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Asymmetric Catalysis | *Very Important Paper* |

trans-Cyclooctenes as Chiral Ligands in Rhodium-Catalyzed Asymmetric 1,4-Additions

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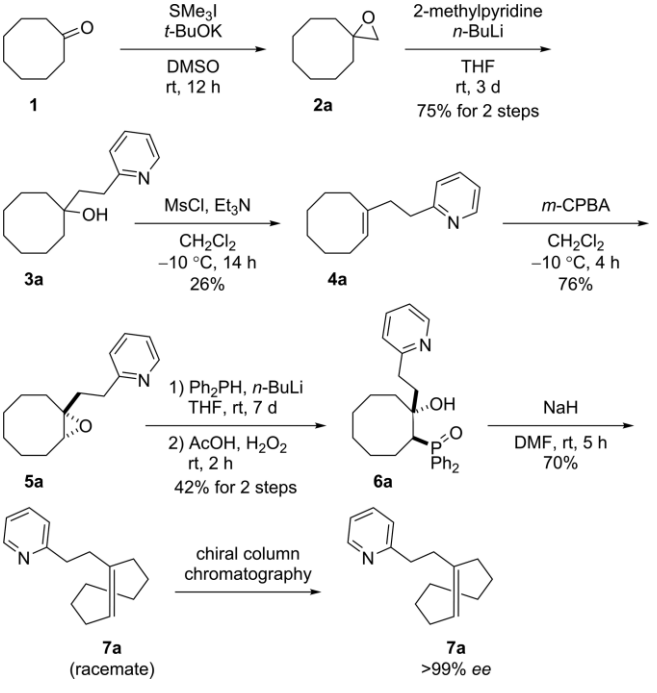
Abstract: *trans*-Cyclooctenes serve as asymmetric ligands for the rhodium-catalyzed 1,4-additions of organotin reagents to enones. We demonstrate, for the first time, that these chiral olefins can provide efficient coordination spheres for asymmetric metal catalysis. As the asymmetric environment around the reaction site is constructed by the *trans*-cyclooctene framework, the introduction of a substituent at the allylic position further improves enantioselectivity to 93 % *ee*. These findings provide new chiral framework designs for the asymmetric ligands of metal catalysts.

Since the discovery of Zeise's salt,[1] metal-olefin complexes have been extensively studied[2] and used in synthetic organic chemistry. In particular, olefins with planar chirality, such as optically active dienes, have contributed significantly to advancements in asymmetric transition-metal catalysis.[3] Among olefins bearing molecular asymmetry, *trans*-cyclooctene, which was the first chiral olefin synthesized,[4] is also known to coordinate to transition metals more strongly than normal olefins due to its strained structure that favors π back donation from a metal atom;[5] its coordination as a substrate to a metal complex bearing a chiral amine ligand was used to synthesize optically active *trans*-cyclooctene.[4b,4c] However, to the best of our knowledge, the behavior of *trans*-cyclooctene derivatives as chiral ligands for asymmetric catalysis is unknown despite their potential as novel molecular-catalyst platforms.[6] Here, we introduce *trans*-cyclooctenes as asymmetric ligands for the rhodium-catalyzed 1,4-additions of organotin reagents and describe their performance, thereby providing new chiral platforms for asymmetric catalysis.

Initially, we designed *trans*-cyclooctene **7a** bearing a pyridyl group as a bidentate ligand, the synthesis of which is shown in Scheme 1.[7] Starting from cyclooctanone (**1**), epoxidation with a sulfur ylide followed by ring opening with (pyridin-2-yl-methyl)lithium yielded **3a**, which was then transformed into *cis*-cyclooctene **4a** by treatment with methanesulfonyl chloride in the presence of triethylamine. Subsequent epoxidation and ring opening with lithium diphenylphosphide followed by oxidation gave the corresponding phosphine oxide **6a**. Finally, treatment with sodium hydride afforded racemic *trans*-cyclooctene **7a**. The enantiomers were subsequently separated by liquid column chromatography with a chiral stationary phase to give optically active **7a** with > 99 % *ee*. Platinum complex **8** was prepared in order to confirm the olefin geometry and absolute configuration of **7a**,[8] and a single crystal was grown for X-ray analysis (Figure 1). The ORTEP drawing unambiguously shows that the alkene is *trans*-configured and is the R_p-enantiomer.[9] In addition, *trans*-cyclooctene **7a** bearing the pyridyl group was shown to be a bidentate ligand.



Scheme 1. Synthesis of *trans*-cyclooctene **7a**.

