JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

COMMUNICATION

pubs.acs.org/JACS

Stereoconvergent Amine-Directed Alkyl−Alkyl Suzuki Reactions of Unactivated Secondary Alkyl Chlorides

Zhe Lu, Ashraf Wilsily, and Gregory C. Fu*

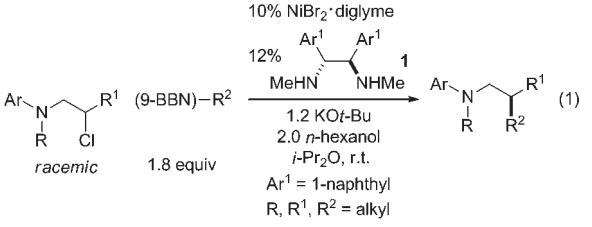
Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, United States

Supporting Information

ABSTRACT: A new family of stereoconvergent cross-couplings of unactivated secondary alkyl electrophiles has been developed, specifically, arylamine-directed alkyl−alkyl Suzuki reactions. This represents the first such investigation to be focused on the use of alkyl chlorides as substrates. Structure−enantioselectivity studies are consistent with the nitrogen, not the aromatic ring, serving as the primary site of coordination of the arylamine to the catalyst. The rate law for this asymmetric cross-coupling is compatible with transmetalation being the turnover-limiting step of the catalytic cycle.

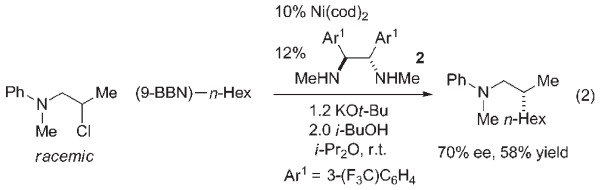
Alkyl−alkyl couplings are among the most challenging of cross-coupling processes, due in part to the potential for intermediates in the catalytic cycle to undergo β-hydride elimination and other undesired reactions.[1,2] The development of highly versatile methods will likely have a substantial impact on organic synthesis,[3] particularly if carbon−carbon bond formation can be accomplished enantioselectively. We have recently begun to pursue this objective with both activated and unactivated secondary alkyl electrophiles.[4−6] Asymmetric cross-couplings of unactivated substrates have proved to be especially difficult, and to date only two families of halides have undergone coupling in good ee (homobenzylic bromides[5a] and acylated bromohydrins (and one chlorohydrin)[5b]). In each instance, a functional group proximal to the electrophilic site (an aryl substituent or a carbonyl oxygen) is likely interacting with the chiral catalyst in the stereochemistry-determining step of the reaction.[7]

Because a wide array of molecules possess nitrogen-containing functional groups, including bioactive compounds such as alkaloids,[8] we sought the development of an amine-directed method for the asymmetric alkyl−alkyl cross-coupling of unactivated electrophiles.[9] In this report, we describe the achievement of this objective, specifically, stereoconvergent Suzuki reactions[10] of racemic secondary alkyl chlorides that bear proximal arylamines (eq 1).

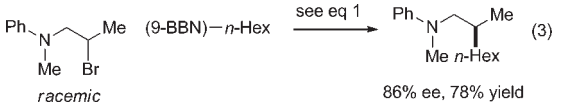


The potential of β-halo *trialkyl*amines to cyclize (e.g., nitrogen mustards[11]) led us to focus on arylamines as the directing group[12] and chlorides as the leaving group for our desired asymmetric alkyl−alkyl Suzuki reaction. We recognized that attenuating the nucleophilicity of the amine toward the halide might also diminish the likelihood that the amine would serve as a directing group and that only a single example of an enantioselective cross-coupling of an unactivated secondary alkyl chloride had been described.[5b]

When we applied the conditions that we had developed earlier for enantioselective Suzuki reactions of homobenzylic bromides[5a] to the cross-coupling of a secondary chloride bearing a pendant arylamine, we obtained a promising lead (eq 2; 70% ee, 58% yield). Optimization of the reaction parameters, primarily through the use of C_2-symmetric 1,2-diamine **1**,[13] provided a method that furnishes the desired alkyl−alkyl coupling product with improved enantioselectivity and yield (Table 1, entry 1).



Under our optimized conditions, an array of stereoconvergent arylamine-directed alkyl−alkyl Suzuki couplings of unactivated secondary chlorides can be achieved with good enantioselectivity (Table 1).[14] The aromatic ring of the arylamine can be un- (entries 1−3), para- (entries 4−6), meta- (entries 7−9), or ortho-substituted (entry 10). Furthermore, it can be fused to another ring (entries 11 and 12). Suzuki reactions of more hindered electrophiles (e.g., entries 2, 3, and 10) sometimes proceed in moderate ee or yield. Functional groups such as ethers, acetals, and aryl fluorides are compatible with the cross-coupling conditions.[15] Although this method was developed for asymmetric Suzuki couplings of unactivated secondary alkyl chlorides, we have determined that it can be applied without modification to the cross-coupling of an alkyl bromide in good ee and yield (eq 3).

