Chemo- and Enantioselective Pd/B Hybrid Catalysis for the Construction of Acyclic Quaternary Carbons: Migratory Allylation of O-Allyl Esters to #-C-Allyl Carboxylic Acids

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J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/jacs.8b02783 • Publication Date (Web): 24 Apr 2018

Chemo- and Enantioselective Pd/B Hybrid Catalysis for the Construction of Acyclic Quaternary Carbons: Migratory Allylation of *O*-Allyl Esters to α-*C*-Allyl Carboxylic Acids

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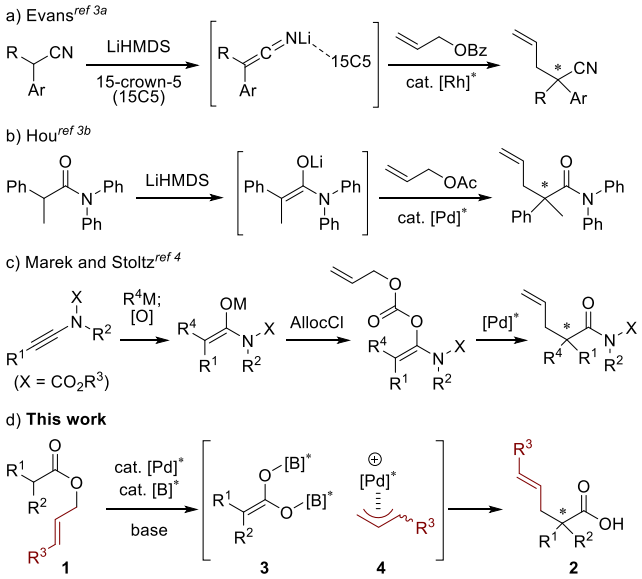
Supporting Information Placeholder

ABSTRACT: We describe herein the asymmetric synthesis of α-allyl carboxylic acids containing an α-quaternary stereocenter by a chiral hybrid catalyst system comprising palladium and boron complexes. The reaction proceeded through palladium-catalyzed ionization of α,α-disubstituted *O*-allyl esters for the generation of chiral π-allyl palladium complex as an electrophile, boron-catalyzed enolization of the carboxylate part for the generation of chiral α,α-disubstituted carboxylic acid-derived enolates as a nucleophile, and enantioselective coupling between the thus-generated nucleophile and electrophile. Proper combinations of chiral ligands for the boron and palladium catalysts were crucial. The reaction proceeded chemoselectively at the α-position of the carboxylic acid group.

Transition metal-catalyzed asymmetric allylic alkylation (AAA) of carbonyl compounds is among the most versatile methods for carbon-skeleton construction of organic molecules concomitant with chirality control. The importance of the reaction is reflected by the number of reports of catalytic AAA reactions of aldehydes, ketones, and 1,3-dicarbonyl compounds (e.g., malonates and β-keto esters).[1] Current major challenges in this reaction category are as follows; (1) expansion of the nucleophile scope to carboxylic acid derivatives containing less acidic α-C–H bonds,[2–6] and (2) construction of all-carbon quaternary stereocenters in acyclic molecules.[3,4,7–9] The methods selected for the generation of geometrically-defined tetrasubstituted enolates or their equivalents in the carboxylic acid oxidation state are critical toward achieving such goals. Evans reported the strategic use of *N*-lithiated prochiral anions derived from α-disubstituted nitriles as equivalents for carboxylic acid-derived enolates (Scheme 1a). Hou reported a reaction using an amide enolate containing a sterically-demanding diphenylamine moiety (Scheme 1b). Stoltz and Marek recently developed an intriguing approach involving the *cis*-carbometalation of ynecarbamates, oxidation, and *O*-allyloxycarbonylation for the generation of geometrically-defined tetrasubstituted *O*-allyloxycarbonyl enolates, followed by a palladium-catalyzed decarboxylative AAA reaction (Scheme 1c).[4] Despite the progress, the functional-group tolerance and atom economy can still be improved. Herein we report an AAA reaction of carboxylic acids promoted by two-component hybrid catalysis comprising palladium and boron complexes that produces α-quaternary carboxylic acids under mild conditions (Scheme 1d).