We next investigated the rhodium-catalyzed 1,4-addition of organotin reagent **10a** to cyclohexenone (**9a**) using 5.0 mol-%

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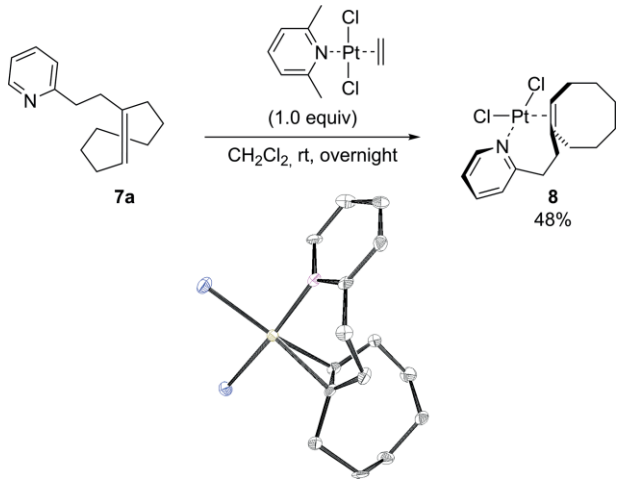
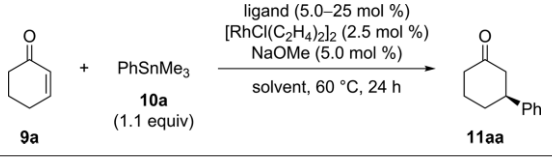


Figure 1. Synthesis and ORTEP drawing of platinum complex **8**.

of **7a**.[10] The reaction proceeded in toluene and ethanol with promising enantioselectivities, while product **11aa** was not obtained in 1,4-dioxane (Table 1, entries 1–3). The enantioselectivities were further improved using 10 mol-% of **7a** (Table 1, entries 4 and 5). In addition, reactions with cyclooctene ligands **12** and **13** did not provide any products (Table 1, entries 6 and 7); the *trans*-cyclooctene framework bearing an additional coordinating group (i.e., pyridyl) was found to be essential for generating an active catalytic species. Furthermore, even higher loadings of **7a** also led to higher enantioselectivities (Table 1, entries 8–10). Cyclooctene ligands see Figure 2.

Table 1. Performance of cyclooctene ligands in rhodium-catalyzed asymmetric 1,4-additions.[a]



Entry	Ligand	Loading of **7** [mol-%]	Solvent	Yield [%][b]	*ee* [%]
1	**7a**	5	1,4-dioxane	< 5	–
2	**7a**	5	toluene	9	71
3	**7a**	5	EtOH	8	77
4	**7a**	10	toluene	8	78
5	**7a**	10	EtOH	10	80
6	**12**	10	EtOH	< 5	–
7	**13**[c]	10	EtOH	< 5	–
8	**7a**	15	EtOH	7	84
9	**7a**	20	EtOH	6	86
10	**7a**	25	EtOH	13	84

[a] Reactions were run using **9a** (0.25 mmol), **10a** (0.28 mmol), $[RhCl(C_2H_4)_2]_2$ (0.0063 mmol), NaOMe (0.013 mmol), and the ligand in the solvents (1.0 mL). [b] NMR yields. [c] A racemate of **13** was used.

Other enones and organotin reagents were also reacted using 10 mol-% of **7a** in ethanol (Scheme 2). While **11ba** and **11ca** were formed with moderate *ee*, cycloheptenone (**9c**) gave **11ca** with higher enantioselectivity (84 % *ee*). In addition, the electron-poor reagent **10b** provided the corresponding product **11ab** in slightly higher enantioselectivity, but the electron-rich reagent **10c** did not give useful amounts of **11ac**. Acyclic enones and other organotin reagents investigated did not provide the corresponding products under these conditions (see Scheme S2 in the Supporting Information for details). The absolute configurations of **11** were determined by comparing their optical rotation with literature values[11] (see the Supporting Information for details).

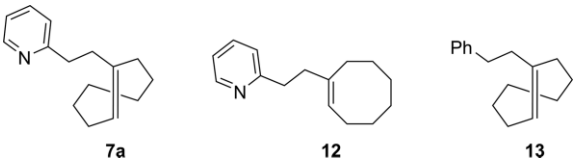
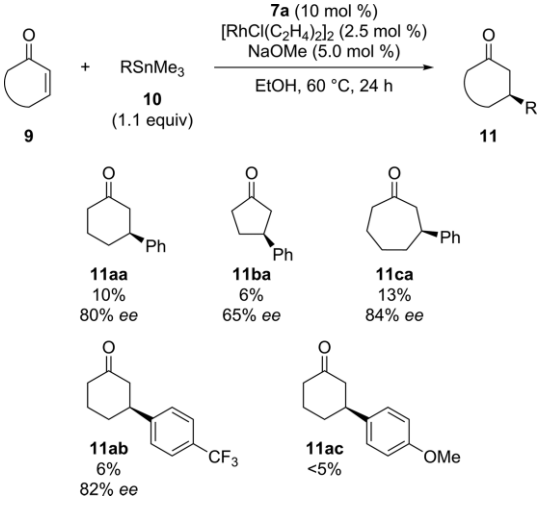
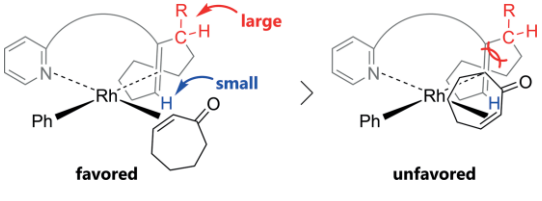


Figure 2. Cyclooctene ligands.



