

有機光酸化還元とキラルクロムハイブリッド触媒により仲介されたアリルC(sp³)-H官能化によるアルケンによるアルデヒドの触媒的不斉アリル化

Metadata	Language: English Publisher: Royal Society of Chemistry Date of Publication: 2019-03-17 Keywords(Ja): " C(sp ³)-H 活性化" " キラル触媒" Keywords(En): "C(sp ³)-H Functionalization" "Chiral Catalysis" Author: 金井求 E-mail: kanai@mol.f.u-tokyo.ac.jp Affiliation: University of Tokyo
URL	
OA Policy	

This work is licensed under a Creative Commons Attribution-NoDerivatives 4.0 International License.



Chemical Science

Accepted Manuscript



This article can be cited before page numbers have been issued, to do this please use: H. Mitsunuma, S. Tanabe, H. Fuse, K. Ohkubo and M. Kanai, *Chem. Sci.*, 2019, DOI: 10.1039/C8SC05677C.



This is an Accepted Manuscript, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this Accepted Manuscript with the edited and formatted Advance Article as soon as it is available.

You can find more information about Accepted Manuscripts in the [author guidelines](#).

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard [Terms & Conditions](#) and the ethical guidelines, outlined in our [author and reviewer resource centre](#), still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.

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,^b and Motomu Kanai^{*a}

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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.¹ 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.² The catalytic asymmetric carbonyl ene reaction is a representative example (Figure 1(a)).³ The electrophile scope of catalytic asymmetric carbonyl ene reactions, however, is limited to highly reactive aldehydes or ketones, such as glyoxylic esters, formaldehyde, fluoral, or ketoesters. In an effort to expand the substrate scope, we envisioned that a reaction mechanism dissected by chiral nucleophilic allylmetal species, which are generated from alkenes via *in-situ* allylic C(sp³)-H bond activation, would be feasible.⁴ 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 (Figure 1(b)).⁵ 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 (Figure 1(c)).⁶ 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 (Figure 1(d)).⁷ 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.^{8,9}

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.¹⁰⁻¹³ 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.⁷ 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 (Figure 1(d)).

^a Graduate School of Pharmaceutical Sciences, The University of Tokyo 7-3-1 Bunkyo-ku, Tokyo 113-0033, Japan. E-mail: h-mitsunuma@mol.f.u-tokyo.ac.jp; kanai@mol.f.u-tokyo.ac.jp

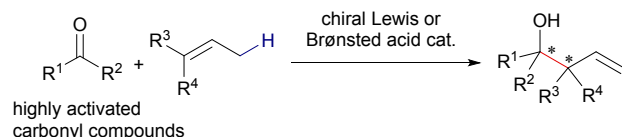
^b Institute for Advanced Co-Creation Studies and Open and Transdisciplinary Research Initiatives, Osaka University, Osaka 565-0871, Japan

† Footnotes relating to the title and/or authors should appear here.

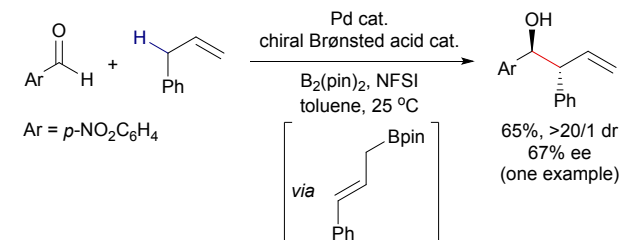
Electronic Supplementary Information (ESI) available: See DOI: 10.1039/x0xx00000x



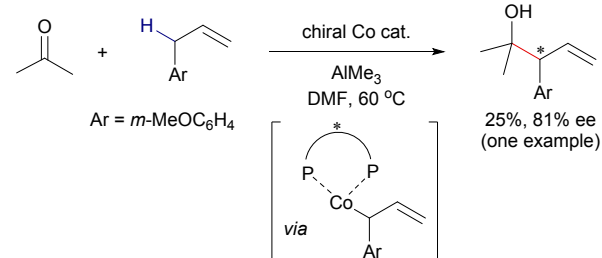
(a) Catalytic asymmetric carbonyl ene reaction



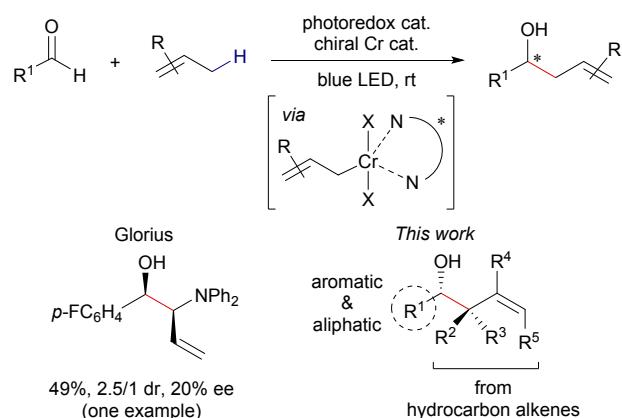
(b) Allylic C-H borylation, followed by catalytic asymmetric allylboration



