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New Directing Groups for Metal-Catalyzed Asymmetric Carbon–Carbon Bond-Forming Processes: Stereoconvergent Alkyl–Alkyl Suzuki Cross-Couplings of Unactivated Electrophiles

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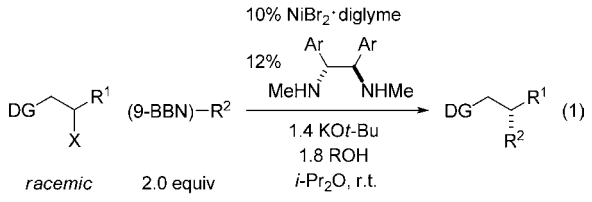
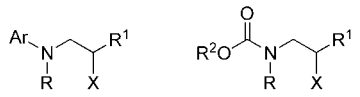
Supporting Information

ABSTRACT: The ability of two common protected forms of amines (carbamates and sulfonamides) to serve as directing groups in Ni-catalyzed Suzuki reactions has been exploited in the development of catalytic asymmetric methods for cross-coupling unactivated alkyl electrophiles. Racemic secondary bromides and chlorides undergo C–C bond formation in a stereoconvergent process in good ee at room temperature in the presence of a commercially available Ni complex and chiral ligand. Structure–enantioselectivity studies designed to elucidate the site of binding to Ni (the oxygen of the carbamate and of the sulfonamide) led to the discovery that sulfones also serve as useful directing groups for asymmetric Suzuki cross-couplings of racemic alkyl halides. To our knowledge, this investigation provides the first examples of the use of sulfonamides or sulfones as effective directing groups in metal-catalyzed asymmetric C–C bond-forming reactions. A mechanistic study established that transmetalation occurs with retention of stereochemistry and that the resulting Ni–C bond does not undergo homolysis in subsequent stages of the catalytic cycle.

Exploiting a "directing" group within a substrate to provide a transient two-point interaction with a chiral reagent/catalyst is a powerful strategy for enantioselective synthesis, since chelation decreases conformational flexibility and can facilitate the effective transmission of stereochemical information from the reagent/catalyst to the substrate.[1] Recently, we have reported the first examples of asymmetric cross-couplings of unactivated alkyl electrophiles, processes that are directed by an aromatic ring, the oxygen of a carbonyl group, or the nitrogen of an arylamine.[2,3] Expanding the scope of enantioselective couplings to other families of functionalized electrophiles is an important objective. In this report, we demonstrate that Ni-catalyzed asymmetric alkyl–alkyl Suzuki reactions can be directed by a diverse array of functional groups, specifically, carbamates, sulfonamides, and sulfones (eq 1); to our knowledge, these represent the first examples of the use of sulfonamides and sulfones as directing groups in metal-catalyzed enantioselective C–C bond-forming processes.

In earlier studies, we determined that racemic secondary halides that bear a proximal arylamine (**1**) undergo asymmetric Suzuki cross-coupling with good ee.[2c] Although this method furnishes access to enantioenriched amines, which are a very important class of bioactive compounds, *aryl*amines are not as pervasive as *alkyl*amines.[4]





To access enantioenriched amines other than tertiary arylamines (**1**), while avoiding the use of nitrogen mustard-like substrates,[5] we decided to examine carbamate-protected halo amines[6] (e.g., **2**) as electrophiles in stereoconvergent alkyl–alkyl Suzuki reactions. We were pleased to determine that a chiral Ni/diamine catalyst can indeed accomplish asymmetric Suzuki couplings of racemic carbamate-protected halo amines with alkylboranes (Table 1). Thus, carbamates derived from secondary dialkylamines (entries 1–3) and from secondary arylamines (entries 4 and 5) cross-couple in good ee at room temperature. The compatibility of this method with an aryl carbamate (entries 1–4) and with an aryl methyl ether (entry 2) is noteworthy, since both functional groups undergo C–O bond cleavage in the presence of other Ni-based catalysts for Suzuki cross-couplings;[7] in contrast, both are inert (>95% recovery in control experiments) to our reaction conditions. The Ni source ($NiBr_2$·diglyme) and the diamine ligand are commercially available.

