COMMUNICATION

Cp*Rh(III)/Boron Hybrid Catalysis for Directed C–H Addition to β-Substituted α,β-Unsaturated Carboxylic Acids

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The C–H bond addition reaction of 2-phenylpyridine derivatives with α,β-unsaturated carboxylic acids catalyzed by Cp*Rh(III)/BH_3·SMe_2 is reported. Activation of C–H bonds with the rhodium catalyst and activation of α,β-unsaturated carboxylic acids with the boron catalyst cooperatively work, and a BINOL-urea hybrid ligand significantly improved the reactivity. With the optimized hybrid catalytic system, various β-disubstituted carboxylic acids were obtained under mild reaction conditions.

Directed C–H functionalization is a powerful tool that enables streamlined syntheses of valuable organic molecules from readily available feedstocks.[1] Trivalent group 9 transition metals bearing pentamethylcyclopentadienyl ligands (Cp*) are versatile and highly active catalysts for directed C–H functionalization.[2] Among a wide variety of reported reactions that employ these catalysts, the formal conjugate addition of aromatic C–H bonds to electron-deficient olefins is an atom- and step-economical synthetic method for alkylated arenes.[3,4] Although these C–H addition reactions have been well-studied over the last decade, the use of α,β-unsaturated carboxylic acids as alkylating agents has received limited attention[5-7] despite the carboxy group being an important and fundamental functional group in organic synthesis. In 2019, Han, Hu, and co-workers reported the C–H alkylation of 2-phenylpyridines with coumarin-3-carboxylic acids, in which a decarboxylation takes place under the reaction conditions (Fig. 1a).[5] Satoh and co-workers reported a Cp*Rh(III)-catalyzed addition of benzamide C–H bonds to the highly electron-deficient α-trifluoromethylacrylic acid in 2020 (Fig. 1a).[6] In both these cases, the α,β-unsaturated carboxylic acids require an additional electron-withdrawing group. Gooßen and co-workers reported a Ru(II)-catalyzed C–H alkylation of benzoic acids, in which a sterically accessible non-substituted acrylic acid was required (Fig. 1b).[7] The limitations of these reactions prompted us to seek a new catalytic system to enable redox-neutral directed C–H alkylations using more general β-substituted α,β-unsaturated carboxylic acids.

Catalytic activation of a carboxy group using a boron reagent/catalyst via the formation of acyloxyboranes has emerged as an attractive method for the functionalization and derivatization of carboxylic acids.[8-14] The electrophilicity of α,β-unsaturated carboxylic acids is also enhanced by this approach (Fig. 1c).[9-12] In 1988, Yamamoto and co-workers reported BH_3•THF-catalyzed Diels–Alder reactions between α,β-unsaturated carboxylic acids and dienes via an acyloxy-borane intermediate.[9] Hall and co-workers demonstrated that aryl boronic acids are efficient catalysts for similar Diels–Alder and cycloaddition reactions.[10] The Takemoto group has developed chiral catalytic systems composed of a boronic acid, thiourea, and amine for asymmetric hetero-Michael addition reactions between α,β-unsaturated carboxylic acids and a variety of nucleophiles.[11] The Ishihara group has reported asymmetric Michael additions between ketones and α,β-unsaturated carboxylic acids catalyzed by a boronic acid and a chiral amine.[12] Inspired by these previous works, we envisaged that the combination a Cp*Rh(III) catalyst and a boron catalyst would enable the directed addition of a C–H bond to various α,β-unsaturated carboxylic acids (Fig. 1d).

