Catalytic Asymmetric Synthesis of Tertiary Alkyl Fluorides: Negishi Cross-Couplings of Racemic α,α-Dihaloketones

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Supporting Information

ABSTRACT: The development of new approaches to the construction of fluorine-containing target molecules is important for a variety of scientific disciplines, including medicinal chemistry. In this Article, we describe a method for the catalytic enantioselective synthesis of tertiary alkyl fluorides through Negishi reactions of racemic α-halo-α-fluoroketones, which represents the first catalytic asymmetric cross-coupling that employs geminal dihalides as electrophiles. Thus, selective reaction of a C–Br (or C–Cl) bond in the presence of a C–F bond can be achieved with the aid of a nickel/bis(oxazoline) catalyst. The products of the stereoconvergent cross-couplings, enantoenriched tertiary α-fluoroketones, can be converted into an array of interesting organofluorine compounds.

INTRODUCTION

Motivated by potential applications in biomedical research and other disciplines,1 substantial effort has been dedicated to the development of methods for the preparation of organofluorine compounds.2 In the case of alkyl fluorides, advances have been described in the catalytic enantioselective synthesis of stereoactive centers that bear a fluorine substituent,3 particularly α to a carbonyl group. Although most studies have addressed the generation of secondary stereocenters,4 a few reports have examined the establishment of tertiary centers; currently, the latter methods are largely limited to either cyclic or doubly activated acyclic α-fluorocarbonyl compounds.5,6 To the best of our knowledge, no general catalytic enantioselective process has been discovered for the synthesis of simple tertiary α-fluorinated acyclic ketones.7−9 During the past decade, we have developed an array of nickel-catalyzed asymmetric cross-coupling methods, employing racemic alkyl electrophiles as reaction partners; to date, all of the electrophiles have been secondary, with Z = H (eq 1).10,11

\[
\text{alkyl} \quad \text{chiral Ni catalyst} \quad \text{alkyl}
\]

This study: Z = F

We have now begun to explore enantioselective couplings of other families of electrophiles, beginning with geminal dihalides (eq 1; Z = F, X = halide).12 such H → F substitutions can have a dramatic impact on reactivity and/or ee.13 If a suitable catalyst could achieve selective cleavage of the C–X bond, along with efficient and highly enanto-enriched C–C bond formation, then this would enable the catalytic asymmetric synthesis of tertiary alkyl fluorides.

In view of the high interest in the enantioselective synthesis of α-fluorocarbonyl compounds,4,5,8,9 as well as the excellent functional-group compatibility of Negishi reactions,14 we chose to examine the coupling of α-halo-α-fluoroketones with organozinc reagents. In this Article, we describe the first catalytic asymmetric cross-coupling that employs geminal dihalides as electrophiles, specifically, a nickel/bis(oxazoline)-catalyzed stereoconvergent Negishi arylation of racemic α-bromo-α-fluoroketones to generate tertiary α-fluorinated acyclic ketones (eq 2).

\[
\text{alkyl} \quad \text{Ar}^1 - \text{ZnCl} \quad 15\% \text{NiCl}_2 \cdot \text{glyme} \quad 16\% \text{L}^* \quad \text{THF/diglyme} \quad -25^\circ C
\]

\[
\text{alkyl} \quad \text{alkyl}
\]

enanto-enriched

\[
15\% \text{NiCl}_2 \cdot \text{glyme} \quad 15\% \text{L}^* \quad \text{THF/diglyme} \quad -25^\circ C
\]

\[
\text{alkyl} \quad \text{Ar}^1 \quad \text{alkyl}
\]

enanto-enriched

RESULTS AND DISCUSSION

At the time that we began our investigation in 2011, we were not aware of any precedent for selective nickel-catalyzed cross-couplings of α-halo-α-fluoro compounds. However, during the course of our studies, Ando reported diastereoselective Kumada reactions of α-bromo-α-fluoro-β-lactams with aryl Grignard reagents,15 employing a NiCl₂·glyme/bis(oxazoline) catalyst.
that we had described for enantioselective couplings of aryl Grignard reagents with α-bromoketones.\textsuperscript{10c}

Unfortunately, our attempts to apply our previous methods for Kumada\textsuperscript{10c} and Negishi\textsuperscript{10d} arylations to the cross-coupling of the racemic α-bromo-α-fluoroketone illustrated in Table 1 were unsuccessful (<2% yield). However, through the appropriate choice of reaction parameters, we were able to achieve the desired α-arylation and to generate the tertiary alkyl fluoride with very good enantioselectivity (97% ee; Table 1, entry 1). NiCl\textsubscript{2}·glyme and bis(oxazoline) \textsuperscript{L}\textsuperscript{*} are commercially available and air-stable.

