Catalytic asymmetric allylation of aldehydes with alkenes through allylic C(sp³)−H functionalization mediated by organophotoredox and chiral chromium hybrid catalysis†

Harunobu Mitsunuma, a Shun Tanabe, a Hiromu Fuse, a Kei Ohkubo a and Motomu Kanai b, *a

We describe a hybrid system that realizes cooperativity between an organophotoredox acridinium catalyst and a chiral chromium complex catalyst, thereby enabling unprecedented exploitation of unactivated hydrocarbon alkenes as precursors to chiral allylchromium nucleophiles for asymmetric allylation of aldehydes. The reaction proceeds under visible light irradiation at room temperature, affording the corresponding homoallylic alcohols with a diastereomeric ratio >20/1 and up to 99% ee. The addition of Mg(ClO₄)₂ markedly enhanced both the reactivity and enantioselectivity.

Introduction

Catalytic asymmetric C(sp³)−H bond functionalization is an emerging synthetic method affording direct access to useful chiral building blocks from stable organic molecules. For example, catalytic asymmetric allylation of aldehydes using unactivated alkenes as pronucleophiles produces enantiomerically-enriched homoallylic alcohols, which act as versatile synthetic intermediates for numerous functional molecules, including various drug leads. The catalytic asymmetric allylic C(sp³)−H bond activation followed by oxida- tion mechanism dissected by chiral nucleophilic allylmetal species, which are generated from alkenes via in situ allylic C(sp³)−H bond activation, would be feasible. Some previous examples related to this strategy are reported. Gong presented a one-pot procedure for asymmetric nucleophilic allylation of an aldehyde with an alkene involving palladium-catalyzed allylic C(sp³)−H borylation of the alkene to generate an allylboronate and chiral phosphoric acid-catalyzed asymmetric allylation of the aldehyde with the thus-generated allylboronate (Fig. 1(b)). Mita and Sato reported a cobalt-catalyzed enantioselective allylation between acetone and an allylarene via nucleophilic chiral allylcobalt(i) species generated through oxidative addition of an allylic C(sp³)−H bond to a low valent cobalt complex (Fig. 1(c)). During our study, Glorius’ group reported an asymmetric allylation between an aldehyde and an allylamine mediated by combining an iridium photoredox catalyst and a chiral chromium catalyst (Fig. 1(d)). Considering the attractive feature of this reaction to generate versatile chiral homoallylic alcohols in a single operation from aldehydes and alkenes, further investigation of this reaction type are highly desirable.

Photocatalyzed C(sp³)−H bond activation followed by oxidative interception of the resulting carbon-centered radical by a metal complex catalyst is a groundbreaking concept for generating organometallic intermediates from substrates traditionally considered inert. Application of organometallic intermediates generated by this method, however, has mainly been limited to cross-coupling reactions. Extension of the chemistry to facilitate the addition of these nucleophiles to polar moieties, such as carbonyl groups, has yet to be explored, except for the recent example by Glorius using electron-rich aromatic- or amine-substituted alkenes. Herein we report an asymmetric hybrid catalyst system comprising an organophotoredox catalyst and a chiral chromium complex catalyst, which enables asymmetric allylation of aldehydes by nucleophilic chiral allylchromium species generated in situ from hydrocarbon feedstock alkenes by C(sp³)−H bond activation (Fig. 1(d)).

Results and discussion

Optimization of reaction conditions

Our mechanistic rationale for this transformation is illustrated in Fig. 2. Based on an earlier report by the Wu laboratory, allyl
radical 4 should be accessible from alkene 1a via electron-transfer oxidation of the π-bond by a photoexcited electron-donor substituted acridinium catalyst (D\textsuperscript{+}−Acr\textsuperscript{−}; D = 2,6-xylyl or mesityl) to generate radical cation 3, followed by deprotonation. A reduced form of the chiral chromium(II) catalyst 5 would then intercept the thus-formed allyl radical 4 to give chiral allyl chromium(III) complex 6. We anticipated that this species would react with aldehydes 2 via a six-membered chair transition state to produce enantiothermically-enriched chromium alkoxide 7 in a syn-selective manner. Protonolysis of 7 would then afford the target homoallylic alcohol 8 and an oxidized chromium(III) complex 9. Finally, electron-transfer reduction of 9 by the reduced form of the photocatalyst (D−Acr\textsuperscript{−}) would regenerate 5 and the oxidized form of the photocatalyst (D−Acr\textsuperscript{+}), thus closing the catalytic cycle.\textsuperscript{15}

