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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]

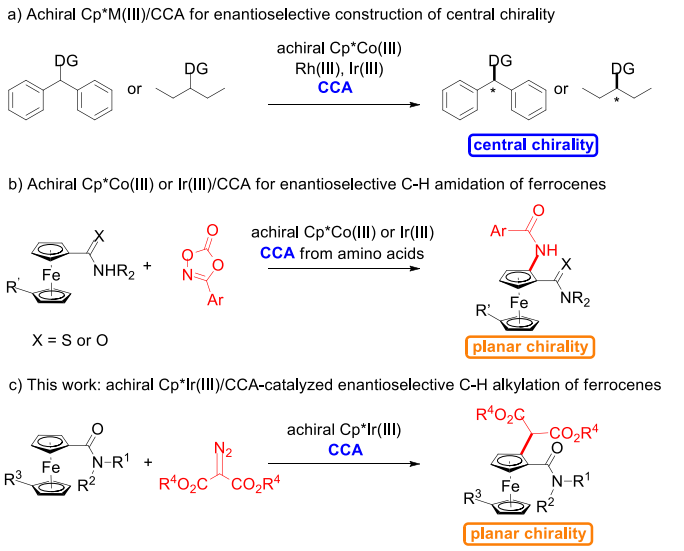

Figure 1. Enantioselective C—H functionalization reaction using achiral Cp*M(III) and CCAs; a) Construction of central chirality; b) Co(III), Ir(III)/CCA-catalyzed C-H asymmetric amidation of ferrocenes; c) this work: Cp*Ir(III)/CCA-catalyzed C-H alkylation of ferrocenes

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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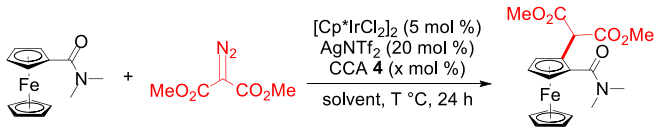
enantioselectivity in achiral Cp*$^{t\mathrm{Bu}}$Ir(III)/amino acid based CCA-catalysed enantioselective C–H amidation of ferrocene carboxamides (Figure 1b).[14b] The reported desymmetrisation reactions of ferrocenes using Cp*M(III)/CCAs were, however, limited to C-H amidation, and so the development 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]

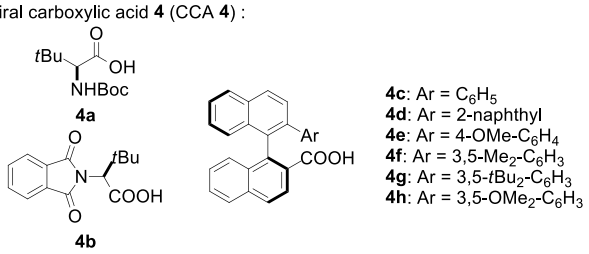


1a **2a** **3aa**

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

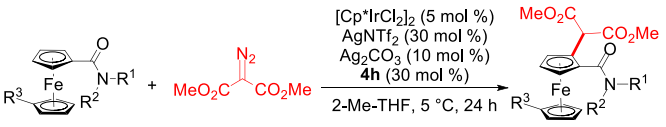
[a]Reaction conditions (unless otherwise stated): **1a** (0.1 mmol), **2a** (0.13 mmol), $[Cp^*IrCl_2]_2$ (5 mol %), $AgNTf_2$ (20 mol %), CCA (20 mol %) in solvent (1.0 mL) at T °C under N_2 for 24 h. [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]$AgNTf_2$ (30 mol %). [e]Ag_2CO_3 (10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

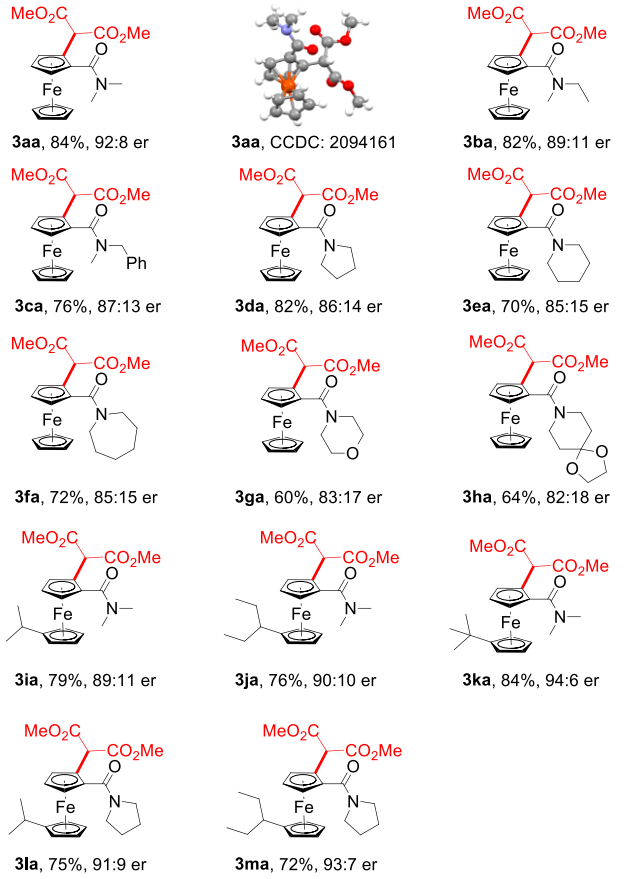
chiral carboxylic acid **4** (CCA **4**) :



