Asymmetric Induction at Remote All-carbon Quaternary Centers of Cyclohexadienones by Rh-catalyzed Conjugate Hydrosilylation

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Abstract: This paper describes the enantioselective desymmetrizing conjugate hydrosilylation of prochiral γ,γ-differently disubstituted cyclohexadienone derivatives **2** to furnish the corresponding cyclohexenones **4** having a remote chiral all-carbon quaternary center at the γ-position. The chiral rhodium-bis(oxazolinyl)phenyl complexes (**1**) were effective catalysts for this transformation. This catalytic system was extended to the asymmetric transformation of cyclohexadienones **5** bearing spirocarbocycles to give the corresponding products **6** with high enantiomeric ratios.

The catalytic asymmetric construction of chiral all-carbon quaternary centers has been recognized as one of the most rewarding accomplishments.[1] Cyclohexane rings having chiral all-carbon quaternary centers are ubiquitous and attractive building blocks found in pharmaceutical agents and natural compounds.[1,2] Major approaches toward the enantioselective synthesis of these structures are based on transformations utilizing reactive cyclohexanones. α-Functionalization of the carbonyl groups involving enantioselective C-C bond forming processes have been well established.[3,4] Furthermore, enantioselective conjugate additions to β-substituted cyclohexenones are the representative strategies to give cyclohexanones with chiral all-carbon quaternary centers at the β-position.[1d] As a whole, the catalytic asymmetric preparation of cyclohexanones bearing chiral all-carbon quaternary centers at the α- or β-positions has been extensively studied.

One of the recent challenges in asymmetric synthesis is the construction of remote chiral quaternary centers distant from such reactive functionalities.[5,6] We aim toward the development of general protocols to furnish optically active cyclohexenone derivatives having a chiral all-carbon quaternary center at the γ-position. The carbon at this position is inherently inert and thus it is difficult to form new C-C bonds here with common transformations. In this context, several research groups have demonstrated an interesting asymmetric desymmetrization of achiral γ,γ-differently disubstituted cyclohexadienones to furnish the corresponding six-membered rings having a chiral all-carbon quaternary center.[7] Intramolecular desymmetrization reactions have been successfully performed,[7,8] while a few of more challenging intermolecular variants were reported with high enantioselectivity with several organocatalysts.[9] We anticipated that the simplest transformation, the desymmetrizing reduction of one side of the C-C unsaturated bond within the γ,γ-disubstituted cyclohexadienones in an enantioselective manner, would furnish a cyclohexenone bearing a chiral all-carbon quaternary center at the γ-position. We addressed this issue by applying transition metal-catalyzed enantioselective conjugate hydrosilylation.[10] Although enantioselective conjugate hydrosilylation of α,β-unsaturated compounds has been well studied,[11,12] the investigation into the construction of remote all-carbon quaternary centers has been rarely conducted. The most challenging feature of this target transformation is that the metal catalyst must discriminate at the steric environment of a quaternary carbon that has inherently no relationship to the reduction event.

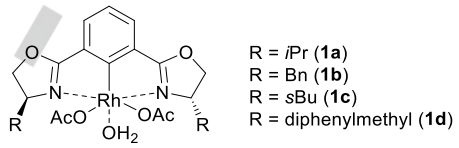

Figure 1. Rh(Phebox-R) (**1**).

We applied chiral rhodium-bis(oxazolinyl)phenyl complexes [Rh(Phebox-R)] (**1**)[13] as catalysts to the enantioselective conjugate hydrosilylation of α,β-unsaturated compounds.[14] The model reaction using 4-methyl-4-phenylcyclohexadienone (**2a**) was carried out first (Table 1). Thus, we ran the reaction of **2a** with triethoxysilane as a reductant in the presence of 2 mol% of catalyst **1a** in toluene at 50 °C (entry 1). After stirring for 1 h, complete formation of the corresponding 2-silyloxy diene **3a** was observed. The noteworthy reason why we did not adopt other reductants such as hydrogen is that the formation of electron-rich intermediate **3a** can suppress the second undesirable reduction of another unsaturated bond. The subsequent treatment of **3a** under acidic condition gave the desired cyclohexenone **4a** with an all-carbon quaternary center at the γ-position in 52% yield (entry 1). Gratifyingly, the non-racemic product was obtained and the enantiomeric ratio of **4a** was 83.5:16.5. Next, we performed the screening of a series of hydrosilanes. Among the alkoxyhydrosilanes, the reaction with trimethoxysilane gave the better result (90% yield, 86.5:13.5 er) (entries 2 and 3). On the other hand, the reaction with diphenylmethylsilane led to a decrease in chemical yield and enantioselectivity (entry 4). The use of dihydrosilanes did not improve the result (entry 5). Next, we examined the substituent effect of [Rh(Phebox-R)] (**1**) (entries 6-8). The use of [Rh(Phebox-*s*Bu)] (**1c**) slightly improved the enantioselectivity (entry 7). In addition, the reaction performed at a lower temperature of 40 °C gave **4a** with the highest enantiomeric ratio (88.5:11.5 er), whereas the reaction at room temperature did not proceed at all (entry 10). The absolute configuration of **4a** was determined as *S* by comparison to reported compounds.[15]

