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Pd-PEPPSI Complexes and the Negishi Reaction

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An overview of Pd-PEPPSI complexes in the Negishi cross-coupling reaction is presented. Preliminary evaluations of differentially substituted imidazolium salts that generate highly active cross-coupling catalysts in situ provide the foundation for the development of an air- and moisture-stable NHC-based precatalyst: Pd-PEPPSI-IPr. The application of Pd-PEPPSI-IPr in sp^3–sp^3, sp^3–sp^2 (and vice versa), and sp^2–sp^2 Negishi cross-couplings is reviewed. This allowed the systematic development of Pd-PEPPSI-IPent, a more sterically demanding, second-generation catalyst that outperforms the IPr analogue in a variety of sp^2–sp^2 Negishi cross-couplings. General routes for the preparation of organozinc reagents are also examined, and an additives study reveals the probable transmetallating species that is operative in these cross-couplings. Mechanistic considerations of the Negishi cross-coupling reaction based on experimental and computational studies are summarized and evaluated.

1. Introduction

Despite both the Negishi[1] and the Suzuki–Miyaura[2,3] reactions having their origins in the seminal papers published by Negishi and co-workers in the late 1970s,[2,4] the former reaction has received considerably less attention. This outcome is a direct consequence of the relative functional group compatibility of organozinc and organoboron reagents, wherein the greater ionic character of the C–Zn bond relative to that of the C–B bond renders the former inherently more basic and nucleophilic. Conversely, it is this same property that renders organozinc reagents better transmetallating species, and so develops a trade-off between more efficient cross-couplings and chemoselectivity. However, this statement is becoming increasingly paradoxical and has been since Reformatsky discovered[5] that zinc enolates are stable entities that efficiently add to ketones and aldehydes in the face of acid/base chemistry.[6] The recent development of milder and more efficient preparative routes for these reagents has also revealed a remarkable tolerance for what was once believed to be incompatible functionality. This has retooled the thinking surrounding organozinc reagents and has provided the impetus for a rekindled interest in organozinc chemistry and the Negishi reaction. The groups of Knochel[7] and Uchiyama[8] independently reported the preparation of organozinc reagents possessing a wide range of unmasked functional groups, including alcohols and aldehydes, by direct zinc insertion with the use of LiCl as a promoter or with the use of $t\mathrm{Bu_4ZnLi_2}$ in a zinc–halogen exchange reaction. Moreover, their efficient one-step, workup-free preparation is well suited for one-pot reaction sequences. These recent findings have the potential to re-establish the Negishi reaction, perhaps in the same limelight as the Suzuki–Miyaura reaction has come to know.

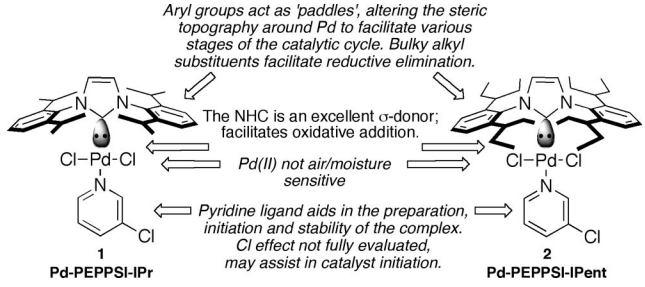

Figure 1. Attributes of the most active Pd-PEPPSI complexes utilized in the Negishi cross-coupling reaction.

Our group was originally interested in the Negishi reaction to achieve efficient cross-couplings between two *unactivated* sp^3 centers by exploiting the inherent reactivity of alkylzinc reagents.[9,10] These preliminary studies eventually led to the development of a series of air- and moisture-stable NHC-Pd^{II} precatalysts, the Pd-PEPPSI series, where PEPPSI stands for pyridine-enhanced precatalyst preparation, stabilization, and initiation (Figure 1).[11–14] Pd-PEPPSI-IPr (**1**) emerged as the first highly active NHC-based catalyst for the Negishi reaction,[12] and subsequent work has shown that Pd-PEPPSI-IPent (**2**) is superior for coupling sterically hindered and heterocyclic substrates.[15,16] Throughout the course of these studies, much mechanistic insight has been garnered. The findings from our work on this general cross-coupling reaction are

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summarized in this microreview, which begins with a brief synopsis of the most efficient preparative routes for organozinc halides.

2. Preparation of Organozinc Halide Reagents

The first known organozinc compound was prepared in 1849, when Frankland reported the oxidative addition of Zn metal into ethyl iodide.[17] The reaction, however, was limited by the low reactivity of the metal, and thus, several methods were developed to increase the reactivity of Zn and to expand the scope of oxidative addition to less reactive C–X bonds. These methods of activation include washing Zn metal with aqueous HCl,[18] addition of 1,2-dibromoethane[19] and/or chlorotrimethylsilane,[20] ultrasound irradiation,[21] metal-solvent co-condensation,[22] and reduction of zinc salts on titanium dioxide.[23] Despite these forays, direct oxidative addition of Zn metal to organic halides has been limited to relatively reactive electrophiles, including alkyl iodides and α-halo esters. To prepare organozinc reagents from less reactive organohalides, including alkyl bromides/chlorides and vinyl and aryl halides, metathesis with organomagnesium or lithium reagents is commonly used (Figure 2, Method A), but this method has limited application due to functional group incompatibility.

As the main benefit of organozinc reagents lies in their functional group tolerance, thereby avoiding the need for extensive protection/deprotection or functional group interconversion methodologies, the direct insertion of Zn metal into a C–X bond (Figure 2, Method B) has become the method of choice, as it is more chemoselective than the metathesis route. Rieke reported a procedure whereby an activated form of Zn metal is produced by the direct reduction of anhydrous Zn salts with potassium or sodium metal in refluxing THF.[24] It was shown that this reactive Zn metal is capable of inserting into alkyl bromides, as well as into aryl bromides and iodides. It was later reported that a preformed solution of lithium naphthalide in THF yielded an even more reactive form of Zn metal (denoted Zn*), which was found to react readily with alkyl bromides at room temperature as well as with aryl bromides and iodides at 65 °C to afford the corresponding organozinc reagents in excellent yields.[25] The scope of this methodology was extended further to include secondary and tertiary alkylzinc bromides in high yields. In the presence of KI, Zn* can insert into alkyl–Cl bonds, presumably through a halo-

Cory Valente was born in Toronto, Canada in 1980. He obtained a HBSc in biological chemistry from York University in 2003 before pursuing a PhD in organic chemistry with Professor Michael G. Organ at the same institution with the aid of an NSERC postgraduate scholarship. His research involved the total synthesis of neodolabellane-type diterpenoids and Pd-catalyzed cross-couplings, in particular with NHC-Pd-type catalysts. In 2009, he moved to Northwestern University to pursue a postdoctoral fellowship with Professor Sir Fraser Stoddart, where he currently enjoys working on the synthesis of new carbon allotropes, on mechanized nanoparticles for therapeutic and diagnostic use and on novel applications of metal-organic frameworks (MOFs).

Matthew E. Belowich was born in River Vale, NJ, USA in 1984. He attended Gettysburg College, where he obtained a B.S. in chemistry under the tutelage of Professor Donald Jameson while working on the synthesis and characterization of Troger's Base derivatives for the self-assembly of novel coordination compounds. In 2007, he moved to Northwestern University to pursue a PhD in organic chemistry with Professor Sir Fraser Stoddart. He is currently working on the synthesis of molecular machines and the template-directed synthesis of polyrotaxanes under thermodynamic control.

Niloufar Hadei was born in Tehran, Iran. She completed undergraduate and master level courses in organic and analytical chemistry at Stockholm University in Sweden. She obtained a PhD under the supervision of Professor Michael G. Organ in organic chemistry at York University in Toronto, Canada, where she explored the use of N-heterocyclic carbenes in Pd-catalyzed cross-couplings, in particular the Negishi reaction. She is currently a postdoctoral fellow in the same laboratory. Her main research interests include transition-metal-catalyzed carbon–carbon and carbon–nitrogen bond-forming reactions, the elucidation of their precise mechanisms and the application of this developed methodology to natural product synthesis.

Professor Michael G. Organ obtained his PhD from the University of Guelph in Guelph, Ontario, Canada, under the supervision of Professor Gordon Lange. His postdoctoral research was conducted in the labs of Barry M. Trost at Stanford University. Prof. Organ's current research focuses on synthetic efficiency and more specifically on the application of tandem-reaction methodology to improve synthetic efficiency. This methodology, focused initially on carbon–carbon bond-forming methods, has been expanded to include carbon–heteroatom bond formation. This has led to his group undertaking and completing the synthesis of a number of natural product targets. Further, progress in tandem-reaction chemistry involving heteroatoms has also allowed Prof. Organ's group to initiate a program in the synthesis of pharmaceutically relevant compounds. 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 and are available through Sigma–Aldrich. Prof. Organ has also developed the concept of microwave-assisted, continuous flow organic synthesis (MACOS, patent pending) that is also being commercialized.

