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Catalytic Asymmetric γ-Alkylation of Carbonyl Compounds via Stereoconvergent Suzuki Cross-Couplings

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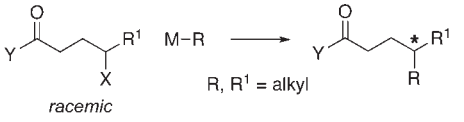
Supporting Information

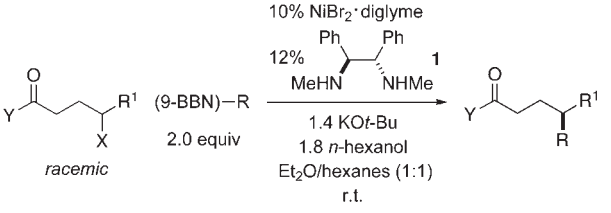
ABSTRACT: With the aid of a chiral nickel catalyst, enantioselective γ- (and δ-) alkylations of carbonyl compounds can be achieved through the coupling of γ-haloamides with alkylboranes. In addition to primary alkyl nucleophiles, for the first time for an asymmetric cross-coupling of an unactivated alkyl electrophile, an arylmetal, a boronate ester, and a secondary (cyclopropyl) alkylmetal compound are shown to couple with significant enantioselectivity. A mechanistic study indicates that cleavage of the carbon−halogen bond of the electrophile is irreversible under the conditions for asymmetric carbon−carbon bond formation.

In comparison with α- and β-alkylation reactions,[1] the range of useful methods for the catalytic enantioselective incorporation of alkyl substituents γ to a carbonyl group is rather limited.[2] One unexplored approach to this objective is the asymmetric coupling of a γ-halocarbonyl compound with an alkylmetal reagent (eq 1).[3,4]



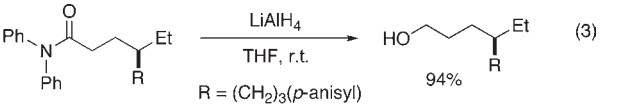
(1)

To date, effective enantioselective cross-couplings of unactivated alkyl electrophiles have been described only for secondary homobenzylic bromides, acylated halohydrins (and one homologue), and β-haloanilines; in each instance, a primary alkylmetal reagent has served as the nucleophilic coupling partner.[5] In this report, we establish that a chiral nickel catalyst can achieve stereoconvergent alkylation reactions of γ-halocarbonyl compounds (eq 2), and we provide the first example of an asymmetric cross-coupling of an unactivated alkyl electrophile with a secondary (cyclopropyl) alkylmetal reagent.

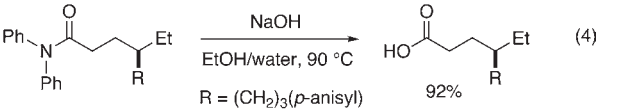


(2)

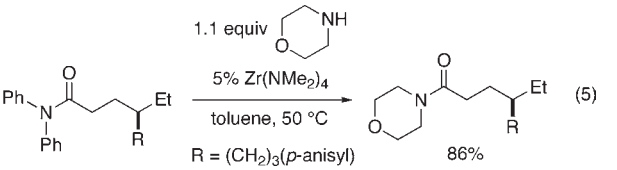
In early studies, we determined that, when the carbonyl group is an *N*,*N*-diphenylamide, good ee's and yields can be obtained for a range of alkyl−alkyl Suzuki cross-couplings (Table 1).[6] Diphenylamides are attractive carboxylic acid derivatives, since reduction and acyl transfer reactions proceed smoothly (eqs 3−5[7]).



(3)



(4)



(5)

As illustrated in Table 1, asymmetric γ-alkylations of a range of unactivated racemic secondary γ-chloroamides can be achieved with an array of alkylboranes, furnishing the alkyl−alkyl Suzuki coupling products with good enantioselectivity. A wide variety of functional groups are compatible with the reaction conditions, including an acetal, silyl ether, aryl ether,[8] indole, and aryl fluoride.[9] Both of the catalyst components ($NiBr_2$·diglyme and ligand **1**) are commercially available.

