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Asymmetric Alkyl−Alkyl Cross-Couplings of Unactivated Secondary Alkyl Electrophiles: Stereoconvergent Suzuki Reactions of Racemic Acylated Halohydrins

Nathan A. Owston and Gregory C. Fu*

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

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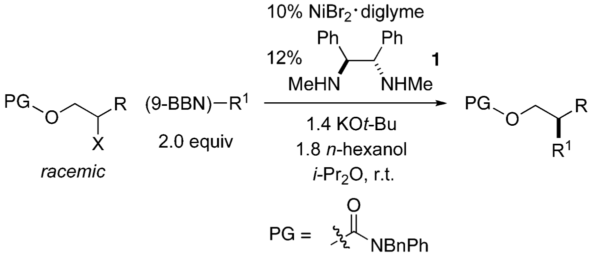
Abstract: A method for asymmetric alkyl−alkyl Suzuki reactions of unactivated secondary alkyl electrophiles, specifically, cross-couplings of racemic acylated halohydrins with alkylborane reagents, has been developed. A range of protected bromohydrins, as well as a protected chlorohydrin and a homologated bromohydrin, are coupled in good ee by a catalyst derived from commercially available components.

During the past several years, there have been substantial advances in the development of methods for metal-catalyzed cross-couplings of secondary alkyl electrophiles.[1] Furthermore, a number of catalytic enantioselective processes have been described; however, with one exception (homobenzylic bromides), this progress has been limited to couplings of *activated* electrophiles (e.g., α-halocarbonyl compounds, benzylic halides, allylic halides, and propargylic halides).[2−4]

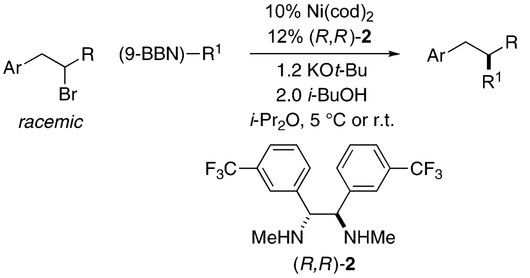
The ability to achieve asymmetric carbon−carbon bond formation with a wide range of *unactivated* halides would greatly enhance the utility of cross-couplings of alkyl electrophiles in organic synthesis. In this report, we describe a method for enantioselective Suzuki reactions[5] of a new family of unactivated secondary alkyl electrophiles, acylated halohydrins (eq 1).



(1)

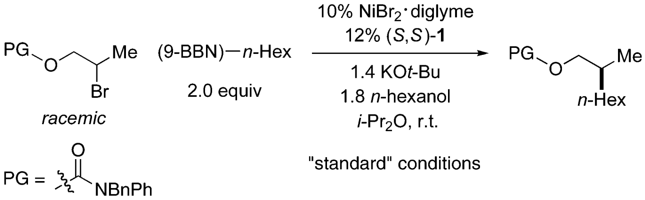
In 2008, we established that homobenzylic bromides serve as suitable substrates for nickel-catalyzed asymmetric Suzuki reactions, thereby furnishing the first examples of enantioselective cross-couplings of unactivated secondary alkyl electrophiles (eq 2).[2] Although this study provided proof-of-principle for such processes, homobenzylic halides are a relatively uncommon substructure in organic molecules. We were therefore intrigued by our observation that low enantioselectivity is obtained when an ether is present in the R substituent of the electrophile (eq 2: 40% ee for R = CH_2OBn, Ar = Ph, and R^1 = n-Hex). We speculated that this anomalous result might be a manifestation of coordination of the ether oxygen to the nickel catalyst.

In view of the pervasiveness of oxygen-containing functional groups in organic molecules, we decided to pursue the possibility that this interaction could be exploited in the development of a method for the asymmetric cross-coupling of oxygenated, unactivated electrophiles. After a series of optimization studies, we determined that a racemic acylated bromohydrin can be coupled with an alkylborane by a chiral nickel/diamine catalyst (both components are commercially available and can be handled in air) in good ee and yield at room temperature (entry 1 of Table 1; 94% ee and 80% yield).



