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

Luqing Lin,* Seiya Fukagawa, Daichi Sekine, Eiki Tomita, Tatsuhiko Yoshino,* and Shigeki Matsunaga*

Abstract: We report an achiral Cp*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*M(III) (Cp = cyclopentadienyl, M = Co, Rh, Ir) complexes are prominent catalysts in this field due to their high reactivity and functional group compatibility.[5] 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* ligands enabled catalytic asymmetric C–H functionalization reactions.[8] However, the derivatization of chiral Cp*M(III) catalysts for the synthesis of complex molecules is still challenging.[9,10] In most cases, C–H activation under Cp*M(III) catalysis is proposed to proceed via a carboxylate-assisted concerted metalation-deprotonation (CMD) mechanism.[4,16] Accordingly, an achiral Cp*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[11] and Cramer’s group,[7b] a chiral Cp* ligand was still essential to obtain high selectivity.[9a] 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.[12-14] However, they would not be suitable for Cp*M(III) catalysts 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.[15] While Cp*M(III) complexes have only three vacant coordination sites.[21]

Supporting information for this article is given via a link at the end of the document.

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Here we report achiral CpxRh(III)/chiral binaphthyl monobenzylcarboxylic 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 amines 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 CpxRh(III) is crucial to achieve this transformation.

We began our investigation by screening several types of CCAs using secondary diarylmethanamines 1a as a model substrate (Table 1).\[25] The reaction conditions selected were based on those previously reported for benzylamine derivatives,\[22] but Ag$_2$CO$_3$ and CCAs were directly used instead of silver carboxylates for easy reaction setup. Two commercially available MPAA's (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 phosphate 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 phosphate 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 the yield and selectivity. With the optimized CCA 6e, we briefly examined the effects of Cp'M ligands (entries 10–12). While a slightly hindered Cp'M$_4$ 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 Ag$_2$SbF$_6$ (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 product 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$_2$CO$_3$ was omitted, albeit in lower yield (entry 18).

Next, we 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 Table 1. Screening of Chiral Carboxylic Acids and Optimization of Reaction Conditions\[18]
In conclusion, we developed an achiral Cp^*Rh(III)/CCA-catalyzed enantioselective C–H functionalization of diarylamines, 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 biphosphines-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^*M(III) and other transition metal catalyses. Furthermore, their synergic effects with chiral Cp^*M(III) catalysts will be promising for achieving highly enantioselective transformations.

Acknowledgements

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

Selected examples of Pd catalyzed asymmetric C–H activation using 


Amino acid derivative was used for enantioselective protodeamination, although only low enantioselectivity (63.37\% ee) was obtained: D. Zell, M. Bursch, V. Müller, S. Grimme, L. Ackermann, Angew. Chem. 2017, 129, 10514-10518; Angew. Chem. Int. Ed. 2017, 56, 10378-10382.

Materials trials using chiral phosphoric acids afforded low enantioselectivities. See Supporting Information.

The use of diethyl diazomalonate and diisopropyl diazomalonate instead of dimethyl diazomalonate lower selectivities. See Supporting Information.


The use of diethyl diazomalonate and disopropyl diazomalonate instead of dimethyl diazomalonate resulted in lower yields and/or lower selectivities. See Supporting Information for the details.

On the use of diethyl diazomalonate and disopropyl diazomalonate instead of dimethyl diazomalonate 2 resulted in lower yields and/or lower selectivities. See Supporting Information for the details.

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For determination of the absolute configuration of 8a, see Supporting Information.

Enantioselective C–H activation-functionalization was achieved using an achiral Cp*Rh(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*Rh(III)/chiral carboxylic acid hybrid catalysis to give 1,4-dihydroisoquinolin-3(2H)-ones in high enantioselectivity.

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