Based on this hypothesis, we began optimizing the reaction conditions using benzaldehyde (2a) and cyclohexene (1a: 2.0 equiv.) as model substrates, and a combination of 5 mol\% CrCl\textsubscript{2} and 2.5 mol\% acridinium photoredox catalysts (2,6-Xyl−Acr\textsuperscript{+}′ClO\textsubscript{4}/Co\textsubscript{0}; 10),\textsuperscript{16} under 430 nm visible light irradiation at room temperature (Table 1). As expected, the desired reaction did not proceed at all in the absence of the chromium complex (entry 1). In the presence of CrCl\textsubscript{2}, however, 8a was obtained in 36% yield with an excellent diastereomeric ratio (dr) of >20/1 (entry 2).

Encouraged by this finding, we then screened various chiral ligands for the chromium catalysts that were previously shown to be effective for asymmetric Nozaki–Hiyama–Kishi reactions (entries 3–6).\textsuperscript{17} The chiral catalysts strongly retarded the reaction, however, with only L1 (ref. 18) affording 8a with diminished yield (12%) and low enantioselectivity (20% ee). Through extensive screening of other chiral ligands, we identified an indane-BOX ligand (L5)\textsuperscript{19} that effectively induced good enantioselectivity (74% ee), although the yield of 8a remained unsatisfactory (8%, entry 7).

We supposed that the low reactivity was due to the high oxidation potential of 1a. Due to the small oxidation potential difference between substrate 1a and photoredox catalyst 10 (see ESI\textsuperscript{†}), only low concentration of cation radical 3 were generated. To improve the reactivity, we investigated the effects of salt additives to stabilize cation radical 3, which would accelerate the overall reaction rate.\textsuperscript{20} Screening of several electrolytes revealed that adding LiBF\textsubscript{4} dramatically enhanced the reactivity; 8a was obtained in 40% yield with 63% ee (entry 8). Moreover, the use of LiClO\textsubscript{4} increased the enantioselectivity up to 99% (entry 9). Further exploration of alkali and alkali-earth metal
Optimization of the reaction conditions

<table>
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<th>Entry</th>
<th>Ligand</th>
<th>Additive</th>
<th>Yield (%)</th>
<th>Dr</th>
<th>ee (%)</th>
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<td>L5</td>
<td>LiClO&lt;4&gt;</td>
<td>44</td>
<td>&gt;20/1</td>
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<td>14</td>
<td>&gt;20/1</td>
<td>99</td>
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<tr>
<td>11</td>
<td>L5</td>
<td>Ca(ClO&lt;4&gt;)_2·xH&lt;2&gt;O</td>
<td>8</td>
<td>&gt;20/1</td>
<td>98</td>
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<tr>
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<td>L5</td>
<td>Mg(ClO&lt;4&gt;)_2</td>
<td>68</td>
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<td>99</td>
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<tr>
<td>13</td>
<td>L5</td>
<td>Mg(ClO&lt;4&gt;)_2</td>
<td>63</td>
<td>&gt;20/1</td>
<td>99</td>
</tr>
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</table>

a General reaction conditions: 2a (0.25 mmol), 1a (5.0 mmol), CrCl<3> (0.0125 mmol), ligand (0.0125 mmol), 10 (0.00625 mmol), and additive (0.25 mmol) were reacted in dichloromethane (DCM; 2.5 mL) at room temperature under 430 nm LED irradiation for 12 h. Yield and diastereomeric ratio were determined by <sup>1</sup>H NMR analysis of the crude mixture using 1,1,2,2-tetrachloroethane as an internal standard. The enantioselectivity of 8a was determined by chiral stationary HPLC analysis after isolation. n.d. = not determined. b Without CrCl<2>, c 10 mol% Et<sub>N</sub>N was added. d 5 mol% Et<sub>N</sub>N was added. e Mes-Acr<sup>+</sup>-ClO<sub>4</sub><sup>-</sup> 11 was used as a photocatalyst.