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]



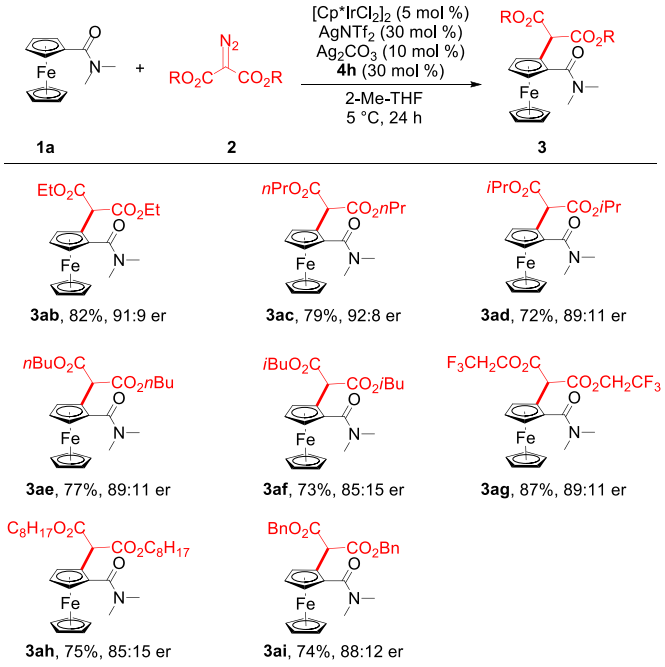


[a]Reaction conditions: **1** (0.1 mmol), **2a** (0.13 mmol), $[Cp^*IrCl_2]_2$ (5 mol %), $AgNTf_2$ (30 mol %), Ag_2CO_3 (10 mol %), **4h** (30 mol %) in 2-Me-THF (0.5 mL) at 5 °C under N_2 for 24 h.

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).

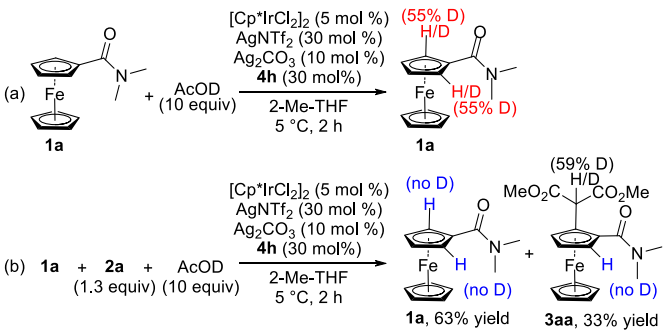
To gain insight on the reaction mechanism, especially the enantio-determining step, we performed H/D-exchange experiments as shown in Scheme 3. In Scheme 3a, **1a** was treated with 10 equiv of deuterated acetic acid-D1 (AcOD) in the absence of diazo malonate **2a** under optimized conditions for short 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]



[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



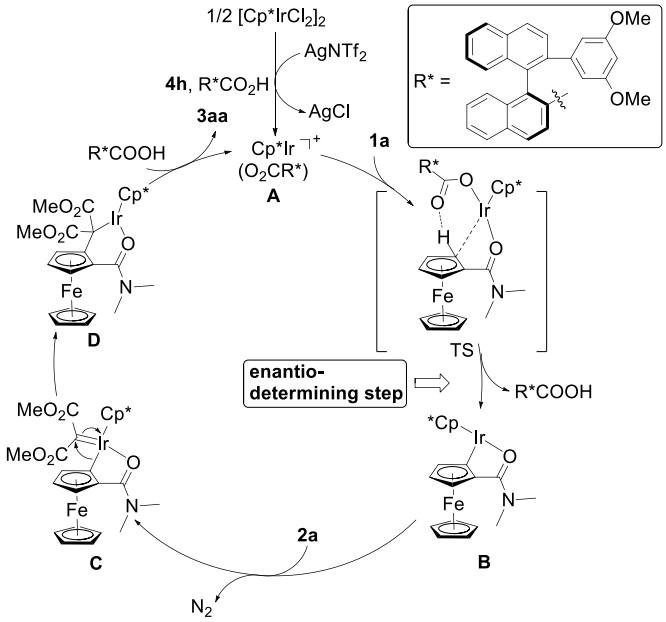
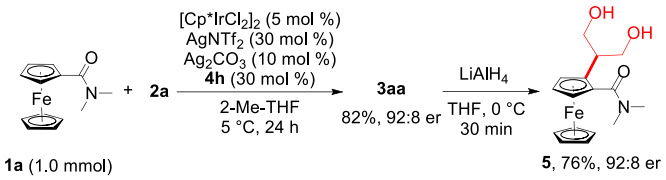


Figure 2. Postulated catalytic cycle of Ir(III)/CCA-catalyzed asymmetric C-H alkylation.

