ARTICLE

Cp*Ir(III)/Chiral Carboxylic Acid-Catalyzed Enantioselective C–H Alkylation of Ferrocene Carboxamides with Diazomalonates

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Enantioselective C–H alkylation of ferrocene carboxamides with diazomalonates using an achiral Cp*Ir(III)/chiral carboxylic acid is described. The combination of achiral Cp*Ir(III) complex and a binaphthyl-based chiral carboxylic acid provided planar chiral alkylated ferrocenes in good yields with moderate to good enantioselectivity (up to 94:6 er).

Introduction

In the past decades, transition-metal-catalysed C–H functionalization reactions have received much attention[1] due to their good atom-[2] and step-economy.[3] Among various transition metal catalysts, trivalent group 9 metal (Co, Rh, Ir) complexes bearing a pentamethylcyclopentadienyl (Cp*) or other related ligands have been widely used for C–H functionalization because of their diverse reactivity, good functional group compatibility, and robustness.[4] The use of these complexes for catalytic enantiocontrol has also attracted much attention over the past decade.[5] Since the pioneering work of Cramer on designing chiral Cp^X ligands[6] and the work of Ward and Rovis on designing artificial metalloenzymes,[7] tremendous progress was achieved on the design of chiral Cp^X ligands.[8] On the other hand, the use of readily available achiral Cp*M(III) in combination with a chiral acid as a sole chiral source has also been investigated as an alternative strategy for enantioinduction.[9-14] Several research groups, including us, reported the utility of chiral sulfonates[12] and/or chiral carboxylic acids (CCAs)[13,14] to realize several asymmetric C-H functionalization reactions. Most of examples using achiral Cp*M(III)/CCAs were, however, limited to the asymmetric construction of central chirality (Figure 1a).[9,12,13] Application of the achiral Cp*M(III)/CCA strategy to the construction of planar chiral compounds was limited.[14]

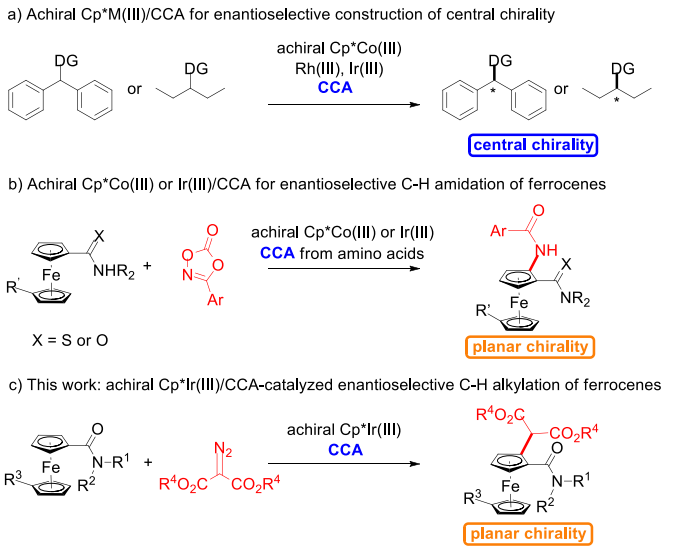

Figure 1. Enantioselective C—H functionalization reaction using achiral Cp*M(III) and CCAs; a) Construction of central chirality; b) Co(III), Ir(III)/CCA-catalyzed C-H asymmetric amidation of ferrocenes; c) this work: Cp*Ir(III)/CCA-catalyzed C-H alkylation of ferrocenes

Ferrocene derivatives have a wide range of applications in materials chemistry, synthetic chemistry, and medicinal chemistry.[15] Especially, planar chiral ferrocenes are often utilized as chiral ligands/catalysts in catalytic asymmetric reactions.[16] The synthesis of planar chiral ferrocene compounds[17] via transition metal-catalysed asymmetric C-H functionalization is potentially the most concise and efficient,[18] and various chiral transition metal catalysts, like Pd, Rh(I), Ir(I), Ni, Pt, Au, Sc, and others, have been utilized.[18,19] The use of Cp*M(III)/CCA system was, however, much less explored. In 2019, Shi and co-workers utilized a Cp*Co(III)/CCA system for the enantioselective amidation of ferrocenes (Figure 1b), but the enantioselectivity was moderate (up to 77.5:22.5 er).[14a] In 2020, the same group significantly improved the

