C–H Activation Hot Paper

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General Enantioselective C–H Activation with Efficiently Tunable Cyclopentadienyl Ligands

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Abstract: *Cyclopentadienyl (Cp) ligands enable efficient steering of various transition-metal-catalyzed transformations, in particular enantioselective C–H activation. Currently only few chiral Cp ligands are available. Therefore, a conceptually general approach to chiral Cp ligand discovery would be invaluable as it would enable the discovery of applicable Cp ligands and to efficiently and rapidly vary and tune their structures. Herein, we describe the three-step gram-scale synthesis of a structurally diverse and widely applicable chiral Cp ligand collection (JasCp ligands) with highly variable and adjustable structures. Their modular nature and their amenability to rapid structure variation enabled the efficient discovery of ligands for three enantioselective Rh^{III}-catalyzed C–H activation reactions, including one unprecedented transformation. This novel approach should enable the discovery of efficient chiral Cp ligands for various further enantioselective transformations.*

The cyclopentadienyl (Cp) ligand and its pentamethyl analogue (Cp*) have emerged as versatile anionic ancillary ligands broadly applicable in transition-metal catalysis.[1] Despite this importance, highly efficient chiral Cp ligands for asymmetric catalysis had remained elusive for a long time and are in high demand.[2,3] Recently, inspired by the rapid development of Cp*Rh^{III}-catalyzed C–H activation, in two complementary strategies, Ward and Rovis et al.[4a] and Cramer and co-workers[4b,c] (Figure 1 a) developed the first classes of chiral Cp ligands, leading to a remarkable development in this field.[5] However, both ligand types face limitations.[3] On the one hand, the proteinaceous ligands developed by the groups of Ward and Rovis can be modified and optimized rapidly by means of molecular biology techniques, but may not be broadly applicable owing to the limitations imposed by the protein, such that only one successful example has been reported to date.[4a] On the other hand, the synthetic organic ligand type developed by the groups of Cramer[4b,c] and You[5k] is broadly applicable but limited in structural variability, and thereby its adaptation to different transformations is difficult owing to its lengthy preparation. As explicitly pointed out by Cramer et al.,[3b] novel chiral Cp ligand types that combine the advantages of

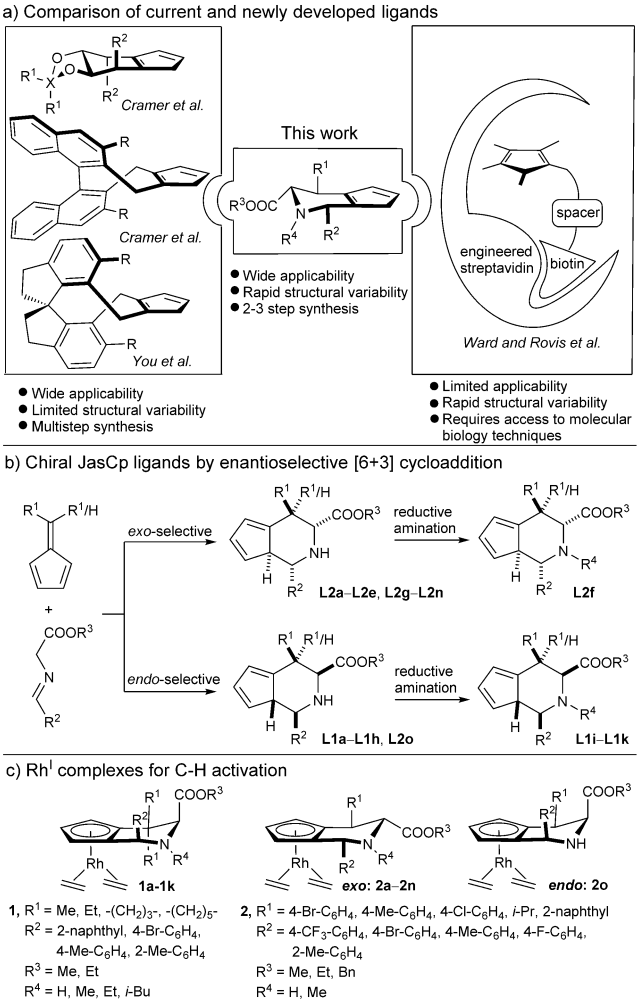

Figure 1. Concept for the discovery and synthesis of a new class of chiral JasCp ligands and the corresponding [$Cp^{I}Rh(C_2H_4)_2$] complexes.