Scheme 1. Catalytic AAA for the Synthesis of α-Quaternary Carboxylic Acid Derivatives

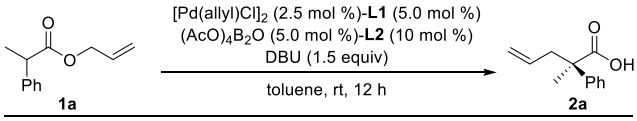


We previously developed a method for chemoselective enolate generation from carboxylic acids using a boron catalyst and amines, enabling carboxylic-acid Mannich and aldol reactions.[10] Chemoselective acidification of the α-C–H bond in carboxylic acid through reversible boron carboxylate formation allowed for the selective generation of a carboxylic acid-derived boron enolate in the presence of a mild amine base. This enolization was applied to a catalytic asymmetric carboxylic-acid Mannich reaction by introducing chiral ligands on the boron atom.[10a] Although the structure of the thus-generated transient boron enolate is unknown, it is hypothesized to be geometrically symmetric diboryl enediolate **3** (Scheme 1d) on the basis of Evans' seminal work.[11] We envisioned that this feature would be advantageous for constructing α-quaternary stereocenters of carboxylic acids, which require geometrically-defined tetrasubstituted enolates.

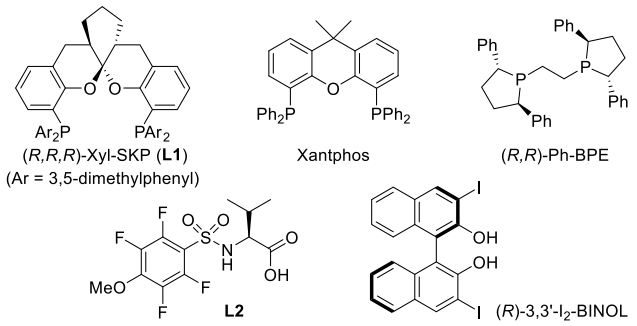
Our reaction design involving Pd/B hybrid catalysis is shown in Scheme 1d.[12,13] We devised allyl esters **1** as a source for both the carboxylic acid and allyl moieties of the target products.[14] Ionization of allyl ester **1** by a palladium catalyst generates π-allylpalladium species **4** concomitant with liberation of the carboxylate moiety, which is trapped and enolized by a boron catalyst and an amine base to generate boryl enediolate **3**. The two reactive species, **3** and **4**, couple to provide α-*C*-allyl carboxylic acid **2**. Because the two asymmetric catalysts cooperate with each

other by introducing independent chiral ligands onto the palladium and boron atoms, respectively, high enantio-induction is possible despite the challenging quaternary carbon construction in an acyclic system.

Table 1. Influence of the Reaction Conditions[a]



entry	deviation from optimized conditions	yield[b]	ee
1[a]	none	(91%)	90%
2	without palladium cat.	0%	-
3	without boron cat.	0%	-
4	xantphos instead of **L1**	92%	30%
5	(*R,R*)-Ph-BPE instead of **L1**	99%	55%
6	without **L2**	99%	32%
7	*ent*-**L2** instead of **L2**	97%	4%
8	(*R*)-3,3'-I_2-BINOL instead of **L2**	22%	69%
9	(*S*)-3,3'-I_2-BINOL instead of **L2**	12%	-
10	BH_3·THF (10 mol %) instead of $(AcO)_4B_2O$	0%	-
11	BCl_3 (10 mol %) instead of $(AcO)_4B_2O$	96%	71%
12	NEt_3 instead of DBU	0%	-
13[c]	*N*-Me-pyrrolidine instead of DBU	55%	97%
14[c,d]	*N*-Me-pyrrolidine instead of DBU	83% (75%)	96%



[a]Optimized reaction conditions: **1a**, $[Pd(allyl)Cl]_2$ (2.5 mol %), **L1** (5 mol %), $(AcO)_4B_2O$ (5 mol %), **L2** (10 mol %), DBU (1.5 equiv), toluene (0.15 M), room temperature, 12 h. Yield was determined by ^1H NMR analysis of a crude mixture using 1,1,2,2-tetrachloroethane as an internal standard. Enantiomeric excess (ee) was determined by chiral HPLC analysis. [b]Yield of isolated product in parenthesis. [c]Reaction time was 24 h. [d]$(AcO)_4B_2O$ (10 mol %) and **L2** (20 mol %) were used.