perchlorates (entries 10–12) identified Mg(ClO<4>)_2 as the optimal additive; 8a was obtained in 68% yield with >20/1 dr and 99% ee (entry 12). Additionally, the use of photocatalyst 11, bearing a mesityl group instead of a xylyl group, did not negatively affect these results (entry 13). It is noteworthy that compared to traditional catalytic asymmetric carbonyl allylations, except for the Krische’s method, this reaction can bypass the pre-activation step of the nucleophile using stoichiometric metal species.

Substrate scope

Under these optimized conditions, we next evaluated the substrate scope (Table 2). The reaction of cyclohexene (1a) with substituted benzaldehydes afforded products 8a–8g with almost complete diastereo- and enantioselectivity (up to >20/1 dr, 99% ee). The reaction well tolerated aryl halide moieties (8b–8d), and proceeded chemoselectively at the aldehyde functional group in the presence of a keto (8e) or an ester (8f) functional group. The method was also easily extended to other cyclic alkenes, with both cyclopentene (1b) and cycloheptene (1c) reacting with excellent stereoselectivity (8h–8k).

Linear alkenes were also competent substrates. Tetrasubstituted alkene 1d reacted with various aldehydes, including ortho-, meta-, and para-substituted benzaldehydes, an electron-rich benzaldehyde, and a heteroaromatic aldehyde, affording the corresponding products 8l–8q (containing an allylic quaternary carbon) with excellent enantioselectivity. The loading of alkene 1d could be reduced to 2 equiv., likely due to the lower oxidation potential of 1d relative to 1a–1c. For less reactive aldehydes such as o-tolualdehyde and p-methoxy benzaldehyde, the chiral chromium alkoxide complex generated from CrCl<3>·3THF and NaOt-Bu<sup>+</sup> exhibited higher catalytic activity than the CrCl<2>-derived species (8m and 8p). We postulate that this is as a result of allylromium species 6 bearing alkoxide ligands (X = OR) with higher nucleophilicity than those bearing electron-withdrawing chloride ligands (X = Cl).<sup>22,23</sup> The reaction of aliphatic aldehydes also proceeded with high enantioselectivity (8r–8u) following minor modifications of the reaction conditions (1,2-dichloroethane [DCE] as the solvent, 20 mol% MgPhPO<sub>3</sub> additive). In the case of asymmetric trisubstituted alkene 1e, an inseparable mixture of 8v and 8w (itself a diastereomixture) was produced with moderate regioselectivity (regioisomeric ratio; rr = 8v/8w = 1.9/1). Nevertheless, both the reactivity and enantioselectivity of 8v were very high: use of 2.5 mol% and 0.5 mol% loadings of the chromium catalyst and photocatalyst 11, respectively, led to the products in 97% combined yield, with 8v in 96% ee. Major isomer 8v presumably derives from prenylchromium species with the chromium atom at the terminal carbon, while minor isomer 8w originates from 2-methyl but-2-enylchromium species with chromium at the terminal carbon. We anticipate that improving the regioselectivity so that the carbon-centered radical can be intercepted by the metal complex in the case of asymmetric alkenes will be a very important avenue for future research. In addition, linear terminal alkenes and disubstituted internal alkenes (e.g. 1-hexene and 2-butene) were unreactive under the current optimal conditions probably due to their high oxidation potentials.

The following experimental results provide key insights into the reaction mechanism (see ESI† for details). First, the addition of TEMPO (2,2,6,6-tetramethylpiperidinyloxyl) as a radical
trapping agent to the reaction between 1a and 2a under otherwise optimized conditions completely inhibited the desired reaction. A TEMPO adduct of 1a at the terminal carbon was detected by 1H NMR analysis of the crude mixture after the workup. This result supports our hypothesis that the reaction proceeds through carbon-centered radicals derived from alkene 1.

