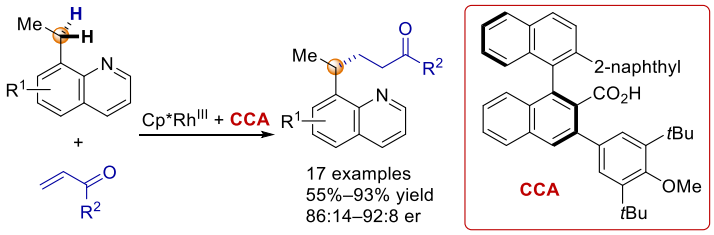
Rhodium(III)/Chiral Carboxylic Acid-Catalyzed Enantioselective C(sp^3)–H Alkylation of 8-Ethylquinolines with α,β-Unsaturated Carbonyl Compounds.

Long-Tao Huang,† Seiya Fukagawa,† Masahiro Kojima,† Tatsuhiko Yoshino,†,* Shigeki Matsunaga†,‡,*

†Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060-0812, Japan.

‡Global Station for Biosurfaces and Drug Discovery, Hokkaido University, Sapporo 060-0812, Japan.

Supporting Information Placeholder



ABSTRACT: The enantioselective C–H alkylation of 8-ethylquinolines with enones or acrolein using a Rh^{III} catalyst and a chiral carboxylic acid is described. Under mild reaction conditions, a binaphthyl-based chiral carboxylic acid enables the enantioselective cleavage of the 8-ethylquinoline C(sp^3)–H bond. The obtained results demonstrate the utility of the combination of a high-valent group 9 metal catalyst and a chiral carboxylic acid for the enantioselective C(sp^3)–H activation and the subsequent C–C bond formation.

In the pursuit of atom-[1] and step-economical[2] organic reactions, direct functionalization of chemically inert C–H bonds has been extensively studied over the past few decades.[3] A wide range of transition metal catalysts have been studied for such C–H functionalization reactions. Among these, high-valent group 9 metals (Co, Rh, Ir) with a pentamethylcyclopentadienyl ligand (Cp*), which exhibit high reactivity, stability, and functional group tolerance, have played a crucial role in the development of such reactions.[4] Following the pioneering work by Cramer and co-workers on the design of chiral Cp^x ligands[5] as well as that by Ward, Rovis, and co-workers on artificial metalloenzymes in 2012,[6] catalytic enantiocontrol using these catalysts has become a priority.[7,8] Whilst the dominant strategy to achieve enantiocontrol has been focused on the development and application of chiral Cp^x ligands,[9] more recent reports have revealed that external chiral sources can effectively control enantioselectivity without the need for a chiral Cp^x ligand.[7c,d,10-13] As C–H activation by high-valent electrophilic transition metals often proceeds via a carboxylate-assisted deprotonation mechanism (AMLA/CMD/BIES),[14] the chiral carboxylic acid-assisted selective functionalization of enantiotopic C–H bonds has been investigated by several research groups, including ours.[10,15] Although the introduction of chiral Cp^x ligands, chiral carboxylic acids (CCAs), and other chiral sources has enabled various enantioselective C(sp^2)–H functionalization reactions (**Figure 1a**), there have been fewer reports on the enantioselective functionalization of less reactive C(sp^3)–H bonds.[10c,e-g,16] In this context, we recently reported the Co^{III}/CCA-catalyzed C–H amidation of thioamides[10c,e] and the Rh^{III}/CCA-catalyzed amidation of 8-alkylquinolines (**Figure 1b**).[10f] However, the enantioselective C–C bond-forming reactions via C(sp^3)–H activation using high-valent group 9 metal catalysts for the construction of carbon skeletons of chiral organic molecules have not yet been reported.

