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Negishi cross-coupling of secondary alkylzinc halides with aryl/heteroaryl halides using Pd–PEPPSI–IPent†

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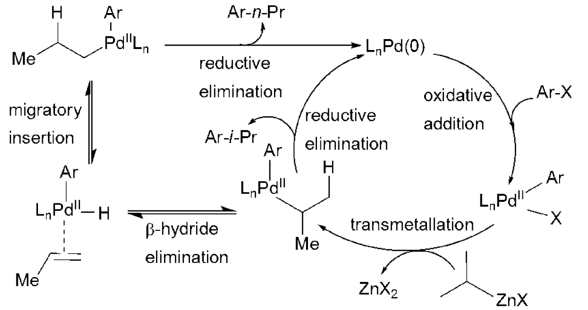
Pd–PEPPSI–IPent has proven to be an excellent catalyst for the Negishi cross-coupling reaction of secondary alkylzinc reagents with a wide variety of aryl/heteroaryl halides. Importantly, β-hydride elimination/migratory insertion of the organometallic leading to the production of isomeric coupling products has been significantly reduced using the highly-hindered Ipent ligand.

Transition metal-catalyzed cross-coupling has seen significant advances in the coupling of sp, sp^2 and sp^3-hybdridized carbon nucleophiles with alkyl, aryl or alkenyl electrophiles.[1] Among these couplings, one of the most challenging remains those between Csp^2 and secondary Csp^3 centres.[2] 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.[3,4] On the other hand, only a handful of studies have been published relating to the analogous cross-coupling of secondary Csp^3-hybridized organometallics with aryl halides. One of the major difficulties in this transformation results from the undesired β-hydride elimination/migratory insertion sequence that competes with reductive elimination leading to isomerised coupling products (Scheme 1). To suppress this isomerisation, the rate of reductive elimination, relative to β-hydride elimination, should be enhanced as much as possible. Several research groups have addressed this issue by employing catalysts containing sterically-bulky phosphine ligands. In 1972 and 1984, Kumada/Tamao and



Scheme 1 Mechanism for the transition metal-catalyzed Negishi cross-coupling of iso-propylzinc halide with an aryl halide.

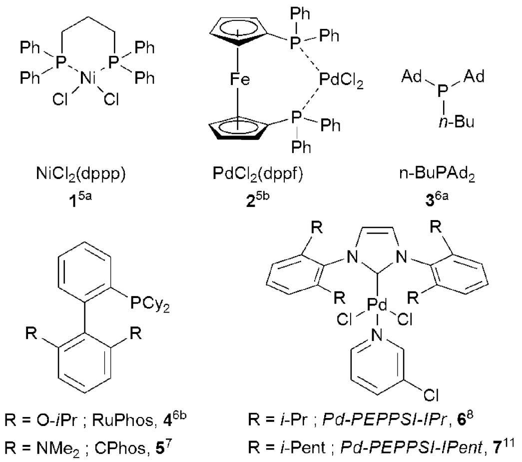
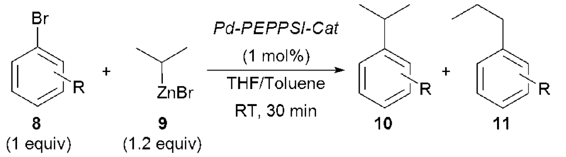


Fig. 1 Previously employed ligands in metal-catalyzed cross-coupling reactions of secondary Csp^3 hybridized organometallics and Pd–PEPPSI complexes.

Table 1 Negishi cross-coupling of isopropylzinc bromide with arylbromides



Entry	Aryl bromide	Catalyst	Yield[a]	**10 : 11**
a	R = 4-CN	**6**	85	3 : 1
		7	92	27 : 1
b	R = 4-CHO	**6**	64	6 : 1
		7	78	39 : 1
c	R = 4-COCH$_3$	**6**	99	6 : 1
		7	98	30 : 1
d	R = 4-CO$_2$CH$_3$	**6**	83	5 : 1
		7	99	40 : 1
e	R = 4-OCH$_3$	**6**	89	2.5 : 1
		7	95	33 : 1
f	R = 3-CN	**6**	77	1 : 1.4
		7	84	11 : 1
g	R = 3-CHO	**6**	78	1.6 : 1
		7	71	22 : 1
h	R = 3-OCH$_3$	**6**	31	3.5 : 1
		7	57	34 : 1
i	R = 2-CN	**6**	99	1 : 8
		7	80	2.4 : 1
j	R = 2-OCH$_3$	**6**	99	1 : 9
		7	46	2 : 1

[a] Isolated yields of mixtures of *i*-Pr and *n*-Pr products; average of two runs.

