Highly Selective Reactions of Unbiased Alkenyl Halides and Alkylzinc Halides: Negishi-Plus Couplings
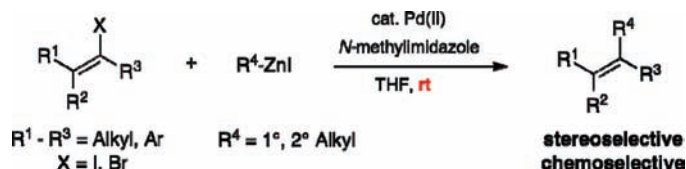
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ABSTRACT

High yielding stereo- and chemoselective Pd-catalyzed cross-couplings in THF at room temperature of alkenyl iodides and bromides with primary and secondary alkyl zinc iodides have been developed with the aid of *N*-methyimidazole as the key additive.

Sp^2–sp^3 cross-couplings of *E*- or *Z*-alkenyl halides with alkylzinc reagents, as described decades ago by Negishi, are among the most important Pd-catalyzed reactions in synthesis.[1] As one of three recently chosen "name" reactions to be awarded the Nobel Prize in Chemistry, these transformations are sure to gain even further in popularity. One of the most challenging types of Negishi couplings is that between alkenyl halides and alkylzinc halides. Associated with such cross-couplings, issues that may arise include concomitant formation of undesired byproducts (Scheme 1), as well as the potential erosion of stereochemistry in the case of a *Z*-alkenyl halide.[2]

Recently, we have shown that addition of TMEDA to a reaction mixture under otherwise standard Negishi conditions[1] prevents losses of stereointegrity in cross-couplings

Scheme 1. Negishi Cross-Couplings of Alkenyl Halides with Alkylzinc Iodides

of *Z*-alkenyl iodides.[3] In this report we disclose new technology that allows for highly stereoselective cross-couplings of alkenyl iodides and bromides with primary and secondary alkyl zinc iodides. Our approach provides consistent maintenance of both *E*- and *Z*-olefin geometry in the products, and excellent levels of efficiency, which exceed results to be expected from traditional additive-free Negishi cross-couplings,[1,2] and even our recently disclosed methodology.[3]

As a representative example, (*Z*)-1-bromooct-1-ene (**1**-*Z*) and *n*-heptylzinc iodide were coupled using 2 mol % of the commonly employed catalyst PdCl$_2$(PPh$_3$)$_2$. Although retention of geometry in the resulting *Z*-olefin was observed, the reaction led to a mixture of products, including significant amounts of protio-quench material and the product of olefin homocoupling (Scheme 1 and Table 1,

(1) (a) *Transition Metals in the Synthesis of Complex Organic Molecules*, 3rd ed.; Hegedus, L. S., Söderberg, B. C. G., Eds.; University Science Books: Sausalito, CA, 2009. (b) *Palladium in Organic Synthesis*; Tsuji, J., Ed.; Springer: Berlin, 2005. (c) Negishi, E.-I.; Gagneur, S. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-VCH: New York, 2002; Vol. 1, p 597. (d) *Metal-Catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. G., Eds.; Wiley-VCH: New York, 1998.

(2) (a) Negishi, E.-I.; Valente, L. F.; Kobayashi, M. *J. Am. Chem. Soc.* **1980**, *102*, 3298. (b) Negishi, E.-I. *Acc. Chem. Res.* **1982**, *15*, 340. (c) Knochel, P; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117. (d) Negishi, E.-I.; Hu, Q.; Huang, Z.; Qian, M.; Wang, G. *Aldrichimica Acta* **2005**, *38*, 71. (e) Negishi, E.-I.; Huang, Z.; Wang, G.; Mohan, S.; Wang, C.; Hattori, H. *Acc. Chem. Res.* **2008**, *41*, 1474.