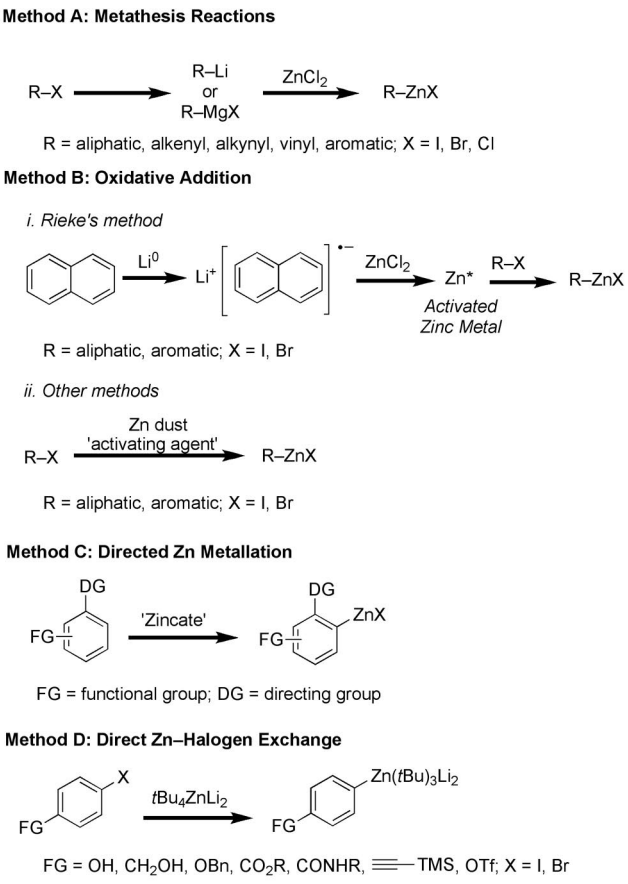


Figure 2. Common methods for the formation of organozinc reagents.

gen substitution reaction followed by direct Zn insertion. More recently, gentler methods utilizing commercially available Zn dust have come to the forefront of this methodology. Knochel and co-workers reported that treatment of alkyl bromides with Zn dust in the presence of a catalytic amount of an alkali metal iodide yields the corresponding alkylzinc reagents in high yield (>85%).[26] In the presence of an excess amount of bromide, this methodology was amenable to the preparation of alkylzinc chlorides, sulfonates, and phosphates. These reaction conditions also effect the conversion of allylic and benzylic derivatives into the corresponding organozinc reagents and tolerate the presence of esters, olefins, and chlorides. Huo reported a remarkably simple and general procedure for the preparation of alkylzinc compounds from unactivated alkyl bromides/chlorides by using a catalytic amount (1–5 mol-%) of I_2 for Zn activation.[27] It was shown that Zn insertion into *n*-octyl bromide occurs with >99% conversion at 80 °C in *N*,*N*-dimethylacetamide (DMA) by using a catalytic amount of I_2 (5 mol-%). In the presence of a stoichiometric amount of LiBr or R_4NBr, alkyl chlorides can also be used. Owing to the greater bond enthalpies, direct Zn insertion into C(sp^2)–X bonds has proven to be more difficult than insertion into C(sp^3)–X bonds. For instance, treatment of iodobenzene with commercial Zn powder, activated by the addition of 1,2-dibromoethane (5 mol-%) and TMSCl (1 mol-%), affords only 5% conversion to phenylzinc iodide after 24 h at 50 °C. However, in the presence of LiCl (1.5 equiv.), full conversion to phenylzinc iodide was observed after 7 h at 50 °C.[7] The presence of an electron-withdrawing group at the *ortho* or *para* positions considerably increases the rate of insertion, allowing the corresponding arylzinc iodides to be prepared at room temperature with >98% conversion. The insertion reaction also displays excellent chemoselectivity, wherein a range of functionalized arylzinc iodides bearing an ester, nitrile, ketone, aldehyde, or amide group were prepared. Moreover, treatment of 4-bromophenyl iodide with Zn/LiCl resulted in insertion exclusively into the C–I bond with 96% conversion. Smooth Zn insertion is also observed for heterocyclic iodides, as well as into C–Br bonds of activated aryl and heteroaryl bromides. Knochel also reported on the efficiency of this method in preparing highly functionalized benzylic zinc chlorides.[28,29] The exact nature of the activating power of LiCl is not known; however, it is believed that LiCl removes the formed organozinc reagent from the metal surface by generating highly soluble RZnX·LiCl complexes, thus allowing subsequent insertion reactions to take place by avoiding the competitive deactivation of the active metal sites.[7]

Directed metallation of (hetero)aromatics is also a valuable method for preparing arylzinc reagents (Figure 2, Method C). Zn complexes of Li amide bases have proven useful for this reaction, particularly in the *ortho*-metallation of various unsaturated systems.[30] Early work in this area by Kondo employed [tBu$_2$Zn(TMP)Li] (TMP = 2,2,6,6-tetramethylpiperidide) as an efficient mixed-metal base for the zincation of functionalized aromatics.[31] The use of this highly active base, however, is not compatible with sensitive functional groups such as aldehydes and nitro groups. More recently, Knochel reported the preparation of the neutral mixed-metal complex $TMP_2Zn·2MgCl_2·2LiCl$ for the directed zincation of base-sensitive (hetero)aromatics.[32] However, in the case of several electron-poor arenes and heteroarenes, these Zn bases were inefficient and provided unsatisfactory yields and selectivities. In the search for a milder and more selective base, Knochel reported the preparation of TMPZnCl·LiCl, which unlike $TMP_2Zn·2MgCl_2·2LiCl$, is stable at room temperature and shows excellent chemoselectivity for the directed zincation of a variety of base-sensitive (hetero)aromatics.[33] Pyridazines, pyrimidines, pyrazines, and purines are cleanly zincated at 25 °C. Caffeine undergoes smooth zincation in the presence of TMPZnCl·LiCl in only 5 min. Less reactive (hetero)aromatics can be zincated with TMPZnCl·LiCl when subjected to microwave irradiation.[34] For example, 1-fluoro-3-methoxybenzene or arenes bearing sensitive functional groups such as ethyl 3-fluorobenzoate could not be metallated at 25 °C; however, under microwave irradiation conditions (160 °C, 2 h), they yielded the desired zincates in yields in excess of 90%.

Recently, Uchiyama and co-workers showed that fine-tuning the ligand environment of organozinc reagents can make direct Zn–halogen exchange (Figure 2, Method D) an

efficient process, even in the presence of an acidic functionality,[8] including unprotected amides and aliphatic and phenolic alcohols. For example, treatment of *p*-iodobenzyl alcohol with tBu_4ZnLi_2 at room temperature provides clean conversion to the corresponding *p*-(Li_2tBu_3Zn)-benzyl alcohol, which can then be trapped with an electrophile or used directly in a Cu- or Pd-catalyzed C–C bond-forming reaction. Additionally, methyl esters, which are generally incompatible with halogen–metal exchange reactions, are suitable substrates under these conditions. This represents an important and practical method for chemoselective metal–halogen exchange, carried out at room temperature and avoiding the need for functional group protection/deprotection strategies.

3. NHC–Pd Catalysts in the Negishi Reaction

3.1. Negishi Cross-Couplings of Two Unactivated sp^3 Centers by an In Situ Generated NHC–Pd Catalyst

Initial studies for the sp^3–**sp^3** (throughout the text, bolded fragments represent the groups originating from the organometallic coupling partners) Negishi reaction were based on the cross-coupling of 1-bromo-3-phenylpropane with *n*BuZnBr (Rieke Metals, Inc.) in the presence of the imidazolium salt IPr·HCl (**3**).[9] Deprotonation of the imidazolium salt under the basic reaction conditions and subsequent capture of the free carbene by Pd generates the active catalyst in situ. Optimization studies revealed that a tetrahydrofuran/*N*-methylpyrrolidinone (THF/NMP) mixed solvent system at room temperature in the presence of $Pd_2(dba)_3$ as the Pd source provided excellent coupling yields. The control reaction, wherein either the imidazolium salt or the Pd source was removed, yielded no reaction (≤0.3% conversion).

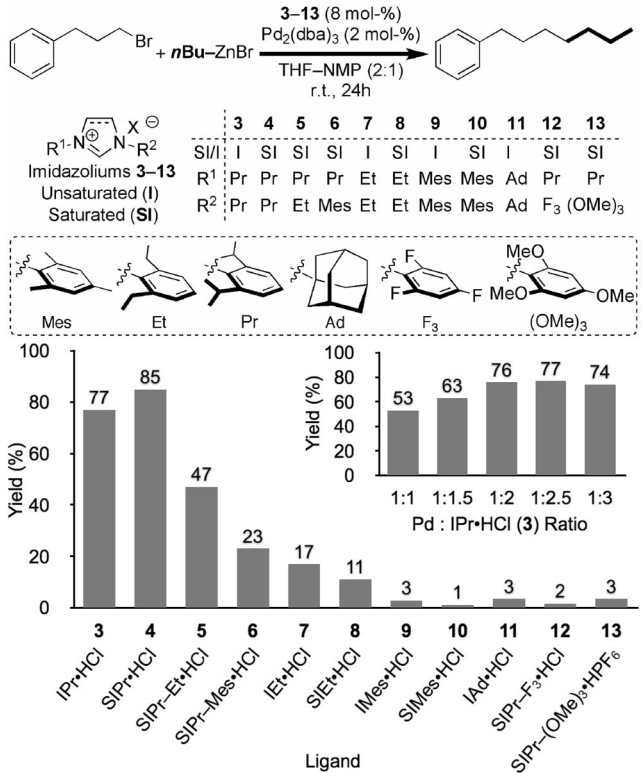
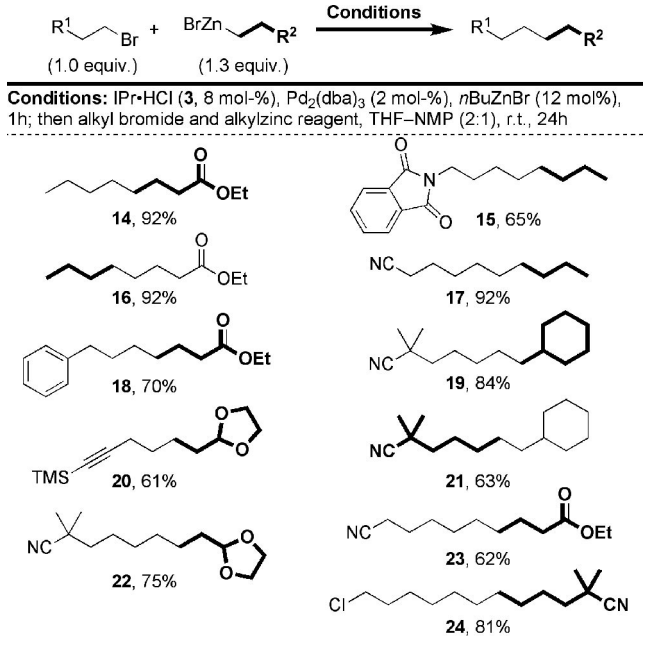