Table 1. Catalytic Asymmetric Synthesis of Tertiary Alkyl Fluorides: Effect of Reaction Parameters\textsuperscript{a}

\begin{tabular}{|c|c|c|c|}
\hline
entry & variation from the “standard” conditions & ee (%)\textsuperscript{b} & yield (%)\textsuperscript{c} \\
\hline
1 & none & 97 & 68 \\
2 & no NiCl\textsubscript{2}·glyme & – & <2 \\
3 & no \textsuperscript{L}\textsuperscript{*} & – & <2 \\
4 & 1, instead of \textsuperscript{L}\textsuperscript{*} & –76 & 11 \\
5 & 2, instead of \textsuperscript{L}\textsuperscript{*} & –70 & 8 \\
6 & 3, instead of \textsuperscript{L}\textsuperscript{*} & – & <2 \\
7 & 4, instead of \textsuperscript{L}\textsuperscript{*} & 52 & 40 \\
8 & 5, instead of \textsuperscript{L}\textsuperscript{*} & – & <2 \\
9 & 10% NiCl\textsubscript{2}·glyme, 11% \textsuperscript{L}\textsuperscript{*} & 97 & 49 \\
10 & 1.2 equiv PhZnCl & 97 & 51 \\
11 & PhMgCl, instead of PhZnCl & – & <2 \\
12 & Ph\textsubscript{2}Zn, instead of PhZnCl & 98 & 56 \\
13 & r.t. & 83 & 17 \\
14 & THF only & 90 & 38 \\
15 & diglyme only & 91 & 19 \\
16 & 0.1 equiv H\textsubscript{2}O & 97 & 65 \\
17 & in air in a closed vial & 94 & 27 \\
\hline
\end{tabular}

\textsuperscript{a}All data are the average of two experiments. \textsuperscript{b}A negative ee value signifies that the major product of the reaction is the opposite (R) enantiomer. \textsuperscript{c}The yields were determined through analysis by \textsuperscript{19}F NMR spectroscopy, with the aid of an internal standard.

were unsuccessful (<2% yield). However, through the appropriate choice of reaction parameters, we were able to achieve the desired α-arylation and to generate the tertiary alkyl fluoride with very good enantioselectivity (97% ee; Table 1, entry 1). NiCl\textsubscript{2}·glyme and bis(oxazoline) \textsuperscript{L}\textsuperscript{*} are commercially available and air-stable.

Table 1 provides information on the impact of various reaction parameters on the efficiency of this catalytic asymmetric synthesis of tertiary alkyl fluorides. In the absence of NiCl\textsubscript{2}·glyme or of ligand \textsuperscript{L}\textsuperscript{*}, essentially no carbon–carbon bond formation is observed (entries 2 and 3). The cis phenyl substituent in the 5 position of the oxazolines plays an important role in enantioselectivity and yield (entry 4), as does the substitution on the one-carbon linker that bridges the oxazolines (entries 5 and 6). A variety of pybox and 1,2-diamine ligands\textsuperscript{10b,d} furnish inferior results (e.g., entries 7 and 8). The use of less catalyst or less nucleophile leads to a modest decrease in yield, although no erosion in ee (entries 9 and 10). Under our optimized conditions, PhMgCl is not a useful coupling partner (entry 11), whereas good enantioselectivity but less-efficient cross-coupling is observed when Ph\textsubscript{2}Zn serves as the nucleophile (entry 12). Conducting the Negishi reaction at room temperature or with a single solvent causes a small drop in ee and a substantial loss in yield (entries 13–15). The presence of water (0.1 equiv) has essentially no impact on the course of the reaction (entry 16), whereas running the reaction under air results in decreased yield (entry 17).

