Catalytic Asymmetric Allylation of Aldehydes with Alkenes Mediated by Organophotoredox and Chiral Chromium Hybrid Catalysis

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Supporting Information Placeholder

ABSTRACT: A hybrid system accomplishing cooperativity between an organophotoredox acidinium catalyst and a chiral chromium complex catalyst was developed, enabling the unprecedented exploitation of unactivated hydrocarbon alkenes as precursors to chiral allylchromium nucleophiles for the asymmetric allylation of aldehydes. The reaction proceeded under visible light irradiation at room temperature and with high functional group tolerance, affording the corresponding homoallylic alcohols with up to >20/1 diastereomeric ratio and 99% ee. The addition of Mg(ClO₄)₂ elicited profound enhancement of both reactivity and enantioselectivity.

The catalytic asymmetric allylation of aldehydes to produce enantiomerically enriched secondary homoallylic alcohols represents a fundamental process in synthetic organic chemistry.¹ The methodology developed to this end thus far can be classified into three main categories. Firstly, chiral Lewis acids, Lewis bases, and Bronsted acids have been used to promote the reaction of preactivated allylmethyl species, such as allylic, -silicon, and -boron reagents (Figure 1(a)).¹ Alternatively, the Nozaki-Hiyama-Kishi (NHK) allylation is a chromium-mediated reductive C-C bond-forming reaction using allylic halides as precursors to nucleophilic allylchromium intermediates.² Despite their high reactivity towards carbonyl groups, these allylchromium species exhibit broad functional group tolerance, enabling the NHK reaction to be extensively applied to multifunctional substrates in complex molecule synthesis.³ Based on the pioneering work by Fürstner,⁴ who developed the first catalytic NHK reaction (using manganese(0) as a stoichiometric reductant and TMSCl as a catalyst turnover facilitator), many catalytic asymmetric variants of the NHK allylation have been reported (Figure 1(b)).³ However, there still remains room for improvement in the two traditional methods represented by Figure 1(a) and 1(b), particularly in their overall efficiency and redox/atom/step economy. To address these issues, Kirsche reported the versatile catalytic asymmetric coupling of primary alcohols with dienes/allenes under transfer hydrogenative conditions (Figure 1(c)), but this powerful method has not yet utilized cyclic dienes as pronucleophiles.⁶ During our study, Glorius’ group reported an elegant diastereoselective allylation of aldehydes mediated by an iridium photoredox/chromium hybrid catalyst. Their racemic reaction utilized electron-rich aromatic- or amine-substituted alkenes as precursors to allylchromium nucleophiles to facilitate photocatalyzed single-electron oxidation. A preliminary application to an asymmetric variant was reported for one substrate combination, but the enantioselectivity was only 20% ee.⁷ Herein we report an asymmetric hybrid catalyst system comprising an organophotoredox catalyst and a chiral chromium complex catalyst, which enables the asymmetric allylation of aldehydes by nucleophilic chiral allylchromium species generated in situ from unactivated hydrocarbon alkenes by C(sp³)–H bond activation (Figure 1(d)).⁸,⁹

Figure 1. Four strategies for catalytic asymmetric allylation of aldehydes. (a) Chiral Lewis acid/base or Bronsted acid-catalyzed reactions using preactivated allylmethyls as nucleophiles. Metal-derived waste is generated, and synthesis of allylmetal reagents requires additional steps. (b) Chiral chromium complex-catalyzed NHK reaction. Halide-, silicon-, and manganese-derived waste is generated. (c) Kirsche reaction. The reaction proceeds with high atom economy, but the scope does not extend to cyclic dienes. (d) This work. The reaction proceeds through photoredox catalyst-mediated allylic C(sp³)–H metatation of unactivated alkenes, generating chiral allylchromium nucleophiles.
Figure 2. Proposed catalytic cycle.

Our mechanistic rationale for this transformation is illustrated in Figure 2. Based on precedent from the Wu laboratory,10 allyl radical 4 should be accessible from alkene 1a via single-electron oxidation of the π-bond by a photoexcited electron-donor substituted acridinium catalyst (D−−⇒Ac)+; D = 2,6-xylyl and 2a,4,6-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. It was anticipated that this species would react with aldehydes 2 via a six-membered chair transition state to produce enantiomerically-enriched chromium alkoxide 7 in a syn-selective fashion. Protonolysis of 7 should then afford the target homoallylic alcohols 8 and an oxidized chromium(III) complex 9. Finally, single-electron reduction of 9 by the reduced form of the photocatalyst (D−−⇒Ac)+ would regenerate 5 and the oxidized form of the photocatalyst (D−−⇒Ac)+, thus closing the catalytic cycle.11 Photocatalyzed C(sp3)−H bond activation followed by oxidative interception of the resulting carbon-centered radical by a metal complex (i.e., corresponding to the process from 1a to 6 in Figure 2) is an emerging method for the catalytic generation of organometallic species from substrates traditionally considered inert.12−14 However, employment of the organometallic intermediates generated by this method has mainly been limited to cross-coupling reactions. Extension of the chemistry to facilitate addition of these nucleophiles to polar moieties, such as carbonyl groups, has been hitherto unexplored with the exception of one recent report by the Glorius group.7,15