Figure 3. Effect of NHC ligand structure and Pd/ligand ratio (inset) on the efficiency of the sp^3–**sp^3** Negishi reaction.

Table 1. Substrate scope for the sp^3–**sp^3** Negishi cross-coupling reaction with use of an in situ generated catalyst from IPr·HCl and $Pd_2(dba)_3$.



Following these preliminary studies, the effect of the NHC sterics on sp^3–**sp^3** Negishi cross-coupling was systematically evaluated (Figure 3).[10] Imidazolium and 4,5-dihydroimidazolium salts **3**–**12** were prepared and evaluated under the optimized reaction conditions described above. Changes to the pendant alkyl groups on the aryl moieties of NHCs have been shown to have little contribution to the electronics of the system – that is, the steric and electronic contributions of NHCs are isolated.[10,14,35] Thus, differences in reaction kinetics and product distributions among the evaluated imidazolium salts are primarily a consequence of altered sterics. A general correlation was observed whereby seemingly subtle changes resulting in decreased sterics of the NHC ligand led to dramatic declines in product yield. For example, removing one methyl moiety from SIPr·HCl (**4**) to yield SIPr–Et·HCl (**5**) induced a drop in product yield from 85 to 47%. Removal of an additional methyl moiety from the ligand [to give SIPr–Mes·HCl (**6**)] further cut the yield in half to 23%. Symmetrical IEt·HCl (**7**) and IMes·HCl (**9**) provided product yields of 17 and 3%, respectively. Despite the size similarity of the ethyl and methoxy groups, SIPr–$(OMe)_3$·HPF_6 (**13**) was comparatively ineffective, as was SIPr–F_3·HCl (**12**). Saturated 4,5-dihydroimidazolium salts provided yields on par with their unsaturated analogues. Whether the bulky IAd·HCl (**11**) ligand was ineffective due to topological considerations or to constraints in generating the active ligated catalyst in situ

remains uncertain. Varying the Pd-to-ligand stoichiometry revealed that at least a 1:2 ratio was required for optimal performance, although a 1:1 ratio was sufficient for adequate catalyst turnover (Figure 3, inset). It is believed that a monoligated catalyst is the active species and that the addition of an excess amount of the imidazolium salt ensures that a greater proportion of active catalyst is formed in situ (vide infra).

A substrate study was carried out subsequently (Table 1) and it was found that under these reaction conditions a variety of functionalized, unactivated primary alkyl bromides and alkylzinc halide reagents were coupled readily (leading to **14**–**24**) in high yields, establishing the effectiveness of an NHC–Pd catalyst in the sp^3–$\mathbf{sp^3}$ Negishi reaction for the first time. Esters (present in **14**, **16**, **18**, **23**), nitriles (present in **17**, **19**, **21**–**24**), acetals (present in **20** and **22**), silylated alkynes (present in **20**), and imides (present in **15**) were found to be compatible functionalities. Importantly, the reaction conditions are exceptionally mild, as all couplings were carried out at room temperature.

3.2. Comparison of an NHC–Pd Precatalyst with Its In Situ Generated Counterpart

The requirement for an excess amount of the imidazolium salt relative to that of Pd for optimal couplings highlights the inefficiency in generating a monoligated NHC–Pd species quantitatively in situ. Moreover, irreproducibility from one experiment to the next is often encountered, as the free carbene is highly susceptible to moisture, to the precise reaction conditions, and to laboratory technique. With the above drawbacks in mind, a Pd^{II} precatalyst that could be activated in situ to yield a monoligated NHC–Pd^0 catalyst, thereby circum venting the need to generate a free carbene, was designed and synthesized.[11,12] Pd-PEPPSI-IPr was compared directly to IPr·HCl/[Pd_2(dba)$_3$] in the sp^3–$\mathbf{sp^3}$ Negishi reaction under the assumption that the active catalytic species in both cases is the monoligated IPr–Pd^0.[12] A rate study revealed that 1 mol-% of Pd-PEPPSI-IPr was much more efficient than 4 mol-% of IPr·HCl/[Pd_2(dba)$_3$] (Figure 4a). Probing this further, it was established that 0.1 mol-% of Pd-PEPPSI-IPr was as effective as a 4 mol-% loading of IPr·HCl/[Pd_2(dba)$_3$], corresponding to turnover numbers of 300 and 7.5, respectively (Figure 4b). This implies that only a small fraction of the theoretical yield of active catalyst is formed in the in situ protocol, which results not only in the waste of precious starting materials but also in uncertainty surrounding the stoichiometry and composition of the active catalytic species.

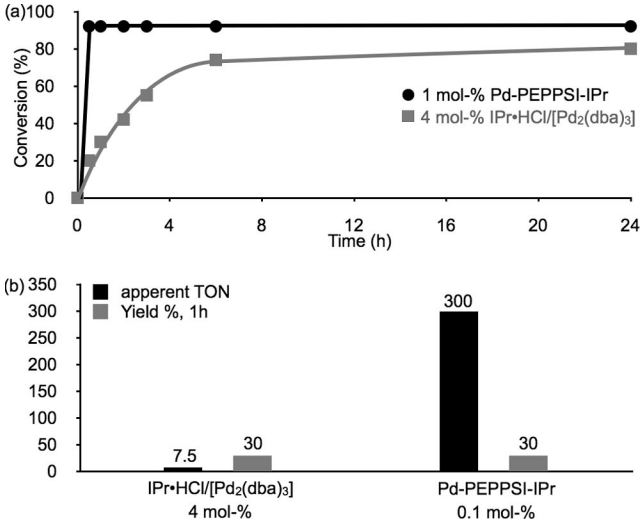


Figure 4. (a) Rate comparison and (b) TON comparison of IPr–Pd^0 prepared in situ from IPr·HCl/[Pd_2(dba)$_3$] or by activation of Pd-PEPPSI-IPr precatalyst in the sp^3–$\mathbf{sp^3}$ Negishi reaction. Substrates and reaction conditions are identical to those that appear in the scheme of Figure 3.

3.3. Effect of LiX Salts on the sp^3–sp^3 Negishi Reaction

The alkylzinc reagents used in the studies carried out up to this point were all prepared by the Rieke protocol.[25] However, enticed by the synthetic ease and reliability of Huo's method,[36] this route was opted for over Reike's method for the preparation of alkylzinc reagents in cross-couplings in the presence of Pd-PEPPSI-IPr.

Intriguingly, initial studies in the Pd-PEPPSI-IPr-catalyzed coupling of 1-bromo-3-phenylpropane with ***n*BuZnBr** revealed a strict dependence on the source of ***n*BuZnBr**, whereby quantitative and 0% yield were obtained by using the Rieke and the Huo protocol, respectively.[12] The mass balance for the latter attempt was entirely 1-bromo-3-phenylpropane, so we reasoned that the lithium halide, a by-product formed in Rieke's method, was a required additive for this reaction. Indeed, quantitative conversion of starting materials into *n*-heptylbenzene was restored upon the addition of LiBr (2.0 equiv.) to Huo's ***n*BuZnBr**. The precise role of additives in transition-metal-mediated cross-couplings remains a topic of interest and conjecture.[37] However, it is generally accepted that additives primarily influence the transmetallation step of the catalytic cycle. Although much work has gone into elucidating the roles of additives in the Suzuki–Miyaura and Stille reactions,[38] significantly less is known about the role of additives in the Negishi reaction. Knochel's[7,28,39] and Oshima's[40] groups found that LiX salts promote transmetallation of organomagnesium and -zinc reagents, perhaps by breaking up polymeric aggregates. Our similar finding prompted us to carry out a titration study in which various stoichiometries of LiBr were doped into the sp^3–$\mathbf{sp^3}$ Negishi cross-coupling (Figure 5).[41] We were intrigued by the finding that the cross-coupling remained dormant until approximately 1.0 equiv. of LiBr (based on ***n*BuZnBr**) was added, at which point an exponential increase in conversion occurred with each successive addition of LiBr (0.1 equiv.) until leveling off in the range of 1.4–2.0 equiv. LiBr. We reason that if the sole purpose of LiBr is to break up polymeric aggregates and/or that the active transmetallating agent is Zn(*n*Bu)Br_2^-, then a substoichiometric quantity of LiBr should suf-

fice. The above finding, however, suggests that a higher-order zincate – of the type $Li_mZn(nBu)Br_3^{(2-m)-}$ – is the active transmetallating agent.