After intensive studies using allyl α-phenylpropionate (**1a**) as a model substrate, we determined the optimized conditions as shown in Table 1, entry 1 (91% yield, 90% ee); (*R,R,R*)-Xyl-SKP (**L1**)[15] as a ligand for the palladium catalyst, *N*-4-MeO-$C_6F_4SO_2$-L-Val (**L2**) as a ligand for the boron catalyst, and DBU (1.5 equiv) as a base. We identified critical parameters during the optimization studies. First, both the palladium and boron catalysts were essential for promoting the reaction (entries 2 and 3); in the absence of either catalyst component, the reaction did not proceed at all. Second, the combination of **L1** and **L2** was critical for the high yield and enantioselectivity (entries 4–9). Replacing **L1** with an achiral ligand (xantphos, entry 4; 92% yield and 30% ee) or (*R,R*)-Ph-BPE (entry 5; 99% yield and 55% ee) significantly diminished the enantioselectivity. The same tendency was observed for the ligands on the boron atom; omitting or replacing **L2** with other ligands[10a] (entries 6–9) diminished the enantioselectivity and/or yield. Specifically, the chirality matching between the two ligands was critical for the high enantioselectivity; the enantiomeric excess of the product was only 4% when the enantiomer of **L2** (***ent*-L2**; *N*-4-MeO-$C_6F_4SO_2$-D-Val) was used in combination with **L1** (entry 7).

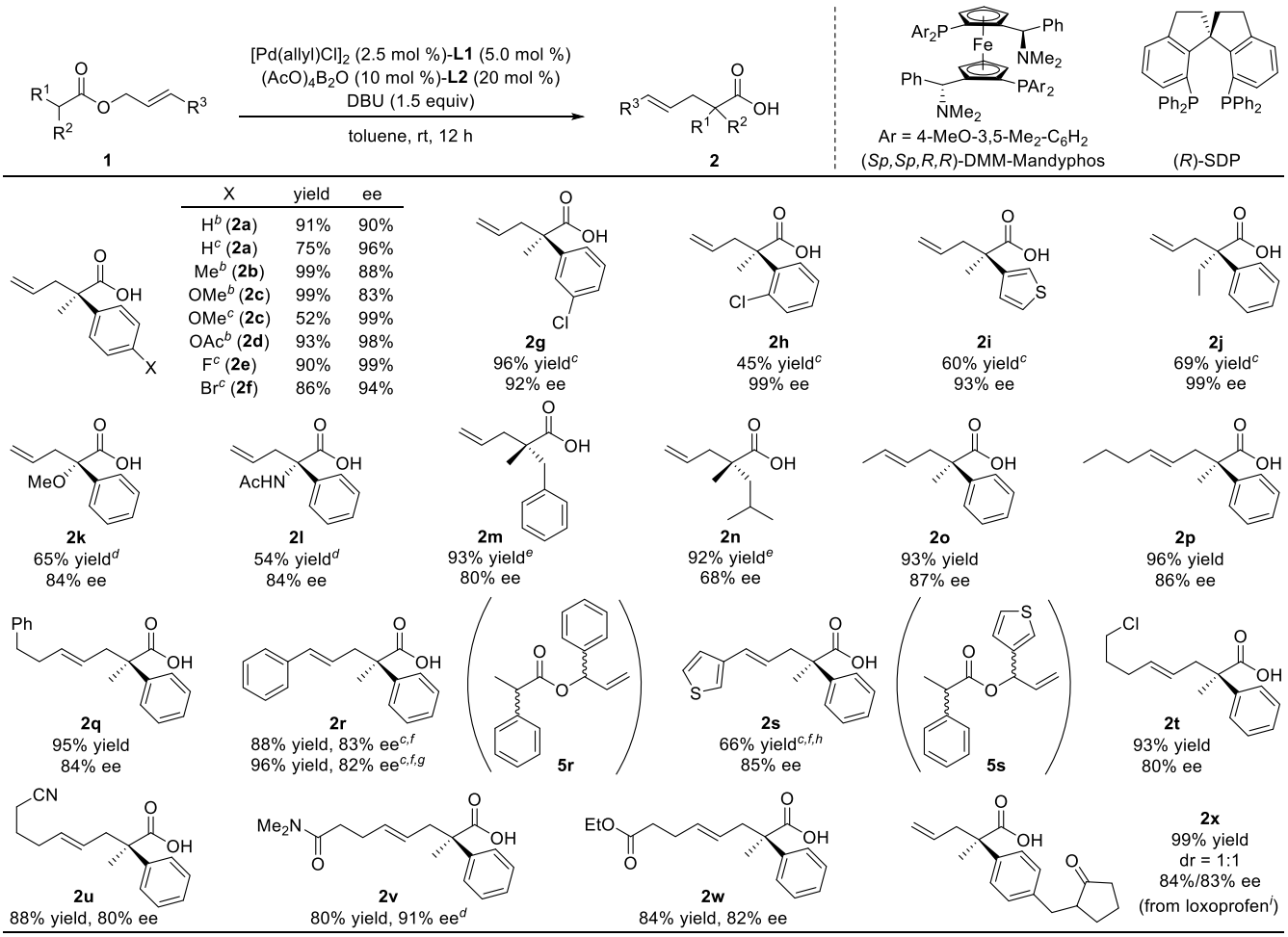
The boron source also affected the reaction (entries 10 and 11). A borane-THF complex (BH_3•THF), which was the best catalyst precursor in Mannich and aldol reactions using carboxylic acids as pronucleophiles,[10] was totally ineffective (entry 10, 0% yield). This was probably because boron carboxylate could not be formed from the carboxylate generated through palladium-catalyzed ionization of **1a**.[13] On the other hand, BCl_3 exhibited reactivity comparable to that of $(AcO)_4B_2O$, although the enantioselectivity was lower (entry 11, 96% yield, 71% ee). Finally, we studied the effects of the base (entries 12–14). Although less basic and sterically-demanding NEt_3 did not promote the reaction (entry 12), sterically less-demanding *N*-methylpyrrolidine provided the product with higher enantioselectivity than DBU (entry 13, 55% yield, 97% ee). The yield was improved by increasing the amount of the boron catalyst (entry 14, 83% yield, 96% ee). Thus, we used either DBU or *N*-methylpyrrolidine as a base, depending on the reactivity of the substrates in the following substrate scope studies.

