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Enantioselective Alkyl−Alkyl Suzuki Cross-Couplings of Unactivated Homobenzylic Halides

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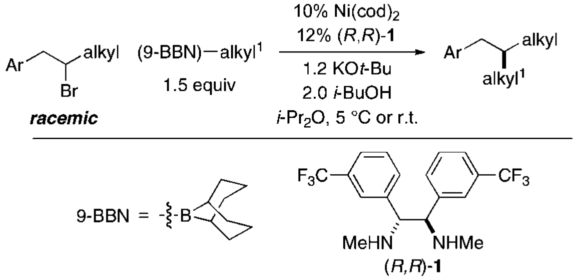
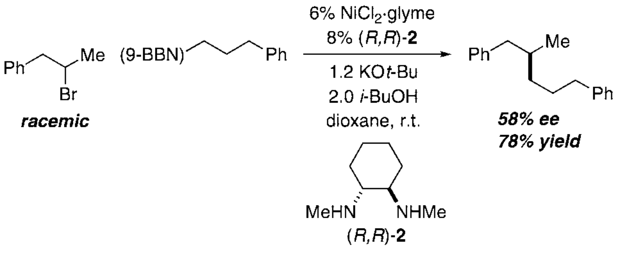
Progress in the development of palladium- and nickel-catalyzed methods for cross-coupling alkyl electrophiles that bear β hydrogens has increased significantly in recent years.[1,2] For reactions of secondary alkyl halides, nickel-based catalysts have proved to be unusually effective.[2a,c,3] Advances have also been described in the development of *chiral* catalysts that achieve cross-couplings of secondary electrophiles with high enantioselectivity, although to date these have been limited to couplings of activated electrophiles (e.g., allylic, benzylic, or α-halocarbonyl) with either organozinc or organosilicon reagents.[4,5] In this report, we expand upon the scope of both reaction partners, specifically, we establish that a chiral nickel catalyst can cross-couple certain *unactivated* alkyl electrophiles with organo*boron* compounds[6] in good enantiomeric excess (eq 1).



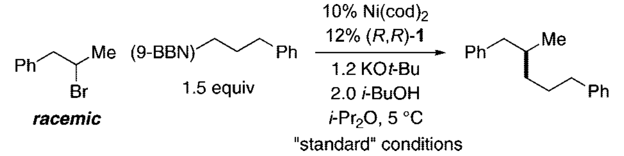
(1)

The conditions that we had employed for asymmetric Negishi and Hiyama reactions were ineffective at cross-coupling 2-bromo-3-phenylpropane with an alkyl-(9-BBN).[4,5] We recently described a method that achieves alkyl−alkyl couplings of secondary electrophiles with organoboron reagents,[3d] and we were pleased to determine that this catalyst can accomplish an asymmetric cross-coupling with promising ee (58% ee; eq 2).



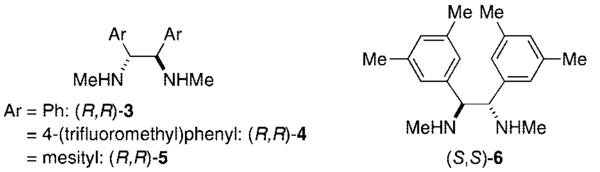
(2)

Table 1. An Asymmetric Suzuki Reaction of an Unactivated Alkyl Bromide: Effect of Reaction Parameters[a]



entry	variation from the standard conditions	ee (%)	yield (%)
1	none	89	85
2	no (*R*,*R*)-**1**	–	<2
3	(*R*,*R*)-**3**, instead of (*R*,*R*)-**1**	85	76
4	(*R*,*R*)-**4**, instead of (*R*,*R*)-**1**	88	66
5	(*R*,*R*)-**5**, instead of (*R*,*R*)-**1**	−6	46
6	(*S*,*S*)-**6**, instead of (*R*,*R*)-**1**	−80	72
7	rt, instead of 5 °C	87	76
8	dioxane at rt, instead of *i*-Pr_2O at 5 °C	60	32
9	5% $Ni(cod)_2$ and 6% (*R*,*R*)-**1**, instead of 10%/12%	89	70

[a] The yield was determined by GC versus a calibrated internal standard. A negative ee value signifies that the opposite enantiomer of the product was formed preferentially.



