Communication

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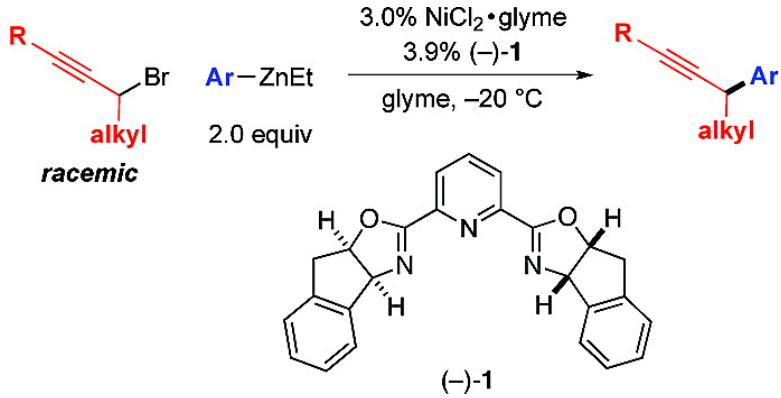

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Nickel-Catalyzed Asymmetric Cross-Couplings of Racemic Propargylic Halides with Arylzinc Reagents

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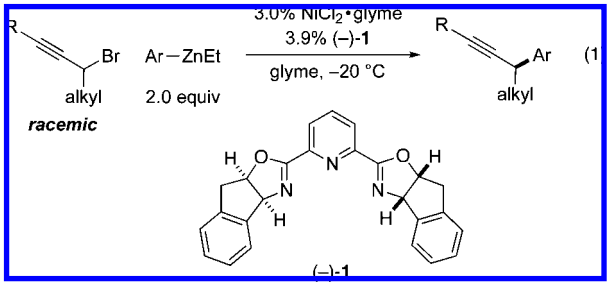
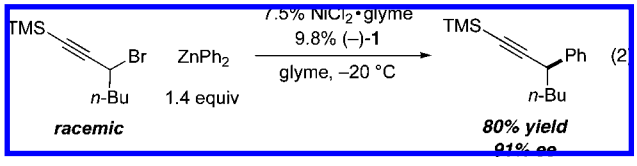
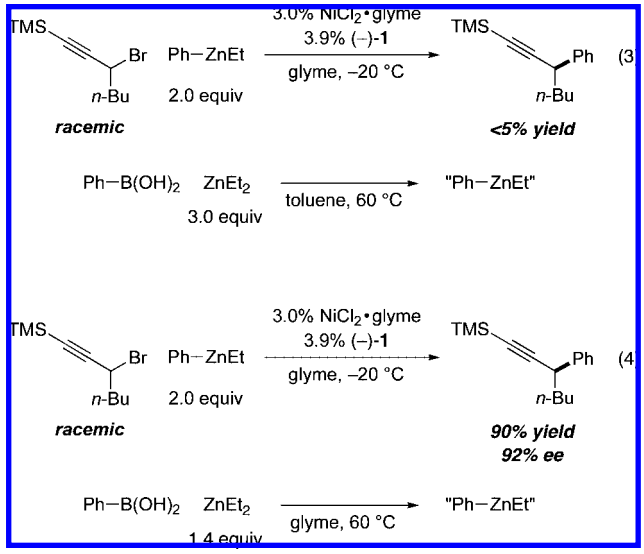
We have recently described the use of chiral nickel complexes to achieve catalytic asymmetric cross-couplings of organozinc,[1,2] -silicon,[3] and -boron[4] reagents with racemic secondary alkyl electrophiles, specifically, α-halocarbonyl compounds and allylic, benzylic, and homobenzylic halides.[5−7] To fully exploit the tremendous potential of enantioselective cross-couplings, it is necessary to expand the scope to other families of reaction partners. With respect to electrophiles, propargylic halides are attractive substrates, since an alkyne is an extremely versatile functional group.[8] In this report, we establish that, in the presence of a chiral Ni/pybox complex, a wide array of racemic propargylic halides can be cross-coupled with arylzinc reagents in a stereoconvergent process (eq 1).



In previous investigations of nickel-catalyzed asymmetric Negishi[9] reactions, we observed that *alkyl*zincs can be coupled with α-bromoesters, 1-haloindanes, and allylic chlorides in good yield and ee.[1] Unfortunately, under the same conditions we were not able to efficiently cross-couple *aryl*zinc reagents with these electrophiles. After extensive studies, we have now determined that enantioselective Negishi reactions of diarylzincs can in fact be achieved by $NiCl_2$•glyme/**1**[10] (both of which are commercially available) in glyme at −20 °C, and that a new family of electrophiles, propargylic halides, are suitable coupling partners (eq 2).



