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# **Pentamethylcyclopentadienyl rhodium(III)/chiral disulfonate hybrid catalysis for enantioselective C-H bond functionalization**

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## **Abstract**

Although Cp<sup>\*</sup>Rh(III) complexes are prominent and versatile catalysts for C-H bond functionalization reactions, catalytic stereocontrol is difficult due to the lack of vacant coordination sites. Here we report a hybrid strategy for inducing chirality without using previously reported chiral Cp<sup>x</sup> ligands. A preformed hybrid catalyst, [Cp<sup>\*</sup>RhL<sub>N</sub>][6,6'-Br-(*S*)-BINSate], catalyzed C-H activation and subsequent conjugate addition of 2-phenylpyridine derivatives to enones in good yield and enantioselectivity (up to 95:5 er). In addition to 2-phenylpyridines, conjugate addition of 6-arylpurines proceeded in up to 91:9 er using [Cp<sup>\*</sup>RhL<sub>N</sub>][(*R*)-SPISate]. The results demonstrated that a chiral organic anion can efficiently control the enantioselectivity of Cp<sup>\*</sup>Rh(III)-catalyzed C-H bond functionalization without a chiral Cp<sup>x</sup> ligand.

Transition metal catalysts cleave inert carbon-hydrogen (C-H) bonds in organic molecules to form reactive organometallic intermediates, enabling catalytic transformation of C-H bonds to desired carbon-carbon and carbon-heteroatom bonds. This catalytic C-H bond functionalization strategy can facilitate the development of atom-<sup>1</sup> and step-economical<sup>2</sup> syntheses of functional molecules, and thus has been intensively investigated over the several decades.<sup>3-16</sup> Among various types of transition metal catalysts studied for catalytic C-H bond functionalization, Rh(III) complexes bearing a pentamethylcyclopentadienyl (Cp\*) or related cyclopentadienyl-type (Cp, Cp<sup>x</sup>) ligand, Cp\*Rh(III) or Cp<sup>x</sup>Rh(III), are outstanding in terms of their reactivity, robustness, and functional group compatibility.<sup>3,5-8</sup> Corresponding cobalt<sup>9,11,12</sup> and iridium<sup>17-19</sup> complexes are also used successfully in catalytic C-H bond functionalization. Over the last decade, a large number of reactions have been reported using these Cp\*M(III) catalysts (M = Rh, Co, and Ir).

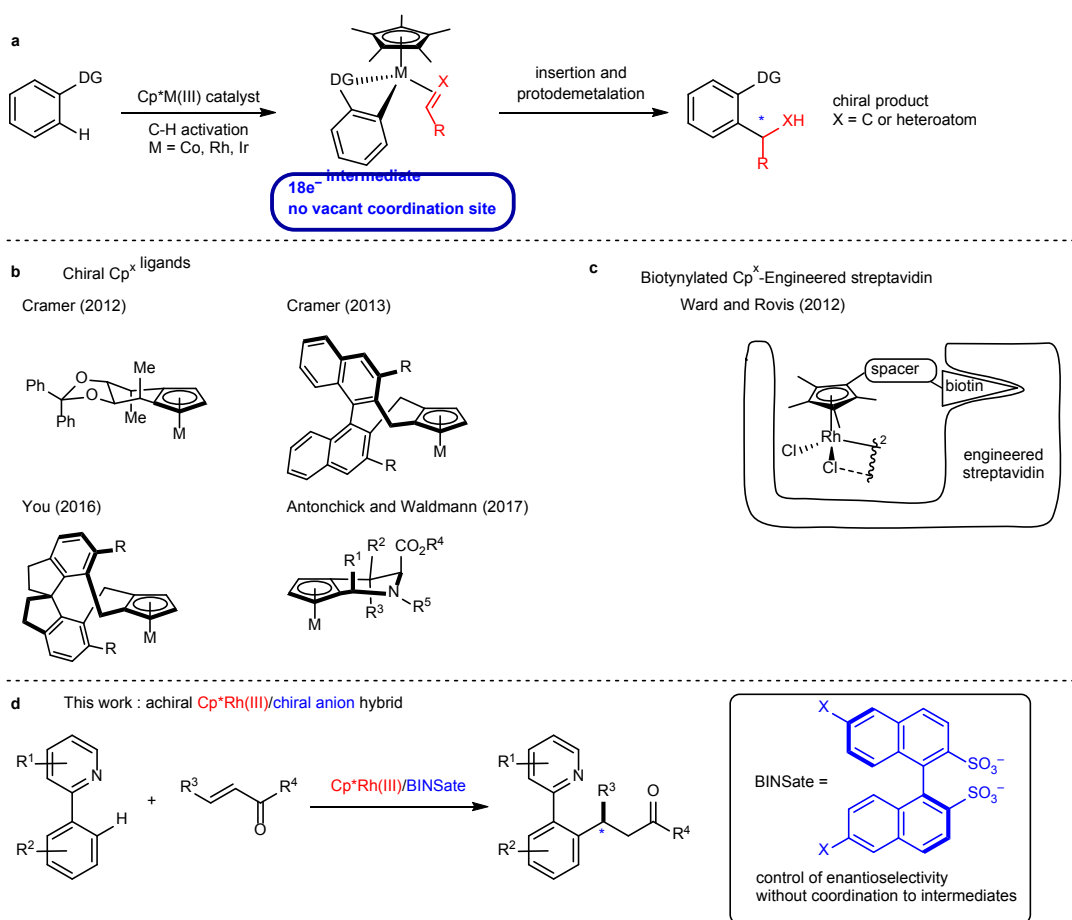
Many catalytic transformations involving functionalization of a C-C or other double bond generate new carbon stereocenters, and therefore, the control of stereoselectivity is an unavoidable task when constructing the desired molecules. In most transition metal-catalyzed reactions, the use of chiral ligands is a well-established strategy for controlling the enantioselectivity. Cp\*M(III)-catalyzed C-H bond functionalization is in difficult situation *because there is no additional vacant coordination site at the insertion step* (Fig. 1a), in contrast to Rh(I), Ir(I), and Pd(0) catalyses, in which standard chiral phosphines are often effective.<sup>14,16</sup> The most straightforward solution to this problem is the use of chiral Cp<sup>x</sup> ligands that require no additional coordination sites (Fig 1b).<sup>8,20-27</sup> In 2012, Ye and Cramer developed precisely designed chiral Cp<sup>x</sup> ligands derived from tartaric acid for asymmetric cyclization of hydroxamic acid derivatives and alkenes.<sup>21</sup> Furthermore, they reported tunable chiral Cp<sup>x</sup> ligands with a binaphthyl backbone,<sup>22</sup> and these tunable ligands were successfully