(c) Asymmetric cobalt(I) catalysis



(d) Photoredox/chiral chromium asymmetric hybrid catalysis



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 enantiomerically-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*) would regenerate **5** and the oxidized form of the photocatalyst (D-Acr⁺), thus closing the catalytic cycle.¹⁵

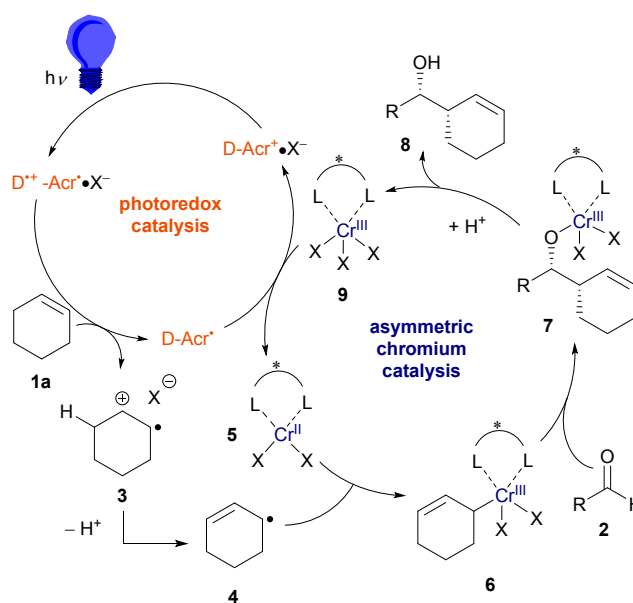


Figure 2. Proposed catalytic cycle.

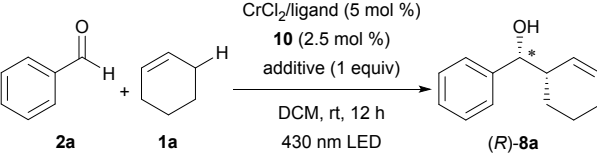
Figure 1. Methods for catalytic asymmetric allylation of carbonyl compounds through C(sp³)-H functionalization of unactivated alkenes as pronucleophiles. (a) Chiral Lewis acid or Brønsted acid-catalyzed carbonyl ene reactions.³ (b) One-pot, stepwise generation of allylboronate followed by chiral Brønsted acid-catalyzed allylboration.⁵ (c) Through chiral allylcobalt species.⁶ (d) Through chiral allylchromium species by Glorius⁷ and our group (this work).

Results and discussion

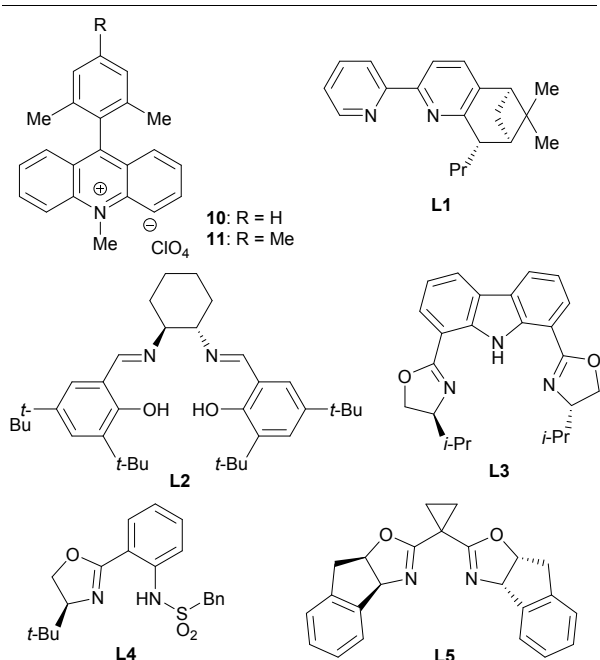
Optimization of reaction conditions

Our mechanistic rationale for this transformation is illustrated in Figure 2. Based on an earlier report by the Wu laboratory,¹⁴ 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⁺-Acr⁺; D = 2,6-xylyl



