J|A|C|S
COMMUNICATIONS

Published on Web 07/08/2005

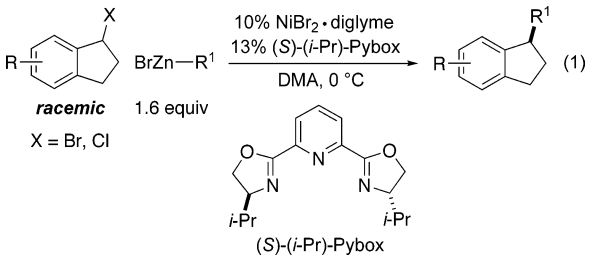
Catalytic Enantioselective Negishi Reactions of Racemic Secondary Benzylic Halides

Forrest O. Arp and Gregory C. Fu*

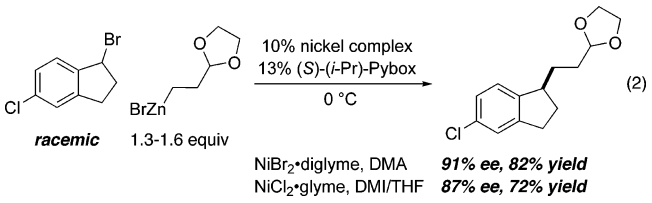
Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

Received June 8, 2005; E-mail: gcf@mit.edu

During the past two years, progress has been achieved in developing nickel-catalyzed cross-coupling reactions of secondary alkyl electrophiles.[1] To fully exploit this family of carbon−carbon bond-forming processes, one must be able to accomplish them enantioselectively. We recently described the first examples of catalytic asymmetric cross-couplings of secondary electrophiles, employing α-bromoamides as substrates.[2] In this report, we establish that a second family of reaction partners, racemic secondary benzylic halides, can be coupled with organozinc reagents in very good enantiomeric excess (eq 1; DMA = *N*,*N*-dimethylacetamide).



Upon investigating a variety of conditions, we determined that Negishi reactions of 1-bromoindanes proceed in good enantiomeric excess and yield in the presence of $NiBr_2$•diglyme/(*i*-Pr)-Pybox in DMA at 0 °C (eq 2; 91% ee, 82% yield). Simultaneously with these studies, we were exploring asymmetric cross-couplings of α-bromoamides;[2] when we applied to 1-bromoindanes the procedure that we had developed for amides, we obtained somewhat lower enantiomeric excess and yield (eq 2; 87% ee, 72% yield; DMI = 1,3-dimethyl-2-imidazolidinone).

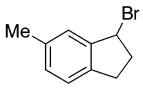
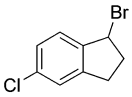
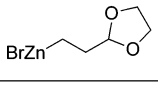
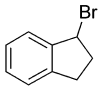
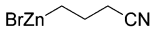
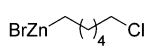
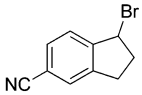
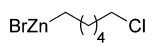
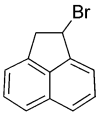
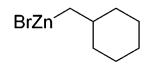
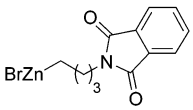
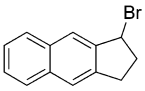
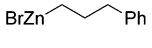
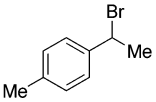
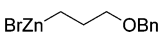


Several features of this method are noteworthy. First, both catalyst components are commercially available and air-stable. Second, while we routinely conduct the cross-couplings under an inert atmosphere, we have determined that the reactions are not highly oxygen- or moisture-sensitive; under identical conditions, couplings run in a capped vial under an atmosphere of air proceed in comparable enantiomeric excess and yield. Third, although nickel complexes can cross-couple aryl halides (including chlorides[3]), our catalyst reacts selectively with an alkyl halide (a benzylic bromide). Fourth, the process is stereoconvergent; both enantiomers of the racemic starting material are preferentially transformed into one enantiomer of the product.[4]

Cross-couplings that illustrate the scope of this method are provided in Table 1.[5,6] Functionalized organozinc reagents, including those that bear a cyano or a chloride group, couple with 1-bromoindanes in very good enantiomeric excess (entries 2−5).[7] 1-Bromoacenaphthene is also a suitable cross-coupling partner (entries 6−8). A branch in the β position of the alkylzinc reagent (entry 6 vs entry 7) or the presence of an imide substituent results in less-efficient carbon−carbon bond formation (entry 8), consistent with our earlier observations.[2] Other 1-bromoindane derivatives undergo highly enantioselective Negishi cross-coupling (entry 9). Thus, for cyclic benzylic bromides, this method consistently furnishes enantiomeric excesses greater than 90% (entries 1−9). We have also obtained a promising lead in a catalytic asymmetric Negishi reaction of an acyclic secondary benzylic bromide with a functionalized organozinc reagent (entry 10).[8]

