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# Catalytic Asymmetric Hiyama Cross-Couplings of Racemic α-Bromo Esters

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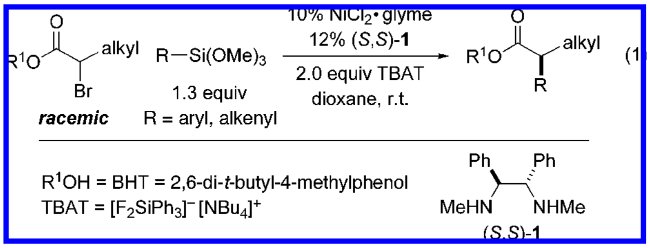
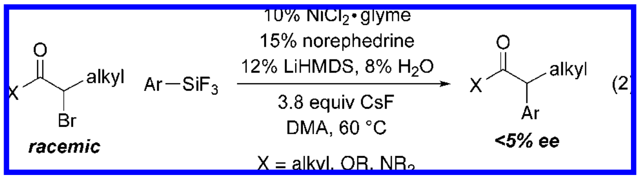
Enantioenriched α-aryl carboxylic acids are an important class of target molecules, due in large part to their bioactivity.[1] The catalytic asymmetric cross-coupling of an α-halo acid derivative with an aryl metal reagent represents a potentially attractive route to this family of structures, but to date no progress has been described toward the achievement of this objective. Indeed, until recently there were virtually no examples of efficient arylations of secondary α-halo carbonyl compounds by a Group 10 catalyst to generate even *racemic* products.[2] In this report, we establish that a nickel/diamine catalyst accomplishes asymmetric Hiyama reactions of α-bromo esters with aryl silanes to provide α-aryl esters in good enantiomeric excess (ee) (eq 1).[3,4]

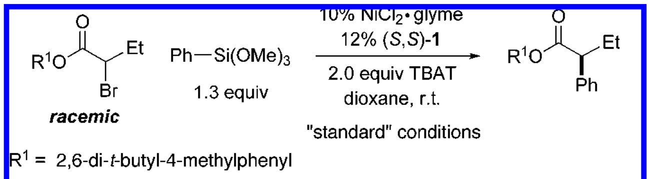


In 2007, we reported that Ni/norephedrine is an effective catalyst for Hiyama arylations of a variety of secondary α-halo carbonyl compounds (e.g., eq 2).[2] Unfortunately, the cross-coupling products were essentially racemic (<5% ee).[5]



However, through adjustment of the reaction parameters, we were able to develop a method that achieves stereoconvergent asymmetric Hiyama couplings of α-halo esters with organosilanes (e.g., Table 1, entry 1). The chiral ligand, fluoride activator, and silane each plays an important role in determining the efficiency of the cross-coupling process (entries 2−5), as does the steric demand of R$^1$ (entries 6−10). A good, but decreased, yield is observed when the catalyst loading is lowered, with little change in the ee (entry 11).

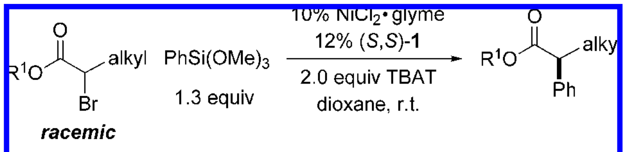
***Table 1.*** Asymmetric Hiyama Reactions: Effect of Reaction Parameters[a]



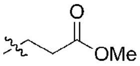
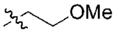
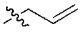
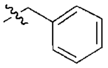
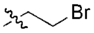
| entry | variation from the "standard" conditions | ee (%) | yield (%) |
|---|---|---|---|
| 1 | none | 99 | 80 |
| 2 | (−)–norephedrine, instead of (*S*,*S*)-**1** | – | 9 |
| 3 | CsF, instead of TBAT | – | <2 |
| 4 | TBAF, instead of TBAT | – | <2 |
| 5 | PhSiF$_3$, instead of PhSi(OMe)$_3$ | 98 | 60 |
| 6 | R$_1$ = Et | 23 | 92 |
| 7 | R$_1$ = *t*-Bu | 33 | 85 |
| 8 | R$_1$ = 2,4,6-trimethylphenyl | 13 | 78 |
| 9 | R$_1$ = 2,6-diisopropylphenyl | 73 | 75 |
| 10 | R$_1$ = 2,6-di-*t*-butyl-4-methoxyphenyl | 95 | 82 |
| 11 | 5% NiCl$_2$•glyme, 6% (*S*,*S*)-**1**, instead of 10%/12% | 98 | 70 |

[a] The yield was determined by GC versus a calibrated internal standard.

