

# Stereoselective Negishi-like Couplings Between Alkenyl and Alkyl Halides in Water at Room Temperature

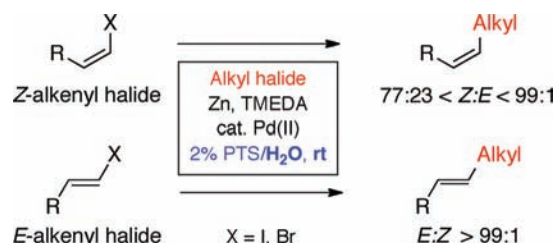
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## ABSTRACT



Mix in water and then stir. That is all that is required in this new approach to stereoselective  $sp^3$ – $sp^2$  cross-couplings between an alkyl and alkenyl halide. Prior formation of organozinc reagents is not required.

Palladium-catalyzed cross-couplings involving *E*- or *Z*-alkenyl halides lie at the very origin of several of the most commonly used ‘name’ reactions.<sup>1</sup> These include Negishi couplings between organozinc halides and alkenyl or aryl halides, usually in THF. Recently, we have shown that by simply combining an aryl bromide with an alkyl iodide in the presence of zinc powder and a palladium catalyst, C–C bond formation smoothly occurs within nanomicelles at room temperature in water.<sup>2</sup> In this report we disclose newly investigated cross-couplings of alkenyl halides. Our approach provides high levels of maintenance of both *E*- and *Z*-olefin geometry in the products of zinc-mediated reactions, which in some cases compare very favorably to traditional two-step Negishi cross-couplings in ethereal media.

Crucial to the success of this technology are the following: (a) the use of TMEDA as additive,<sup>3</sup> presumably functioning as both a surface-cleaning/activating agent for the metal and ligand for the in situ-formed organozinc reagent; (b) the palladium(II) precursor PdCl<sub>2</sub>(Amphos)<sub>2</sub>;<sup>4</sup> other sources of Pd(0) or Pd(II) catalysts led to inferior results; (c) the amphiphile PTS (the diester made from PEG-600,  $\alpha$ -Tocopherol, Sebacic acid),<sup>5</sup> which presumably supplies the hydrophobic pocket in which the in situ generated water-sensitive organozinc halide reacts;<sup>6</sup> and (d) Zn dust, rather than powder. Only 2 equiv of the corresponding alkyl halide and 1 mol % of PdCl<sub>2</sub>(Amphos)<sub>2</sub> are required for high levels of conversion and good isolated yields under mild, ambient temperatures.

In the case of cross-couplings of stereoisomerically pure *E*-alkenyl halides (Table 1, entries 1 and 2), complete retention of *E*-stereochemistry was observed. Mixtures of

(1) (a) Negishi, E.-I.; Gagneur, S. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley: New York, 2002; Vol. 1, p 597. (b) Negishi, E.-I. *Acc. Chem. Res.* **1982**, *15*, 340. (c) Negishi, E.-I.; Hu, Q.; Huang, Z.; Qian, M.; Wang, G. *Aldrichimica Acta* **2005**, *38*, 71. (d) Negishi, E.-I.; Huang, Z.; Wang, G.; Mohan, S.; Wang, C.; Hattori, H. *Acc. Chem. Res.* **2008**, *41*, 1474. (e) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117.

(2) Krasovskiy, A.; Duplais, C.; Lipshutz, B. H. *J. Am. Chem. Soc.* **2009**, *131*, 15592.

(3) Without TMEDA, no product is formed.

(4) PdCl<sub>2</sub>(Amphos)<sub>2</sub> (dichlorobis(*p*-dimethylaminophenyl- $\pi$ -di-*tert*-butylphosphine)palladium(II)) is commercially available from Johnson Matthey.

(5) Lipshutz, B. H.; Ghorai, S. *Aldrichimica Acta* **2008**, *41*, 59.

(6) In the absence of PTS, low levels of conversion (<20%) were observed after 48 h.

**Table 1.** Representative Couplings of *E*-Alkenyl Halides in PTS/H<sub>2</sub>O<sup>a</sup>

entry	coupling partners	product <sup>b</sup>	<i>E/Z</i> <sup>c</sup>
1	R = CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	(89%)	>99/1
2	R = OCH <sub>2</sub> Ph	(85%)	>99/1
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3		(83%) <sup>d</sup>	96/4
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4		(92%) <sup>d</sup>	91/9

<sup>a</sup> Conditions: alkyl halide (2 mmol), alkenyl halide (1 mmol), PdCl<sub>2</sub>(Amphos)<sub>2</sub> (0.01 mmol), zinc dust (3 mmol), TMEDA (2 mmol), 2% PTS/H<sub>2</sub>O (2 mL), rt, 24 h. <sup>b</sup> Isolated yields. <sup>c</sup> Determined by proton NMR and GC of the crude. <sup>d</sup> 12 h.