Table 1. Optimization of the Reaction Conditions^a


entry	ligand	additive	yield (%)	dr	ee (%)
1 ^b	none	none	0	n.d.	n.d.
2	none	none	36	>20/1	n.d.
3	L1	none	12	>20/1	20
4 ^c	L2	none	0	n.d.	n.d.
5 ^d	L3	none	0	n.d.	n.d.
6 ^d	L4	none	0	n.d.	n.d.
7	L5	none	8	>20/1	74
8	L5	LiBF ₄	40	>20/1	63
9	L5	LiClO ₄	44	>20/1	99
10	L5	NaClO ₄	14	>20/1	99
11	L5	Ca(ClO ₄) ₂ ·xH ₂ O	8	>20/1	98
12	L5	Mg(ClO ₄) ₂	68	>20/1	99
13 ^e	L5	Mg(ClO ₄) ₂	63	>20/1	99



^a 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 diastereomeric ratio were determined by ¹H 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 CrCl₂. ^c 10 mol % Et₃N was added. ^d 5 mol % Et₃N was added. ^e Mes-Acr⁺•ClO₄⁻ **11** was used as a photocatalyst.

Based on this hypothesis, we began optimizing the reaction conditions using benzaldehyde (**2a**) and cyclohexene (**1a**: 20

equiv) as model substrates, and a combination of 5 mol % CrCl₂ and 2.5 mol % acridinium photoredox catalysts (**2,6**-Xyl-Acr⁺•ClO₄⁻; **10**),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 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 screened various chiral ligands for the chromium catalysts that were previously shown to be effective for asymmetric Nozaki-Hiyama-Kishi reactions (entries 3–6).¹⁷ The chiral catalysts strongly retarded the reaction, however, with only **L1**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**)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 Supplementary Information), 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.²⁰ Screening of several electrolytes revealed that adding LiBF₄ dramatically enhanced the reactivity; **8a** was obtained in 40% yield with 63% ee (entry 8). Moreover, the use of LiClO₄ increased the enantioselectivity up to 99% (entry 9). Further exploration of alkali and alkali-earth metal perchlorates (entries 10–12) identified Mg(ClO₄)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 xyl group, did not negatively affect these results (entry 13). It is noteworthy that compared to traditional catalytic asymmetric carbonyl allylations,² except for the Krische's method,^{21,p} this reaction can bypass the preactivation 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 ketone (**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**).


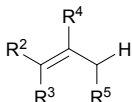
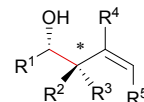

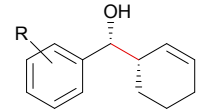
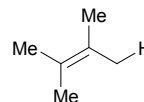
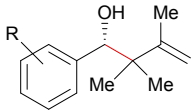

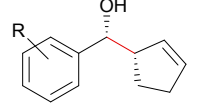
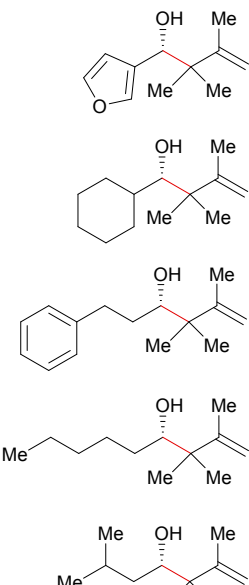

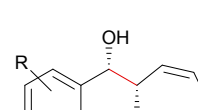
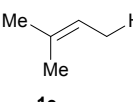
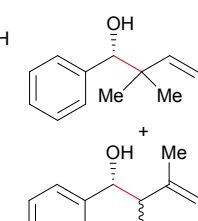
Linear alkenes were also competent substrates. Tetrasubstituted alkene **1d** reacted with various aldehydes, including *ortho*-, *meta*-, and *para*-substituted benzaldehydes, an electron-rich benzaldehyde, and a heteroaromatic aldehyde, affording the corresponding products **8l–8q** (containing an 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 $\text{CrCl}_3 \cdot 3\text{THF}$ and NaOt-Bu^{21} exhibited higher catalytic activity than the CrCl_2 -derived species (**8m** and **8p**). We postulate that this is as a result of allylchromium species **6** bearing alkoxide ligands ($\text{X} = \text{OR}$) with higher nucleophilicity than those bearing electron-withdrawing chloride ligands ($\text{X} = \text{Cl}$).^{22,23} The reaction of aliphatic aldehydes also proceeded with high enantioselectivity (**8r–8u**) following minor modifications of the reaction conditions (dichloroethane [DCE] as the solvent, 20 mol % MgPhPO_3 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; $\text{rr} = \mathbf{8v/8w} = 1.9/1$). 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.