(3) Krasovskiy, A.; Lipshutz, B. H. *Org. Lett.* **2011,** in press.

entry 1). Among many screened mono- and bidentate ligands (Figure 1), only conformationally flexible dppf and DPEPhos (entries 2 and 3), both having large bite angles,[4] proved to be effective for the desired Pd-catalyzed transformation. While the restricted geometry characteristic of XantPhos led to stereoretention (entry 4), a poor yield was obtained.
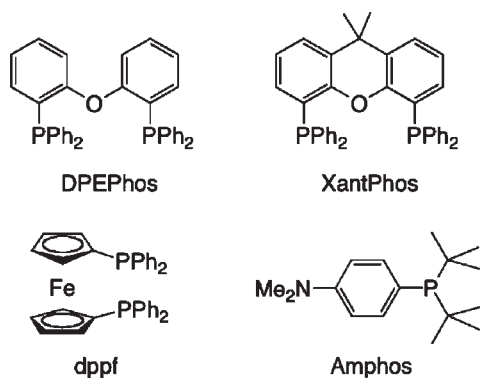

Figure 1. Ligands associated with Pd catalysts screened.

Remarkably, in the presence of N,N,N',N'-tetramethyl-ethane-1,2-diamine (TMEDA, 1.1 equiv vs substrate) or N-methylimidazole[5] (N-MeIm, 2.0 equiv vs substrate) under otherwise identical and standard Negishi conditions[1] with the simplest monodentate catalyst PdCl$_2$-(PPh$_3$)$_2$, virtually complete stereoretention and high yields were realized (Table 1, entries 5 and 6). The overall efficiency can be further enhanced using bidentate ligand-containing catalyst PdCl$_2$(DPEPhos) leading to the desired cross-coupled product in essentially quantitative yield (entry 7).

These newly discovered ligand/additive effects can also be applied to Negishi cross-couplings of (E)-1-bromooct-1-ene (**1**-E) with n-heptylzinc iodide. The results obtained follow the same trend as seen in the case of isomeric Z-alkenyl bromide **1**-Z (entries 8−12). Complete conversion of starting alkenyl bromide **1**-E to the desired product **2**-E was observed using the PdCl$_2$(DPEPhos)/N-MeIm pair (entry 12).

Cross-coupling of secondary alkyl zinc iodides proved to be more demanding. Use of either PdCl$_2$(PPh$_3$)$_2$ or PdCl$_2$-(DPEPhos) alone led to only traces of final product (entries 13, 14, 20). Under the best conditions of PdCl$_2$(DPEPhos)/N-MeIm found for couplings with primary alkylzinc

(4) Burello, E.; Rothenberg, G. *Adv. Synth. Catal.* **2005**, *347*, 1969.

(5) For reports of enhanced reactivity of an alkylzinc reagent in the presence of N-MeIm, see: (a) Inoe, S.; Furukawa, K. *J. Organomet. Chem.* **1972**, *37*, 25. (b) Inoe, S.; Imanaka, Y. *J. Organomet. Chem.* **1972**, *35*, 1. (c) Inoe, S.; Yokoo, Y. *J. Organomet. Chem.* **1972**, *39*, 11. (d) Zhou, J.; Fu, C. G. *J. Am. Chem. Soc.* **2003**, *125*, 12527.

(6) (Amphos)$_2$PdCl$_2$ (CAS #887919-35-9) obtained from Johnson Matthey (Amphos = p-dimethylaminophenyl-di-*tert*-butyllphosphine): Guram, A. S.; King, A. O.; Allen, J. G.; Wang, X.; Schenkel, L. B.; Chan, J.; Bunel, E. E.; Faul, M. M.; Larsen, R. D.; Martinelli, M. J.; Reider, P. J. *Org. Lett.* **2006**, *8*, 1787.

Table 1. Effect of Catalyst and Additives on Reactions of Alkenyl Bromide **1** with a *Primary* and *Secondary* Alkylzinc Iodides[a]

entry	1	catalyst	Z/E^b	yield (%)^c
1	Z	PdCl$_2$(PPh$_3$)$_2$	99/1	64
2	Z	PdCl$_2$(dppf)	99/1	92
3	Z	PdCl$_2$(DPEPhos)	99/1	94
4	Z	PdCl$_2$(XantPhos)	98/2	72
5	Z	PdCl$_2$(PPh$_3$)$_2$ + TMEDA^e	99/1	91
6	Z	PdCl$_2$(PPh$_3$)$_2$ + N-MeIm^f	99/1	93
7	**Z**	**PdCl$_2$(DPEPhos)** + N-**MeIm**^{f}	**99/1**	**>99 (96)**^{d}
8	E	PdCl$_2$(PPh$_3$)$_2$	1/99	34
9	E	PdCl$_2$(DPEPhos)	1/99	90
10	E	PdCl$_2$(PPh$_3$)$_2$ + TMEDA^e	1/99	72
11	E	PdCl$_2$(PPh$_3$)$_2$ + N-MeIm^f	1/99	82
12	**E**	**PdCl$_2$(DPEPhos)** + N-**MeIm**^{f}	**1/99**	**>99 (95)**^{d}

