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Special Issue

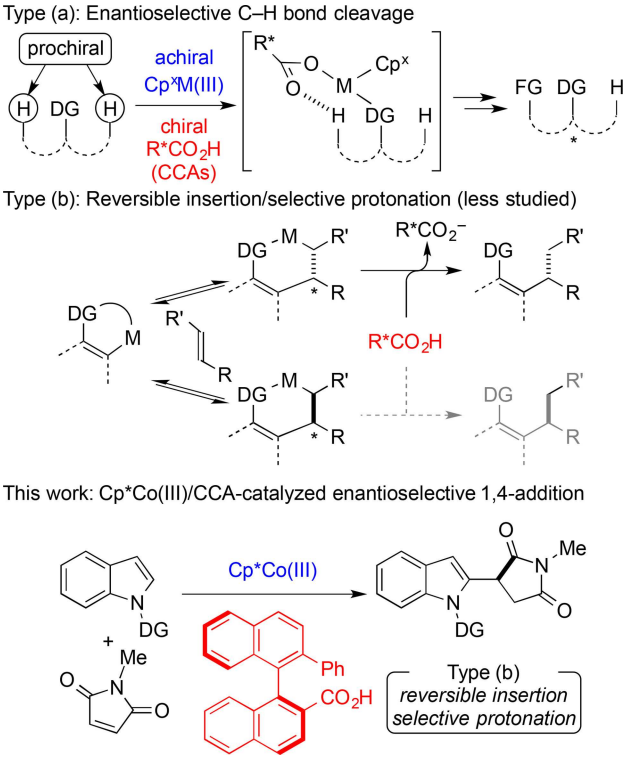
Cp^*Co^{III}/Chiral Carboxylic Acid-Catalyzed Enantioselective 1,4-Addition Reactions of Indoles to Maleimides

Takumaru Kurihara, Masahiro Kojima, Tatsuhiko Yoshino,* and Shigeki Matsunaga*[a]

Abstract: We report enantioselective 1,4-addition reactions of indoles to maleimides via a C2-selective C–H activation catalyzed by an achiral Cp^*Co^{III}/chiral carboxylic acid system. In these reactions, a BINOL-derived chiral carboxylic acid enables the enantioselective reactions as the sole chiral source.

C–H functionalization reactions have emerged as a promising strategy for the formation of C–C or C-hetero atom bonds, and can lead to atom-[1] and step-economical[2] organic syntheses.[3] Although cationic complexes of group 9 metals (Co, Rh, Ir) with a pentamethylcyclopentadienyl (Cp*) or related (Cp^x) ligands can catalyze C–H functionalization reactions quite efficiently, catalytic stereocontrol is difficult to accomplish due to the lack of vacant coordination sites for additional chiral ligands.[4] In this context, the development of well-designed chiral Cp^x ligands that require no additional coordination site and elegantly enable asymmetric C–H functionalization reactions was pioneered by Cramer and co-workers[5] followed by other research groups.[6–9]

More recently, combinations of achiral $Cp^xM(III)$ complexes and chiral carboxylic acids (CCAs) have been exploited for enabling asymmetric C–H functionalization reactions.[10] In Cp*M(III)-catalyzed C–H functionalization reactions, a carboxylic acid or its salt can accelerate the C–H bond activation[11] and/or protodemetallation step;[12] thus, the use of CCAs could potentially induce enantioselectivity in these two steps. Enantioselective C–H activation using a CCA,[13] in which two prochiral C–H bonds of a substrate are distinguished by a CCA and one of them is cleaved selectively, has been explored by Chang,[14] our group,[15] and Shi[16] (Scheme 1: Type (a)). On the other hand, enantio-induction by selective protodemetallation has been reported by Ackermann,[17] who achieved Cp*Co(III)/CCA-catalyzed asymmetric C–H alkylations using alkenes via a selective protodemetallation (Scheme 1: Type (b)). In this case, the reversible insertion of an alkene after C–H activation generates two enantiotopic intermediates, one of which is selectively protonated by the CCA, thus leading to enantioselective alkylation.[18] Compared to enantioselective C–H activations, enantioselective alkylations via the reversible insertion/selective protonation mechanism have received less attention, and the reactions to which it has been applied are relatively limited.[17,19]



Scheme 1. Enantioselective C–H functionalization reactions catalyzed by achiral Cp^xM^{III} (M = Co, Rh, Ir) and chiral carboxylic acids (CCAs). DG = directing group.

