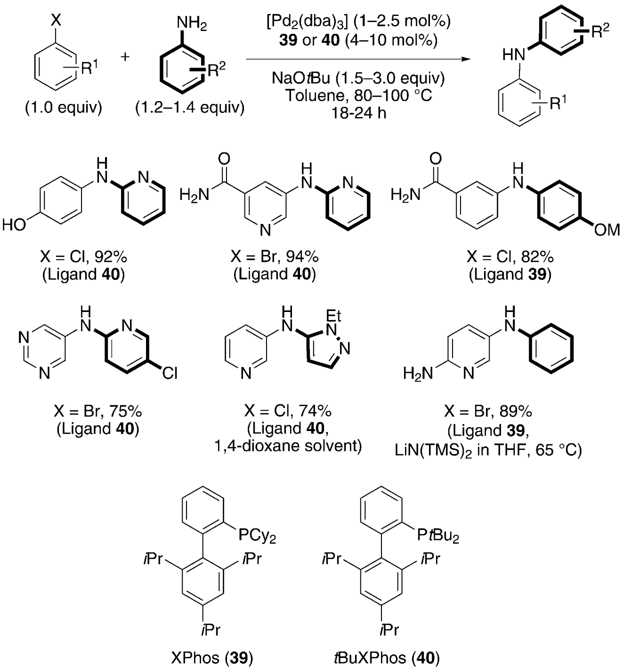
Entry	Ar-R^1	X	R^2	Cat. [%]	Yield [%]
1	2-Py	Cl	octyl	0.01	98
2	3-Py	Cl	octyl	0.05	98
3	3-Py	Cl	4-tolylamino	0.1	66
4	Ph	Cl	octyl	0.05	99
5	4-Tol	Cl	*i*Bu	0.02	99
6	2-Py	Br	octyl	0.01	92
7	3-Py	Br	Bn	0.01	99
8	Ph	Br	Bn	0.005	99
9	3-Py	I	*i*Bu	0.2	99
10	2-Tol	I	cyclohexyl	0.05	93

To this end, Buchwald and co-workers developed a method for the coupling of electron-deficient anilines with aryl chlorides using K$_2$CO$_3$ base at 110 °C (Scheme 21).[72] Presumably, electron-withdrawing substituents act to lower the pK_a of the palladium ammonium complex into a range suitable for deprotonation by the "weaker" carbonate base. Another efficient method was developed by the same research group that allowed an array of (hetero)aryl mesylates to be transformed into the corresponding *N*-aryl amides in moderate-to-excellent yields (Scheme 22).[73] Recently, Pd-PEPPSI-IPr (**14**) has been shown to be an effective and versatile precatalyst for aryl aminations in the presence of Cs$_2$CO$_3$ in DME.[21]

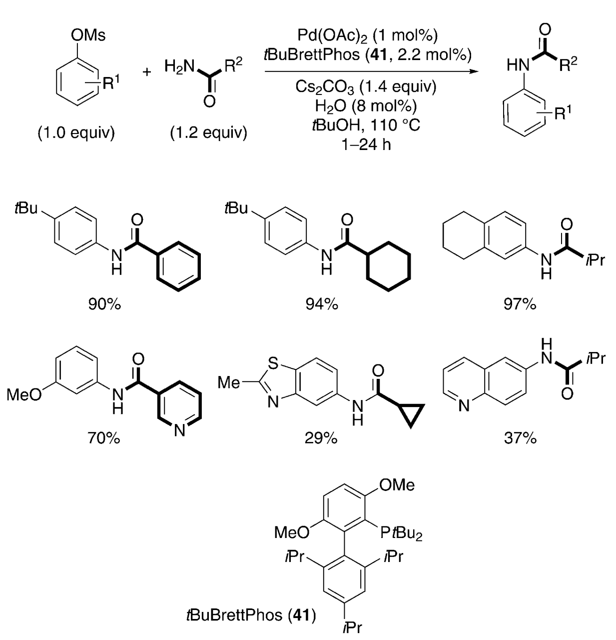


Scheme 21.