Table 1. Optimization of Reaction Conditions

<table>
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<tr>
<th>entry</th>
<th>ligand</th>
<th>additive</th>
<th>yield (%)</th>
<th>dr</th>
<th>ee (%)</th>
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<td>Ca(ClO4)2⋅xH2O</td>
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<td>&gt;20/1</td>
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<td>Mg(ClO4)2</td>
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<td>Mg(ClO4)2</td>
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<td>&gt;20/1</td>
<td>99</td>
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<td>L5</td>
<td>MgCla2</td>
<td>63</td>
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<td>99</td>
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General reaction conditions: 2a (0.25 mmol), 1a (5.0 mmol), CrCl2 (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 dr were determined by 1H NMR analysis of the crude mixture using 1,1,2,2-tetrachloroethane as an internal standard. The ee of 8a was determined by chiral stationary HPLC analysis after isolation, n.d. = Not determined. *Without CrCl2, 10 mol % EtN was added. **5 mol % EtN was added. *2,4,6-Mes-Acr+·ClO4− 11 was used as photocatalyst.

Based on this hypothesis, we commenced optimization of the reaction conditions using benzaldehyde (2a) and cyclohexene (1a; 20 equiv) as model substrates, and a combination of 5 mol % CrCl2 and 25 mol % acridinium photocatalysts (2.6-Xyl-Acr+·ClO4−),10 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 chromium complex (entry 1). In the presence of CrCl2, however, 8a was obtained in 36% yield with an excellent diastereomeric ratio (dr) of >20/1 (entry 2). Encouraged by this finding, we then trialed various chiral ligands for the chromium catalysts, which have previously proven effective for asymmetric NHK reactions (entries 3–6).5 However, this resulted in strong retardation of the reaction, with only L117 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)18 which was effective for inducing good enantioselectivity (74% ee), although the yield of 8a remained unsatisfactory (8%, entry 7).
To improve both the reactivity and enantioselectivity, we next investigated the effect of additives. While the addition of LiCl\textsuperscript{19} or LiBr\textsuperscript{20} was not beneficial (entries 8 and 9), LiBF\textsubscript{4} dramatically enhanced the reactivity; \textit{8a} was obtained in 40\% yield with 63\% ee (entry 10). Following screening of related cationic lithium salts, we were delighted to discover that addition of LiClO\textsubscript{4} increased the enantioselectivity up to 99\% ee (entry 11). Further exploration of alkali and alkali-earth metal perchlorates (entries 12–14) identified as MgClO\textsubscript{4} the optimal additive; \textit{8a} was obtained in 68\% yield with >20/1 dr and 99\% ee (entry 14).\textsuperscript{21,22} Additionally, use of photocatalyst \textit{11}, bearing a mesityl group instead of a xyllyl group, did not prove detrimental to these results (entry 15).

With these optimized conditions in hand, our attention turned to the substrate scope. The reaction of cyclohexene (\textit{1a}) with substituted benzaldehydes afforded products \textit{8a}–\textit{8g} with almost complete diastereo- and enantioselectivity (up to >20/1 dr, 99\% ee). The reaction exhibited notable tolerance of aryl halide moieties (\textit{8b}–\textit{8d}), and proceeded chemoselectively at the aldehyde functional group in the presence of a ketone (\textit{8e}) or an ester (\textit{8f}) group. The method was also easily extended to other cyclic alkenes, with both cyclopentene (\textit{1b}) and cycloheptene (\textit{1c}) reacting with excellent stereoselectivity (\textit{8h}–\textit{8k}).

