Chiral Carboxylic Acid-Enabled Achiral Rhodium(III)-Catalyzed Enantioselective C−H Functionalization

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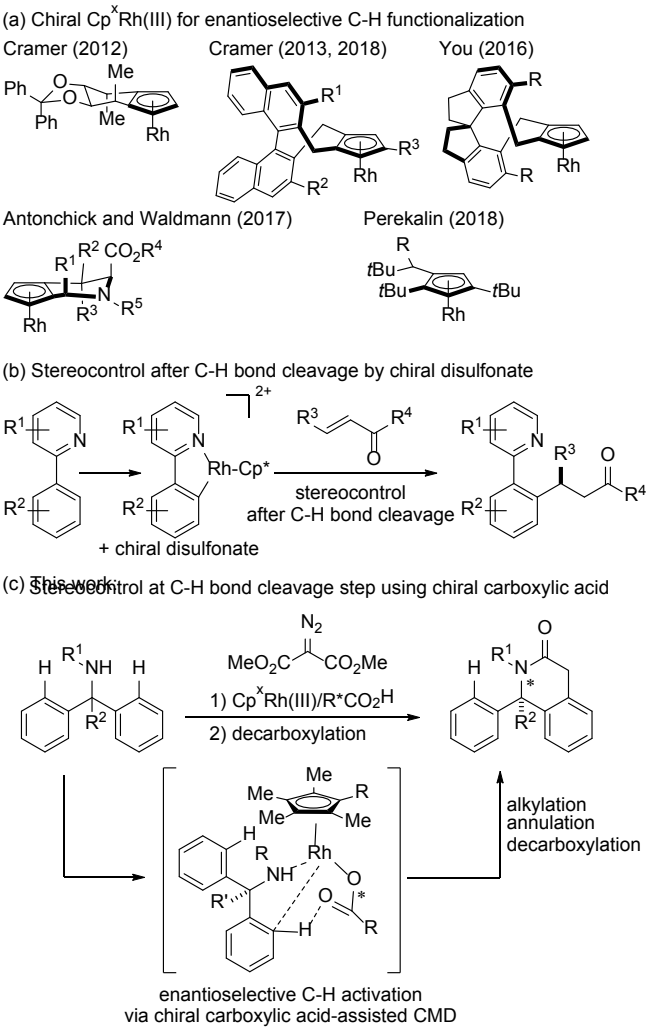
Abstract: We report an achiral Cp^{x}Rh(III)/chiral carboxylic acid-catalyzed asymmetric C–H alkylation of diarylmethanamines with a diazomalonate followed by cyclization and decarboxylation to afford 1,4-dihydroisoquinolin-3(*2H*)-one. Secondary alkylamines as well as non-protected primary alkylamines underwent the transformation with high enantioselectivities (up to 98.5/1.5 er) by using a newly developed chiral carboxylic acid as the sole chiral source to achieve enantioselective C–H cleavage via a CMD mechanism.

Transition metal-catalyzed direct C–H functionalization has been investigated as an atom-[1] and step-economical[2] strategy in organic synthesis over the last few decades.[3-5] Group 9 Cp^{x}M(III) (Cp = cyclopentadienyl, M = Co, Rh, Ir) complexes are prominent catalysts in this field due to their high reactivity and functional group compatibility.[4] Enantioselective C–H functionalization has recently attracted much attention for the synthesis of complex molecules including chiral stereocenters.[5] In this context, Cramer's group reported that Rh(III)[6] and Ir(III)[7] complexes bearing precisely designed chiral Cp^x ligands enabled catalytic asymmetric C–H functionalization reactions.[8] You's group[9] and Antonchick and Waldmann's group[10] also developed different types of chiral Cp^x ligands. These designed Cp^x ligands greatly facilitated the development of enantioselective C–H functionalization reactions (Scheme 1a).[11] However, the derivatization of chiral Cp^{x}M(III) catalysts for optimizing the desired reaction can potentially be problematic, although some easily accessible chiral Cp^x ligands[10,12] and Cp^{x}Rh complexes[13] were recently developed. Therefore, new approaches to achieve enantioselective C–H functionalization using more easily available achiral Cp^{x}M(III) complexes in combination with external chiral sources are highly demanded.[14]