***Table 2.*** Asymmetric Hiyama Reactions: Phenylations of α-Bromo Esters[a]



R$^1$OH = BHT = 2,6-di-*t*-butyl-4-methylphenol

| entry | alkyl | ee (%) | yield (%) |
|---|---|---|---|
| 1 | Me | 89 | 84 |
| 2 | Et | 99 | 80 |
| 3 | Bu | 92 | 76 |
| 4 | *i*-Bu | 93 | 64 |
| 5[b] | *i*-Pr | 75 | 72 |
| 6 |  OMe | 92 | 80 |
| 7 |  OMe | 99 | 68 |
| 8 |  | 80 | 78 |
| 9 |  | 84 | 72 |
| 10 |  Br | 86 | 70 |

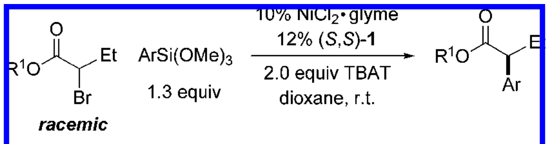
[a] All data are the average of two experiments. Isolated yields are reported. [b] The 2,6-diisopropylphenyl ester was used.

An array of racemic α-bromo esters can be cross-coupled with PhSi(OMe)$_3$ with good enantioselectivity in the presence of NiCl$_2$• glyme and diamine **1** (Table 2). The highest ee's are obtained with smaller alkyl substituents (e.g., Me → *i*-Bu; entries 1−4). In the case of a bulky *i*-Pr group, relatively little of the desired product is generated if a BHT ester is employed; use of a less hindered aryl ester leads to cross-coupling, albeit in moderate ee (entry 5). Functional groups such as esters, ethers, olefins, and unactivated alkyl bromides are compatible with the reaction conditions (entries 6−10).[6] It is noteworthy that both of the catalyst components are air-stable and that the cross-couplings proceed at room temperature.

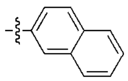
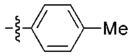
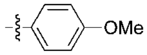
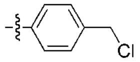
This method for catalytic asymmetric Hiyama reactions is not limited to *phenylations* of α-bromo esters. Substituted aryl silanes,

10.1021/ja8009428 CCC: $40.75

**Table 3.** Asymmetric Hiyama Reactions: Arylations of α-Bromo Esters[a]

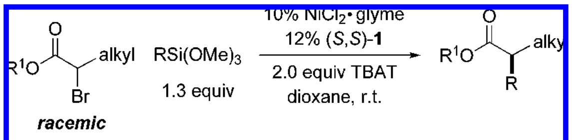


$R^1OH$ = BHT = 2,6-di-*t*-butyl-4-methylphenol

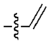
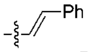
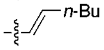
| entry | Ar | ee (%) | yield (%) |
|---|---|---|---|
| 1 |  | 89 | 74 |
| 2 |  | 92 | 76 |
| 3 |  | 87 | 64 |
| 4 |  | 94 | 72 |

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

**Table 4.** Asymmetric Hiyama Reactions: Alkenylations of α-Bromo Esters[a]



$R^1OH$ = BHT = 2,6-di-*t*-butyl-4-methylphenol

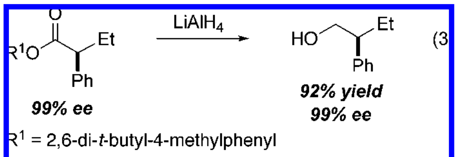
| entry | alkyl | R | ee (%) | yield (%) |
|---|---|---|---|---|
| 1 | *n*-Bu |  | 93 | 66 |
| 2 | *n*-Bu |  | 92 | 72 |
| 3 | Et |  | 91 | 70 |