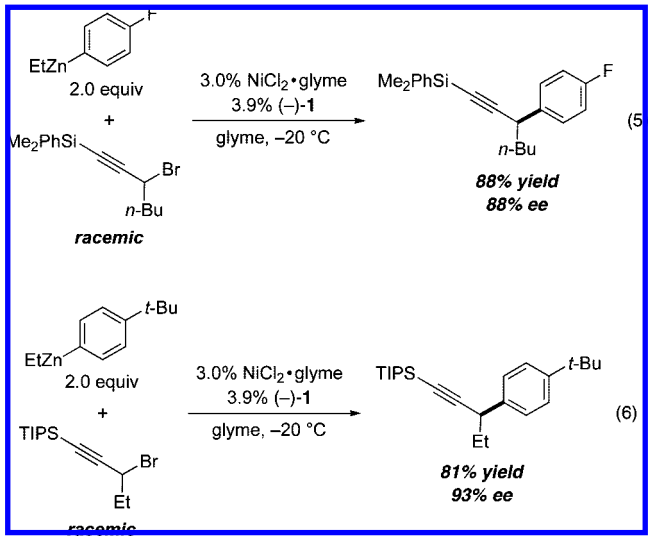
We next turned our attention to exploring the scope of the catalytic asymmetric arylation of propargylic halides. Few diarylzinc reagents are commercially available, and diarylzincs generated in situ by transmetalation of arylmagnesium or aryllithium compounds did not furnish results comparable to eq 2, due in part to interference by the residual magnesium or lithium salts.[11] Since arylzinc halides also were not suitable coupling partners under these conditions, we examined the use of arylzinc reagents produced by treatment of readily available arylboronic acids with diethylzinc.[12] Although the published procedure was not effective (eq 3), we were pleased to determine that, by employing a modified protocol, the coupling of an arylzinc with a propargylic halide can be achieved in very good yield and ee (eq 4).



With straightforward access to a useful family of arylzinc reagents, we examined the scope of this method for enantioselective Negishi cross-coupling, focusing initially on TMS-substituted propargylic bromides (Table 1), because of their ready deprotection. We have established that asymmetric carbon−carbon bond formation occurs smoothly in the presence of functional groups such as acetals, ethers, esters, and olefins. Reactions of hindered substrates proceed in modest yield (but high ee; e.g., entry 4).

Ni/**1** can be applied to asymmetric Negishi reactions of propargylic bromides that bear silyl protecting groups other than TMS (eq 5 and eq 6). Thus, under the same conditions, Me_2PhSi- and TIPS-substituted electrophiles also undergo enantioselective cross-coupling in good yield and ee.

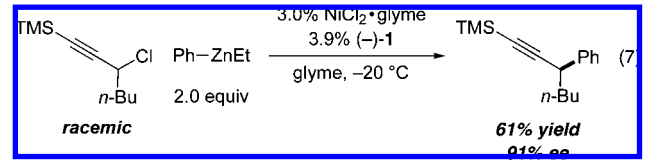
Furthermore, without modification this stereoconvergent method can be employed for asymmetric Negishi couplings of alkyl- and aryl-substituted propargylic bromides (Table 2); the alkyl substituent can range in size from methyl to *t*-butyl (entries 1−5). Carbon−carbon bond formation proceeds in generally good yield and enantioselectivity with an array of functionalized arylzinc reagents, including compounds that contain heterocycles. An



unactivated primary alkyl chloride is essentially inert to these conditions (entry 5).[13,14]

Not only propargylic bromides, but also chlorides, undergo cross-coupling under our standard conditions (eq 7). Although the yield is somewhat lower, the ee is essentially identical to that observed for the reaction of the corresponding bromide (see eq 4).

Wright and Anderson recently described a series of novel inhibitors of dihydrofolate reductase (from *Cryptosporidium*

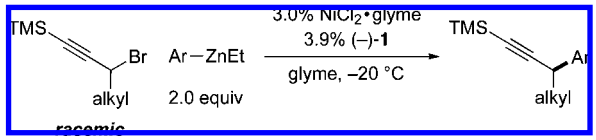


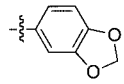
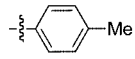
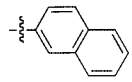
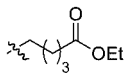
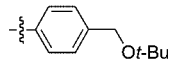
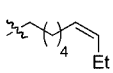
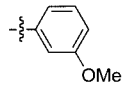
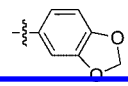
hominis and *Toxoplasma gondii*, two parasitic protozoa), the most active of which was pyrimidine **2** (Scheme 1).[15] They synthesized target compound **2** via a Sonogashira reaction of alkyne **3**, which was prepared in five steps (22% yield) from arylacetic acid **4**, by attachment and then removal of an Evans chiral oxazolidinone.