Our group recently developed a Cp*Rh(III)/chiral disulfonate-catalyzed enantioselective conjugate addition of aromatic C–H bonds to enones, in which the chiral disulfonate enabled stereocontrol during the insertion step after C–H bond cleavage (Scheme 1b).[15] On the other hand, stereocontrol at the C-H bond cleavage step still requires chiral Cp^x ligands.[6g,h,7b] In most cases, C–H activation under Cp^{x}M(III) catalysis is proposed to proceed via a carboxylate-assisted concerted metalation-deprotonation (CMD) mechanism.[4,16] Accordingly, an achiral Cp^{x}M(III)/chiral carboxylic acid (CCA) hybrid system should be able to achieve asymmetric C–H activation. Although CCAs were investigated in Ir(III)-catalyzed C-H amidation reactions of phosphine oxides by Chang's group[17] and Cramer's group,[7b] a chiral Cp^x ligand was still essential to obtain high selectivity.[7b] In Pd catalysis, mono-*N*-protected amino acids (MPAAs) and related ligands, mainly developed by Yu's group, are effective for asymmetric C–H activation.[18-20] However, they would not be suitable for Cp^{x}M(III) catalyses because these ligands require at least four coordination sites, i.e., two for ligands, a directing group, and a C–H bond to be cleaved,[19] while Cp^{x}M(III) complexes have only three vacant coordination sites.[21]



Scheme 1. Different Approaches for Enantioselective C–H Functionalization Using Cp^{x}M(III) Catalysts.

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Here we report achiral $Cp^xRh(III)$/chiral binaphthyl monocarboxylic acid hybrid catalysts for enantioselective C–H alkylation of diarylmethanamines with diazomalonate followed by cyclization and decarboxylation (Scheme 1c).[22] Both secondary and non-protected primary alkylamines functioned as a directing group in our catalytic system. Directed C–H alkylation reactions with diazo compounds are well investigated using Cp*M(III) catalysts,[23] but Pd-catalyzed conditions have not been reported,[24] and thus the development of CCAs specifically optimized for $Cp^xRh(III)$ is crucial to achieve this transformation.

We began our investigation by screening several types of CCAs using secondary diarylmethanamine **1a** as a model substrate (Table 1).[25] The reaction conditions selected were based on those previously reported for benzylamine derivatives,[22] but Ag_2CO_3 and CCAs were directly used instead of silver carboxylates for easy reaction setup. Two commercially available MPAAs (**4a**, **4b**) were selected for the initial trials (entries 1, 2). The desired product **3a** was obtained in moderate yield after Krapcho decarboxylation, but the enantioselectivity was low in both cases. We next focused on CCAs based on a binaphthyl backbone. As the simple binaphthyl monocarboxylic acid **5a**[26] exhibited almost no enantioselectivity (entry 3), we considered that increasing the steric hindrance around the carboxylic acid moiety would improve the enantioselectivity. CCA **5b**, with a phenyl group at the 2'-position, resulted in 37/63 er (entry 4), partially supporting our assumption. Therefore, we next screened binaphthyl carboxylic acids with a diaryl phosphine oxide group, which is bulky and easy to modify, at the 2'-position (**6**).[27] As expected, the addition of **6a** delivered **3a** in good yield with moderate enantioselectivity (entry 5, 75.5/24.5 er). The aryl groups on the phosphine oxide (**6b**, **6c**) had only minor effects on the selectivity (entries 6, 7). To further increase the steric hindrance, a 3,5-di-*tert*-butyl-4-methoxy-phenyl (DTBM) group was introduced at the *ortho*-position of the carboxylic acid by directed C–H arylation (**6d**, **6e**).[28] The use of **6d** dramatically improved the selectivity to 94.5/5.5 er with a modest yield (entry 8). Changing the 3,5-bis(trifluoromethyl)phenyl groups of **6d** to 3,4,5-trifluorophenyl groups (**6e**, entry 9) increased both the yield and selectivity. With the optimized CCA **6e**, we briefly examined the effects of Cp^x ligands (entries 10–12). While a slightly less hindered Cp^{Me4} ligand afforded almost the same selectivity and reactivity (entry 10), sterically more hindered ligands exhibited lower reactivity and enantioselectivity (entries 11, 12). We also investigated other silver sources, but only very low yields were observed when using AgOTf or $AgSbF_6$ (entries 13, 14). Thus, the reaction conditions in entry 9 were identified to be optimal. We performed several control experiments to elucidate the importance of each component of the catalytic system (entry 15–18). The desired reaction did not proceed without $[Cp^*RhCl_2]_2$ or **6e** (entry 15, 16). The use of ester **6f** instead of carboxylic acid **6e** afforded no desired product (entry 17), indicating that the carboxylic acid moiety is essential. On the other hand, the product was obtained when Ag_2CO_3 was omitted, albeit in lower yield (entry 18).

