RESEARCH ARTICLE

Photoinduced Direct β-Allylation of Carboxylic Acids Enabled by Boron Catalysis with a Mixed Two-Ligand System

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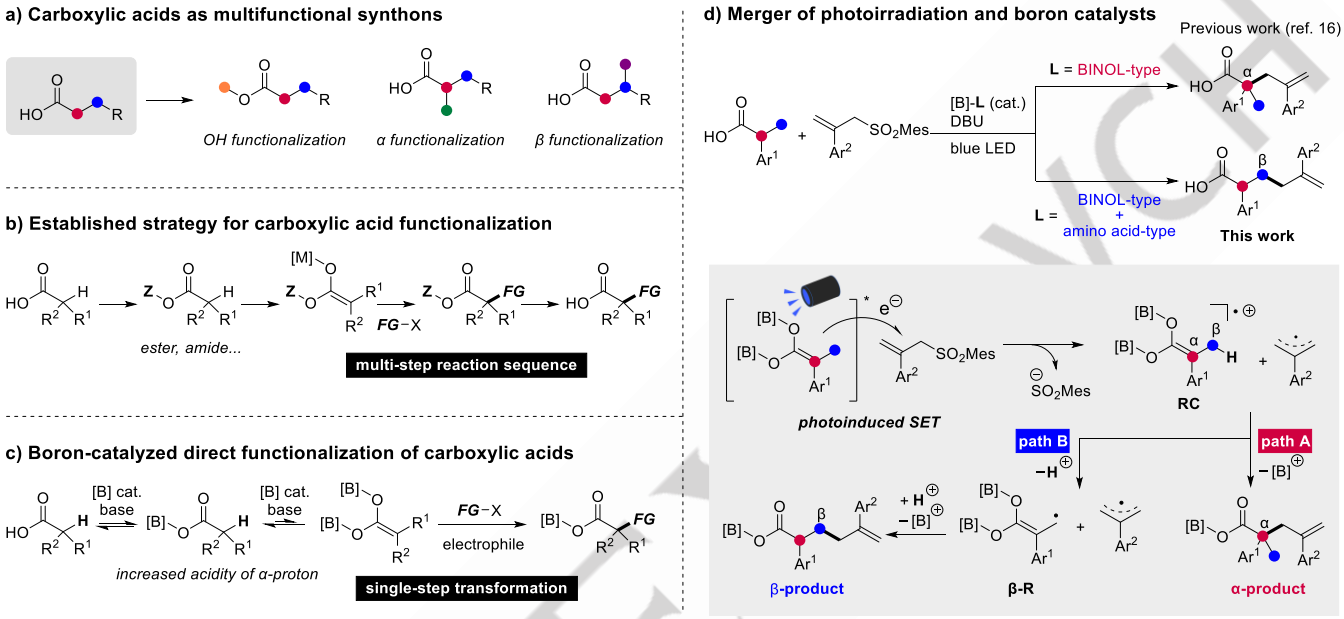
Abstract: A visible light-induced, boron-catalyzed direct β-allylation of carboxylic acids with allylsulfones was developed. The selective promotion of β-allylation over the competing α-allylation was achieved by the combined use of a bulky binaphthol derivative and a *N*-sulfonyl valine derivative as ligands for the boron catalyst. Photoexcitation of catalytically generated diboron ene-1,1-diolates induces single-electron transfer to the allylsulfones, and ensuing deprotonation of the resulting radical cations generates β-radicals, directing C–C bond formation at the β-position. The versatility of this catalysis was demonstrated through its application to various pharmaceutical compounds. Furthermore, by leveraging the unique features of the carboxy group preserved in the products, subsequent transformations were successfully achieved, showcasing the capability of the boron catalysis in rapidly increasing the molecular complexity of carboxylic acids.

Introduction

Carboxylic acids are versatile and readily available building blocks in organic synthesis as well as ubiquitous motifs in biologically active molecules, including natural products, pharmaceuticals, and agrochemicals. Hence, transformations of feedstock carboxylic acids to value-added compounds through direct derivatization are highly demanded (Scheme 1a, b).[1-3] In this regard, α-functionalization of carboxylic acids through the formation of an enolate intermediate has been the classical and most reliable approach, where novel methods have been continuously reported.[4-19] In comparison, direct functionalization at positions more distal to the carboxy group has received less attention but would represent an attractive strategy to allow for rapid increase in molecular complexity from simple starting materials. Recently, carboxy group-directed palladium-catalyzed β- and γ-functionalizations of aliphatic carboxylic acids have emerged as promising strategies, realizing arylation,[20-30] olefination,[31-33] alkynylation,[34] and installation of heteroatoms.[35-38] Despite these significant developments, a C(sp^3)–C(sp^3) coupling at the distal positions has remained as a formidable challenge but would represent a desirable pathway to construct stereochemically enriched molecules.[39,40]

