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Visible Light Driven α -Allylation of Carboxylic Acids

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KEYWORDS. carboxylic acid, boron catalyst, visible light, single-electron transfer, radical, allylation

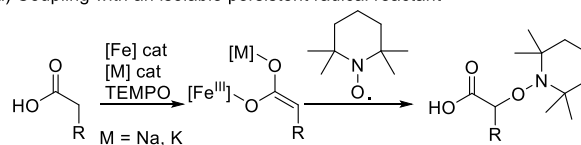
ABSTRACT: A boron-catalyzed α -allylation of carboxylic acids with allylsulfones under blue LED irradiation conditions is developed. We propose that photoexcitation of catalytically generated boron enediolates induces single-electron transfer to the allylsulfones. Subsequent C-C bond formation through a radical reaction constructs sterically demanding quaternary carbon centers at the position α to the carboxy group. The π -extended ligand on the boron atom is likely the key for efficient photoexcitation of the boron enediolates.

Carboxylic acids are versatile feedstock compounds abundantly available from natural resources.¹ Hence, efficient methods, especially catalytic methods, for upgrading the feedstock carboxylic acids to value-added compounds are of great interest. While catalytic α -functionalization of carbonyl compounds has been studied extensively for decades, mild and catalytic methods applicable to carboxylic acids are rare despite their utility.²⁻⁵ The difficulty stems mainly from the low acidity of the carboxylic acid α -protons, which hampers the formation of enolates required for application to polar reactions.⁶ Moreover, radical reactions, which exhibit intriguing reactivity complementary to polar reactions,⁷ have largely been neglected partly due to their tendency for decarboxylation.⁸ Recently, Ohshima and Yazaki developed a catalytic α -oxygenation of carboxylic acids through a radical process by hybrid catalysis, comprised of an iron catalyst and alkali metal catalysts derived from molecular sieves (Scheme 1a).⁴ The proposed heterobimetallic enediolate reacted with an isolable persistent radical, TEMPO, to produce α -oxycarboxylic acids. However, there are limited numbers of readily available isolable persistent radical species. Therefore, a catalytic α -functionalization of carboxylic acids in a radical process that enables coupling with non-radical substrates is a highly attractive target.

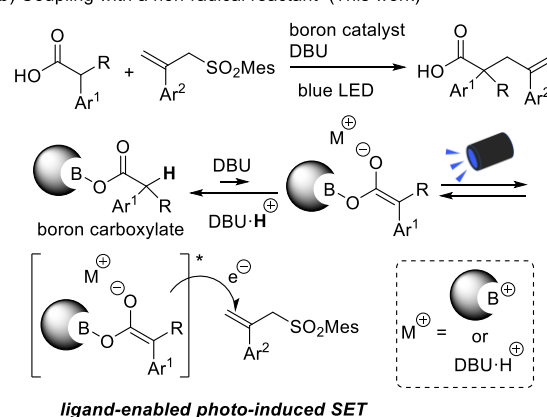
Photoinduced single-electron transfer between an electron-rich enolate or enamine and electron-deficient reagents followed by a radical reaction sequence has emerged as a powerful tool in α -functionalization of carbonyl compounds.⁹ We previously developed boron-catalyzed α -functionalizations of free carboxylic acids with polarized electrophiles, such as imines, trifluoromethyl

Scheme 1. Catalytic α -functionalization of carboxylic acids *via* radical processes.

a) Coupling with an isolable persistent radical reactant



b) Coupling with a non-radical reactant (This work)



ketones and so on.⁵ The outcomes of these reactions can be rationalized by assuming the ionization of boron carboxylates through α -deprotonation by an organic base such as DBU. The resulting boron enediolate can be in the form of either a diboron enediolate or a monoboron enediolate anion with an onium counteranion. The structural ambiguity for the enolate intermediate is mostly due to low concentration of the ionized species in the equilibrium mixture.¹⁰ Irrespective of the nature of the

counteraction, the ene moiety of the enolate is formally π -conjugated with the ligand of the boron catalyst through the oxygen and boron atoms. Thus, we envisioned that extending the π system of the ligand would enhance the photosensitivity of the intrinsically electron-rich boron enediolate, thereby facilitating single-electron transfer to electron-accepting reagents followed by a radical reaction sequence. Herein, we report a boron-catalyzed α -allylation of α -aryl carboxylic acids with readily available allylsulfones under blue LED irradiation conditions, constructing a sterically congested quaternary carbon center at the position α to the carboxy group (Scheme 1b).

