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Asymmetric Nickel-Catalyzed Negishi Cross-Couplings of Secondary α-Bromo Amides with Organozinc Reagents

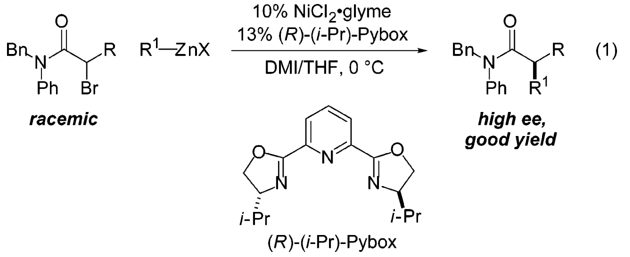
Christian Fischer and Gregory C. Fu*

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

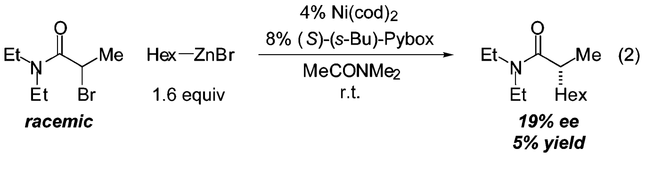
Received February 1, 2005; E-mail: gcf@mit.edu

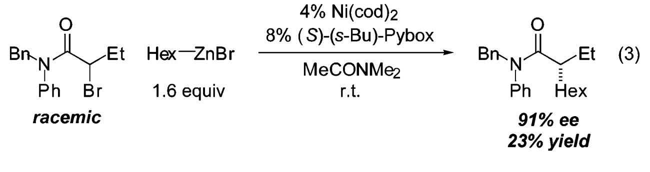
Recently, considerable progress has been described in the quest for catalysts that can cross-couple alkyl electrophiles.[1] Although most investigations have focused on reactions of primary electrophiles, there have also been noteworthy advances in the development of catalysts that achieve couplings of secondary alkyl electrophiles.[2,3]

For cross-couplings of unsymmetrical secondary electrophiles, a stereocenter may be produced at the carbon that bears the leaving group. This stereochemical aspect adds an important new dimension to these carbon−carbon bond-forming processes, control of which would greatly increase their utility. In this report, we describe the first catalytic enantioselective cross-couplings of secondary alkyl electrophiles (eq 1; DMI = 1,3-dimethyl-2-imidazolidinone).[4]



In 2003, we reported that Ni(cod)$_2$/(*s*-Bu)-Pybox catalyzes Negishi reactions of secondary alkyl bromides and iodides.[3a] Our observation that the cross-couplings proceed particularly well in the presence of (*s*-Bu)-Pybox clearly opened the door to the possibility of achieving an asymmetric variant.[5] Upon exploring several different families of secondary alkyl electrophiles, we obtained promising results with α-bromo amides (for some illustrative data, see eqs 2 and 3). Optimization of the reaction conditions led to a catalyst system that furnishes the desired product in both high enantiomeric excess and yield (eq 4).[6]





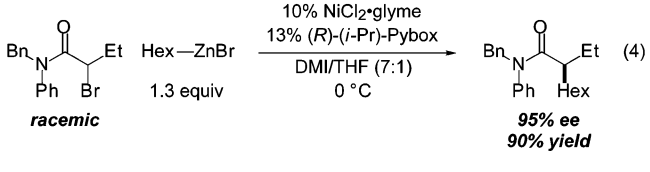
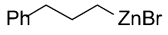
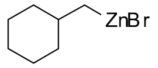
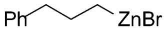
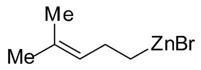
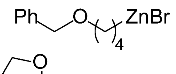
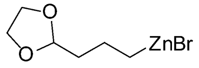
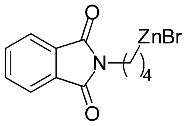
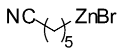