We have previously developed a boron catalyst that enables facile generation of carboxylic acid enolates (Scheme 1c).[10-19] The reversible formation of B–O covalent bond between the carboxylic acids and the Lewis-acidic boron catalysts increases the acidity of the α-proton, enabling smooth deprotonation by the aid of the other boron catalyst to generate the key diboron enediolate intermediates under mildly basic conditions. The strategy has been successfully applied to various α-functionalizations. A notable example is a photoinduced boron-catalyzed direct α-allylation of carboxylic acids, where the key step features a single-electron transfer (SET) from the photoexcited boron enolate to electron-accepting allylsulfones (Scheme 1d).[16] The resulting enolate-derived radical cation **RC** then undergoes a radical-radical coupling with the allyl radical to form the C–C bond at the α-position (path A). We questioned whether this mechanism can be adapted to switch the reactive site from the α-position to the β-position. It is conceivable that a deprotonation of the radical cation intermediate **RC** would generate a β-radical **β-R**, and efficient coupling with this intermediate would unlock an exciting pathway

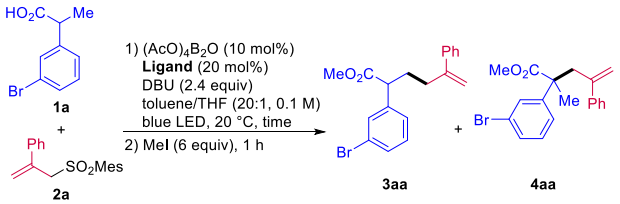
leading to β-allylation of carboxylic acids (path B). This switch of selectivity is expected to be challenging as this radical transposition process ought to compete with the α-functionalization reaction. Additionally, the resulting β-radical can be prone to undergo oxidation that ultimately leads to α, β-unsaturated carboxylic acids or other side products. Presumably due to these complications, this strategy has so far proved effective only for aldehydes and ketones,[41-44] and to date, there are no examples of direct β-functionalization of carboxylic acids or their derivatives under this mechanism.[45] Herein, we report our successful development of a new boron catalytic system that enables the β-selective direct C(sp^3)–C(sp^3) coupling of carboxylic acids for the first time. Key to this success is a mixed two-ligand system combining a binaphthol (BINOL)-derivative and an amino acid-derivative, which we showed to promote the β-allylation predominantly over the competing α-functionalization through both electronic and steric ligand effects.



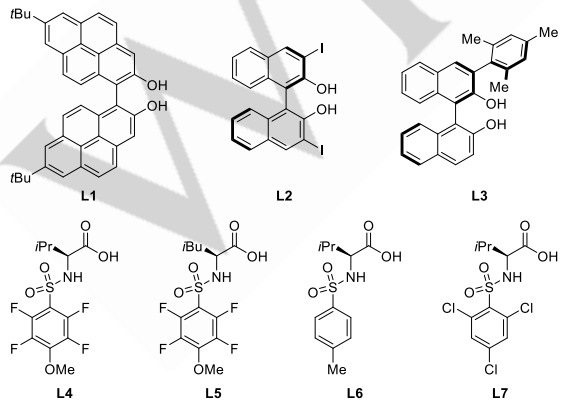
Scheme 1. Boron-catalyzed α- and β-functionalizations of carboxylic acids.

Given the essential role of BINOL-type ligands in our previous photoinduced boron-catalyzed α-allylation of carboxylic acids,[16] we first investigated various structural derivatives using 2-(3-bromophenyl)propanoic acid (**1a**) and allylsulfone **2a** as the substrates, together with $(AcO)_4B_2O$ as a boron source (Table 1). Upon careful analysis of the reaction with bipyrenol ligand **L1**,[46,47] which was optimal for the α-allylation, a small amount of β-allylation product **3aa** (7% yield) was detected along with α-product **4aa** (69% yield). Further exploration of various BINOL-type ligands only led to a trace amount of **3aa**, and **4aa** remained as the major product (entry 2 and Supporting Information). Nonetheless, results of ligands bearing bulky substituents at 3- or 3,3'-position, such as **L3** (entry 3), attracted our attention: formation of **4aa** was significantly suppressed while **3aa** was still produced in a detectable level. It is hypothesized that the bulky substituents might disfavor α-allylation due to steric repulsion between the ligand and allyl radical, thus encouraging C–C bond formation at the slightly more distal β-position. L-Valine-derived ligand **L4**, a competent ligand for the non-photochemical α-functionalizations of carboxylic acids,[18] provided **3aa** in 6% yield while suppressing the formation of **4aa** to <1% (entry 4). The high β-allylation selectivity would be ascribed to the electron withdrawing ability of **L4** for facilitating the β-deprotonation by increacing Lewis acidity of a boron catalyst. Next, we expected that improved reactivity for β-allylation may be achieved by employing two complementary ligands: **L3** for sterically inhibiting α-allylation (entry 3) and **L4** for electronically promoting β-allylation (entry 4). To our delight, combined use of **L3** (10 mol%) and **L4** (10 mol%) substantially improved the yield of β-allylation product **3aa** (27%) while avoiding the formation of α-allylation product **4aa** (<1%) (entry 5). The yield of **3aa** was improved to 37% by prolonging the reaction time to 4 h with a modified photoirradiation setup (entry 6). On the other hand, replacing **L4** with leucine-derived ligand **L5** (entry 7) or with other *N*-sulfonyl valines **L6** and **L7** (entries 8-9) was not effective in improving the efficiency of β-allylation. Further investigation revealed that changing the solvent to *o*-xylene with the use of an increased amount of DBU (3.2 equiv) improved the yield to 52% while achieving >25:1 β/α selectivity (entry 10). The yield decreased slightly when the enantiomer of **L4** was used as the ligand (entry 11, 47%), which can be ascribed to a minor chirality mismatch between **L3** and ***ent*-L4** in a hetero-ligated boron ene-1,1-diolate intermediate. Finally, through the control experiment, we confirmed that the lignads **L3** and **L4** are essential for promoting the photoinduced allylation reaction (entry 12).