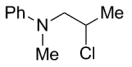
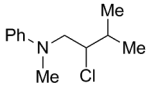
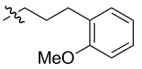
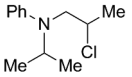
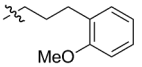
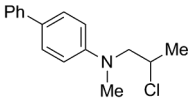
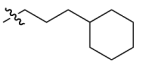
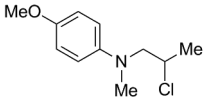
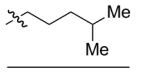
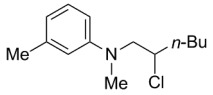
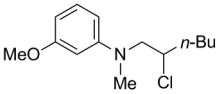
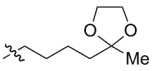
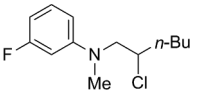
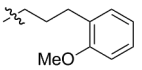
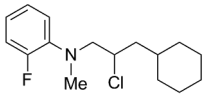
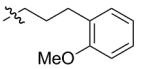
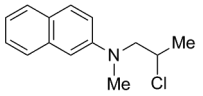
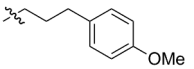
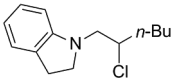
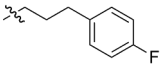


The spatial relationship between the arylamine and the chloride is important for obtaining good enantioselectivity. Thus, if an additional methylene unit is introduced between the arylamine and the chloride (**3**), then the cross-coupling product is generated with essentially no ee (<5%). Furthermore, a secondary

Received: April 18, 2011
Published: May 10, 2011

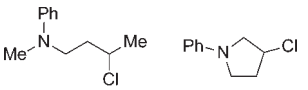
   dx.doi.org/10.1021/ja203560q | J. Am. Chem. Soc. 2011, 133, 8154–8157

Table 1. Stereoconvergent Amine-Directed Alkyl−Alkyl Suzuki Reactions of Unactivated Secondary Alkyl Chlorides (for the reaction conditions, see eq 1)[a]

entry	electrophile	R^2	ee (%)	yield (%)[b]
1		*n*-Hex	88	84
2[c]			96	52
3			82	72
4			85	68
5		*n*-Hex	87	76
6			84	78
7		$(CH_2)_3OTBS$	91	63
8			94	86
9			92	70
10			71	82
11			83	70
12			92	57

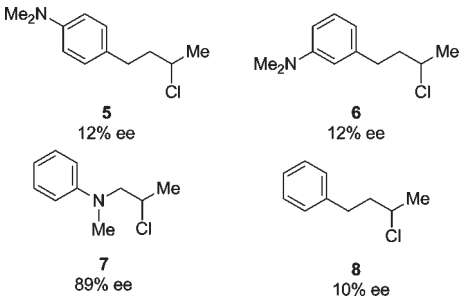
[a] All data are the average of two experiments. [b] Yield of purified product. [c] Catalyst loading: 20% $NiBr_2$•diglyme, 24% **1**.

alkyl chloride that bears a conformationally constrained arylamine (**4**) couples with only modest enantioselectivity.[16]



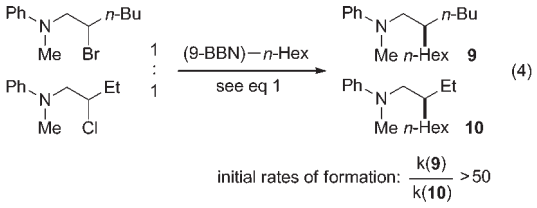
3 <5% ee **4** 41% ee

We hypothesize that the effective asymmetric induction in the Suzuki cross-couplings illustrated in Table 1 arises from complexation of the arylamine to the chiral nickel catalyst in the stereochemistry-determining step of the catalytic cycle. In order to gain insight into whether this interaction is primarily through the aromatic ring[5a] or through the nitrogen[12] of the arylamine, we examined enantioselective Suzuki reactions of arylamines **5** and **6**. We determined that these electrophiles undergo cross-coupling with very modest ee (cf. **7**), comparable to a substrate that lacks an amino substituent altogether (**8**).[17] Collectively, these data are consistent with our new Suzuki couplings being *nitrogen*-directed processes. They therefore complement the only two previous examples of asymmetric cross-couplings of unactivated alkyl electrophiles, which are directed by carbon- (aromatic ring)[5a] and oxygen-based (carbonyl)[5b] functional groups.