Table 2. Substrate Scope of Catalytic Asymmetric Allylation^a

		$\text{CrCl}_2/\text{L5}$ (2.5–20 mol %) 10 or 11 (0.5–5 mol %) Mg source (20–100 mol %)							
	+		$\xrightarrow[\text{430 nm LED}]{\text{DCM, rt, 12–48 h}}$						
1	8	yield (%)	ee (%)	1	8	yield (%)	ee (%)		
 1a		8a: R = H	65 ^b	99	 1d		8l: R = H	86 ^c	88
		8b: R = <i>p</i> -Cl	82	99			8m: R = <i>o</i> -Me	50 ^d	96
		8c: R = <i>p</i> -Br	81	98			8n: R = <i>m</i> -Me	85 ^e	90
		8d: R = <i>p</i> -I	46	99			8o: R = <i>p</i> -Me	97 ^e	95
		8e: R = <i>m</i> -COMe	46	99			8p: R = <i>p</i> -MeO	39 ^d	96
		8f: R = <i>p</i> -CO ₂ Me	80	99					
		8g: R = <i>p</i> -CF ₃	63	99					
 1b		8h: R = H	59	99		8q	33 ^f	93	
		8i: R = <i>p</i> -Cl	55	99		8r	90 ^g	99	
 1c		8j: R = H	56 ^b	99		8s	69 ^h	86	
		8k: R = <i>p</i> -Cl	47	99		8t	95 ^h	85	
 1e		8v	96			8u	78 ^h	85	
		8w							
		97 ^c		1.9/1 rr					

^a General reaction conditions: aldehyde **2** (0.25 mmol), alkene **1** (5.0 mmol), CrCl_2 (0.0125 mmol), **L5** (0.0125 mmol), **10** (0.00625 mmol), and $\text{Mg}(\text{ClO}_4)_2$ (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 enantioselectivity was determined by chiral stationary HPLC analysis after isolation. ^b CrCl_2 (10 mol %) and **L5** (10 mol %) were used. ^c Alkene (2 equiv), CrCl_2 (2.5 mol %), **L5** (2.5 mol %), **11** (0.5 mol %), $\text{Mg}(\text{ClO}_4)_2$ (1 equiv), and DCM (0.125 M)



were used. *d* Alkene (20 equiv), $\text{CrCl}_3 \cdot 3\text{THF}$ (10 mol %), NaOt-Bu (30 mol %), **L5** (10 mol %), **11** (1.25 mol %), $\text{Mg}(\text{ClO}_4)_2$ (1 equiv), and DCM (0.0625 M) were used. *e* Alkene (5 equiv), CrCl_2 (10 mol %), **L5** (10 mol %), **11** (1.25 mol %), $\text{Mg}(\text{ClO}_4)_2$ (1 equiv), and DCM (0.0625 M) were used. *f* Alkene (20 equiv), CrCl_2 (20 mol %), **L5** (20 mol %), **11** (5 mol %), $\text{Mg}(\text{ClO}_4)_2$ (1 equiv), and DCM (0.0625 M) were used. *g* Alkene (5 equiv), CrCl_2 (10 mol %), **L5** (10 mol %), **11** (5 mol %), $\text{Mg}(\text{ClO}_4)_2$ (1 equiv), and DCE (0.05 M) were used. *h* Alkene (20 equiv), CrCl_2 (20 mol %), **L5** (20 mol %), **11** (5 mol %), MgPhPO_3 (20 mol %), and DCE (0.1 M) were used. Reaction time was 48 h.

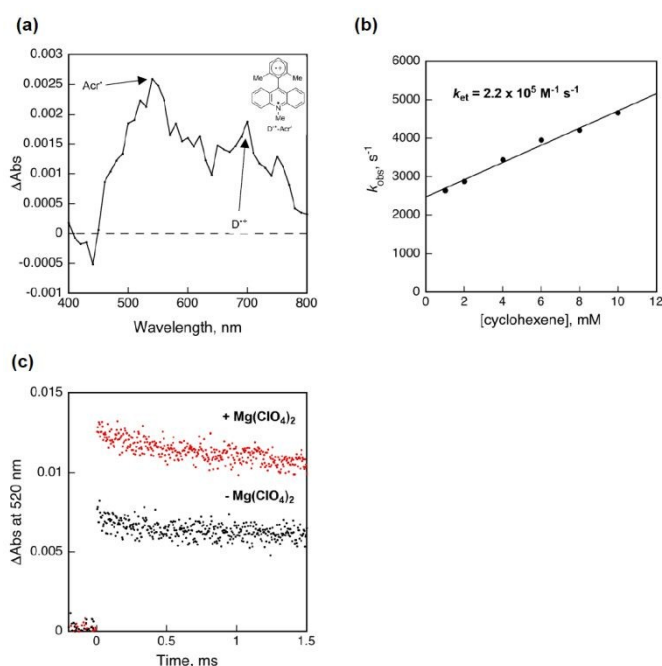
The following experimental results provide key insights into the reaction mechanism (see Supplementary Information for details). First, the addition of TEMPO (2,2,6,6-tetramethylpiperidinyloxy) as a radical trapping agent to the reaction between **1a** and **2a** under otherwise optimized conditions 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 Figure 2.