Optimization of this initial lead provided a method that achieves the desired carbon−carbon bond formation in a stereoconvergent process in very good ee and yield (89% ee, 85% yield; Table 1, entry 1). From a practical point of view, it is noteworthy that both of the catalyst components, $Ni(cod)_2$ and (*R*,*R*)-**1**, are commercially available. In the absence of the diamine, essentially no cross-coupling occurs (entry 2). An array of related ligands in which the aromatic ring is unsubstituted, para-substituted, or meta-substituted furnishes slightly to modestly lower enantioselectivities and yields (e.g., entries 3, 4, and 6), whereas the presence of a hindered mesityl group leads to nearly racemic product and less efficient carbon−carbon bond formation (entry 5). If the cross-coupling is conducted at room temperature, rather than at −5 °C, a small erosion in yield is observed (entry 7), and replacement of *i*-Pr_2O with dioxane is deleterious (entry 8).[7] Finally, if half of the “standard” catalyst loading is employed, the yield of the coupling is somewhat diminished.

We have examined the scope of this asymmetric Suzuki cross-coupling process with respect to the electrophile (Table 2). For alkyl groups that range in steric demand from methyl to isopropyl, very good ee is generally observed (e.g., entries 1−4). The presence of an electron-rich aromatic group leads to higher ee than an electron-poor substituent (entry 5 vs entry 6), and a hindered *o*-tolyl group is tolerated (entry 7). It is noteworthy that these asymmetric Suzuki reactions of unactivated alkyl bromides proceed under unusually mild conditions (i.e., below room temperature).[8,9]

Our current hypothesis is that the chiral Ni/**1** complex differentiates between the two alkyl groups (CH_2Ar vs alkyl in Table 2) of the unactivated halide via a secondary interaction between the CH_2Ar substituent and the catalyst. Consistent with the suggestion that proper positioning of the aromatic group is important for obtaining good ee,

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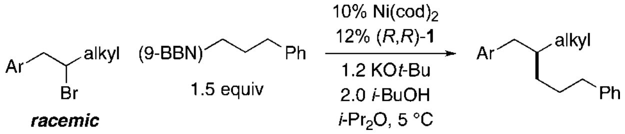
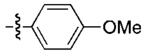
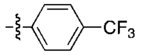
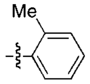
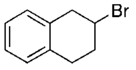
Table 2. Asymmetric Suzuki Reactions of Unactivated Alkyl Bromides: Variation of the Electrophile



entry	Ar	alkyl	ee (%)	yield (%)[a]
1	Ph	Me	90	78
2	Ph	n-Bu	94	84
3	Ph	CH_2CH_2Ph	90	68
4	Ph	i-Pr	88	74
5		Me	90	84
6		Me	70	82
7		Me	86	86

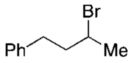
[a] Isolated yield. All data are the average of two experiments.

bromides **7** and **8** undergo Suzuki cross-coupling with low enantioselectivity under our standard conditions.[10]



7

5% ee

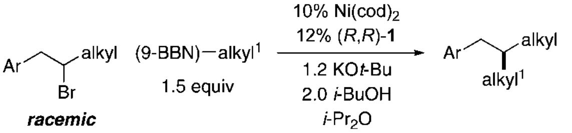


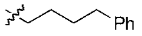
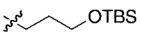
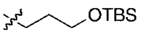
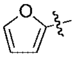
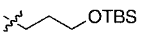
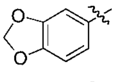
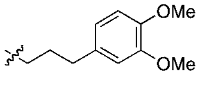
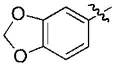
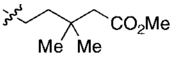
8

14% ee

Additional examples that illustrate the scope of this method for asymmetric Suzuki reactions of unactivated alkyl halides are provided in Table 3. Thus, a range of heteroatom-containing electrophiles and alkylboranes serve as suitable cross-coupling partners (e.g., entries 2−7), although the reactions generally proceed in somewhat lower ee than for less functionalized substrates.[11,12]