2-Phenylpropionic acid (**1a**) was selected as a model substrate for the following reasons. First, the α -aryl carboxylic acid is a ubiquitous motif in biologically active compounds such as anti-inflammatory drugs.¹¹ Second, an enediolate derived from an α,α -disubstituted acetic acid is an electron-rich species, which would be favorable for single-electron transfer. Third, the resulting radical is stabilized by multiple substituents. Thus, the reaction between **1a** and 2-phenylallylsulfone **2a**¹² with boron catalysts was investigated under blue LED irradiation conditions ($\lambda_{\text{max}} = 465 \text{ nm}$) (Table 1). Intensive studies led to the optimized conditions, using allylmesitylsulfone **2a** (2 equiv) as a reactant, DBU (2.4 equiv) as a base, $(\text{AcO})_4\text{B}_2\text{O}$ as a boron source, and bipyrenol (**L1**·2H)¹³ as a proligand in toluene/THF (20/1) mixed solvent (entry 1, 69% NMR yield, 65% isolated yield). The boron catalyst, blue LED irradiation, and the base were all essential for this reaction to produce **3aa**.¹⁴

Ligands on the boron atom were highly influential as shown in Table 1. The reaction without a ligand produced **3aa** in only 7% yield (entry 2). Valine-derived ligand **L2**, which was a suitable ligand for the non-irradiated ionic reactions in our previous studies,^{3b,3d,3e} did not exhibit a meaningful effect (entry 3, 2% yield). In sharp contrast, simple binaphthol (**L3**·2H) gave promising reactivity (entry 4, 29% yield). Introduction of iodine atoms at the 3,3'-positions of the binaphthol scaffold (**L4**) increased the yield to 43% (entry 5). The yield dropped significantly when the binaphthyl scaffold of **L4** was changed to biphenyl (**L5**) (entry 6, 8%). On the other hand, extension of the π -system with biphenanthryl as in **L6** imparted a positive effect (entry 7, 56% yield). Thus, **L1**, which had the widest π -system among the ligands examined, was identified as the optimal ligand (entry 1, 69% yield).¹⁵

With the optimal conditions in hand, the substrate scope of the reaction was investigated (Table 2). The introduction of electron-donating *tert*-butyl and methoxy substituents at the *para*-position of the phenyl ring of 2-phenylpropanoic acid resulted in adverse effects (**3ba** 37% yield, and **3ca** 43% yield), while the effect of an electron-withdrawing chloro substituent was not significant (**3da** 51% yield). Although *meta*-substituted carboxylic acids such as **1e** and **1f** were suitable substrates for the reaction with **2a** (**3ea** 47% yield, and **3fa** 69% yield), the *ortho*-methyl substituent in **1g** prohibited the reaction. Carboxylic acids with α -heteroaryl groups also reacted in moderate yields (**3ha** 48% yield, and **3ia** 43% yield) with **L4** as the optimal ligand. The α -ethyl substrate **1j** underwent the reaction with **2a** with reactivity comparable to α -methyl substrate **1a** (**3ja**

Table 1. Ligand effect on photo-induced α -allylation of carboxylic acid.^a

Entry	Ligand	Yield (%)
1	L1	69 (65)
2	without ligand	7
3	L2	2
4	L3	29
5	L4	43
6	L5	8
7	L6	56