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.

Acknowledgements

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Notes and references

1 Selected recent reviews: (a) J. He, M. Wasa, K. S. L. Chan, Q. Shao and J.-Q.Yu, Palladium-Catalyzed Transformations of Alkyl C-H Bonds. *Chem. Rev*. 2017, **117**, 8754-8786; (b) C. G. Newton, S.-G. Wang, C. C. Oliveira and N. Cramer, Catalytic Enantioselective Transformations Involving C-H Bond Cleavage by Transition-Metal Complexes. *Chem. Rev*., 2017, **117**, 8908-8976; (c) J. R. Hummel, J. A. Boerth and J. A. Ellman, Transition-Metal-Catalyzed C-H Bond Addition to Carbonyls, Imines, and Related Polarized π Bonds. *Chem. Rev*., 2017, **117**, 9163-9227; (d) R. R. Karimov and J. F. Hartwig, Transition-Metal-Catalyzed Selective Functionaliza-tion of C(sp^3)-H Bonds in Natural Products. *Angew. Chem. Int. Ed*., 2018, **57**, 4234-4241; (e) J. Loup, U. Dhawa, F. Pesciaioli, J. Wencel-Delord and L. Ackermann, Enantioselective C-H Activation

with Earth-Abundant 3d Transition Metals. *Angew. Chem. Int. Ed.*, 2019, **58**, 12803-12818; (f). Ł. Wozniak, J.-F. Tan, Q.-H. Nguyen, A. Vigné, V. Smal, Y.-X. Cao and N. Cramer, Catalytic Enantioselective Functionalizations of C-H Bonds by Chiral Iridium Complexes. *Chem. Rev.* 2020, **120**, 10516-10543; (g) Q. Gu, Z.-J. Wu and S.-L. You, Recent Advances in Enantioselective Direct C-H Addition to Carbonyls and Michael Acceptors. *Bull. Chem. Soc. Jpn.,* 2021, **94**, 641-647; (h) G. Liao, T. Zhang, Z.-K. Lin and B.-F. Shi, Transition Metal-Catalyzed Enantioselective C-H Functionalization via Chiral Transient Directing Group Strategies. *Angew. Chem. Int. Ed.*, 2020, **59**, 19773-19786; (i) Q. Zhang and B.-F. Shi, 2-(Pyridin-2-yl)isopropyl (PIP) Amine: An Enabling Directing Group for Divergent and Asymmetric Functionalization of Unactivated Methylene C(sp^3)–H Bonds. *Acc. Chem. Res.*, 2021, **54**, 2750-2763.

2 B. M. Trost, The Chemistry Reaction and Atom Economy. *Science*, 1991, **254**, 1471-1477.

3 P. A. Wender and B. L. Miller, Synthesis at the Molecular Frontier. *Nature*, 2009, **460**, 197-201.

4 For selected reviews on Cp*M(III)-catalysed C-H functionalization, see: (a) T. Satoh and M. Miura, Oxidative Coupling of Aromatic Substrates with Alkynes and Alkenes under Rhodium Catalysis. *Chem. Eur. J.*, 2010, **16**, 11212-11222; (b) G. Song, F. Wang and X. Li, C-C, C-O and C-N Bond Formation via Rhodium(III)-catalyzed Oxidative C-H Activation. *Chem. Soc. Rev.*, 2012, **41**, 3651-3678; (c) N. Kuhl, N. Schröder and F. Glorius, Formal S_N-Type Reactions in Rhodium(III)-Catalyzed C-H Bond Activation. *Adv. Synth. Catal.*, 2014, **356**, 1443-1460; (d) G. Song and X. Li, Substrate Activation Strategies in Rhodium(III)-Catalyzed Selective Functionalization of Arenes. *Acc. Chem. Res.*, 2015, **48**, 1007-1020; (e) S. Wang, S.-Y. Chen and X.-Q. Yu, C-H Functionalization by High-valent Cp*Co(III) Catalysis. *Chem. Commun.*, 2017, **53**, 3165-3180; (f) T. Yoshino and S. Matsunaga, (Pentamethylcyclopentadienyl)cobalt(III)-Catalyzed C-H Bond Functionalization: From Discovery to Unique Reactivity and Selectivity. *Adv. Synth. Catal.*, 2017, **359**, 1245-1262; (g) J. Park and S. Chang, Comparison of the Reactivities and Selectivities of Group 9 [Cp*M^{III}] Catalysts in C-H Functionalization Reactions. *Chem. Asian J.*, 2018, **13**, 1089-1102; (h) T. Piou and T. Rovis, Electronic and Steric Tuning of a Prototypical Piano Stool Complex: Rh(III) Catalysis for C-H Functionalization. *Acc. Chem. Res.*, 2018, **51**, 170-180; (i) T. Yoshino and S. Matsunaga, Cp*Co^{III}-Catalyzed C-H Functionalization and Asymmetric Reactions Using External Chiral Sources. *Synlett*, 2019, **30**, 1384-1400; (j) R. Manoharan and M. Jeganmohan, Recent Advancements in Allylic C(sp^3)-H Functionalization of Olefins Catalyzed by Rh(III) or Ir(III) Complexes. *Eur. J. Org. Chem.*, 2020, 7304-7319. (k) Y. Nishii and M. Miura, Cp*M-Catalyzed Direct Annulation with Terminal Alkynes and Their Surrogates for the Construction of Multi-Ring Systems. *ACS Catal.*, 2020, **10**, 9747-9757.