The stereochemistry of the catalyst, not of an alkoxy substituent of the carbamate, determines the stereochemical outcome of this carbamate-directed asymmetric C–C bond-forming process (eqs 2 and 3). Furthermore, under identical conditions, a racemic secondary alkyl *chloride* cross-couples in good ee and yield (eq 4). Perhaps predictably, increasing the distance between the directing group and the electrophilic site leads to an erosion in enantioselectivity when the standard

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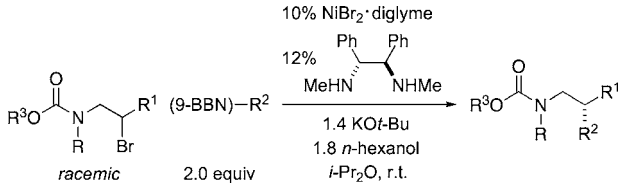
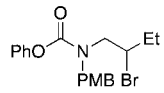
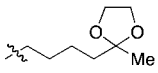
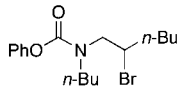
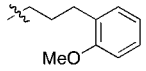
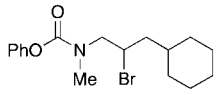
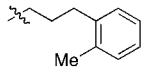
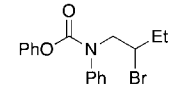
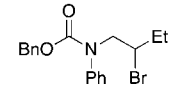
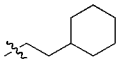
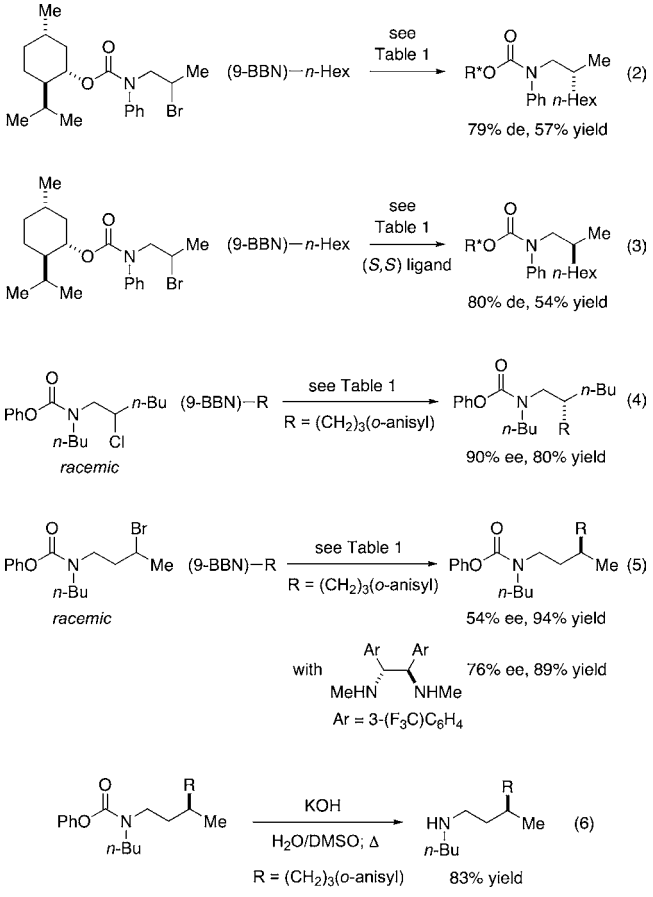
Table 1. Catalytic Asymmetric Suzuki Cross-Couplings of Unactivated Alkyl Electrophiles To Generate Carbamate-Protected Amines[a]



entry	electrophile	R^2	ee (%)	yield (%)[b]
1			91	56
2			90	83
3			90	74
4		*n*-Hex	90	56
5			80	66