L1·2H

L2·2H

L3·2H

L4·2H

L5·2H

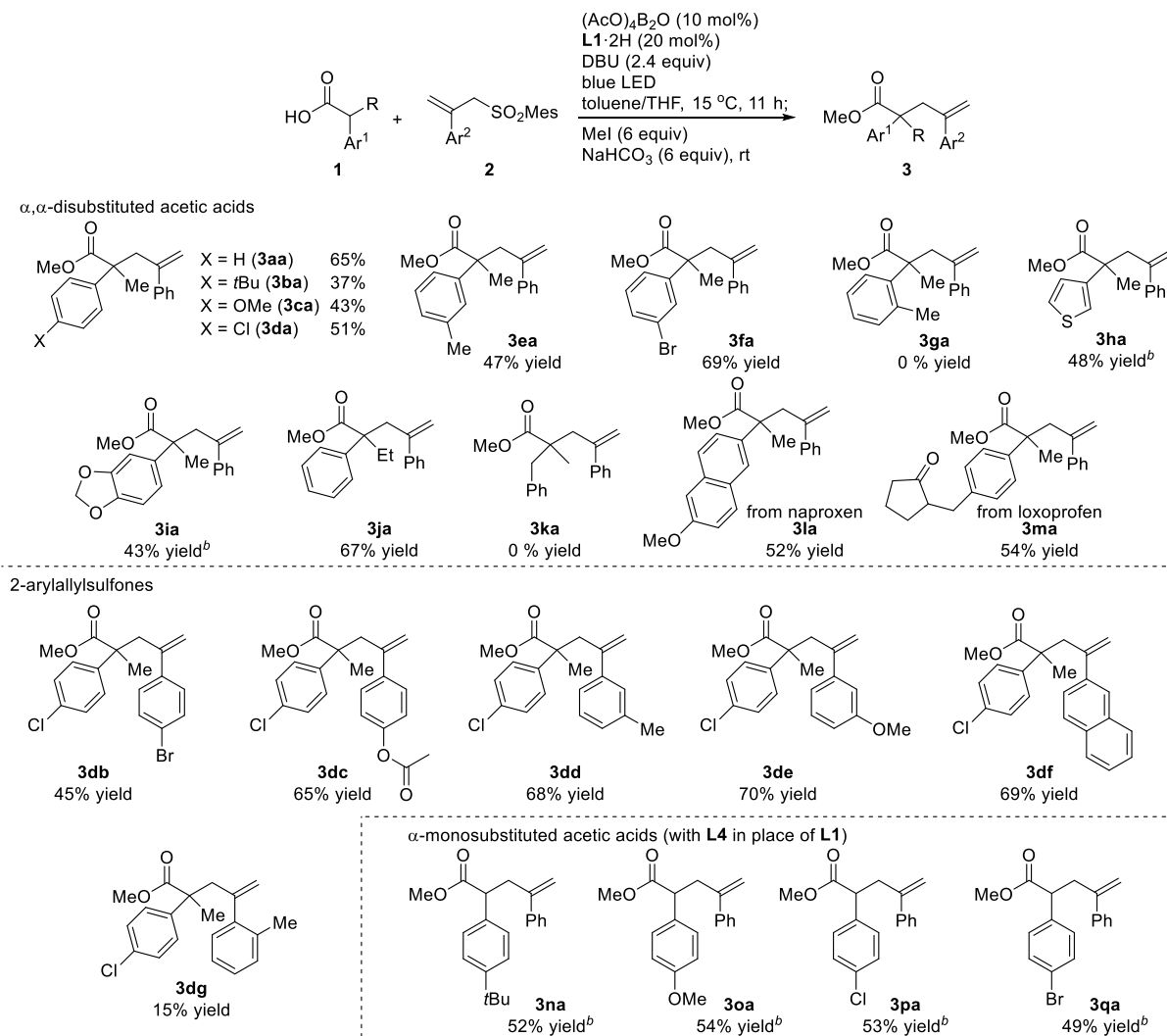
L6·2H

^a**1a** (0.1 mmol), **2a** (0.15 mmol), $(\text{AcO})_4\text{B}_2\text{O}$ (0.01 mmol), **Ligand**·2H (0.02 mmol), DBU (0.24 mmol), toluene/THF (20/1, 0.1 M), 40 W blue LED, 15 °C, 11 h. Yield was determined by ¹H NMR analysis using tetrachloroethane as an internal standard. Yield of the isolated product is described in parentheses.

67% yield). α,α -Dialkyl carboxylic acid **1k**, however, did not react at all and was recovered completely.

The reaction was applicable to the direct conversion of drug molecules containing a carboxy group (Table 2). The allylation of an anti-inflammatory drug, naproxen **1l**, provided **3la** in 52% yield. Loxoprofen **1m**, which contains a ketone moiety, reacted chemoselectively at the position α to the carboxy group to give **3ma** in 54% yield.