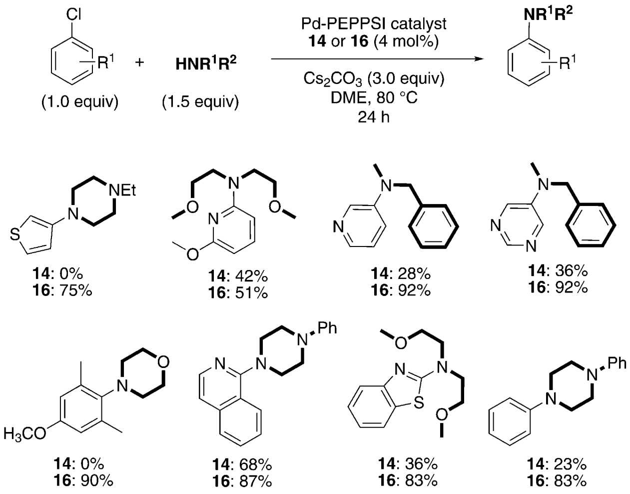
Using the optimized conditions developed for Pd-PEPPSI-IPr (**14**),[21] a variety of challenging aryl chlorides were coupled with secondary amines (Scheme 23). Consistently, Pd-PEPPSI-IPent (**16**) outperformed Pd-PEPPSI-IPr (**14**).[67] While **14** showed no activity in the coupling of morpholine to 2-chloro-5-methoxy-1,3-dimethylbenzene,



Scheme 20.



Scheme 22.



Scheme 23.

which is both electronically and sterically disfavored, **16** provided excellent yields.

To shed some light on the differences in the catalytic performance between Pd-PEPPSI-IPr (**14**) and Pd-PEPPSI-IPent (**16**) with alkyl amine substrates, a rate study was conducted (Figure 7) for the amination of a range of *p*-substituted aryl chlorides with morpholine.[67a] The bulkier Pd-PEPPSI-IPent outperformed Pd-PEPPSI-IPr in each test case and in all instances, **16** reached maximum turnover in a shorter timeframe, and coupled even the most electron-rich aryl chlorides where Pd-PEPPSI-IPr (**14**) failed.

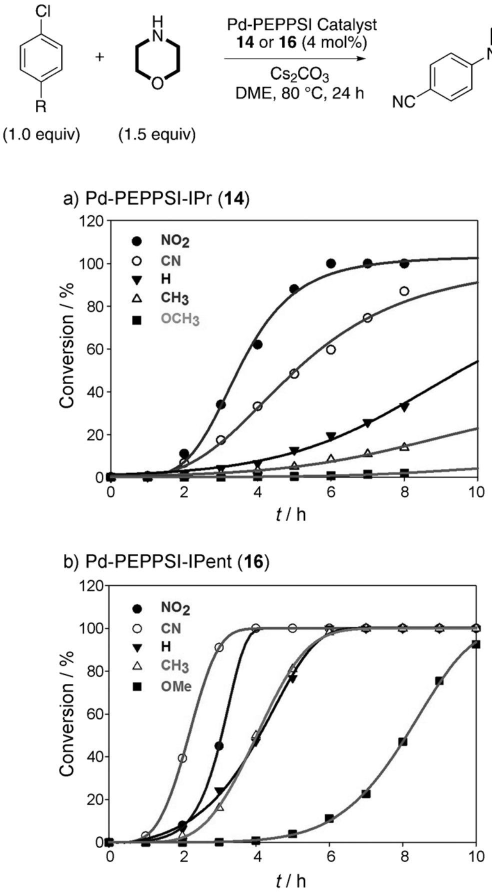


Figure 7. Substituent effects on the rate of amination of *para*-substituted aryl chlorides with morpholine catalyzed by a) Pd-PEPPSI-IPr (**14**) or b) Pd-PEPPSI-IPent (**16**).