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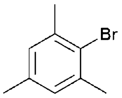
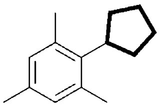
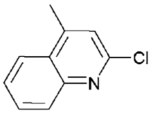
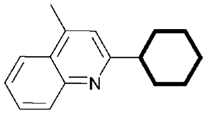
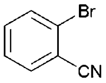
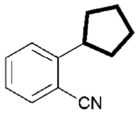
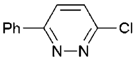
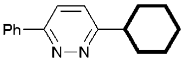
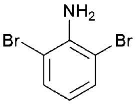
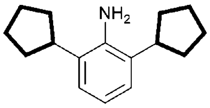
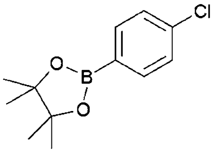
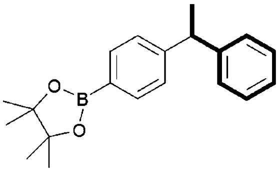
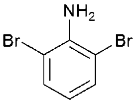
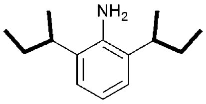
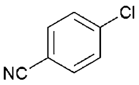
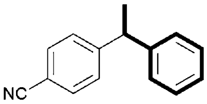
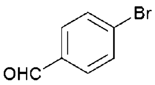
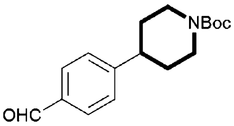
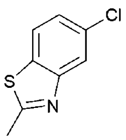
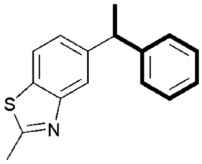
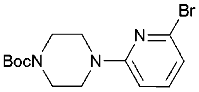
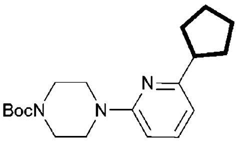
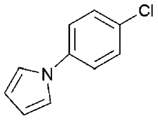
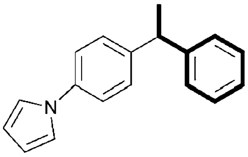
Hayashi, respectively, reported that NiCl$_2$(dppp) (**1**, Fig. 1) and PdCl$_2$(dppf) (**2**, Fig. 1) can couple secondary alkyl Grignards with a limited array of aryl and vinyl halides.[5] In 2008, Molander and Hoogenband independently reported the Suzuki–Miyaura coupling of secondary alkyltrifluoroborates with aryl halides in the presence of *n*-BuPAd$_2$ (**3**, Fig. 1) and RuPhos (**4**, Fig. 1), respectively.[6] These publications described efficient coupling of cyclic alkyltrifluoroborates, although when linear alkyltrifluoroborates were used the ratio of desired- (non-isomerised) to isomerised-product was moderate and functional group incompatibilities surfaced. Recently, Han and Buchwald published a report detailing the Pd-catalysed coupling of secondary alkylzinc halides with aryl bromides and activated aryl chlorides using the bulky CPhos ligand (**5**, Fig. 1).[7] Under their optimal conditions good ratios of secondary to primary alkyl couplings with several substrates were observed although the β-hydride elimination pathway could not be fully eliminated.

We have been systematically evaluating the steric and electronic properties of Pd–N-heterocyclic carbene (NHC) complexes (*e.g.*, **6** and **7**, Fig. 1) in an effort to enhance their catalytic performance in various cross-coupling reactions.[8] NMR studies that we have performed on these metal complexes are suggestive that increases in bulk on the *N*-phenyl substituent lead to enhanced positive charge on the Pd metal.[9] It is generally true that electron-poor metal centers tend to undergo reductive processes faster than electron-rich ones. Further, metal complexes containing more-sterically-hindered ligands undergo reductive elimination faster than complexes with less-hindered ancillary ligands.[10] Thus, we reasoned that sterically-bulky Pd–PEPPSI–IPent (**7**, Fig. 1)[11] could perform well in the coupling of secondary Csp^3-hybridized organometallics with aryl halides where the rate of reductive elimination would have to be significantly faster than β-hydride elimination. We have shown by experiment,[8a–c] supported and explained by calculation,[8d–f] that Pd–PEPPSI–IPr does not readily undergo