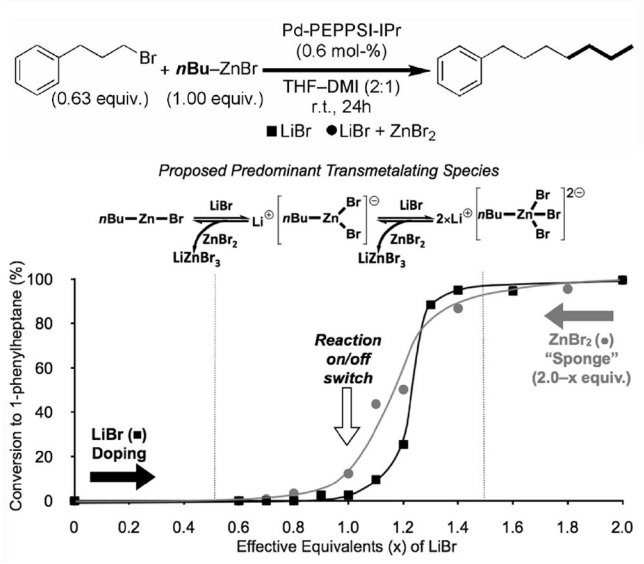


Figure 5. A double titration study in which various stoichiometries of the additives LiBr (■, *x* equiv.) and LiBr plus $ZnBr_2$ (●, 2.0 equiv. LiBr, 2.0 – *x* equiv. $ZnBr_2$) were added to the sp^3–**sp³** Negishi cross-coupling reaction.

Koszinowski and Böhrer recently used anion-mode electrospray ionization (ESI) mass spectrometry to examine mixtures of organozinc(ate) species generated by either (i) LiCl-assisted oxidative addition of Zn^0 into organic halides[42] or (ii) metathesis between organolithium compounds and $ZnCl_2$ in THF.[43] Analysis of a 1:1 mixture of *n*BuLi and $ZnCl_2$ in THF revealed mononuclear $ZnCl_3^-$ and $Zn(nBu)Cl_2^-$ species and polynuclear $Zn_2(nBu)Cl_4^-$ and $LiZn_2(nBu_2)Cl_4^-$ species in significant quantities, alongside smaller amounts of $LiZnCl_4^-$ and $LiZn(nBu)Cl_3^-$. The last species is analogous to $Li_mZn(nBu)Br_3^{(2-m)-}$, the intermediate we postulate as the active transmetallating agent in the sp^3–**sp³** Negishi cross-coupling. Its occurrence in small amounts at a 1:1 stoichiometry of *n*BuLi/$ZnCl_2$ is consistent with the finding that the cross-coupling initiates at a 1:1 ratio of LiBr/*n*BuZnBr. Importantly, it is evident that complex equilibria are operational, and that species comparable to those deduced by Koszinowski and Böhrer are likely to also be present in some relative stoichiometry in our system.

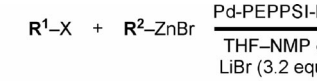
To further probe the role of LiBr in this cross-coupling, we opted to dope in various quantities of $ZnBr_2$ to act as a sponge for LiBr. Given that $ZnBr_2$ is more Lewis-acidic, it should bind Br^- better than *n*BuZnBr. The ability of $ZnBr_2$ to sequester Br^- is known.[44] As the $ZnBr_2$ is doped in, a proportion of LiBr is sequestered away, leaving fewer "effective equivalents" of LiBr in solution (Figure 5, ● data points). A very similar conversion versus effective equivalents of LiBr curve is produced relative to the one wherein LiBr is successively added in the absence of exogenous $ZnBr_2$ (■ data points). This supports the proposal that as LiBr is removed from solution, the concentration of $Li_mZn(nBu)Br_3^{(2-m)-}$ decreases and at or below 1.0 equiv. of the "effective" LiBr threshold, the reaction is switched off.

3.4. Scope of Pd-PEPPSI-IPr in the Negishi Cross-Coupling Reaction

An assessment of the reactivity and generality of Pd-PEPPSI-IPr was carried out through the use of an expanded substrate scope (Tables 2 and 3).[12] Functionalized organozinc and organohalide substrates possessing sp^3 and/or sp^2 hybridization at the reactive C–Zn or C–X centers, respectively, were "mixed and matched" to give the trends presented in Table 2. Alkyl chlorides, bromides, iodides, tosylates and mesylates were compatible electrophiles with both alkyl- and arylzinc reagents. Aryl chlorides, bromides, iodides, and triflates were also compatible in all cross-couplings; however, in contrast to their alkyl counterparts, aryl tosylates and mesylates were inert, providing no trace of their target products.

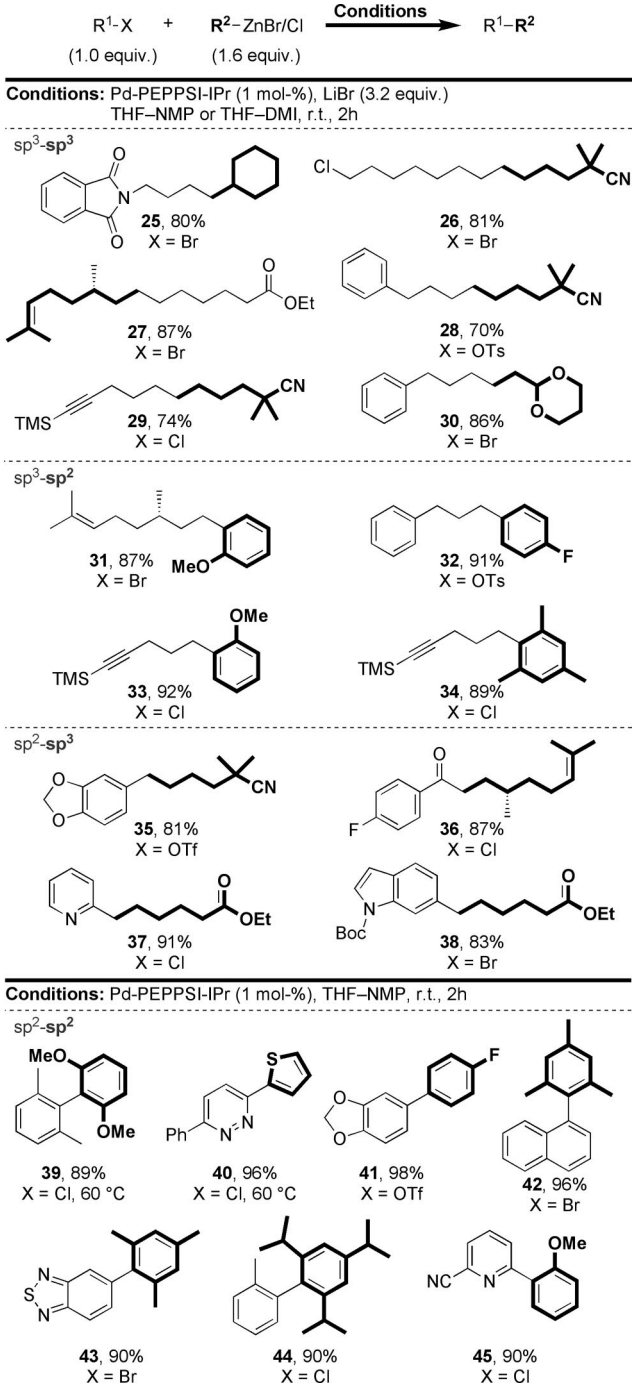
One hypothesis is that that alkyl tosylates and mesylates are converted in situ into their more reactive alkyl derivatives by virtue of the presence of LiBr/Cl and/or $ZnBr_2$/Cl_2, a process that is not available to aryl pseudohalides. Additives and solvent polarity had dramatic effects on select cross-couplings. Whereas alkylzinc reagents required the addition of a twofold excess of LiBr/Cl, arylzinc reagents did not. This is an artefact of the preparation of the organozinc reagent, as a stoichiometric quantity of MgX_2 is generated in the preparation of arylzinc halides, which circumvents the need for LiX (vide supra). In general, when arylzinc reagents were coupled, a less polar solvent media was required relative to that required for alkylzinc reagents. Surprisingly, a solvent polarity switch was found to be crucial to the success of the reaction when alkyl or aryl bromides were coupled in three of the four hybridization mix/match settings (Table 2, bolded entries). We remain uncer-

Table 2. Substrate compatibility, solvent ratio and additive table for the Negishi reaction catalyzed by Pd-PEPPSI-IPr.



		R² = Alkylzinc LiBr Req'd		Arylzinc LiBr NOT Req'd	
R¹	X	Compatible	THF–DMI	Compatible	THF–NMP
Alkyl	Cl	✓	1 : 3	✓	2 : 1
	Br	✓	**2 : 1**	✓	**1 : 2**
	I	✓	1 : 3	✓	2 : 1
	OTs	✓	1 : 3	✓	2 : 1
	OMs	✓	1 : 3	✓	2 : 1
Aryl	Cl	✓	1 : 2	✓	2 : 1
	Br	✓	**2 : 1**	✓	2 : 1
	I	✓	1 : 2	✓	2 : 1
	OTs	✘	1 : 2	✘	2 : 1
	OMs	✘	1 : 2	✘	2 : 1
	OTf	✓	1 : 2	✓	2 : 1

Table 3. Selected results showcasing the substrate scope of the Negishi reaction in the presence of the precatalyst Pd-PEPPSI-IPr.