A more detailed kinetic study for alkyl amines was conducted wherein the loading of **14** was held constant while the concentrations of 4-chlorobenzonitrile, morpholine, and Cs_2CO_3 were systematically varied (Figure 8). When the concentration of morpholine was doubled (Figure 8b), the

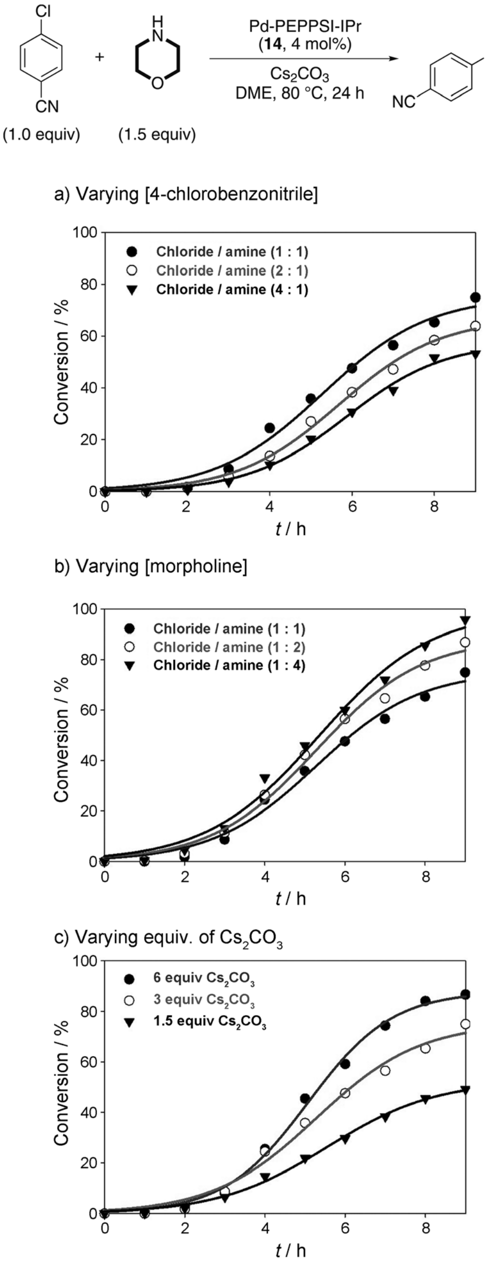


Figure 8. Determining the effect of electrophile, nucleophile, and base on the rate of amination of *para*-chlorobenzonitrile with morpholine catalyzed by Pd-PEPPSI-IPr (**14**). a) Base and morpholine held constant while varying [*para*-chlorobenzonitrile]. b) *para*-Chlorobenzonitrile and base held constant while varying [morpholine]. c) *para*-Chlorobenzonitrile and morpholine held constant while varying [Cs_2CO_3].

maximum rate increased by approximately 20%, suggesting that amine coordination to palladium is relevant, but not rate-limiting. While the reaction was marginally less than zero order in aryl chloride, the rate was significantly influenced by increasing the equivalents of Cs_2CO_3 (Figure 8c). Doubling the base equivalents resulted in an approximate doubling of the maximum rate, which is consistent with the deprotonation step being rate limiting in the catalytic cycle.

To get a more detailed analysis of aminations involving aniline derivatives, which are far less basic and therefore more acidic, rate studies were again carried out.[67b] The consequence of substituent effects on the rate of the aryl amination reaction with aniline and electronically dissimilar aryl chlorides was found to follow the expected trajectories for both Pd-PEPPSI-IPr (**14**) and Pd-PEPPSI-IPent (**16**) (Figure 9). As was found in the coupling with morpholine, aryl chloride concentration has little effect on the reaction rate (Figure 10a), which is unsurprising given the strong σ-donating properties of the NHC ligand. However, it was found that both the concentration of aniline and the equivalents of base had an apparent first-order effect on the rate of reaction (Figure 10b and c). In combination with the morpholine-based rate studies, it appears that the nature of the amine determines whether the formation of the palladium ammonium complex or deprotonation of this complex is rate-limiting. Intuitively this situation can be rationalized in that the more nucleophilic the amine (i.e., morpholine relative to aniline), the easier it is to overcome the energy barrier to yield the palladium ammonium complex, which should be more stable from a standpoint of inductive effects. On the other hand, aniline and its derivatives have a lower pK_a (ca. 25) relative to morpholine (ca. 36) and thus their corresponding palladium ammonium complexes (pK_a much less than 10) are

