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

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

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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

\[
\begin{align*}
\text{racemic} & \quad R_1, R_1' = \text{alkyl} \\
R & \quad \gamma-	ext{haloester}
\end{align*}
\]

(1)

To date, effective enantioselective cross-couplings of unactivated alkyl electrophiles have only been described 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.

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Supporting Information. Experimental procedures and compound characterization data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.
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). Diphenylamides are attractive carboxylic acid derivatives, since reduction and acyl transfer reactions proceed smoothly (eq 3–5).

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, indole, and aryl fluoride. Both of the catalyst components (NiBr2•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-chloro diphenylamides. Thus, the corresponding bromides are also suitable electrophiles (eq 6; not optimized). Furthermore, under the standard conditions, good ee is observed for the stereocoupling of a homologue of a γ-chloro amide, thereby achieving enantioselective δ-alkylation (eq 7). Finally, the carbonyl group need not be a diphenylamide; for example, the cross-coupling of a γ-chloro Weinreb amide.
proceeds with promising ee, and a preliminary study provides evidence that enhanced enantioselectivity will be possible through further optimization (eq 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. We have obtained encouraging enantioselectivities when coupling a γ-chloro amide with an arylborane (eq 9), a boronate ester (eq 10), and a secondary (cyclopropyl) alkylborane (eq 11). These data illustrate the potential for an important expansion in the scope of asymmetric cross-couplings of unactivated alkyl electrophiles.
Regarding the pathway for these Suzuki reactions, our current working hypothesis is depicted in Scheme 1. This builds on pioneering mechanistic studies by Vicic and by Phillips of nickel/terpyridine-catalyzed Negishi cross-couplings of unactivated alkyl halides. Interestingly, the computational investigation of Phillips suggests that the formation of $B$ may be reversible for the coupling of MeZnI and $i$-PrI, specifically, that $\Delta G^\neq = 11$ kcal/mol for $B \rightarrow A$ and $\Delta G^\neq = 13$ kcal/mol for $B \rightarrow C$.

In order to gain insight into whether the initial step of oxidative addition ($A \rightarrow B$) is reversible under our Suzuki cross-coupling conditions, we monitored the reaction of each enantiomer of a $\gamma$-haloamide (eq 12). We observe essentially no erosion in the ee of the electrophile during the course of the reaction, which is consistent with the conclusion that halide abstraction ($A \rightarrow B$) is irreversible, in contrast to the Phillips study of a Negishi reaction.

In conclusion, we have developed a method for the catalytic enantioselective $\gamma$- (and $\delta$-) alkylation of carbonyl compounds through the cross-coupling of $\gamma$-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.

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

**Acknowledgments**

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References


2. For a recent example, see: Smith SW, Fu GC. J Am Chem Soc. 2009; 131:14231–14233. [PubMed: 19772285]


6. Notes: (a) The catalytic enantioselective γ-alkylation illustrated in entry 4 of Table 1 proceeds in 89% ee and 79% yield on a gram scale (1.1 g of product). (b) The cross-coupling depicted in entry 3 of Table 1 proceeds in 89% ee and 57% yield when conducted with a lower catalyst loading (5% NiBr2•diglyme/6% ligand 1 on a 0.5 mmol scale). (c) Under the standard conditions (eq 2), essentially no carbon–carbon bond formation is observed in the absence of NiBr2•diglyme or of 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.


10. Under the standard conditions (eq 2), a β-chloroamide is not a suitable coupling partner, due to 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-couple with ee’s 1–15% lower than the diphenylamide.


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


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


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Scheme 1.
Outline of a Possible Reaction Pathway (for the sake of simplicity, all of the elementary steps are drawn as irreversible).
**Table 1**

Catalytic Enantioselective γ-Alkylation of \(N,N\)-Diphenylamides via Stereoconvergent Suzuki Cross-Couplings of Secondary Alkyl Chlorides (for the reaction conditions, see eq 2)\(^a\)

<table>
<thead>
<tr>
<th>entry</th>
<th>(R^1)</th>
<th>(R)</th>
<th>ee (%)</th>
<th>yield (%)</th>
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<tr>
<td>1</td>
<td>Me</td>
<td></td>
<td>85</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>2(^c)</td>
<td>Me</td>
<td></td>
<td>90</td>
<td>54</td>
<td></td>
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<tr>
<td>3</td>
<td>Et</td>
<td>(CH(_2)_3–OTBS)</td>
<td>91</td>
<td>74</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Et</td>
<td></td>
<td>89</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Et</td>
<td>(CH(_2)_2–N)</td>
<td>90</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>6(^d)</td>
<td>Et</td>
<td>(CH(_2)_2–CN)</td>
<td>69</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>(n)-Bu</td>
<td></td>
<td>90</td>
<td>64</td>
<td></td>
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<tr>
<td>8</td>
<td>CH(_2)CH(_2)Ph</td>
<td></td>
<td>88</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>(i)-Bu</td>
<td>(CH(_2)_3–Ph)</td>
<td>82</td>
<td>61</td>
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\(^a\) All data are the average of two experiments.

\(^b\) Yield of purified product.

\(^c\) 20% NiBr\(_2\) • diglyme and 24% 1 were used.

\(^d\) The reaction was conducted in \(i\)-Pr\(_2\)O at 60 °C.