Table 1. Optimization of β-allylation of carboxylic acid.[a]



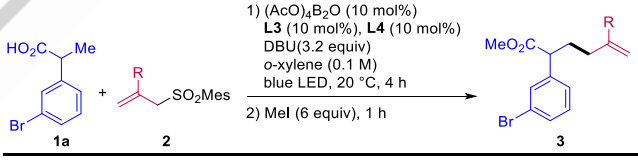
entry	Ligand	time (h)	yield of **3aa** (%)	yield of **4aa** (%)
1	**L1**	2	7	69
2	**L2**	2	1	47
3	**L3**	2	5	5
4	**L4**	2	6	<1
5	**L3** (10 mol%) **L4** (10 mol%)	1	27	<1
6[b]	**L3** (10 mol%) **L4** (10 mol%)	4	37	4
7[b]	**L3** (10 mol%) **L5** (10 mol%)	4	6	22
8[b]	**L3** (10 mol%) **L6** (10 mol%)	4	9	34
9[b]	**L3** (10 mol%) **L7** (10 mol%)	4	7	7
10[b][c]	**L3** (10 mol%) **L4** (10 mol%)	4	52	2
11[b][c]	**L3** (10 mol%) ***ent*-L4** (10 mol%)	4	47	3
12[b][c]	none	4	<1	<1



[a]**1a** (0.1 mmol), **2a** (0.2 mmol), DBU (0.24 mmol), $(AcO)_4B_2O$ (0.01 mmol), ligand (0.02 mmol in total), toluene/THF (20:1, 0.1 M), Lumidox II blue LED, 20 °C. Subsequent methyl esterification was conducted by adding MeI (0.6 mmol) to the reaction mixture. Yield was determined by ^{1}H NMR analysis using tetrabromoethane as the standard. [b] Kessil Tuna Blue was used as the LED. [c] *o*-Xylene (0.1 M) solvent and 3.2 equiv DBU were used.

Having the optimized conditions in hand, scope of allylsulfones was investigated using **1a** as the carboxylic acid substrate (Table 2). Since the separation of positional isomers **3** and **4** was extremely challenging in most cases, NMR yields of **3** were shown in the table. The isolated yields of **3** was calculated from the purified products with the **3**/**4** ratios shown. This reaction can be scaled up to 1-mmol of **1a** using the identical photochemical setup with slight reduction in efficiency, affording β-product **3aa** in 31% isolated yield. A *para*-bromo derivative of 2-arylallylsulfone (**2b**) provided an excellent 68% yield (entry 3). *para*-Phenyl variant (**2c**) afforded 63% yield of the β-coupled products, which contained an isomer of the internal olefin conjugated with the biphenyl group (**3ac'**) as a result of facile double bond isomerization of **3ac** during the work-up (entry 4). Methoxy and methyl substituents at the *meta*-position were tolerated to provide **3ad** and **3ae** in 53% and 42% yield, respectively (entries 5 and 6). A π-extended naphthyl group was compatible, giving **3af** in 35% yield (entry 7). However, the aryl group at the C2 position of the allylsulfone was essential, as **2g**, which bears a methyl group at the C2 position instead, was totally unreactive (entry 8). Since the reduction potential of **2g** (–2.37 V vs SCE) was lower than those of **2a** (–2.27 V vs SCE) and **2b** (–2.15 V vs SCE), the necessity of the aryl substituents in the allylsulfones would be ascribed to their higher propensity to undergo single-electron reduction as compared to the alkyl-substituted variants (see Supporting Information for details).

Table 2. Scope of allylsulfones.[a]



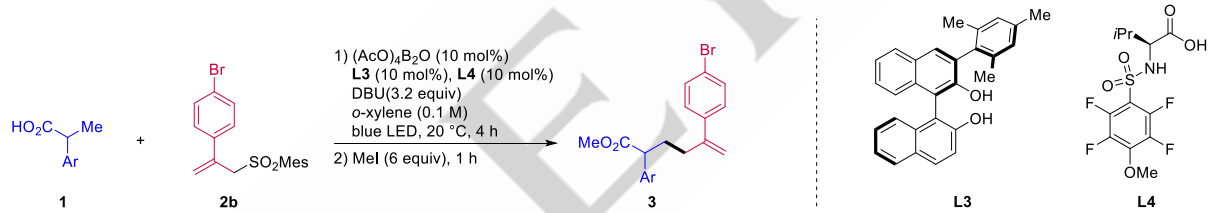
entry	R	NMR yield of **3** (%) (**3**/**4**)[b]	Isolated yield of **3** (%) (**3**/**4**)[c]
1	Ph (**3aa**)	52 (21.5/1)	40 (>50/1)
2[d]	Ph (**3aa**)	35 (14.8/1)	31 (28.1/1)
3	4-Br-C_6H_4 (**3ab**)	68 (17.8/1)	54 (35.4/1)
4	4-Ph-C_6H_4 (**3ac**)	63 (12.4/1)[e]	45 (>50/1)[f]
5	3-MeO-C_6H_4 (**3ad**)	53 (16.4/1)	50 (35.2/1)
6	3-Me-C_6H_4 (**3ae**)	42 (8.6/1)	36 (>50/1)
7	2-naphthyl (**3af**)	35 (10.5/1)	36 (25.0/1)
8	Me (**3ag**)	0	–