Table 1. Asymmetric Negishi Cross-Couplings of Secondary α-Bromo Amides with Organozinc Reagents (eq 1; all data are the average of two experiments)

entry	R	R^1—ZnX	yield (%)[a]	ee (%)
1	Et	Hex—ZnBr	90	96
2	Et	MeZnI	90	91
3	Et		84	96
4[b]	Et		58	92
5	*n*-Bu	Hex—ZnBr	85	96
6	*n*-Bu		79	96
7	*i*-Bu	MeZnI	78	87
8	Et		78	95
9	Et		77	96
10[c]	Me		66 (60)	77 (>98)
11	Et		51	96
12	Et		70	93

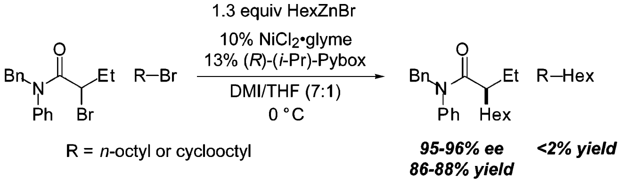
[a] Isolated yield. [b] The coupling was conducted at room temperature. [c] For the second run (data given in parentheses), the product was recrystallized, which leads to an enrichment of the enantiomeric excess of the product.

This method has proved to be general for catalytic asymmetric Negishi cross-couplings of a range of α-bromo amides with an array of organozinc reagents (Table 1).[7] Not only unfunctionalized (entries 1−7) but also functionalized (entries 8−12) organozincs serve as useful coupling partners, affording the target compounds in very good enantiomeric excess. Thus, asymmetric carbon−carbon bond formation proceeds smoothly in the presence of groups such as an olefin (entry 8), a benzyl ether (entry 9), an acetal (entry 10), an imide (entry 11), and a nitrile (entry 12).[8]

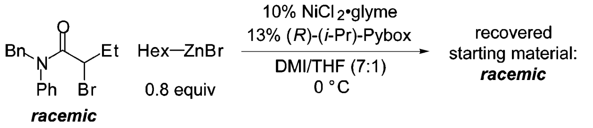
Several other observations are worthy of note. First, this catalyst system is highly selective for coupling an α-bromo amide in the presence of either an unactivated primary or secondary alkyl bromide (eq 5). Second, there is no evidence for kinetic resolution during the catalytic asymmetric cross-coupling (eq 6). Third, the amide can be converted into other useful functional groups (eq 7).

We have not yet had the opportunity to systematically investigate the mechanism(s) of the nickel-based catalysts that we have described for cross-coupling alkyl electrophiles.[3] Recently, Vicic suggested that, for Negishi reactions, carbon−carbon bond forma-

10.1021/ja0506509 CCC: $30.25



(5)



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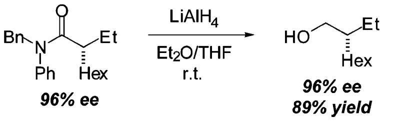

(7)

tion may proceed via radical−radical coupling.[9] In view of the high enantioselectivity that we observe under the conditions described in eq 1, we believe that for this system the Vicic mechanism is unlikely to be operative.

In conclusion, we have developed the first method that achieves catalytic asymmetric cross-couplings of alkyl electrophiles. These Ni/(*i*-Pr)-Pybox-catalyzed reactions of secondary α-bromo amides with organozinc reagents are tolerant of an array of functional groups and generally proceed in good yield and in high enantiomeric excess. This advance further highlights the potential impact of cross-couplings of alkyl electrophiles on synthetic organic chemistry.

Acknowledgment. This paper is dedicated to our colleague, Prof. Richard R. Schrock, on the occasion of his 60th birthday. Support has been provided by the National Institutes of Health (National Institute of General Medical Sciences, R01-GM62871), the German Academic Exchange Service (postdoctoral fellowship to C.F.), Merck Research Laboratories, and Novartis. Funding for the MIT Department of Chemistry Instrumentation Facility has been furnished in part by the National Science Foundation (CHE-9808061 and DBI-9729592).