With respect to the electrophile, the scope of these asymmetric alkylations is not limited to cross-couplings of γ-chlorodiphenylamides. Thus, the corresponding bromides are also suitable electrophiles (eq 6; not optimized). Furthermore, under the standard conditions, good ee was observed for the stereoconvergent coupling of a homologue of a γ-chloroamide, thereby achieving enantioselective δ-alkylation (eq 7).[10] Finally, the carbonyl group need not be a diphenylamide;[11] for example, the cross-coupling of a γ-chloro Weinreb amide[12] proceeded with promising ee, and a preliminary study provided evidence

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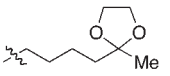
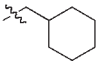
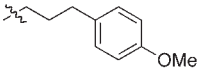
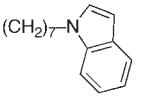
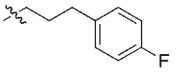
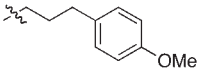
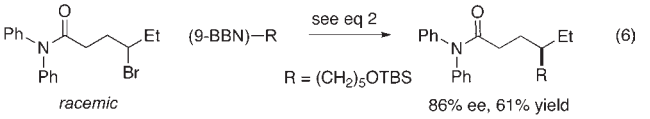
Table 1. Catalytic Enantioselective γ-Alkylation of *N*, *N*-Diphenylamides via Stereoconvergent Suzuki Cross-Couplings of Secondary Alkyl Chlorides[a]

entry	R^1	R	ee (%)	yield (%)[b]
1	Me		85	63
2[c]	Me		90	54
3	Et	$(CH_2)_5$–OTBS	91	74
4	Et		89	80
5	Et		90	63
6[d]	Et	$(CH_2)_5$–CN	69	51
7	*n*-Bu		90	64
8	CH_2CH_2Ph		88	83
9	*i*-Bu	$(CH_2)_3$–Ph	82	61

[a] For the reaction conditions, see eq 2. All data are averages of two experiments. [b] Yields of purified products. [c] 20% $NiBr_2$·diglyme and 24% **1** were used. [d] The reaction was conducted in *i*-Pr_2O at 60 °C.

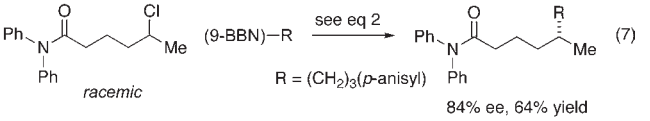
that enhanced enantioselectivity should be possible through further optimization (eq 8).

Alkyl bromide:



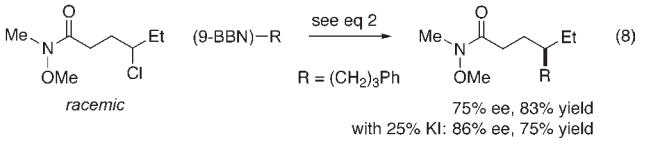
(6)

Homologue:



(7)

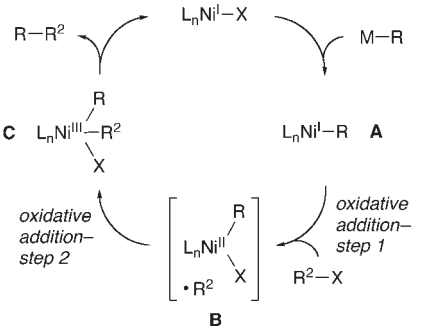
Weinreb amide:



(8)

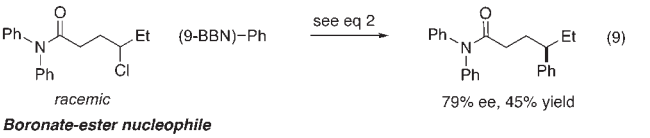
With respect to the nucleophilic coupling partner, previous studies of asymmetric cross-couplings of unactivated secondary electrophiles have focused exclusively on *primary alkyl-(9-BBN)* derivatives.[5] We obtained encouraging enantioselectivities when a γ-chloroamide was coupled with an *aryl*borane (eq 9), a *boronate ester* (eq 10), or a *secondary* (cyclopropyl) alkylborane (eq 11).[13] These data illustrate the potential for an important expansion in the scope of asymmetric cross-couplings of unactivated alkyl electrophiles.

