Enantioselective Barbier-type allylation of ketones using allyl halide and indium in water†

Shuichi Nakamura,∗ab Yoshichika Hara,a Takashi Furukawaa and Tsunehisa Hirashitaa

We disclose herein an efficient enantioselective Barbier-type allylation of ketones using allyl halide and indium metal in water. The reaction was catalysed by chiral bis(midazoline) to afford homoallylic alcohols having quaternary stereocenters in good yield with moderate to good enantioselectivity. Based on experimental investigation, a possible transition state has been proposed to explain the origin of the asymmetric induction.

Optically active tertiary homoallylic alcohols are an important class of synthetic intermediates because they often act as useful chiral building blocks for the synthesis of biologically active compounds. One of the most efficient methods for the synthesis of optically active tertiary homoallylic alcohols would be the catalytic enantioselective allylation of ketones. Although there are many papers on the catalytic enantioselective allylation of aldehydes, catalytic enantioselective allylation of ketones have been far less explored probably due to their low reactivity and the difficulty in enantiofacial discrimination of ketones.1 Recently, catalytic enantioselective allylations of ketones using stannanes,2 silanes,3 boron reagents,4 allyl alcohols,5 and manganese compounds6 using various chiral catalysts have been reported. However, these reactions rely on strictly anhydrous conditions or on the use of corrosive or toxic reagents. On the other hand, Barbier-type allylation using allyl halide and indium metal has shown to be an effective method for the synthesis of homoallylic alcohols, because organoindium compounds have low toxicity, and they have the ability to tolerate the reaction in water.7 Therefore, there are several papers on the enantioselective Barbier-type allylation of ketones with allyl halides using a stoichiometric amount of chiral additives and indium metal in an organic solvent.8 However, there is no report on the catalytic enantioselective Barbier-type allylation of ketones in water using indium metal and allyl halides.9 Recently, Kobayashi and co-workers first reported the catalytic enantioselective allylation of ketones in water using allylboronate and a catalytic amount of indium(0) and bis(midazoline) catalyst to give a product with 52% ee.10 Despite the pioneering progress achieved in enantioselective reaction of allylation with ketones in water, the development of novel catalyst systems with acceptable catalytic activity and stereoselectivity still remains a major challenge. On the other hand, we recently reported the enantioselective three-component synthesis of optically active propargylamines in water15 and the enantioselective alkylation of ketimines using chiral bis(imidazoline) catalysts.12 Therefore, our research interest was expanded to the catalytic enantioselective Barbier-type

![Table 1 Enantioselective Barbier-type allylation of 3-bromoacetoephone 1a using various allyl halides 2a–c, indium, and bis(imidazoline) catalyst 4a–d†](image)

<table>
<thead>
<tr>
<th>Run</th>
<th>X</th>
<th>Additive (equiv.)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
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<tr>
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<tr>
<td>2</td>
<td>Br</td>
<td>4a</td>
<td>18</td>
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<td>3</td>
<td>I</td>
<td>4a</td>
<td>18</td>
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<tr>
<td>4</td>
<td>I</td>
<td>4b</td>
<td>18</td>
<td>5</td>
<td>16</td>
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<tr>
<td>7</td>
<td>I</td>
<td>4a</td>
<td>24</td>
<td>75</td>
<td>16</td>
</tr>
<tr>
<td>8</td>
<td>I</td>
<td>4a SDS (0.2)</td>
<td>18</td>
<td>99</td>
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</tr>
<tr>
<td>9</td>
<td>Br</td>
<td>4a NaI (3.9)</td>
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<td>99</td>
<td>86</td>
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</tbody>
</table>

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c7ra01038a

a Reaction conditions: 1a (0.10 mmol), allyl halide (3.0 equiv.), In (2.0 equiv.), and 4 (10 mol%) in water (0.10 M) were used. b In THF. c Sodium dodecyl sulfate.
allylation using allyl halide and indium metal using chiral bis(imidazoline) catalysts in water.

First, we examined the enantioselective Barbier-type allylation of 3-bromoacetophenone with various allyl halides (3.0 equiv.) and indium powder (2.0 equiv.) using 10 mol% of chiral bis(imidazoline) ligand in water. The results are shown in Table 1.

To our delight, the reaction using allyl iodide as allyl halide afforded product 3a in high yield with moderate enantioselectivity, although the reaction using allyl chloride or bromides gave product 3a in low yield (Table 1, entries 1–3). Although we investigated the effect of the substituent on imidazoline catalysts, changing the substituent on nitrogen in imidazoline catalysts from a tert-butylcarbonyl group to an acetyl, benzoyl or tosyl group could not improve the enantioselectivity of product 3a (Table 1, entries 4–6). When the reaction was carried out in THF instead of water, the enantioselectivity was significantly reduced (Table 1, entry 7). In order to improve yield and enantioselectivity, we added some additives. Sodium dodecyl sulfate (SDS) was added to the reaction mixture as a surfactant, but stereoselectivity could not be improved (Table 1, entry 8). On the other hand, the addition of 3.9 equiv. of NaI to the reaction of allyl bromide 2b and 1a improved the yield and enantioselectivity of 3a (Table 1, entry 9 vs. 2).