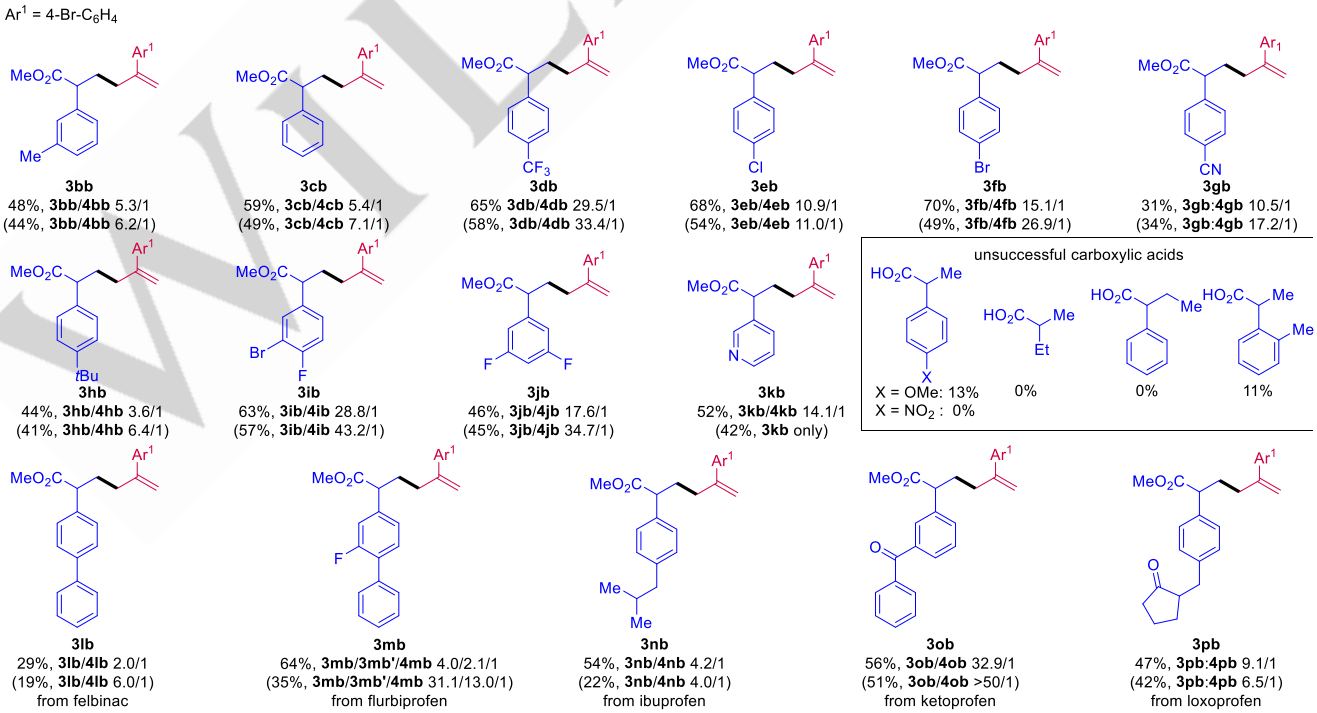
[a] **1a** (0.1 mmol), **2** (0.2 mmol), DBU (0.32 mmol), $(AcO)_4B_2O$ (0.01 mmol), **L3** (0.01 mmol), **L4** (0.01 mmol), *o*-xylene (0.1 M), Kessil Tuna Blue LED, 20 °C. Subsequent methyl esterification was conducted by adding MeI (0.6 mmol) to

the reaction mixture. [b] Yields were determined by ^{1}H NMR analysis using tetrabromoethane as the standard. [c] Isolated yields of **3** were calculated from the purified samples with the **3**/**4** ratios (determined by ^{1}H NMR analysis) shown. [d] The reaction was carried out with 1 mmol of **1a**. [e] Including 35% of the internal-olefin isomer **3ac'**. [f] **3ac**/**3ac'** 1.3/1.