applied in a series of catalytic asymmetric C-H bond functionalization reactions catalyzed by Rh(III)<sup>8,20,23</sup> and Ir(III).<sup>24</sup> After these pioneering reports, You's group<sup>25,26</sup> and Antonchick and Waldmann's group<sup>27</sup> reported new chiral Cp<sup>x</sup>Rh(III) catalysts exhibiting high enantioselectivity. As another approach, Ward, Rovis, and co-workers reported that a biotinylated Cp<sup>x</sup>Rh complex combined with an engineered streptavidin catalyzes enantioselective reactions using electron-deficient alkenes (Fig 1c).<sup>28</sup> These two approaches significantly advanced the field, but the design and preparation of the catalysts are not trivial, although some chiral Cp<sup>x</sup> ligands were recently synthesized in shorter steps.<sup>27,29,30</sup> In Rovis and Ward's case, the substrate generality is limited, and the optimization of streptavidin for each substrate would be necessary.<sup>28</sup> Accordingly, new approaches for catalytic stereocontrol of Cp<sup>\*</sup>M(III)-catalyzed C-H bond functionalization are still in high demand.

On the other hand, hybridization of organocatalysts with transition metals is an emerging method in asymmetric catalysis.<sup>31-36</sup> This strategy is quite attractive because an organocatalyst component can realize enantioselective transformation without using chiral ligands. The application of an organo/metal hybrid system in transition metal-catalyzed C-H bond activation has mainly focused on enantioselective C-H bond cleavage<sup>13,14,19,37</sup> in which an organocatalyst component, often regarded as an anionic ligand, functions as a base for concerted metalation deprotonation (CMD).<sup>38,39</sup> In this context, Chang and co-workers reported enantioselective amidation of phosphine oxides using a chiral carboxylic acid and a Cp<sup>\*</sup>Ir(III) catalyst, but the observed enantioselectivities were less than 66:34 er.<sup>19</sup> The only successful examples of controlling the enantioselectivity of the following insertion and related steps are the combination of palladium catalysts and chiral phosphoric acids in oxidative allylic substitution reactions.<sup>40,41</sup> Ackermann and co-workers recently reported their attempt to control the enantioselectivity of alkene insertion/protodemetalation steps by a

Cp\*Co(III)/chiral carboxylic acid system, but the enantioselectivity was only moderate (63:37 er) even with a stoichiometric amount of the chiral source.<sup>42</sup>