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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(2) For pioneering studies of iron-, copper-, and cobalt-catalyzed couplings of Grignard reagents, see: (a) Brinker, U. H.; König, L. *Chem. Ber.* **1983**, *116*, 882−893 (iron). (b) Donkervoort, J. G.; Vicario, J. L.; Jastrzebski, J. T. B. H.; Gossage, R. A.; Cahiez, G.; van Koten, G. *J. Organomet. Chem.* **1998**, *558*, 61−69 (copper). (c) Tsuji, T.; Yorimitsu, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2002**, *41*, 4137−4139 (cobalt). (d) Nakamura, M.; Matsuo, K.; Ito, S.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 3686−3687 (iron). (e) Nagano, T.; Hayashi, T. *Org. Lett.* **2004**, *6*, 1297−1299 (iron). (f) Martin, R.; Fürstner, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 3955−3957 (iron).

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(5) For reviews of applications of oxazoline-based chiral ligands, including pybox, in asymmetric catalysis, see: (a) McManus, H. A.; Guiry, P. J. *Chem. Rev.* **2004**, *104*, 4151−4202. (b) Nishiyama, H. In *Advances in Catalytic Processes*; Doyle, M. P., Ed.; JAI Press: Greenwich, CT, 1997; Volume 2, pp 153−188.

(6) Notes: (a) $NiCl_2$•glyme, unlike $Ni(cod)_2$, is air-stable; both are commercially available. $NiBr_2$•diglyme and $NiCl_2$•diglyme can also be used, although they are somewhat less effective. (b) (*i*-Pr)-Pybox, unlike (*s*-Bu)-Pybox, is commercially available. (c) We have not been able to employ commercially available HexZnBr (Aldrich) in this process. We recommend that pure organozinc reagents be prepared from the corresponding alkyl bromides according to the straightforward procedure of Huo: Huo, S. *Org. Lett.* **2003**, *5*, 423−425. (d) At room temperature, the product is generated in 91% ee. At −20 °C, the cross-coupling process is slow.

(7) General Procedure for Table 1: In the air (no special precautions are necessary), a 10 mL Schlenk flask was charged with $NiCl_2$•glyme (22.0 mg, 0.100 mmol), (*R*)-(*i*-Pr)-Pybox (39.2 mg, 0.130 mmol), and the α-bromo amide (1.00 mmol). The flask was purged with argon for 5 min, and then DMI (2.2 mL) and THF (0.5 mL) were added. The resulting orange solution was stirred at room temperature for 20 min, and then the flask was placed into a 0 °C bath. The reaction mixture was stirred for 10 min, and then the organozinc reagent (1.0 M in DMI; 1.3 mL, 1.3 mmol) was added. The resulting dark-brown reaction mixture was stirred for 12 h at 0 °C. Then, the excess organozinc reagent was quenched by the addition of ethanol (0.5 mL), and the brown mixture was passed through a plug of silica gel (eluted with Et_2O) to remove inorganic salts and most of the DMI. The filtrate was concentrated, and the resulting orange oil was purified by flash chromatography.

(8) Notes: (a) The yield of the reaction is sensitive to the steric demand of the coupling partners. Thus, we have not been able to efficiently cross-couple a secondary organozinc reagent or an α-isopropyl−α-bromo amide. (b) Under the standard conditions, benzylzinc reagents are not suitable substrates. (c) For the cross-coupling illustrated in entry 1 of Table 1, when the reaction is run on a 10 mmol scale, we obtain the product in 88% yield (3.0 g) and 95% ee. (d) The process is not highly sensitive to oxygen or moisture; when we conduct a coupling under air in a closed vial with 1.6 equiv of the organozinc reagent, we obtain essentially identical yield and enantiomeric excess. (e) Under identical conditions, α-bromoesters furnish lower yield and lower enantiomeric excess.

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JA0506509