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both current approaches, that is, efficient modification of the ligand structure and wide applicability under different conditions for rapid adaptation to different transformations, are highly desirable. Herein, we describe the development and implementation of a general strategy for the synthesis of a new class of chiral Cp ligands (JasCp ligands) and their application in enantioselective C–H activation reactions (Figure 1 a). The chiral JasCp ligands embody four adjustable positions and can be accessed efficiently in three steps on gram scale from commercially available starting materials with an enantioselective [6+3] cycloaddition as the key step, as previously reported by our group.[6] To demonstrate and validate the generality of the concept and the efficiency of the ligand development, a library of corresponding Rh^I catalysts was synthesized and employed for the highly enantioselective catalysis of two reactions previously described with the complementary chiral cyclopentadienyl ligands mentioned above[4b,c] and an unprecedented transformation yielding axially chiral biaryl compounds.

For the implementation of a general and efficient strategy for catalyst discovery and development, a variety of chiral Cp ligands must be readily accessible in a few steps and in high enantiopurity, and the Cp ligands must be equipped with stereogenic centers and functional groups that can both be flexibly varied to allow for catalyst optimization depending on the transformation to be steered enantioselectively. In light of these requirements, we employed enantioselective [6+3] cycloadditions of imino esters with fulvenes to efficiently access chiral Cp derivatives (Figure 1 b).[6] The modular nature of these Cp derivatives enables rapid structural variation by employment of different amino acids, aldehydes, and fulvenes. Different chiral Cp (JasCp) derivatives are available through enantioselective *endo*- and *exo*-selective transformations (**L1**, **L2**; see the Supporting Information for details). By means of this robust asymmetric synthesis methodology, a wide range of chiral Cp ligands were prepared using commercial catalysts for the [6+3] cycloadditions (see the Supporting Information, Table S1). We prepared the corresponding $[Cp^JRh(C_2H_4)_2]$ complexes and divided them into two categories (**1** and **2**) based on mono- or disubstitution with R^1 (Figure 1 c and Table S2). A notable feature of the developed $[Cp^JRh(C_2H_4)_2]$ complexes is the presence of a nucleophilic nitrogen atom in their structure.

To explore the potential of the novel catalysts, we investigated the C–H functionalization of hydroxamates with alkenes catalyzed by Rh^{III} (see Figure 2) that was initially reported by the groups of Glorius[7a] and Fagnou,[7b] and for which the first chiral version was developed by Ward and Rovis et al.[4a] and the Cramer group[4b] employing chiral Cp ligands (see Figure 1 a). To develop an efficient, streamlined process for catalyst optimization, we chose commercial catalysts for the synthesis of the chiral JasCp ligands by asymmetric [6+3] cycloaddition[6a,b] with moderate to excellent enantioselectivity. As the JasCp ligands were not obtained as pure enantiomers in these cycloadditions, the concept of chirality transfer (CT) was introduced to rapidly evaluate the efficiency of chirality induction by a given ligand (Table S3). In this concept, enantiomerically enriched ligands are employed and a linear relationship between the enantiopurity of the employed Cp catalyst and the enantiopurity of the products of the targeted reaction is assumed.[8] The validity of this assumption was subsequently confirmed by successful catalyst optimization (Figure S1). For ligand optimization, a standard reaction was employed with R^1 substituents originating from different ketones or aldehydes (Table S3, entries 1–6). The methyl group was identified to be optimal for disubstitution with R^1, and the corresponding Rh^I complex **1a** gave the desired product with 68 % CT in 90 % yield. Other groups, such as ethyl, cyclobutyl, or cyclohexyl moieties, resulted in either lower reactivity or lower enantioselectivity. Sequentially, intensive screening of R^2 was conducted by making use of commercially available aldehydes, including aromatic substitutions with different electronic properties on all positions (Table S3, entries 7–9). The R^2 group was identified to be critical for the enantioselectivity and the 2-naphthyl group turned out to be optimal. Furthermore, investigations of the possible effect of R^3 on the ester group revealed that big groups such as ethyl resulted in lower reactivity for this specific reaction although the enantioselectivity remained comparable (Table S3, entry 10). The corresponding ligand in optically pure form can be prepared