Our optimized conditions can be applied to the catalytic asymmetric Negishi arylation of a variety of racemic α-bromo-α-fluoroketones, furnishing tertiary alkyl fluorides in generally good ee (Table 2).\textsuperscript{16} The R group of the ketone can vary in size, although a lower ee is observed with a bulky isopropyl substituent (entries 1–6). High enantioselectivity is typically obtained whether the aromatic group (Ar) is para-, meta-, or ortho-substituted, and whether it is electron-rich or electron-poor (entries 7–16); we have not previously observed high ee in related nickel-catalyzed cross-couplings with ortho-substituted Ar groups (entries 14 and 15; previously: ≤75% ee)\textsuperscript{10c,d,17}

Table 2. Catalytic Asymmetric Synthesis of Tertiary Alkyl Fluorides: Scope with Respect to the Electrophile\textsuperscript{a}

\begin{tabular}{|c|c|c|c|c|}
\hline
entry & Ar & R & ee (%)\textsuperscript{b} & yield (%)\textsuperscript{c} \\
\hline
1 & Ph & Et & 97 & 62 \\
2 & Ph & CH\textsubscript{2}Ph & 98 & 73 \\
3 & Ph & & 97 & 43 \\
4 & Ph & & 91 & 59 \\
5 & Ph & & 82 & 55 \\
6 & Ph & CH\textsubscript{2}Cl & 98 & 62 \\
7 & Ph & X=O\textsubscript{Me} & CH\textsubscript{2}Ph & 96 & 62 \\
8 & Ph & t-Bu & CH\textsubscript{2}Cl & 98 & 76 \\
9 & Ph & Et & 96 & 54 \\
10 & Ph & F & CH\textsubscript{2}Cl & 97 & 63 \\
11 & X=O\textsubscript{Me} & & Et & 97 & 54 \\
12 & X=O\textsubscript{Me} & & CH\textsubscript{2}Ph & 97 & 59 \\
13 & Ph & & Et & 97 & 65 \\
14 & Ph & X=O\textsubscript{Me} & Et & 92 & 62 \\
15 & Ph & X=O\textsubscript{Me} & Me & CH\textsubscript{2}Ph & 94 & 70 \\
16 & Ph & & Et & 97 & 51 \\
\hline
\end{tabular}

\textsuperscript{a}All data are the average of two experiments. \textsuperscript{b}Yield of purified product.
Functional groups such as an olefin, alkyl chloride, alkyl methyl ether, and aryl fluoride are compatible with the reaction conditions.

The scope of this method for the catalytic asymmetric synthesis of tertiary alkyl fluorides is also fairly broad with respect to the nucleophile (ArZnCl; Table 3).

Table 3. Catalytic Asymmetric Synthesis of Tertiary Alkyl Fluorides: Scope with Respect to the Nucleophile

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>Ar</th>
<th>ee (%)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₂Ph</td>
<td>TBSO</td>
<td>97</td>
<td>67</td>
</tr>
<tr>
<td>2</td>
<td>Et</td>
<td>i-Pr</td>
<td>97</td>
<td>71</td>
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<tr>
<td>3c</td>
<td>CH₂Ph</td>
<td>F</td>
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<tr>
<td>4c</td>
<td>CH₂Ph</td>
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<td>70</td>
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<tr>
<td>5</td>
<td>CH₂Ph</td>
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<td>99</td>
<td>78</td>
</tr>
<tr>
<td>6</td>
<td>Et</td>
<td>i-Pr</td>
<td>97</td>
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<tr>
<td>9</td>
<td>Cl</td>
<td></td>
<td>98</td>
<td>58</td>
</tr>
</tbody>
</table>

All data are the average of two experiments. Yield of purified product. Reaction temperature: −20 °C.

Moreover, regioselective Baeyer–Villiger oxidation of the enantioenriched α-fluoroketones can be achieved, thereby providing access to either an alkyl ester or an aryl ester by controlling the relative migratory aptitudes of the ketone substituents (eqs 6 and 7). This oxidation thereby enables, to our knowledge, the first asymmetric synthesis of acylated fluorohydrins (eq 6), as well as an indirect method for the catalytic enantioselective synthesis of tertiary α-fluoroesters (eq 7) and amides.