*E/Z*-alkenyl halides led to slight increases of the resulting *E/Z*-isomer ratio in the final products (entries 3, 4). This observation is expected based on relative rates of cross-couplings between *E*- and *Z*-disubstituted isomers. We could clearly observe much faster consumption of the *E*-isomer by monitoring reactions by GC. A second explanation relies on isomerization of either the starting material or final product during the course of the reaction to the more thermodynamically stable *E*-isomer. Lastly, isomerization could happen after generation of a Pd(II) intermediate following a likely stereospecific<sup>7</sup> Pd-insertion/transmetalation.

To gain further insight, cross-couplings of *Z*-alkenyl halides were studied (Table 2). In all representative cases examined, ≥95% retention of *Z*-stereochemistry was observed. Various functionalized *Z*-olefins could be prepared in good to excellent yields (entries 1–14, Table 2). When both substrates are unactivated, the “homohalide” pairs such as alkenyl iodide + alkyl iodide (entry 1) and alkenyl bromide + alkyl bromide (entry 4), led to efficient cross-couplings with anticipated *Z*-stereochemistry (entries 1, 4). Curiously, the “mixed halide” pairs (entries 2, 3), under otherwise identical conditions, gave low levels of conversion and/or significant amounts of the

(7) Jutand, A.; Negry, S. *Organometallics* **2003**, *22*, 4229.

**Table 2.** Representative Couplings of *Z*-Alkenyl Halides in PTS/H<sub>2</sub>O<sup>a</sup>

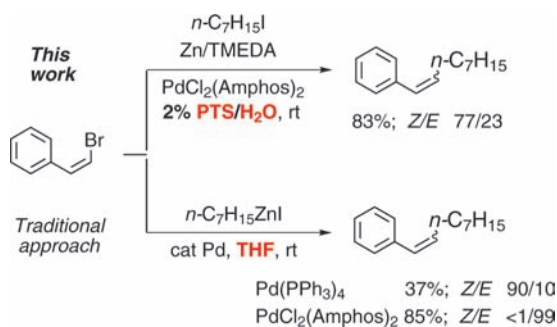
entry	coupling partners	product <sup>b</sup>	<i>Z/E</i> <sup>c</sup>
1	X = I, Y = I	(93%) <sup>d</sup>	99/1
2	X = I, Y = Br	(67%) <sup>e</sup>	96/4
3	X = Br, Y = I	(51%) <sup>f</sup>	95/5
4	X = Br, Y = Br	(87%) <sup>g</sup>	96/4
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5	X, Y = Br	(86%)	97/3
6	X, Y = I	(79%)	99/1
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7	R = H	(52%) <sup>h</sup>	98/2
8	R = <i>n</i> -C <sub>5</sub> H <sub>11</sub>	(93%)	97/3
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9	R = Cl	(85%) <sup>i</sup>	97/3
10	R = C <sub>2</sub> H <sub>5</sub>	(90%) <sup>i</sup>	98/2
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11	X = Br	(94%) <sup>d</sup>	99/1
12	X = I	(95%) <sup>d</sup>	99/1
-----			
13	n = 2	(74%)	96/4
14	n = 3	(85%)	99/1

<sup>a</sup> Conditions: alkyl halide (2 mmol), alkenyl halide (1 mmol), PdCl<sub>2</sub>(Amphos)<sub>2</sub> (0.01 mmol), zinc dust (3 mmol), TMEDA (2 mmol), 2% PTS/H<sub>2</sub>O (2 mL), rt, 48 h. <sup>b</sup> Isolated yields. <sup>c</sup> Determined by proton NMR and GC of the crude. <sup>d</sup> 12 h. <sup>e</sup> ~20% reduction of alkenyl iodide. <sup>f</sup> 60% conversion. <sup>g</sup> 81% yield with 1.5 equiv of alkyl bromide. <sup>h</sup> GC yield 94%. <sup>i</sup> 24 h.

product of alkenyl halide reduction. In one case (entry 2), competitive zinc insertion occurs with the alkenyl iodide, while, in the other case (entry 3), consumption of the alkyl iodide is too rapid leading to competitive protio quenching. Nonetheless, stereoselectivity is unaffected. As illustrated in entries 7–9 and 11–14, functional groups such as benzyl ether, ketone, chloride, ester, and trimethylsilyl are tolerated within the starting halides.<sup>8</sup>

$\beta$ -Bromostyrene showed anomalous behavior in PTS/H<sub>2</sub>O, losing 21–30% of its originally all *Z* constitution (Scheme 1, top). Stirring this reaction for one additional day after

