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The First Negishi Cross-Coupling Reaction of Two Alkyl Centers Utilizing a Pd–N-Heterocyclic Carbene (NHC) Catalyst[†]

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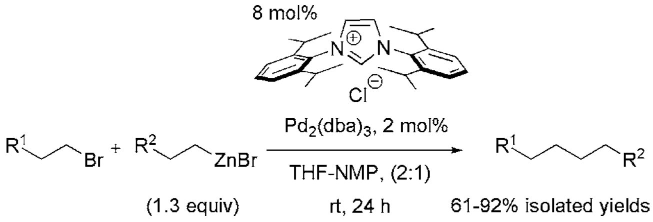
ABSTRACT



The development of an NHC-based system capable of cross-coupling sp^3–sp^3 centers in high yield has been a long-standing challenge. This communication describes the use of a Pd–NHC catalytic system that achieves room-temperature Negishi cross-couplings of unactivated, primary bromides and alkyl organozinc reagents with a variety of functionality.

Palladium-catalyzed cross-coupling reactions of unsaturated organohalides and sulfonates with organometallic reagents are well established and powerful methods for construction of carbon−carbon bonds.[1] While coupling of alkyl organometallic reagents has been known for some time, the use of unactivated alkyl chlorides, bromides, or tosylates as coupling partners posed a greater challenge,[2] isolated early examples notwithstanding.[3] Until recently, there was no general and efficient catalytic protocol for alkyl−alkyl cross-coupling reactions.

Previous work by Fu and co-workers demonstrated that $Pd(PR_3)_2$ (R = cyclohexyl, cyclopentyl) is an effective catalyst for Negishi[4] and Suzuki[5] cross-couplings of primary alkyl halides (Cl, Br, I) and tosylates. Kambe and co-workers disclosed Pd−1,3-diene catalysts for Kumada couplings of unactivated alkyl halides (Cl, Br) and tosylates.[6] In addition,

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[†] This study was first disclosed at the Canadian Society for Chemistry National Meeting (Saskatoon, Saskatchewan, Canada, May 29, 2005); Abstract #73: *Multicomponent Synthesis: Metals, Microwaves and Microchannels.*

(1) (a) *Metal-Catalyzed Cross-Coupling Reactions*, 2 ed.; de Meijere, A., Diederich, F., Eds.; John Wiley & Sons: New York, 2004. (b) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; John Wiley & Sons: New York, 2002.

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(5) (a) Kirchhoff, J. H.; Netherton, M. R.; Hills, I. D.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 13662−13663. (b) Kirchhoff, J. H.; Dai, C.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 1945−1947. (c) Netherton, M. R.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 3910−3912. (d) Netherton, M. R.; Dai, C.; Neuschütz, K.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 10099−10100.

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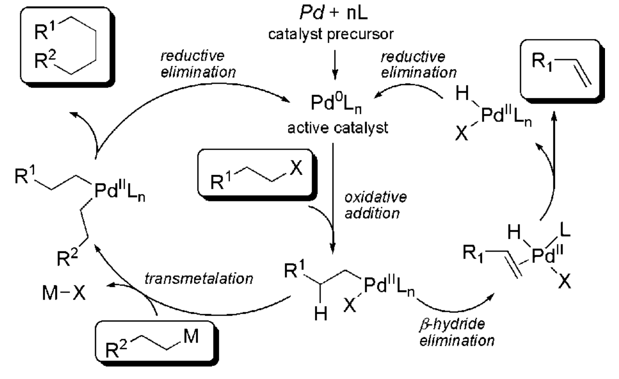
catalysts based on Ni[6,7] or other transition metals (Fe, Cu)[3,8] have been used successfully in alkyl−alkyl cross-coupling protocols.

The main problems when attempting to couple haloalkanes are the reluctance of saturated carbon−halogen bonds to undergo oxidative addition[2b] compared to aryl, vinyl, or allyl halides and competing *β*-H elimination from the oxidative addition intermediate, which results in unwanted alkene formation (Scheme 1). A viable process must overcome these obstacles. Recent mechanistic studies suggest that palladium insertion into an alkyl halide bond (oxidative addition) occurs via an S_N2-type mechanism and is enhanced by an electron-rich palladium center.[9] Effective reductive elimination is dependent on the catalyst's steric environment.[10]

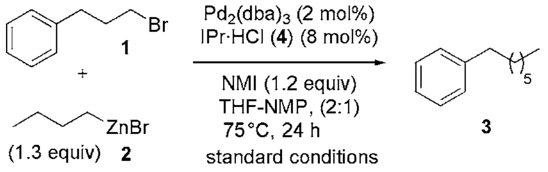
Scheme 1. General, Simplified Mechanism for Pd-Catalyzed Alkyl−Alkyl Cross-Coupling Reactions