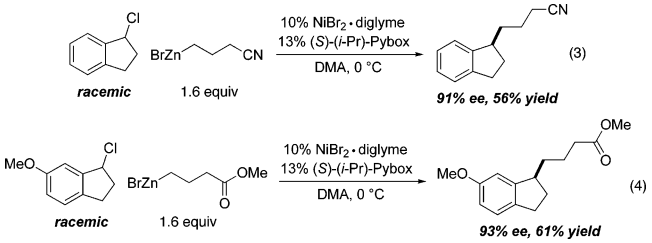
Until now, we have not described success in employing nickel catalysts in any cross-couplings (e.g., Negishi, Suzuki, Hiyama, or Stille reactions) of secondary chlorides.[9] We were, therefore, pleased to observe that $NiBr_2$/Pybox achieves reactions of benzylic chlorides with functionalized organozincs with excellent enantioselectivity (eqs 3 and 4).

Table 1. Catalytic Enantioselective Negishi Reactions of Racemic Secondary Benzylic Bromides[a]

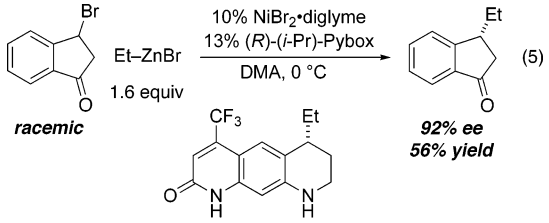
entry	R–X	R^1–ZnBr	yield (%)	ee (%)
1		BrZn–Hex	89	96
2			82	91
3			64	91
4			69	94
5			47	91
6		BrZn–Bu	72	98
7[b]			39	96
8[b]			41	99
9			76	98
10			63	75

[a] For the reaction conditions, see eq 1. All data are the average of two experiments. [b] The coupling was performed at room temperature.

10.1021/ja053751f CCC: $30.25



Chiral indanes have served as intermediates in the synthesis of a variety of bioactive compounds,[10,11] and we have established that our new method provides ready access to such targets. For example, Ligand Pharmaceuticals' route to LG 121071, the first orally active, nonsteroidal androgen receptor agonist, proceeds via (*R*)-3-ethylindanone, which was generated in three steps from propiophenone via a copper-catalyzed enantioselective conjugate reduction (86% ee).[12,13] Through a nickel-catalyzed asymmetric Negishi cross-coupling, we can synthesize the key intermediate in 92% ee in two steps from commercially available 1-indanone (eq 5).



MacLeod has employed racemic *trans*-1,3-dimethylindane in his syntheses of *trans*-trikentrin A[14] and iso-*trans*-trikentrin B,[15] both of which have been isolated from the marine sponge *Trikentrion flabelliforme* and exhibit antibacterial activity. We have established that this indane can be prepared enantioselectively using two Negishi cross-couplings (Figure 1). Both diastereomers of intermediate **A** react to generate the desired *trans*-1,3-dimethylindane.[16]

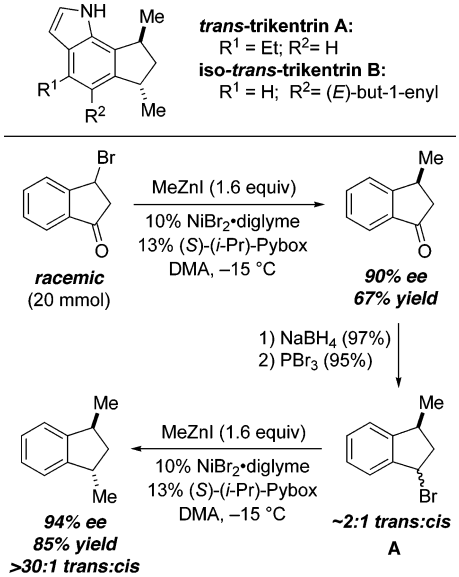


Figure 1. Catalytic enantioselective synthesis of *trans*-1,3-dimethylindane.

In conclusion, we have described the first highly enantioselective cross-couplings of secondary benzylic halides, specifically, Negishi reactions of racemic bromides and chlorides with organozinc reagents. Our method employs commercially available catalyst components and is not highly air- or moisture-sensitive. Current efforts are directed at further expanding the scope of nickel-catalyzed coupling reactions of alkyl electrophiles.

Acknowledgment. We thank Jianrong (Steve) Zhou for important preliminary studies. Support has been provided by the National Institutes of Health (National Institute of General Medical Sciences, R01-GM62871), 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.

References

(1) For recent reviews, see the following: (a) Metal-catalyzed cross-coupling reactions of unactivated alkyl halides: Frisch, A. C.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 674−688. (b) Nickel-catalyzed couplings of unactivated alkyl electrophiles: Netherton, M. R.; Fu, G. C. *Adv. Synth. Catal.* **2004**, *346*, 1525−1532.