Herein, we report our investigations into enantioselective Cp*Co(III)/CCA-catalyzed 1,4-addition reactions of indoles to maleimides via C–H activation (Scheme 1: This work). Directing group-assisted C–H activation of indoles enables site-selective C–C bond formations at the C2-position, overriding the inherent nucleophilic reactivity at the C3-position with polar electrophiles.[20] Li, Ackermann, and co-workers have reported the racemic variants of this reaction, in which the addition of a catalytic amount of an achiral carboxylate dramatically enhanced the reactivity.[21] We hypothesized that the rate enhancement could be due to the acceleration of the final protodemetallation step, and that the use of a CCA could enable enantioselective addition reactions.

[a] *T. Kurihara, M. Kojima, T. Yoshino, Prof. Dr. S. Matsunaga*
Faculty of Pharmaceutical Sciences
Hokkaido University
Kira-ku, Sapporo 060-0812 (Japan)
E-mail: tyoshino@pharm.hokudai.ac.jp
smatsuna@pharm.hokudai.ac.jp

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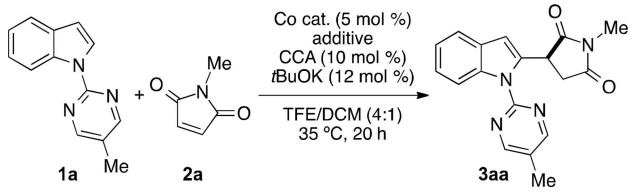
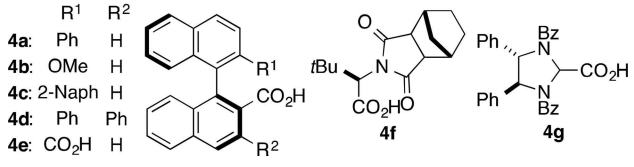
We selected pyrimidyl-protected indole **1a** and maleimide **2a** as model substrates for the screening of several types of CCAs (Table 1). Our initial trial using BINOL-derived CCA **4a** afforded the product **3aa** in excellent yield and in an enantiomeric ratio (*er*) of 75:25 (entry 1), supporting our hypothesis (*vide supra*). We next examined the effect of different substituents on the binaphthyl backbone on the reaction. Using a CCA with a sterically less hindered methoxy group at the 2′ position (**4b**), as well as one carrying a 2-naphthyl group (**4c**) at the same location, resulted in decreased selectivity (entries 2 and 3). Unfortunately, the introduction of a substituent at the *ortho*-position of the carboxylic acid moiety (**4d**) decreased both the yield and enantioselectivity (entry 4), although a similar modification was effective in our previous work.[15a] Dicarboxylic acid **4e**[22] and two CCAs with non-binaphthyl backbones (**4f**, **4g**)[15b,17b] that were used in previously reported Cp*Co(III)/CCA-catalyzed enantioselective C–H functionalization reactions did not afford better results than **4a** (entries 5–7). Based on these results, we selected **4a** as the optimal CCA and turned our attention to optimizing the reaction conditions. Carrying out the reaction at lower temperature for a longer time (10 °C, 48 h) improved the enantioselectivity to 80:20 *er*, but diminished the yield (entry 8). Changing the cobalt catalyst to $[Cp^*Co(CH_3CN)_3](SbF_6)_2$/MS13X improved the reactivity without any loss of selectivity (entry 9, 94%, 81:19 *er*). The MS13X molecular sieves would be able to adsorb the acetonitriles coordinating to the Co center, effectively generating an active cationic Co species.