**Scheme 1.** Negishi-like Couplings in Water and in THF



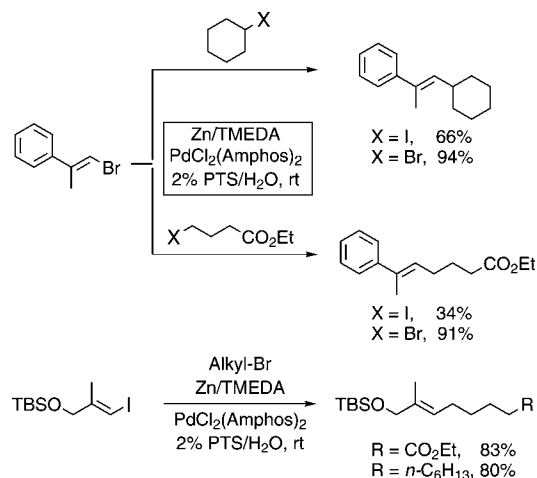
completion led to only 5% *Z*→*E* isomerization. Moreover, a control experiment run in the absence of an alkyl halide also showed insignificant isomerization of the starting material alkenyl halide under these reaction conditions. By way of comparison, in THF, Pd(PPh<sub>3</sub>)<sub>4</sub> as catalyst leads mainly to the *Z*-isomer, albeit in low isolated yield, while PdCl<sub>2</sub>(Amphos)<sub>2</sub> gave virtually all *E*-olefinic product (Scheme 1).<sup>9</sup> Clearly, further experimental and theoretical studies on the role of ligands and reaction media in Negishi cross-couplings seem warranted.

Also noteworthy are the couplings with unsymmetrical 2,2-disubstituted alkenyl halides, found to readily undergo cross-coupling reactions under our conditions with complete retention of configuration (Scheme 2). Both primary and

(8) General Procedure: In a 5 mL round-bottom flask under argon containing zinc dust (197 mg, 3 mmol) and PdCl<sub>2</sub>(Amphos)<sub>2</sub> (7 mg, 0.01 mmol) was added 2% PTS solution in water (2 mL). *N,N,N',N'*-Tetraethylethylenediamine (TMEDA, 232 mg, 2 mmol) was added at rt followed by the addition of the alkyl halide (2 mmol) and the vinyl halide (1 mmol). The flask was stirred vigorously at rt for the indicated time. The product was extracted with EtOAc. Silica gel (1 g) was added to the combined organic phase, and solvents were removed under vacuum. The resulting dry, crude silica was introduced on top of a silica gel chromatography column to purify the product.

(9) Rare examples of cross-couplings between alkylzinc reagents and *Z*-vinyl halides: (a) Negishi, E.-I.; Luo, F.-T.; Rand, C. L. *Tetrahedron Lett.* **1982**, 23, 27. (b) Koumaglo, K.; Chan, T. H. *Tetrahedron Lett.* **1984**, 25, 717. (c) Chan, T. H.; Koumaglo, K. *J. Organomet. Chem.* **1985**, 285, 109. (d) Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1986**, 27, 83. (e) Tamaru, Y.; Ochiai, H.; Nakamura, T.; Yoshida, Z. *Tetrahedron Lett.* **1986**, 27, 955. (f) Millar, J. G. *Tetrahedron Lett.* **1989**, 30, 4913. (g) Negishi, E.-I.; Ay, M.; Gulevich, Y. V.; Noda, Y. *Tetrahedron Lett.* **1993**, 34, 1437. (h) Meyer, C.; Marek, I.; Courtemanche, G.; Normant, J.-F. *J. Org. Chem.* **1995**, 60, 863. (i) Nakamura, E.; Aoki, S.; Sekiya, K.; Oshino, H.; Kuwajima, I. *J. Am. Chem. Soc.* **1987**, 109, 8056.

**Scheme 2.** Stereoselective Coupling of 2,2-Disubstituted Alkenyl Halides



secondary alkyl halides react smoothly, although use of alkyl bromides is preferred for more sterically hindered disubstituted alkenyl halides. In these latter cases, alkyl iodides were readily consumed; however, a considerable amount of their homocoupled Wurtz-type side products were formed. Under our reaction conditions, dimerization products from starting alkenyl halides were not observed. These overall trends seem to be general for both alkenyl bromides and alkenyl iodides. On the other hand, we were unable to obtain reasonable yields with more sterically hindered  $\alpha$ -substituted cyclic or acyclic alkenyl halides.

In summary, a new micellar technology is described for effecting net Negishi-like cross-couplings of stereodefined alkenyl halides with alkyl halides. This method not only is an alternative to the generally accepted two-step procedures that rely on initial generation of stoichiometric organozinc reagents but also allows replacement of organic solvent with water as the only medium.

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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>.

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