To clarify the electron-transfer dynamics between **1a** and the photoexcited **10**, we examined the transient absorption measurements as shown in Figure 3a. Laser flash irradiation ($\lambda = 355$ nm) of **10** gave the electron-transfer state ($\text{Acr}^+-\text{Xyl}^{*+}$). The spectrum furnished absorption peaks at $\lambda_{\text{max}} = 520$ nm²⁴ and 700 nm,²⁵ which attributed to the acridinyl radical moiety (Acr^*) and the xylyl radical cation moiety (Xyl^{*+}), respectively (Figure 3(a)). The time profiles of the decay at 700 nm due to the Xyl^{*+} moiety obeyed pseudo-first-order kinetics. The decay rate constant (k_{obs}) linearly increased with the concentration of **1a** (Figure 3(b)). The rate constant of electron transfer from **1a** to the acridinyl radical moiety of $\text{Acr}^+-\text{Xyl}^{*+}$ was determined from the linear plot to be $2.2 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$. Thus, electron transfer efficiently occurred to yield **3** and the reduced **10** (Acr^+-Xyl) as the initial step of the photocatalytic redox process.

Furthermore, to confirm that the dramatically increased reactivity in the presence of additive $\text{Mg}(\text{ClO}_4)_2$ 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** ($\text{Acr}^+-\text{Xyl}^{*+}$), we monitored the initial transient absorption intensities due to Acr^+-Xyl ($\lambda_{\text{max}} = 520$ nm) generated by laser irradiation of **10** with a large excess of **1a** (300 mM) in the absence and presence of $\text{Mg}(\text{ClO}_4)_2$ (Figure 3(c)). The initial intensity in the presence of $\text{Mg}(\text{ClO}_4)_2$ was 1.9 times higher than that in the absence of $\text{Mg}(\text{ClO}_4)_2$ (Figure 3(c)). The radical pair is efficiently stabilized in the presence of $\text{Mg}(\text{ClO}_4)_2$ salt by the electrostatic interaction of **3** with ClO_4^- .²⁰ Therefore, the concentration of cation radical **3** is enhanced by the presence of $\text{Mg}(\text{ClO}_4)_2$, and this is likely the reason for the

dramatically higher product yield in the presence of $\text{Mg}(\text{ClO}_4)_2$ (Table 1, entry 7 vs. 12).²⁶

Figure 3. Detection of radical intermediates in the



photocatalytic redox cycle. (a) Transient absorption spectrum of **10** (50 μM) measured in DCM at 200 μs after laser excitation at 355 nm. (b) Relationship between the decay rate constant (k_{obs}) of the Xyl^{*+} moiety observed at 700 nm and the concentration of **1a**. (c) Time profiles at 520 nm of Acr^+-Xyl generated by photoexcitation of Acr^+-Xyl (50 μM) with cyclohexene (300 mM) in the absence (black) and presence (red) of $\text{Mg}(\text{ClO}_4)_2$.

Conclusions

In conclusion, we developed the first catalytic asymmetric allylation of aldehydes using unactivated hydrocarbon alkenes as pronucleophiles. The reaction enabled direct access to enantiomerically 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 catalysis 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 $\text{C}(\text{sp}^3)\text{-H}$ 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

This work was supported in part by JSPS KAKENHI Grant Numbers JP17H06442 (M.K.) (Hybrid Catalysis), 17H01522 (M.K.), 17K19479 (M.K.), 18H05969 (H.M.), and 18H04650 (K.O.) (Hybrid Catalysis). Authors deeply thanks to Prof. Shunichi Fukuzumi (Ewha Womans University, Korea) for the useful discussion and transient absorption measurements.