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

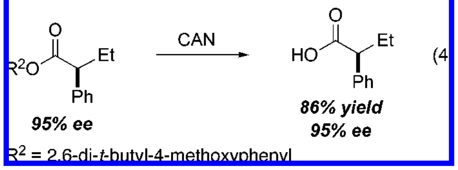
including one that bears a benzylic chloride, undergo cross-coupling in good ee (Table 3).[7]

Furthermore, the catalyst system can be applied without modification to highly enantioselective *alkenylations* of α-bromo esters (Table 4). Thus, vinyltrimethoxysilane (entry 1), as well as more substituted vinylsilanes (entries 2 and 3), can be employed as coupling partners.[8]

The BHT ester can be reduced to a primary alcohol without racemization (eq 3). If a carboxylic acid is desired, an oxidatively cleavable aryl ester may be used (eq 4; see entry 10 of Table 1).[9]



$R^1$ = 2,6-di-*t*-butyl-4-methylphenyl



$R^2$ = 2,6-di-*t*-butyl-4-methoxyphenyl

In conclusion, we have developed the first catalytic asymmetric cross-couplings of α-halo carbonyl compounds with aryl metal reagents, thereby generating synthetically useful α-aryl carboxylic acid derivatives in good ee; this method can also be applied to enantioselective alkenylation reactions. To the best of our knowledge, with regard to asymmetric cross-couplings of alkyl electrophiles, there have been no prior reports of success with organosilanes or with arylations/vinylations, nor have diamines been employed as chiral ligands. Additional investigations 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.

## References

(1) For leading references to their pharmacology, see: Landoni, M. F.; Soraci, A. *Curr. Drug Metab.* **2001**, *2*, 37−51.
(2) Strotman, N. A.; Sommer, S.; Fu, G. C. *Angew. Chem., Int. Ed.* **2007**, *46*, 3556−3558.
(3) For reviews of the Hiyama reaction, see: (a) Denmark, S. E.; Sweis, R. F. In *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: New York, 2004; Chapter 4. (b) Hiyama, T.; Shirakawa, E. *Top. Curr. Chem.* **2002**, *219*, 61−85.
(4) See the following for previous reports of catalytic asymmetric cross-couplings of alkyl electrophiles. (a) α-Halo amides: Fischer, C.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 4594−4595. (b) Benzylic halides: Arp, F. O.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 10482−10483. (c) Allylic halides: Son, S.; Fu, G. C. *J. Am. Chem. Soc.*, ASAP. In each case, a chiral *pybox* ligand and an *alkylzinc* reagent are employed.
(5) The susceptibility of α-aryl carbonyl compounds to racemization can complicate the development of catalytic asymmetric methods for their synthesis. For example, to date, highly enantioselective arylations of enolates have been limited to the formation of quaternary stereocenters. For an early study, see: Ahman, J.; Wolfe, J. P.; Troutman, M. V.; Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 1918−1919. For leading references, see: Liao, X.; Weng, Z.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 195−200.
(6) Notes: (a) In a gram-scale reaction, the cross-coupling illustrated in entry 1 of Table 2 proceeds in 80% yield and 90% ee. (b) The ee of the product correlates linearly with the ee of the ligand. (c) The ee of the product is constant during the course of the reaction. (d) In the absence of an organosilane, no phenylation by TBAT is observed.
(7) Notes: Under our standard conditions, (a) a cross-coupling with (4-$CF_3$)$C_6H_4Si(OMe)_3$ furnished racemic product, perhaps due to the lability of the α stereocenter (in the case of aryl groups that are not electron-poor, control experiments establish that racemization of the product does not occur); (b) a reaction with (1-naphthyl)$Si(OMe)_3$ was unsuccessful; (c) (4-F)$C_6H_4Si(OMe)_3$ underwent cross-coupling in moderate yield (44%) and ee (63%).
(8) Under our standard conditions, *n*-hexyltrimethoxysilane and allyltrimethoxysilane did not participate in asymmetric Hiyama cross-couplings in good ee/yield.
(9) Hydrolysis of BHT esters generally requires vigorous reaction conditions. For an example, see: Hattori, T.; Hayashizaka, N.; Miyano, S. *Synthesis* **1995**, 41−43.

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