5 Reviews: (a) B. Ye and N. Cramer, Chiral Cyclopentadienyls: Enabling Ligands for Asymmetric Rh(III)-Catalyzed C-H Functionalizations. *Acc. Chem. Res.*, 2015, **48**, 1308-1318; (b) T. Yoshino, S. Satake and S. Matsunaga, Diverse Approaches for Enantioselective C-H Functionalization Reactions Using Group 9 Cp^xM^{III} Catalysts. *Chem. Eur. J.*, 2020, **26**, 7346-7357; (c) S. Shaaban, C. Davies and H. Waldmann, Applications of Chiral Cyclopentadienyl (Cp^x) Metal Complexes in Asymmetric Catalysis. *Eur. J. Org. Chem.*, 2020, **2020**, 6512-6524; (d) J. Mas-Rosello, A. G. Herraiz, B. Audic, A. Laverny and N. Cramer, Chiral Cyclopentadienyl Ligands: Design, Syntheses, and Applications in Asymmetric Catalysis. *Angew. Chem., Int. Ed.*, 2021, ***60***, 13198-13224; (e) Q. Wang, C.-X. Liu, Q. Gu and S.-L. You, Chiral Cp^xRh Complexes for C-H Functionalization Reactions. *Sci. Bull.,* 2021, **66**, 210-213.

6 (a) B. Ye and N. Cramer, Chiral Cyclopentadienyl Ligands as Stereocontrolling Element in Asymmetric C-H Functionalization. *Science*, 2012, **338**, 504-506; (b) B. Ye and N. Cramer, A Tunable Class of Chiral Cp Ligands for Enantioselective Rhodium(III)-Catalyzed C-H Allylations of Benzamides. *J. Am. Chem. Soc.*, 2013, **135**, 636-639.

7 (a) T. K. Hyster, L. Knörr, T. R. Ward and T. Rovis, Biotinylated Rh(III) Complexes in Engineered Streptavidin for Accelerated Asymmetric C-H Activation. *Science*, 2012, **338**, 500-503; (b) I. Hassan, A. Ta, M. Danneman, N. Semakul, M. Burns, C. Basch, V. Dippon, B. McNaughton and T. Rovis, Asymmetric δ-Lactam Synthesis with a Monomeric Streptavidin Artificial Metalloenzyme. *J. Am. Chem. Soc.*, 2019, **141**, 4815-4819.