Herein, we report the Rh^{III}/CCA-catalyzed enantioselective C(sp^3)–H alkylation of 8-ethylquinolines (**1**) with α,β-unsaturated ketones or acrolein (**2**, **Figure 1c**). Catalytic C–H activation and a subsequent addition to an electron-deficient olefin, Michael acceptor, can be regarded as a conjugate addition with the formal transfer of a non-acidic proton. This atom-economical transformation has been achieved using several transition metal catalysts, including Rh^{III} and Co^{III} catalysts.[17] The C–H alkylation of 8-alkylquinolines with Michael acceptors was first reported by Kim and co-workers using a Rh^{III} catalyst in 2016.[18a] Since then, similar conjugate addition reactions of 8-alkylquinolines have been developed using either Rh^{III} or Co^{III} catalysts.[18,19] These precedents for the racemic reactions, combined with our previous work on the enantioselective C–H amidation of 8-alkylquinolines,[10f] prompted us

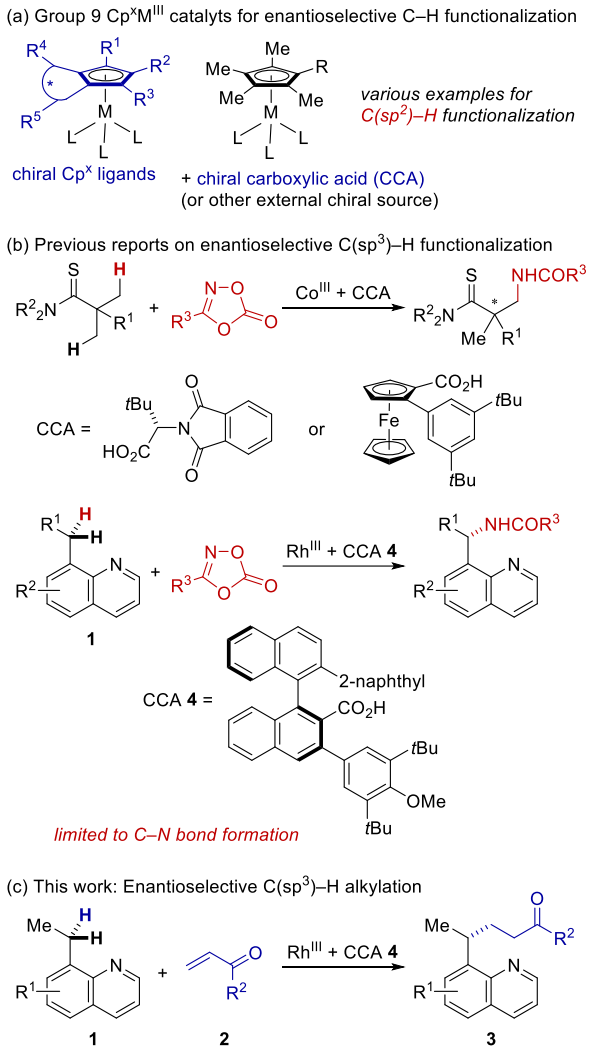
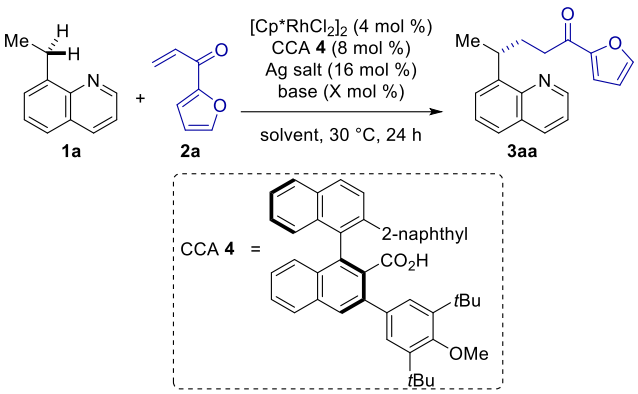


Figure 1. Enantioselective C–H functionalization reactions using high-valent group 9 metal catalysts.

to investigate the enantioselective conjugate addition of 8-ethylquinolines.