entry	1	catalyst	Z/E^b	yield (%)^c
13	Z	PdCl$_2$(PPh$_3$)$_2$	ND	<5
14	Z	PdCl$_2$(DPEPhos)	ND	<5
15	Z	PdCl$_2$(PPh$_3$)$_2$ + TMEDA^e	94/6	40
16	Z	PdCl$_2$(PPh$_3$)$_2$ + N-MeIm^f	96/4	69
17	Z	PdCl$_2$(DPEPhos) + N-MeIm^f	96/4	83
18	**Z**	**PdCl$_2$(Amphos)$_2$** + N-**MeIm**^{f}	**99/1**	**>99 (96)**^{d}
19	E	PdCl$_2$(PPh$_3$)$_2$	1/99	49
20	E	PdCl$_2$(DPEPhos)	1/99	~10
21	E	PdCl$_2$(PPh$_3$)$_2$ + TMEDA^e	1/99	66
22	E	PdCl$_2$(PPh$_3$)$_2$ + N-MeIm^f	1/99	81
23	E	PdCl$_2$(DPEPhos) + N-MeIm^f	1/99	93
24	**Z**	**PdCl$_2$(Amphos)$_2$** + N-**MeIm**^{f}	**1/99**	**>99 (98)**^{d}

^{a} Conditions: n-heptylzinc iodide or cyclohexylzinc iodide (1.1 mmol, 1.0 M in THF), alkenyl bromide (1.0 mmol), Pd catalyst (2 mol %). Reactions were run at 0.33 M at rt, 24 h. ^{b} Z/E ratio determined by NMR and GC on crude material. ^{c} GC yield. ^{d} Isolated yield. ^{e} 1.1 equiv. ^{f} 2.0 equiv.

halides (*vide supra*), full conversion was not observed (entries 17, 23).

Additional screening of ligands ultimately led to an especially efficient combination: PdCl$_2$(Amphos)$_2$[6]/N-MeIm. This catalyst/additive system affords both excellent yields and essentially total stereoretention (entries 18, 24).
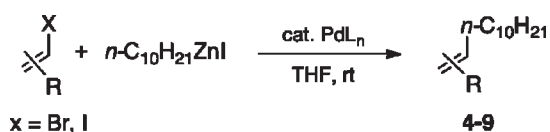
To further explore the scope of these cross-coupling reactions, several alkenyl halides containing varying

Table 2. Cross-Couplings of *n*-Decylzinc Iodide with Representative Alkenyl Bromides[a]

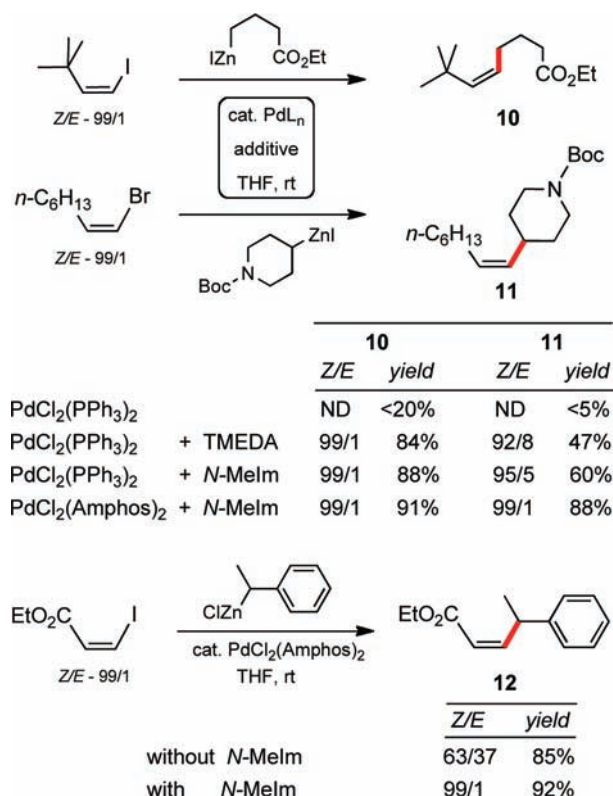| entry	X	product		yield (%)[b]
1	Br	Ph / n-C₁₀H₂₁	**4**	92
2	Br	n-C₁₀H₂₁ / Ph	**5**	77[c]
3	I	n-C₁₀H₂₁ / OH[d]	**6**	89
4	I	(bicyclic structure) / n-C₁₀H₂₁	**7**	95
5	I	n-C₃H₇ / n-C₃H₇ / n-C₁₀H₂₁	**8**	94
6	I	(cyclohexenyl) / n-C₁₀H₂₁	**9**	86