Table 2 Negishi cross-coupling of secondary alkylzinc halides with aryl/heteroaryl halides[a]

$$\underset{\text{(1 equiv)}}{\text{Ar-X}} \;+\; \underset{\text{(1.5 equiv)}}{\textbf{sec-AlkylZnX}} \xrightarrow[\text{THF/Toluene, RT, 20h}]{\textit{Pd-PEPPSI-IPent}\text{ (2 mol\%)}} \text{Ar-}\textbf{Alkyl}$$

Entry	Aryl halide	Product	Yield (%)	Entry	Aryl halide	Product	Yield (%)
1			80	7			92
2			70	8			94
3			82[b]	9			61
4			76[b,c]	10			95
5			40[d]	11			82
6			90	12			83

[a] Isolated yields; average of two runs. [b] 3.4 equivalents of the alkylzinc reagent was used. [c] 16/1 branched/linear. [d] 6/1 desired/isomerized.

β-hydride elimination, hence the reason for its great success in 1° alkyl–1° alkyl couplings. We have proposed that through-space interactions between the electron-poor Pd centre (following oxidative addition) and the electron-rich C–H bonds of the isopropyl substituent keep the metal coordinatively saturated and mitigate the necessity for agostic interactions that lead to β-hydride elimination.[8d,e] Here in we set out to investigate the use of Pd–PEPPSI–IPent in Negishi cross-coupling of secondary alkylzinc halides with aryl/heteroaryl halides.

In order to see the clear-cut connection between steric bulk of the NHC ligand and catalytic performance of *PEPPSI* complexes, we compared the reactivity of Pd–PEPPSI–IPr (**6**) with Pd–PEPPSI–IPent (**7**). We first prepared isopropylzinc bromide in THF using Knochel's method[12] and examined its coupling with *p*-cyano-bromobenzene. After a short optimization study, it was found that in the presence of 1 mol% of either Pd–PEPPSI precatalyst (*i.e.*, **6** or **7**), coupling was completed within 30 minutes at room temperature. We were pleased that **7** gave rise to good yield, but more importantly it exhibited excellent selectivity for the branched (non-isomerized) product. Conversely, while conversion was also high with **6**, the ratio of branched to linear product was dramatically lower (Table 1, **10** : **11**). The same trend was observed when a variety of *ortho*-, *meta*-, and *para*-substituted aryl bromides were subjected to the optimized reaction conditions (Table 1). Moreover, an interesting trend emerged between selectivity for the branched product and the sterics of the oxidative addition partner. Selectivity for the branched product decreased in the following order: *para*- > *meta*- > *ortho*- (see Table 1, entries a, f and i for –CN; entries b and g for –CHO; entries e, h, and j for –OMe). Remarkably, while reduced, Ipent (**7**) still showed a preference for the non-isomerized product with *ortho*-substituted aryl chlorides, while Ipr (**6**) inverted selectivity in favour of the linear, less sterically-crowded isomerised product (entries i and j). Additionally, electronic properties of the aryl group on the relative rate of reductive elimination was not significant in our study, as was the case in the report by Han and Buchwald.[7] These results are in agreement with the report of Culkin and Hartwig who studied the rate of reductive elimination from DPPBz-ligated arylpalladium alkyl complexes and reported that aryl group electronic properties had a minor effect on the rate of reductive elimination.[13]

Following these promising results, **7** was further evaluated using a variety of cyclic and acylic alkylzinc reagents that were effectively coupled with several aryl halides (Table 2), including sterically-bulky mesityl (entry 1), nitrile (entries 2 and 10), aniline (entries 3 and 4), aldehyde (entry 5) and pinacol boronic acid (entry 9). It is noteworthy that the acidic aniline moiety could be coupled with the secondary zinc reagent, further illustrating the selectivity and utility of the Negishi cross-coupling reaction.[14] Heteroaryl halides including pyridine (entry 6), quinoline (entry 7), pyridazine (entry 8) and benzothiazole (entry 11) were also coupled in high yields. Moreover, when acyclic alkylzinc reagents were employed the ratio for branched to isomerized products was good to excellent (entries 4, 9 and 10).

Sterically-bulky Pd–PEPPSI–IPent (**7**) has proven to be an excellent precatalyst for the Negishi cross-coupling of secondary alkylzinc reagents with a wide variety of aryl/heteroaryl halides. Under the optimized conditions, the rate of reductive elimination relative to β-hydride elimination was suitable to almost eliminate the formation of isomerized projects, which is a significant problem for this transformation.

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