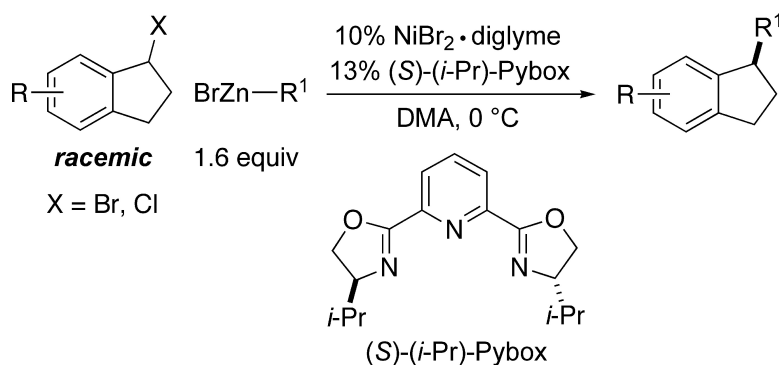


Catalytic Enantioselective Negishi Reactions of Racemic Secondary Benzylic Halides

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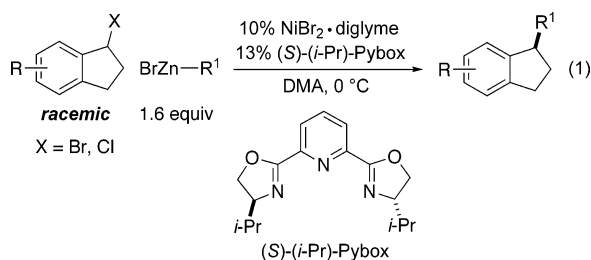
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Forrest O. Arp and Gregory C. Fu*

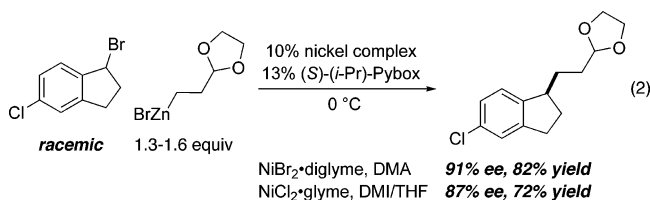
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During the past two years, progress has been achieved in developing nickel-catalyzed cross-coupling reactions of secondary alkyl electrophiles.¹ To fully exploit this family of carbon–carbon bond-forming processes, one must be able to accomplish them 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 NiBr₂·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 chlorides³), 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-bro-

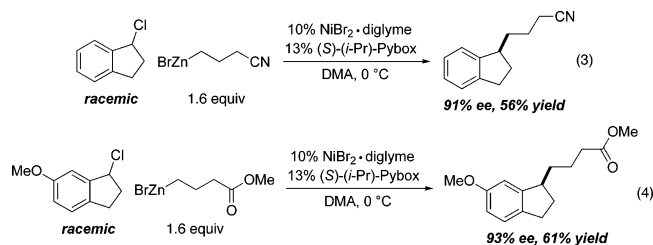
Table 1. Catalytic Enantioselective Negishi Reactions of Racemic Secondary Benzylic Bromides^a

entry	R–X	R ¹ –ZnBr	yield (%)	ee (%)
1		BrZn–Hex	89	96
2		BrZn–CH ₂ CH ₂ CH ₂ –O–CH ₂ CH ₂ –O	82	91
3		BrZn–CH ₂ CH ₂ –CN	64	91
4		BrZn–CH ₂ (CH ₂) ₄ –Cl	69	94
5		BrZn–CH ₂ (CH ₂) ₄ –Cl	47	91
6		BrZn–Bu	72	98
7 ^b		BrZn–CH ₂ CH ₂ –C ₆ H ₁₁	39	96
8 ^b		BrZn–CH ₂ (CH ₂) ₃ –N–C(=O)–C ₆ H ₄ –C(=O)–N	41	99
9		BrZn–CH ₂ CH ₂ CH ₂ –Ph	76	98
10		BrZn–CH ₂ CH ₂ CH ₂ –O–Bn	63	75

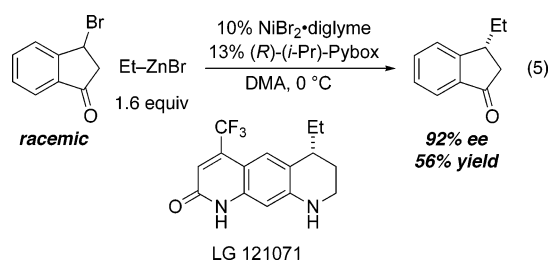
^a For the reaction conditions, see eq 1. All data are the average of two experiments. ^b The coupling was performed at room temperature.

moindanes in very good enantiomeric excess (entries 2–5).⁷ 1-Bromoacene 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 NiBr₂/Pybox achieves reactions of benzylic chlorides with functionalized organozinc reagents with excellent enantioselectivity (eqs 3 and 4).



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 A¹⁴ and *iso-trans*-trikentrin B,¹⁵ both of which have been isolated from the marine sponge *Trikentron 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 inter-

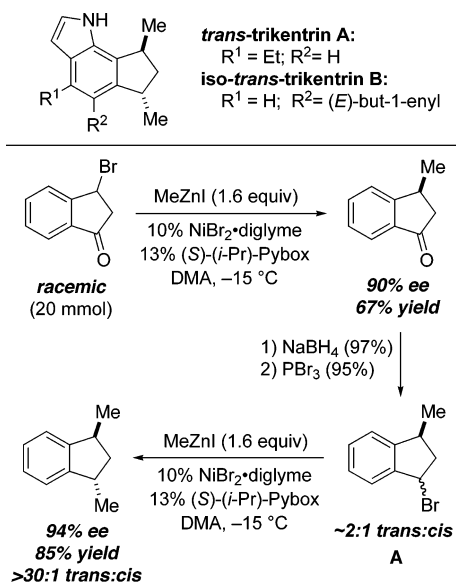


Figure 1. Catalytic enantioselective synthesis of *trans*-1,3-dimethylindane.

mediate **A** react to generate the desired *trans*-1,3-dimethylindane.¹⁶

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.

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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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- (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 NiBr₂·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 NiBr₂·diglyme. (c) Under our standard conditions, we cannot effectively (yield and/or ee) cross-couple 1,3-dibromoindane, 1-bromotetralin, benzylzincs, or arylzincs.
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