As a demonstration of our new Negishi cross-coupling method, we have applied it to a catalytic asymmetric synthesis of alkyne **3**. Thus, on a gram-scale, the propargylic bromide derived from commercially available 4-trimethylsilyl-3-butyn-2-ol was coupled with arylzinc reagent **5** (generated from a commercially available arylboronic acid) to furnish the key carbon–carbon bond in 93% ee.

In conclusion, we have developed a stereoconvergent method for the catalytic asymmetric Negishi cross-coupling of racemic secondary propargylic halides with arylzinc reagents. Neither family of compounds has previously been shown to be a suitable partner in such coupling processes. From a practical point of view, it is noteworthy that the catalyst components ($NiCl_2$•glyme

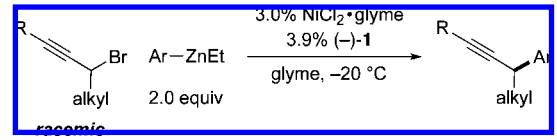
Table 1. Asymmetric Cross-Couplings of TMS-Protected Propargylic Bromides with Arylzinc Reagents[c]

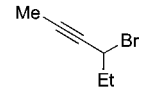
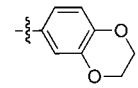
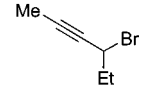
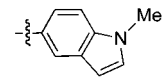
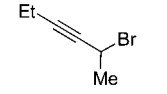
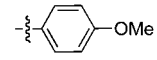
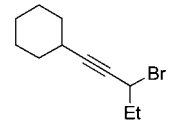
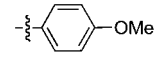
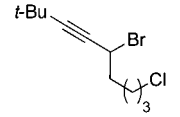
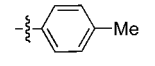
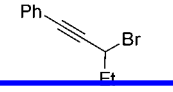


entry	alkyl	Ar	yield (%)[a]	ee (%)
1	Me		71	93
2	*n*-Bu		92	93
3[b]	*n*-Bu		70	93
4	*n*-Bu		39	92
5			76	94
6			79	94
7	*i*-Bu		71	93

[a] Yield of purified product. [b] Run using 6.0% $NiCl_2$•glyme, 7.8% (−)-**1**, and 3.0 equiv of ArZnEt. [c] All data are the average of two experiments.

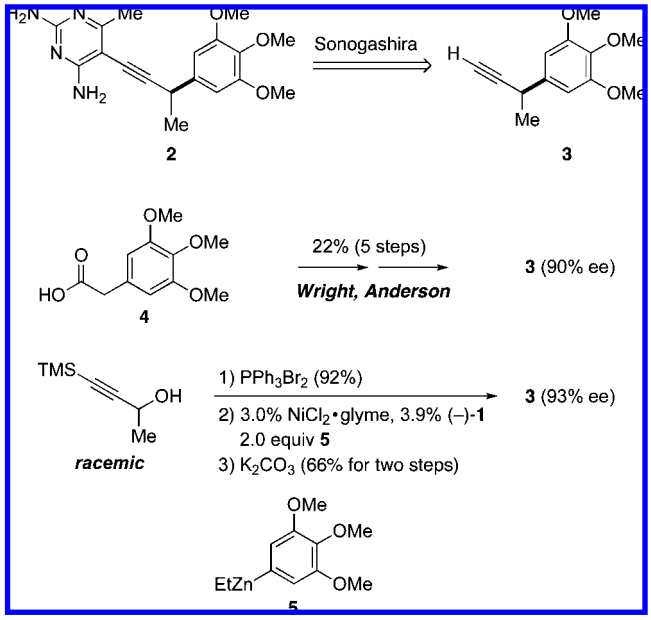
Table 2. Asymmetric Cross-Couplings of Propargylic Bromides with Arylzinc Reagents[c]



entry	electrophile	Ar	yield (%)[a]	ee (%)
1			81	88
2[b]			78	84
3			76	91
4			63	89
5			81	92
6			83	89

[a] Yield of purified product. [b] Run using 6.0% $NiCl_2$•glyme, 7.8% (−)-**1**, and 3.0 equiv of ArZnEt. [c] All data are the average of two experiments.

