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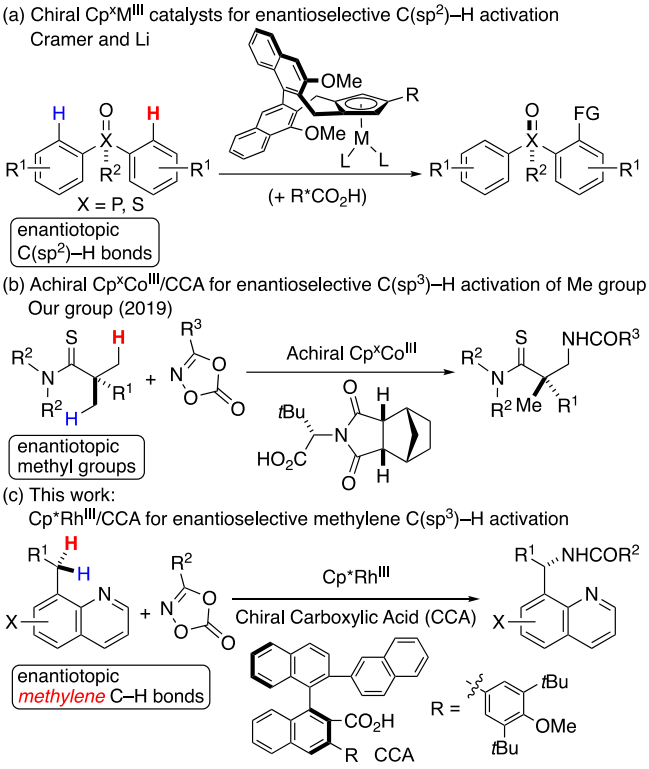
Catalytic Enantioselective Methylene C(sp^3)–H Amidation of 8-Alkylquinolines Using Cp*Rh^{III}/Chiral Carboxylic Acid System

Seiya Fukagawa, Masahiro Kojima, Tatsuhiko Yoshino,* and Shigeki Matsunaga*

Abstract: The catalytic enantioselective directed methylene C(sp^3)–H amidation reactions of 8-alkylquinolines using a Cp*Rh^{III}/chiral carboxylic acid (CCA) hybrid catalytic system is described. A binaphthyl-based chiral carboxylic acid efficiently differentiates between the enantiotopic methylene C–H bonds, which leads to the formation of C–N bonds in good enantioselectivity.

Transition-metal-catalyzed C–H functionalization[1] is an attractive approach to develop atom-[2] and step-economical[3] synthetic routes for organic molecules. Among various metal catalysts employed in directing group-assisted C–H functionalization reactions, group 9 metals wtih a cyclopentadienyl-type ligand, i.e., Cp^{x}M^{III} (M = Co, Rh, or Ir), exhibit high reactivity, broad substrate generality, and robustness, realizing a wide range of synthetically valuable transformations[4]. In particular, when one wishes to functionalize enantiotopic C–H bonds of prochiral substrates to generate chiral products, stereocontrol at the C–H bond cleavage step, i.e. an enantioselective C–H activation, is crucial. Cramer and co-workers, followed by Li and co-workers, have achieved such enantioselective C–H activation/functionalization reactions by using well-designed chiral Cp^{x}M^{III} catalysts[5–9] (Scheme 1a), where a chiral carboxylic acid was sometimes employed as a secondary chiral source. [7c,d,f,g] Although this strategy is successful for the enantioselective functionalization of C(sp^2)–H bonds, functionalization of less reactive enantiotopic C(sp^3)–H bonds has not yet been achieved. On the other hand, our group has recently reported enantioselective C–H functionalization reactions catalyzed by readily available achiral Cp^{x}M^{III} catalysts that were combined with external chiral sources.[10–12] Notably, our hybrid approach using an achiral Cp^{x}Co^{III} catalyst and a chiral amino acid derivative has been successfully applied to enantioselective C(sp^3)–H functionalization reactions via the differentiation of two enantiotopic methyl groups[10c,d] (Scheme 1b). However, enantioselective functionalization reactions of methylene C(sp^3)–H bonds, which are more challenging but also more attractive from a synthetic point of view, were unsuccessful using this previously reported catalytic system.