Furthermore, linear alkenes were also competent substrates. Tetrasubstituted alkenes \textit{1d} reacted with various aldehydes including \textit{ortho}-, \textit{meta}-, and \textit{para}-substituted benzaldehydes, an electron-rich benzaldehyde, and a heteroaromatic aldehyde, affording the corresponding products \textit{8l}–\textit{8q} (containing an allylic quaternary carbon) with excellent enantioselectivity. The loading of alkenes \textit{1d} could be reduced to 2 equiv, likely due to a lowered oxidation potential of \textit{1d} relative to \textit{1a}–\textit{1c}. For less reactive aldehydes, such as \textit{o}-tolualdehyde and \textit{p}-methoxy benzaldehyde, the chiral chromium alkoxide complex generated from CrCl\textsubscript{3}•3THF and NaOr-Bu\textsuperscript{23} exhibited higher catalytic activity than the CrCl\textsubscript{3}-derived species (\textit{8m} and \textit{8p}). We postulate that this is as a result of allylchromium species \textit{6} bearing alkoxide ligands (X = OR) possessing higher nucleophilicity than those bearing electron-withdrawing chloride ligands (X = Cl).\textsuperscript{24,25} The reaction of aliphatic aldehydes also proceeded with high enantioselectivity (\textit{8r}–\textit{8u}) following minor modifications of the reaction conditions (dichloroethane (DCE) as solvent, 20 mol \% MgPhPO\textsubscript{4} additive). In the case of unsymmetric trisubstituted alkenes \textit{1e}, an inseparable mixture of \textit{8v} and \textit{8w} (itself as a diastereomixture) was produced with moderate regioselectivity (regioisomeric ratio; \textit{r} = 8v/8w = 1.9/1). Nevertheless, both the reactivity and enantioselectivity of \textit{8v} were very high: using 2.5 mol \% and 0.5 mol \% loadings of the chromium catalyst and photocatalyst \textit{11} respectively, products were obtained in 97\% combined yield, with \textit{8v} in 95\% ee. Major isomer \textit{8v} presumably derives from prenylchromium species with the chromium atom at the terminal carbon, while minor isomer \textit{8w} originates from 2-methyl but-2-enylchromium species with chromium at the terminal carbon. We anticipate that improvement of the regioselectivity for interception of the symmetric-centered radical by the metal complex in the case of unsymmetric alkenes will constitute a very important avenue for future research.

| Table 2. Substrate Scope of Catalytic Asymmetric Allylation\textsuperscript{a} |

\begin{tabular}{|c|c|c|}
\hline
Entry & Substrate & Yield (\%) & ee (\%) \\
\hline
1 & \textit{8a} & 55 & 99 \\
2 & \textit{8b} & 82 & 99 \\
3 & \textit{8c} & 81 & 98 \\
4 & \textit{8d} & 46 & 99 \\
5 & \textit{8e} & 46 & 99 \\
6 & \textit{8f} & 80 & 99 \\
7 & \textit{8g} & 63 & 99 \\
8 & \textit{8h} & 59 & 99 \\
9 & \textit{8i} & 55 & 99 \\
10 & \textit{8j} & 43 & 99 \\
11 & \textit{8k} & 47 & 99 \\
12 & \textit{8l} & 86 & 88 \\
13 & \textit{8m} & 50 & 96 \\
14 & \textit{8n} & 85 & 90 \\
15 & \textit{8o} & 97 & 95 \\
16 & \textit{8p} & 39 & 96 \\
17 & \textit{8q} & 33 & 93 \\
18 & \textit{8r} & 90 & 99 \\
19 & \textit{8s} & 69 & 86 \\
20 & \textit{8t} & 47 & 85 \\
21 & \textit{8u} & 78 & 85 \\
22 & \textit{8v} & 95 & \\
23 & \textit{8w} & 1.9/1 rr \\
\hline
\end{tabular}

\textsuperscript{a}General reaction conditions: aldehyde 2 (0.25 mmol), alkene 1 (5.0 mmol), CrCl\textsubscript{3} (0.0125 mmol), L\textsubscript{5} (0.0125 mmol), L\textsubscript{9} (0.00625 mmol), and Mg(ClO\textsubscript{4})\textsubscript{2} (0.25 mmol) were reacted in DCM (2.5 mL) at room temperature under 430 nm LED irradiation for 12 h. Yield was isolated yield. The dr was >20/1 in each case (\textit{8a}–\textit{8k}), as determined by \textsuperscript{1}H NMR analysis of the crude mixture. The ee was determined by chiral stationary HPLC analysis after isolation. \textsuperscript{b}Alkene (2 equiv), CrCl\textsubscript{2} (2.5 mol \%), L\textsubscript{5} (2.5 mol \%), L\textsubscript{11} (0.5 mol \%), Mg(ClO\textsubscript{4})\textsubscript{2} (1 equiv), and DCM (0.125 M) were used. \textsuperscript{c}Alkene (20 equiv), CrCl\textsubscript{3}•3THF (10 mol \%), NaOr-Bu (30 mol \%), L\textsubscript{5} (10 mol \%), L\textsubscript{11} (1.25 mol \%), Mg(ClO\textsubscript{4})\textsubscript{2} (1 equiv), and DCM (0.0625 M) were used. \textsuperscript{d}Alkene (5 equiv), CrCl\textsubscript{2} (10 mol \%), L\textsubscript{5} (10 mol \%), L\textsubscript{11} (1.25 mol \%), Mg(ClO\textsubscript{4})\textsubscript{2} (1 equiv), and DCM (0.0625 M) were used. \textsuperscript{e}Alkene (20 equiv), CrCl\textsubscript{2} (20 mol \%), L\textsubscript{5} (20 mol \%), L\textsubscript{11} (5 mol \%), Mg(ClO\textsubscript{4})\textsubscript{2} (1 equiv), and DCE (0.05 M) were used. \textsuperscript{f}Alkene (20
equiv), CrCl₂ (20 mol %), L₅ (20 mol %), MgPhPO₃ (20 mol %), and DCE (0.1 M) were used. Reaction time was 48 h.