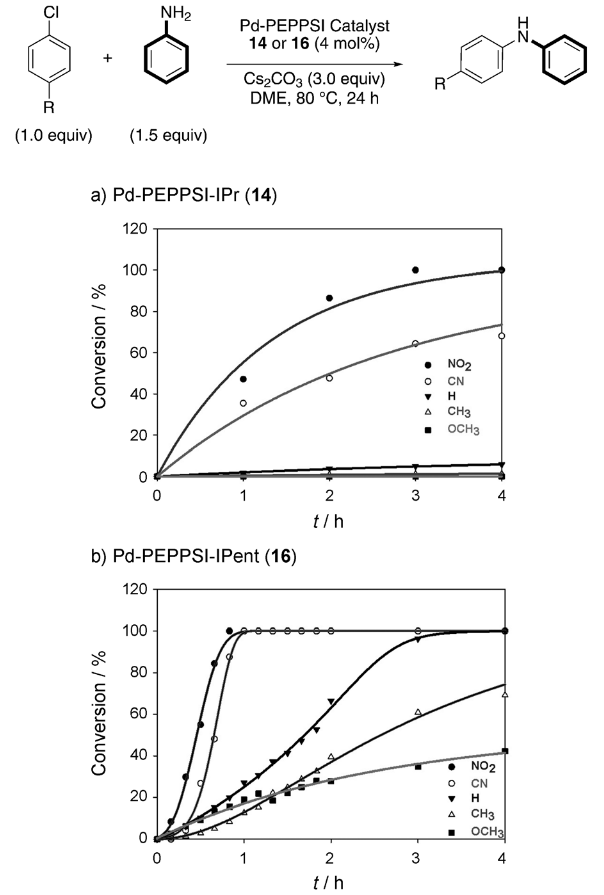


Figure 9. Substituent effects on the rate of the aryl amination reaction of *para*-substituted aryl chlorides with aniline as catalyzed by a) Pd-PEPPSI-IPr (**14**) and b) Pd-PEPPSI-IPent (**16**).