Herein, we report directed enantioselective methylene C(sp^3)–H functionalization reactions using a Cp*Rh^{III}/chiral carboxylic acid (CCA) hybrid catalytic system (Scheme 1c), in which a binaphthyl-based CCA assists the enantioselective cleavage of methylene C(sp^3)–H bonds to construct a C–N bond at the stereocenter. Although such directing-group-asssited catalytic



Scheme 1. Enantioselective C–H functionalization reactions with stereocontrol at the C–H cleavage step using Cp^{x}M^{III} catalysts (M = Co, Rh, Ir).

C–H activation with the differentiation of methylene C(sp^3)–H bonds have been intensively studied using palladium and other metal catalysts over the past years, most studies have focused on C–C or C–B bond formation reactions[13–19], leaving enantioselective C–N bond formation reactions barely explored.[16a–c,20,21]

Our investigation on the enantioselective methylene C–H amidation of 8-ethylquinoline **1a** using dioxazolone **2a** to afford **3aa** started with attempting to identify an appropriate CCA under the Cp*Rh^{III} catalysis (Table 1).[22] The combination of [Cp*RhCl$_2$]$_2$ and AgSbF$_6$ was selected as the precursor for an active cationic [Cp*Rh^{III}] catalyst. Initially, we tested H$_2$-BHTL **4**, which is the best CCA for the enantioselective C(sp^3)–H amidation of thioamides using a Co^{III} catalyst (entry 1).[10c] The desired reaction proceeded in excellent yield, albeit with low enantioselectivity. Thus, we were motivated to evaluate other types of CCAs. Gratifyingly, binaphthyl-based CCA **5a** exhibited a promising level of selectivity (entry 2, 68:32 *er*), which prompted us to fine-tune the binaphthyl structure. We found that a Ph group at the *ortho* position relative to the carboxylic acid group had a positive effect on the enantioselectivity (**5b**; entry 3), and therefore continued to examine other substituents. While a 4-OMe-C$_6$H$_4$ group at the same position was not effective (**5c**;

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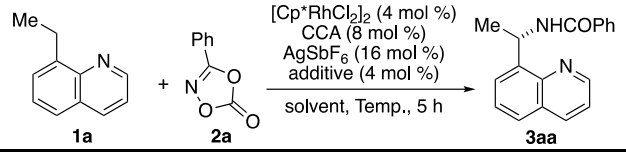
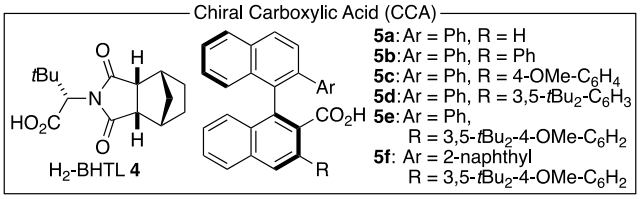
Table 1. Screening of chiral carboxylic acids and optimization of the reaction conditions[a]