The scope of allylsulfones was examined using **1d** as the carboxylic acid donor. The results are also shown in Table 2. Bromo and acetoxy substituents at the *para*-position of the phenyl ring of the 2-phenylallylsulfones were competent (**3db** 45% yield, and **3dc** 65% yield). It is noteworthy that the reaction occurred site-selectively in the presence of an enolizable ester group in the allylsulfone substrate (**2c**). *meta*-Methyl and methoxy substituents and a sterically demanding 2-naphthyl substituent were also tolerated (**3dd** 68% yield, **3de** 70% yield, and **3df** 69% yield). On the

Table 2. Substrate scope.^a

^a**1** (0.1 mmol), **2** (0.2 mmol), (AcO)₄B₂O (0.01 mmol), **L1**·2H (0.02 mmol), DBU (0.24 mmol), toluene/THF (20/1, 0.1 M), 40 W blue LED, 15 °C, 11 h. Subsequent methyl esterification was conducted by adding MeI (0.6 mmol) and NaHCO₃ (0.6 mmol) to the reaction mixture. Yields of the isolated products were described. ^b**L4**·2H was used instead of **L1**·2H.

other hand, the *ortho*-methyl substituent in **2g** significantly inhibited the reaction (**3dg** 15% yield). Moreover, when the aryl substituent at the C2 position of the allylsulfone was changed to H, Me, or Cl, no allylation product was obtained, suggesting the importance of the conjugation of the aryl group with the allyl system for promoting the allylation.

α-Monosubstituted acetic acids (**1n**, **1o**, **1p** and **1q**), which were expected to be less reactive compared to α,α-disubstituted acetic acids in terms of both electron density of the corresponding enediolates and stability of the radical intermediates, were also applicable (Table 2). Re-evaluation of the ligand revealed that **L4** was suitable for this class of substrates.¹⁴ Both electron-donating and -withdrawing substituents at the *para*-position of the phenyl ring were tolerated under the reaction conditions (**3na** 52% yield, **3oa** 54% yield, **3pa** 53% yield, and **3qa** 49% yield).

Product formation and substrate consumption were monitored by ¹H NMR spectroscopy using tetramethyl silane as an internal standard in C₆D₆ solvent with

intermittent photoirradiation (Figure 1). The reaction progress was only observed during the photoirradiation periods. The absence of product formation during the dark conditions confirmed the requirement of photoirradiation.¹⁶ Product yield reached a maximum at 70% even though both **1a** and **2a** continued to decrease upon photoirradiation. This observation indicates the occurrence of catalyst deactivation during the progress of the reaction. Detection of a thiosulfonate by GC-MS spectrometry suggests that the water formed by disproportionation of the liberated sulfinate¹⁷ hydrolyzed and deactivated the catalyst.¹⁸

We assumed two possible species for a photo-excited single-electron reductant of the reaction. One is the boron enediolate and the other is phenoxy anion **L1**. However, the boron enediolate could not be detected by NMR, UV-Vis and fluorescence measurements because it exists in very low concentration in a complex equilibrium mixture. Therefore, to confirm whether the photo-excited phenoxy anion **L1** is

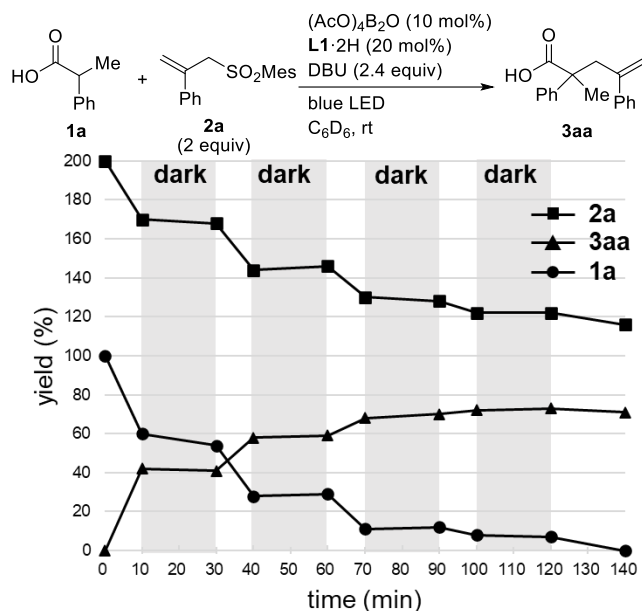
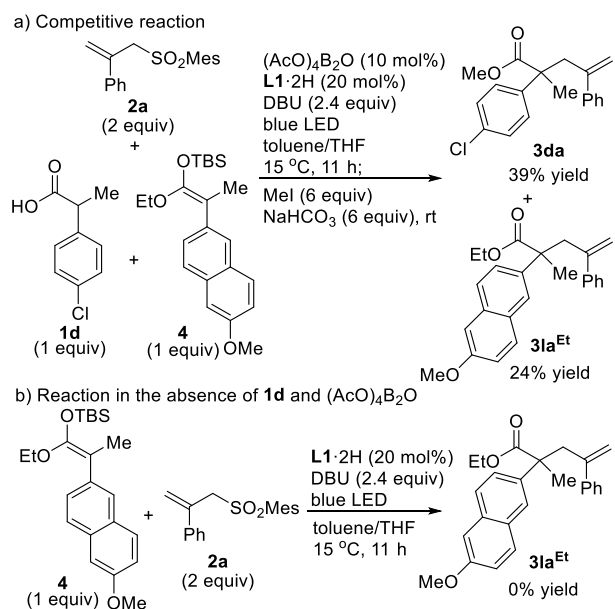