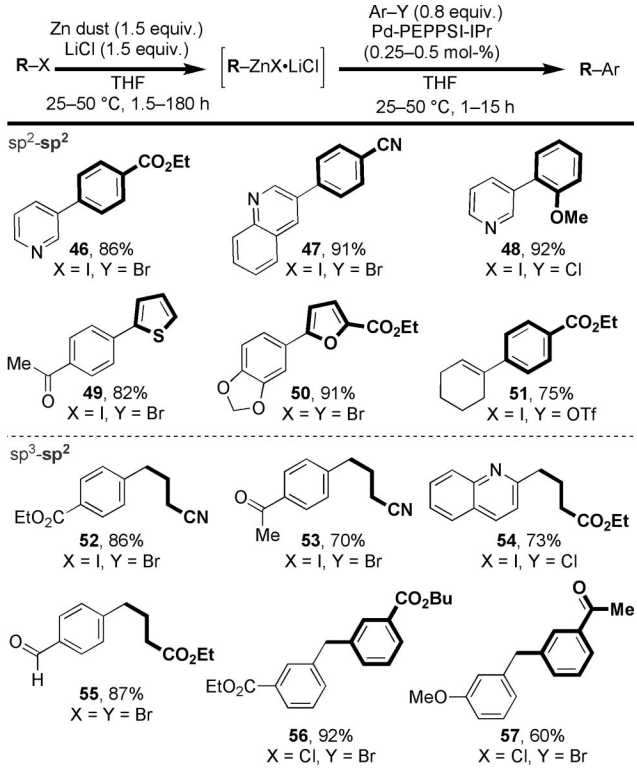


tain as to what consequence this required solvent polarity switch has for the mechanism of this particular cross-coupling reaction.

A wide range of functionalized substrates, leading to cross-coupled products **25**–**45** (Table 3), was well-tolerated under the developed reaction conditions. Functional groups including imides (present in **25**), esters (present in **27**, **37**, **38**), and nitriles (present in **26**, **28**, **29**, **35**, **45**) were inert to the organozinc reagents and reaction conditions, rendering these cross-couplings chemoselective. Acetal (present in **30**, **35**, **41**), trimethylsilyl (present in **29**, **33**, **34**), and *tert*-butoxycarbonyl (present in **38**) protecting groups remained intact. Control studies revealed that aryl acid chlorides marginally reacted with alkylzinc reagents in the absence of Pd but were cleanly cross-coupled in the presence of Pd-PEPPSI-IPr to provide their corresponding ketones (see **38**) in high yields. Heteroaryls including substituted pyridines (**37** and **45**), indoles (**38**), pyridazines (**40**), and 2,1,3-benzothiadiazoles (piazthioles, **43**) were also well-tolerated. In terms of sterics, Pd-PEPPSI-IPr was capable of coupling substrates to provide tri-*ortho*-substituted biaryls **42** and **44** and single tetra-*ortho*-substituted derivative **39**.

Knochel and co-workers developed a one-pot Negishi cross-coupling reaction (Table 4) in which the organozinc reagent is prepared in situ from the corresponding (hetero)aryl, alkyl and benzylic halides by using Zn dust and LiCl.[45] In the presence of Pd-PEPPSI-IPr, a range of functionalized aryl bromides, chlorides, and triflates were coupled smoothly in good-to-excellent yields (providing **46**–**57**). Esters (present in **46**, **50**–**52**, **54**–**56**), nitriles (present in **47**), methyl ketones (present in **49**, **53**, **57**), and aldehydes (present in **55**) were among the functional groups tolerated. Moreover, Pd-PEPPSI-IPr was found to be more efficient for these cross-couplings than $Pd(PPh_3)_4$ – arguably the most widely used homogeneous catalysts for cross-couplings – requiring shorter reaction times to achieve higher yields.

Table 4. Selected results for one-pot cross-couplings between aryl- and alkylzinc reagents prepared in situ and aryl halides or pseudohalides in the presence of Pd-PEPPSI-IPr.



3.5. Pd-PEPPSI-IPent in the Negishi Cross-Coupling Reaction

The recently disclosed second-generation PEPPSI precatalyst Pd-PEPPSI-IPent has been shown to be better suited to the coupling of sterically challenging substrates in the Suzuki–Miyaura[16] and Stille[46] reactions. This trend follows for the Negishi reaction,[15] where in a head-to-head competition experiment (Figure 6), Pd-PEPPSI-IPent outperformed Pd-PEPPSI-IPr, providing quantitative conversion into tetra-*ortho*-substituted biaryl **61** in under 5 h at room temperature. Pd-PEPPSI-IPr was much more sluggish but steadily turned over product during the course of the study. A more detailed analysis of Pd-PEPPSI-IPent versus Pd-PEPPSI-IPr, in addition to the well-tailored dialkylbiaryl phosphane ligands **62** and **63** [Pd source = $Pd_2(dba)_3$], was carried out (Figure 7). Each reaction in the study 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. As demonstrated in Figure 7, Pd-PEPPSI-IPent outperforms the IPr analogue. Turnover by all catalysts was achieved by heating the reaction mixtures to 70 °C in the THF/NMP cosolvent system (turnover likely begins below this temperature), wherein Pd-PEPPSI-IPr, **62** and **63** provided similar results. The desired product was formed in approximately 45–55% conversion, with homocoupling of the aryl bromide constituting the mass balance of the electrophile. The homocoupled aryl bromide presumably forms through disproportionation of the mesitylzinc bromide (**59**) with 2-bromo-*m*-xylene (**60**), a process likely to be accelerated with heating. The equilibrium of this disproportionation provides two arylzinc reagents that are equally suited for transmetallation with the oxidative addition adduct, Xy–Pd(L)–Br. Omitting NMP yields conditions that have been reported to be optimal for **62** and **63**.[47] However, this had a detrimental effect on this cross-coupling reaction, where the desired product yields dropped across the board. Again, Pd-PEPPSI-IPr, **62**, and **63** performed similarly. The extent of the disproportionation appears to be attenuated, as unreacted 2-bromo-*m*-xylene (**60**) is present. However, this is still an operating pathway as the mass balance of the electrophile is accounted for in homocoupled byproduct **64** and *m*-xylene (**66**). The presence of starting material and intermediates, along with the lower yields of **61** and **64**, suggests that the catalytic cycle is slowed for each of these catalyst systems relative to that when NMP is employed as a co-solvent. Thus, solvent polarity appears to affect the proficiency of metal exchange processes, including (1) disproportionation of the organometallic reagent and/or (2) transmetallation with Pd, which serves as the bottleneck for the catalytic cycle.

Pd-PEPPSI-IPent, however, fairs much better, and transmetallation with the active catalyst appears to be less dependent on solvent polarity. It cannot be ruled out that oxidative addition is also affected by solvent polarity. When Pd-PEPPSI-IPr, **62** or **63** was used, homocoupled organozinc **65** (approximately 10% for each case) was also formed. The formation of this byproduct may be accounted for by a second transmetallation step that Lei, Wu and co-workers have documented,[48] in which transmetallation of $\mathbf{Ar^2}$ZnX with Ar^1–Pd–$\mathbf{Ar^2}$ (Ar^1 comes from the electrophile) competes with reductive elimination of the latter species to yield $\mathbf{Ar^2}$–Pd–$\mathbf{Ar^2}$.

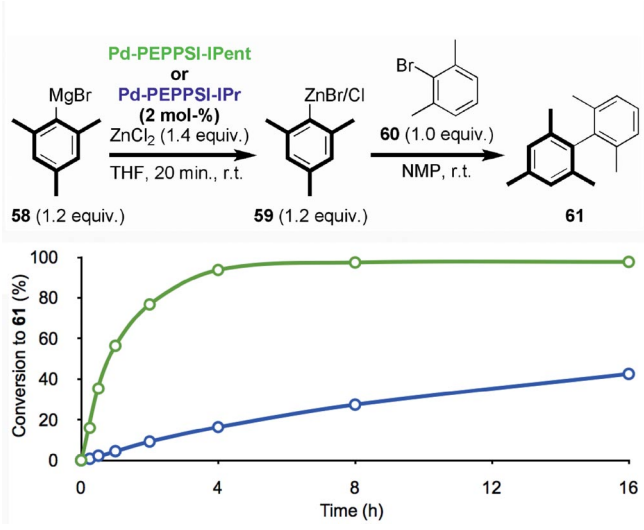


Figure 6. A comparative rate study of Pd-PEPPSI-IPent and Pd-PEPPSI-IPr in the Negishi cross-coupling of sterically encumbered substrates.