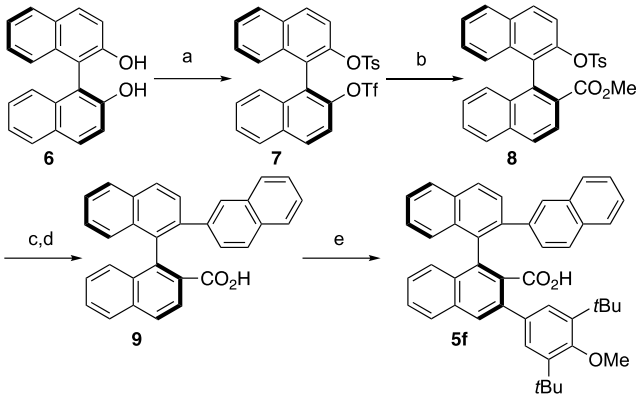


Entry	CCA	Temp.	Solvent	Additive	Yield[b]	*Er*[c]
1	**4**	80 °C	DCM	none	94%	57/43
2	**5a**	80 °C	DCM	none	90%	68/32
3	**5b**	80 °C	DCM	none	73%	71/28
4	**5c**	80 °C	DCM	none	83%	69/31
5	**5d**	80 °C	DCM	none	68%	78/22
6	**5e**	80 °C	DCM	none	78%	81/19
7	**5f**	80 °C	DCM	none	75%	85/15
8	**5f**	80 °C	$PhCF_3$	none	66%	86/14
9	**5f**	80 °C	PhCl	none	69%	87/13
10	**5f**	30 °C	PhCl	none	53%	90/10
11	**5f**	30 °C	PhCl	Ag_2CO_3	93%	91/9
12[d]	**5f**	4 °C	PhCl	Ag_2CO_3	93%	92/8
13[d,e]	**5f**	4 °C	PhCl	Ag_2CO_3	0%	–
14[d,f]	**5f**	4 °C	PhCl	Ag_2CO_3	0%	–



[a] Reaction conditions (unless otherwise stated): **1a** (0.05 mmol), **2a** (0.06 mmol), $[Cp^*RhCl_2]_2$ (0.002 mmol), and CCA **4** or **5** (0.004 mmol), $AgSbF_6$ (0.008 mmol), and additive (0.002 mmol) in the indicated solvent (0.075 M). [b] Determined by ^1H NMR analysis of the crude mixture using dibenzyl ether as the internal standard. [c] Determined by chiral HPLC analysis. [d] 0.2 M, 18 h. [e] $Cp^*CoI_2(CO)$ (8 mol %) was used instead of $[Cp^*RhCl_2]_2$. [f] $[Cp^*IrCl_2]_2$ (4 mol %) was used instead of $[Cp^*RhCl_2]_2$.

entry 4), a sterically more demanding aryl group enhanced the enantiomeric ratio to 78:22 (**5d**; entry 5). Finally, we discovered that a 3,5-di-*tert*-butyl-4-methoxy-phenyl (DTBM) group afforded the best results (**5e**; entry 6). In addition, changing the Ph group at the 2'-position to a 2-naphthyl group improved the selectivity (**5f**; entry 7). As shown in Scheme 2, binaphthyl-based CCA **5f** can be synthesized from BINOL **6** in five steps via a Ni-catalyzed Suzuki-Miyaura cross-coupling[23] and carboxylic acid-directed Ru-catalyzed C–H arylation,[24] indicating that further derivatization in order to expand the scope of application would be facile. Subsequently, we optimized the reaction conditions using **5f**. A screening of other halogenated solvents revealed that PhCl was the most suitable solvent in terms of enantioselectivity (entries 7–9). Lowering the reaction temperature to 30 °C improved the enantioselectivity further, albeit under concomitant decrease of the reactivity (entry 10). The addition of a catalytic amount of Ag_2CO_3, which is expected to deprotonate CCA **5f** to facilitate the formation of the