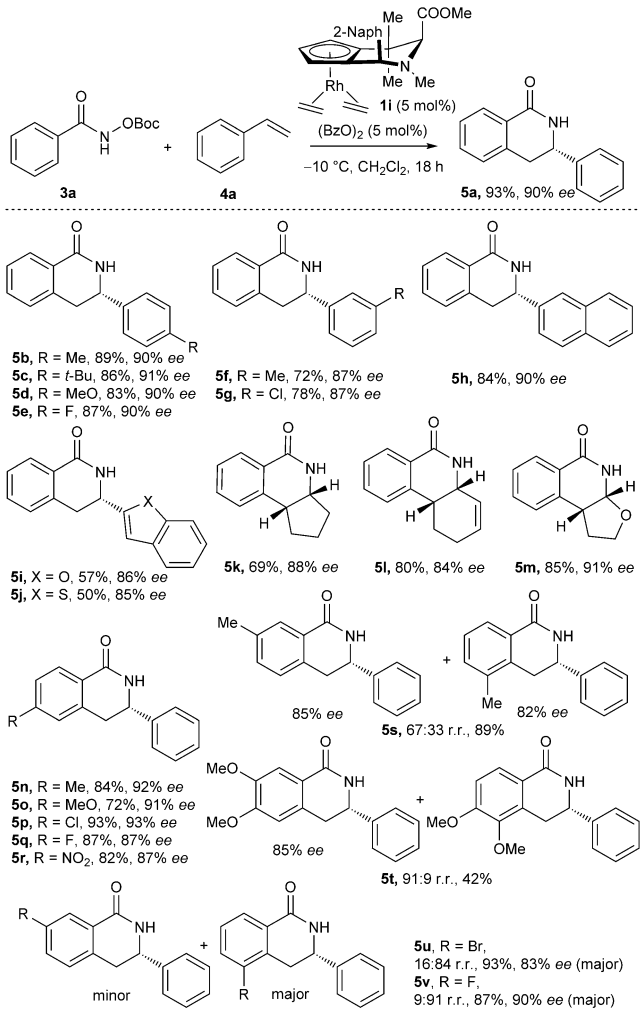

Figure 2. Enantioselective synthesis of isoquinolinones.[10] Bz = benzoyl.

by using preparative HPLC on a chiral stationary phase for racemate separation on gram scale or by using a known enantioselective [6+3] cycloaddition.[6c] With this optically pure ligand in hand, we investigated the importance of the protective group on the secondary amine. Several N-alkylated ligands were readily synthesized by reductive amination with various aldehydes. Among those, the N-methylated catalyst **1i** afforded the desired product in 90% yield and with 83% *ee*. Further enhancement of steric hindrance by introduction of an ethyl or an isobutyl substituent led to a decrease in both reactivity and enantioselectivity (Table S3, entries 11–13). The structure and absolute configuration of catalyst **1i** were unambiguously determined by crystal-structure analysis (Figure S3).[9]

Having an optimized catalyst (**1i**) in hand, we optimized the reaction conditions (Table S4). The solvent had no obvious effect on the enantioselectivity, but significantly influenced the reactivity. Moreover, up to 90% *ee* could be reached by lowering the temperature to −10 °C (Figure 2 and Table S4, entry 3). Having established optimized reaction conditions, the substrate scope was explored. As shown in Figure 2, various styrenes, even those with heterocyclic substituents or cyclic alkenes, are tolerated in this enantioselective transformation, yielding the desired products with excellent regio- and enantioselectivity (see **5a**–**5j** and **5k**–**5m**, respectively). Aryl hydroxamates with substituents with different electronic and steric properties proved to be suitable for this reaction and yielded the desired products **5n**–**5v**. The absolute configuration of product **5m** was assigned by vibrational circular dichroism (VCD) spectroscopy (Figure S4).[10]