Our investigation started with application of the combination of $[Cp^*RhCl_2]_2$ and CCA **4**,[10f] which has previously exhibited good enantioselectivity for the C–H amidation of 8-ethylquinoline (**1a**), to the reaction of **1a** and vinyl ketone **2a** (**Table 1**, entry 1). To our satisfaction, the desired alkylated product (**3aa**) was obtained in promising enantioselectivity (87:13), albeit in low yield. With this result in hand, we subsequently screened the reaction conditions to enhance the reactivity. We first examined a variety of cationic silver salts, which abstract chloride ligands from $[Cp^*RhCl_2]_2$. While $AgSbF_6$, $AgPF_6$, and $AgNTf_2$ afforded similar results (entries 1, 2, 4), the use of AgOTf significantly diminished the reactivity (entry 3), probably due to the comparatively high coordinating ability of the triflate anion. Due to the enantioselectivity exhibited in entry 2, $AgPF_6$ was selected for the subsequent screening of the reaction solvent (entries 5–9). Unfortunately, all examined reactions resulted in lower yields when any solvent other than PhCl was used. Although substituting Ag_2CO_3 with other carbonates decreased reactivity (entries 10–12), increasing the amount of Ag_2CO_3 drastically improved the

Table 1. Optimization of the reaction conditions.[a]

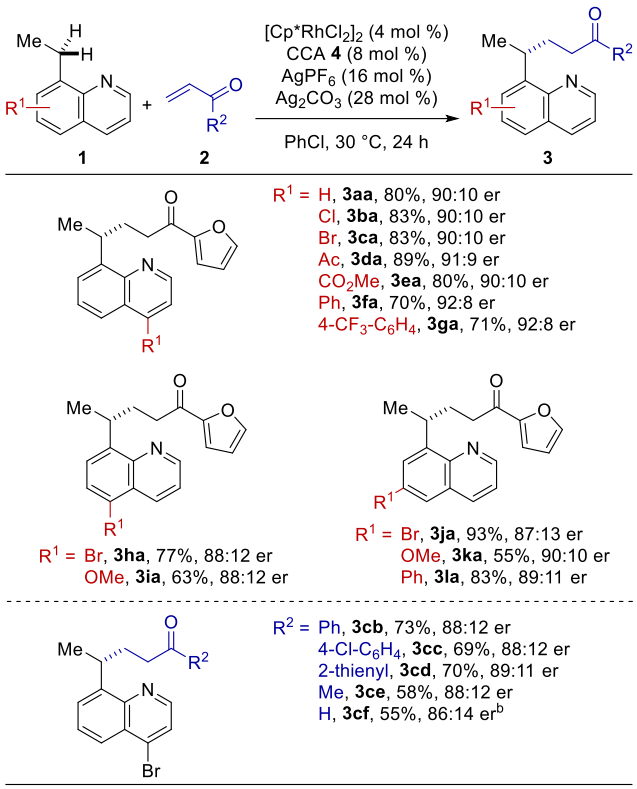


Entry	Ag salt	Base (mol %)	Solvent	Yield[b] (%)	Er[c]
1	$AgSbF_6$	Ag_2CO_3 (4)	PhCl	26	87:13
2	$AgPF_6$	Ag_2CO_3 (4)	PhCl	30	89:11
3	AgOTf	Ag_2CO_3 (4)	PhCl	0	n.d.
4	$AgNTf_2$	Ag_2CO_3 (4)	PhCl	38	88:12
5	$AgPF_6$	Ag_2CO_3 (4)	CH_2Cl_2	10	85:15
6	$AgPF_6$	Ag_2CO_3 (4)	DCE	17	85:15
7	$AgPF_6$	Ag_2CO_3 (4)	THF	6	88:12
8	$AgPF_6$	Ag_2CO_3 (4)	Toluene	25	89:11
9	$AgPF_6$	Ag_2CO_3 (4)	HFIP	<5%	n.d.
10	$AgPF_6$	Na_2CO_3 (4)	PhCl	15	89:11
11	$AgPF_6$	K_2CO_3 (4)	PhCl	8	89:11
12	$AgPF_6$	Cs_2CO_3 (4)	PhCl	12	88:12
13	$AgPF_6$	Ag_2CO_3 (28)	PhCl	80	89:11
14	$AgPF_6$	Na_2CO_3 (28)	PhCl	8	89:11
15	$AgPF_6$	K_2CO_3 (28)	PhCl	18	89:11
16	$AgPF_6$	Cs_2CO_3 (28)	PhCl	4	89:11
17	$AgNTf_2$	Ag_2CO_3 (28)	PhCl	56	89:11
18[d]	$AgPF_6$	Ag_2CO_3 (28)	PhCl	57	90:10
19[e]	$AgPF_6$	Ag_2CO_3 (28)	PhCl	80[f]	90:10