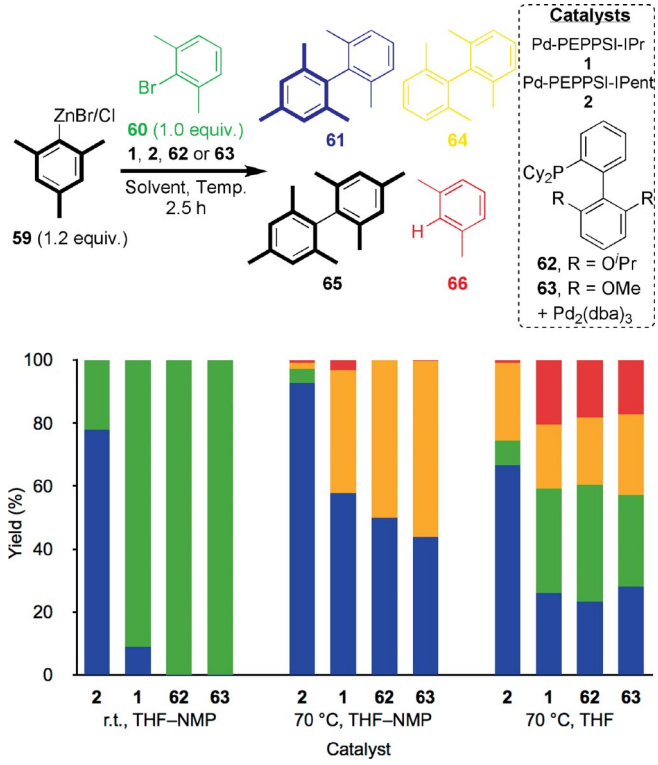
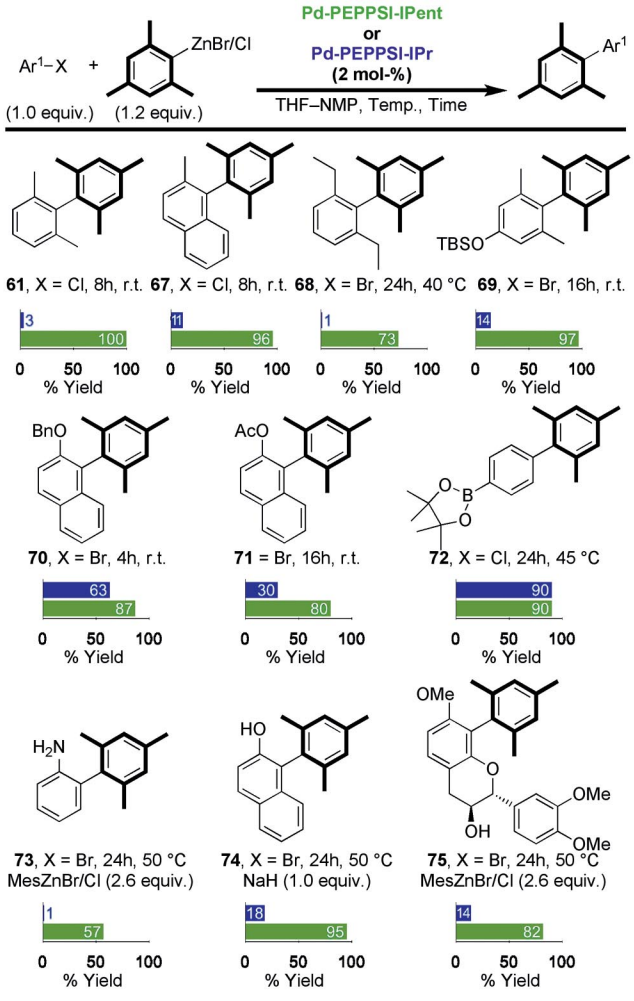


Figure 7. Solvent and temperature effects on the product distribution in the Negishi cross-coupling of sterically hindered substrates with the aid of NHC- and phosphane-ligated catalysts.

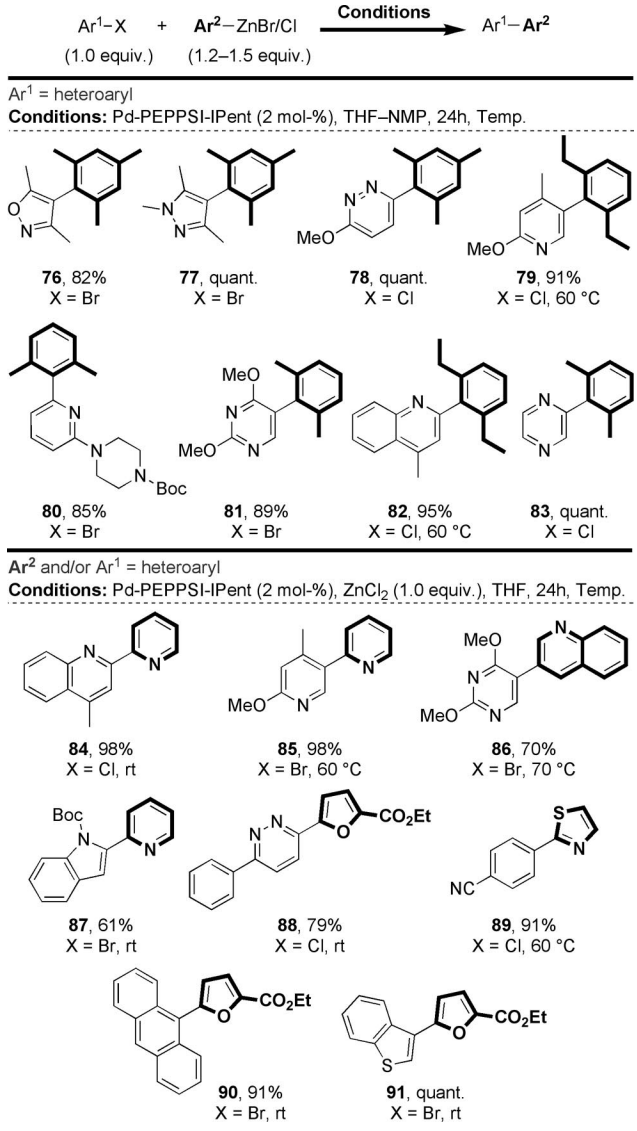
Pd-PEPPSI-IPent was evaluated more generally in its ability to couple electrophiles possessing varied steric bulk with **Mes**ZnBr/Cl (Table 5). In all cases in which the electrophile possesses sterics *ortho* to the oxidative addition site, the IPent analogue considerably outperformed the IPr analogue (leading to **61** and **67**–**75**). Unmasked anilines and alcohols (leading to **73**–**75**) were tolerated; however, an excess amount of **Mes**ZnBr/Cl or NaH was required as a proton sponge.

Table 5. Substrate study for the sp^2–$\mathbf{sp^2}$ Negishi cross-coupling of sterically hindered electrophiles with **Mes**ZnBr/Cl in the presence of Pd-PEPPSI-IPent and Pd-PEPPSI-IPr.



Pd-PEPPSI-IPent was also evaluated in terms of its ability to couple heteroaryl halides with heteroarylzinc halides (Table 6). The reaction was found to be quite general, and tolerated a wide range of heteroaryls, leading to cross-coupled products **76**–**91**, containing pyrazine, quinoline, isoxazole, pyrazole, pyrimidine, pyridazine, pyridine, indole, thiophene, furan, and thiazole frameworks. The majority of couplings were carried out at room temperature, with a select few cross-couplings requiring mild heating. When heteroarylzinc halides were used, omission of NMP proved beneficial, as did the addition of $ZnCl_2$ (1 equiv.). Overall, Pd-PEPPSI-IPent is a general and efficient catalyst for Negishi cross-coupling reactions of both sterically hindered and heterocyclic substrates.

Table 6. Substrate study for the sp^2–$\mathbf{sp^2}$ Negishi cross-coupling of (hetero)aryl halides with arylzinc halides (top half) and heteroarylzinc halides (bottom half).



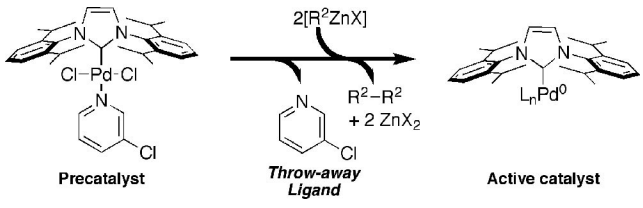
4. Mechanistic Considerations

The precise mechanism of a particular cross-coupling reaction depends on many variables, which include organometallic and ligand structure, additives, solvent, temperature and the transition metal. For example, both Pd and Ni are routinely used as effective catalysts in Negishi cross-couplings, but they operate through different pathways. Pd-mediated couplings occur by the generally accepted oxidative addition (OA), transmetallation (TM) and reductive elimination (RE) sequence, through a Pd^0/Pd^{II} redox process.[37] Ni-mediated couplings, although they also contain these three basic steps, operate under a Ni^I/Ni^{III} redox cycle

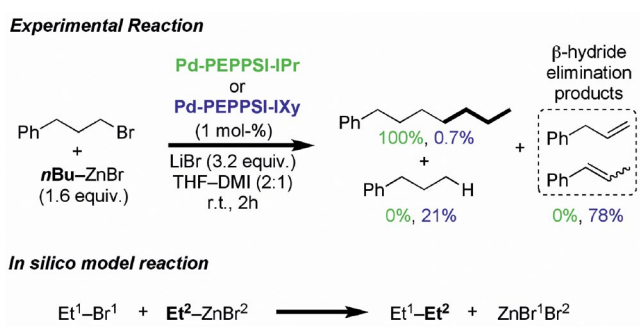
that initiates and propagates through a radical chain mechanism.[49] Cardenas and co-workers have investigated this mechanism in some detail, building on the earlier work of Knochi,[50] and a recent review nicely summarizes the scope and mechanism of the Ni-catalyzed Negishi cross-coupling reaction.[51] Alternatively, Casares and Espinet have shown that ZnRX and ZnR_2 undergo TM with *trans*-[PdRfCl(PPh_3)$_2$] (R_f = 3,5-dichloro-2,4,6-trifluorophenyl) to give the *cis*- and *trans*-[PdRfMe(PPh_3)$_2$] complexes, respectively.[52] Only the *cis* isomer is capable of RE, and isomerization of the *trans* isomer must occur before the catalytic cycle can resume. This isomerization was found to be ligand-dependent and slow, permitting alternative side processes to take over in place of RE. As such, the structure of the TM species can have drastic effects on the outcome of the cross-coupling.

