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Catalytic Enantioselective Methylene C(sp³)–H Amidation of 8-Alkylquinolines Using Cp*RhIII/Chiral Carboxylic Acid System

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

Abstract: The catalytic enantioselective directed methylene C(sp³)–H amidation reactions of 8-alkylquinolines using a Cp*RhIII/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 is an attractive approach to develop atom- and step-economical synthetic routes for organic molecules. Among various metal catalysts employed in directing group-assisted C–H functionalization reactions, group 9 metals with a cyclopentadienyl-type ligand, i.e., Cp*MIII (M = Co, Rh, or Ir), exhibit high reactivity, broad substrate generality, and robustness, realizing a wide range of synthetically valuable transformations. 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/functionlization reactions by using well-designed chiral Cp*MIII catalysts, where a chiral carboxylic acid was sometimes employed as a secondary chiral source. Although this strategy is successful for the enantioselective functionalization of C(sp³)–H bonds, functionalization of less reactive enantiotopic C(sp³)–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*MIII catalysts that were combined with external chiral sources. Notably, our hybrid approach using an achiral Cp*CoIII catalyst and a chiral amino acid derivative has been successfully applied to enantioselective C(sp³)–H functionalization reactions via the differentiation of two enantiotopic methyl groups (Scheme 1b). However, enantioselective functionalization reactions of methylene C(sp³)–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(sp³)–H functionalization reactions using a Cp*RhIII/chiral carboxylic acid (CCA) hybrid catalytic system (Scheme 1c), in which a binaphthyl-based CCA assists the enantioselective cleavage of methylene C(sp³)–H bonds to construct a C–N bond at the stereocenter. Although such directing-group-assisted catalytic

Scheme 1. Enantioselective C–H functionalization reactions with stereocontrol at the C–H cleavage step using Cp*MIII catalysts (M = Co, Rh, Ir).

C–H activation with the differentiation of methylene C(sp³)–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, leaving enantioselective C–N bond formation reactions barely explored.

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*RhIII catalysis (Table 1). The combination of [Cp*RhCl2]2 and AgSbF6 was selected as the precursor for an active cationic [Cp*Rh]3+ catalyst. Initially, we tested H2-BHTL 4, which is the best CCA for the enantioselective C(sp³)–H amidation of thiocyanides using a CoIII catalyst (entry 1). The desired reaction proceeded in excellent yield, albeit with low enantioselectivity. Thus, we were motivated to evaluate other types of CCAAs. 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-C6H4 group at the same position was not effective (5c;
entry 4), a stericly more demanding aryl group enhanced the enantioemeric 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 5f in five steps via a Ni-catalyzed Suzuki-Miyaura cross-coupling[23] and carboxylic acid-directed Ru-catalyzed C–H amination,[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 Ag₂CO₃, which is expected to deprotonate CCA 5f to facilitate the formation of the 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, Cp²CoCl₂(CO) or Cp²IrCl₂ 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 (3aa and 3da) in good to high yield and good selectivity. Electron-deficient 8-ethylquinolines (1c, 1e–1l) 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 dioazolones 2 using 4-chloro-8-ethylquinoline 1e. Dioazolones 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 dioazolone (3eb). Heteroaromatic and aliphatic dioazolones also afforded the corresponding products (3ee–3eh) in 78–97% yield and 93:7–94:5 er.

To further expand the substrate scope of this reaction, we also investigated amidation reactions of other 8-alkyquinolines (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 Ag₂CO₃ 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 CH₃CO₂D, 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.

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

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.\[52\]

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 enantioselectively by using a binaphthyl-based chiral carboxylic acid (5f), which provides modular and concise design capability and may find new applications in the future.

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

References:


For the absolute configuration of 3, see the Supporting Information for details.

Enantioselective cleavage of methylene C(sp³)–H bonds has been achieved using an achiral Cp*RhIII 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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