Our investigation started with the reaction of model substrates 2-phenylpyridine **1a** and α,β-unsaturated carboxylic acid **2a** in the presence of the metal catalyst $[Cp^*RhCl_2]_2$/$AgSbF_6$, and the boron precatalyst BH_3·SMe_2 (Table 1). Solvent screening (entries 1–5) revealed that the desired product **3aa** was obtained when using DMF at 50 °C, albeit in a low yield (entry 5). Other solvents were not suitable for this reaction. We next examined other boron catalysts, such as $B(OH)_3$, $PhB(OH)_2$, and $(AcO)_4B_2O$, but the desired reaction did not proceed (entries 6–8). In the absence of BH_3·SMe_2, **3aa** was not obtained, indicating that activation of **2a** with the boron catalyst is essential for a successful reaction (entry 9). To improve the reactivity, we added a ligand for the boron catalyst. When we used Ts-L-Val -

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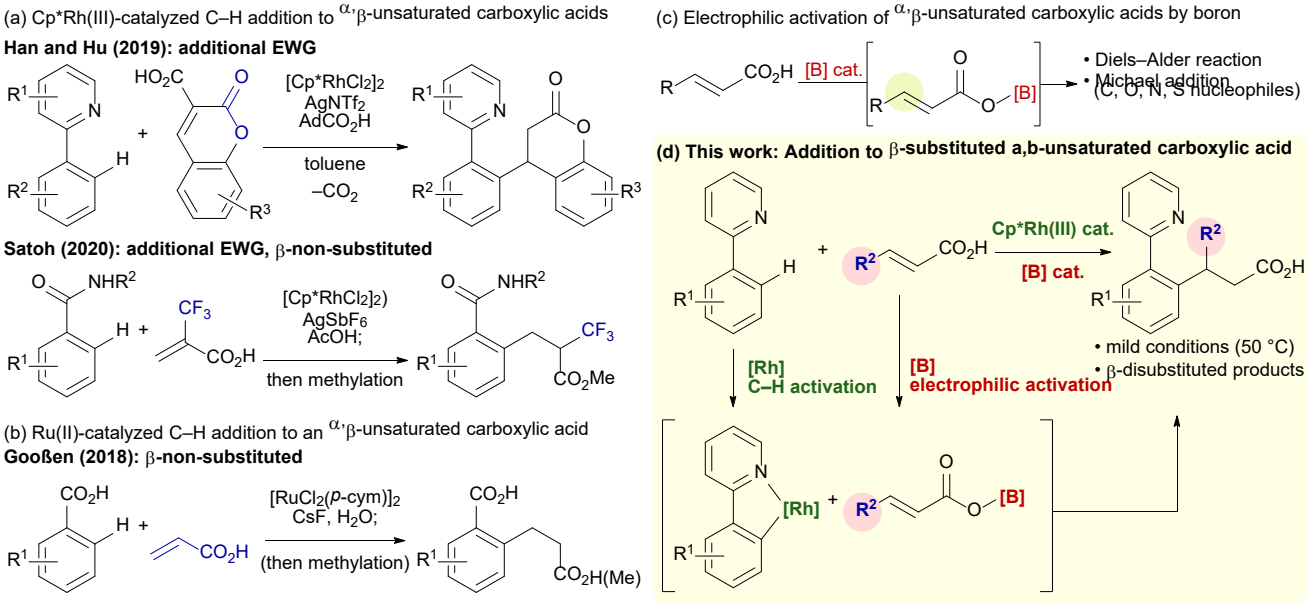
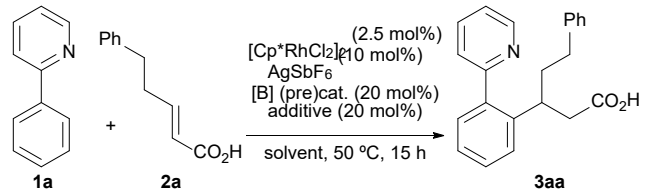


Fig. 1 (a)(b) Previous examples of directed C–H addition to α,β-unsaturated carboxylic acids; (c) boron catalysis for activation of α,β-unsaturated carboxylic acids; (d) the reaction presented in this work.

