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# Catalytic Enantioselective Cyclization/Cross-Coupling with Alkyl Electrophiles

Huan Cong<sup>†,‡</sup> and Gregory C. Fu<sup>\*,†,‡</sup>

<sup>†</sup>Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, United States

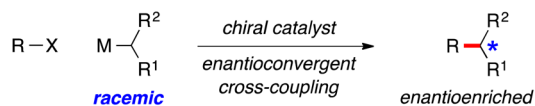
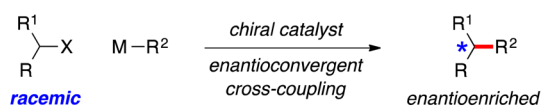
<sup>‡</sup>Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, United States

**S** Supporting Information

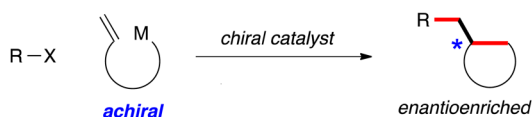
**ABSTRACT:** As part of our ongoing effort to expand the scope of cross-coupling reactions of alkyl electrophiles, we have pursued a strategy wherein the nucleophilic coupling partner includes a pendant olefin; after transmetalation by such a substrate, if  $\beta$ -migratory insertion proceeds faster than direct cross-coupling, an additional carbon–carbon bond and stereocenter can be formed. With the aid of a nickel/diamine catalyst (both components are commercially available), we have established the viability of this approach for the catalytic asymmetric synthesis of 2,3-dihydrobenzofurans and indanes. Furthermore, we have applied this new method to the construction of the dihydrobenzofuran core of fasiglifam, as well as to a cross-coupling with a racemic alkyl electrophile; in the latter process, the chiral catalyst controls two stereocenters, one that is newly generated in a  $\beta$ -migratory insertion and one that begins as a mixture of enantiomers.

In recent years, significant progress has been reported on the development of methods for the transition-metal-catalyzed cross-coupling of alkyl electrophiles to generate carbon–carbon bonds, including enantioselective processes.<sup>1</sup> To date, most investigations of asymmetric catalysis have focused on stereoconvergent reactions of racemic secondary electrophiles,<sup>2</sup> although an advance has also been described with a racemic secondary nucleophile (top of Figure 1).<sup>3</sup>

**Previous work:**



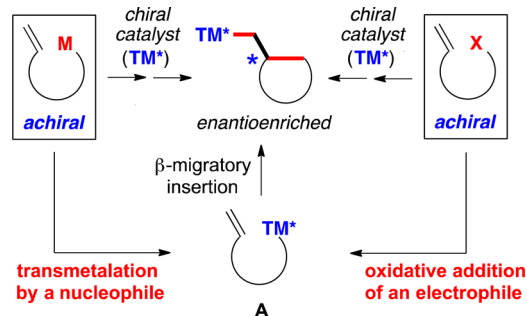
**This study:**



— : new carbon–carbon bond

**Figure 1.** Asymmetric cross-couplings of alkyl electrophiles.

As part of our ongoing effort to expand the scope of enantioselective cross-couplings of alkyl electrophiles, we are pursuing an approach wherein an organometallic reagent that bears a pendant olefin is employed as the nucleophilic coupling partner (bottom of Figure 1).<sup>4–6</sup> In the presence of a chiral catalyst, transmetalation and then  $\beta$ -migratory insertion (left side of Figure 2), followed by alkyl–alkyl coupling, could lead