8 For selected examples of designing chiral Cp^x ligands, see: (a) J. Zheng, W.-J. Cui, C. Zheng and S.-L. You, Synthesis and Application of Chiral Spiro Cp Ligands in Rhodium-Catalyzed Asymmetric Oxidative Coupling of Biaryl Compounds with Alkenes. *J. Am. Chem. Soc.,* **2016**, *138*, 5242-5245; (b) Z.-J. Jia, C. Merten, R. Gontla, C. Daniliuc, A. Antonchick and H. Waldmann, General Enantioselective C-H Activation with Efficiently Tunable Cyclopentadienyl Ligands. *Angew. Chem., Int. Ed.*, 2017, **56**, 2429-2434; (c) E. Trifonova, N. Ankudinov, A. Mikhaylov, D. Chusov, Y. Nelyubina and D. Perekalin, A Planar-Chiral Rhodium(III) Catalyst with a Sterically Demanding Cyclopentadienyl Ligand and Its Application in the Enantioselective Synthesis of Dihydroisoquinolones. *Angew. Chem., Int. Ed.*, 2018, **57**, 7714-7718; (d) K. Ozols, Y.-S. Jang and N. Cramer, Chiral Cyclopentadienyl Cobalt(III) Complexes Enable Highly Enantioselective 3d-Metal-Catalyzed C-H Functionalizations. *J. Am. Chem. Soc.*, 2019, **141**, 5675-5680; (e) C. Farr, A. Kazerouni, B. Park, C. Poff, J. Won, K. Sharp, M. Baik and S. Blakey, Designing a Planar Chiral Rhodium Indenyl Catalyst for Regio- and Enantioselective Allylic C-H Amidation. *J. Am. Chem. Soc.*, 2020, **142**, 13996-14004; (f) L. Hao, L. Vasamsetty, T. Li, J. Jiang, X. Pang and J. Wang, A New Class of C_2-Symmetric Chiral Cyclopentadienyl Ligand Derived from Ferrocene Scaffold: Design, Synthesis and Application. *Chem. Eur. J.*, 2020, **26**, 14546; (g) G. Li, X. Yan, J. Jiang, H. Liang, C. Zhou and J. Wang, Chiral Bicyclo[2.2.2]octane-Fused CpRh Complexes: Synthesis and Potential Use in Asymmetric C-H Activation. *Angew. Chem., Int. Ed.*, 2020, **59**, 22436-22440; (h) R. Pototskiy, A. Kolos, Y. Nelyubina and D. Perekalin, Rhodium Catalysts with a Chiral Cyclopentadienyl Ligand Derived from Natural R-Myrtenal. *Eur. J. Org. Chem.*, 2020, **38**, 6019-6025; (i) W.-J. Cui, Z.-J. Wu, Q. Gu and and S.-L. You, Divergent Synthesis of Tunable Cyclopentadienyl Ligands and Their Application in Rh-Catalyzed Enantioselective Synthesis of Isoindolinone. *J. Am. Chem. Soc.*, 2020, **142**, 7379-7385; (j) C. Pan, S.-Y. Yin, S.-B. Wang, Q. Gu and S.-L. You, Oxygen-Linked Cyclopentadienyl Rhodium(III) Complexes-Catalyzed Asymmetric C-H Arylation of Benzo[*h*]quinolines with 1-Diazonaphthoquinones. *Angew. Chem., Int. Ed.*, 2021, **60**, 15510-15516. For other applications, see refs. 5.

9 Review: T. Yoshino and S. Matsunaga, Chiral Carboxylic Acid Assisted Enantioselective C-H Activation with Achiral Cp^xM^{III} (M = Co, Rh, Ir) Catalysts. *ACS Catal.* 2021, **11**, 6455-6466.

10 For a seminal work and selected examples of Pd(II)-catalysed enantioselective C–H functionalization reactions using mono-protected amino acids derivatives, see: (a) B.-F. Shi, N. Maugel, Y.-H. Zhang and J.-Q. Yu, Pd^{II}-Catalyzed Enantioselective Activation of C(sp^2)-H and C(sp^3)-H Bonds Using Monoprotected Amino Acids as Chiral Ligands. *Angew. Chem. Int. Ed.*, 2008, **47**, 4882-4886; (b) F.-L. Zhang, K. Hong, T.-J. Li, H. Park and J.-Q. Yu, Functionalization of C(sp^3)-H bonds using a Transient Directing Group. *Science,* 2016, **351**, 252-256; (c) G. Chen, W. Gong, Z. Zhuang, M. S. Andrä, Y.-Q. Chen, X. Hong, Y.-F. Yang, T. Liu, K. N. Houk and J.-Q. Yu, Radiative Human Body Cooling by Nanoporous Polyethylene Textile. *Science,*

2016, **353**, 1023-1027; (d) P. Jain, P. Verma, G. Xia and J.-Q. Yu, Enantioselective Amine α-functionalization via Palladium-catalysed C-H Arylation of Thioamides. *Nat. Chem.*, 2017, **9,** 140-144.

11 For examples of Ru(II)-catalysed enantioselective C–H functionalization reactions Using similar CCAs, see: (a) U. Dhawa, R. Connon, J. Oliveira, R. Steinbock and L. Ackermann, Enantioselective Ruthenium-Catalyzed C-H Alkylations by a Chiral Carboxylic Acid with Attractive Dispersive Interactions. *Org. Lett.* **2021**, *23*, 2760-2765; (b) T. Zhou, P.-F. Qian, J.-Y. Li, Y.-B. Zhou, H.-C. Li, H.-Y. Chen and B.-F. Shi, Efficient Synthesis of Sulfur-Stereogenic Sulfoximines via Ru(II)-Catalyzed Enantioselective C-H Functionalization Enabled by Chiral Carboxylic Acid. *J. Am. Chem. Soc.*, **2021**, *143*, 6810-6816; (c) L.-T. Huang, Y. Hirata, Y. Kato, L. Lin, M. Kojima, T. Yoshino and S. Matsunaga, Ru(II)/Chiral Carboxylic Acid-Catalyzed Enantioselective C-H Functionalization of Sulfoximines. *Synthesis*, **2021**, *accepted article* [DOI: 10.1055/a-1588-0072].