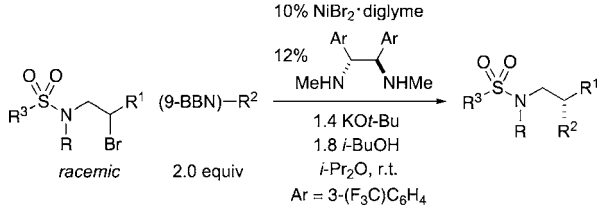
[a]All data are the average of two experiments. [b]Yield of purified product.

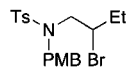
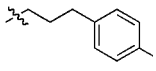
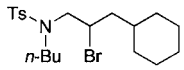
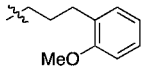
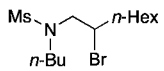
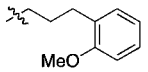
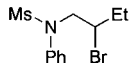
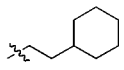


method is applied; however, it is clear that it will be possible to address this shortcoming through appropriate modification of the reaction conditions (eq 5). The carbamate, which serves as both a protecting group and a directing group, can be hydrolyzed in good yield to liberate the secondary amine (eq 6).

To further expand access to enantioenriched amines via asymmetric cross-couplings of alkyl electrophiles, we chose to pursue sulfonamide-directed processes. The achievement of this objective would be noteworthy not only in the context of the asymmetric synthesis of amines, but also more broadly since, to our knowledge, there are no examples of metal-catalyzed enantioselective C−C bond-forming reactions directed by a sulfonamide. The conditions that we had employed for couplings of carbamate-protected amines (Table 1) furnished promising results for a racemic sulfonamide, and optimization of the reaction conditions provided an enhancement in enantioselectivity and yield (Table 2; the diamine ligand is commercially available).

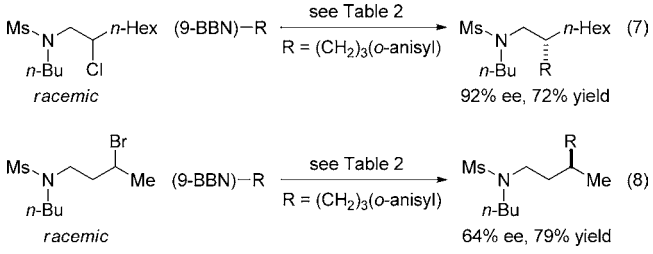
Table 2. Sulfonamide-Directed Catalytic Asymmetric Suzuki Cross-Couplings of Unactivated Alkyl Electrophiles[a]



entry	electrophile	R^2	ee (%)	yield (%)[b]
1			90	58
2			90	54
3			90	76
4			72	68

[a]All data are the average of two experiments. [b]Yield of purified product.

As illustrated in Table 2, both tosyl- and mesyl-protected secondary dialkylamines are suitable cross-coupling partners, undergoing stereoconvergent C−C bond formation in good ee at room temperature (entries 1−3).[8,9] A sulfonamide derived from an arylamine couples with more moderate enantioselectivity, perhaps due to the diminished Lewis basicity of the sulfonamide (entry 4). As observed for carbamate-directed asymmetric Suzuki reactions (eqs 4 and 5), the sulfonamide-directed cross-coupling of a corresponding unactivated secondary chloride also proceeds in good ee and yield (eq 7), whereas a homologous alkyl bromide couples with modest enantioselectivity (eq 8).