Having established the reaction conditions, Barbier-type allylation of various ketones with allyl bromide, indium powder and NaI using 10 mol% of chiral bis(imidazoline) ligand 4a in water was examined (Table 2). The reaction of acetophenone 1b afforded product 3b in good yield with moderate enantioselectivity (Table 2, entry 2). The reaction of electron-deficient ketone 1e–g having fluoro, chloro, or bromo groups in the para or meta position were tolerated in this reaction condition and gave products 3c–g with good stereoselectivity (59–89% ee, Table 2, entries 3–7), although the reaction of ortho-substituted ketone 1f gave product 3f in low yield and enantioselectivity (Table 2, entry 6). Ketones 1h, i having an electron-donating methyl and methoxy group gave corresponding products 3h, i in high yield with good enantioselectivity (Table 2, entries 8 and 9). Ketones 1j, k having a naphthyl or heteroaryl group such as the thienyl group also afforded products 3j, k in moderate yield with good enantioselectivity (Table 2, entries 10 and 11). These reaction conditions were also applicable to the reaction of trifluoromethyl ketones 1l (Table 2, entry 12). The absolute configurations of products 3a–d, f–l were determined in comparison with the value of the specific rotation reported in the literature (see ESI†). To our knowledge, these results are the first examples for the indium-mediated catalytic enantioselective Barbier-type allylation of ketones in water.

In order to clarify the reaction mechanism, we conducted spectroscopic analysis. The 1H NMR spectrum for the mixture of 2b, 4a, NaI, and indium powder showed a new methylene signal at 2.85 ppm (see ESI†). Chan and co-workers reported that 1H NMR peaks for allylindium(III) and allylindium(I) in water were observed at 2.8 ppm and 1.7 ppm, respectively, and that allylindium(III) make a allylindium sesquihalide species.14 Furthermore, the ESI-mass spectroscopic analysis for the reaction mixture of 2b, 4a, NaI, and indium powder showed complex A (Fig. 1: cation mode, calcd for C51H57I3InN5O3 as complex 4a, 1398.0 found: 1397.7). This signal implied a complex between allylindium(III) sesquihalide and 2b.15

From the above consideration and absolute stereochemistry of the products, the assumed transition state for the enantioselective

![Fig. 1](Image)

**Fig. 1** ESI mass spectrum for the mixture of 4a, 2b, NaI and indium in water.

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![Fig. 2](Image)

**Fig. 2** Assumed transition state for the Barbier-type allylation of 1 using 4a.

**Table 2** Enantioselective Barbier-type allylation of various ketones 1a–l using various allyl bromide 2b, indium, and bis(imidazoline) catalyst 4a

<table>
<thead>
<tr>
<th>Entry</th>
<th>R1</th>
<th>R2</th>
<th>Time (h)</th>
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<td>1</td>
<td>3-BrC6H5</td>
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<tr>
<td>2</td>
<td>Ph</td>
<td>CH3</td>
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<td>3-FC6H5</td>
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<td>18</td>
<td>89</td>
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<td>CH3</td>
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<tr>
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<td>3-IC6H4</td>
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<td>18</td>
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<tr>
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<td>Ph</td>
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</tbody>
</table>

*Reaction conditions: 1 (0.10 mmol), 2b (3.0 equiv.), NaI (3.9 equiv.), In (2.0 equiv.), and 4a (10 mol%) in water (0.10 M) were used.*
Barbier-type allylation of ketones using 4a in water is shown in Fig. 2. The allylation of ketones would proceed through a six-membered transition state including In(III) species.26 Allyldinium sesquihalide dissociates to monomeric allyl halide by coordination to bisimidazolines, then indium(III) cation coordinates to ketones. In this transition state, indium(III) makes an octahedral structure, and the allyl group approaches the re-face of ketones avoiding steric repulsion between the phenyl group in 4a and substituents for ketones to give (R)-homoallylic alcohols. Further studies are required to fully elucidate the mechanistic detail of the Barbier-type allylation reaction of ketones with 4a.

In conclusion, we developed an enantioselective allylation of ketones using chiral bisimidazolines catalysts. To our knowledge, this is the first example of the highly enantioselective allylation of ketones using Barbier-type allylation of allyl halide and indium in water. Further experiments are in progress to study the scope of the asymmetric synthesis in water using bisimidazolines catalyst to other reactions.

Acknowledgements
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Notes and references
enantioselective Barbier-type allylation of hydrazones, see: 

10 (a) U. Schneider, M. Ueno and S. Kobayashi, J. Am. Chem. Soc., 2008, 130, 13824. See also: 
(b) U. Schneider and S. Kobayashi, Angew. Chem., Int. Ed., 2007, 46, 5909; 


13 We also examined reactions with various additives, such as ammonium bromide, cetyltrimethylammonium bromide and 18-crown-6, however the yield and enantioselectivity of the product was low (see ESI†).


15 We also examined the enantioselective allylation reaction using various ratios of allyl bromide and indium. The best result was obtained in the reaction using allyl bromide and indium in a 3 : 2 ratio (see ESI†). This result supports the formation of indium(III) sesquihalide species.

(c) K. Koszinowski, J. Am. Chem. Soc., 2010, 132, 6032. See also ref. 7b and c.

17 (a) M. Yasuda, M. Haga and A. Baba, Organometallics, 2009, 28, 1998; 
(b) M. Yasuda, K. Kiyokawa, K. Osaki and A. Baba, Organometallics, 2009, 28, 132.