We then examined the substrate scope of the reaction (Table 2). Because of the unsatisfactory reactivity in most of the substrates compared with **1a**, we increased boron catalyst loading to 10 mol % $(AcO)_4B_2O$ and 20 mol % **L2**, while maintaining the palladium catalyst loading (2.5 mol % $[Pd(allyl)Cl]_2$ and 5 mol % **L1**). Substrates with α-aryl groups containing various substitution patterns and electronic characteristics afforded good reactivity and high enantioselectivity when using the proper base, DBU or *N*-methylpyrrolidine (**2a**–**2i**). The yield of α-ethyl-substituted **2j** was slightly lower than that of α-methyl-substituted **2a**; but the enantiomeric excess of **2j** was higher than that of **2a** (69% yield and 99% ee for **2j** *vs.* 75% yield and 96% ee for **2a**). α-Hetero atom-substituted substrates were also competent (**2k** and **2l**).

α,α-Dialiphatic-substituted ester **1m** is a particularly challenging substrate due to the difficulties in sterically and electronically differentiating the two substituents at the α-carbon, as well as the greater pK_a value of the α-proton compared with α-aryl-substituted substrates. The standard combination of chiral ligands **L1** and **L2** was not effective; **2m** was obtained up to 23% yield at 60 °C. Further exploration of the chiral ligands revealed that (S_p,S_p,*R,R*)-DMM-Mandyphos was the best ligand for the palladium catalyst in combination with ***ent*-L2** for the boron catalyst; **2m** was obtained in 93% yield with 80% ee. The same conditions were applicable to **1n**, providing **2n** in 92% yield with 68% ee.

When the allyl group contained an aliphatic substituent (R^3 = aliphatic), the reaction proceeded under the standard conditions with complete terminal position-selectivity of the allyl group (**2o**, **2p**, and **2q**). When R^3 was an aromatic group (**2r** and **2s**), however, (*R*)-Ph-SDP afforded better results than **L1**.[16] It should be noted that **5r**, which contains a branched allyl group as a 1:1 diastereomixture, can be convergently transformed to linear **2r** with high enantioselectivity comparable to that obtained when using linear allyl ester **1r** as the starting material. This result supports our hypothesis that the reaction proceeds *via* two independent active species, boron enolate **3** and π-allyl palladium **4**, and not *via* Ireland-Claisen rearrangement (see below).

Table 2. Substrate Scope[a]



[a]General reaction conditions: **1** (300 μmol), $[Pd(allyl)Cl]_2$ (7.5 μmol), **L1** (15 μmol), $(AcO)_4B_2O$ (30 μmol), **L2** (60 μmol), DBU (450 μmol), toluene (2.0 mL), room temperature, 12 h. Isolated yield is shown. [b]$(AcO)_4B_2O$ (5 mol %) and **L2** (10 mol %) were used. [c]*N*-Me-pyrrolidine was used instead of DBU and the reaction time was 24 h. [d]Isolated yield was determined after conversion of the product into methyl ester. [e](S_p,S_p,*R*,*R*)-DMM-Mandyphos and *ent*-**L2** were used instead of **L1** and **L2**, respectively. [f](*R*)-Ph-SDP was used instead of **L1**. [g]From **5r**. The reaction time was 20 h. [h]From **5s**. [i]1:1 diastereomixture.