In this article, we report Cp\*Rh(III)/BINSate<sup>43-45</sup>-catalyzed enantioselective conjugate addition of aromatic C-H bonds to  $\alpha,\beta$ -unsaturated ketones (BINSate = 1,1'-binaphthyl-2,2'-disulfonate) (Fig. 1d). The hybridization of the achiral Cp\*Rh(III) and the chiral anion exhibited high enantioselectivity in the C-H bond functionalization reactions (up to 95:5 er), demonstrating the viability of this hybrid system as an alternative strategy to chiral Cp<sup>x</sup> ligands and protein-conjugate catalysts. Conjugate addition of organometallic nucleophiles to electron-deficient alkenes is fundamental and important C-C bond formation in organic synthesis.<sup>46,47</sup> Realizing a similar process via C-H bond activation can circumvent the use of stoichiometric amounts of organometallic reagents. A series of racemic reactions were reported using Cp\*Rh(III)<sup>48-50</sup> and Cp\*Co(III)<sup>51-53</sup> catalysts, but catalytic stereocontrol was achieved only in the reaction with nitroalkenes using a chiral Cp<sup>x</sup>Rh(III) catalyst.<sup>50</sup>

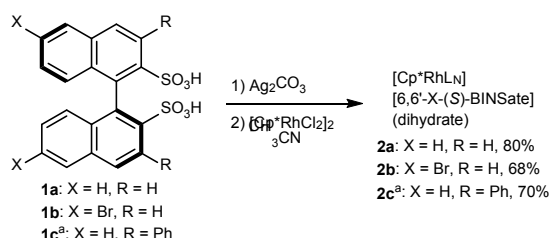


**Figure 1.  $\text{Cp}^*\text{Rh(III)}$  or  $\text{Cp}^x\text{Rh(III)}$ -catalyzed asymmetric reactions.** (a) General scheme of  $\text{Cp}^*\text{Rh(III)}$ -catalyzed C-H bond functionalization generating a new chiral center via insertion/protodemetalation. DG = directing group. (b) Chiral  $\text{Cp}^x$  ligands reported for  $\text{Cp}^x\text{M(III)}$ -catalyzed asymmetric C-H bond functionalization. M = metal. (c) Biotinylated  $\text{Cp}^x\text{Rh}$ /streptavidin system for catalytic asymmetric C-H bond functionalization. (d) This report:  $\text{Cp}^*\text{Rh(III)}$ /BINSate hybrid catalysis for enantioselective conjugate addition of aromatic C-H bonds to  $\alpha,\beta$ -unsaturated ketones.

## Results

**Design and preparation of catalysts.** We envisioned that a  $\text{Cp}^*\text{Rh(III)}$  complex bearing a dianion of BINSa (BINSate) as a counteranion or a ligand would be an active

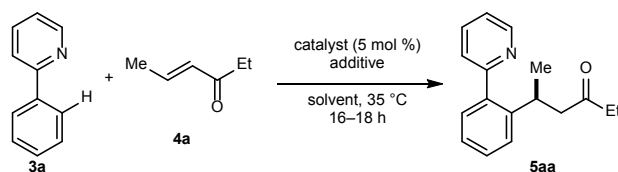
catalyst for C-H bond functionalization because the BINSate can easily dissociate from the metal center to provide vacant coordination sites due to its high acidity.<sup>45</sup> Treatment of (*S*)-BINSa **1a** with Ag<sub>2</sub>CO<sub>3</sub> followed by [Cp\*RhCl<sub>2</sub>]<sub>2</sub> in CH<sub>3</sub>CN afforded [Cp\*RhL<sub>N</sub>][(*S*)-BINSate] **2a** (Fig. 2). NMR analysis revealed the formation of a 1:1 composite of Cp\*Rh(III) and (*S*)-BINSate without coordination of CH<sub>3</sub>CN. Elemental analysis indicated that **2a** would exist as a dihydrate form, although the exact structure and the coordinating ligand are unclear. A catalyst possessing Br substituents at the 6,6'-positions **2b**, and a catalyst possessing phenyl substituents at the 3,3'-positions **2c** were also synthesized by a similar procedure.<sup>45</sup>



**Figure 2. Preparation of [Cp\*RhL<sub>N</sub>][(*S*)-BINSate] **2**.** Detailed reaction conditions for each catalyst are provided in Supplementary Methods. <sup>a</sup>(*R*)-Isomer.

**Optimization for 1,4-addition.** Conjugate addition of 2-phenylpyridine **3a** to enone **4a** to give **5aa**<sup>48,49</sup> was selected as a model reaction to evaluate catalyst **2**. We carried out the reactions using **2a** in various solvents (Table 1, entries 1–7). The reaction in toluene and Et<sub>2</sub>O afforded moderate to good selectivity, albeit in low yield (entries 1,2). Halogenated solvents, CH<sub>2</sub>Cl<sub>2</sub> and 1,2-dichloroethane (DCE), were suitable regarding both reactivity and selectivity (entries 4,5). While acetone produced results comparable to DCE (entry 6), MeOH afforded lower enantioselectivity (entry 7). After DCE was identified as the optimal solvent considering its inertness, several organic bases were screened as additives to improve the enantioselectivity (entries 8–12), with the expectation that they would form an ammonium salt and interact with the BINSate to modulate the chiral environment.<sup>44,45</sup> The addition of pyridine completely inhibited the