Summary, we have developed the first catalytic asymmetric cross-coupling method that employs geminal dihalides as electrophiles. Specifically, we have established that nickel/bis(oxazoline)-catalyzed stereocconvergent Negishi reactions of racemic α-halo-α-fluoroketones provide access to enantioenriched tertiary alkyl fluorides, thereby complementing earlier catalytic asymmetric methods for the synthesis of organofluorine compounds, which have typically focused on the generation of secondary alkyl fluorides. The α-fluoroketones that are produced in these Negishi couplings can be transformed into a variety of interesting families of organofluorine target molecules. Additional investigations of catalytic enantioselective cross-couplings of alkyl electrophiles are underway.

CONCLUSIONS

In summary, we have developed the first catalytic asymmetric cross-coupling method that employs geminal dihalides as electrophiles. Specifically, we have established that nickel/bis(oxazoline)-catalyzed stereocconvergent Negishi reactions of racemic α-halo-α-fluoroketones provide access to enantioenriched tertiary alkyl fluorides, thereby complementing earlier catalytic asymmetric methods for the synthesis of organofluorine compounds, which have typically focused on the generation of secondary alkyl fluorides. The α-fluoroketones that are produced in these Negishi couplings can be transformed into a variety of interesting families of organofluorine target molecules. Additional investigations of catalytic enantioselective cross-couplings of alkyl electrophiles are underway.
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The authors declare no competing financial interest.

REFERENCES


(9) For an example with esters, see: Tengeji, A.; Shina, I. Molecules 2012, 17, 7356–7378.


(16) Under our standard conditions: (a) On a gram-scale, the asymmetric Negishi cross-coupling illustrated in entry 2 of Table 2 furnished the desired tertiary alkyl fluoride in 97% ee and 66% yield (1.41 g of product). (b) Hydrodeborination of the electrophile was a side reaction (the secondary alkyl fluoride was produced in ∼5% ee). (c) During the course of a cross-coupling, no kinetic resolution of the electrophile was detected (<5% ee), and the ee of the product was constant. (d) The cross-coupling product was stable (no further reaction and no erosion in ee). (e) A cyclic ketone (α,α-tetralone-derived) and a 2-thienyl ketone were not suitable electrophiles.

(17) A ketone in which the aromatic group (Ar) was mesityl did not undergo cross-coupling under our standard conditions.

(18) For an example of a nickel-catalyzed cross-coupling of an unactivated alkyl chloride, see ref 10b.


(21) Our standard conditions were not effective for the cross-coupling of a thiencyclic reagent or a Knoevenagel-type arylic reagent: Krasovskiy, A.; Malakhov, V.; Gavryushin, A.; Knochel, P. Angew. Chem., Int. Ed. 2006, 45, 6040–6044.

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Essentially no carbon–carbon bond formation was observed when o-tolylzinc chloride was employed as the nucleophile under our standard conditions.

Nickel-catalyzed Negishi reactions of aryl halides are well-established; for examples, see: Phapale, V. B.; Cárdenas, D. J. Chem. Soc. Rev. 2009, 38, 1598–1607. Interestingly, under the conditions described in eq 2, essentially no coupling of PhZnCl with an aryl iodide or an aryl bromide was observed (≥95% recovery of 4-bromotoluene and 4-iodotoluene).

The stereochemistry of each product (eqs 4 and 5) has been determined by X-ray crystallography (see the Supporting Information). Reduction of the ketone with NaBH₄ also proceeded with high diastereoselectivity (>20:1) and in good yield (>99%). However, we have not yet been able to establish the relative stereochemistry of the major diastereomer.


For the Baeyer–Villiger reactions illustrated in eqs 6 and 7, the selectivity is ≥20:1 for the indicated bond cleavage.


The aryl ester (eq 7) can readily be converted into an amide by treatment with an amine (e.g., pyrrolidine: 70% isolated yield). We are not aware of reports of direct methods for the catalytic enantioselective synthesis of tertiary α-fluorinated acyclic amides.