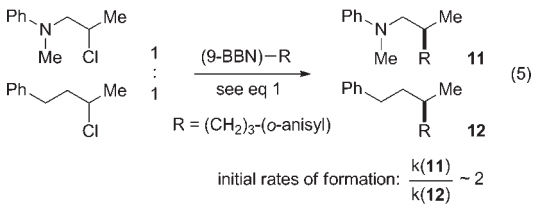
5 12% ee **6** 12% ee **7** 89% ee **8** 10% ee

To date, the rate law has not been determined for any enantioselective cross-coupling of an unactivated secondary alkyl halide. For the Suzuki reaction of an arylamine-containing secondary chloride (entry 1 of Table 1), we have established that the rate law is first order in the catalyst and in the organoborane but zeroth order in the electrophile,[18] which is consistent with a catalytic cycle in which transmetalation is the turnover-limiting step (e.g., Scheme 1[19]). In a competition experiment, the catalyst cross-couples an alkyl bromide in preference to a chloride with very high selectivity (eq 4), indicating that, if complexation of the amine to nickel precedes oxidative addition, the complexation is likely reversible vis-à-vis oxidative addition.[20] The data illustrated in eq 5 are further consistent with the suggestion that the arylamine does not play a dominant role in determining relative *reactivity* in these Suzuki couplings of alkyl halides.



(4)

initial rates of formation: $\frac{k(\mathbf{9})}{k(\mathbf{10})} > 50$



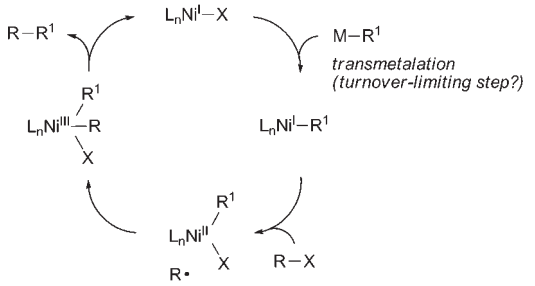
(5)

initial rates of formation: $\frac{k(\mathbf{11})}{k(\mathbf{12})} \sim 2$

In summary, a new family of stereoconvergent cross-couplings of unactivated secondary alkyl electrophiles has been developed. These nitrogen-directed enantioselective Suzuki reactions represent the third example of such processes, complementing previous reports of couplings directed by carbon- (arenes) and oxygen-based functional groups, as well as the first investigation focused on the use of unactivated alkyl *chlorides* as substrates. Structure−enantioselectivity studies indicate that the likely primary site of coordination of the arylamine to the catalyst is the nitrogen, not the aromatic ring. The rate law for an asymmetric

dx.doi.org/10.1021/ja203560q | *J. Am. Chem. Soc.* 2011, 133, 8154–8157

Scheme 1. Outline of a Possible Pathway for a Nickel-Catalyzed Cross-Coupling of a Simple Unactivated Alkyl Electrophile



cross-coupling of an unactivated alkyl electrophile has been determined for the first time, and the data are consistent with transmetalation being the turnover-limiting step of the catalytic cycle. Additional catalyst-development and mechanistic investigations of enantioselective alkyl−alkyl cross-couplings 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.

■ AUTHOR INFORMATION

Corresponding Author
gcf@mit.edu

■ ACKNOWLEDGMENT

This study is dedicated to the memory of Prof. David Y. Gin. Support has been provided by the National Institutes of Health (National Institute of General Medical Sciences, Grant R01-GM62871), Eli Lilly (fellowship to Z.L.), and the Martin Family Society of Fellows for Sustainability (fellowship to Z.L.).

■ REFERENCES

(1) For leading references on metal-catalyzed cross-coupling reactions of alkyl electrophiles, see: Rudolph, A.; Lautens, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 2656–2670.

(2) For reviews of metal-catalyzed cross-coupling reactions, see: (a) *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley−VCH: New York, 2004. Denmark, S. E. (p 191): "Alkyl−alkyl cross-coupling reactions have historically been the most difficult to realize." (b) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-i., Ed.; Wiley Interscience: New York, 2002.

(3) (a) For examples of applications of alkyl−alkyl Suzuki cross-couplings in the total synthesis of natural products, see: Keaton, K. A.; Phillips, A. J. *Org. Lett.* **2007**, *9*, 2717–2719. Griggs, N. D.; Phillips, A. J. *Org. Lett.* **2008**, *10*, 4955–4957. (b) For examples of applications of alkyl−alkyl Negishi cross-couplings in the synthesis of C-alkyl glycosides, see: Gong, H.; Gagné, M. R. *J. Am. Chem. Soc.* **2008**, *130*, 12177–12183.