Table 1. Screening CCAs and optimizing reaction conditions.[a]



entry	Co cat.	additive	CCA	yield [%][b]	er
1	$Cp^*Co(CO)I_2$	$AgSbF_6$	**4a**	>95	75:25
2	$Cp^*Co(CO)I_2$	$AgSbF_6$	**4b**	>95	61:39
3	$Cp^*Co(CO)I_2$	$AgSbF_6$	**4c**	>95	69:31
4	$Cp^*Co(CO)I_2$	$AgSbF_6$	**4d**	63	49:51
5	$Cp^*Co(CO)I_2$	$AgSbF_6$	**4e**[c]	>95	54:46
6	$Cp^*Co(CO)I_2$	$AgSbF_6$	**4f**	>95	64:36
7	$Cp^*Co(CO)I_2$	$AgSbF_6$	**4g**	77	50:50
8[d]	$Cp^*Co(CO)I_2$	$AgSbF_6$	**4a**	65	80:20
9[d]	$[Cp^*Co(CH_3CN)_3](SbF_6)_2$	MS13X	**4a**	94	81:19

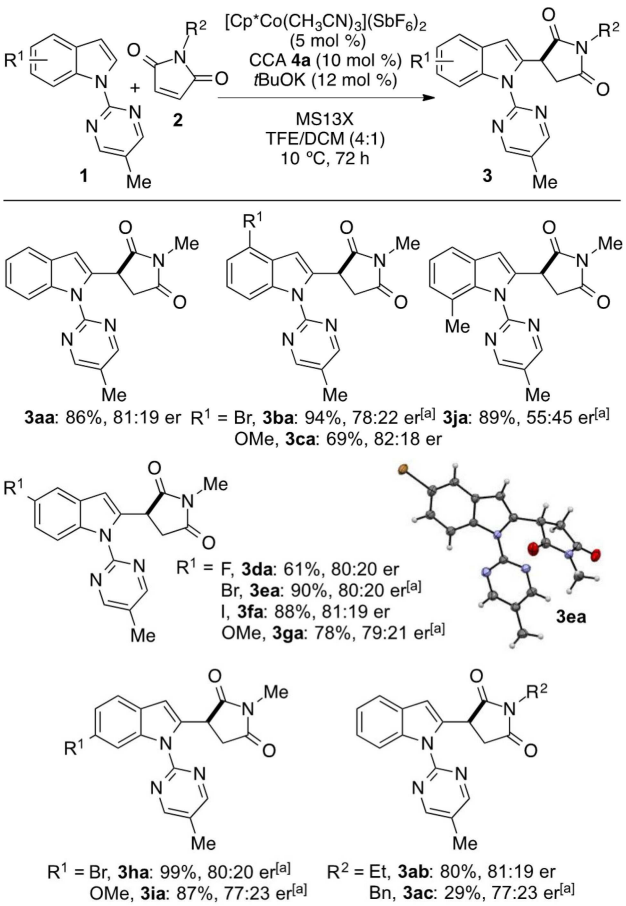
Chiral Carboxylic Acid (CCA)



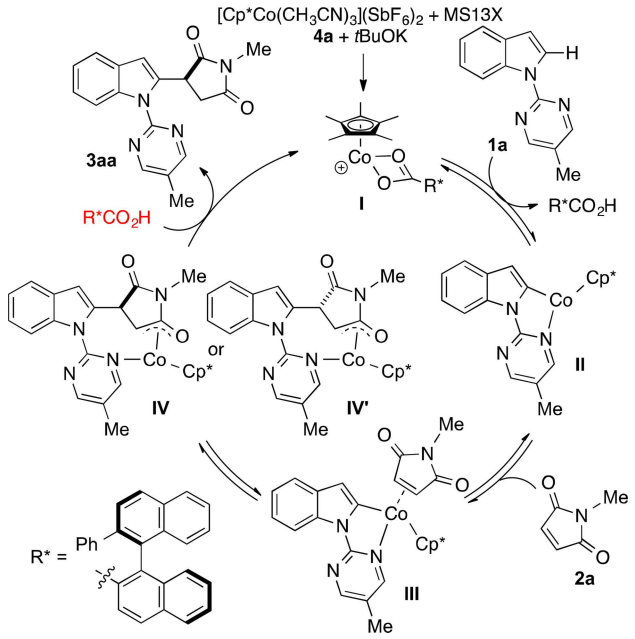
[a] Unless otherwise noted, reactions were carried out using **1a** (0.05 mmol), **2a** (0.10 mmol), Cp*Co cat. (0.0025 mmol, 5 mol%), CCA (0.005 mmol, 10 mol%), *t*BuOK (0.006 mmol, 12 mol%), and $AgSbF_6$ (0.005 mmol, 10 mol%) or MS13X (10 mg, 200 mg/mmol of **1a**) in TFE/DCM (4:1) (0.25 mL) at 35 °C for 20 h [b] Determined by ^1H NMR analysis of the crude reaction mixture. [c] 5 mol%. [d] 10 °C, 48 h. TFE = 2,2,2-trifluoroethanol, DCM = dichloromethane.