Although N-heterocyclic carbenes (NHCs) have received considerable attention as an alternative to phosphines due to their excellent *σ*-donor properties, ease of synthesis, and variable steric bulk,[11] there has been limited success in using Pd−NHC catalytic protocols for alkyl−alkyl cross-coupling reactions. Fu and co-workers reported low yields when NHC ligands related to **5** were employed in Negishi[4] or Suzuki[5b] couplings. Caddick, Cloke et al. reported an alkyl−alkyl Suzuki reaction utilizing **4** with moderate yields.[12a] Despite these disappointing results, we still believed that the NHC ligand platform should be effective for alkyl−alkyl coupling reactions.

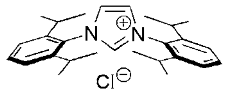
To this end, we submitted **4** to Negishi conditions developed by Fu et al.,[4] assuming that the alkylzinc reagent would facilitate the formation of active catalyst (Table 1).

Table 1. Effect of Reaction Conditions on the Yield of Alkyl−Alkyl Negishi Coupling

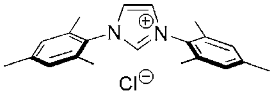


entry	change from standard conditions	yield (%)[a]
1	none	75
2	no ligand (**4**)	0.3
3	no $Pd_2(dba)_3$	0.0
4	no NMI	75
5	substituted toluene for NMP	2
6	substituted CH_2Cl_2 for NMP	2
7	substituted THF for NMP	2
8	substituted DME for NMP	3
9	substituted DMF for NMP	4
10	substituted DMA for NMP	50
11	substituted ligand **5** for **4**	8

[a] GC yield against a calibrated internal standard (undecane); reactions were performed in duplicate, and the average yield is reported.



4



5

We were delighted to find that cross-coupling occurred in high yield (Table 1, entry 1). Further examination of the conditions revealed that **5** was inactive (Table 1, entry 11) and *N*-methylimidazole (NMI) was not a necessary additive in these experiments (Table 1, entry 4). However, a solvent study revealed the same dependence on 1-methyl-2-pyrrolidinone (NMP) to achieve high yields (Table 1, entries 5−10) as reported by Fu et al.[4]

Following our initial success, we conducted a more detailed investigation of the coupling conditions (Table 2). Screening of the Pd:IPr (**4**) ratio confirmed that a 1:2 ratio was optimal (Table 2, entries 1−4). The impressively high yield was retained when the reaction was conducted at room temperature (Table 2, entry 6).

Evaluation of the source of palladium demonstrated that $Pd_2(dba)_3$ and $Pd(OAc)_2$ were equally effective at 75 °C and room temperature (Table 2, entries 7−8), while other Pd precursors were less effective (Table 2, entries 9−11).

A variety of substrates were coupled in good to excellent yields at room temperature using the optimal conditions developed for the Negishi alkyl−alkyl coupling reaction.[13] The results (Table 3) indicate that a number of functional

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(8) Nakamura, M.; Matsuo, K.; Ito, S.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 3686−3687.

(9) Hills, I. D.; Netherton, M. R.; Fu, G. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 5749−5752.

(10) Hadei, N.; Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. G. *Org. Lett.* **2005**, *7*, 1991−1994.

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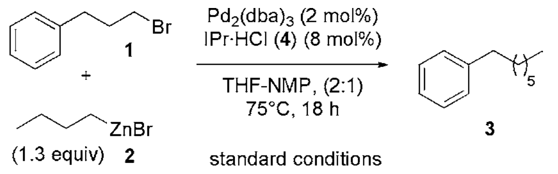
(12) (a) Arentsen, K.; Caddick, S.; Cloke, F. G. N.; Herring, A. P.; Hitchcock, P. B. *Tetrahedron Lett.* **2004**, *45*, 3511−3515. NHC ligands have also been employed in Sonogashira and Kumada reactions of alkyl bromides; see: (b) Eckhardt, M.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 13642−13643. (c) Frisch, A. C.; Rataboul, F.; Zapf, A.; Beller, M. *J. Organomet. Chem.* **2003**, *687*, 403−409.