To demonstrate the generality of the approach and the flexible applicability of our ligand library, we investigated the asymmetric C–H allylation of benzamides (Figure 3) that had previously been rendered enantioselective by Cramer and coworkers with chiral binaphthyl-substituted Cp ligands.[4c] This seminal work showed that the cyclohexyl-substituted chiral Cp ligands successfully applied in the synthesis of isoquinolinones[4b] (Figure 2) failed to induce high enantioselectivity in this transformation.[4c] A preliminary experiment showed that only 24% *ee* could be achieved with catalyst **1i**, which had proven best in steering the reaction described above (Figure 2 and Table S5, entry 3). Gratifyingly, screening with our ligand collection rapidly revealed that catalyst **2a**, which is based on a chiral Cp ligand obtained from *exo*-selective [6+3] cycloaddition and equipped with two aryl groups, is very efficient in this process, yielding up to 86% CT without diminishing the reactivity (Table S5, entry 6). Although Rh^I complex **2a** was obtained as a 60:40 mixture of diastereomers owing to the face selectivity of Rh complexation (Table S2), we decided to directly use this mixture of Rh^I complexes for further ligand optimization to streamline the catalyst screening process. Systematic variation of the R^1 and R^2 groups in the ligand demonstrated that excellent enantioselectivity was observed if ligands with *para*- or *meta*-substituted aryl groups were used (Table S5). The R^3 group did not have a significant effect on the enantioselectivity (Table S5, entries 8, 17, and 18). In sharp contrast to catalyst **1i**, which performed best in the isoquinolinone synthesis (Figure 2), R^4 = Me led to a sluggish

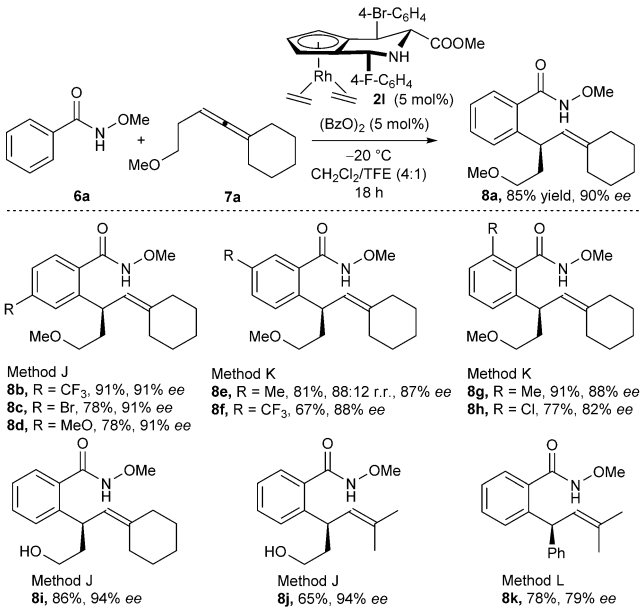

Figure 3. Enantioselective allylation of benzamides.[10] Method J: Benzamides **6** (0.12 mmol, 1.20 equiv) and allenes **7** (0.10 mmol, 1.00 equiv) were used with 0.5 mL of DCM/TFE mixture as the solvent. Method K: Benzamides **6** (0.10 mmol, 1.00 equiv) and allenes **7** (0.12 mmol, 1.20 equiv) were used. Method L: 0.1 mL of DCM/TFE.

reaction and decreased enantioselectivity (Table S5, entry 11). Ultimately, catalyst **2l** turned out to be best. Subsequent optimization of the reaction conditions revealed that the solvent has a dramatic effect on the reactivity, but only a slight influence on the enantioselectivity (Table S6). A 4:1 combination of dichloromethane (DCM) and trifluoroethanol (TFE) proved to be optimal, affording the desired product in 85% yield and with 90% *ee* within 18 h at −20 °C (Figure 3). Examination of the possible difference between the two diastereomers of the Rh^I complex surprisingly revealed that both diastereomers of catalyst **2l** yielded the product with the same stereoselectivity. This finding was confirmed for catalyst **2n** (Figure S2). Therefore, Rh^I complex **2l** was employed as a mixture of two diastereomers in all further transformations. Evaluation of the substrate scope (Figure 3) showed that benzamides bearing different substitution patterns were well tolerated, affording products **8a**–**8h** with good to excellent *ee* values and yields. Furthermore, various allenes can be employed in this reaction (**8i**–**8k**).