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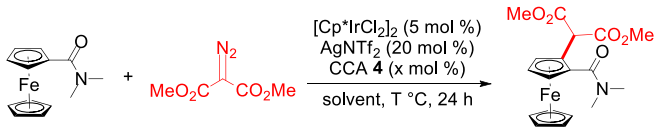
enantioselectivity in achiral Cp*$^{t\text{Bu}}$Ir(III)/amino acid based CCA-catalysed enantioselective C–H amidation of ferrocene carboxamides (Figure 1b).[14b] The reported desymmetrisation reactions of ferrocenes using Cp*M(III)/CCAs were, however, limited to C-H amidation, and so the development of other C-H functionalization of ferrocenes is highly desirable. Herein, we report Cp*Ir(III)/a binaphthyl based CCA-catalysed C-H alkylation of ferrocene amides with diazomalonates.[20]

Results and discussion

On the basis of our recent report on Cp*Rh(III)-catalyzed directed C–H alkylation of ferrocene carboxamides with diazomalonates[21] and Cp*Rh(III)/CCA catalysed-desymmetrization of amines with diazomalonates,[13b] we commenced our study with *N,N*-dimethylferrocene carboxamide (**1a**) and diazomalonate (**2a**) as the model substrate. Initial attempts indicated that Cp*Ir(III) gave more promising enantioselectivity than Cp*Rh(III).[22] Thus, detailed optimization studies were performed using $[Cp^*IrCl_2]_2$ and $AgNTf_2$ in combination with CCAs (Table 1). As shown in entries 1-3, CCAs derived from amino acids **4a**, **4b** and binaphthyl based CCA **4c** were used and the binaphthyl chiral acid **4c** showed slightly better enantioselectivity (64:36 er, entry 3). We envisoned that the substituent at 2'-position of the binaphthyl unit would be effective to modify the chiral environment, and screened more binaphthyl-based CCAs. While sterically more hindered 2-naphthyl unit in **4d** resulted in low er (entry 4), an electron-donating -OMe unit at *p*-position in **4e** improved enantioselectivity (entry 5, 69:31 er). The similar tendency was observed with di-substituted benzene ring of binaphthyl carboxylic acids. Sterically hindered **4f** and **4g** afforded **3aa** in good yield, but in poor enantioselectivity (entries 6,7). 3,5-Di-methoxy-phenyl-substituted **4h** resulted in the best selectivity, 71:29 er (entry 8).[23] Therefore, further optimization of the reaction conditions was performed with **4h**. By changing the reaction temperature from 100 °C to 40 °C, enantiomeric ratio increased to 75:25 er (entry 9). The choice of solvent had a significant influence on the enantioselectivity (entries 9-14), and the ether solvents generally gave better selectivity than dichchloroethane. 2-Me-THF was determined as optimal solvent, producing **3aa** in 62% yield with 88:12 er (entry 14). The reaction proceeded even at to 5 °C, and the selectivity reached 91:9 er (entry 15). To improve the yield at 5 °C, the amount of catalyst components and other parameter were modified in entries 16-18. 30 mol % of CCA **4h** (entry 16) and $AgNTf_2$ (entry 17) increased the yield with only little effects on enantioselectivity. Finally, the addition of Ag_2CO_3 (10 mol %) at concentrated conditions (0.2 M) gave **3aa** in 84% yield with 92:8 er (entry 18).[24]

Table 1. Optimization studies of Cp*Ir(III)/CCA-catalyzed asymmetric C-H alkylation.[a]

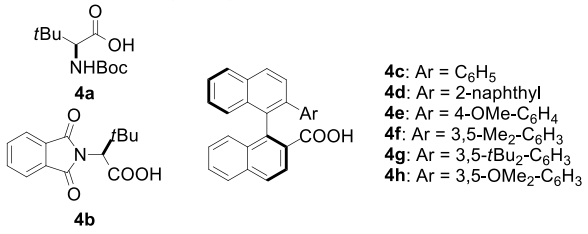


1a **2a** **3aa**

Entry	CCA (x mol %)	Solvent	T (°C)	%Yield[b]	Er[c]
1	**4a** (20)	DCE	100	65	52:48
2	**4b** (20)	DCE	100	84	53:47
3	**4c** (20)	DCE	100	92	64:36
4	**4d** (20)	DCE	100	86	56:44
5	**4e** (20)	DCE	100	85	69:31
6	**4f** (20)	DCE	100	87	57:43
7	**4g** (20)	DCE	100	89	55:45
8	**4h** (20)	DCE	100	83	71:29
9	**4h** (20)	DCE	40	64	75:25
10	**4h** (20)	$PhCF_3$	40	54	74:26
11	**4h** (20)	MTBE	40	53	86:14
12	**4h** (20)	DME	40	65	78:22
13	**4h** (20)	THF	40	75	80:20
14	**4h** (20)	2-Me-THF	40	62	88:12
15	**4h** (20)	2-Me-THF	5	57	91:9
16	**4h** (30)	2-Me-THF	5	72	90:10
17[d]	**4h** (30)	2-Me-THF	5	90	90:10
18[d,e]	**4h** (30)	2-Me-THF	5	84	92:8