Under the optimized reaction conditions (Table 1, entry 9), the scope and limitations of the enantioselective 1,4-addition of the pyrimidylindoles **1**[23] to maleimides **2**[24] were investigated (Scheme 2). Indoles bearing an electron-withdrawing group or electron-donating group at the 4-, 5-, and 6-position (**1b**–**1i**) provided the corresponding products (**3ba**–**3ia**) in 61–99% yields with 77:23–82:18 *er*. The absolute configuration of the major isomer of **3ea** was determined to be (*S*) by single-crystal X-ray diffraction analysis. Although **1j**, which contains a methyl group at the 7-position, was converted to the corresponding product (**3ja**) in high yield, the enantioselectivity was low. This was attributed to steric repulsion between the methyl group and the pyrimidyl directing group, which would distort the conformation of the metallacycle intermediate, leading to the lower selectivity. In addition to *N*-methylmaleimide **2a**, *N*-ethylmaleimide **2b** afforded the corresponding product (**3ab**) in 80% yield with 81:19 *er*, while *N*-benzylmaleimide **2c** exhibited lower reactivity (29% yield, 77:23 *er*).

A plausible catalytic cycle for this enantioselective 1,4-addition is shown in Scheme 3.[21,25] Initially, cationic Cp*Co(III) species **I** would be generated from $[Cp^*Co(CH_3CN)_3](SbF_6)_2$,



Scheme 2. Scope and limitations of the enantioselective 1,4-addition of pyrimidylindoles **1** and maleimides **2**. Unless otherwise noted, reactions were carried out using **1** (0.20 mmol), **2** (0.40 mmol), $[Cp^*Co(CH_3CN)_3](SbF_6)_2$ (0.01 mmol, 5 mol%), **4a** (0.02 mmol, 10 mol%), *t*BuOK (0.024 mmol, 12 mol%), and MS13X (40 mg, 200 mg/mmol of **1**) in TFE/DCM (4:1) (1.0 mL) at 10 °C for 72 h. [a] 20 °C.



Scheme 3. Plausible catalytic cycle for the CCA (**4a**)-induced enantioselectivity.

MS13X, **4a**, and *t*BuOK. C–H bond cleavage of indole **1** would then occur via a concerted metallation-deprotonation (CMD) mechanism[11,26] to form a metallacycle intermediate **II**. After the coordination of maleimide **2** to **II**, which would generate intermediate **III**, the insertion of the C–C double bond would afford intermediate **IV** or **IV′**. Although this insertion step seemingly determines the stereochemistry, intermediate **III** does not contain an extra coordination site that can accommodate CCA **4a** or its anion. Therefore, it is more likely that the reaction proceeds via a reversible insertion/selective protodemetallation mechanism.[17,19] Specifically, the insertion of the C–C double bond is expected to be reversible, which would afford the enantiomeric metallacycles **IV** and **IV′** in equilibrium, while a selective protonation of **IV** by CCA **4a** would proceed to furnish the product in an enantioselective fashion and regenerate **I**. Although we cannot completely deny a mechanism in which CCA **4a** activates maleimide **2a** as a chiral acid catalyst to promote enantioselective insertion of the C–C double bond, we consider that the reversible insertion/selective protodemetallation mechanism would be more likely because the reasonable enantioselectivity was observed in TFE, which is highly polar and would not be suitable for the recognition of substrates via hydrogen-bonding with CCAs.

In summary, we have developed an enantioselective Cp*Co^{III}/CCA-catalyzed 1,4-addition reaction of indoles **1** and maleimides **2**, which proceeds via a C–H activation process. In these reactions, a chiral carboxylic acid (CCA) derived from BINOL (**4a**) serves as the sole chiral source for the enantioselective addition, albeit the observed enantioselectivity leaves room for improvement. Further investigations, including the development of new classes of CCAs, are ongoing in our group.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: C–H activation · cobalt · chiral carboxylic acids · asymmetric 1,4-addition · indoles

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