Notes and references

- For selected recent reviews on catalytic enantioselective C(sp³)-H bond functionalization, see: (a) R. Giri, B.-F. Shi, K. M. Engle, N. Maugelc and J.-Q. Yu, *Chem. Soc. Rev.* **2009**, *38*, 3242. (b) Q. Lu and F. Glorius, *Angew. Chem. Int. Ed.* **2017**, *56*, 49. (c) T. G. Saint-Denis, R.-Y. Zhu, G. Chen, Q.-F. Wu and J.-Q. Yu, *Science* **2018**, *359*, eaa04798.
- For selected recent reviews on stereoselective allylation of carbonyl compounds, see: (a) P. V. Ramachandran, *Aldrichimica Acta* **2002**, *35*, 23. (b) S. E. Denmark and J. Fu, *Chem. Rev.* **2003**, *103*, 2763. (c) C.-M. Yu, J.-s. Youn and H.-K. Jung, *Bull. Korean Chem. Soc.* **2006**, *27*, 463. (d) I. Marek and G. Sklute, *Chem. Commun.* **2007**, 1683. (e) D. G. Hall, *Synlett* **2007**, *11*, 1644. (f) G. C. Hargaden and P. J. Guiry, *Adv. Synth. Catal.* **2007**, *349*, 2407. (g) H. Yamamoto and M. Wadamoto, *Chem. - Asian J.* **2007**, *2*, 692. (h) H. Lachance and D. G. Hall, *Org. React.* **2009**, *73*, 1. (i) S. B. Han, I. S. Kim and M. J. Krische, *Chem. Commun.* **2009**, 7278. (j) M. Yus, J. C. Gonzalez-Gomez and F. Foubelo, *Chem. Rev.* **2011**, *111*, 7774. (k) J. Moran and M. J. Krische, In *Asymmetric Synthesis: More Methods and Applications*; M. Christmann and S. Bräse, Eds.; Wiley-VCH: Weinheim, Germany, 2012; pp 187. (l) M. Yus, J. C. Gonzalez-Gomez and F. Foubelo, *Chem. Rev.* **2013**, *113*, 5595. (m) H.-X. Huo, J. R. Duvall, M.-Y. Huang and R. Hong, *Org. Chem. Front.* **2014**, *1*, 303. (n) Q. Tian and G. Zhang, *Synthesis* **2016**, *48*, 4038. (o) P. Kumar, D. Tripathi, B. M. Sharma and N. Dwivedi, *Org. Biomol. Chem.* **2017**, *15*, 733. (p) S. W. Kim, W. Zhang and M. J. Krische, *Acc. Chem. Res.* **2017**, *50*, 2371. (q) P.-S. Wang, M.-L. Shen and L.-Z. Gong, *Synthesis* **2018**, *50*, 956. (r) D. M. Sedgwick, M. N. Grayson, S. Fustero and P. Barro, *Synthesis* **2018**, *50*, 1935. (s) K. Spielmann, G. Niel, R. M. de Figueiredo and J.-M. Campagne, *Chem. Soc. Rev.* **2018**, *47*, 1159. (t) M. Holmes, L. A. Schwartz and M. J. Krische, *Chem. Rev.* **2018**, *118*, 6026.
- For selected reviews on catalytic asymmetric carbonyl ene reactions, see: (a) K. Mikami and M. Shimizu, *Chem. Rev.* **1992**, *92*, 1021. (b) D. J. Berrisford and C. Bolm, *Angew. Chem. Int. Ed.* **1995**, *34*, 1717. (c) In: K. Mikami, M. Terada, E. N. Jacobsen, A. Pfaltz and H. Yamamoto, eds. *Comprehensive Asymmetric Catalysis*. Berlin, Heidelberg: Springer; **1999**: pp.1143. (d) L. C. Dias, *Curr. Org. Chem.* **2000**, *4*, 305. (e) K. Mikami, T. Nakai, In: I. Ojima, ed. *Catalytic Asymmetric Synthesis*. New York: Wiley-VCH; **2000**: pp.543. (f) M. L. Clarke and M. B. France, *Tetrahedron* **2008**, *64*, 9003.
- Catalytic allylic C(sp³)-H activation reported so far mainly generates electrophilic π -allylmetal complexes. For selected reviews of allylic C(sp³)-H activation, see: (a) T. Jensen and P. Fristrup, *Chem. Eur. J.* **2009**, *15*, 9632. (b) G. Liu and Y. Wu, *Top. Curr. Chem.* **2010**, *292*, 195. (c) G. J. Engelin and P. Fristrup, *Molecules* **2011**, *16*, 951. (d) C. Liu, H. Zhang, W. Shi and A. Lei, *Chem. Rev.* **2011**, *111*, 1780. (e) C. S. Yeung and V. M. Dong, *Chem. Rev.* **2011**, *111*, 1215. (f) B. J. Li and Z. J. Shi, *Chem. Soc. Rev.* **2012**, *41*, 5588. (g) F. Liron, J. Obble, M. M. Lorion and G. Poli, *Eur. J. Org. Chem.* **2014**, 5863. (h) C. Zheng and S. L. You, *RSC Adv.* **2014**, *4*, 6173. (i) C. G. Newton, S. G. Wang, C. C. Oliveira and N. Cramer, *Chem. Rev.* **2017**, *117*, 8908.