(2) Fischer, C.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 4594−4595.

(3) For a few examples, see: (a) Tamao, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 4374−4376. (b) Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 6054−6058. (c) Lipshutz, B. H.; Blomgren, P. A. *J. Am. Chem. Soc.* **1999**, *121*, 5819−5820.

(4) Our current hypothesis is that the benzylic halide is transformed into a benzylic radical, which then combines with nickel to generate a benzylnickel intermediate.

(5) General procedure: In the air (no special precautions are necessary), a 4 mL glass vial was charged with $NiBr_2$·diglyme (35.3 mg, 0.100 mmol), (*S*)-(*i*-Pr)-Pybox (39.2 mg, 0.130 mmol), and the benzylic halide (1.00 mmol). The vial was fitted with a septum cap and purged with argon for 15 min. DMA (1.75 mL) was added, and the resulting orange mixture was placed in a 0 °C bath and stirred for 15 min. The organozinc reagent (1.6 M in DMA; 1.0 mL, 1.6 mmol) was added in a single portion, and the resulting homogeneous brown solution was stirred at 0 °C for 24 h. Then, the remaining organozinc reagent was quenched by the addition of ethanol (0.3 mL), and the resulting orange solution was purified directly by flash chromatography.

(6) Notes: (a) Use of a commercially available organozinc reagent (Aldrich) led to a lower enantiomeric excess and yield. We recommend that organozinc reagents be prepared from the corresponding alkyl bromides according to the straightforward procedure of Huo: Huo, S. *Org. Lett.* **2003**, *5*, 423−425. (b) Less than 2% of the desired product is generated in the absence of $NiBr_2$·diglyme. (c) Under our standard conditions, we cannot effectively (yield and/or ee) cross-couple 1,3-dibromoindane, 1-bromotetralin, benzylzincs, or arylzincs.

(7) The product of the Negishi reaction depicted in entry 4 (Table 1) has been used as an intermediate in the synthesis of selective σ ligands: Berardi, F.; Ferorelli, S.; Colabufo, N. A.; Leopoldo, M.; Perrone, R.; Tortorella, V. *Bioorg. Med. Chem. Lett.* **2001**, *9*, 1325−1335.

(8) The product of the coupling illustrated in entry 10 (Table 1) has been employed in the total synthesis of natural products such as (+)-nuciferol and (+)-nuciferal. The two previous routes to this compound proceeded in 13 steps from mannitol (Takano, S.; Goto, E.; Ogasawara, K. *Tetrahedron Lett.* **1982**, *23*, 5567−5570) and 9 steps from *trans*-2-butene-1,4-diol (Takano, S.; Sugihara, T.; Samizu, K.; Akiyama, M.; Ogasawara, K. *Chem. Lett.* **1989**, 1781−1784).

(9) (a) Negishi: Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 14726−14727. (b) Suzuki: Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 1340−1341. (c) Hiyama: Powell, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 7788−7789. (d) Stille: Powell, D. A.; Maki, T.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 510−511.

(10) (a) For a review of the synthesis of indanes, see: Hong, B.-C.; Sarshar, S. *Org. Prep. Proc. Int.* **1999**, *31*, 1−86. (b) For a review of indane derivatives of biological interest, see: Ganellin, C. R. *Adv. Drug Res.* **1967**, *4*, 163−249.

(11) (a) For leading references to progress on the catalytic asymmetric hydrogenation of indenes, see: Halterman, R. L. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 2004; Supplement 2, pp 1−6. (b) For a specific example, see: Troutman, M. V.; Appella, D. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 4916−4917.

(12) (a) Hamann, L. G.; Mani, N. S.; Davis, R. L.; Wang, X.-N.; Marschke, K. B.; Jones, T. K. *J. Med. Chem.* **1999**, *42*, 210−212. (b) Mani, N. S.; Wu, M. *Tetrahedron: Asymmetry* **2000**, *11*, 4687−4691.

(13) For a five-step synthesis of (*S*)-3-ethylindanone, see: (a) Stephan, E.; Rocher, R.; Aubouet, J.; Pourcelot, G.; Cresson, P. *Tetrahedron: Asymmetry* **1994**, *5*, 41−44. (b) Brienne, M.-J.; Ouannes, C.; Jacques, J. *Bull. Soc. Chim. Fr.* **1967**, 613−623.

(14) MacLeod, J. K.; Monahan, L. C. *Aust. J. Chem.* **1990**, *43*, 329−337.

(15) MacLeod, J. K.; Ward, A.; Willis, A. C. *Aust. J. Chem.* **1998**, *51*, 177−187.

(16) To the best of our knowledge, this is the first synthesis of enantioenriched *trans*-1,3-dimethylindane.

JA053751F