Figure 1. Effect of blue LED irradiation on the reaction profile. Conditions: **1a** (38 μmol), **2a** (76 μmol), $(\text{AcO})_4\text{B}_2\text{O}$ (3.8 μmol), **L1**·2H (7.6 μmol), DBU (91 μmol), C_6D_6 (0.1 M), 40 W blue LED.

the actual reductant that generates an allyl radical species,¹⁹ a reaction between ketene silyl acetal **4** and allylsulfone **2a** was conducted. As a competitive reaction, 1 equiv. of **4** was added to the standard catalytic conditions for the reaction of the free carboxylic acid **1d** and **2a** (Scheme 2a). This reaction produced the allylation product **3da** derived from the carboxylic acid (**1d**) as the major product in 39% yield along with **3la^{Et}** derived from the ketene silyl acetal (**4**) in 24% yield. On the other hand, the allylation of the ketene silyl acetal (**4**) did not occur at all in the absence of the carboxylic acid and $(\text{AcO})_4\text{B}_2\text{O}$ (Scheme 2b). These results provided two important insights. First, the allyl radical species is generated under the catalytic conditions and

Scheme 2. Control reactions with ketene silyl acetal 4.



reacts with the ketene silyl acetal **4** to give **3la^{Et}**. Second, the active single-electron reductant is not the photo-excited phenoxy anion **L1**. This result is consistent with a fluorescence quenching experiment of **L1** with varying concentration of **2a**, which showed no decrease in fluorescence intensity upon addition of **2a**.¹⁴ Thus the actual single-electron reductant in the reaction is likely a photoexcited boron enediolate species.

Based on the above results and considerations, the following catalytic mechanism can be proposed (Figure 2). Energetically unfavorable α -deprotonation of the boron carboxylate **A** with DBU forms a small amount of electron-rich boron enediolate **B**, and this species is photoexcited (**B*) by blue LED irradiation. Single-electron transfer from the excited boron enediolate (**B*) to allylsulfone **2** followed by elimination of the sulfinate anion from the resulting anion radical **2^{-•}** generates a radical pair consisting of the cation radical (**B^{+•}**) of the boron enediolate and the allyl radical **C[•]**.²⁰ The generated allyl radical **C[•]** may react with either the cation radical (**B^{+•}**) or the closed shell species **B**. In the former case, immediate radical-radical coupling of the radical pair (**B^{+•}/C[•]**) affords the α -allylation product **D**.^{21,22} Finally, the exchange of the carboxylate groups between **D** and the DBU salt of the starting material (**1**·DBU) produces the α -allylated carboxylic acid (**3**·DBU) as a DBU salt with regeneration of the boron carboxylate **A** to close the catalytic cycle. Alternatively, the allyl radical **C[•]** may react with the closed shell **B** to propagate a radical chain process, while it can exist in only a very low concentration as discussed before. If this is the case, a highly electron-rich α,α -dioxycarbon radical (**E[•]**) would form and undergo single-electron reduction of allylsulfone **2** to produce the boron carboxylate **D** and the allyl radical **C[•]**.²³****