Next, the scope of carboxylic acids was explored utilizing allylsulfone **2b** as the coupling partner (Scheme 2, NMR yields of **3** are shown along with isolated yields of **3** in the parentheses). *meta*-Tolyl (**1b**) and simple phenyl (**1c**) substituents, instead of the *meta*-bromophenyl group in **1a**, afforded the corresponding products in moderate yields (**3bb**: 48%, **3cb**: 59%). 2-Arylpropanoic acid (**1d**) with an electron-withdrawing trifluoromethyl group at the *para*-position was a competent substrate, giving β-allylation product **3db** in 65% yield. The reactions of **1e** and **1f** bearing a *para*-chloro or -bromo substituent also proceeded in good yields (**3eb**: 68%, **3fb**: 70%). *para*-Cyano- (**1g**) and *tert*-butyl substituent (**1h**), however, decreased the yields (**3gb**: 31%, **3hb**: 44%). 3,4- and 3,5-Dihalogenated aryl groups were compatible, providing **3ib** and **3jb** in 63% and 46% yield, respectively. The tolerance of halogen substitution opens the possibility for subsequent derivatization. Furthermore, the boron catalysis was applicable to a carboxylic acid bearing a 3-pyridyl group, providing **3kb** in 52% yield. Through the investigation of various carboxylic acid substrates, limitation of the method was revealed as follows. Substituents which exhibit strongly electron-donating (OMe) and -withdrawing (NO_2) properties due to resonance effects significantly hampered the reaction, supposedly due to their impact on the acidity of the α- and β-protons or stability of the β-radical. When 2-ethylpropionic acid was subjected to the optimized conditions, the desired product was not obtained at all, suggesting that the conjugation of the α-aryl group with the generated diboron enediolate is essential to promoting the reaction. 2-Phenylbutanoic acid bearing a β-methyl group was not reactive despite the ability to generate a more stable secondary β-radical. This result shows the sensitivity to steric environment at the β-position, presumably in relation to the deprotonation of the allylic C–H of the radical cation to produce the β-radical. Similarly, sterically demanding *o*-methyl substitution on the phenylpropionic acid inhibited the reaction (See Supporting Information for other unsuccessful examples).

Given the prevalence of 2-arylcarboxylic acid structures in bioactive compounds, we were pleased to find that this reaction was applicable to a series of drug molecules (**1l**-**1p**), demonstrating its versatility as a late-stage editing method of complex molecules. The keto groups in ketoprofen **1o** and loxoprofen **1p** were tolerated, and no competing allylation at the α- and β-position to the keto group of **1p** was observed. The reactivity difference between distinct carbonyl groups showcases the power of this catalytic system in selectively activating the carboxylic acids through the intermediacy of boron ene-1,1-diolates.





Scheme 2. Scope of carboxylic acids. **1** (0.1 mmol), **2b** (0.2 mmol), DBU (0.32 mmol), $(AcO)_4B_2O$ (0.01 mmol), **L3** (0.01 mmol), **L4** (0.01 mmol), *o*-xylene (0.1 M), Kessil Tuna Blue LED, 20 °C. Subsequent methyl esterification was conducted by adding MeI (0.6 mmol) to the reaction mixture. NMR yields were determined by ^{1}H NMR analysis using tetrabromoethane as the standard, and isolated yields of **3** were calculated from the purified samples with the **3/4** ratios (determined by ^{1}H NMR analysis) shown in parentheses.

The broad range of compatible substrates thus encouraged us to establish a quantitative structure-reactivity relationship for informing applicable carboxylic acids in this methodology. To identify molecular parameters crucial to the chemical yields, we adopted a DFT-featurization approach, where the carboxylic acids were first computed by density-functional theory (DFT).[48] Descriptors derived from the DFT calculations were then used to build models that provided the best fit with experimental yields, where the NMR yields were employed to exclude the influence of the isolation efficiency of the products. In addition to the successful substrates, poorly performing carboxylic acids were also included for generality (see Scheme 2 and Supporting Information for details). Among all the models examined, logistic regression-type functions were found to be the most suitable in capturing both high-yielding substrates as well as those giving <5% yields. Upon screening 40 representative parameters, we discovered that a combination of **NBOaH** (NBO charges on α-H), **HLG** (HOMO-LUMO energy gap), **BDBHH** (highest NBO electron occupations of βC-βH σ-bond), and **APTbHH** (highest APT charge on β-H) provided an excellent level of fitting: $R^2 = 0.93$ and $Q^2 = 0.87$ for leave-one-out (LOO) validation (Figure 1 and Supporting Information). The success in connecting the quantifiable electronic descriptors of the carboxylic acids to the chemical yields of this reaction thus points to the possibility of further predicting suitable substrates for this β-allylation method.

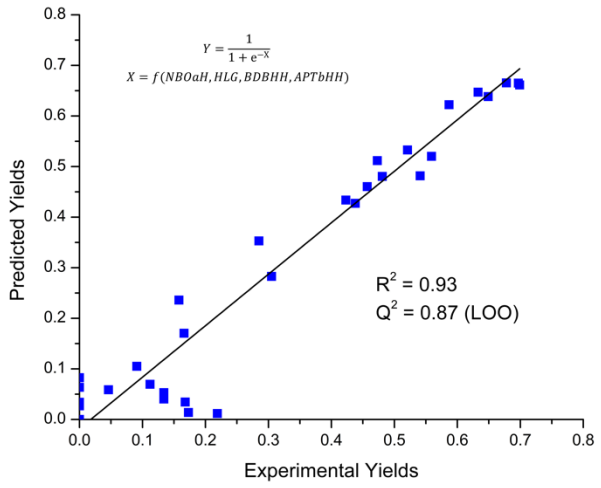
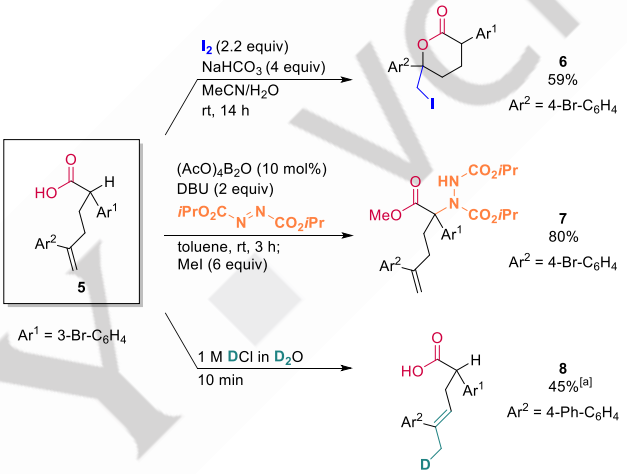