Scheme 1. Catalytic Asymmetric Synthesis of a Potent Dihydrofolate Reductase Inhibitor (**2**)



and pybox ligand **1**) are commercially available. Additional studies of enantioselective nickel-catalyzed cross-coupling reactions are underway.

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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.

References

(1) (a) Fischer, C.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 4594–4595. (b) Arp, F. O.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 10482–10483. (c) Son, S.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 2756–2757.

(2) For examples of applications by others of Ni/pybox catalysts to cross-coupling reactions of alkyl electrophiles, see: (a) Gong, H.; Sinisi, R.; Gagne, M. R. *J. Am. Chem. Soc.* **2007**, *129*, 1908–1909. (b) Phapale, V. B.; Bunuel, E.; Garcia-Iglesias, M.; Cardenas, D. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 8790–8795.

(3) Dai, X.; Strotman, N. A.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 3302–3303.

(4) Saito, B.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 6694–6695.

(5) 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. *Topics in Organometallic Chemistry: Palladium in Organic Synthesis*; Tsuji, J., Ed.; Springer: New York, 2005; pp 85–108. (c) Netherton, M. R.; Fu, G. C. *Adv. Synth. Catal.* **2004**, *346*, 1525–1532.

(6) 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.

(7) For mechanistic studies of nickel-catalyzed couplings of unactivated alkyl electrophiles, see: (a) Jones, G. D.; Martin, J. L.; McFarland, C.; Allen, O. R.; Hall, R. E.; Haley, A. D.; Brandon, R. J.; Konovalova, T.; Desrochers, P. J.; Pulay, P.; Vicic, D. A. *J. Am. Chem. Soc.* **2006**, *128*, 13175–13183. (b) Lin, X.; Phillips, D. L. *J. Org. Chem.* **2008**, *73*, 3680–3688.

(8) For some leading references to the chemistry of alkynes, see: (a) *Acetylene Chemistry*; Diederich, F., Stang, P. J., Tykwinski, R. R., Eds.; Wiley–VCH: New York, 2005. (b) *The Chemistry of Triple-Bonded Functional Groups*; Patai, S., Ed.; Wiley: New York, 1994.

(9) For a review of the Negishi reaction, see: (a) Negishi, E.-i.; Hu, Q.; Huang, Z.; Wang, G.; Yin, N. In *The Chemistry of Organozinc Compounds*; Rappoport, Z., Marek, I., Eds.; Wiley: New York, 2006; Chapter 11.

(10) For nickel-catalyzed asymmetric cross-coupling reactions of alkyl electrophiles, we have generally found that the use of a slight excess of ligand, relative to nickel, leads to improved yield and/or ee.

(11) Better, but still unsatisfactory, results were obtained if the magnesium/lithium salts were removed prior to cross-coupling.

(12) (a) Bolm, C.; Rudolph, J. *J. Am. Chem. Soc.* **2002**, *124*, 14850–14851. (b) Schmidt, F.; Stemmler, R. T.; Rudolph, J.; Bolm, C. *Chem. Soc. Rev.* **2006**, *35*, 454–470. (c) For a discussion of boron-to-zinc transmetalation, see: (ca) Jimeno, C.; Sayalero, S.; Fjermestad, T.; Colet, G.; Maseras, F.; Pericas, M. A. *Angew. Chem., Int. Ed.* **2008**, *47*, 1098–1101.

(13) Notes: (a) Under our standard conditions, vinylation and alkylation reactions of propargylic bromides do not proceed in high yield/ee. (b) During the course of these asymmetric Negishi cross-couplings, the ee of the unreacted propargylic bromide is less than 5% and the ee of the product remains constant. (c) In the absence of $NiCl_2$•glyme or pybox ligand **1**, essentially none of the desired alkyne is formed.

(14) Palladium-catalyzed cross-couplings of propargylic electrophiles with organometallic reagents typically furnish the allene, not the alkyne, as the major product. See: (a) Tsuji, J.; Mandai, T. In *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley–VCH: New York, 2004; Chapter 10; Ma, S. *Eur. J. Org. Chem.* **2004**, 1175–1183. The regioselectivity of carbon–carbon bond formation for the corresponding nickel-catalyzed processes has not been thoroughly investigated. For all of the Negishi reaction catalyzed by Ni/**1** that are reported herein, essentially none of the allene is formed (<5%), regardless of the choice of R.

(15) Pelphrey, P. M.; Popov, V. M.; Joska, T. M.; Beierlein, J. M.; Bolstad, E. S. D.; Fillingham, Y. A.; Wright, D. L.; Anderson, A. C. *J. Med. Chem.* **2007**, *50*, 940–950.

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