[a] Conditions: *n*-decylzinc iodide (1.1 mmol, 1.0 M in THF), alkenyl halide (1.0 mmol), PdCl₂(Amphos)₂ (2 mol %), *N*-MeIm (2.0 mmol). Reactions run at 0.33 M at rt, 3 h (12 h for entries 4 and 5). [b] Isolated yield. [c] From 90% technical grade α-bromostyrene. [d] *n*-Decylzinc iodide (2.4 equiv) used.

substitution patterns were examined (Table 2). Thus, in addition to the β-substituted alkenyl halides illustrated in Table 1, both β,β- (entry 1), α- (entries 2, 3), and α,β-substituted (entries 4, 5) alkenyl halides coupled smoothly at room temperature under these newly found conditions. Also noteworthy is the case of highly labile (*Z*)-1-(2-iodoethenyl)cyclohexene (entry 6), found to readily undergo cross-coupling with complete retention of configuration. While both alkenyl bromides and iodides react smoothly, use of alkenyl iodides is preferred for reactivity and stability reasons.[7]

The well-known functional group tolerance of organozinc reagents,[8] together with the exceptionally mild

conditions developed for these stereoselective cross-couplings, should allow for the synthesis of a variety of functionalized isomerically pure alkenes. As illustrated in Scheme 2, functional groups such as Boc- and an ester are tolerated within the starting organozinc reagents. Noteworthy is the high yield and isomeric purity of very sterically hindered alkene **10** derived from (*Z*)-1-iodo-3,3-dimethylbut-1-ene.[9] Here again, experiments utilizing different catalysts and additives, including TMEDA, were not consistently as effective as the PdCl₂(Amphos)₂/*N*-MeIm combination.[10]

Scheme 2. Cross-Couplings of Functionalized Reagents[a]

		10		**11**	
		Z/E	yield	Z/E	yield
PdCl₂(PPh₃)₂		ND	<20%	ND	<5%
PdCl₂(PPh₃)₂	+ TMEDA	99/1	84%	92/8	47%
PdCl₂(PPh₃)₂	+ *N*-MeIm	99/1	88%	95/5	60%
PdCl₂(Amphos)₂	+ *N*-MeIm	99/1	91%	99/1	88%

	Z/E	yield
without *N*-MeIm	63/37	85%
with *N*-MeIm	99/1	92%

[a] Conditions: organozinc halide (1.1 mmol, 1.0 M in THF), alkenyl halide (1.0 mmol), Pd catalyst (2 mol %), TMEDA (1.1 mmol), N-MeIm (2.0 mmol). Reactions were run at 0.33 M at rt, 24 h (3 h for 12). Z/E ratio determined by NMR and GC on crude material. Isolated yields.

In general, reactions of alkylzinc halides leading to various undesired products (Scheme 3) has been addressed by using bidentate ligands to ensure saturation of the coordination sphere of Pd,[11] thus discouraging pathways such as β-H elimination and homocoupling via ligand

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(8) (a) Rieke, R. D.; Hanson, M. V. *Tetrahedron* **1997**, *53*, 1925. (b) *Organozinc Reagents, A Practical Approach*; Knochel, P., Jones, P., Eds.; Oxford: New York, 1999. (c) *Handbook of Functionalized Organometallics. Applications in Synthesis*; Knochel, P., Ed.; Wiley: Weinheim, 2005.