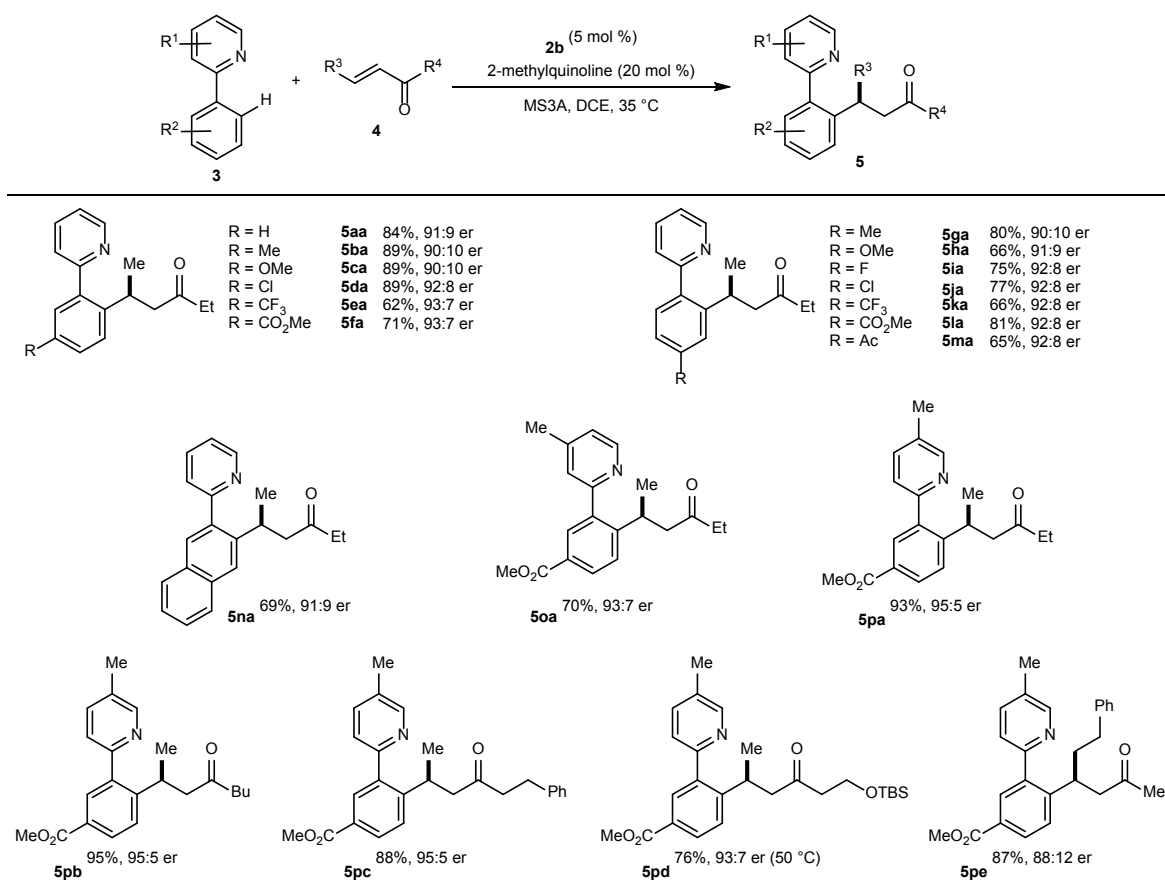
reaction, probably due to its strong coordination with the metal center to occupy the vacant coordination sites (entry 8), while more sterically hindered bases altered the reactivity and enantioselectivity. Among the bases screened, 2-methylquinoline was the best additive in terms of the balance between reactivity and enantioselectivity (entry 12, 86% yield, 86:14 er). The addition of molecular sieves 3A further improved the enantioselectivity, although the yield was diminished (entry 13). Catalyst **2b**, derived from 6,6'-dibromo BINSA, afforded slightly better enantioselectivity (entry 14), while catalyst **2c**, derived from 3,3'-diphenyl BINSA, provided an almost racemic mixture (entry 15). Finally, the yield was recovered by changing the ratio of **3a** and **4a** to 1:1.1 and prolonging the reaction time to afford **5aa** in 84% isolated yield and 91:9 er (entry 16).