[a]Reaction conditions (unless otherwise stated): **1a** (0.05 mmol), **2a** (0.10 mmol), $[Cp^*RhCl_2]_2$ (0.002 mmol), CCA **4** (0.004 mmol), Ag salt, and base in the indicated solvent (0.5 mL) at 30 °C. [b]Determined by ^1H NMR analysis of the crude mixture using 1,1,2,2-tetrabromoethane as the internal standard. [c]Determined by chiral HPLC analysis. [d]The reaction was performed at 4 °C for 48 h. [e]The reaction was performed in 0.20 mmol (for **1a**) scale. [f]Isolated yield.

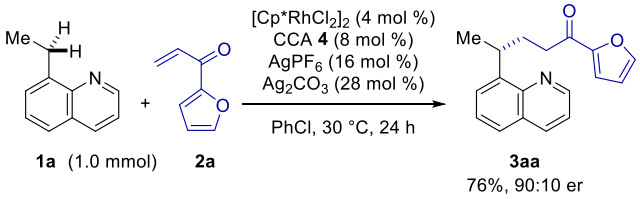
reactivity without compromising the enantioselectivity (entry 13). In contrast, the addition of the increased amount of other carbonate bases resulted in decreased reactivity (entries 14–16). We again tested $AgNTf_2$, which provided slightly better yield than $AgPF_6$ (entries 2 and 4), but no improvement was observed at this point (entry 17). Decreasing the reaction temperature to 4 °C significantly deteriorated the reaction rate with only negligible improvement of the selectivity (entry 18).

Scheme 1. Substrate scope of Rh^{III}/CCA 4-catalyzed enantioselective C(sp^3)–H alkylation reactions of 1.[a]



[a]Reaction conditions: **1** (0.20 mmol), **2** (0.40 mmol), $[Cp^*RhCl_2]_2$ (0.008 mmol), CCA **4** (0.016 mmol), $AgPF_6$ (0.0032 mmol), and Ag_2CO_3 (0.056 mmol) in PhCl (2 mL) at 30 °C for 24 h. Isolated yields after chromatographic purification were given. [b]The reaction was performed using **2f** (0.60 mmol) at 5 °C for 48 h.

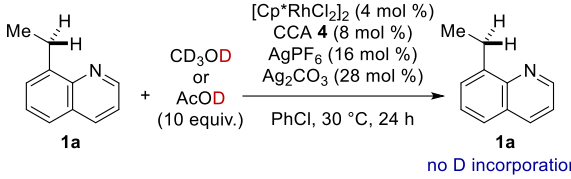
Scheme 2. Preparative scale reaction.



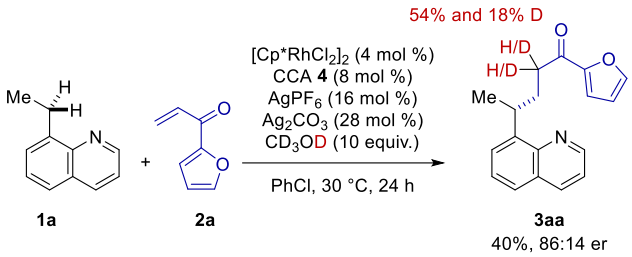
Finally, **3aa** was isolated in 80% yield with 90:10 er under the optimized conditions shown in entry 19.

We next examined the substrate scope of the reaction with respect to 8-ethylqunolines (**1**) and the α,β-unsaturated carbonyl compounds (**2**) (Scheme 1). 8-Ethylquinolines that bear various substituents at the 4-, 5-, or 6-positions provided the corresponding alkylated products (**3aa**–**3la**) in 55%–93% yield with 87:13–92:8 er. Halogen- and carbonyl-substituted substrates are well tolerated under these reaction conditions (**3ba**–**3ea**, **3ha**, **3ja**), offering the opportunity for further manipulation and derivatization of the products. When the electrophile was changed to other α,β-unsaturated carbonyl compounds, moderate to good yields with similarly good enantioselectivities were observed (**3cb**–**3cf**). In addition to enones, the relatively unstable acrolein (**2f**) afforded the desired

Scheme 3. H/D exchange experiments.