Scheme 1. Outline of a Possible Reaction Pathway[a]



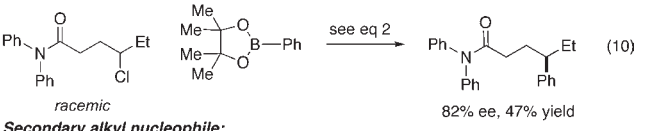
[a] For the sake of simplicity, all of the elementary steps are drawn as irreversible.

Aryl nucleophile:



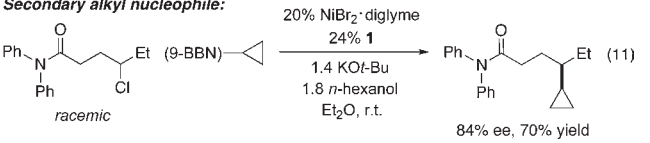
(9)

Boronate-ester nucleophile



(10)

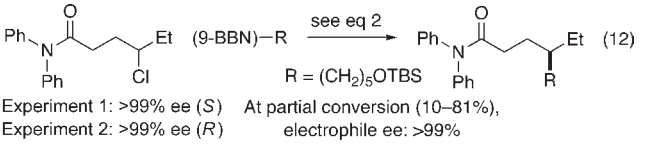
Secondary alkyl nucleophile:



(11)

Our current working hypothesis regarding the pathway for these Suzuki reactions is depicted in Scheme 1. This builds on pioneering mechanistic studies of nickel/terpyridine-catalyzed Negishi cross-couplings of unactivated alkyl halides by Vicic[14a] and Phillips.[14b] Interestingly, the computational investigation by Phillips suggests that the formation of **B** may be reversible for the coupling of MeZnI and *i*-PrI, specifically, that $\Delta G^{\ddagger} = 11$ kcal/mol for **B** → **A** and $\Delta G^{\ddagger} = 13$ kcal/mol for **B** → **C**.

To gain insight into whether the initial step of oxidative addition (**A** → **B**) is reversible under our Suzuki cross-coupling conditions, we monitored the reaction of each enantiomer of a γ-haloamide and observed essentially no erosion in the ee of the electrophile during the course of the reaction (eq 12). This is consistent with the conclusion that halide abstraction (**A** → **B**) is *irreversible*, in contrast to the results of Phillips' study of a Negishi reaction.[15,16]



(12)

In conclusion, we have developed a method for the catalytic enantioselective γ- (and δ-) alkylation of carbonyl compounds

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through the cross-coupling of γ-haloamides with alkylboranes. With regard to the family of products that is generated, this study differs from previous reports of asymmetric couplings of unactivated secondary alkyl electrophiles, which furnished substituted benzenes, protected alcohols, and anilines. Both alkyl chlorides and alkyl bromides are suitable electrophilic cross-coupling partners, and for the first time an arylmetal, a boronate ester, and a secondary (cyclopropyl) alkylmetal compound are shown to serve as nucleophilic partners and to couple with substantial enantioselectivity. A mechanistic study indicates that carbon−halogen bond cleavage is irreversible under the reaction conditions. Further investigations of cross-couplings of alkyl electrophiles are underway.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, compound characterization data, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENT

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(1) (a) For leading references on catalytic, enantioselective α-alkylation reactions, see: MacMillan, D. W. C.; Watson, A. J. B. α-Functionalization of Carbonyl Compounds. In *Science of Synthesis*; De Vries, J. G., Molander, G. A., Evans, P. A., Eds.; Thieme: Stuttgart, Germany, 2010; Vol. 3, pp 677−745. (b) For leading references on catalytic enantioselective β-alkylation reactions, see: Nguyen, B. N.; Hii, K. K.; Szymanski, W.; Janssen, D. B. Conjugate Addition Reactions. In *Science of Synthesis*; De Vries, J. G., Molander, G. A., Evans, P. A., Eds.; Thieme: Stuttgart, Germany, 2010; Vol. 1, pp 571−688.