Table 3. Asymmetric Suzuki Reactions of Unactivated Alkyl Bromides



entry	Ar	alkyl	alkyl[1]	ee (%)	yield (%)[a]
1[b]	Ph	Me		80	68
2[c]	Ph	Me		78	68
3[c]	Ph	n-Bu		82	64
4[b]	Ph	CH_2OBn	n-Hex	40	69
5[c]		Me		66	62
6[c]		Et		85	74
7[c]		Et		76	73

[a] Isolated yield. [b] Run at 5 °C. [c] Run at rt. All data are the average of two experiments.

In summary, we have developed the first effective method for asymmetric cross-couplings of *unactivated* alkyl electrophiles, specifically, a nickel-based catalyst for stereoconvergent Suzuki reactions of homobenzylic bromides with alkylboranes. It is noteworthy that there are no other examples of enantioselective Suzuki couplings of alkyl electrophiles and that the catalyst components are commercially available. Although the process has limitations, its discovery demonstrates that unactivated alkyl electrophiles, a very important family of coupling partners, can begin to be considered as potential substrates for enantioselective cross-couplings. In view of the potential impact of such reactions on organic synthesis, efforts to develop more versatile catalysts are underway.

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

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(1) For two of the pioneering investigations of palladium- and nickel-catalyzed cross-couplings of unactivated alkyl electrophiles, see: (a) Ishiyama, T.; Abe, S.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1992**, 691–694. (b) Devasagayaraj, A.; Stüdemann, T.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2723–2725.

(2) For reviews of cross-coupling reactions of alkyl electrophiles, see: (a) Frisch, A. C.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 674–688. (b) Netherton, M. R.; Fu, G. C. In *Topics in Organometallic Chemistry: Palladium in Organic Synthesis*; Tsuji, J., Ed.; Springer: New York, 2005. (c) Netherton, M. R.; Fu, G. C. *Adv. Synth. Catal.* **2004**, *346*, 1525–1532.

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(4) For asymmetric Negishi reactions of activated alkyl electrophiles, see: (a) α-Bromo amides: Fischer, C.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 4594–4595. (b) Benzylic bromides and chlorides: Arp, F. O.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 10482–10483. (c) Allylic chlorides: Son, S.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 2756–2757.

(5) For asymmetric Hiyama reactions of α-bromo esters, see: Dai, X.; Strotman, N. A.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 3302–3303.

(6) For reviews of the Suzuki reaction, see: (a) Miyaura, N. In *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: New York, 2004; Chapter 2. (b) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-i., Ed.; Wiley-Interscience: New York, 2002. (c) Miyaura, N. *Top. Curr. Chem.* **2002**, *219*, 11–59.

(7) In initial studies, related solvents such as t-BuOMe and glyme were inferior to i-Pr_2O.

(8) To the best of our knowledge, these are the first examples of nickel-catalyzed Suzuki reactions of unactivated alkyl electrophiles that proceed below room temperature.

(9) Notes: (a) In a gram-scale reaction, the asymmetric Suzuki cross-coupling illustrated in entry 1 of Table 2 was accomplished in 89% ee and 95% yield. (b) During the course of a coupling reaction, the ee of the starting material is less than 10%, and the ee of the product is essentially constant. (c) The ee of the product correlates linearly with the ee of the ligand. (d) For the cross-couplings depicted in Table 2, all of the alkyl bromide has been consumed.

(10) For the substrate illustrated in entry 3 of Table 2, the catalyst is effectively differentiating between a benzyl and a homobenzyl substituent.

(11) Under our standard conditions, alkylboranes derived from the hydroboration of disubstituted olefins are not suitable reaction partners, and the cross-coupling of a phthalimide-containing alkylborane proceeded in modest yield (~40%).

(12) We speculate that the modest ee observed in entry 4 of Table 3 may be due to competitive coordination of the ether oxygen to the catalyst. Studies directed at exploring this hypothesis are underway.

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