Scheme 4. Deuterium incorporation to the product.



product (**3cf**) in 55% yield and 86:14 er when the reaction was performed at 5 °C. We also performed a reaction between **1a** and enone **2a** on a preparative 1.0 mmol scale, which furnished **3aa** in 76% yield and 90:10 er (Scheme 2). Unfortunately, 8-propylquinline and 8-pentylquinoline are less reactive under the current conditions and failed to give the products in synthetically meaningful yield. We also examined other electron-deficient olefins as well as dimethyl diazomalonate as the alkylation reagents, but none of them are successful (See Supporting Information for the details).

To clarify the enantio-determining step of these reactions, the reversibility of the C–H activation was examined (Scheme 3). When **1a** was reacted with CD_3OD or AcOD under the optimized reaction conditions except that **2** was omitted, almost no H/D exchange was observed, indicating that the C–H activation is irreversible. Although CCAs or chiral sulfonates can potentially control the enantioselectivity of C–H alkylation reactions via a reversible insertion/selective protonation mechanism,[11,12] such a mechanism can be excluded from these experimental results. The reaction in the presence of CD_3OD afforded the desired product with some deuterium incorporation at the α-position (Scheme 4), supporting the formation of an enolate intermediate. In addition, by the single crystal X-ray diffraction analysis of **3ja** (CCDC 2025508), the absolute configuration of **3** was unambiguously determined to be the same as that observed for the C–H amidation of 8-ethylquinolines (**1**) in our previous study using the same CCA (**4**),[10f] and the enantiomeric ratios were also comparable. These observations also indicate that CCA **4** is mainly responsible for the enantioselective C–H activation to irreversibly generate metallacycle **5** both in the current C–H alkylation reactions and previously reported C–H amidation reactions (Figure 2).[10f] In the C–H alkylation reaction, insertion of enone **2** generates enolate **6**, which is further protonated possibly by CCA **4** to give the product.

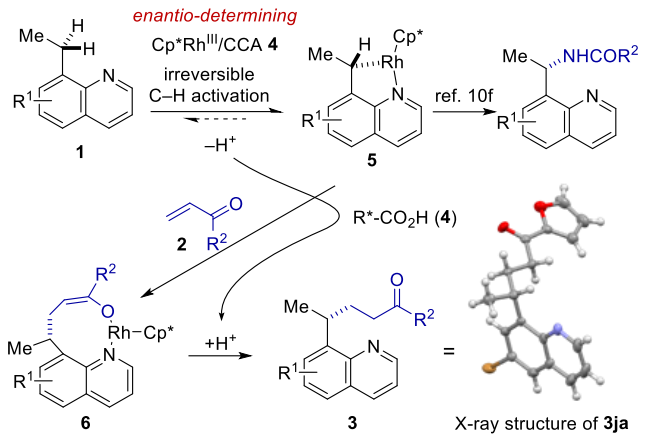


Figure 2. Mechanistic consideration on the enantio-determining step.

In summary, we have developed enantioselective C–H alkylation of 8-ethylquinolines (**1**) via the conjugate addition to enones or acrolein (**2**). The reactions proceeded under mild conditions with good functional group compatibility. Our results demonstrate further utility of the combination of a high-valent group 9 metal catalyst and a chiral carboxylic acid (CCA) for the selective functionalization of enantiotopic C(sp^3)–H bonds to furnish C–C bonds, which complements the previously established C–N bond-forming reactions.

ASSOCIATED CONTENT

Supporting Information

Experimental details and copies of spectroscopic data of the synthesized compounds (PDF).

AUTHOR INFORMATION

Corresponding Author

Corresponding Authors
*E-mail: tyoshino@pharm.hokudai.ac.jp.
*E-mail: smatsuna@pharm.hokudai.ac.jp.

ORCID

Masahiro Kojima: 0000-0002-4619-2621
Tatsuhiko Yoshino: 0000-0001-9441-9272
Shigeki Matsunaga: 0000-0003-4136-3548

Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

This work was supported in part by JSPS KAKENHI Grant Number JP20H02730 (S.M.), JP20H04794 in Hybrid Catalysis (T.Y), and JP19K16306 (T.Y.).

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