(9) (*Z*)-1-Iodo-3,3-dimethylbut-1-ene as a starting material was chosen over the corresponding bromide due to the volatility of the latter compound.
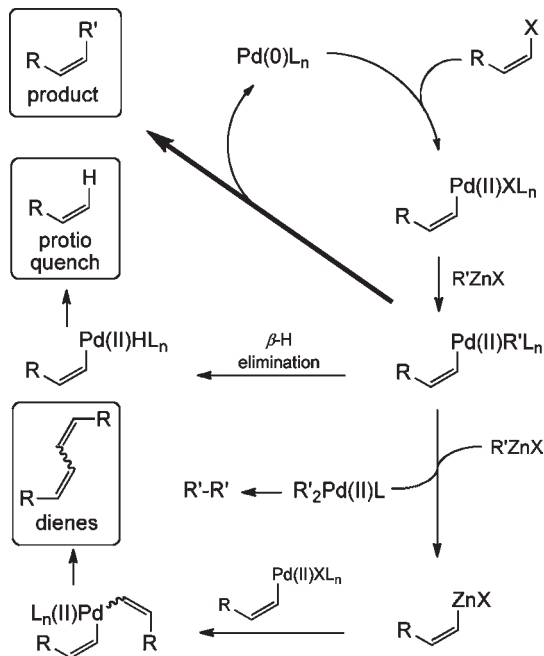
(10) See Supporting Information.

(11) (a) Zuideveld, M. A.; Swennenhuis, B. H. G.; Boele, M. D. K.; Guari, Y.; van Strijdonck, G. P. F.; Reek, J. N. H.; Kamer, P. C. J.; Goubitz, K.; Fraanje, J.; Lutz, M.; Spek, A. L.; van Leeuwen, P. W. N. M. *J. Chem. Soc., Dalton Trans.* **2002**, 2308. (b) Chass, G. A.; O'Brien, C. J.; Hadei, N.; Kantchev, E. A. B.; Mu, W.-H.; Fang, D.-C.; Hopkinson, A. C.; Csizmadia, I. G.; Organ, M. G. *Chem.—Eur. J.* **2009**, *15*, 4281.

scrambling. We assume that addition of stoichimetric amounts of N-methylimidazole, or TMEDA, serves the same purpose, thus allowing use of simple monodentate ligand-containing catalysts such as $PdCl_2(Amphos)_2$. Presumably, the presence of these additives in stoichiometric amounts provides a coordinating ligand for both catalytic palladium[12] and stoichiometric zinc.[13]

It is known that β-H elimination is also responsible for the formation of isomerized cross-coupled products in the

case of secondary alkyl zinc reagents.[14] Our preliminary studies showed that addition of N-methylimidazole also suppresses this undesired transformation leading to branched products **13**–**14** in excellent yields without detectable formation of isomerized byproducts (Scheme 4).[15]

Scheme 4. Cross-Couplings of Aryl Halides with sec-$C_4H_9ZnI^a$

13 R = OMe, 96%
14 R = CO_2Et, 98%
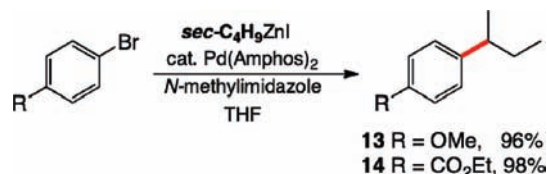
^{a} Conditions: organozinc halide (1.1 mmol, 1.0 M in THF), aryl bromide (1.0 mmol), $Pd(Amphos)_2$ (2 mol %), N-MeIm (2.0 mmol), 6 h at 40 °C for **13** and 3 h at rt for **14**. Isolated yields.

In summary, a new catalyst system has been identified that offers a general solution to fundamental problems that can be encountered in Negishi couplings: that is, protio-quenching and homocoupling that can dramatically impact yields and stereochemical issues, most notably when Z-alkenyl educts are involved. These "Negishi-Plus" reactions involve a combination of catalytic $PdCl_2(Amphos)_2$ together with stoichiometric N-methylimidazole; when used in THF at room temperature, cross-couplings between 1° and 2° alkylzinc reagents and variously substituted alkenyl iodides or bromides take place in high yields.

Supporting Information Available. Experimental procedures and product spectral data are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) (a) Han, C.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 7532. (b) Kondolff, I.; Doucet, H.; Santalli, M. *Organomet.* **2006**, *25*, 5219. (c) Çalimsiz, S.; Organ, M. G. *Chem. Commun.* **2011**, *47*, 5181.

(15) Use of $Pd(Amphos)_2$ instead of $PdCl_2(Amphos)_2$ in this case was nessesary to achieve full conversion.