**Table 1.** Optimization of reaction conditions for conjugate addition to enone.

| Entry           | Catalyst  | Additive                                   | Solvent                         | Yield (%)       | er    |
|-----------------|-----------|--------------------------------------------|---------------------------------|-----------------|-------|
| 1               | <b>2a</b> | –                                          | toluene                         | 21              | 66:34 |
| 2               | <b>2a</b> | –                                          | Et <sub>2</sub> O               | 3               | 88:12 |
| 3               | <b>2a</b> | –                                          | THF                             | 79              | 80:20 |
| 4               | <b>2a</b> | –                                          | CH <sub>2</sub> Cl <sub>2</sub> | >95             | 80:20 |
| 5               | <b>2a</b> | –                                          | DCE                             | >95             | 81:19 |
| 6               | <b>2a</b> | –                                          | Acetone                         | >95             | 81:19 |
| 7               | <b>2a</b> | –                                          | MeOH                            | 12              | 63:37 |
| 8               | <b>2a</b> | pyridine (20 mol %)                        | DCE                             | 0               | –     |
| 9               | <b>2a</b> | 2,6-dimethylpyridine (20 mol %)            | DCE                             | 47              | 87:13 |
| 10              | <b>2a</b> | 2,4,6-trimethylpyridine (20 mol %)         | DCE                             | <5              | 86:14 |
| 11              | <b>2a</b> | 2,6-di- <i>t</i> -butylpyridine (20 mol %) | DCE                             | >95             | 82:18 |
| 12              | <b>2a</b> | 2-methylquinoline (20 mol %)               | DCE                             | 86              | 86:14 |
| 13              | <b>2a</b> | 2-methylquinoline (20 mol %), MS3A         | DCE                             | 59              | 90:10 |
| 14              | <b>2b</b> | 2-methylquinoline (20 mol %), MS3A         | DCE                             | 60              | 92:8  |
| 15              | <b>2c</b> | 2-methylquinoline (20 mol %), MS3A         | DCE                             | 5%              | 46:54 |
| 16 <sup>a</sup> | <b>2b</b> | 2-methylquinoline (20 mol %), MS3A         | DCE                             | 84 <sup>b</sup> | 91:9  |

Reaction conditions: **3a** (0.06 mmol), **4a** (0.05 mmol), catalyst **2** (0.0025 mmol, 5 mol%) in solvent (0.25 mL) at 35 °C for 16-18 h. Yields are determined by <sup>1</sup>H-NMR analysis of the crude mixture using dibenzyl ether as an internal standard unless otherwise noted. Enantiomeric ratios (er) were determined by chiral HPLC analysis. <sup>a</sup>**3a** (0.10 mmol), **4a** (0.11 mmol), 48 h. <sup>b</sup>Isolated yield after silica gel column chromatography.

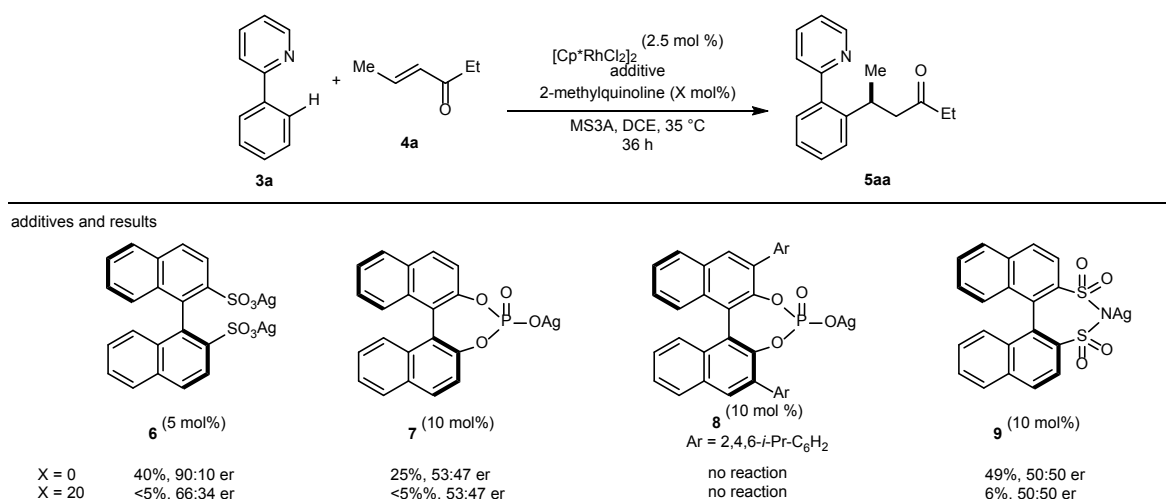
**Substrate generality.** With the optimized conditions in hand, we next investigated the substrate generality (Fig. 3). 2-Phenylpyridine derivatives containing both electron-donating and electron-withdrawing groups on the phenyl moiety were suitable substrates to afford good yields and enantioselectivity (**5aa–5ma**). These substituents had only minor effects on the enantioselectivity (90:10–93:7 er) although the reactivity was dependent on the substituents. For substrates having meta-substituents, less hindered C-H bonds were selectively functionalized under the optimal conditions (**5aa–5fa**, **5na–5pa**). Substituted pyridyl groups also worked as a directing group, and the products were obtained in 93:7 to 95:5 er (**5oa**, **5pa**). Enones bearing a longer alkyl chain as well as functionalized enone also tolerated to give the products (**5pb–5pd**) with good enantioselectivity. A bulkier substituent at the  $\beta$ -position exhibited only minor effect on the reactivity and selectivity to afford a reasonably good result (**5pe**). In all cases, the pendant functional groups remained intact, reflecting the efficient functional group compatibility of the current system.