Scheme 2. Reactions with various organotin reagents and substrates.

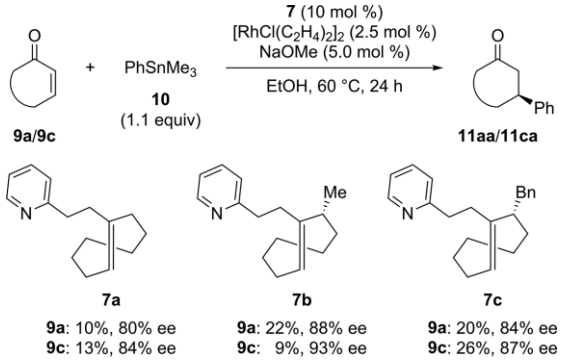
On the basis of the absolute configurations of the obtained products and previous studies,[3,12] these reactions are proposed to proceed through the formation of the rhodium complexes shown in Scheme 3. The pyridyl group and the alkene constitute a bidentate ligand; the enone approaches *syn* to the *trans*-cyclooctene moiety, and the asymmetric environment around the reaction site is constructed by the *trans*-cyclooctene framework (highlighted in red and blue in Scheme 3), noting that the methylene group (R = H) is sterically bulkier than a hydrogen atom. Therefore, the enone preferentially approaches in a manner that avoids the bulkier group, which results in high enantioselectivity.



Scheme 3. Proposed reaction pathway.

This mechanistic insight inspired us to introduce substituents at the allylic position (R ≠ H) in order to further improve enantioselectivity; hence, ligands **7b** and **7c** were synthesized, and the reactions of **9a** and **9c** with these ligands were investigated

(Scheme 4).[13] As expected, enantioselectivities were improved in all cases, and especially for the reaction of **9c** with **7b**, which afforded **9c** with 93 % *ee*, suggesting that these *trans*-cyclooctenes are appropriately designed asymmetric ligands.[14]



Scheme 4. Reactions using **7a** and 8-substituted *trans*-cyclooctene ligands **7b** and **7c**.

In summary, we demonstrated that *trans*-cyclooctenes serve as asymmetric ligands in the rhodium-catalyzed 1,4-additions of organotin reagents to enones. These chiral olefins provide high enantioselectivities and can create efficient coordination spheres for asymmetric metal catalysis. Although further studies are required to improve catalytic activity, these findings offer new avenues for the design of novel asymmetric metal catalysts. Studies into more sophisticated ligands and applications to a variety of metal catalysts are currently underway in our laboratory.

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Keywords: *trans*-Cyclooctene · Planar chirality · Chiral ligands · Rhodium · 1,4-Addition

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[9] Deposition Numbers 2024941–2024942 contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.
[10] Although 1,4-addition using phenylboronic acid was also investigated, the enantioselectivity was much lower than that obtained using the organotin reagents. See Scheme S1 in the Supporting Information for details.
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[12] Small nonlinear effects were observed (see Scheme S3 in the Supporting Information for details), consistent with a previous report that used chiral phosphine-olefin ligands. See ref.[3g].
[13] *trans*-Cyclooctene ligand **7d** bearing a 2-methylbenzyl group was also synthesized and investigated. See Scheme S4 in the Supporting Information for details.
[14] *trans*-Cyclooctene to *cis*-cyclooctene isomerization was also detected at the end of these catalytic reactions, and may be one of the reasons for the observed low chemical yields. As **7a** isomerizes faster at higher loadings, isomerization may be caused by the coordination of two molecules of **7a** to a rhodium center. Actually, the isomerizations of **7b** and **7c** were suppressed to some extent, and the yields from the reactions catalyzed by **7b** and **7c** were slightly higher than those catalyzed by **7a** (Scheme 4), which suggests that the bulkiness of the ligand also inhibits the extra coordination of **7** in addition to constructing a better asymmetric environment. See Scheme S5 in the Supporting Information for details.

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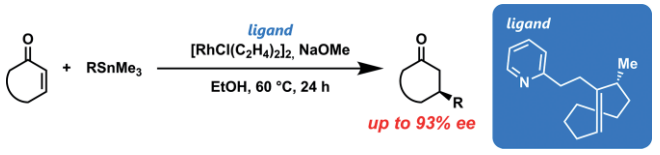

trans-Cyclooctenes serve as asymmetric ligands during the rhodium-catalyzed 1,4-additions of organotin reagents to enones. The potentials of these chiral olefins to provide efficient coordination spheres for asymmetric metal catalysis are demonstrated for the first time. These findings provide chiral frameworks for the design of asymmetric ligands for metal catalysts.

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