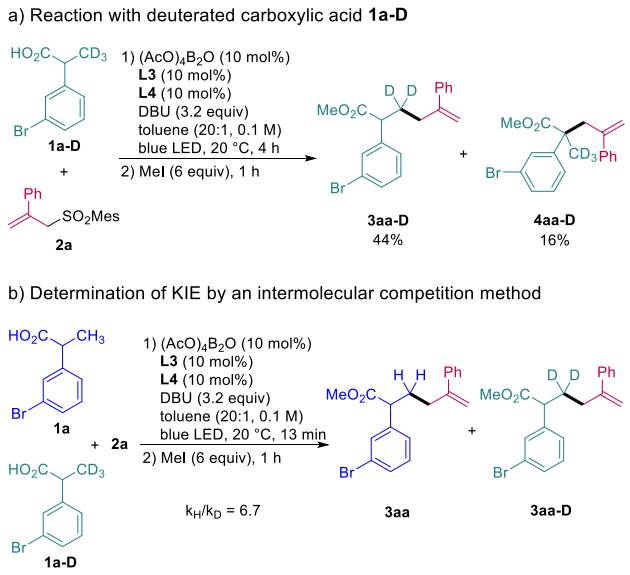
Figure 1. Regression models for correlating the reaction yields (NMR) and carboxylic acid structures.

The β-allylation products in Table 2 and Scheme 2 were isolated as the corresponding methyl esters for ease of purification, but the true synthetic utility of this method would be manifested when the carboxy group is preserved for subsequent transformations. For instance, taking advantage of the carboxylic acid and olefin moieties in product **5**, an iodocyclization was successfully achieved to afford **6** in 59% yield (Scheme 3). In addition, **5** has one remaining α-proton to form the boron enolate to allow for a subsequent boron-catalyzed α-amination,[14] providing **7** in 80% yield. Furthermore, leveraging the facile isomerization of the terminal double bond to the internal position under acidic conditions, a selective deuteration at the terminal position was accomplished by treating **5** with 1 M DCl in D_2O to produce **8** in 45% yield. Thus, these three exemplary transformations showcase the power of this method to directly functionalize the unprotected carboxylic acids, enabling rapid increase of the molecular complexity to multifunctional value-added derivatives.



Scheme 3. Transformations of β-allylation products. [a] Yield was determined by ^{1}H NMR analysis using tetrabromoethane as the standard.

Arguably, the most important step in this reaction is the proposed β-deprotonation (**RC** to **β-R** in Scheme 1d). To gain mechanistic insights into this elementary step, deuterium-labelling experiments were carried out. First, β-deuterated carboxylic acid **1a-D** was subjected to the optimized conditions, providing the deuterated products **3aa-D** and **4aa-D** in 44% and 16% yields, respectively (Scheme 4a). No scrambling of β-hydrogens was observed, indicating that the β-deprotonation step is irreversible. It should be noted that the ratio of α-allylation product **4aa-D** over β-allylation product **3aa-D** increased markedly compared to that in the reaction with non-deuterated carboxylic acid **1a** (Table 1, entry 10: **3aa** 52%, **4aa** 2%). This result is consistent with a slower β-deprotonation causing an increased generation of the competing α-allylation product. When the same reaction was conducted without blue LED irradiation, **1a-D** with 100% D at the β-position was completely recovered, suggesting that no β-deprotonation is possible with any intermediates prior to the photoexcitation step. Moreover, an KIE value of 6.7 obtained by the reaction with 1:1 mixture of **1a** and **1a-D** clearly shows that the β-deprotonation step critically influences the overall reaction rate of the β-allylation process (Scheme 4b).[49]



Scheme 4. Probing β-deprotonation step with deuterated carboxylic acid **1a-D**.