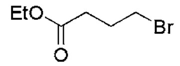
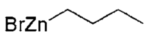
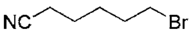
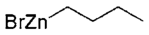
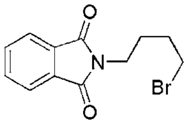
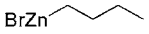
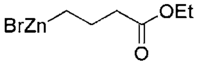
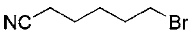
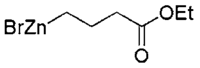
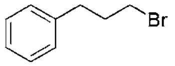
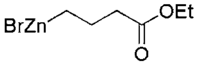
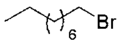
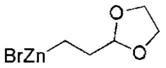
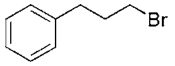
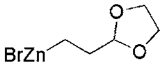
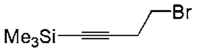
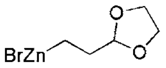
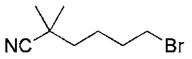
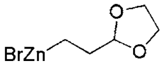
Table 2. Optimization of Catalyst Composition and Temperature



entry	change from standard conditions	yield (%)[a]
1	Pd:IPr (**4**) = 1:1	60
2	none (Pd:IPr (**4**) = 1:2)	75
3	Pd:IPr (**4**) = 1:2.5	70
4	Pd:IPr (**4**) = 1:3	50
5	55 °C	70
6	rt	77
7	$Pd(OAc)_2$	75
8	$Pd(OAc)_2$, rt	75
9	$Pd(OCOCF_3)_2$, rt	40
10	$PdCl_2$, rt	19
11	$[(\pi\text{-allyl})PdCl]_2$, rt	6

[a] GC yield against a calibrated internal standard (undecane); reactions were performed in duplicate, and the average yield is reported.

Table 3. Room-Temperature Negishi Cross-Coupling Reactions of Unactivated Alkyl Bromides with Alkyl Zinc Reagents[a]

entry	alkyl bromide	alkylzinc reagent	yield (%)[b]	
1			**6**	92 (83)
2			**7**	92 (92)
3			**8**	65 (65)
4			**6**	92 (75)
5			**9**	62 (66)
6			**10**	76
7			**11**	66
8			**12**	70
9			**13**	61
10			**14**	75

[a] $Pd_2(dba)_3$ (2 mol %), IPr•HCl (8 mol %), *n*-butylzinc bromide (0.5 M in THF, 12 mol %), stirred for 1 h, alkyl bromide (0.5 mmol), alkylzinc reagent (0.5 M in THF, 0.65 mmol) in THF−NMP (2:1), rt, 24 h. [b] Isolated yield at room temperature; isolated yield at 75 °C in parentheses. Reactions were performed in duplicate, and the average yield is reported.

groups (esters, nitriles, amides, alkynes, and acetals) were tolerated. The addition of a small amount (12 mol %) of *n*-butylzinc bromide appeared to be necessary in order to achieve reproducible catalyst formation.[14] That said, we have one example that demonstrates that excellent yields may be obtained when *n*-butylzinc bromide activation is not employed.[15] It is noteworthy that the yields at room temperature were generally higher when compared to reactions performed at 75 °C (Table 3, entries 1−5).

In conclusion, we have demonstrated the first high-yielding Negishi cross-coupling reaction utilizing NHC ligands. Further, this is also the first reported room-temperature palladium-catalyzed Negishi alkyl−alkyl coupling reaction. We are currently expanding the scope of the Pd−NHC Negishi protocol to aryl and vinyl halides, pseudo-halides, and more elaborate zinc reagents

Acknowledgment. We would like to thank the ORDCF and NSERC (Canada) for financially supporting our program and Varian Canada for their collaborative in-kind donation (in part) of the GC/MS/MS 4000 to conduct the analyses in this report.

Supporting Information Available: Experimental procedures for Tables 2 and 3 and characterization data for the cross-coupling products (Table 3). This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Coupling of the chloride and tosylate analogues of **1** with *n*-butylzinc bromide led to unsatisfactory yields (≤30%) of **3**. However, coupling of tosylates can be achieved if the organozinc halide is prepared from Rieke zinc made from $ZnBr_2$. See: Rieke, R. D.; Hanson, M. V.; Brown, J. D.; Niu, Q. J. *J. Org. Chem.* **1996**, *61*, 2726−2730. Zhu, L.; Wehmeyer, R. M.; Rieke, R. D. *J. Org. Chem.* **1991**, *56*, 1445−1453. We believe this is due to the bromide ion from LiBr (produced as a byproduct in Rieke zinc fromation) displacing the tosylate group (GC/MS). Indeed, when we used commercially available organozinc reagent (Rieke Metals, Inc., which contains LiCl), we observed significant formation of the alkyl chloride (GC/MS).

(14) Steric nature of the organozinc reagent could affect the formation of the active catalyst. We observed significant variation in yield when the organozinc reagent participating in the cross-coupling reaction was used alone.

(15) Reaction depicted in Table 3, entry 4, yielded 87% of the cross-coupled product when *n*-butylzinc bromide catalyst activation was not employed.