(2)

Table 1. Asymmetric Alkyl−Alkyl Suzuki Reactions of Unactivated Alkyl Electrophiles: Racemic Acylated Bromohydrins[a]



entry	variation from the "standard" conditions	ee (%)	yield (%)[b]
1	none	94	80
2	no $NiBr_2$•diglyme	−	<2
3	no (*S*,*S*)-**1**	−	<2
4	no KO*t*-Bu	−	<2
5	conditions in eq 2 (rt)	94	18
6	$Ni(cod)_2$, instead of $NiBr_2$•diglyme	94	38
7	(*S*,*S*)-**2**, instead of (*S*,*S*)-**1**	91	47
8	*i*-BuOH, instead of *n*-hexanol	95	67
9	TBME, instead of *i*-Pr_2O	90	79
10	1.5 equiv of alkylborane	94	61
11	5% $NiBr_2$•diglyme, 6% (*S*,*S*)-**1**	94	37
12	PG = $CONEt_2$	87	66
13	PG = CONMePh	91	79
14	PG = $CONPh_2$	95	71
15	PG = COAr (Ar = *p*-anisyl)	83	81

[a] All data are the average of two experiments. [b] The yield was determined by GC analysis versus a calibrated internal standard.

Table 1 provides information about the effect of a number of reaction parameters on the efficiency of this new stereoconvergent Suzuki reaction. In the absence of $NiBr_2$•diglyme, ligand **1**, or KO*t*-Bu, essentially no cross-coupling is observed (entries 2−4). The conditions that were developed for asymmetric Suzuki couplings of homobenzylic bromides (eq 2) furnish only a small amount of product (18% yield; entry 5), due to the inferiority of $Ni(cod)_2$, ligand **2**, and *i*-BuOH, relative to $NiBr_2$•diglyme, ligand **1**, and *n*-hexanol (entries 6−8). TBME can be employed in place of *i*-Pr_2O as the solvent, at the expense of a slight erosion in ee (entry 9). Use of less alkylborane or catalyst results in a lower yield (entries 10 and 11). Other acyl protecting groups can be utilized, although there is a modest erosion in enantioselectivity and/or yield (entries 12−15).

We have examined the scope of this catalytic asymmetric alkyl−alkyl cross-coupling with respect to both the electrophilic and the nucleophilic partner (Table 2).[6] In the case of the racemic electrophile, for R substituents that range in size from methyl to isobutyl, the Suzuki reaction proceeds with uniformly good ee (≥90% ee; entries 1−10).

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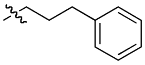
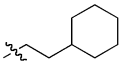
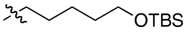
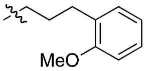
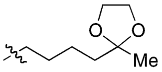
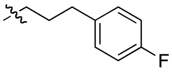
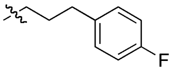
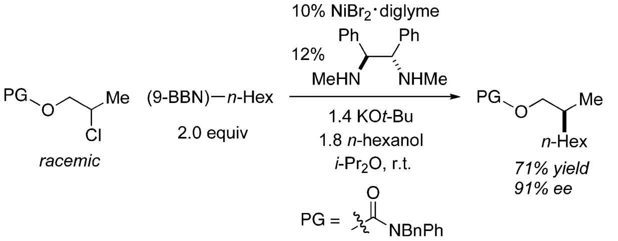
In addition, an array of alkylboranes serve as suitable nucleophiles, including substrates that bear a silyl ether (entry 3), an aryl alkyl ether (entry 4), an acetal (entry 6), and an aryl fluoride (entries 7 and 10).[7]

Table 2. Asymmetric Alkyl–Alkyl Suzuki Cross-Couplings of Racemic Acylated Bromohydrins: Scope (for the reaction conditions, see eq 1)[a]

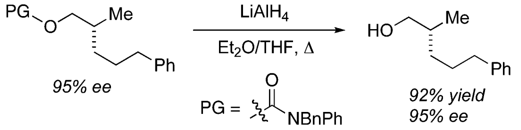
entry	R	R^1	ee (%)	yield (%)[b]
1	Me		94	80
2	Me		96	62
3	Me		94	66
4	Me		92	82
5	Et	*n*-Hex	96	74
6	Et		96	66
7	*n*-Hex		98	70
8[c]	CH$_2$Ph	*n*-Hex	90	54
9[c]	*i*-Bu	*n*-Hex	98	54
10	*i*-Bu		98	66

[a] All data are the average of two experiments. [b] Yield of purified product. [c] 15% NiBr$_2$·diglyme and 18% (*S*,*S*)-**1** were used.

This new stereoconvergent method is effective for asymmetric alkyl–alkyl Suzuki reactions not only of racemic acylated bromohydrins but also of chlorohydrins (eq 3); this represents the first example of an enantioselective cross-coupling of an unactivated secondary alkyl chloride. The carbamate protecting group can be cleaved in very good yield without eroding the ee (eq 4).