Table 1 Optimization of the reaction conditions for the C–H addition reaction of **1a** with **2a**.[a]



Entry	[B] (pre)cat.	Additive	Solvent	Yield (%)[b]
1	$BH_3{\cdot}SMe_2$	–	DCE	0
2	$BH_3{\cdot}SMe_2$	–	Toluene	0
3	$BH_3{\cdot}SMe_2$	–	1,4-dioxane	0
4	$BH_3{\cdot}SMe_2$	–	HFIP	0
5	$BH_3{\cdot}SMe_2$	–	DMF	7
6	$B(OH)_3$	–	DMF	0
7	$PhB(OH)_2$	–	DMF	0
8	$(AcO)_4B_2O$	–	DMF	0
9	–	–	DMF	0
10	$BH_3{\cdot}SMe_2$	Ts-L-Val	DMF	52
11	$BH_3{\cdot}SMe_2$	(*S*)-BINOL	DMF	32
12	$BH_3{\cdot}SMe_2$	**4**	DMF	20
13	$BH_3{\cdot}SMe_2$	**4** + (*S*)-BINOL	DMF	48
14	$BH_3{\cdot}SMe_2$	**5**	DMF	86
15	–	**5**	DMF	0
16	$BH_3{\cdot}SMe_2$	***rac*-5**	DMF	73

[a] The reactions were run using **1a** (0.1 mmol), **2a** (0.1 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol%), $AgSbF_6$ (10 mol%), boron catalyst (20 mol%), and an additive in the indicated solvent (0.5 M). [b] Determined by ^1H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard

(entry 10) or (*S*)-BINOL (entry 11), the reactivity was greatly enhanced, as reported by Shimizu, Kanai, and co-workers,[14b,c]

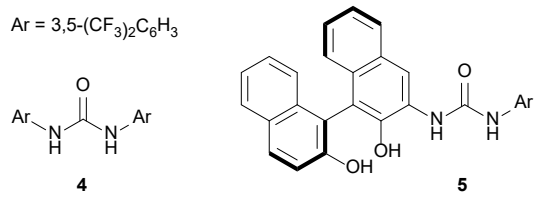
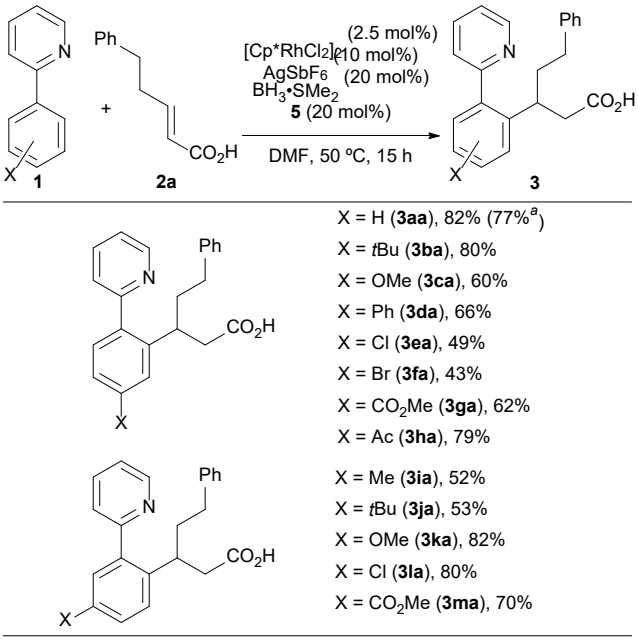


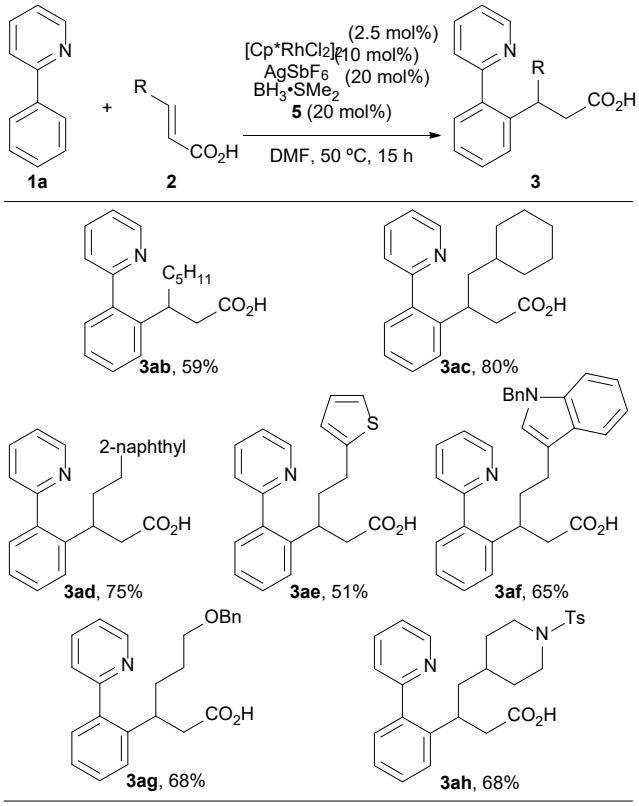
Fig. 2 Structure of additive/ligand used in Table 1.