The following experimental results provide key insights regarding the reaction mechanism (see Supporting Information for details). Firstly, the addition of TEMPO (2,2,6,6-tetramethylpiperidinyl oxide) as a radical trapping agent to the reaction between 1d and 2a under otherwise optimized conditions completely inhibited the desired reaction. A TEMPO adduct of 1d at the terminal carbon was detected by ²H NMR analysis of the crude mixture after workup. This result supports our hypothesis that the reaction proceeds through carbon-centered radicals derived from alkene 1. Secondly, a radical clock experiment using 2-phenylcyclopropylcarbalddehyde 1d and 2a was performed. The reaction proceeded in 77% yield without any cyclopropane ring-opening. Thus, ketyl radicals derived from aldehydes are not involved in the catalytic cycle. These results, together with the observation that the presence of the chromium complex was essential for the reaction (Table 1, entry 1), are all consistent with our working hypothesis for the reaction mechanism depicted in Figure 2.

In conclusion, we have developed the first catalytic asymmetric allylation of aldehydes using unactivated hydrocarbon alkenes as pronucleophiles. The reaction enabled direct access to enantio-merically and diastereomerically-enriched homomannolysis with high functional group tolerance, starting from readily available and stable substrates. Critical for success 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 catalytic generation of chiral and nucleophilic (i.e., polar) organometallic species from simple alkenes via allylic C(sp³)–H activation. Studies to improve the efficiency of the process further, fully elucidate the reaction mechanism, and expand the substrate scope are currently ongoing.

ASSOCIATED CONTENT
Supporting Information
The Supporting Information is available free of charge on the ACS Publications website.

Experimental details and characterization data (PDF)

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Notes
The authors declare no competing financial interests.

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REFERENCES


(8) The reaction may be classified as a catalytic asymmetric carbonyl ene reaction in a general sense. Substrate scope of the previously-reported carbonyl ene reactions, however, is limited to highly electrophilic aldehydes (e.g. glyoxal esters) or intramolecular reactions. For reviews of catalytic asymmetric carbonyl ene reactions, see; Clarke, M. L. E.; France, M. B. The Carbonyl Ene Reaction. *Tetrahedron* **2008**, *64*, 9003-9031.


(11) For a discussion of the feasibility of the working hypothesis shown in Figure 2 based on the redox potential of each intermediate, see Supporting Information.

(12) For related methods for the generation of organonickel species, see:


(m) Go, S. Y.; Lee, G. S.; Hong, S. H. Highly Regioselective and Visible-Light-Induced Hydroalkylation of Aliphatic C–H Bonds via Photooxidation Mediated/In Situ Prepared Copper(II)-Mediated Refor-


(21) For the formation of Mg(ClO_2)_3 is yet to be fully elucidated. We speculate that aldehydes coordinate to Mg(ClO_2)_3 acting as a Lewis acid, resulting in the activation of the electrophile. In addition, Mg(ClO_2)_3 may stabilize ion pair 3 favoring the single-electron photooxidation of I. See; (a) Thompson, P. A.; Simon, J. D. Electrospray in the energetics and dynamics of intermolecular electron transfer reactions. *J. Am. Chem. Soc.* **1993**, *115*, 5657-5664.


(22) We assume that chiral ligand L_5 remains coordinately to the chromium atom during the reaction in the presence of stoichiometric Mg(ClO_2)_3; the reaction between 1a and 2a did not proceed at all by premixing of L_5 with Mg(ClO_2)_3. See Supporting Information for details. Studies are ongoing to clarify the role of Mg(ClO_2)_3.


(25) In the reaction of p-methoxy benzaldehyde and 1d, NMR yields of 8p were 33% and 62% by using CeCl_3 and CeCl_3·3THF–NaOrBu catalysts, respectively.
Aromatic & aliphatic aldehydes + hydrocarbon alkenes

Visible light

Asymmetric Hybrid Catalysis

Mg(OtBu)_2

85-99% ee >20/1 dr (22 examples)