12 S. Satake, T. Kurihara, K. Nishikawa, T. Mochizuki, M. Hatano, K. Ishihara, T. Yoshino and S. Matsunaga, Pentamethylcyclopentadienyl Rhodium(III)-chiral Disulfonate Hybrid Catalysis for Enantioselective C-H Bond Functionalization. *Nat. Catal.*, 2018, **1**, 585-591.

13 (a) D. Gwon, S. Park and S. Chang, Dual Role of Carboxylic Acid Additive: Mechanistic Studies and Implication for the Asymmetric C-H Amidation. *Tetrahedron*, 2015, **71**, 4504-4511. (b) L. Lin, S. Fukagawa, D. Sekine, E. Tomita, T. Yoshino and S. Matsunaga, Chiral Carboxylic Acid Enabled Achiral Rhodium(III)-Catalyzed Enantioselective C-H Functionalization. *Angew. Chem., Int. Ed.*, 2018, **57**, 12048-12052; (c) F. Pesciaioli, U. Dhawa, J. Oliveira, R. Yin, M. John and L. Ackermann, Enantioselective Cobalt(III)-Catalyzed C-H Activation Enabled by Chiral Carboxylic Acid Cooperation. *Angew. Chem., Int. Ed.*, 2018, **57**, 15425-15429; (d) S. Fukagawa, Y. Kato, R. Tanaka, M. Kojima, T. Yoshino and S. Matsunaga, Enantioselective C(sp^3)-H Amidation of Thioamides Catalyzed by a $Cobalt^{III}$/Chiral Carboxylic Acid Hybrid System. *Angew. Chem., Int. Ed.*, 2019, **58**, 1153-1157; (e) S. Fukagawa, M. Kojima, T. Yoshino and S. Matsunaga, Catalytic Enantioselective Methylene C(sp^3)-H Amidation of 8-Alkylquinolines Using a Cp^*Rh^{III}/Chiral Carboxylic Acid System. *Angew. Chem., Int. Ed.*, 2019, **58**, 18154-18158; (f) D. Sekine, K. Ikeda, S. Fukagawa, M. Kojima, T. Yoshino and S. Matsunaga, Chiral 2-Aryl Ferrocene Carboxylic Acids for the Catalytic Asymmetric C(sp^3)-H Activation of Thioamides. *Organometallics*, 2019, **38**, 3921-3926; (g) L.-T. Huang, S. Fukagawa, M. Kojima, T. Yoshino and S. Matsunaga, Rhodium(III)/Chiral Carboxylic Acid Catalyzed Enantio-selective C(sp^3)-H Alkylation of 8-Ethylquinolines with α,β-Unsaturated Carbonyl Compounds. *Org. Lett.*, 2020, **22**, 8256-8260; (h) W. Liu, W. Yang, J. Zhu, Y. Guo, N. Wang, J. Ke, P. Yu and C. He, Dual-Ligand-Enabled Ir(III)-Catalyzed Enantioselective C-H Amidation for the Synthesis of Chiral Sulfoxides. *ACS Catal.*, 2020, **10**, 7207-7215 (i) Y. Kato, L. Lin, M. Kojima, T. Yoshino and S. Matsunaga, Development of Pseudo-C_2-symmetric Chiral Binaphthyl Monocarboxylic Acids for Enantioselective C(sp^3)-H Functionalization Reactions under Rh(III) Catalysis. *ACS Catal.*, 2021, **11**, 4271-4277. For other examples, see ref. 9.

14 (a) Y.-H. Liu, P.-X. Li, Q.-J. Yao, Z.-Z. Zhang, D.-Y. Huang, M. Le, H. Song, L. Liu and B.-F. Shi, Cp*Co(III)/MPAA-Catalyzed Enantioselective Amidation of Ferrocenes Directed by Thioamides under Mild Conditions. *Org. Lett.*, 2019, **21**, 1895-1899; (b) L. Liu, H. Song, Y.-H. Liu, L.-S. Wu and B.-F. Shi, Achiral Cp^xIr(III)/Chiral Carboxylic Acid Catalyzed Enantioselective C-H Amidation of Ferrocenes under Mild Conditions. *ACS Catal.*, 2020, **10**, 7117-7122; (c) L. Jin, Q.-J. Yao, P.-P. Xie, Y. Li, B.-B. Zhan, Y.-Q. Han, X. Hong and B.-F. Shi, Atropselective Synthesis of Axially Chiral Styrenes via Aymmetric C-H Functionalization Strategy. *Chem*, 2020, **6**, 497-511; For the use of chiral Cp^xRh(III), see: (d) S.-B. Wang, J. Zheng and S.-L. You, Synthesis of Ferrocene-Based Pyridinones through Rh(III)-Catalyzed Direct C-H Functionalization Reaction. *Organometallics*, 2016, **35**, 1420-1425.