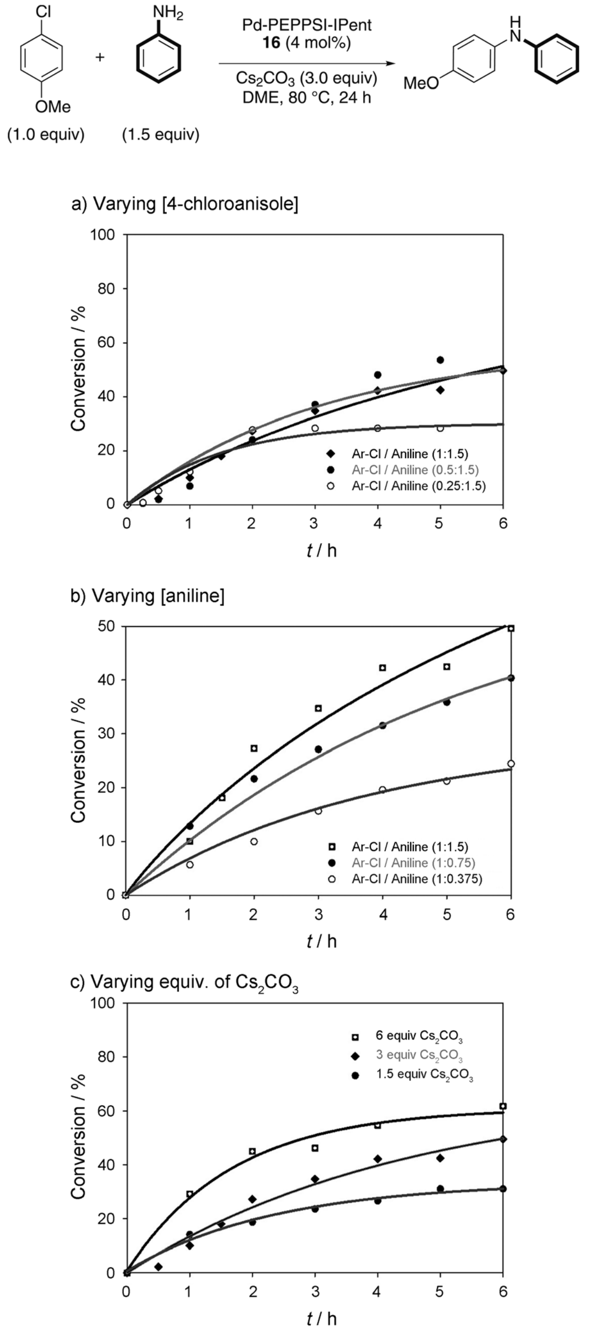


Figure 10. Determining the effect of electrophile, nucleophile, and base on the rate of aryl amination of *para*-anisole with aniline catalyzed by Pd-PEPPSI-IPent (**16**). a) Base and aniline held constant while varying [*para*-anisole]. b) *para*-Anisole and base held constant while varying [aniline]. c) *para*-Anisole and aniline held constant while varying [Cs_2CO_3].

more readily deprotonated. Looking more closely, a rate study on the amination of chlorobenzene with various *para*-substituted anilines reveals that electron-poor anilines perform poorly in the presence of either Pd-PEPPSI-IPr (**14**) or Pd-PEPPSI-IPent (**16**; Figure 11). Given that electron-poor anilines are more acidic, this study suggests that amine coordination to palladium may be more crucial than deprotonation.

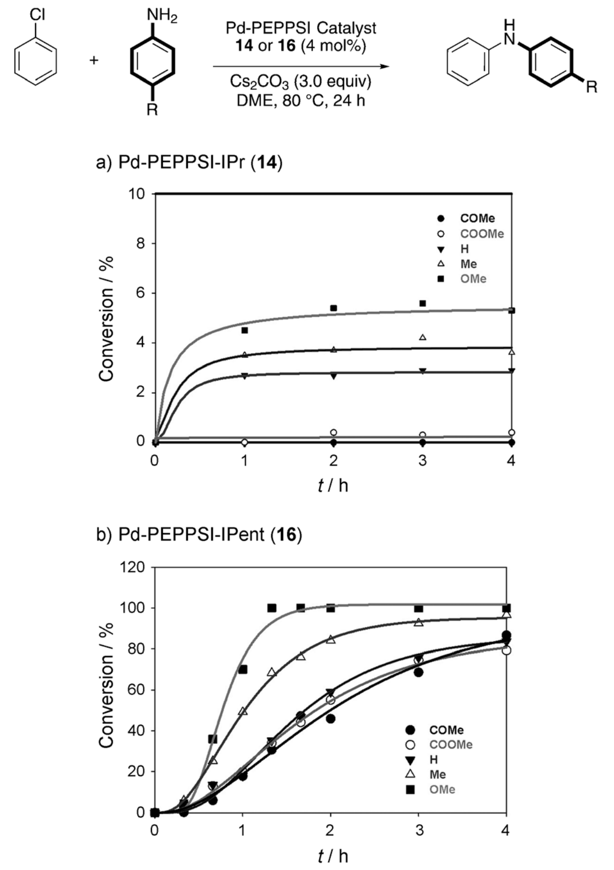
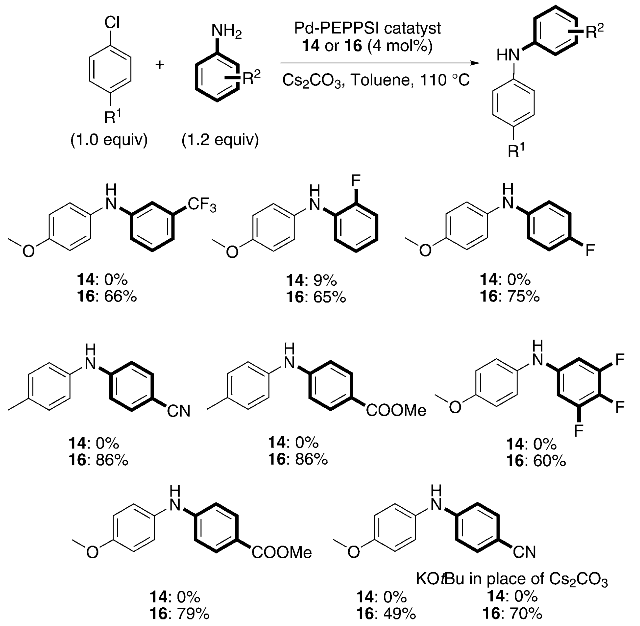