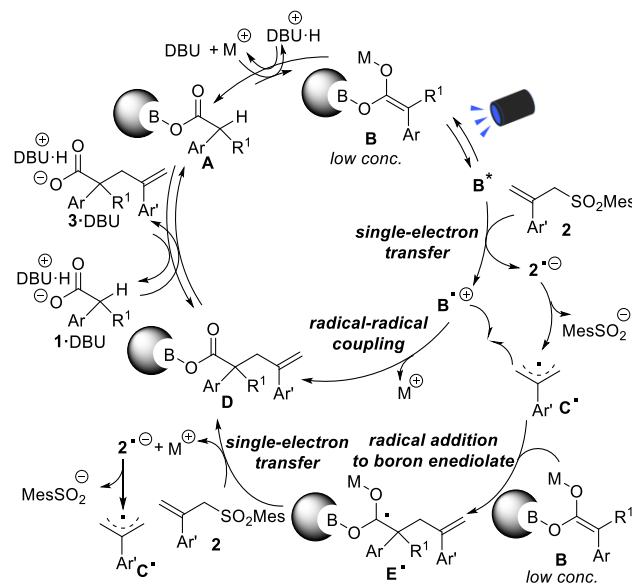
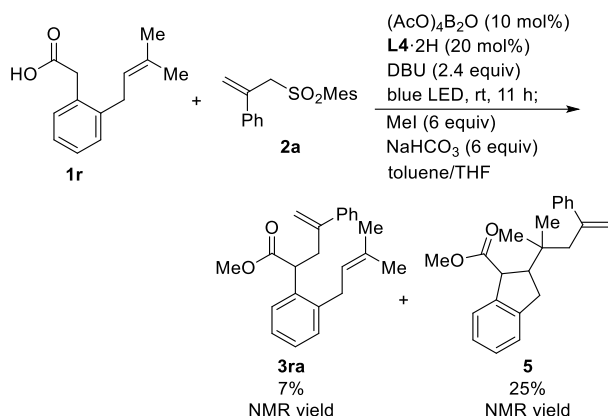


Figure 2. Proposed mechanism.

To shed light on the radical nature of the postulated radical cation (**B^{+•}**), a radical clock experiment was conducted with alkene-tethered phenylacetic acid **1r** and **2a** as a substrate couple in the presence of the boron/**L4** catalyst system (Scheme 3). This reaction afforded an indenyl compound **5** in 25% yield as a major product along

with minor formation of the direct α -allylation product **3ra** in 7% yield, confirming the radical nature of the boron enediolate moiety under the photoirradiation conditions.

Scheme 3. Radical clock experiment.



In summary, we have developed a ligand-enabled boron-catalyzed α -allylation of carboxylic acids using allylsulfones as a coupling partner under blue LED irradiation. The reaction produced sterically demanding quaternary carbon centers. Requirement for the blue LED irradiation strongly suggests that the reaction proceeds through a radical process: photoexcitation of *in situ* generated boron enediolates followed by single-electron transfer to the allylsulfones. The extended π -system of the ligand bound to the boron atom was essential as the photoexcitation moiety for the reaction. Further exploration of photo-induced chemoselective transformations of carboxylic acids is ongoing in our laboratory.

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Author Contributions

The manuscript was written through contributions of all authors. // These authors contributed equally.

ASSOCIATED CONTENT

Supporting Information

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

Detailed experimental procedures, characterization data, UV-Vis spectra, fluorescence spectra, cyclic voltammogram, NMR spectra, HPLC chart.

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(10) We tried to confirm the formation of this boron enediolate species by NMR spectroscopy, but no spectral change was observed upon addition of DBU to a CDCl_3 solution of the boron carboxylate species. Although spectroscopic evidence for the formation of diboron enediolates has not been obtained due to the low concentration of the carboxylic acid enolate species under the boron catalysis conditions, we postulate the diboron enediolate species as the most probable structure. Deprotonation of the α -proton of the *in situ* generated boron carboxylate should be facilitated by a second boron catalyst as a Lewis acid, giving the diboron enediolate. Generation of diboron enediolates from carboxylic acids is also discussed in the following seminal reports, which describe carboxylic acid aldol reactions, see: (a) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. Stereoselective Aldol Condensations via Boron Enolates. *J. Am. Chem. Soc.* **1981**, *103*, 3099–3111. (b) Ramachandran, P. V.; Chanda, P. M.; Otoo, B. *anti*-Selective Enolboration-Aldolization of Propanoic Acid. *Tetrahedron Lett.* **2014**, *55*, 1289–1291. In addition, non-linear effect was observed in boron-catalyzed asymmetric Mannich-type reaction, see: (c) Fujita, T.; Yamane, M.; Sameera, W. M. C.; Mitsunuma, H.; Kanai, M. ChemRxiv 2021. Siloxy Esters as Traceless Activator of Carboxylic Acids: Boron-Catalyzed Chemoselective Asymmetric Aldol Reaction. [10.26434/chemrxiv.14683485.v1](https://doi.org/10.26434/chemrxiv.14683485.v1) This content is a preprint and has not been peer-reviewed.