We next investigated the substrate scope of the secondary diarylmethanamines **1** (Scheme 2). Substrates **1a**–**1h** bearing an electron-withdrawing group or electron-donating group at the *para*-position were efficiently converted to the corresponding products **3a**–**3h** with high enantioselectivities (91.5/8.5–96/4 er). The sterically less hindered C–H bond was selectively

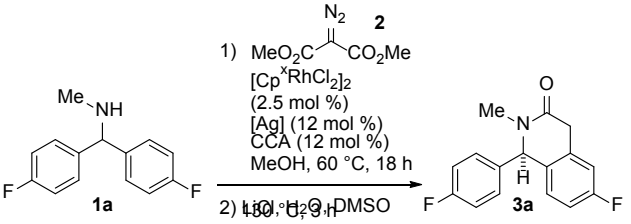
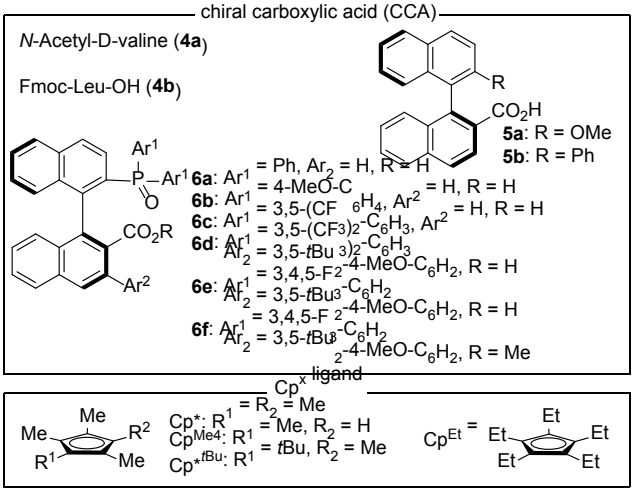
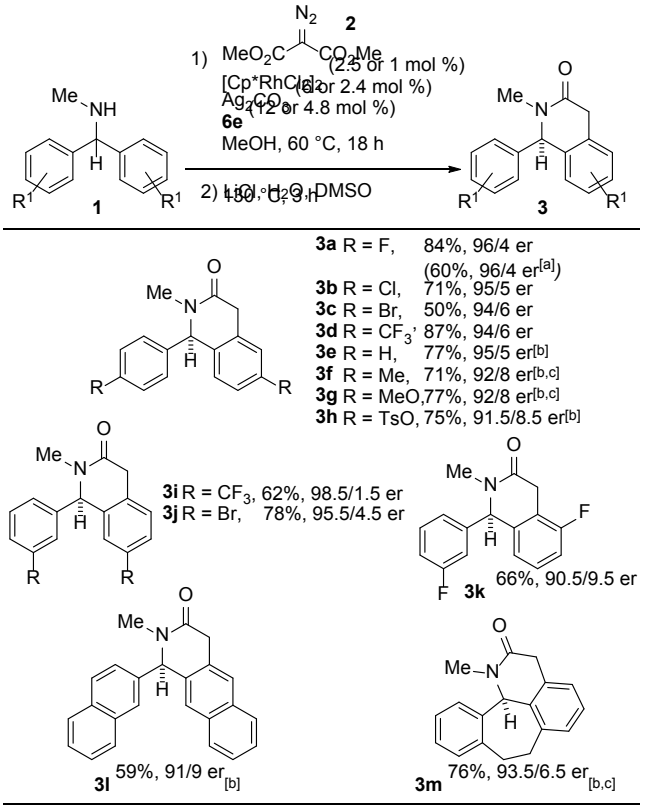