Figure 11. Substituent effects on the rate of the aryl amination reaction of chlorobenzene with *para*-substituted anilines as catalyzed by a) Pd-PEPPSI-IPr (**14**) and b) Pd-PEPPSI-IPent (**16**).

Regardless of the mechanistic underpinnings, an array of electron-deficient anilines were successfully coupled with electron-rich aryl chlorides in good-to-excellent yields (Scheme 24). This is a noteworthy set of reactions as it represents, based on the rate studies, the worst electronic-pairing scenario (electron-rich aryl chlorides and electron-deficient anilines) for this transformation. This highlights the high reactivity of Pd-PEPPSI-IPent (**16**) in the aryl amination reaction. Relating to the point made above about coordination being more important for anilines owing to their poor basicity, it is of note that Pd-PEPPSI-IPr (**14**) failed to provide any product for *p*-cyanoaniline when the strong base KO*t*Bu was used whereas Pd-PEPPSI-IPent (**16**) provided a 70% yield for this identical transformation. Strikingly, **16** provided 50% yield even when carbonate base was used! This result is strongly suggestive that there may be more than just steric effects around the metal center at play that gives **16** some of its high reactivity in this transformation.



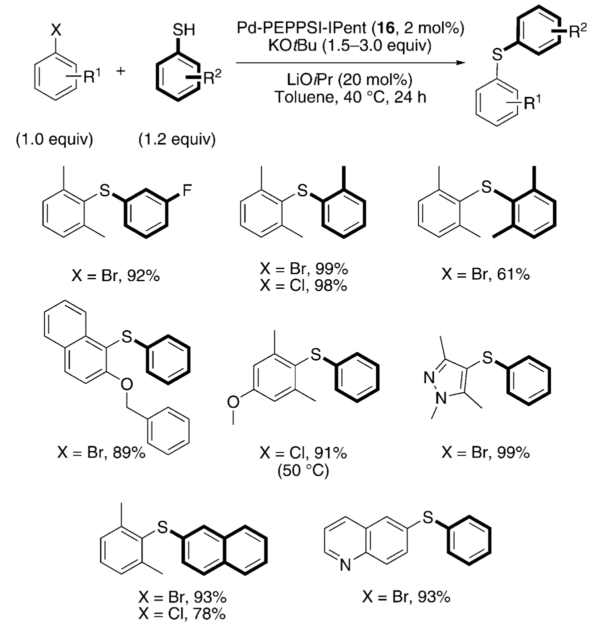
Scheme 24.