**Figure 2.** Complementary approaches to generating a precursor (A) for catalytic enantioselective cyclizations.

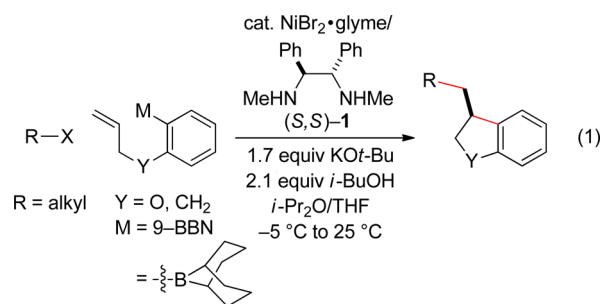
to the formation of two carbon–carbon bonds and a new stereocenter (bottom of Figure 1). This strategy complements asymmetric coupling processes wherein an intermediate of type A is generated through oxidative addition of an electrophile (right side of Figure 2).<sup>7</sup>

In this report, we establish that a transmetalation–insertion sequence can indeed be used to generate two, rather than one, carbon–carbon bonds in a cross-coupling with an alkyl electrophile and that this process can be achieved with good enantioselectivity. Specifically, we describe couplings of arylboron reagents that bear a pendant olefin with unactivated alkyl halides, thereby furnishing 2,3-dihydrobenzofurans<sup>8,9</sup> and indanes<sup>10,11</sup> in high ee (eq 1).

In order to enhance the likelihood of cyclization ( $\beta$ -migratory insertion) prior to coupling with the electrophile, we chose to focus on an organometallic coupling partner that could form a five-membered ring upon insertion, since such cyclizations are often facile. At the outset, it was unclear what catalyst would enable the desired sequence of bond-forming processes, much less achieve high enantioselectivity.

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Interestingly, we have determined that a nickel/1,2-diamine-based catalyst, which we have found to be useful for enantioconvergent alkyl-alkyl couplings,<sup>3,12</sup> is also effective for the desired cyclization/cross-coupling sequence (Table 1,

**Table 1. Catalytic Enantioselective Cyclization/Cross-Coupling with an Alkyl Electrophile: Influence of Reaction Parameters<sup>a</sup>**

10%  $\text{NiBr}_2 \cdot \text{glyme}$   
 12%  $(S,S)$ -**1**  
 1.7 equiv KOt-Bu  
 2.1 equiv *i*-BuOH  
*i*-Pr<sub>2</sub>O/THF; 25 °C  
 "standard" conditions

entry	variation from the "standard" conditions	ee (%) <sup>a</sup>	yield (%) <sup>b</sup>
1	none	96	82
2	no $\text{NiBr}_2 \cdot \text{glyme}$	—	<5
3	no $(S,S)$ - <b>1</b>	—	<5
4	no <i>i</i> -BuOH	—	<5
5	1.5 equiv of arylboron reagent	81	67
6	$(S,S)$ - <b>2</b> , instead of $(S,S)$ - <b>1</b>	39	64
7	$(S,S)$ - <b>3</b> , instead of $(S,S)$ - <b>1</b>	—	<5
8	$(S,S)$ - <b>4</b> , instead of $(S,S)$ - <b>1</b>	61	33
9	$\text{BnCH}_2\text{CH}_2\text{Cl}$ , instead of $\text{BnCH}_2\text{CH}_2\text{Br}$	—	<5

$\text{F}_3\text{C}$   $\text{CF}_3$   
 $\text{MeHN}$   $\text{NHMe}$   
 $(S,S)$ -**2**

$i$ -Pr  $i$ -Pr  
 $(S,S)$ -**3**

$\text{Ph}$   $\text{Me}$   $\text{Me}$   
 $(S,S)$ -**4**

<sup>a</sup>All data are the average of two experiments. <sup>b</sup>The yield was determined by GC analysis with the aid of a calibrated internal standard.

entry 1). Thus, in the presence of  $\text{NiBr}_2 \cdot \text{glyme}$  and ligand **1**, both of which are commercially available, the target 2,3-dihydrobenzofuran is generated in good ee and yield. Under these conditions, essentially none of the product of direct cross-coupling (without cyclization of the nucleophile) or of endo cyclization is observed (<5%).