Table 1. Screening of Chiral Carboxylic Acids and Optimization of Reaction Conditions[a]

Entry	$[Cp^xRhCl_2]_2$	CCA	[Ag]	Yield[b]	Er
1	$[Cp^*RhCl_2]_2$	**4a**	Ag_2CO_3	63%	43.5/56.5
2	$[Cp^*RhCl_2]_2$	**4b**	Ag_2CO_3	61%	54/46
3	$[Cp^*RhCl_2]_2$	**5a**	Ag_2CO_3	43%	49.5/50.5
4	$[Cp^*RhCl_2]_2$	**5b**	Ag_2CO_3	20%	37/63
5	$[Cp^*RhCl_2]_2$	**6a**	Ag_2CO_3	67%	75.5/24.5
6	$[Cp^*RhCl_2]_2$	**6b**	Ag_2CO_3	56%	70.5/29.5
7	$[Cp^*RhCl_2]_2$	**6c**	Ag_2CO_3	82%	71/29
8	$[Cp^*RhCl_2]_2$	**6d**	Ag_2CO_3	54%	94.5/5.5
9	$[Cp^*RhCl_2]_2$	**6e**	Ag_2CO_3	84%[c]	96/4
10	$[Cp^{Me4}RhCl_2]_2$	**6e**	Ag_2CO_3	80%[c]	96/4
11	$[Cp^{*tBu}RhCl_2]_2$	**6e**	Ag_2CO_3	34%	91/9
12	$[Cp^{Et}RhCl_2]_2$	**6e**	Ag_2CO_3	51%	93.5/6.5
13	$[Cp^*RhCl_2]_2$	**6e**	AgOTf	19%	95/5
14	$[Cp^*RhCl_2]_2$	**6e**	$AgSbF_6$	15%	95/5
15	–	**6e**	Ag_2CO_3	0%	–
16	$[Cp^*RhCl_2]_2$	–	Ag_2CO_3	0%	–
17	$[Cp^*RhCl_2]_2$	**6f**	Ag_2CO_3	0%	–
18	$[Cp^*RhCl_2]_2$	**6e**	–	63%	96/4



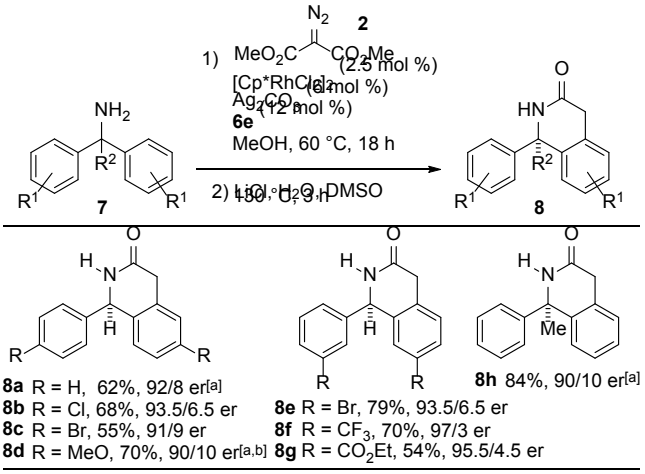
[a] See Supporting Information for the general conditions. [b] Determined by ^1H NMR analysis of the crude mixture. [c] Isolated yields



Scheme 2. Substrate Scope of Secondary Diarylmethanamines. See Supporting Information for the general conditions. [a] $[Cp^*RhCl_2]_2$ (1 mol %), Ag_2CO_3 (2.4 mol %), **6e** (4.8 mol %) were used. [b] $[Cp^{Me4}RhCl_2]_2$ was used instead of $[Cp^*RhCl_2]_2$. [c] AgOTf (12 mol %) was used instead of Ag_2CO_3.