2.6. Carbon–Sulfur Bond Formation at Low Temperature

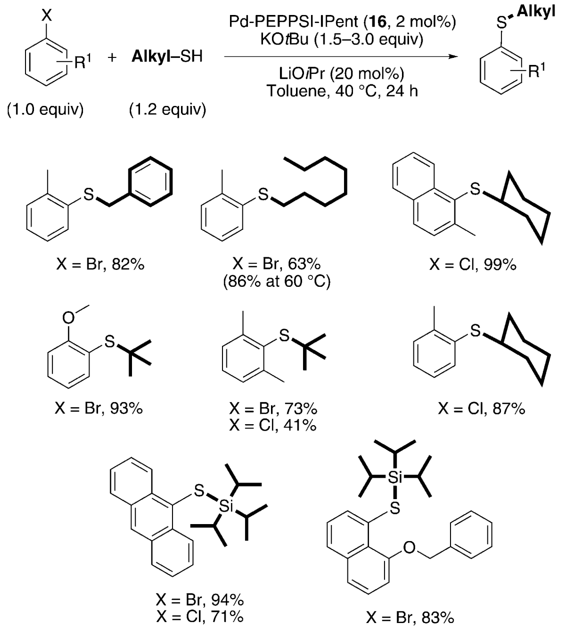
Carbon-heteroatom bond formation in cross-couplings is dominated by aryl aminations, however examples exist for the formation of aryl ethers and thioethers which themselves are important and common functional groups in natural products and pharmaceuticals.[74] Cross-coupling methods to produce thioethers typically require elevated reaction temperatures to achieve useful conversion into products,[75] with the Josiphos ligand (**35**) being the most generally applied ligand.[75e,76] Building on the reasoning presented in the preceding Sections, Pd-PEPPSI-IPent (**16**) was examined for its ability to perform the thiolation of electrophiles at room temperature or below. An impediment in this class of cross-coupling reactions is the thiolate-derived siphoning of palladium away from the catalytic cycle into catalytically inactive palladium adducts (i.e., $[ArPd(SR)_2]^-$ and the dimeric thiolate-bridged $[(ArPdSR)_2]$).[76c] To circumvent these resting states, reductive elimination must be fast and this would be aided by the ideal steric topography of **16**.

Sulfination of (hetero)aryl halides with aryl sulfides proceeded efficiently at 40 °C to provide various diaryl thioethers under the mildest reactions conditions reported to date for this transformation (Scheme 25).[77] Both aryl bromides and aryl chlorides (the chlorides required additional base for optimal results) possessing heteroatoms and/or steric bulk were routinely coupled to provide high yields of product.

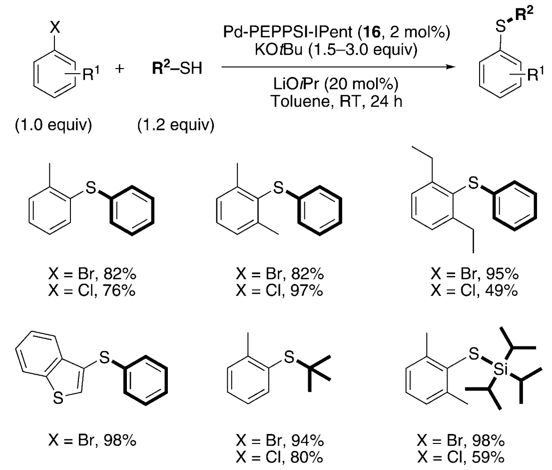
Alkyl thiols, which are known to be sluggish coupling partners, were found to be as effective as aryl thiols in this cross-coupling methodology (Scheme 26); all substitution patterns, including primary, secondary, and tertiary alkyl



Scheme 25.



Scheme 26.



Scheme 27.

thiols were tolerated.[77] The functional triisopropylsilanethiol, a masked form of sulfur, was also routinely coupled despite its significant steric component and, as pioneered by Hartwig and co-workers, is a viable route to install free thiols onto sp^2-hydridzied carbon centers.[78]

A rate study revealed that most cross-couplings were complete within 4–5 h, despite the standard reaction being run for a full 24 h. This encouraged the evaluation of aryl sulfinations at room temperature, and even sterically hindered substrates fared well (Scheme 27). This developed route is the mildest and most generally applicable set of reaction conditions reported to date for the formation of thiol ethers by metal-catalyzed sulfinations.

3. Summary

Since their first reported use as ligands for palladium in cross-coupling reactions just over a decade ago, NHCs have come a long way from chemical curiosities to mainstream, commercially available ligands for catalysis. The NHC metal precatalyst complexes are very stable to air and moisture and have shown superb reactivity in a growing number of applications. Increased steric bulk on the NHC that buries the metal deep within its fold has been linked to heightened reactivity in cross-coupling procedures. Detailed analysis of these structural studies has led to the creation of a number of unique imidazole-based carbene palladium complexes in which the degree of steric bulk has been steadily increased. This approach has led to the creation of Pd-PEPPSI-IPent (**16**), which has been demonstrated to be among the most reactive and general catalysts for Suzuki–Miyaura, Negishi, and Stille–Migita couplings for carbon–carbon bond formation and in amination and sulfination reactions for carbon–heteroatom bond formation.

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