A number of cross-couplings are plagued by homocoupling of the electrophile and/or nucleophile and reduction of the organohalide. These side reactions are ligand-dependent, but little investigation has gone into elucidating the mechanism by which these byproducts form. Wu and Lei have recently completed an experimental and theoretical study that sheds light on these processes.[48] The cross-couplings were all carried out with $PdCl_2$(dppf) as the catalyst. They found that a second TM step competes with RE, in which Ar^1–Pd–$\mathbf{Ar^2}$ reacts with $\mathbf{Ar^2}$ZnX to give $\mathbf{Ar^2}$–Pd–$\mathbf{Ar^2}$ and Ar^1ZnX. These last two species account for the formation of homocoupled product and reduction of the aryl halide. This second TM step is highly dependent on the structures both of Ar^1 and of Ar^2, and proceeds most efficiently when Ar^1 has an *ortho* substituent.

We were interested in more thoroughly defining the contributions from NHCs in Pd-mediated cross-couplings. Moreover, there are no computational studies on either the complete catalytic cycle of any Pd-mediated sp^3–**sp^3** coupling or the Pd-mediated Negishi reaction. To fill this void, nontruncated models were used in a density functional theory [DFT, supported by atoms-in-molecules (AIM) analyses] investigation of the sp^3–**sp^3** Negishi reaction catalyzed by NHC–Pd complexes.[53] The active catalytic species both for the catalyst generated in situ and for Pd-PEPPSI-IPr is the monoligated NHC–Pd^0 species. Pd-PEPPSI precatalysts are activated in situ by shedding of the throwaway ligand and a double TM and RE sequence (Scheme 1). Both IPr–Pd and IXy–Pd were experimentally and computationally analyzed, as the latter species is a poor catalyst for the sp^3–**sp^3** Negishi reaction and leads predominately to the β-hydride elimination product and reduction of the alkyl halide (Scheme 2). As there is no difference in the electronic contributions from these two NHCs,[10,14,35] sterics is the contributing factor for the varied catalyst performance. For both catalysts, it was found that TM is the rate-determining step of the catalytic cycle. Thus, both systems are sufficiently electron-rich to readily undergo OA, and as such, variation in proficiencies towards OA is not the source of the observed differences in catalyst performance. In the IPr–Pd analogue, four weak C–H···Pd agostic interactions (Figure 8), originating from the isopropyl substituents on the aryl fragments of the NHC, are present. These interactions, which contribute entropically to the various stages of the catalytic cycle, are (i) absent in the IXy–Pd model, (ii) amenable throughout the catalytic cycle, and (iii) primarily responsible for the marked differences in catalyst performance. For example, these agostic interactions coordinatively saturate Pd in the OA adduct, and thus curtail β-hydride elimination. The success of the reaction also depends on the approach of Et^1Br^1 to the NHC–Pd^0 species. The "steric wall" created by the IPr ligand guides the electrophile into the coordination sphere of Pd through a side-*syn* approach (in which Br^1 ends up *syn* to the NHC). On the other hand, approach from the front places Br^1 *anti* to the NHC, leading to an energetically favorable OA adduct, due to Coulombic repulsion between the NHC and Br^1. A front-*anti* approach is favored by 10.2 kJ mol^{-1} over a top-*syn* approach for IXy–Pd, so the OA adduct falls into a stable "*anti*-trap" from which TM cannot occur. Effectively, the catalytic cycle stalls, allowing deleterious side reactions, such as β-hydride elimination, to take over. In the



Scheme 1. Proposed activation of Pd-PEPPSI complexes.



Scheme 2. A comparison of Pd-PEPPSI-IPr and Pd-PEPPSI-IXy in the sp^3–**sp^3** Negishi cross-coupling reaction (top) and the in silico model reaction (bottom).

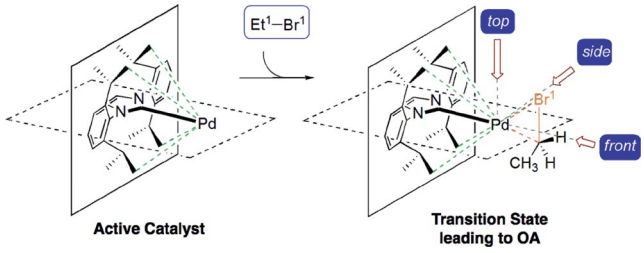


Figure 8. The approach of Et^1Br^1 to the NHC–Pd^0 species can occur from the top, side or front of the NHC–Pd bond. The green dotted lines indicate H···Pd interactions. In this case, the electrophile approaches from the side and Br^1 ends up *syn* to Pd. See text for a more detailed analysis.

case of IPr–Pd, the front-*anti* transition state lies higher on the energy diagram profile, and so avoids this "*anti*-trap". Instead, a side-*syn* approach is energetically favored, and the resulting OA adduct is destabilized due to the agostic IPr···Pd interactions, facilitating TM. The third piece of information gleaned from this study was that $ZnBr_2$ remains in the coordination sphere of IPr–Pd and is shed after RE. This produces greater congestion in the steric environment around Pd after TM and, therefore, aids in RE by pushing the two alkyl substituents closer together.

5. Conclusions

A review of Pd-PEPPSI complexes in the Negishi reaction has been presented. Pd-PEPPSI-IPr and Pd-PEPPSI-IPent are the two most active precatalysts, with the latter being better suited for the cross-coupling of sterically hindered and heterocycle-containing substrates. These precatalysts have high turnover numbers relative to those of the NHC–Pd species formed through an in situ protocol (IPr·HCl/[$Pd_2(dba)_3$]), illustrating the inefficiency involved in forming the active catalyst by the latter approach. In the sp^3–**sp³** Negishi cross-coupling reaction, it was found that LiBr is an essential additive. A titration study revealed that more than 1.0 equiv. of LiBr was required for adequate turnover of the catalytic cycle, leading to the hypothesis that $Li_mZn(n\text{Bu})Br_3^{(2-m)-}$ is the active transmetalation species. Computational studies revealed that (i) transmetallation is the rate-determining step, (ii) four weak C–H···Pd agostic interactions present in IPr–Pd are primarily responsible for the improved catalyst performance relative to the IXy–Pd analogue, and (iii) that $ZnBr_2$ remains in the coordination sphere of Pd and is not shed until after reductive elimination.

[1] a) A. O. King, N. Okukado, E.-i. Negishi, *J. Chem. Soc., Chem. Commun.* **1977**, 683–684; b) E.-i. Negishi, A. O. King, N. Okukado, *J. Org. Chem.* **1977**, *42*, 1821–1823.

[2] E.-i. Negishi in *Aspects of Mechanism and Organometallic Chemistry* (Ed.: J. H. Brewster), Plenum, New York, **1978**, p. 285.

[3] a) A. Suzuki, *J. Organomet. Chem.* **1999**, *576*, 147–168; b) N. Miyaura, *Top. Curr. Chem.* **2002**, *219*, 11–59; c) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457–2483.

[4] E.-i. Negishi, *J. Organomet. Chem.* **2002**, *653*, 34–40.

[5] S. Reformatsky, *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 1210–1211.

[6] M. W. Rathke, *Org. React.* **1975**, *22*, 423–458.

[7] A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 6040–6044.

[8] a) M. Uchiyama, T. Furuyama, M. Kobayashi, Y. Matsumoto, K. Tanaka, *J. Am. Chem. Soc.* **2006**, *128*, 8404–8405; b) T. Furuyama, M. Yonehara, S. Arimoto, M. Kobayashi, Y. Matsumoto, M. Uchiyama, *Chem. Eur. J.* **2008**, *14*, 10348–10356.

[9] N. Hadei, E. A. B. Kantchev, C. J. O'Brien, M. G. Organ, *Org. Lett.* **2005**, *7*, 3805–3807; N. Hadei, E. A. B. Kantchev, C. J. O'Brien, M. G. Organ, *J. Org. Chem.* **2005**, *70*, 8503–8507.

[10] C. J. O'Brien, E. A. B. Kantchev, G. A. Chass, N. Hadei, A. C. Hopkinson, M. G. Organ, D. H. Setiadi, T.-H. Tang, D.-C. Fang, *Tetrahedron* **2005**, *61*, 9723–9735.

[11] C. J. O'Brien, E. A. B. Kantchev, C. Valente, N. Hadei, G. A. Chass, A. Lough, A. C. Hopkinson, M. G. Organ, *Chem. Eur. J.* **2006**, *12*, 4743–4748.

[12] M. G. Organ, S. Avola, I. Dubovyk, N. Hadei, E. A. B. Kantchev, C. J. O'Brien, C. Valente, *Chem. Eur. J.* **2006**, *12*, 4749–4755.