(2) For a recent example, see: Smith, S. W.; Fu, G. C. *J. Am. Chem. Soc.* **2009**, *131*, 14231–14233.

(3) For leading references on metal-catalyzed alkyl−alkyl cross-couplings, see: Rudolph, A.; Lautens, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 2656–2670.

(4) For leading references on enantioselective cross-couplings of alkyl electrophiles, see: (a) Glorius, F. *Angew. Chem., Int. Ed.* **2008**, *47*, 8347–8349. (b) Owston, N. A.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 11908–11909.

(5) (a) Saito, B.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 6694–6695. (b) Reference 4b. (c) Lu, Z.; Wilsily, A.; Fu, G. C. *J. Am. Chem. Soc.* **2011**, *133*, 8154–8157.

(6) Notes: (a) The catalytic enantioselective γ-alkylation illustrated in entry 4 of Table 1 proceeded in 79% yield with 89% ee on a gram scale (1.1 g of product). (b) The cross-coupling depicted in entry 3 of Table 1 proceeded in 57% yield with 89% ee when conducted with a lower catalyst loading (5% $NiBr_2$·diglyme/6% **1** on a 0.5 mmol scale). (c) Under the standard conditions (eq 2), essentially no carbon−carbon bond formation was observed in the absence of $NiBr_2$·diglyme or ligand **1**. (d) During the course of a γ-alkylation, the unreacted electrophile remains essentially racemic (<5% ee), and the ee of the product is virtually constant. (e) For a substrate bearing a methyl group α to the amide, one isomer of the product was observed when the "matched" ligand was employed, and a 1.7:1 ratio of diastereomers was generated when the "mismatched" ligand was used (substrate control). (f) In addition to the desired cross-coupling, minor amounts of the electrophile undergo β-elimination and hydrodehalogenation.

(7) For zirconium-catalyzed transamidation, see: Stephenson, N. A.; Zhu, J.; Gellman, S. H.; Stahl, S. S. *J. Am. Chem. Soc.* **2009**, *131*, 10003–10008.

(8) For leading references on nickel-catalyzed Suzuki reactions of aryl alkyl ethers, see: Yu, D.-G.; Li, B.-J.; Shi, Z.-J. *Acc. Chem. Res.* **2010**, *43*, 1486–1495.

(9) For examples of nickel-catalyzed Suzuki reactions of aryl fluorides (perfluorinated arenes), see: Schaub, T.; Backes, M.; Radius, U. *J. Am. Chem. Soc.* **2006**, *128*, 15964–15965.

(10) Under the standard conditions (eq 2), a β-chloroamide is not a suitable coupling partner because of its propensity to lose HCl and form an α,β-unsaturated amide.

(11) Under the standard cross-coupling conditions (eq 2), a variety of dialkyl and diarylamides cross-coupled with ee's 1−15% lower than those for the diphenylamide.

(12) For a review of the utility of Weinreb amides in organic synthesis, see: Balasubramaniam, S.; Aidhen, I. S. *Synthesis* **2008**, 3707–3738.

(13) On the other hand, (9-BBN)-cyclopentyl is not a suitable substrate under these conditions.

(14) (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.

(15) An alternative but in our view less likely explanation is that interconversion of **A** and **B** proceeds without erosion of the enantiomeric excess of the electrophile.

(16) For related studies addressing the potential reversibility of oxidative addition for nickel-catalyzed cross-couplings of *activated* alkyl halides, see: (a) Suzuki reactions of α-haloamides (irreversible oxidative addition): Lundin, P. M.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 11027–11029. (b) Negishi reactions of benzylic halides (computational study; reversible oxidative addition): Lin, X.; Sun, J.; Xi, Y.; Liu, D. *Organometallics* **2011**, *30*, 3284–3292.