15 Reviews: (a) T. Hayashi, A. Togni, *Ferrocenes;* VCH: Weinheim, Germany, 1995; (b) D. R. van Staveren and N. Metzler-Nolte, Bioorganometallic Chemistry of Ferrocene. *Chem. Rev.*, 2004, **104**, 5931-5986; (c) T. Moriuchi and T. Hirao, Design of Ferrocene-Dipeptide Bioorganometallic Conjugates to Induce Chirality-Organized Structures. *Acc. Chem. Res.*, 2010, **43**, 1040-1051; (d) G. Jaouen, A. Vessieres and S. Top, Ferrocifen Type Anti Cancer Drugs. *Chem. Soc. Rev.*, 2015, **44**, 8802-8817; (e) Z. Huang, H.-J. Yu, L. Wang, X.-W. Liu, T.-F. Lin, F. Haq, S. Vatsadze and D. Lemenovskiy, Ferrocene-contained Metal Organic Frameworks: From Synthesis to Applications. *Coord. Chem. Rev.*, 2021, **430**, 213737.

16 Reviews: (a) L.-X. Dai and X.-L. Hou, *Chiral Ferrocenes in Asymmetric Catalysis;* Wiley-VCH: Weinheim, Germany, 2010; (b) G.-C. Fu, Enantioselective Nucleophilic Catalysis with "Planar-Chiral" Heterocycles. *Acc. Chem. Res.*, 2000, **33**, 412-420; (c) L.-X. Dai, T. Tu, S.-L. You, W.-P. Deng and X.-L. Hou, Asymmetric Catalysis with Chiral Ferrocene Ligands. *Acc. Chem. Res.*, 2003, **36**, 659-667; (d) G. C. Fu, Asymmetric Catalysis with "Planar-Chiral" Derivatives of 4-(Dimethyl-amino)pyridine. *Acc. Chem. Res.*, 2004, **37**, 542-547; (e) R. Arrayás, J. Adrio, J. Carretero, Recent Applications of Chiral Ferrocene Ligands in Asymmetric Catalysis. *Angew. Chem. Int. Ed.*, 2006, *45*, 7674-7715; (f) S. Arae and M. Ogasawara, Catalytic Asymmetric Synthesis of Planar-Chiral Transition-Metal Complexes. *J. Synth. Org. Chem., Jpn.*, 2012, **70**, 593-605;.

17 General Review: D. Schaarschmidt and H. Lang, Selective Syntheses of Planar-Chiral Ferrocenes. *Organometallics*, 2013, **32**, 5668-5704.

18 Reviews on asymmetric C-H functionalization of ferrocenes: (a) C.-X. Liu, Q. Gu and S.-L. You, Asymmetric C-H Bond Functionalization of Ferrocenes: New Opportunities and Challenges. *Trends in Chem.*, 2020, **2**, 737-749; (b) D.-W. Gao, Q. Gu, C. Zheng and S.-L You, Synthesis of Planar Chiral Ferrocenes via Transition-Metal-Catalyzed Direct C-H Bond Functionalization. *Acc. Chem. Res.*, 2017, **50**, 351-365.

19 For selected examples, see: (a) D.-W. Gao, Y.-C. Shi, Q. Gu, Z.-L. Zhao and S.-L. You, Enantioselective Synthesis of Planar Chiral Ferrocenes via Palladium-Catalyzed Direct Coupling with Arylboronic Acids. *J. Am. Chem. Soc.*, 2013, **135**, 86-89; (b) C. Pi, Y. Li, X.-L. Cui, H. Zhang, Y.-B. Han and Y.-J. Wu, Redox of Ferrocene Controlled Asymmetric Dehydrogenative Heck Reaction via Palladium-catalyzed Dual C-H Bond Activation. *Chem. Sci.*, 2013, **4**, 2675-2679; (c) Y.-C. Shi, R.-F. Yang, D.-W. Gao and S.-L. You, Enantioselective Synthesis of Planar Chiral Ferrocenes via Palladium-Catalyzed Annulation with Diarylethynes. *Beilstein J. Org. Chem.*, 2013, **9**, 1891-1896; (d) R. Deng, Y. Huang, X. Ma, G. Li, R. Zhu, B. Wang, Y.-B. Kang and Z. Gu, Palladium-Catalyzed Intramolecular Asymmetric C-H Functionalization/Cyclization Reaction of Metallocenes: An Efficient Approach toward the Synthesis of Planar Chiral Metallocene Compounds. *J. Am. Chem. Soc.*, 2014, **136**, 4472-4475; (e) C. Pi, X.-L. Cui, X.-Y. Liu, M.-X. Guo, H.-Y. Zhang and Y.-J. Wu, Synthesis of Ferrocene Derivatives with Planar Chirality via Palladium-Catalyzed Enantio-selective C-H Bond Activation. *Org. Lett.*, 2014, **16**, 5164-5167; (f) X. Ma and Z. Gu, Palladium-catalyzed Intramolecular Cp-H Bond Functionalization/Arylation: An Enantioselective Approach to Planar Chiral Quinilinoferrocenes. *RSC Adv.*, 2014, **4**, 36241-36244; (g) T. Shibata and T. Shizuno, Iridium-Catalyzed