[a]Reaction conditions (unless otherwise stated): **1a** (0.1 mmol), **2a** (0.13 mmol), $[Cp^*IrCl_2]_2$ (5 mol %), $AgNTf_2$ (20 mol %), CCA (20 mol %) in solvent (1.0 mL) at T °C under N_2 for 24 h. [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]$AgNTf_2$ (30 mol %). [e]Ag_2CO_3 (10 mol %) was added, 2-Me-THF (0.5 mL).

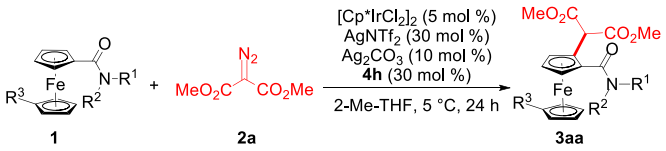
chiral carboxylic acid **4** (CCA **4**) :



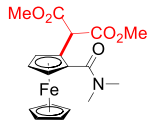
4c: Ar = C_6H_5
4d: Ar = 2-naphthyl
4e: Ar = 4-OMe-C_6H_4
4f: Ar = 3,5-Me_2-C_6H_3
4g: Ar = 3,5-tBu$_2$-C_6H_3
4h: Ar = 3,5-OMe_2-C_6H_3

With the optimal conditions in hand, we set out to explore the scope of ferrocenes first. The substrates **1a**–**c** bearing the amides derived from acyclic amines efficiently produced the corresponding alkylated products (**3aa**–**3ca**) in 76–84% yield with 87:13–92:8 er. Ferrocene caboxamides derived from simple cyclic amines also resulted in the similar enantioselectivity (85:15–86:14 er) and good yield (**3da**–**3fa**), while functionalized amides **1g** and **1h** gave products in moderate selectivity, **3ga** (60%, 83:17er) and **3ha** (64%, 82:18 er). The reaction was applicable to ferrocenes with additional substituent on the other ring (**1i**–**1m**), giving good enantioselectivity (**3ia**–**3ma:** 89:11–94:6 er). The presence of the additional substituent was beneficial for the enantioselectivity in the case of ferrocene substrates containing cyclic amides (**3la**, **3ma** vs **3da**). The absolute configuration of **3aa** was unequivocally determined by the single crystal X-ray diffraction analysis (CCDC 2094161), and those of others were determined by analogy.

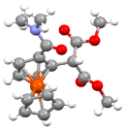
Scheme 1. Scope of Ferrocene Carboxamides[a]



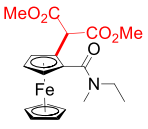
1 2a 3aa



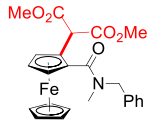
3aa, 84%, 92:8 er



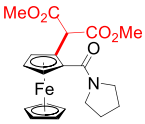
3aa, CCDC: 2094161



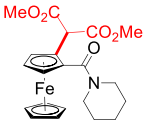
3ba, 82%, 89:11 er



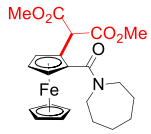
3ca, 76%, 87:13 er



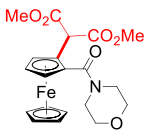
3da, 82%, 86:14 er



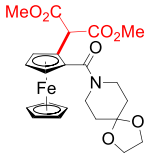
3ea, 70%, 85:15 er



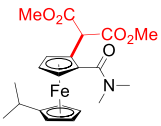
3fa, 72%, 85:15 er



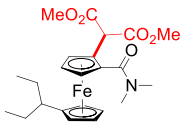
3ga, 60%, 83:17 er



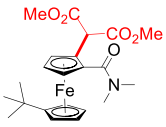
3ha, 64%, 82:18 er



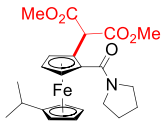
3ia, 79%, 89:11 er



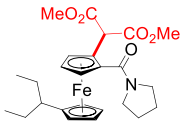
3ja, 76%, 90:10 er



3ka, 84%, 94:6 er



3la, 75%, 91:9 er



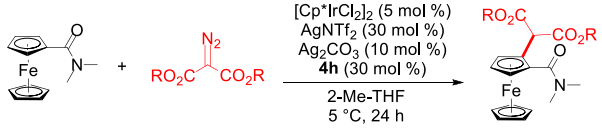
3ma, 72%, 93:7 er

[a]Reaction conditions: **1** (0.1 mmol), **2a** (0.13 mmol), $[Cp^*IrCl_2]_2$ (5 mol %), $AgNTf_2$ (30 mol %), Ag_2CO_3 (10 mol %), **4h** (30 mol %) in 2-Me-THF (0.5 mL) at 5 °C under N_2 for 24 h.