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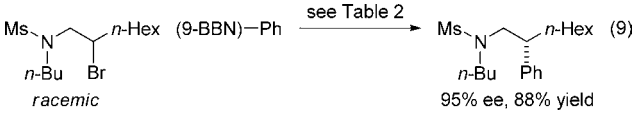
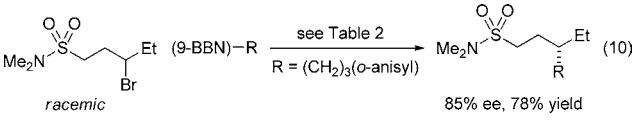
In our previous studies of asymmetric cross-couplings of unactivated alkyl halides, we focused our attention on the use of *alkyl* nucleophiles as coupling partners. However, we recently described modest success when an arylboron reagent was employed in an amide-directed Suzuki reaction (82% ee, 47% yield).[2d] In the case of sulfonamide-directed cross-couplings, for the first time we have achieved an arylation of an unactivated electrophile with excellent enantioselectivity and yield (eq 9).

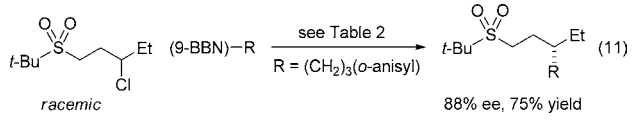


Given that we have observed both nitrogen-[2c] and oxygen-directed[2b,d] asymmetric cross-couplings of unactivated alkyl halides, we sought insight into which heteroatom is the more likely binding site to Ni in these sulfonamide-directed processes. When we "reverse" the sulfonamide such that the distance between the sulfonamide oxygens and the electrophilic carbon remains virtually the same, but the nitrogen and the electrophilic carbon are now separated by two additional atoms, the cross-coupling nevertheless proceeds with good



enantioselectivity (eq 10). In view of our previous observations that the distance between the directing group and the electrophilic site generally has a significant impact on ee (e.g., eqs 5 and 8), we believe that the sulfonamide *oxygen* is likely binding to Ni in the asymmetric Suzuki reactions illustrated in Table 2.

Further support for the suggestion of oxygen as the site of complexation is provided by our observation that unactivated secondary alkyl electrophiles that bear *sulfones* also undergo stereoconvergent C−C bond formation in good ee; both alkyl bromides (Table 3)[10] and alkyl chlorides (eq 11)[11] are suitable



coupling partners. To our knowledge, these are the first examples of sulfone-directed, metal-catalyzed enantioselective C−C bond-forming processes.

Although KO *t*-Bu is employed as a stoichiometric additive in the Suzuki couplings described above, the conditions are not highly Brønsted-basic. For example, when enantioenriched ketone **3** is included in a reaction mixture, it can be recovered at the end of the cross-coupling with virtually no erosion in enantiomeric excess. In contrast, in the absence of the trialkylborane, the ketone is completely racemized. By ^{11}B NMR spectroscopy, we have determined that an "ate" complex (**4**) is generated under the cross-coupling conditions, which significantly attenuates the Brønsted basicity of the reaction medium.[12]

Our current hypothesis is that these asymmetric cross-couplings of secondary alkyl electrophiles follow the pathway depicted in Figure 1.[13] To gain insight into the transmetalation

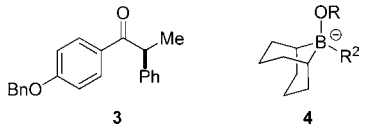
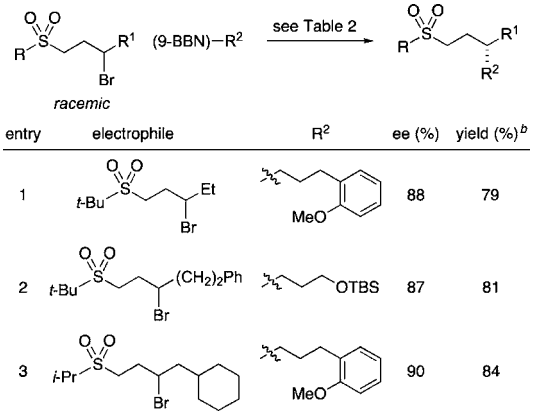


Table 3. Sulfone-Directed Catalytic Asymmetric Suzuki Cross-Couplings of Unactivated Alkyl Electrophiles[a]



[a]All data are the average of two experiments. [b]Yield of purified product.