**Figure 3. Substrate generality of conjugate addition to  $\alpha,\beta$ -unsaturated ketones.** Reaction conditions: **3** (0.10 mmol), **4** (0.11–0.13 mmol), **2b** (0.005 mmol), 2-methylquinoline (0.02 mmol), MS3A (4 mg) in DCE (0.50 mL) at 35 °C unless otherwise noted. The isolated yields and enantiomeric ratios determined by chiral HPLC analysis are shown. The structure of the starting materials and detailed reaction conditions for each substrate are provided in Supplementary Information.

**Comparison with other chiral organic anions.** Other chiral organic anions were investigated for the same conjugate addition reaction, and compared with BINSate (Fig. 4). For this study, the hybrid catalysts were generated in situ by mixing [Cp\*RhCl<sub>2</sub>]<sub>2</sub> and Ag salts of chiral acids. The use of Ag-BINSate **6** in the absence of 2-methylquinoline afforded the desired product in an enantiomeric ratio of 90:10, indicating that the same active catalyst would be generated. 2-Methylquinoline totally

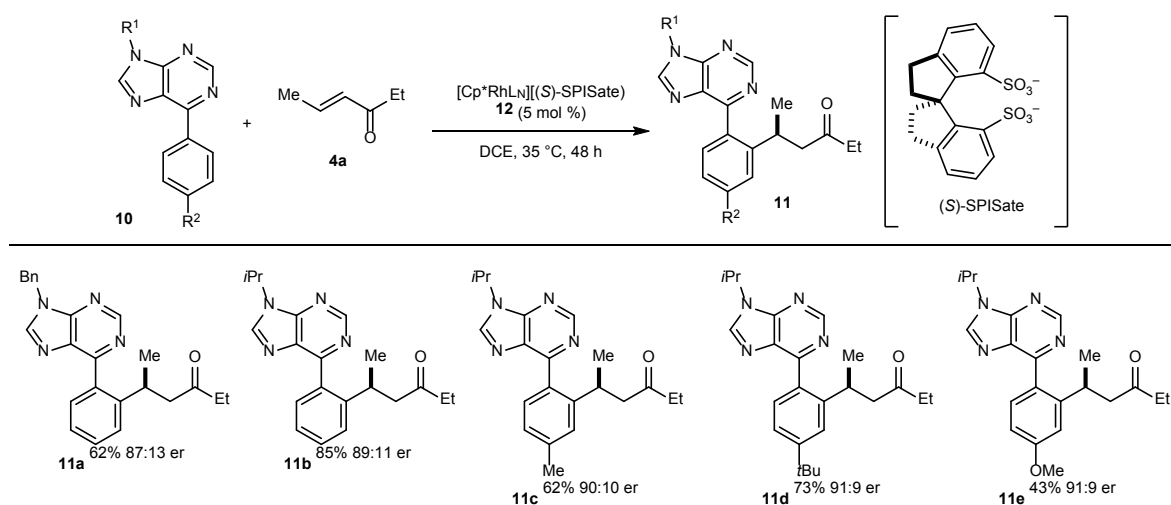
inhibited the reaction under these in situ catalyst generation conditions. Ag salts of chiral acid **7** and **9** instead of **6** also promoted the reaction, but almost no enantioselectivity was observed whether or not 2-methylquinoline was added, while the use of Ag-TRIP **8** afforded no desired product.



**Figure 4. Evaluation of other chiral organic anions.** Reaction conditions: **3a** (0.050 mmol), **4a** (0.065 mmol),  $[\text{Cp}^*\text{RhCl}_2]_2$  (0.00125mmol), additive, 2-methylquinoline (0.01 mmol for X = 20), MS3A (2 mg) in DCE (0.25 mL) at 35 °C for 36 h. Yields were determined by <sup>1</sup>H NMR analysis of the crude mixture using dibenzyl ether as an internal standard. The enantiomeric ratios were determined by chiral HPLC analysis.

**Conjugate addition of 6-arylpurines to  $\alpha,\beta$ -unsaturated ketone.** To expand the scope of our concept, we investigated substrates other than 2-phenylpyridines. When we used 6-arylpurine **10a**<sup>54</sup> under the optimized conditions for 2-phenylpyridines, addition to enone **4a** proceeded to give **11a** with diminished enantioselectivity (78:22 er, Supplementary Figure 2). A slightly better enantioselectivity was observed when the reaction was performed without any additives (84:16 er, Supplementary Figure 3). The selectivity was further improved to 87:13 er by employing (*S*)-SPISate<sup>55</sup> as the counteranion (see Supplementary Information for preparation of catalyst **12**). Several 6-arylpurines were investigated under the newly optimized reactions conditions (Figure

5). 6-Arylpurines with an isopropyl group at the N9-position gave better enantioselectivity (**11b–11e**, 89:11 to 91:9 er). 6-Arylpurines are important compounds in medicinal chemistry due to their biological activities, and C-H bond functionalization of these compounds can increase the diversity of the accessible structure.<sup>54</sup> These results indicate that our concept can be potentially applied to other substrates with different directing groups by optimizing the counteranion depending on the substrate structure.