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(13) (a) Rajbangshi, S.; Sugiura, K.-I. An Alternative Synthesis of Bipyrenol: A High-Yield Oxidative Coupling Reaction of a Pyrene Derivative with $\text{Cu}(\text{BF}_4)_2 \cdot n\text{H}_2\text{O}$. *Synthesis* **2017**, *49*, 3145–3148. (b) Hassan, K.; Yamashita, K.-I.; Hirabayashi, K.; Shimizu, T.; Nakabayashi, K.; Imai, Y.; Matsumoto, T.; Yamano, A.; Sugiura, K.-I. π -Expanded Axially Chiral Biaryls and Their Emissions: Molecular Design, Syntheses, Optical Resolution, Absolute Configuration, and Circularly Polarized Luminescence of 1,1'-Bipyrene-2,2'-diols. *Chem. Lett.* **2015**, *44*, 1607–1609.

(14) See Supporting Information for details.

(15) When the chiral variants of selected ligands (**L1**, **L4**, and **L6**) were examined under the same conditions, modest enantioselectivities were observed in the reactions with (*R*)-**L4** (52% ee) and (*R*)-**L6** (21% ee). These results are indicative of the involvement of the boron catalysts modified with chiral ligands in the enantioselectivity-determining transition state. In contrast, the reaction with (*R*)-**L1** afforded racemic **3aa**. Although the absolute configuration of chiral **3aa** has not yet been determined, these results suggest the importance of steric effects in the vicinity of the boron atoms of the boron enediolate for the enantiocontrol.

(16) A radical chain process cannot be ruled out only by the result of light/dark experiment. Cismesia, M. A.; Yoon, T. P. Characterizing Chain Processes in Visible Light Photoredox Catalysis. *Chem. Sci.* **2015**, *6*, 5426–5434.

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(18) When 20 mol% of H_2O was added to the reaction between **1a** and **2a**, **3aa** was obtained in only 33% yield with 20% recovery of **1a**. Thus, generation of water should have a detrimental effect on the catalyst. Although identification of byproducts was not possible, decarboxylation is one of the possible degradation pathways, which would be promoted by the deactivated boron catalyst.

(19) Liang, K.; Liu, Q.; Shen, L.; Li, X.; Wei, D.; Zheng, L.; Xia, C. Intermolecular oxyarylation of olefins with aryl halides and TEMPOH catalyzed by the phenolate anion under visible light. *Chem. Sci.* **2020**, *11*, 6996–7002.

(20) The allyl radical formation is also supported by detection of a trace amount of hexa-1,5-diene-2,5-diylidibenzene by GC-MS analysis of the crude mixture and by isolation of the diene.

(21) For Lewis acid-mediated Mukaiyama-Michael reaction, Fukuzumi proposed a mechanism involving single-electron transfer from an electron-rich ketene silyl acetal to a Lewis acid activated enone followed by radical-radical coupling. See: (a) Sato, T.; Wakahara, Y.; Otera, J.; Nozaki, H.; Fukuzumi, S. Importance of Lewis Acid Mediated Electron Transfer in Mukaiyama-Michael Reaction of Ketene Silyl Acetals. *J. Am. Chem. Soc.* **1991**, *113*, 4028–4030. (b) Otera, J.; Fujita, Y.; Sakuta, N.; Fujita, M.; Fukuzumi, S. Mechanism of Mukaiyama-Michael Reaction of Ketene Silyl Acetal: Electron Transfer or Nucleophilic Addition? *J. Org. Chem.* **1996**, *61*, 2951–2962.

(22) Since the aryl substituent on the C-2 position of the allylsulfone **2** is crucial, the aryl substituent may endow persistency to the allyl radical **C'** to enable the radical-radical coupling. See: Leifert, D.; Studer, A. The Persistent Radical Effect in Organic Synthesis. *Angew. Chem. Int. Ed.* **2020**, *59*, 74–108.

(23) When the reaction of **1d** (0.1 mmol) and **2a** (0.2 mmol) in toluene-*d*₈/THF-*d*₈ was performed under light irradiation with 460 nm bandpass filter (29.6 mW intensity of the light, and 22% transmittance at the wavelength) for 30 min, the product was obtained in 15% yield. Thus, the quantum yield of the reaction is estimated to be 9%. Although the value is small for long radical chain, involvement of radical chain as a minor pathway cannot be ruled out only by the quantum yield.

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