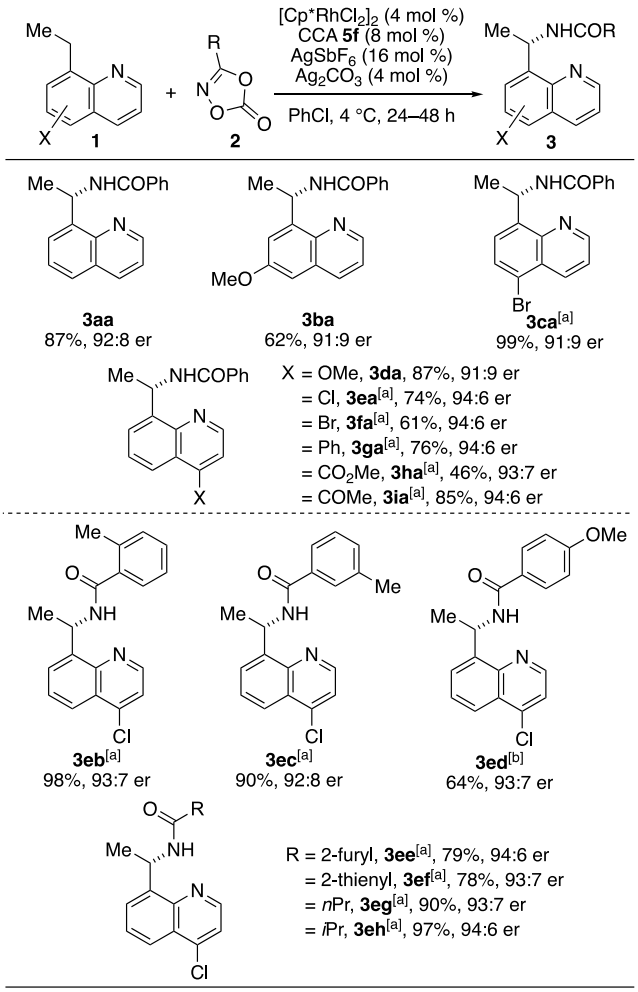
Scheme 2. Synthetic route of **5f**. Reagents and conditions: a) TsCl, Et_3N, DMAP, DCM, then Tf_2O, 91%; b) $Pd(OAc)_2$, dppp, iPr_2NEt, CO, MeOH, DMSO, 80%; c) 2-naphthaleneboronic acid, $Ni(cod)_2$, PCy_3, K_3PO_4, THF; d) KOH, $EtOH/H_2O$, 80% over 2 steps; e) 5-bromo-1,3-di-*tert*-butyl-2-methoxybenzene, $[RuCl_2(p\text{-cymene})]_2$, $PEt_3{\bullet}HBF_4$, K_2CO_3, NMP, 89%.

corresponding chiral carboxylate, drastically improved the reactivity without decreasing the selectivity (entry 11). The reaction proceeded even at 4 °C, and the product (**3aa**) was obtained in 93% yield with 92:8 *er* under the optimized conditions (entry 12). Under the identical conditions, $Cp^*CoI_2(CO)$ or $[Cp^*IrCl_2]_2$ instead of the rhodium catalyst did not afford the desired product (entries 13 and 14).

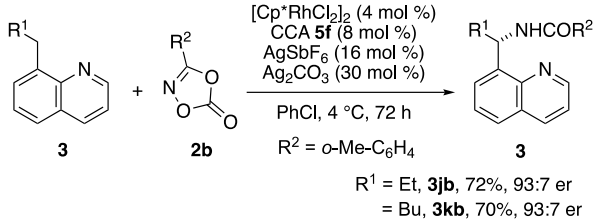
With the optimized reaction conditions in hand, we investigated the substrate scope with respect to the 8- ethylquinolines **1** (Scheme 3). 8-Ethylquinolines with an electron-donating methoxy group at the C4- or C6-positions (**1b** and **1d**) furnished the desired products (**3ba** and **3da**) in good to high yield and good selectivity. Electron-deficient 8-ethylquinolines (**1c**, **1e**–**1i**) reacted even at –10 °C, providing the corresponding products (**3ca**, **3ea**–**3ia**) in 46–99% yield with 91:9–94:6 *er*.[25] Carbonyl groups and halogen substituents were not affected under the applied reaction conditions. Next, we examined the scope of dioxazolones **2** using 4-chloro-8-ethylquinoline **1e**. Dioxazolones bearing a substituent at different positions on the phenyl ring were tolerated and afforded the products (**3eb**–**3ed**) in 64–98% yield and 92:8–93:7 *er*. The C–H amidation proceeded smoothly, even when using a sterically hindered dioxazolone (**3eb**). Heteroaromatic and aliphatic dioxazolones also afforded the corresponding products (**3ee**–**3eh**) in 78–97% yield and 93:7–94:6 *er*.

