

Cross-Couplings of Alkyl Electrophiles under "Ligandless" Conditions: Negishi Reactions of Organozirconium Reagents

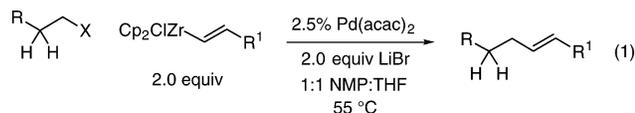
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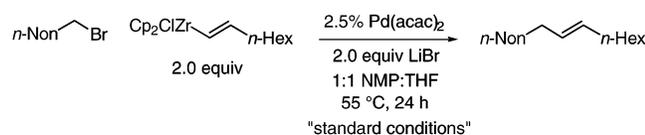
During the past few years, considerable effort has been devoted to expanding the scope of palladium- and nickel-catalyzed cross-coupling reactions¹ so as to include unactivated, β -hydrogen-containing alkyl electrophiles as partners.² For such processes, whereas the composition of nickel-based catalysts has been diverse,^{3,4} with the exception of an early report by Suzuki describing the use of Pd(PPh₃)₄ for couplings of alkyl iodides with organoboranes,⁵ all effective palladium-based catalysts have employed very bulky, electron-rich ligands (i.e., trialkylphosphines,^{6,7} alkyl-diaminophosphines,⁸ and carbenes⁹).

In this Communication, we provide an impetus for looking beyond such ligands in future efforts at catalyst development. Specifically, we establish that simple, "ligandless" palladium complexes¹⁰ can catalyze the first zirconium-Negishi reactions^{11,12} of alkyl electrophiles (eq 1). Such ligandless processes are attractive from the standpoints of cost, simplicity, and ease of purification.



As illustrated in Table 1, we have determined that Pd(acac)₂ is effective for the cross-coupling of 1-bromodecane with an alkenylzirconium reagent (entry 1). Other palladium complexes can also be employed (entries 2 and 3), but nickel complexes are only modestly efficient under these conditions (entries 4 and 5); without Pd(acac)₂, no cross-coupling is observed (entry 6). A halide source other than LiBr can be used (e.g., LiI; entry 7), whereas the coupling proceeds poorly if no activator is present (entry 8). Finally, the cross-coupling is less effective at lower temperature (entry 9) or with less catalyst (entry 10).¹³

Table 1. Effect of Reaction Parameters on the Cross-Coupling of an Alkyl Bromide with an Organozirconium Reagent



entry	change from the "standard conditions"	yield (%) ^a
1	none	99
2	PdBr ₂	100
3	Pd ₂ (dba) ₃	100
4	NiBr ₂	57
5	Ni(cod) ₂	62
6	no Pd(acac) ₂	0
7	LiI	100
8	no LiBr	20
9	room temp	14
10	1.0% Pd(acac) ₂	80

^a Yield according to GC, versus a calibrated internal standard (average of two runs).

Table 2. Zirconium-Negishi Cross-Couplings of Alkyl Bromides under Ligandless Conditions^a

entry	alkyl bromide	zirconium reagent	yield (%)
1			99
2			86
3			96
4			72
5			99
6			73 ^b
7			82
8			97
9			68
10			77
11			77
12			74
13			60 ^b
14			85
15			76 ^c

^a All yields are isolated yields (average of two runs). ^b 5% Pd(acac)₂ was used. ^c 5% Pd(acac)₂ was used. Reaction time: 48 h.

Pd(acac)₂ is effective for cross-coupling a range of functionalized alkyl bromides and alkenylzirconium reagents in generally good yield (Table 2). A variety of groups are compatible with the reaction conditions, including esters, alkyl and silyl ethers, nitriles, amides, acetals, and olefins. A somewhat hindered, β -branched alkyl bromide can be coupled, albeit in more modest yield (entry 13). Furthermore, sterically demanding alkenylzirconium reagents that are derived from the hydrozirconation of internal alkynes can be cross-coupled (entries 14 and 15).¹⁴ When the coupling illustrated

Table 3. Zirconium-Negishi Cross-Couplings of Other Alkyl Electrophiles under Ligandless Conditions^a

entry	alkyl halide	yield (%)
1		82
2		83
3		46

^a All yields are isolated yields (average of two runs).

in entry 1 is conducted under microwave conditions (100 °C, 15 min; 30 W), an excellent isolated yield of the product is obtained (94%).

The activity of this simple, ligandless catalyst for zirconium-Negishi couplings is not limited to reactions of alkyl bromides. Under the same set of conditions, functionalized alkyl iodides and alkyl tosylates undergo clean cross-coupling with alkenylzirconium reagents (Table 3, entries 1 and 2).¹⁵ Finally, reactions of alkyl chlorides can also be achieved, although less efficiently (entry 3).

At this stage, we have not determined the nature of the active catalyst. Interestingly, we have found that the addition of mercury to a cross-coupling shuts down the process, an observation consistent with the presence of a heterogeneous species in the reaction mixture.^{16,17}

In conclusion, we have described the first ligandless palladium-based method for cross-coupling alkyl electrophiles: Pd(acac)₂-catalyzed reactions of functionalized alkyl halides/tosylates with organozirconium reagents. In view of the attractiveness of ligandless catalysts (cost, simplicity, and ease of purification), these observations add a significant and intriguing new dimension to the development of effective processes for coupling alkyl electrophiles.

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Supporting Information Available: Experimental procedures and compound characterization data (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (10) By “ligandless”, we are simply indicating that typical ligands such as phosphines are not present. For a discussion of other ligandless catalysts for cross-coupling reactions, see: *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998; pp 26, 208, 214, 233.
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- (13) Notes: (a) The cross-coupling proceeds efficiently in NMP alone, but not in THF. (b) Under otherwise identical conditions, if the alkenylzirconium reagent is replaced with nonylzinc bromide, we observe essentially no cross-coupling (<2%). (c) In addition to zirconium-Negishi reactions of primary alkyl electrophiles, these conditions are also effective for couplings of aryl bromides (but not aryl chlorides).
- (14) Under these conditions, secondary alkyl bromides are not suitable substrates.
- (15) Under the cross-coupling conditions, some RCH₂X (X = Br, I, OTs) is converted to RCH₂Cl (the chloride originates from the alkenylzirconium reagent). We believe that one of the roles of LiBr is to transform RCH₂Cl into more reactive RCH₂Br.
- (16) (a) For example, see: Whitesides, G. M.; Hackett, M.; Brainard, R. L.; Lavalleye, J. P. P. M.; Sowinski, A. F.; Izumi, A. N.; Moore, S. S.; Brown, D. W.; Staudt, E. M. *Organometallics* **1985**, *4*, 1819–1830. Pd/C catalyzes these zirconium-Negishi cross-couplings, although less effectively than Pd(acac)₂. Visually, the Pd(acac)₂-catalyzed reactions appear to be homogeneous. For an excellent discussion, including leading references, of approaches to distinguishing between homogeneous and heterogeneous catalysis, see: Widegren, J. A.; Bennett, M. A.; Fink, R. G. *J. Am. Chem. Soc.* **2003**, *125*, 10301–10310. (b) For an example of a coupling catalyzed by palladium nanoparticles, see: Reetz, M. T.; Westermann, E. *Angew. Chem., Int. Ed.* **2000**, *39*, 165–168.
- (17) The cross-coupling proceeds in the presence of radical traps.

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