(4) For enantioselective cross-couplings of *activated* secondary alkyl electrophiles, see: (a) An initial study: Fischer, C.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 4594–4595. (b) Work by others: Caeiro, J.; Sestelo, J. P.; Sarandeses, L. A. *Chem.—Eur. J.* **2008**, *14*, 741–746. (c) A recent investigation and leading references: Lundin, P. M.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 11027–11029. (d) Multigram reactions: Lou, S.; Fu, G. C. *Org. Synth.* **2010**, *87*, 317–329; Lou, S.; Fu, G. C. *Org. Synth.* **2010**, *87*, 330–338.

(5) For enantioselective cross-couplings of *unactivated* secondary alkyl electrophiles, see: (a) Saito, B.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 6694–6695. (b) Owston, N. A.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 11908–11909.

(6) For leading references on enantioselective cross-couplings of secondary alkyl electrophiles, see: Glorius, F. *Angew. Chem., Int. Ed.* **2008**, *47*, 8347–8349.

(7) For reviews of "directed" reactions, see: (a) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307–1370. (b) Rousseau, G.; Breit, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 2450–2494.

(8) *The Alkaloids: Chemistry and Biology*; Cordell, G. A., Ed.; Elsevier: San Diego, 2010.

(9) For a review of methods for the enantioselective synthesis of amines, see: *Chiral Amine Synthesis*; Nugent, T. C., Ed.; Wiley−VCH: Weinheim, Germany, 2010.

(10) (a) The Suzuki reaction is the most broadly used cross-coupling process. For reviews, see ref 2. (b) For a pioneering study of alkyl−alkyl Suzuki cross-couplings, see: Ishiyama, T.; Abe, S.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1992**, 691–694.

(11) Koller, M.; Szinicz, L. In *Clinical Toxicological Analysis*; Külpmann, W.-R., Ed.; Wiley−VCH: Weinheim, Germany, 2009; Vol. 2, pp 679−743.

(12) (a) We are aware of only one report of a metal-catalyzed asymmetric reaction that is directed by a tertiary arylamine (Khan, H. A.; Kou, K. G. M.; Dong, V. M. *Chem. Sci.* **2011**, *2*, 407–410); the paucity of such processes may be due in part to the diminished Lewis basicity of the nitrogen as a result of delocalization of the "lone pair". (b) For an example of a catalytic enantioselective reaction that is directed by a *secondary* arylamine, wherein the proton is lost during binding, see: Worthy, A. D.; Joe, C. L.; Lightburn, T. E.; Tan, K. L. *J. Am. Chem. Soc.* **2010**, *132*, 14757–14759.

(13) (a) The synthesis of racemic diamine **1** has been described: Alexakis, A.; Aujard, I.; Mangeney, P. *Synlett* **1998**, 873–874. (b) The synthesis of enantiopure diamine **1** has not been reported, but it is readily prepared through the method of Chin: Chin, J.; Mancin, F.; Thavarajah, N.; Lee, D.; Lough, A.; Chung, D. S. *J. Am. Chem. Soc.* **2003**, *125*, 15276–15277. (c) Kim, H.; So, S. M.; Chin, J.; Kim, B. M. *Aldrichimica Acta* **2008**, *41*, 77–88.

(14) Notes: (a) During the course of an asymmetric cross-coupling, the unreacted electrophile remains racemic, and the ee of the product is constant. (b) The stereoconvergent Suzuki reaction illustrated in entry 1 of Table 1 proceeds: in 88% ee and 86% yield on a gram scale (1.2 g of product); in 88% ee and 74% yield with 5% $NiBr_2$•diglyme/6% **1**. (c) Under the standard cross-coupling conditions: essentially no carbon−carbon bond formation is observed in the absence of $NiBr_2$•diglyme or ligand **1**; the presence of an ortho or a strongly electron-withdrawing substituent on the arylamine generally leads to lower ee and/or yield; the use of TBME or Et_2O as the solvent results in formation of the cross-coupling product in comparable ee but somewhat diminished yield (65−70%); a small amount of unreacted alkyl halide is sometimes observed.

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

(16) The coupling partner for electrophiles **3** and **4**: (9-BBN)-$(CH_2)_3$(*p*-anisyl).

(17) The coupling partner for electrophiles **5**−**8**: (9-BBN)$(CH_2)_3$-(*o*-anisyl).

(18) In contrast, for a *non*asymmetric cross-coupling of an unactivated secondary alkyl chloride, the rate *is* dependent on the concentration of the electrophile: Lu, Z.; Fu, G. C. *Angew. Chem., Int. Ed.* **2010**, *49*, 6676–6678.

(19) For a related mechanistic proposal for Ni/terpyridine-catalyzed Negishi cross-couplings, 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.

(20) We speculate that oxidative addition of the electrophile proceeds via binding of nitrogen to nickel, followed by oxidative addition to form a metalacycle.