**Figure 5. Conjugate addition of 6-arylpurines to  $\alpha,\beta$ -unsaturated ketone.** Reaction conditions: **10** (0.12 mmol), **4a** (0.10 mmol), and **12** (0.005 mmol) in DCE (0.50 mL) at 35 °C for 48 h.

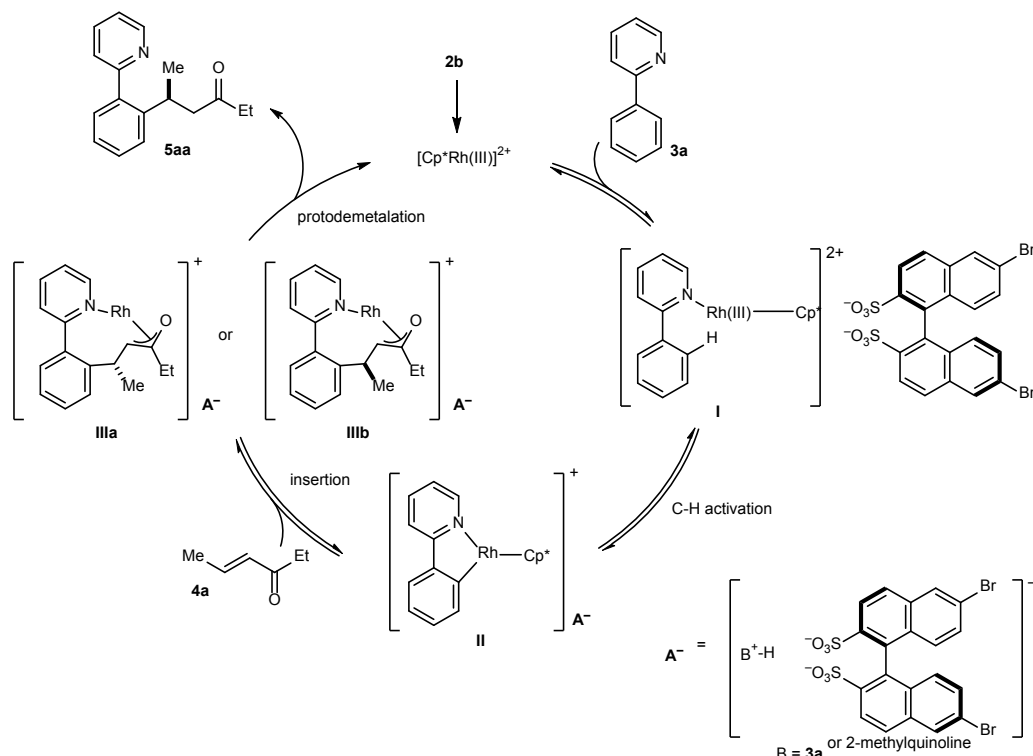
## Discussion

The proposed catalytic cycle for **5aa** based on previous reports on racemic reactions is shown in Fig 5.<sup>49</sup> Dissociation of the coordinating water and/or BINSate from **2b** liberates a coordinatively unsaturated  $\text{Cp}^*\text{Rh(III)}$  species, and C-H activation via CMD mechanism<sup>38,39</sup> or aromatic electrophilic substitution generates metallacycle intermediate **II**. The C-H activation step releases  $\text{H}^+$ , which is trapped by **3a** or 2-methylquinoline to form ammonium-BINSate species **A**<sup>−</sup>. Subsequent insertion of **4a** or protodemetalation to afford product **5aa** is an enantio-determining step of this