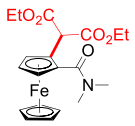
Subsequently, we examined the reactivity and selectivity of various diazomalonates with **1a**. Diazomalonates with linear alkyl ester units (**2b**, **2c**, **2e**) afforded good yields and enantiomeric ratios. Relatively unstable **2h** with longer alkyl unit gave product (**3ah**) in 75% yield, but in decreased selectivity, 85:15 er. Branched esters, such as isopropyl (**2d**) and isobutyl (**2f**) were also tolerated. Benzyl diazomalonate **2i** gave **3ai** in 74% yield and 88:12 er. Diazomalonate **2g** bearing electron-withdrawing groups also reacted smoothly to give the alkylation product in high yield (**3ag**, 87%, 89:11 er).

To gain insight on the reaction mechanism, especially the enantio-determining step, we performed H/D-exchange experiments as shown in Scheme 3. In Scheme 3a, **1a** was treated with 10 equiv of deuterated acetic acid-D1 (AcOD) in the absence of diazo malonate **2a** under optimized conditions for short time (2 h), resulting in the recovery of **1a** with 55% D at *ortho*-positions. In contrast, when the reaction was performed in the presence of diazo malonate **2a** and AcOD (10 equiv) for 2 h, H/D exchange was not observed at ortho-positions of **3aa** and recovered **1a** (Scheme 3b, no D). These results indicate that the Ir(III)-catalyzed C-H cleavage step can potentially become reversible (Scheme 3a), while the C-H cleavage step in the presence of highly reactive diazo malonate **2a** becomes irreversible (Scheme 3b). Thus, enantioselectivity is speculated to be determined under kinetic control at the C-H cleavage step.

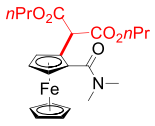
Scheme 2. Scope of Diazomalonates[a]



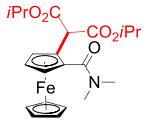
1a 2 3



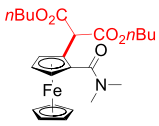
3ab, 82%, 91:9 er



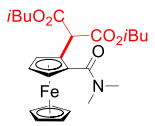
3ac, 79%, 92:8 er



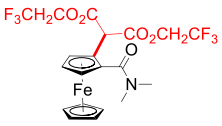
3ad, 72%, 89:11 er



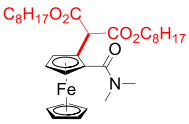
3ae, 77%, 89:11 er



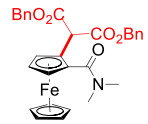
3af, 73%, 85:15 er



3ag, 87%, 89:11 er



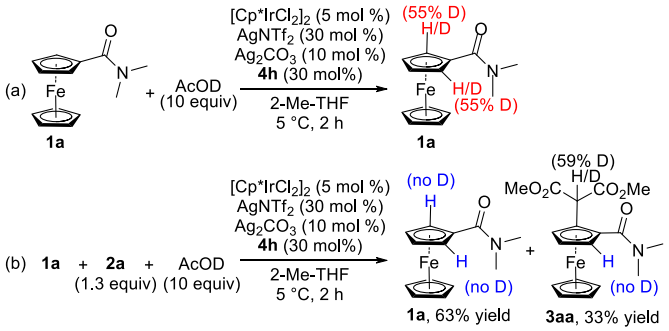
3ah, 75%, 85:15 er



3ai, 74%, 88:12 er

[a]Reaction conditions: **1a** (0.1 mmol), **2** (0.13 mmol), $[Cp^*IrCl_2]_2$ (5 mol %), $AgNTf_2$ (30 mol %), Ag_2CO_3 (10 mol %), **4h** (30 mol %) in 2-Me-THF (0.5 ml) at 5 °C under N_2 for 24 h.