- Z.-L. Tao, X.-H. Li, Z.-Y. Han and L.-Z. Gong, *J. Am. Chem. Soc.* **2015**, *137*, 4054.
- T. Mita, S. Hanagata, K. Michigami and Y. Sato, *Org. Lett.* **2017**, *19*, 5876.
- J. L. Schwarz, F. Schäfers, A. Tlahuext-Aca, L. Lückemeier and F. Glorius, *J. Am. Chem. Soc.* **2018**, *140*, 12705. The racemic variant exhibited broad substrate scope and excellent diastereoselectivity.
- For chiral Brønsted base-catalyzed enantioselective allylation of ketones with special hydrocarbon alkenes (i.e., skipped enynes), see: X.-F. Wei, X.-W. Xie, Y. Shimizu and M. Kanai, *J. Am. Chem. Soc.* **2017**, *139*, 4647.
- For Brønsted base-catalyzed racemic allylation of imines with hydrocarbon alkenes, see: W. Bao, H. Kossen and U. Schneider, *J. Am. Chem. Soc.* **2017**, *139*, 4362.
- For related methods for the generation of organonickel species, see: (a) C. L. Joe and A. G. Doyle, *Angew. Chem. Int. Ed.* **2016**, *55*, 4040. (b) D. T. Ahneman and A. G. Doyle, *Chem. Sci.* **2016**, *7*, 7002. (c) D. R. Heitz, J. C. Tellis and G. A. Molander, *J. Am. Chem. Soc.* **2016**, *138*, 12715. (d) B. J. Shields and A. G. Doyle, *J. Am. Chem. Soc.* **2016**, *138*, 12719. (e) M. H. Shaw, V. W. Shurtleff, J. A. Terrett, J. D. Cuthbertson and D. W. C. MacMillan, *Science* **2016**, *352*, 1304. (f) X. Zhang and D. W. C. MacMillan, *J. Am. Chem. Soc.* **2017**, *139*, 11353. (g) Y.-Y. Gui, L.-L. Liao, L. Sun, Z. Zhang, J.-H. Ye, G. Shen, Z.-P. Lu, W.-J. Zhou and D.-G. Yu, *Chem. Commun.* **2017**, *53*, 1192. (h) Y.-Y. Gui, X.-W. Chen, W.-J. Zhou and D.-G. Yu, *Synlett* **2017**, *28*, 2581. (i) C. Le, Y. Liang, R. W. Evans, X. Li and D. W. C. MacMillan, *Nature* **2017**, *547*, 79. (j) H.-P. Deng, X.-Z. Fan, Z.-H. Chen, Q.-H. Xu and J. Wu, *J. Am. Chem. Soc.* **2017**, *139*, 13579. (k) Y.-Y. Gui, Z.-X. Wang, W.-J. Zhou, L.-L. Liao, L. Song, Z.-B. Yin, J. Li and D.-G. Yu, *Asian J. Org. Chem.* **2018**, *7*, 537. (l) H. Fuse, M. Kojima, H. Mitsunuma and M. Kanai, *Org. Lett.* **2018**, *20*, 2042. (m) S. Y. Go, G. S. Lee and S. H. Hong, *Org. Lett.* **2018**, *20*, 4691. (n) J. Twilton, M. Christensen, D. A. DiRocco, R. T. Ruck, I. W. Davies and D. W. C. MacMillan, *Angew. Chem. Int. Ed.* **2018**, *57*, 5369. (o) L. Huang and M. Rueping, *Angew. Chem. Int. Ed.* **2018**, *57*, 10333. (p) I. B. Perry, T. W. Brewer, P. J. Sarver, D. M. Schlutz, D. A. DiRocco and D. W. C. MacMillan, *Nature* **2018**, *560*, 70. (q) Y. Shen, Y. Gu and R. Martin, *J. Am. Chem. Soc.* **2018**, *140*, 12200. (r) L. K. G. Ackerman, J. I. M. Alvarado and A. G. Doyle, *J. Am. Chem. Soc.* **2018**, *140*, 14059. (s) D.-M. Yan, C. Xiao and J.-R. Chen, *Chem* **2018**, *4*, 2496. (t) L. Zhang, X. Si, Y. Yang, M. Zimmer, S. Witzel, K. Sekine, M. Rudolph and A. S. K. Hashmi, *Angew. Chem. Int. Ed.* **2018**, *57*, 10.1002/anie.201810526.
- For related methods for the generation of organopalladium species, see: (a) S. Kato, Y. Saga, M. Kojima, H. Fuse, S. Matsunaga, A. Fukatsu, M. Kondo, S. Masaoka and M. Kanai, *J. Am. Chem. Soc.* **2017**, *139*, 2204. (b) U. K. Sharma, H. P. L. Gemoets, F. Schröder, T. Noël and E. V. Van der Eycken, *ACS Catal.* **2017**, *7*, 3818.