One of the most noteworthy features of this catalytic system is the combined use of **L3** and **L4** for promoting the selective β-allylation. Since the experiments with **1a-D** revealed the importance of the β-deprotonation step (**RC** to **β-R** in Scheme 1d), we decided to determine the pK_a values of the radical cations **RC1**, **RC1'** (bearing **L3** and **L4**), and **RC2** (bearing two molecules of **L3**) for comparison by DFT calculations, referencing known pK_a values of a series of anilines in acetonitrile.[50] The calculated pK_a values of **RC1**, **RC1'**, and **RC2** were 5.9, 6.5 and 7.6, respectively (Figure 2a). As these values are lower than that of a strong acid, TsOH (pK_a = 8.6),[51] deprotonation of the β-proton by DBU should be thermodynamically favorable in all cases, with the **L3**/**L4**-complexation resulting in more acidic β-protons in **RC1** and **RC1'**. Next, we looked into the steric effects of the ligands on the plausible intermediates, namely radical cations (**RC1**, **RC1'**, and **RC2**) and β-radicals (**β-R1**, **β-R1'**, and **β-R2**), calculated at the (U)CAM-B3LYP/6-31+G(d,p) SMD(toluene) level of theory. All the optimized structures of **RC** illustrate that the ligands sufficiently shield the boron atoms and the α-carbons, preventing the generation of neutral α-radicals through O–B bond cleavage as well as the direct α-allylation of the radical cations. Similarly, the β-protons of **RC1'** were located at the sterically hindered position, preventing the generation of **β-R1'** by β-deprotonation. In sharp contrast, β-protons are located at the position accessible to base in **RC1** and **RC2**, leading to preferential β-deprotonation rather than α-allylation. The two viable β-radicals, **β-R1** and **β-R2**, exhibited notable differences in their steric environments, particularly around the β-carbons. In **β-R2**, two mesityl groups of **L3** flank the β-carbon, blocking the approach of any reactant. On the other hand, the β-carbon of **β-R1** is accessible from the side of **L4**, enabling C–C bond formation with allyl radicals. Thus, the advantage of the **L3**/**L4** two-ligand system is largely due to steric effects, where shielding of the boron atoms and the α-carbon by the bulky **L3** ligand results in inhibition of the α-allylation, while at the same time, leaving space for the β-allylations.

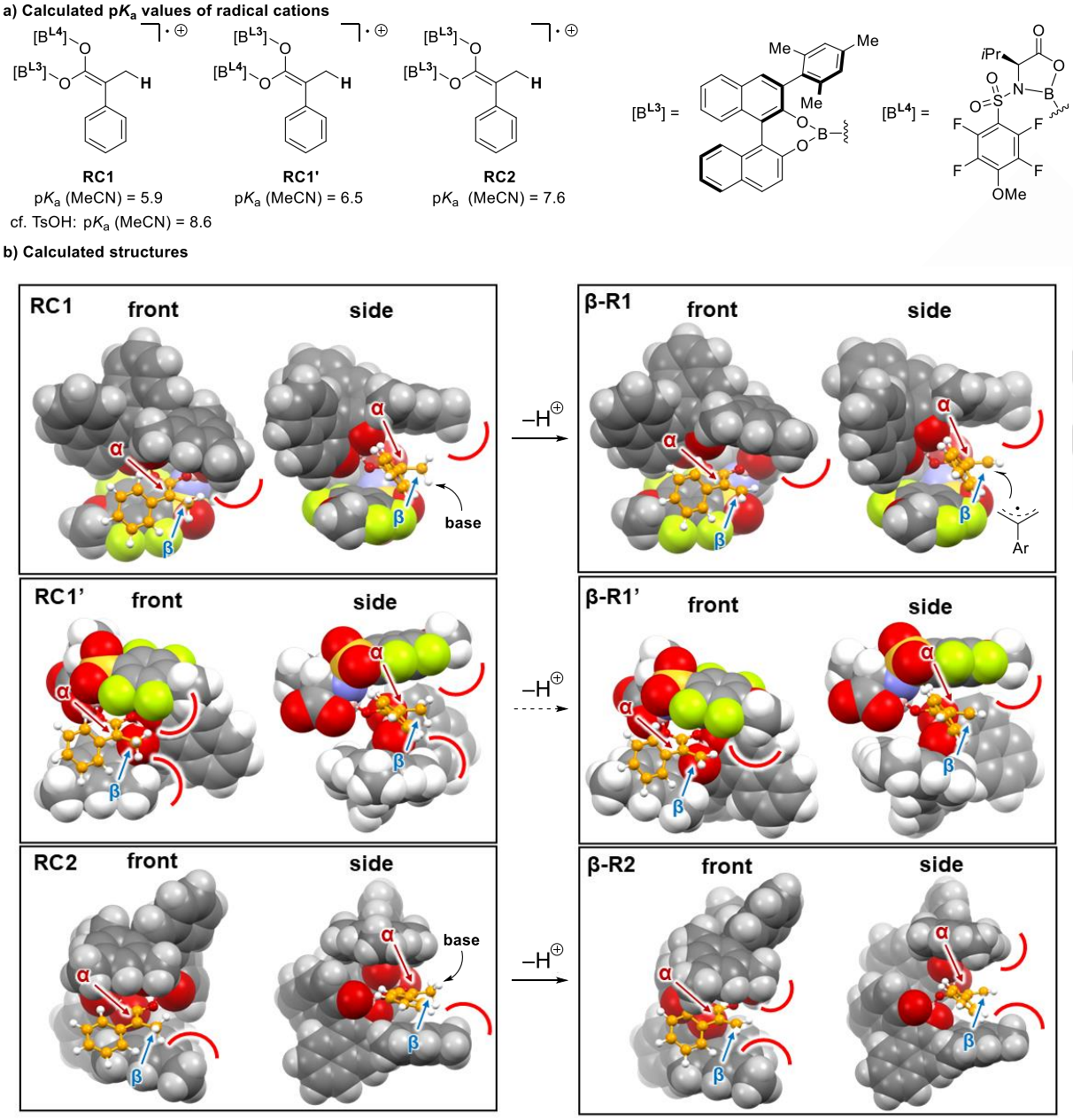
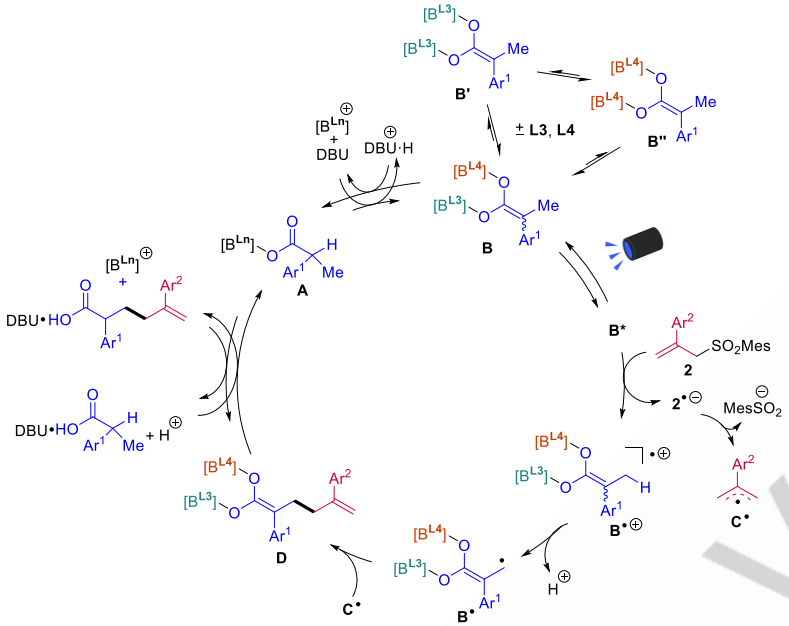