Second, we performed a radical clock experiment using 2-phenylcyclopropylcarbaldehyde and 1d. The reaction proceeded with 77% yield without any cyclopropane ring-opening, indicating that ketyl radicals derived from aldehydes are not involved in the catalytic cycle. These findings, together with the observation that the presence of the chromium complex was essential for the reaction (Table 1, entry 1), are consistent with our working hypothesis for the reaction mechanism depicted in Fig. 2.

To clarify the electron-transfer dynamics between 1a and the photoexcited 10, we examined the transient absorption measurements as shown in Fig. 3(a). Laser flash irradiation (λ = 355 nm) of 10 gave the electron-transfer state (Acr<sup>-</sup>–Xyl<sup>+</sup>). The spectrum furnished absorption peaks at λ<sub>max</sub> = 520 nm (ref. 24) and 700 nm, which attributed to the acridinyl radical moiety (Acr<sup>-</sup>) and the xylyl radical cation moiety (Xyl<sup>+</sup>), respectively (Fig. 3(a)). The time profiles of the decay at 700 nm due to the Xyl<sup>+</sup> moiety obeyed pseudo-first-order kinetics. The decay rate

### Table 2: Substrate scope of catalytic asymmetric allylation<sup>a</sup>

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
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<tbody>
<tr>
<td>1a</td>
<td>R = H</td>
<td>65&lt;sup&gt;b&lt;/sup&gt;</td>
<td>99</td>
</tr>
<tr>
<td>1b</td>
<td>R = p-Cl</td>
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<td>99</td>
</tr>
<tr>
<td>1c</td>
<td>R = p-Br</td>
<td>56&lt;sup&gt;c&lt;/sup&gt;</td>
<td>99</td>
</tr>
<tr>
<td>1d</td>
<td>R = p-I</td>
<td>47</td>
<td>99</td>
</tr>
<tr>
<td>1e</td>
<td>R = m-COMe</td>
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<td>99</td>
</tr>
<tr>
<td>1f</td>
<td>R = p-COMe</td>
<td>63</td>
<td>99</td>
</tr>
<tr>
<td>1g</td>
<td>R = p-CF&lt;sub&gt;3&lt;/sub&gt;</td>
<td>63</td>
<td>99</td>
</tr>
</tbody>
</table>

<sup>a</sup> General reaction conditions: aldehyde 2 (0.25 mmol), alkene 1 (5.0 mmol), CrCl<sub>2</sub> (0.0125 mmol), L5 (0.0125 mmol), 10 (0.00625 mmol), and Mg(ClO<sub>4</sub>)<sub>2</sub> (0.25 mmol) were reacted in DCM (2.5 mL) at room temperature under 430 nm LED irradiation for 12 h. Yield is isolated yield. The diastereomeric ratio was >20/1 in each case (8a–8k), as determined by 1H NMR analysis of the crude mixture. The enantiomeric excess was determined by chiral stationary HPLC analysis after isolation. <sup>b</sup> CrCl<sub>2</sub> (10 mol%) and L5 (10 mol%) were used. <sup>c</sup> Alkene (2 equiv.), CrCl<sub>2</sub> (2.5 mol%), L5 (2.5 mol%), 11 (0.5 mol%), Mg(ClO<sub>4</sub>)<sub>2</sub> (1 equiv), and DCM (0.125 M) were used. <sup>d</sup> Alkene (20 equiv.), CrCl<sub>3</sub>·3THF (10 mol%), NaOt-Bu (30 mol%), L5 (10 mol%), 11 (1.25 mol%), Mg(ClO<sub>4</sub>)<sub>2</sub> (1 equiv), and DCM (0.0625 M) were used. <sup>e</sup> Alkene (5 equiv.), CrCl<sub>2</sub> (10 mol%), L5 (10 mol%), 11 (1.25 mol%), Mg(ClO<sub>4</sub>)<sub>2</sub> (1 equiv), and DCM (0.0625 M) were used. <sup>f</sup> Alkene (20 equiv.), CrCl<sub>2</sub> (20 mol%), L5 (20 mol%), 11 (5 mol%), Mg(ClO<sub>4</sub>)<sub>2</sub> (1 equiv), and DCE (0.05 M) were used. <sup>g</sup> Alkene (20 equiv.), CrCl<sub>2</sub> (20 mol%), L5 (20 mol%), 11 (5 mol%), MgPhPO<sub>3</sub> (20 mol%), and DCE (0.1 M) were used. Reaction time was 48 h.