In the absence of  $\text{NiBr}_2 \cdot \text{glyme}$ , ligand **1**, or *i*-BuOH, the desired cyclization/cross-coupling product did not form in appreciable yield (Table 1, entries 2–4).<sup>13</sup> Furthermore, the use of a smaller excess of the arylboron reagent led to a somewhat lower ee and yield (entry 5).<sup>14</sup> Other ligands that we have found to be useful for enantioconvergent couplings of alkyl electrophiles were not effective for this new asymmetric cross-coupling with an alkyl halide (entries 6–8).<sup>15</sup> If the alkyl

bromide was replaced with the corresponding alkyl chloride, essentially no 2,3-dihydrobenzofuran was observed (entry 9).<sup>16</sup>

We next examined the scope of this method for asymmetric cyclization/cross-coupling with alkyl bromides (Table 2).<sup>17</sup> A

**Table 2. Catalytic Enantioselective Cyclization/Cross-Coupling with Alkyl Electrophiles<sup>a</sup>**

R-Br  
 M = 9-BBN  
 Table 1

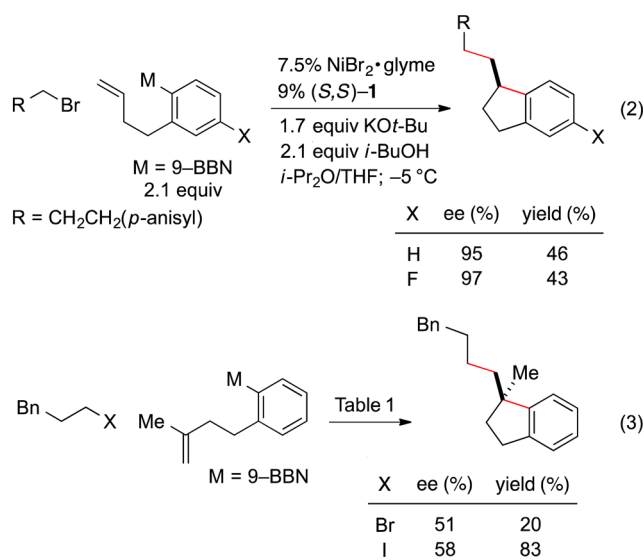
entry	product	ee (%)	yield (%) <sup>b</sup>
1		95	77
2		96	47
3		97	69
4		97	67
5		94	45 <sup>c</sup>
6		96	58
7		96	52

<sup>a</sup>All data are the average of two experiments. <sup>b</sup>Yield of purified product. <sup>c</sup>15%  $\text{NiBr}_2 \cdot \text{glyme}$  and 17% ligand **1** were used.

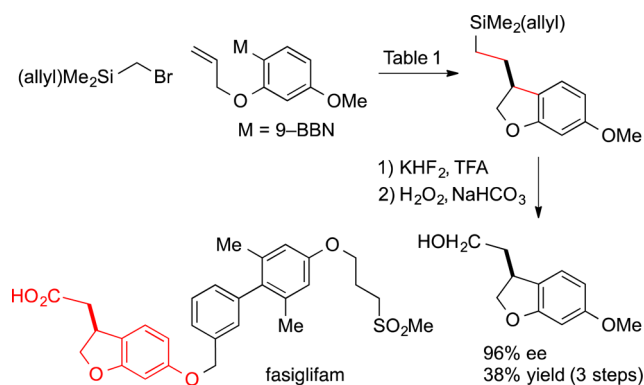
range of functionalized electrophiles serve as suitable reaction partners, furnishing the desired 2,3-dihydrobenzofuran in very good enantiomeric excess. A silane, an acetal, and an imide are compatible with the reaction conditions. The method is not limited to unhindered primary alkyl bromides; a  $\beta$ -branched primary and a secondary bromide also undergo cyclization/cross-coupling (entries 6 and 7).