Enantioselective C-H Alkylation of Ferrocenes with Alkenes Using Chiral Diene Ligands. *Angew. Chem. Int. Ed.*, 2014, **53**, 5410-5413; (h) Q.-W. Zhang, K. An, L.-C. Liu, Y. Yue and W. He, Rhodium-Catalyzed Enantioselective Intramolecular C-H Silylation for the Syntheses of Planar-Chiral Metallocene Siloles. *Angew. Chem. Int. Ed.*, 2015, **54**, 6918-6921; (i) M. Murai, K. Matsumoto, Y. Takeuchi, and K. Takai, Rhodium-Catalyzed Synthesis of Benzosilolo-Metallocenes via the Dehydrogenative Silylation of C(sp^2)-H Bonds. *Org. Lett.*, 2015, **17**, 3102-3105; (j) A. Urbano, G. Hernández, A. Hoyo, A. Carrión and M. Carreño, Mild Access to Planar-Chiral Ortho-Condensed Aromatic Ferrocenes via Gold(I)-Catalyzed Cycloisomerization of Ortho-Alkynylaryl Ferrocenes. *Chem. Commun.*, 2016, **52**, 6419-6422; (k) T. Shibata, N. Uno, T. Sasaki and K. Kanyiva, Pt-Catalyzed Enantioselective Cycloisomerization for the Synthesis of Planar-Chiral Ferrocene Derivatives. *J. Org. Chem.*, 2016, **81**, 6266-6272; (l) Z.-J. Cai, C.-X. Liu, Q. Gu and S.-L. You, Thioketone-Directed Palladium(II)-Catalyzed C-H Arylation of Ferrocenes with Aryl Boronic Acids. *Angew. Chem. Int. Ed.*, 2018, **57**, 1296-1299; (m) J.-C. Xu, Y. Liu, J.-L. Zhang, X.-H. Xua and Z. Jin, Palladium-Catalyzed Enantioselective C(sp^2)-H Arylation of Ferrocenyl Ketones Enabled by a Chiral Transient Directing Group. *Chem. Commun*., 2018, **54**, 689-692; (n) Z.-J. Cai, C.-X. Liu, Q. Wang, Q. Gu and S.-L. You, Thioketone-directed Rhodium(I) Catalyzed Enantioselective C-H Bond Arylation of ferrocenes. *Nat. Commun.*, 2019, **10**, article number 4168; (o) J. Gair, B. Haines, A. Filatov, D. Musaev and J. Lewis, Di-Palladium Complexes are Active Catalysts for Mono-N-Protected Amino Acid-Accelerated Enantioselective C-H Functionalization. *ACS Catal*., 2019, **9**, 11386-11397; (p) H. Chen, Y.-X. Wang, Y.-X. Luan and M. Yuan, Enantioselective Twofold C-H Annulation of Formamides and Alkynes without Built-in Chelating Groups *Angew. Chem. Int. Ed.*, 2020, **59**, 9428-9432; (q) S.-J. Lou, Q.-D. Zhuo, M. Nishiura, G. Luo and Z. Hou, Enantioselective C-H Alkenylation of Ferrocenes with Alkynes by Half-Sandwich Scandium Catalyst. *J. Am. Chem. Soc.*, 2021, **143**, 2470-2476; (r) P.-C. Zhang, Y.-L. Li, J.-F. He, H.-H. Wu, Z.-M. Li and J.-L. Zhang, Simultaneous Construction of Axial and Planar Chirality by Gold/TY-Phos-Catalyzed Asymmetric Hydroarylation. *Nat. Comm.*, 2021, **12**, 4609; For other examples, see reviews in refs 17,18.

20 Reviews: (a) C. Pan, S.-Y. Yin, Q. Gu and S. You, $Cp^xM(III)$-Catalyzed Enantioselective C-H Functionalization through Migratory Insertion of Metal-Carbenes/Nitrenes. *Org. Biomol. Chem.*, 2021, **19**, 7264-7275; (b) Y. Xia, D. Qiu and J.-B. Wang, Transition-Metal-Catalyzed Cross-Couplings through Carbene Migratory Insertion. *Chem. Rev.*, 2017, **117**, 13810-13889.

21 L.-L. Zhang, J.-K. Zhao, Q. Mou, D.-W. Teng, X.-T. Meng and B. Sun, Rhodium(III)-Catalyzed Direct C-H Alkylation of Ferrocenes with Diazo Compounds under Weakly Coordinating Approach. *Adv. Synth. Catal*., 2020, **4**, 955-959.

22 The reaction with $[Cp^*RhCl_2]_2$ (5 mol %), $AgNTf_2$ (20 mol %), and CCA **4c** (20 mol %) in DCE at 100 °C for 24 h gave **3aa** in 85% yield and 52:48 er.

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.