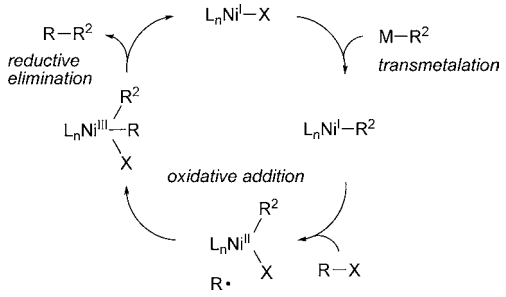
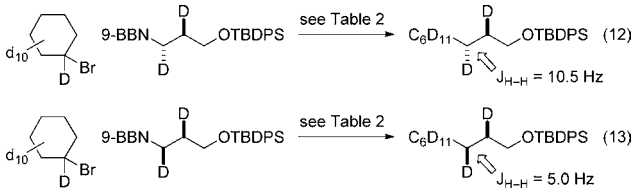


Figure 1. Outline of a mechanism for Ni-catalyzed enantioselective Suzuki cross-couplings of unactivated secondary alkyl halides.

process, which is likely the turnover-limiting step in these Suzuki reactions,[14] we examined the cross-coupling of an unactivated secondary halide with a diastereomerically enriched alkyl-(9-BBN) reagent under the conditions described in Table 2 (eqs 12 and 13).[15,16] Analysis of the appropriate coupling



constants revealed that the alkyl group of the organoborane is transferred to the reaction product with retention of configuration at carbon, consistent with transmetalation with retention, as well with structural integrity for the Ni−R^2 bond (e.g., toward homolytic cleavage) during the catalytic cycle.[17,18]

In summary, we have established that two families of *protecting* groups for amines can also serve as effective *directing* groups, thereby enabling enantioselective Suzuki reactions of unactivated secondary alkyl halides. Thus, a readily available Ni catalyst achieves asymmetric alkyl−alkyl cross-couplings of racemic carbamate- and sulfonamide-protected halo amines in

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good ee at room temperature. In contrast with our earlier method for the catalytic asymmetric synthesis of amines, which exclusively produced arylamines and was *nitrogen*-directed,[2c] for carbamate- and sulfonamide-directed cross-couplings, *oxygen* is the likely site of coordination to Ni. In particular, a structure−enantioselectivity study of sulfonamides is consistent with binding by oxygen, as is our observation that sulfones can function as a directing group in these stereoconvergent Suzuki reactions. This investigation has thus established for the first time that sulfonamides and sulfones can serve as effective directing groups in metal-catalyzed asymmetric C−C bond-forming processes. With respect to the mechanism of Ni-catalyzed Suzuki cross-couplings of unactivated secondary alkyl electrophiles, we have determined that the stereochemistry of the boron-bound carbon of a chiral trialkylborane is preserved in the reaction product, consistent with transmetalation with retention of stereochemistry and with structural integrity for the resulting Ni−C bond in subsequent stages of the catalytic cycle. A wide range of additional studies of cross-coupling reactions of alkyl electrophiles are underway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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(6) Enantioselective Suzuki reactions of carbamate-protected halo alcohols (halohydrins): ref 2b.

(7) Leading references to Ni-catalyzed Suzuki cross-couplings: (a) Of aryl carbamates and aryl methyl ethers: Yu, D.-G.; Li, B.-J.; Shi, Z.-J. *Acc. Chem. Res.* **2010**, *43*, 1486. (b) Of aryl carbamates: Quasdorf, K. W.; Antoft-Finch, A.; Liu, P.; Silberstein, A. L.; Komaromi, A.; Blackburn, T.; Ramgren, S. D.; Houk, K. N.; Snieckus, V.; Garg, N. K. *J. Am. Chem. Soc.* **2011**, *133*, 6352. (c) Of aryl methyl ethers: Tobisu, M.; Shimasaki, T.; Chatani, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 4866. (d) Of oxygen leaving groups: Rosen, B. M.; Quasdorf, K. W.; Wilson, D. A.; Zhang, N.; Resmerita, A.-M.; Garg, N. K.; Percec, V. *Chem. Rev.* **2011**, *111*, 1346.