[13] a) M. G. Organ, M. Abdel-Hadi, S. Avola, N. Hadei, J. Nasielski, C. J. O'Brien, C. Valente, *Chem. Eur. J.* **2007**, *13*, 150–157; b) M. G. Organ, M. Abdel-Hadi, S. Avola, I. Dubovyk, N. Hadei, E. A. B. Kantchev, C. J. O'Brien, C. Valente, *Chem. Eur. J.* **2008**, *14*, 2443–2452; c) C. Valente, S. Baglione, D. Candito, C. J. O'Brien, M. G. Organ, *Chem. Commun.* **2008**, 735–737.

[14] M. G. Organ, G. A. Chass, D.-C. Fang, A. C. Hopkinson, C. Valente, *Synthesis* **2008**, 2776–2797.

[15] S. Çalimsiz, M. Sayah, D. Mallik, M. G. Organ, *Angew. Chem. Int. Ed.* **2010**, *49*, 2014–2017.

[16] M. G. Organ, S. Çalimsiz, M. Sayah, K. H. Hoi, A. J. Lough, *Angew. Chem. Int. Ed.* **2009**, *48*, 2383–2387.

[17] E. Frankland, *Justus Liebigs Ann. Chem.* **1849**, *71*, 171–213.

[18] a) R. L. Shriner, *Org. React.* **1942**, *1*, 1–37; b) J. W. Cornforth, R. H. Cornforth, G. Popjak, I. Y. Gore, *Biochem. J.* **1958**, *69*, 146–155.

[19] a) E. Erdik, *Tetrahedron* **1987**, *43*, 2203–2212; b) P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390–2392.

[20] a) J. K. Gawronski, *Tetrahedron Lett.* **1984**, *25*, 2605–2608; b) G. Picotin, P. Miginiac, *J. Org. Chem.* **1987**, *52*, 4796–4798.

[21] a) B.-H. Han, P. Boudjouk, *J. Org. Chem.* **1982**, *47*, 5030–5032; b) R. F. Abdulla, *Aldrichimica Acta* **1988**, *21*, 31–42.

[22] a) T. O. Murdock, K. J. Klabunde, *J. Org. Chem.* **1976**, *41*, 1076–1077; b) K. J. Klabunde, T. O. Murdock, *J. Org. Chem.* **1979**, *44*, 3901–3908.

[23] H. Stadtmüller, B. Greve, K. Lennick, A. Chair, P. Knochel, *Synthesis* **1995**, 69–72.

[24] L. Zhu, R. M. Wehmeyer, R. D. Rieke, *J. Org. Chem.* **1991**, *56*, 1445–1453.

[25] R. D. Rieke, M. V. Hanson, J. D. Brown, Q. J. Niu, *J. Org. Chem.* **1996**, *61*, 2726–2730.

[26] C. Jubert, P. Knochel, *J. Org. Chem.* **1992**, *57*, 5425–5431.

[27] S. Huo, *Org. Lett.* **2003**, *5*, 423–425.

[28] A. Metzger, M. A. Schade, P. Knochel, *Org. Lett.* **2008**, *10*, 1107–1110.

[29] A. Metzger, F. M. Piller, P. Knochel, *Chem. Commun.* **2008**, 5824–5826.

[30] a) V. Snieckus, *Chem. Rev.* **1990**, *90*, 879–933; b) J. Clayden, C. C. Stimson, M. Keenan, *Chem. Commun.* **2006**, 1393–1394; c) M. Schlosser, *Angew. Chem. Int. Ed.* **2005**, *44*, 376–393; d) K. W. Henderson, W. J. Kerr, *Chem. Eur. J.* **2001**, *7*, 3431–3437; e) A. Turck, N. Plé, F. Mongin, G. Quéguiner, *Tetrahedron* **2001**, *57*, 4489–4505; f) F. Mongin, G. Quéguiner, *Tetrahedron* **2001**, *57*, 4059–4090; g) F. Levoux, P. Jeschke, M. Schlosser, *Chem. Rev.* **2005**, *105*, 827–856; h) M. Kauch, D. Hoppe, *Synthesis* **2006**, 1578–1589; i) W. Clegg, S. H. Dale, E. Hevia, G. W. Honeyman, R. E. Mulvey, *Angew. Chem. Int. Ed.* **2006**, *45*, 2370–2374; j) D. M. Hodgson, S. M. Miles, *Angew. Chem. Int. Ed.* **2006**, *45*, 935–938; k) M. Yus, F. Foubelo in *Handbook of Functionalized, Organometallics Vol. 1* (Ed.: P. Knochel), Wiley-VCH, Weinheim, **2005**.

[31] a) Y. Kondo, H. Shilai, M. Uchiyama, T. Sakamoto, *J. Am. Chem. Soc.* **1999**, *121*, 3539–3540; b) T. Imahori, M. Uchiyama, Y. Kondo, *Chem. Commun.* **2001**, 2450–2451; c) P. F. H. Schwab, F. Fleischer, J. Michl, *J. Org. Chem.* **2002**, *67*, 443–449; d) M. Uchiyama, T. Miyoshi, Y. Kajihara, T. Sakamoto, Y. Otani, T. Ohwada, Y. Kondo, *J. Am. Chem. Soc.* **2002**, *124*, 8514–8515.

[32] a) S. H. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7685–7688; b) M. Mosrin, P. Knochel, *Chem. Eur. J.* **2009**, *15*, 1468–1477.

[33] M. Mosrin, P. Knochel, *Org. Lett.* **2009**, *11*, 1837–1840.

[34] M. Mosrin, G. Monzon, T. Bresser, P. Knochel, *Chem. Commun.* **2009**, 5615–5617.

[35] a) N. Hadei, E. A. B. Kantchev, C. J. O'Brien, M. G. Organ, *Org. Lett.* **2005**, *7*, 1991–1994; b) A. R. Chianese, X. Li, M. C.

Janzen, J. W. Faller, R. H. Crabtree, *Organometallics* **2003**, *22*, 1663–1667; c) R. Dorta, E. D. Stevens, N. M. Scott, C. Costabile, L. Cavallo, C. D. Hoff, S. P. Nolan, *J. Am. Chem. Soc.* **2005**, *127*, 2485–2495.

[36] S. Hou, *Org. Lett.* **2003**, *5*, 423–425.

[37] E.-i. Negishi in *Handbook of Organopalladium Chemistry for Organic Synthesis*, Wiley, New York, **2002**.

[38] a) K. Matos, J. A. Soderquist, *J. Org. Chem.* **1998**, *63*, 461–470; b) N. Miyaura, *J. Organomet. Chem.* **2002**, *653*, 54–57; c) V. Farina, V. Krishnamurthy, W. J. Scott, *Org. React.* **1997**, *50*, 1–652.

[39] a) H. Ren, G. Dunet, P. Mayer, P. Knochel, *J. Am. Chem. Soc.* **2007**, *129*, 5376–5377; b) N. Boudet, S. Sase, P. Sinha, C.-Y. Liu, A. Krasovskiy, P. Knochel, *J. Am. Chem. Soc.* **2007**, *129*, 12358–12359; c) A. Krasovskiy, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 3333–3336.

[40] H. Ochiai, M. Jang, K. Hirano, H. Yorimitsu, K. Oshima, *Org. Lett.* **2008**, *10*, 2681–2683.

[41] G. T. Achonduh, N. Hadei, C. Valente, S. Avola, C. J. O'Brien, M. G. Organ, *Chem. Commun.* **2010**, *46*, 4109–4111.

[42] K. Koszinowski, P. Böhrer, *Organometallics* **2009**, *28*, 100–110.

[43] K. Koszinowski, P. Böhrer, *Organometallics* **2009**, *28*, 771–779.

[44] T. J. Anderson, D. A. Vicic, *Organometallics* **2004**, *23*, 623–625.

[45] S. Sase, M. Jaric, A. Metzger, V. Malakhov, P. Knochel, *J. Org. Chem.* **2008**, *73*, 7380–7382.

[46] M. Dowlut, D. Mallik, M. G. Organ, *Chem. Eur. J.* **2010**, *16*, 4279–4283.

[47] J. E. Milne, S. L. Buchwald, *J. Am. Chem. Soc.* **2004**, *126*, 13028–13032.

[48] Q. Liu, Y. Lan, J. Liu, G. Li, Y.-D. Wu, A. Lei, *J. Am. Chem. Soc.* **2009**, *131*, 10201–10210.

[49] a) V. B. Phapale, M. Guisán-Ceinos, E. Buñuel, D. J. Cárdenas, *Chem. Eur. J.* **2009**, *15*, 12681–12688; b) H. Gong, M. R. Gagné, *J. Am. Chem. Soc.* **2008**, *130*, 12177–12183; c) X. Lin, D. L. Phillips, *J. Org. Chem.* **2008**, *73*, 3680–3688; d) V. B. Phapale, E. Buñuel, M. Garcia-Iglesias, D. J. Cárdenas, *Angew. Chem. Int. Ed.* **2007**, *46*, 8790–8795.

[50] J. Knochi, *Pure Appl. Chem.* **1980**, *52*, 571–605.

[51] V. B. Phapale, D. J. Cárdenas, *Chem. Soc. Rev.* **2009**, *38*, 1598–1607.

[52] J. A. Casares, P. Espinet, B. Fuentes, G. Salas, *J. Am. Chem. Soc.* **2007**, *129*, 3508–3509.

[53] G. A. Chass, C. J. O'Brien, N. Hadei, E. A. B. Kantchev, W.-H. Mu, D.-C. Fang, A. C. Hopkinson, I. G. Csizmadia, M. G. Organ, *Chem. Eur. J.* **2009**, *15*, 4281–4288.

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