To confirm that our approach also enables the discovery of chiral catalysts for unprecedented reactions, a novel C–H activation reaction was realized that yields valuable axially chiral biaryl compounds with excellent enantioselectivity (Figure 4). Despite the prevalence of atropisomerism in natural products,[11] pharmaceuticals,[12] and chiral catalysts/ligands,[13] the corresponding catalytic enantioselective approaches have not reached the state of the art for the establishment of chirality established for other compound classes, and novel methods are in high demand.[14] Especially in the field of asymmetric transition-metal catalysis enabled by chiral Cp ligands, only two classes of transformations have been documented.[2d-f,5c,k] In contrast, biaryl compounds have

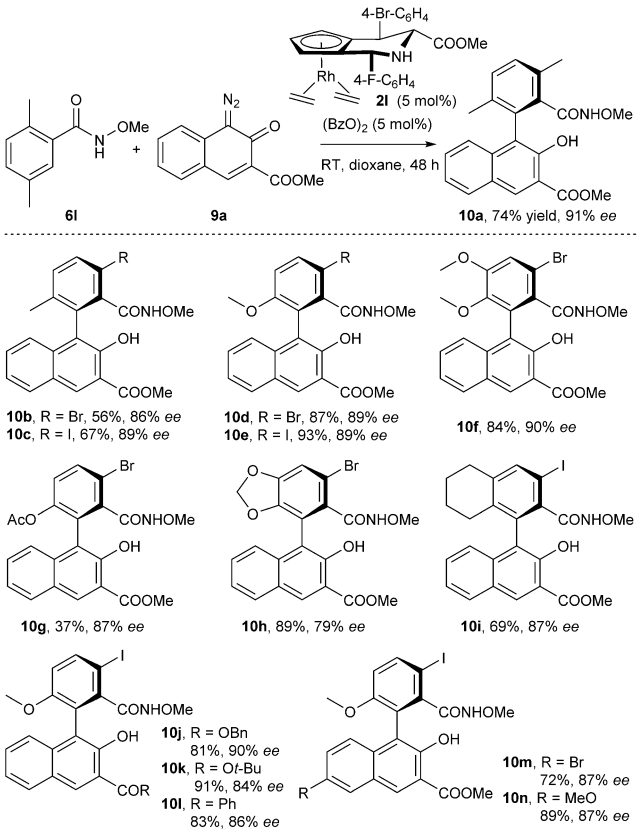

Figure 4. Synthesis of axially chiral compounds.[10]

efficiently been synthesized through direct C–H arylation enabled by rhodium(III) complexes with achiral Cp and Cp* ligands.[15] Although such strategies represent one of the most efficient approaches to construct aryl–aryl bonds, a catalytic enantioselective version has not been reported thus far. Based on this consideration, we envisioned that the chiral JasCp ligands could also enable the synthesis of axially chiral biaryls by direct C–H arylation. Benzamides **6** and diazonaphthoquinones **9** were chosen as promising coupling partner candidates (Figure 4).[16] Aside from their considerable reactivity, diazo compounds **9** can provide two *ortho* substituents adjacent to aryl–aryl bonds in the resulting biaryl products **10**, thus contributing to the stabilization of the axial chirality. After preliminary optimization, the reaction of benzamide **6l** and **9a** afforded the desired substituted product **10a** in 74% yield with up to 91% *ee* using **2l** as the catalyst (Figure 4). Subsequent investigation of the substrate scope revealed that various electron-rich substituents in the *meta* position of the benzamide were tolerated well, affording chiral biaryl compounds **10b**–**10i** in good to excellent yields and enantioselectivities. To prohibit further coupling of biaryl product **10** with diazonaphthoquinone **9**, various *ortho* substituents, such as methyl, bromo, and iodo groups, were installed on the benzamide, and also found to be compatible with this transformation. Furthermore, reactions with **9** bearing various substituents proceeded well and provided compounds **10j**–**10n** with high enantioselectivity. The absolute configuration of **10a** was assigned by vibrational circular dichroism (VCD) spectroscopy (Figure S5).[10]

To rationalize the observed regio- and enantioselectivity, computational studies[17] were performed for the isoquinolinone synthesis (Figure 2; for details, see the Supporting Information). There are four possible stereoisomers based on two regioisomers with the phenyl group at the 3- and 4-positions, of which only the 3-substituted regioisomer **5a** with *S* configuration was found experimentally. The excellent regioselectivity can be rationalized by our calculations as all pathways to the 4-substituted regioisomers feature transition-state barriers that are approximately 2 kcal mol^{-1} higher in energy than those leading to the 3-substituted regioisomers (Figure S6 and Table S7). Hence, from a kinetic perspective and in agreement with the experimental findings, the pathways leading to the 4-substituted regioisomer can be excluded from the analysis. Regarding the enantioselectivity of the formation of the 3-substituted regioisomers, previous mechanistic considerations suggested a preferred structure for the rhodacycle intermediate in which the Boc protective group is located on the sterically less hindered side, and styrene approaches the rhodacycle intermediate from the open side with the phenyl group pointing away from the Cp ligand to avoid unfavorable steric interactions.[4b] Accordingly, in the present case, the Boc moiety would point towards the 2-naphthyl group (substituent R^2) bearing side of the ligand to avoid unfavorable steric interactions with the methyl group (substituent R^1; intermediate **B**, Figure 5). Styrene should