and **3aa** was obtained in 52% and 32% yield, respectively. We also investigated the effect of adding urea **4** (Fig. 2), which can potentially activate an acyloxyborane intermediate via hydrogen bonding.[11] As expected, urea **4** improved the product yield, with respect to entry 5, to 20% (entry 12). The combination of **4** and (*S*)-BINOL led to a further improvement of the reactivity (entry 13). Following this promising result, we synthesized a BINOL-urea hybrid ligand **5** (Fig. 2; see the ESI for details) and examined its catalytic activity. To our delight, the yield increased to 86% when this new ligand was used (entry 14). We confirmed that, even when using **5**, no reaction proceeded in the absence of $BH_3{\cdot}SMe_2$ (entry 15), while a racemic BINOL-urea ligand (***rac*-5**) exhibited a similar reactivity (entry 16). Under these conditions, the second C–H alkylation from **3aa** was not observed possibly due to the relatively low reaction temperature (50 °C).

Under the optimized reaction conditions, we examined the scope of the 2-aryl pyridines (Scheme 1). The desired products were successfully isolated without esterification of the carboxy group. 2-Aryl pyridines bearing various substituents provided the corresponding products **3** in moderate to good yields. The reaction tolerated *t*-Bu (**3ba**, **3ja**), methoxy (**3ca**, **3ka**), halogen (**3ea**, **3fa**, **3la**), and carbonyl (**3ga**, **3ha**, **3ma**) substituents at both the *para* and *meta* positions. In case the substrate had a *meta*-substituent, the sterically less hindered C–H bond was



Scheme 1 Scope of 2-aryl pyridines. The reactions were run using **1** (0.3 mmol) and **2a** (0.3 mmol). [a] 1 mmol scale.



Scheme 2 Scope of α,β-unsaturated carboxylic acids. The reactions were run using **1a** (0.3 mmol) and **2** (0.3 mmol).

selectively functionalized (**3ia**–**3ma**). When we performed a preparative-scale (1 mmol) reaction using **1aa** as the substrate, **3aa** was obtained without significant loss of yield.

Subsequently, the scope of the α,β-unsaturated carboxylic acids was examined (Scheme 2). An α,β-unsaturated carboxylic