- For a related method for the generation of organocobalt species, see: S. M. Thullen and T. Rovis, *J. Am. Chem. Soc.* **2017**, *139*, 15504.
- 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 benzylic 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 10(q).
- 14 R. Zhou, H. Liu, H. Tao, X. Yu and J. Wu, *Chem. Sci.* **2017**, 8, 4654.
 - 15 For a discussion of the feasibility of the working hypothesis shown in Figure 2 based on the redox potential of each intermediate, see Supplementary Information.
 - 16 T. Tsudaka, H. Kotani, K. Ohkubo, T. Nakagawa, N. V. Tkachenko, H. Lemmetyinen and S. Fukuzumi, *Chem. Eur. J.* **2017**, 23, 1306.
 - 17 For selected examples of catalytic asymmetric Nozaki-Hiyama-Kishi allylation reaction, see: (a) M. Bandini, P. G. Cozzi, P. Melchiorre and A. Umani-Ronchi, *Angew. Chem. Int. Ed.* **1999**, 38, 3357. (b) A. Berkessel, D. Menche, C. A. Sklorz, M. Schröder and I. Paterson, *Angew. Chem. Int. Ed.* **2003**, 42, 1032. (c) M. Inoue, T. Suzuki and M. Nakada, *J. Am. Chem. Soc.* **2003**, 125, 1140. (d) M. Kurosu, M.-H. Lin and Y. Kishi, *J. Am. Chem. Soc.* **2004**, 126, 12248. (e) J.-Y. Lee, J. J. Miller, S. S. Hamilton and M. S. Sigman, *Org. Lett.* **2005**, 7, 1837. (f) G. Xia and H. Yamamoto, *J. Am. Chem. Soc.* **2006**, 128, 2554. (g) J. J. Miller and M. S. Sigman, *J. Am. Chem. Soc.* **2007**, 129, 2752. (h) Z. Zhang, J. Huang, B. Ma and Y. Kishi, *Org. Lett.* **2008**, 10, 3073. (i) Q.-H. Deng, H. Wadepohl and L. H. Gade, *Chem. Eur. J.* **2011**, 17, 14922.
 - 18 C. Chen, K. Tagami and Y. Kishi, *J. Org. Chem.* **1995**, 60, 5386.
 - 19 G. Desimoni, G. Faita and K. A. Jørgensen *Chem. Rev.* **2006**, 106, 3561.
 - 20 (a) P. A. Thompson and J. D. Simon, *J. Am. Chem. Soc.* **1993**, 115, 5657. (b) T. M. Bockman, S. M. Hubig and J. K. Kochi, *J. Am. Chem. Soc.* **1998**, 120, 2826. (c) T. Yabe and J. K. Kochi, *J. Am. Chem. Soc.* **1992**, 114, 4491. (d) V. N. Grosso, C. M. Previtali and C. A. Chesta, *Photochem. Photobiol.* **1998**, 68, 481. (e) R. A. Marcus, *J. Phys. Chem. B* **1998**, 102, 10071. (f) T. Kluge and H. Knoll, *Photochem. Photobiol. A* **2000**, 130, 95. (g) E. V. Vakarin, M. F. Holovko and P. Piotrowiak, *Chem. Phys. Lett.* **2002**, 363, 7. (h) K. Okamoto, K. Ohkubo, K. M. Kadish and S. Fukuzumi, *J. Phys. Chem. A* **2004**, 108, 10405.
 - 21 K. N. Mahendra and R. C. Mehrotra, *Synth. React. Inorg. Met.-Org. Chem.* **1990**, 20, 963.
 - 22 K. Sugimoto, S. Aoyagi and C. Kibayashi, *J. Org. Chem.* **1997**, 62, 2322.
 - 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.
 - 24 S. Fukuzumi, H. Kotani, K. Ohkubo, S. Ogo, N. V. Tkachenko and H. Lemmetyinen, *J. Am. Chem. Soc.* **2004**, 126, 1600.
 - 25 K. Ohkubo, K. Suga, K. Morikawa and S. Fukuzumi, *J. Am. Chem. Soc.* **2003**, 125, 12850.
 - 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 Supplementary Information for details.

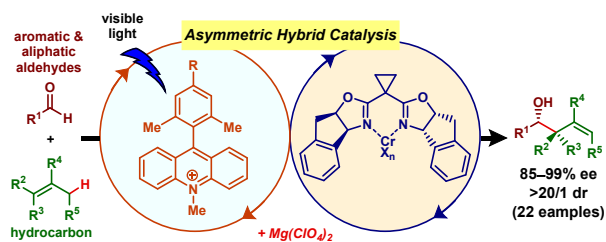


Journal Name

View Article Online
DOI: 10.1039/C8SC05677C

ARTICLE

A table of contents entry



We have developed a catalytic asymmetric nucleophilic allylation of aldehydes using simple alkenes as pronucleophiles without relying on stoichiometric metals.