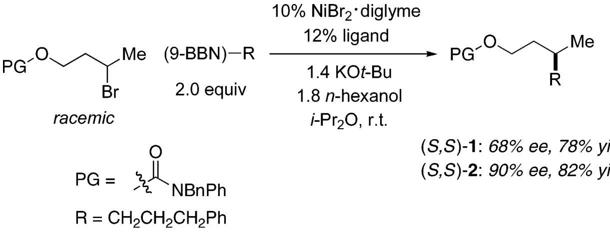
(3)



(4)

We have begun to investigate asymmetric Suzuki reactions of homologues of the acylated halohydrin electrophiles described above. In an initial study, we determined that, under the conditions optimized for bromohydrins, we obtain promising ee and yield for the cross-coupling of a racemic acylated homologue (eq 5).[8] Importantly, simply by modifying the structure of the ligand, the desired stereoconvergent alkyl–alkyl Suzuki coupling can be accomplished with very good enantioselectivity (eq 5; ligand **2** is commercially available).

In summary, we have developed a method for asymmetric alkyl–alkyl Suzuki reactions of unactivated secondary alkyl electrophiles, specifically, cross-couplings of racemic acylated halohydrins with alkylborane reagents. A range of protected bromohydrins, as well as a protected chlorohydrin and a homologated bromohydrin, are coupled in good ee by a catalyst derived from commercially available components. This investigation is only the second report of an asymmetric cross-coupling of an unactivated secondary alkyl electrophile, and it represents an advance with respect to utility, enantioselectivity, and versatility. Additional efforts to develop useful new coupling reactions of alkyl electrophiles are underway.



(5)

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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.

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(1) For leading references, see: Rudolph, A.; Lautens, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 2656–2670.

(2) For a report on catalytic asymmetric cross-couplings of *unactivated* secondary alkyl electrophiles, see: Saito, B.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 6694–6695. (Suzuki alkylations of homobenzylic bromides)

(3) For reports on catalytic asymmetric cross-couplings of *activated* secondary alkyl electrophiles, see: (a) Negishi alkylations of α-bromoamides: Fischer, C.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 4594–4595. (b) Negishi alkylations of 1-haloindanes: Arp, F. O.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 10482–10483. (c) Negishi alkylations of allylic chlorides: Son, S.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 2756–2757. (d) Hiyama arylations and vinylations of α-bromoesters: Dai, X.; Strotman, N. A.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 3302–3303. (e) Negishi arylations of propargylic halides: Smith, S. W.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 12645–12647. (f) Couplings of alkynylindiums with benzylic bromides: Caeiro, J.; Perez Sestelo, J.; Sarandeses, L. A. *Chem.—Eur. J.* **2008**, *14*, 741–746. (g) Negishi arylations of α-bromoketones: Lundin, P. M.; Esquivias, J.; Fu, G. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 154–156. (h) Kumada arylations of α-bromoketones: Lou, S.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 1264–1266. (i) Zirconium Negishi alkenylations of α-bromoketones: Lou, S.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 5010–5011. (j) Suzuki arylations of α-haloamides: Lundin, P. M.; Fu, G. C. *J. Am. Chem. Soc.*, ASAP (DOI: 10.1021/ja105148g).

(4) For overviews and leading references, see: (a) Glorius, F. *Angew. Chem., Int. Ed.* **2008**, *47*, 8347–8349. (b) Reference 1.

(5) The Suzuki reaction is perhaps the most widely used cross-coupling process. For leading references, see: (a) *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: New York, 2004. (b) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-i., Ed.; Wiley Interscience: New York, 2002.

(6) Notes: (a) During the course of a cross-coupling, no kinetic resolution of the secondary alkyl bromide is detected, and the ee of the product is constant. (b) On a gram-scale, the reaction illustrated in entry 1 of Table 2 proceeds in 95% ee and 76% yield. (c) In preliminary experiments under our standard conditions, an alkylboronic acid and a secondary alkyl-(9-BBN) reagent were not suitable cross-coupling partners, and the reaction of a hindered (R = *i*-Pr) and of an ether-containing (R = CH$_2$OMe) electrophile proceeded in good ee (>90%) but low yield (~30%) even in the presence of 15% NiBr$_2$·diglyme/18% ligand **1**. (d) Except in the case of entries 8 and 9 of Table 2 (20–30% recovered starting material; heating was not beneficial), little or no starting material remained when these cross-couplings were terminated. Hydrodebromination of the electrophile was observed as a side reaction. (e) For a proposed mechanism for Ni/terpyridine-catalyzed Negishi cross-couplings of unactivated alkyl electrophiles, see: 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. Lin, X.; Phillips, D. L. *J. Org. Chem.* **2008**, *73*, 3680–3688.

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(8) In contrast, in the case of the other example of an asymmetric cross-coupling of an unactivated secondary alkyl electrophile (ref 2), the reaction of a homologue proceeded in low ee (14%).

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