Under similar conditions, indane derivatives can also be produced in high ee, although modest yield (eq 2).<sup>17c</sup> An attempt to generate a quaternary stereocenter furnished a promising initial result (eq 3).

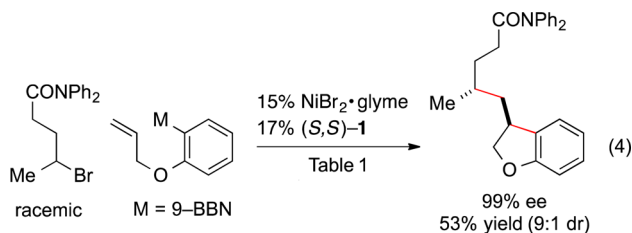
A number of optically active 2,3-dihydrobenzofurans exhibit interesting biological activity,<sup>8,9</sup> including fasiglifam (Takeda Pharmaceuticals: TAK-875), which progressed to phase 3 clinical trials for type 2 diabetes until being withdrawn due to concerns about liver safety.<sup>18</sup> We have applied our method to a catalytic asymmetric synthesis of the dihydrobenzofuran core of fasiglifam (Scheme 1).



Scheme 1. Catalytic Asymmetric Synthesis of the 2,3-Dihydrobenzofuran Core of Fasiglifam



In view of the similarity of the optimized conditions for this new asymmetric cyclization/cross-coupling process to those for our stereoselective cross-coupling of racemic  $\gamma$ -haloamides,<sup>12d</sup> we investigated the possibility that a single chiral catalyst could accomplish two distinct enantioselective transformations: create a new stereocenter through the cyclization of an achiral nucleophile, as well as control the absolute stereochemistry of a second stereocenter through an enantioconvergent coupling of a racemic electrophile. As illustrated in eq 4, this objective can indeed be achieved (minor diastereomer: 86% ee).



In summary, we have expanded the scope of cross-coupling reactions of alkyl electrophiles by incorporating an olefin in the nucleophilic partner, which leads to the formation of an additional carbon-carbon bond and stereocenter, when compared with a simple cross-coupling. With the aid of a nickel/diamine catalyst (both components are commercially

available), we have established that this strategy enables the synthesis of highly enantioenriched 2,3-dihydrobenzofurans and indanes through couplings with a range of alkyl halides. We have applied this new method to the generation of the dihydrobenzofuran core of fasiglifam, as well as to a transformation wherein the chiral catalyst controls the stereochemistry of two rather different processes: a  $\beta$ -migratory insertion and an enantioconvergent coupling of a racemic alkyl halide. Ongoing studies are directed at further enlarging the scope of cross-coupling reactions of alkyl electrophiles, as well as elucidating the mechanisms of these transformations.

## 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

gcfu@caltech.edu

### Notes

The authors declare no competing financial interest.

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(13) The failure to observe a significant amount of the cross-coupling product in the absence of *i*-BuOH (entry 4 of Table 1) could be due to less effective transmetalation in the absence of a less bulky alkoxide.

(14) Some of the nucleophile is consumed in the reduction of the Ni(II) precatalyst to the active catalyst. A small amount also undergoes protodeborylation under the reaction conditions.

(15) For example, see: (a) Pybox ligand: Fischer, C.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 4594–4595. (b) Bis(oxazoline) ligand: Lou, S.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 1264–1266.

(16) The alkyl chloride is largely intact at the end of the reaction (>95%).

(17) Notes: Under our standard conditions (Table 1): (a) The coupling illustrated in Table 2, entry 1 proceeded in 96% ee and 67% yield on a gram scale (1.07 g of product). (b) An initial attempt to form a six-membered ring through cyclization/cross-coupling of a homologated arylboron reagent was not successful. (c) In general, the primary undesired side reactions are reduction (hydrodehalogenation) and electrophile homocoupling. (d) PhBr is not a suitable electrophile. (e) An indoline can be generated with promising enantioselectivity and yield (54% ee, 40% yield).

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