transformation. There are two possible mechanisms by which enantioselectivity is induced by the BINSate. The first is reversible insertion of **4a** and selective protodemetalation by a chiral proton source  $\mathbf{A}^-$ .<sup>42</sup> In this case, intermediates **IIIa** and **IIIb** are in equilibrium, and protodemetalation of **IIIa** is faster than that of **IIIb**. The second possibility is that the formation of a contact ion pair between cationic intermediate **II** and chiral anion  $\mathbf{A}^-$  constructs a chiral environment for enantioselective insertion of **4a** to afford **IIIa**, leading to **5aa**. The combination of a chiral anion and a cationic metal catalyst is an established catalytic system, especially in gold(I) and palladium catalysis.<sup>32,33,56-58</sup> An earlier study<sup>32</sup> reported a clear dependency of the enantioselectivity on the polarity of the reaction medium; less polar solvents resulted in higher enantioselectivity due to the effective formation of a contact ion pair.<sup>56</sup> On the other hand, our studies of the solvent effects (Table 1, entries 1-7) revealed no such consistency, and reasonable selectivity was observed even in MeOH (entry 7). Accordingly, chiral induction via the contact ion pairing mechanism is unlikely, and the reversible insertion/selective protonation mechanism is more plausible. Huang and co-workers reported that the use of acidic solvents greatly enhanced the reactivity of the C-H bond addition of 2-phenylpyridines to enones catalyzed by  $\text{Cp}^*\text{Rh(III)}$  probably because the protodemetalation step would be slow in non-acidic solvents,<sup>49</sup> which also supports the reversible insertion/selective protonation mechanism. The low enantioselectivity obtained by using Ag salts of other chiral acids having similar backbones **7** and **9** (Figure 4) indicated that the dianionic BINSate is essential in this system, and we assumed that the monoanionic property of chiral proton source  $\mathbf{A}^-$  may be important for selective protodemetalation of cationic intermediate **III**.

The present finding demonstrated that a chiral organic anion can efficiently control the enantioselectivity of  $\text{Cp}^*\text{Rh(III)}$ -catalyzed C-H bond functionalization without a chiral  $\text{Cp}^x$  ligand. Further investigation and application of  $\text{Cp}^*\text{M(III)}$ /chiral anion or

Cp\*M(III)/other chiral organocatalyst hybrid systems are ongoing in our laboratory.



**Figure 6. Proposed catalytic cycle.** The catalytic cycle involves C-H activation, insertion, and protodemetalation. Insertion/protodemetalation should be an enantio-determining step.

## Methods

**Synthesis of  $[\text{Cp}^*\text{RhL}_N][(\text{S})\text{-6,6'-Br}_2\text{-BINSate}]$  2b.** To a stirred solution of (S)-6,6'-Br<sub>2</sub>-BINSa **1b** (114 mg, 0.20 mmol) in CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>CN (1:1, 4 mL) was added Ag<sub>2</sub>CO<sub>3</sub> (110 mg, 0.40 mmol) at 40 °C. After stirring for 24 h in dark, the reaction mixture was filtered through a Celite pad, and washed with CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>CN (1:1). The filtrate was evaporated in *vacuo* to furnish Ag<sub>2</sub>-(S)-6,6'-Br<sub>2</sub>-BINSate (142 mg, 90%) as an orange solid, which was directly used for the next step without purification. To a flame-dried Schlenk flask were added  $[\text{Cp}^*\text{RhCl}_2]_2$  (50 mg, 0.081 mmol), Ag<sub>2</sub>-(S)-6,6'-Br<sub>2</sub>-BINSate (142 mg, 0.18 mmol), CH<sub>3</sub>CN (1.8 mL) in a glovebox. The flask was taken out of the glovebox, and the mixture was stirred at room temperature

and under argon atmosphere. After 48 h, the resulting precipitates were removed by filtration through a Celite pad and washed with CH<sub>3</sub>CN. The filtrate was concentrated in *vacuo* and the residue was dissolved in CH<sub>3</sub>CN (1 mL). To this solution was added Et<sub>2</sub>O dropwise, and the resulting orange precipitates were collected by filtration, washed with Et<sub>2</sub>O, and dried in *vacuo* to afford [Cp\*RhL<sub>N</sub>][(S)-6,6'-Br<sub>2</sub>-BINSate] **2b** (115 mg, 67% as trihydrate).

**General procedure of asymmetric 1,4-addition via C–H activation.** To a dried screw-capped vial were added **2b** (4.3 mg, 5 μmol, 5 mol %), MS3A (4 mg), and DCE (0.5 mL) under argon atmosphere in a glovebox. To the resulting mixture were successively added 2-phenylpyridine derivative **3** (0.10 mmol), 2-methylquinoline (2.7 μL, 0.02 mmol, 20 mol %), and enone **4** (0.11 or 0.13 mmol). The vial was capped, taken out of the glovebox, and the mixture was heated at 35 °C with stirring under argon atmosphere. Upon completion, as judged by TLC analysis of the reaction mixture, the reaction mixture was directly purified by silica gel column chromatography to afford the desired product **5**. The enantiomeric ratio was determined by chiral HPLC analysis (Chiralpak ID, hexane/*i*-PrOH = 9:1, 1.0 mL/min, 254 nm).

Other experimental details and characterization data are provided in. Supplementary Methods. The data that support the findings of this study are available from the corresponding authors upon reasonable request.

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## Author contributions

S.S., T.K., K.N., T.M., and T.Y. performed experiments and analyzed the data. S.S., M.H., K.I., T.Y., and S.M. conceived and designed the experiments, and prepared the manuscript. All authors contributed to discussions and commented on the manuscript.

**Competing financial interest**

The authors declare no competing financial interests.