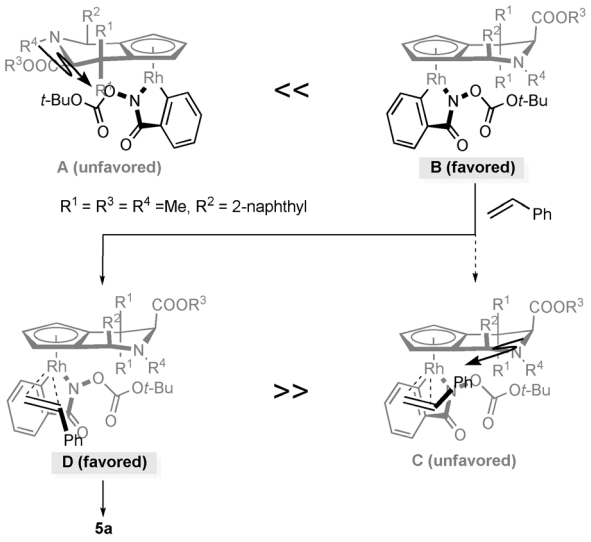

Figure 5. Stereochemical model for the isoquinolinone synthesis.

approach in the same way (intermediate **D**, Figure 5) while the other orientation of styrene would be less favorable (intermediate **C**, Figure 5). For the calculations, we also considered that the hydroxamate is in its presumably less favored orientation with the Boc group pointing towards the methyl groups (substituents R^1, intermediate **A**, Figure 5). In addition, we took into account two different orientations of the Boc carbonyl group (Figure S8), so that in total four conformers of the rhodacycle intermediate were investigated. Furthermore, two opposite ways for the approach of styrene to the rhodacycle intermediate were also taken into consid-

eration (intermediates **C** and **D**, Figure 5). Analysis of the free-energy profiles of all pathways strongly supported the stereochemical model previously proposed by the Cramer group.[4b]

In conclusion, we have developed a conceptually novel general approach to chiral Cp ligand discovery that unites the advantages of previously developed ligand classes, namely wide applicability and the possibility for rapid structural variation. The chiral JasCp ligands can be readily synthesized in three steps on gram scale from commercially available starting materials, and both their structures and configurations can be efficiently adjusted by means of flexible enantioselective [6+3] cycloaddition reactions. Further modification of the secondary amine embodied in the [6+3] cycloadducts enlarges the ligand pool significantly, and more importantly proves to be critical for the enantiocontrol of different reactions. Investigation of a chiral JasCp ligand collection with modular nature, and therefore with highly variable and adjustable structures and absolute and relative configurations, enabled the efficient discovery of chiral ligands for different enantioselective Rh^{III}-catalyzed C–H activation reactions. Our results suggest that this approach should enable the discovery of efficient chiral JasCp ligands for various further enantioselective transformations.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: asymmetric synthesis · C–H activation · cycloadditions · cyclopentadienyl ligands · rhodium

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Communications

C–H Activation

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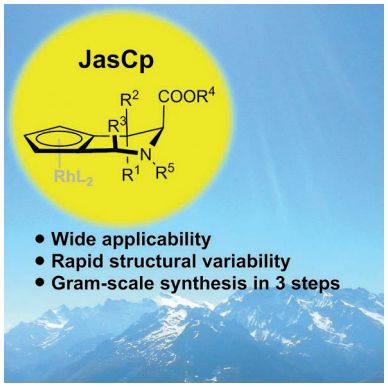
General Enantioselective C–H Activation with Efficiently Tunable Cyclopentadienyl Ligands



The discovery of chiral Cp ligands that unite the advantages of previously developed ligand classes is enabled by a novel approach. They can be readily synthesized on gram scale, and both their structures and configurations can be efficiently adjusted by means of flexible enantioselective [6+3] cycloaddition reactions. With these ligands, three rhodium(III)-catalyzed C–H activation reactions were rendered highly enantioselective.