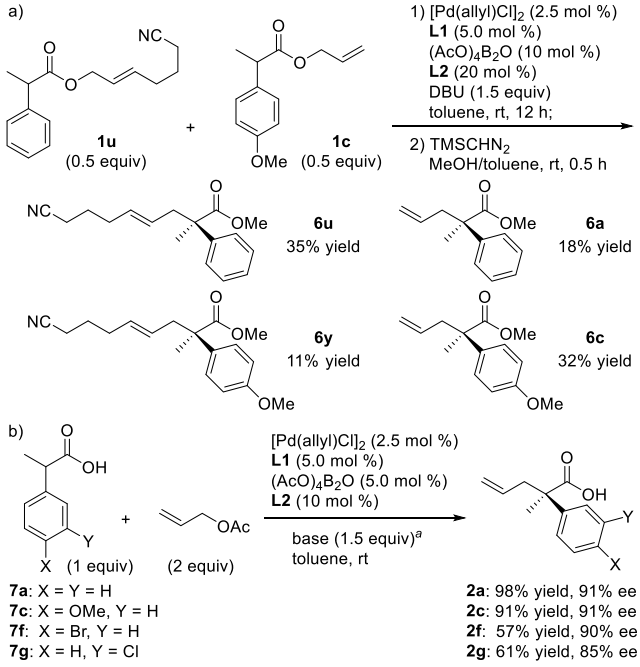
Next, we assessed the functional group compatibility. The alkyl chloride group was intact; byproducts derived from elimination or substitution of the chloride, which should proceed under strongly basic conditions, were not observed at all (**2t**).[17] Other enolizable functional groups, i.e., nitrile (**1u**), amide (**1v**), ester (**1w**), and ketone (**1x**), were all compatible. Importantly, the allyl group was introduced chemoselectively at the α-position of the carboxylic acid functionality. This selectivity is due to chemoselective enolate formation from the carboxylic acid moiety by the boron catalyst. The conditions were applicable to an anti-inflammatory drug, loxoprofen (**1x**), indicating that this method can be used for late-stage structural diversification of drug lead compounds.

Because the reaction is a formal rearrangement, we assessed whether or not the allyl transfer is an intramolecular process. We conducted a shuffling experiment under the standard conditions using an equimolar mixture of **1u** and **1c** (Scheme 2a). The reaction produced all four possible products, **6u**, **6a**, **6y**, and **6c** in excellent total yield (96%). This result indicates that the lifetimes of boron enolate **3** and π-allyl palladium **4**, generated through ionization of allyl ester substrate **1**, were long enough to escape from the solvent cage and combine in an intermolecular fashion.

This finding led us to investigate an intermolecular variant of the catalytic enantioselective α-*C*-allylation of carboxylic acids **7** using allyl acetate as an allyl donor (Scheme 2b). The reaction proceeded under the standard conditions for migratory allylation shown in Table 2, and the enantioselectivity of the products was comparable between the two conditions.[18] These results support our notion that both the migratory allylation in Table 2 and intermolecular allylation in Scheme 2b proceed through the same reactive species (**3** and **4**).

In summary, we developed a boron/palladium hybrid catalysis for an asymmetric migratory α-*C*-allylation of allyl esters. The combined use of two distinct chiral catalysts allowed us to fine tune the asymmetric environment during C–C bond formation for the construction of acyclic chiral quaternary carbon centers with generally high enantioselectivity. The allylation reaction proceeded chemoselectively at the α-position of the carboxylic acid functionality despite the presence of intrinsically more-readily enolizable functional groups such as nitrile, amide, ester, and ketone. The finding might be useful for late-stage, chemoselective asymmetric introduction of an allyl group into multifunctional molecules.

Scheme 2. Support for the Intermolecular Nature of the Allylation Step and Application to Intermolecular AAA



[a]For **7a** and **7c**, base = DBU, 12 h. For **7f** and **7g**, base = *N*-Me-pyrrolidine, 24 h.

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.

ACKNOWLEDGMENT

This work was supported by JSPS KAKENHI Grant Number JP17H06442 (MK) (Hybrid Catalysis), Grant-in-Aid for Scientific Research (C) from JSPS (YS), and the research grant of Astellas Foundation for Research on Metabolic Disorders (YS). TF and HC thank Tobe Maki Scholarship and Kobayashi International Scholarship, respectively, for their fellowships.

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(16) When **L1** was used, **2r** was obtained in 85% yield and 70% ee.

(17) When the corresponding substrate containing more reactive bromide was used, however, the target product was not obtained.

(18) Substrate scope of the intermolecular reaction is slightly narrower than migratory allylation. See SI for more details.