(8) (a) Under the standard asymmetric cross-coupling conditions: (1) lower ee and/or yield are obtained when arylsulfonamides in which the aromatic group is hindered (mesityl) or very electron-poor (nosyl) are employed as substrates; (2) during the course of a reaction, the unreacted electrophile remains racemic, and the ee of the product is constant; (3) essentially no C−C bond formation is observed in the absence of $NiBr_2$·diglyme, the ligand, or KO*t*-Bu. (b) For the stereoconvergent Suzuki reaction illustrated in entry 3 of Table 2: (1) the use of TBME, Et_2O, or toluene, rather than *i*-Pr_2O, as solvent results in formation of the product in comparable ee but somewhat diminished yield (∼65%); (2) on a gram scale, the coupling proceeds in 90% ee and 79% yield; (3) with 5% $NiBr_2$·diglyme/6% ligand, the cross-coupling product is generated in 90% ee and 42% yield; (4) the reaction is not highly water-sensitive (the addition of 0.1 equiv of water leads to no loss in ee or yield); (5) use of 1.3 equiv of alkylborane results in comparable enantioselectivity (89%) but lower yield (53%).

(9) Examples of Ni-catalyzed Suzuki cross-couplings of aryl fluorides (perfluorinated arenes): Schaub, T.; Backes, M.; Radius, U. *J. Am. Chem. Soc.* **2006**, *128*, 15964.

(10) In a preliminary study, when the R group of the sulfone was Me or aryl, lower enantioselectivity was observed (∼80% ee).

(11) A homologue ((*t*-Bu)$SO_2(CH_2)_3CHClMe$) cross-coupled in 49% ee and 85% yield.

(12) A previous report of the formation of an "ate" complex under somewhat different conditions: Saito, B.; Fu, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 9602.

(13) (a) Related mechanistic proposals for Ni/terpyridine-catalyzed Negishi reactions: 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. Lin, X.; Phillips, D. L. *J. Org. Chem.* **2008**, *73*, 3680. (b) Overview of mechanistic issues regarding Ni-catalyzed cross-couplings of unactivated alkyl halides: Hu, X. *Chem. Sci.* **2011**, *2*, 1867.

(14) For the cross-coupling illustrated in entry 3 of Table 2, we determined that the rate law is first order in the Ni catalyst and in the organoborane, but zeroth order in the electrophile.

(15) To simplify the analysis of the coupling constants, we chose to employ perdeuterated cyclohexyl bromide as the unactivated secondary alkyl electrophile.

(16) A pioneering example of the use of this coupling-constant strategy in the context of elucidating the mechanism of organometallic reactions: Bock, P. L.; Boschetto, D. J.; Rasmussen, J. R.; Demers, J. P.; Whitesides, G. M. *J. Am. Chem. Soc.* **1974**, *96*, 2814.

(17) After our mechanistic study was complete, Jarvo independently reported that transmetalation in a Ni-catalyzed *primary−primary* Suzuki cross-coupling, under conditions initially described by us (Saito, B.; Fu, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 9602.), proceeds with retention of stereochemistry: Taylor, B. L. H.; Jarvo, E. R. *J. Org. Chem.* **2011**, *76*, 7573.

(18) Analogous studies of the mechanism of transmetalation in *palladium*-catalyzed Suzuki reactions of *aryl* electrophiles: (a) Ridgway, B. H.; Woerpel, K. A. *J. Org. Chem.* **1998**, *63*, 458. (b) Matos, K.; Soderquist, J. A. *J. Org. Chem.* **1998**, *63*, 461.