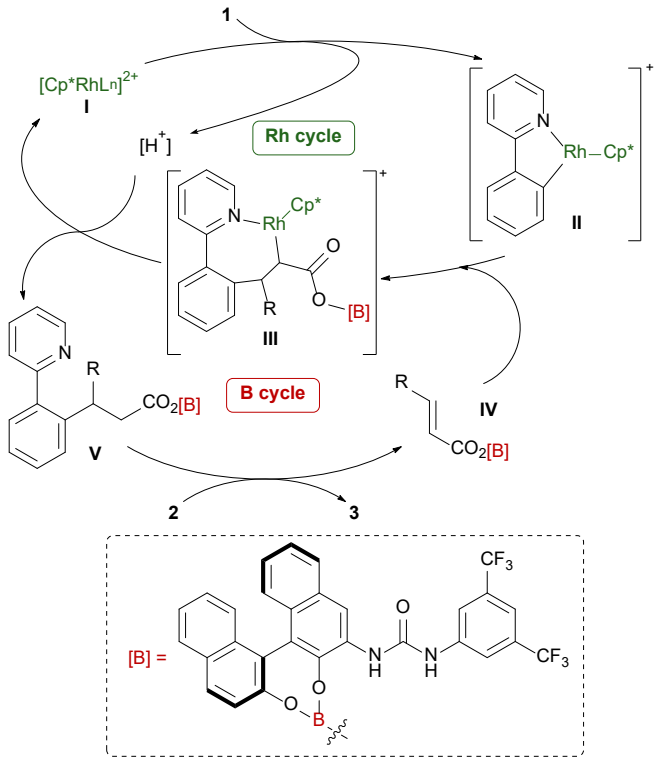


Fig 3. A hypothetical catalytic cycle.

acid bearing a linear alkyl group (**2b**) afforded **3ab** in 59% yield. The reaction also proceeded smoothly when using a carboxylic acid bearing a sterically hindered branched alkyl group (**3ac**). α,β-Unsaturated carboxylic acids bearing a naphthyl group or a heterocycle, such as a thiophene or indole, are also compatible under these reaction conditions, providing the desired products in moderate to good yields (**3ad**–**3af**). A Bn-protected alcohol and a Ts-protected amine were also tolerated and afforded the desired products in moderate yields (**3ag**, **3ah**). On the other hand, 3,3-dimethylacrylic acid, which bears two β-substituents, did not afford the desired product under the same conditions.

A hypothetical catalytic cycle is shown in Fig. 3. An active rhodium species (**I**) is generated from $[Cp^*RhCl_2]_2$ and $AgSbF_6$ and reacts with **1** to form metallacycle **II** via deprotonative C–H activation. Meanwhile, $BH_3{\cdot}SMe_2$ would react with **2** and **5** to form an active electrophile (**IV**), which coordinates to **II** and inserts into the C–Rh bond to produce **III**. Protonation of **III** and subsequent dissociation regenerates **I** with concomitant release of **V**. Finally, a B–O bond exchange reaction between **V** and **2** affords the product **3** and regenerates **IV**.[9-12] Although the role of the urea functional group of **5** has not yet been experimentally proved, we expect that intramolecular hydrogen bonding with the carbonyl group in intermediate **IV** might enhance the reactivity of the electron-deficient C–C double bond. A computational conformation search of **IV** (R = CH_2CH_2Ph; **2a**) at a the semi-empirical level suggested that most of stable conformers involve similar intermolecular hydrogen bonding The most stable conformation was further optimized

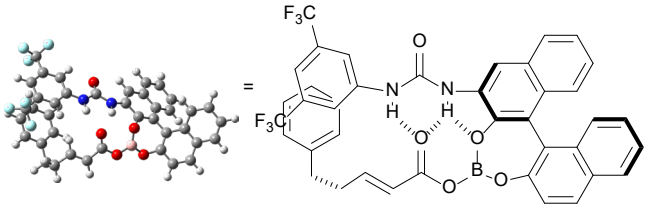


Fig 4. Calculated structure of acyloxyborane intermediate **IV**.

by DFT calculation (see the ESI for details) and the structure is shown in Fig 4. In addition to hydrogen bonding activation of the carbonyl group by the urea, the NH moiety can interact with the phenolic oxygen, which can also enhance the Lewis acidity of the borane catalyst.[15] Meanwhile, the current catalytic system, unfortunately, only produced a racemic product, which can be rationalized by the rather planar structure of **IV** and large distance between the binaphthyl chirality and the reactive β-carbon.

In summary, we have demonstrated that a combination of Cp*Rh(III)/boron/BINOL-urea catalytic system enables the directed addition of an aryl C–H bond to β-substituted α,β-unsaturated carboxylic acids, which provides β-disubstituted carboxylic acids. The hybrid catalysis was essential to realize this transformation under mild reaction conditions. Although a 2-pyridyl directing group is required and additional tuning of the catalytic system and reaction conditions would be necessary for expanding the substrate scope to more synthetically valuable molecules, the current results may lead to the further development of novel hybrid catalytic systems that facilitate the use of β-substituted α,β-unsaturated carboxylic acids for metal-catalyzed C–H functionalization reactions.

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