Figure 2. Calculated pK_a values of radical cations and the structures of radical cations and β-radicals.

Based on the experimental and computational results, the following catalytic cycle is conceivable for the boron-catalyzed β-allylation of carboxylic acids (Scheme 5). Deprotonation of in-situ generated boron carboxylate **A** forms a boron enediolate **B**. Since two ligands, **L3** and **L4**, are present in the reaction, three possible combinations should be considered. However, bis-**L3** intermediate **B'** would not be productive due to the above-mentioned steric reason, and bis-**L4** intermediate **B''** is less efficient to be excited by visible-light irradiation as it lacks extended π-systems (see Supporting Information). Hence, the hetero-ligated intermediate **B** is most likely the productive intermediate to proceed forward. Single-electron transfer from the photoexcited species **B*** to allylsulfone **2** generates radical cation $\mathbf{B}^{\bullet+}$ and radical anion $\mathbf{2}^{\bullet-}$, which releases allyl radical $\mathbf{C}^{\bullet}$ through an elimination of the sulfinate anion. On the other hand, deprotonation of radical cation $\mathbf{B}^{\bullet+}$ produces β-radical $\mathbf{B}^{\bullet}$ that couples with $\mathbf{C}^{\bullet}$ to yield the enolate **D**. Finally, protonation of **D** and ligand exchange on the boron atom produced the DBU salt of β-allylated product **5** accompanied by the regeneration of the boron carboxylate **A**.



Scheme 5. Plausible catalytic cycle.

Conclusion

We have developed a visible-light induced, boron-catalyzed direct β-allylation of carboxylic acids. By implementing a two-ligand system consisting of a BINOL-derivative and an amino-acid derivative, the desired selective β-functionalization was able to outcompete the existing α-allylation pathway. Mechanistic experiments provided support for the key role of β-deprotonation, and DFT calculations suggested that the combined use of two ligands is crucial for β-radical generation via electronically facilitating the β-deprotonation as well as for hampering α-allylation by sterically shielding the α-position. The versatility of this catalytic system was demonstrated by the direct derivatization of a wide collection of carboxylic acids, including drug molecules. Moreover, the product can be further converted into multifunctional carboxylic acid compounds, showcasing the capability of the boron catalysis for rapid increment of molecular complexity.

Supporting Information

The authors have cited additional references within the Supporting Information.[52-56]

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Keywords: carboxylic acid • boron catalysis • photochemical reaction • β-allylation • radical

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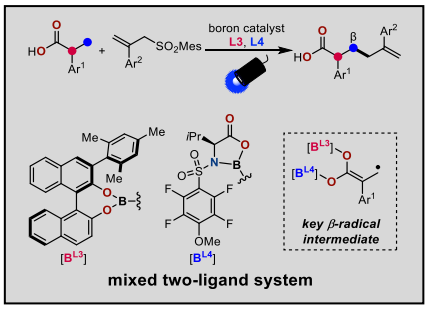
Entry for the Table of Contents



A photoinduced, boron-catalyzed direct β-allylation of carboxylic acids was developed. The mixed two-ligand system, consisting of a binaphthol derivative and a valine derivative, was essential. Photoexcitation of catalytically generated diboron ene-1,1-diolates induces single-electron transfer to the allylsulfones, generating radical cations. Subsequent deprotonation forms β-radicals, enabling C(sp^3)–C(sp^3) bond formation at the β-position.

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