To further expand the substrate scope of this reaction, we also investigated amidation reactions of other 8-alkylquinolines (Scheme 4). Although the presence of a larger alkyl group at the reactive site decreased the reactivity, reasonable conversion was achieved by increasing the amount of Ag_2CO_3 and prolonging the reaction time. Under such modified reaction conditions, 8-propylquinoline **1j** and 8-pentylquinoline **1k** afforded the amidated products (**3jb** and **3kb**) in 70–72% yield and 93:7 *er*.

We conducted H/D exchange experiments in order to confirm whether a C–H activation step is reversible or not (Scheme 5). When we performed the C–H amidation reaction of **1a** using **2a** in the presence of a catalytic amount of CCA **5f** and an excess amount of CH_3CO_2D, only a very small amount of deuterium was incorporated into the product (**3aa**) and recovered **1a**



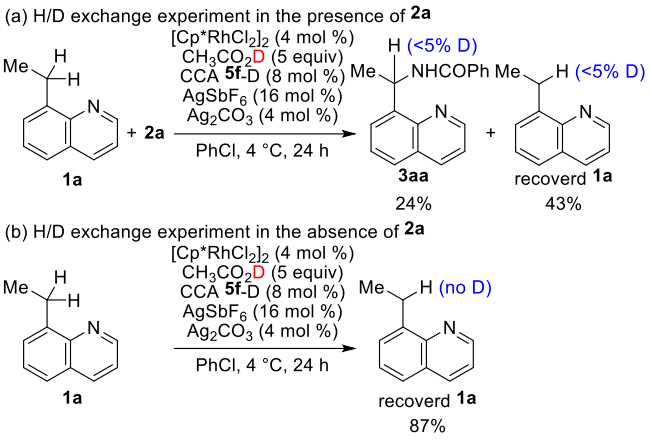
Scheme 3. Substrate scope. Yields of the isolated products were given. For detailed reaction conditions: see the Supporting Information. [a] –10 °C. [b] –20 °C.



Scheme 4. Enantioselective C–H amidation of other 8-alkylquinolines. For detailed reaction conditions: see the Supporting Information.

(Scheme 5a). Furthermore, deuterium incorporation was not observed in the absence of **2a** (Scheme 5b). These results suggest that the C–H activation step is almost irreversible and thus determines the enantioselectivity. CCA **5f** would be involved in a carboxylate-assisted C–H activation process.[26]

In summary, we have demonstrated that a Cp*Rh^{III}/CCA catalytic system enables the enantioselective cleavage of methylene C(sp^3)–H bonds. Enantioselective amidation reactions of 8-alkylquinolines using dioxazolones **2** proceeded in good yield and enantioselectivity by using a binaphthyl-based



Scheme 5. H/D exchange experiments to check the reversibility of the C–H activation step.

chiral carboxylic acid (**5f**), which provides modular and concise design capability and may find new applications in the future.

Acknowledgements

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Keywords: C-H activation • asymmetric catalysis • rhodium • quinoline • chiral carboxylic acid

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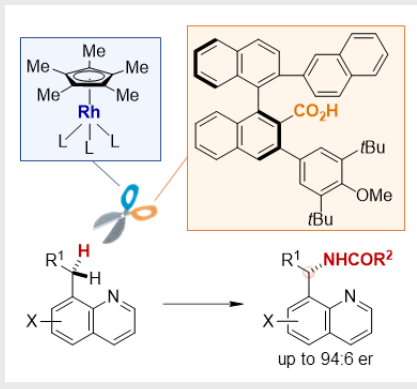
COMMUNICATION

Enantioselective cleavage of methylene C(sp^3)–H bonds has been achieved using an achiral Cp*Rh^{III} catalyst combined with a binaphthyl-based chiral carboxylic acid. Directing group-assisted C–H amidation reactions of 8-alkylquinolines with dioxazolones proceed in high enantioselectivity under mild conditions in the presence of various functional groups.



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