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<sup>24</sup> Ref. 24.
constant ($k_{obs}$) linearly increased with the concentration of 1a (Fig. 3(b)). The rate constant of electron transfer from 1a to the acryldehyde moiety of Acr$^+$ was determined from the linear plot to be $2.2 \times 10^5$ M$^{-1}$ s$^{-1}$. Thus, electron transfer efficiently occurred to yield 3 and the reduced 10 (Acr$^-$) as the initial step of the photocatalytic redox process.

Furthermore, to confirm that the dramatically increased reactivity in the presence of additive Mg(ClO$_4$)$_2$ was due to the increased concentration of the radical pair (3 and Acr$^-$-Xyl) generated by electron transfer from 1a to the electron-transfer state of 10 (Acr$^+$-Xyl$^+$), we monitored the initial transient absorption intensities due to Acr$^+$-Xyl ($\lambda_{max} = 520$ nm) generated by laser irradiation of 10 with a large excess of 1a (300 mM) in the absence and presence of Mg(ClO$_4$)$_2$ (Fig. 3(c)). The initial intensity in the presence of Mg(ClO$_4$)$_2$ was 1.9 times higher than that in the absence of Mg(ClO$_4$)$_2$ (Fig. 3(c)). The radical pair is efficiently stabilized in the presence of Mg(ClO$_4$)$_2$ salt by the electrostatic interaction of 3 with ClO$_4^-$.$^{26}$ Therefore, the concentration of cation radical 3 is enhanced by the presence of Mg(ClO$_4$)$_2$, and this is likely the reason for the dramatically higher product yield in the presence of Mg(ClO$_4$)$_2$ (Table 1, entry 7 vs. 12).$^{26}$

### Conclusions

In conclusion, we developed the first catalytic asymmetric allylation of aldehydes using unactivated hydrocarbon alkenes as pronucleophiles. The reaction enabled direct access to enantio- and diastereomerically-enriched homoallylic alcohols, starting from readily available and stable substrates. Critical to the success of the reaction was the development of an asymmetric hybrid catalyst system comprising an acridinium photoredox catalyst and a chiral chromium complex catalyst. The hybrid catalyst enabled a key radical–polar crossover process involving the catalytic generation of chiral and nucleophilic (i.e., polar) organometallic species from simple alkenes via allylic C(sp$^3$)–H activation. Further studies to improve the efficiency of the process, fully elucidate the reaction mechanism, and expand the substrate scope are ongoing.

### Conflicts of interest

There are no conflicts to declare.

### Acknowledgements

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### Notes and references


13 For the generation of chiral organometallic species through homolytic cleavage of a stable C(sp³)–H bond and subsequent oxidative trap by a chiral metal complex, which was applied to a catalytic asymmetric coupling reaction (oxidative benzyllic C(sp³)–H cyanation), see: W. Zhang, F. Wang, S. D. McCann, D. Wang, P. Chen, S. S. Stahl and G. Liu, *Science*, 2016, 353, 1014. One preliminary example (54% ee) with this reaction pattern was also described in ref. 10q.


15 For a discussion of the feasibility of the working hypothesis shown in Fig. 2 based on the redox potential of each intermediate, see ESI.*


23 In the reaction of p-methoxy benzaldehyde and 1d, NMR yields of 8p were 33% and 62% by using CrCl₂ and CrCl₃·3THF–NaOt-Bu catalysts, respectively.


26 On the other hand, the role of Mg(ClO₄)₂ (or perchlorate in general, see Table 1, entry 7 vs. 9–12) in enhancing the enantioselectivity is still unclear. We assume that chiral ligand L₅ remains coordinated to the chromium atom during the reaction in the presence of stoichiometric Mg(ClO₄)₂; the reaction between 1a and 2a did not proceed at all by premixing of L₅ with Mg(ClO₄)₂. See ESI† for details.