Scheme 3. H/D Exchange Experiments



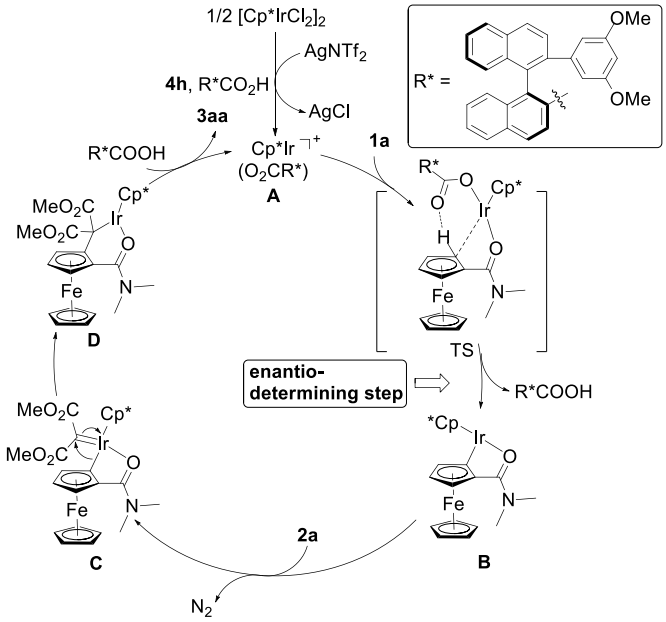
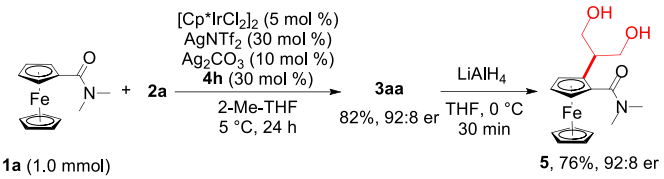


Figure 2. Postulated catalytic cycle of Ir(III)/CCA-catalyzed asymmetric C-H alkylation.

Postulated catalytic cycle of the asymmetric C-H alkylation is shown in Figure 2. Halogen abstraction of $[Cp^*IrCl_2]_2$ with $AgNTf_2$ affords the coordinatively unsaturated cationic Cp*Ir-chiral carboxylate complex **A**. Based on the previous related reports, we assume that carboxylate-assisted concerted metalation-deprotonation of **1a** would proceed under kinetic control via TS in Figure 2 to afford the chiral metalacyclic intermediate **B**. The step from **A** to **B** is speculated to be enantio-determining as supported by the experiments in Scheme 3. The reaction of **B** with diazomalonate **2a** would proceed smoothly to afford the Ir-carbene species **C**. In Scheme 2, the enantioselectivity slightly changed depending on the diazomalonates used. The results in Scheme 2 implies that the undesired reversible protonation from **B** to **A** might somewhat compete when using less reactive diazomalonates, resulting in slight loss of enantioselectivity in chiral intermediate **B**. Migratory insertion affords intermediate **D** and the last proto-demetalation with CCA **4h** would afford **3aa** and regenerate active species **A**.

To demonstrate the practicality and potential synthetic applications of the reaction, we performed the reaction of ferrocene carboxamide **1a** with **2a** on a preparative 1.0 mmol scale. As shown in Scheme 4, the reaction proceeded without any problems and **3aa** was obtained in 82% yield and 92:8 er. Reduction of **3aa** with $LiAlH_4$ gave diol **5** in 76% yield without loss of enantiopurity.

Scheme 4. Preparative Scale Reaction and Derivatization



Conclusions

In summary, we demonstrated the utility of achiral Cp*Ir(III)/a binaphthyl-based chiral carboxylic acid for catalytic asymmetric synthesis of planar chiral ferrocenes. Cp*Ir(III) and the appropriately tuned binaphthyl-based chiral carboxylic acid system promoted the C-H alkylation of ferrocene carboxamides at 5 °C, giving alkylated products in up to 94:6 er. Further application of the binaphthyl-based CCAs in asymmetric C-H functionalization is ongoing in our laboratory.

Author Contributions

Q. Mou, R. Zhao, R. Niu, S. Fukagawa, and T. Shigeno performed the experiments and analysed the data. Q. Mou, T. Yoshino, S. Matsunaga and B. Sun prepared the manuscript and ESI. All authors discussed the results and contributed to finalize the manuscript.

Conflicts of interest

There are no conflicts to declare.

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23 Chiral carboxylic acids bearing one more aromatic ring at 3-position of **4h** resulted in much lower enantioselectivity in this reaction.

24 For results using other silver salts, see Electronic Supplementary Information.