Published in final edited form as:

Org Lett. 2011 August 5; 13(15): 3822–3825. doi:10.1021/ol201307y.

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

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Abstract

High yielding stereo- and chemo-selective 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-methylimidazole as the key additive.

Sp²-sp³ 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 conditions¹ prevents losses of stereointegrity in cross-couplings of *Z*-alkenyl iodides.³

In this report we disclose new technology that allows for highly stereo- and chemoselective 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 chemoselectivity, 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 PdCl₂(PPh₃)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, entry 1). Among many screened mono- and bidentate ligands (Figure 1), only conformationally flexible dppf and DPEPhos (entries 2 and 3), both

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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>.

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), poor chemoselectivity resulted.

Remarkably, in the presence of *N,N,N',N'*-tetramethylethane-1,2-diamine (TMEDA, 1.1 equiv vs. substrate) or *N*-methylimidazole⁵ (*N*-MeIm, 2.0 equiv vs. substrate) under otherwise identical and standard Negishi conditions¹ with the simplest monodentate catalyst PdCl₂(PPh₃)₂, virtually complete stereo- and chemoselectivity were realized (Table 1, entries 5 and 6). The chemoselectivity can be further enhanced using bidentate ligand-containing catalyst PdCl₂(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 PdCl₂(DPEPhos)/*N*-MeIm pair (entry 12).

Cross-coupling of secondary alkyl zinc iodides proved to be more demanding. Use of either PdCl₂(PPh₃)₂ or PdCl₂(DPEPhos) alone led to only traces of final product (entries 13, 14, 20). Under the best conditions of PdCl₂(DPEPhos)/*N*-MeIm found for couplings with primary alkylzinc halides (*vide supra*), full conversion was not observed (entries 17, 23).

Additional screening of ligands ultimately led to an especially efficient combination: PdCl₂(Amphos)₂⁶/*N*-MeIm. This catalyst / additive system affords both excellent chemoselectivity and essentially total stereoretention (entries 18, 24).

To further explore the scope of these cross-coupling reactions, several alkenyl halides containing varying 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 both 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 Boc- and 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

In general, chemoselectivity in 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 scrambling. We assume that addition of stoichiometric amounts of *N*-methylimidazole, or TMEDA, serves the same purpose, thus allowing use of simple monodentate ligand-containing catalysts such as PdCl₂(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.¹⁵

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 PdCl₂(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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Financial support provided by the NIH is warmly acknowledged. We are grateful to Johnson Matthey for generously supplying PdCl₂(Amphos)₂, and to Boulder Scientific for the Cp₂ZrCl₂ used to make the alkenyl halides used in this study.

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Figure 1.
Ligands associated with Pd catalysts screened

Scheme 1.

Negishi cross-couplings of alkenyl halides with alkylzinc iodides.

Scheme 2. Cross-couplings of functionalized reagents. ^a

^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*-Melm (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.

Scheme 3.

Sequence leading to the desired “product” when $\text{Pd}(0)\text{L}_n = \text{PdCl}_2(\text{Amphos})_2/\text{N}$ -methylimidazole, or product mixtures using other catalysts/additives.

Scheme 4.

Cross-couplings of aryl halides with *sec*-C₄H₉ZnI. ^a

^a Conditions: organozinc halide (1.1 mmol, 1.0 M in THF), aryl halide (1.0 mmol), Pd catalyst (2 mol %), *N*-MeIm (2.0 mmol), 6 h at 40 °C for **13** and 3 h at rt for **14**. Isolated yields.

Table 1

Effect of catalyst and additives on reactions of alkenyl bromide **1** with a *primary* and *secondary* alkylzinc iodides. ^a

entry	1	catalyst	<i>Z/E</i> ^b	yield (%) ^c
1	<i>Z</i>	PdCl ₂ (PPh ₃) ₂	99/1	64
2	<i>Z</i>	PdCl ₂ (dppf)	99/1	92
3	<i>Z</i>	PdCl ₂ (DPEPhos)	99/1	94
4	<i>Z</i>	PdCl ₂ (XantPhos)	98/2	72
5	<i>Z</i>	PdCl ₂ (PPh ₃) ₂ + TMEDA ^e	99/1	91
6	<i>Z</i>	PdCl ₂ (PPh ₃) ₂ + <i>N</i> -MeIm ^f	99/1	93
7	<i>Z</i>	PdCl₂(DPEPhos) + <i>N</i>-MeIm^f	99/1	>99 (96)^d
8	<i>E</i>	PdCl ₂ (PPh ₃) ₂	1/99	34
9	<i>E</i>	PdCl ₂ (DPEPhos)	1/99	90
10	<i>E</i>	PdCl ₂ (PPh ₃) ₂ + TMEDA ^e	1/99	72
11	<i>E</i>	PdCl ₂ (PPh ₃) ₂ + <i>N</i> -MeIm ^f	1/99	82
12	<i>E</i>	PdCl₂(DPEPhos) + <i>N</i>-MeIm^f	1/99	>99 (95)^d

entry	1	catalyst	<i>Z/E</i> ^b	yield (%) ^c
13	<i>Z</i>	PdCl ₂ (PPh ₃) ₂	ND	<5
14	<i>Z</i>	PdCl ₂ (DPEPhos)	ND	<5
15	<i>Z</i>	PdCl ₂ (PPh ₃) ₂ + TMEDA ^e	94/6	40
16	<i>Z</i>	PdCl ₂ (PPh ₃) ₂ + <i>N</i> -MeIm ^f	96/4	69
17	<i>Z</i>	PdCl ₂ (DPEPhos) + <i>N</i> -MeIm ^f	96/4	83
18	<i>Z</i>	PdCl₂(Amphos)₂ + <i>N</i>-MeIm^f	99/1	>99 (96)^d
19	<i>E</i>	PdCl ₂ (PPh ₃) ₂	1/99	49
20	<i>E</i>	PdCl ₂ (DPEPhos)	1/99	~10
21	<i>E</i>	PdCl ₂ (PPh ₃) ₂ + TMEDA ^e	1/99	66
22	<i>E</i>	PdCl ₂ (PPh ₃) ₂ + <i>N</i> -MeIm ^f	1/99	81
23	<i>E</i>	PdCl ₂ (DPEPhos) + <i>N</i> -MeIm ^f	1/99	93

entry	1	catalyst	Z/E ^b	yield (%) ^c
24	Z	PdCl ₂ (Amphos) ₂ + <i>N</i> -MeIm ^f	1/99	>99 (98) ^d

^aConditions: *n*-decylzinc 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.

^bZ/E-ratio determined by NMR and GC on crude material.

^cGC yield.

^dIsolated yield.

^e1.1 equiv.

^f2.0 equiv.

Table 2Cross-couplings of *n*-decylzinc iodide with representative alkenyl bromides. ^a

entry	X	product	yield (%) ^b
1	Br		4 92
2	Br		5 77 ^c
3	I		6 89
4	I		7 95
5	I		8 94
6	I		9 86

^aConditions: *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).

^bIsolated yield.

^cFrom 90% technical grade α -bromostyrene.

^d*n*-Decylzinc iodide (2.4 equiv) used.