functionalized to furnish **3i** and **3j** in 98.5/1.5 er and 95.5/4.5 er, respectively, while a *meta*-fluorine-substituted substrate **1k** reacted selectively at the more acidic C–H bond *ortho* to the fluorine, providing **3k** in 66% yield and 90.5/9.5 er. A substrate with two enantiotopic naphthyl groups **1l** and a tricyclic amine **1m** also afforded the products (**3l**, **3m**) with good enantioselectivities.[29] For several substrates, the use of $[Cp^{Me4}RhCl_2]_2$ instead of $[Cp^*RhCl_2]_2$ and AgOTf instead of Ag_2CO_3 was slightly beneficial to obtain higher enantioselectivity. Even when the catalyst loading was decreased to 1 mol % of $[Cp^*RhCl_2]_2$ and 4.8 mol % of **6e** using **1a** as a substrate, the enantioselectivity was maintained (96/4 er) with moderate yield.

Our $Cp^xRh(III)$/CCA catalytic system was successfully applied not only to secondary amines **1**, but also to primary amines **7** (Scheme 3). Non-protected primary alkyl amines are common and synthetically attractive functional groups, but their use as directing groups in C–H functionalization is challenging, probably due to their strong coordinating ability leading to catalyst deactivation.[30] To our delight, non-protected primary amines **7** exhibited good reactivity and enantioselectivity under the optimal conditions. Substrates bearing various substituents afforded product **8a**–**8g** in 55%–79% yields with 90/10–97/3 enantioselectivities.[31] A substrate with a methyl group at the α-position of the nitrogen was also applicable to give product **8h** in 90% yield and 90/10 er.



Scheme 3. Primary Non-Protected Amines as Substrates. See Supporting Information for the general conditions. [a] $[Cp^{Me4}RhCl_2]_2$ was used instead of $[Cp^*RhCl_2]_2$. [b] AgOTf (12 mol %) was used instead of Ag_2CO_3.

In conclusion, we developed an achiral $Cp^xRh(III)$/CCA-catalyzed enantioselective C–H functionalization of diarylmethanamines, including non-protected primary amines, to afford potentially bioactive 1,4-dihydroisoquinolin-3(*2H*)-ones[32] (see Supporting Information for a proposed catalytic cycle). Enantioselective C–H bond cleavage via a CMD mechanism was achieved using a newly developed binaphthyl-based chiral mono-carboxylic acid as the sole chiral source. The developed CCAs will be useful for further development of reactions involving enantioselective C–H activation and protonation under $Cp^xM(III)$ and other transition metal catalyses. Furthermore, their synergic effects with chiral $Cp^xM(III)$ catalysts will be promising for achieving highly enantioselective transformations.

Acknowledgements

This work was supported in part by JSPS KAKENHI Grant Number JP15H05802 in Precisely Designed Catalysts with Customized Scaffolding, JSPS KAKENHI Grant Number JP18H04637 in Hybrid Catalysis, JSPS KAKENHI Grant Number JP17H03049, JP17K15417, and JP16F16409, JST ACT-C Grant Number JPMJCR12Z6, and The Asahi Glass Foundation and Naito Foundation (S.M.).

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

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[29] The use of diethyl diazomalonate and diisopropyl diazomalonate instead of dimethyl diazomalonate **2** resulted in lower yields and/or lower selectivities. See Supporting Information for the details.

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[31] For determination of the absolute configuration of **8a**, see Supporting Information.

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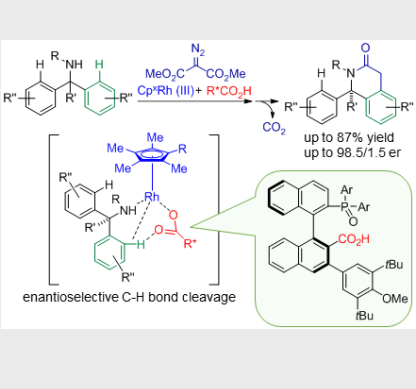
COMMUNICATION

Enantioselective C–H activation/functionalization was achieved using an achiral $Cp^xRh(III)$ catalyst with a newly developed binaphthyl monocarboxylic acid as the sole chiral source. Both secondary and primary diarylmethanamines reacted with a diazomalonate under the $Cp^xRh(III)$/chiral carboxylic acid hybrid catalysis to give 1,4-dihydroisoquinolin-3(*2H*)-ones in high enantioselectivity.



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