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[**] This research was supported by Grants-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (Nos. 15H03808 and 15K21063).

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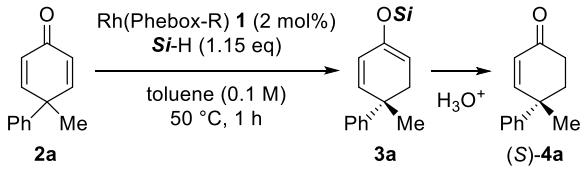
Table 1. Optimization of reaction conditions.[a]

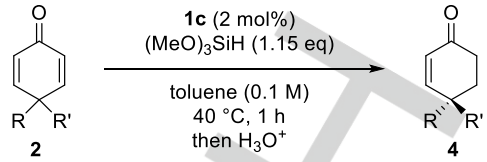


Entry	1	*Si*-H	Yield [%][b]	*e.r.* [%]
1	**1a**	$(EtO)_3SiH$	52	83.5:16.5
2	**1a**	$(EtO)_2MeSiH$	87	77.5:22.5
3	**1a**	$(MeO)_3SiH$	90	86.5:13.5
4	**1a**	$PhMe_2SiH$	13	72.5:27.5
5	**1a**	Ph_2SiH_2	57	81.5:18.5
6	**1b**	$(MeO)_3SiH$	99	85.5:14.5
7	**1c**	$(MeO)_3SiH$	97	87:13
8	**1d**	$(MeO)_3SiH$	91	75.5:24.5
9[c]	**1c**	$(MeO)_3SiH$	82	88.5:11.5
10[d]	**1c**	$(MeO)_3SiH$	No reaction	---

[a] Reaction conditions: **2a** (0.1 mmol), hydrosilane (0.115 mmol), **1** (2 mol%), toluene (1 mL), 50 °C, 1 h. [b] Isolated yield. [c] 40 °C. [d] Room temperature.

Next, we examined the scope of 4-methyl-4-arylcyclohexadienones (**2**) (Table 2). Since we initially hypothesized that the Rh-H species would approach from the less hindered prochiral face of **2a** to avoid the large phenyl ring, we carried out the reaction with 4-methyl-4-arylcyclohexadienones **2b-g** bearing various substituents on the phenyl ring to gain steric bulkiness. Concerning the position of the substituent, the introduction of *meta*- or *ortho*-substituents tended to slightly diminish the enantioselectivity, contrary to expectations (entries 2-4). To examine the electronic effect of the substituents, we conducted the reaction with compounds **2e** and **2f** (entries 5 and 6). The introduction of an electron-donating group improved the er whereas the introduction of electron-withdrawing group resulted in lower er. For the ring size of the large aromatic substituent, the reaction of compound **2g** gave a similar er to the standard compound **2a** (entry 7). We next performed the reaction of 4-ethyl-4-phenylcyclohexadienone (**2h**) to investigate the steric importance of the alkyl side chain of **2a** (entry 8). The er of **4h** was dramatically decreased to 68.5:31.5. Finally, the reaction of **2i** with different two alkyl groups (cyclohexyl and Me) gave product **4i** with moderate enantioselectivity (entry 9). The absolute configuration of the product **4e** was determined as *S* by comparison to reported compounds.[15] For unreported compounds **4**, the absolute configuration was tentatively assigned by analogy.

Table 2. Reaction of 4-alkyl-4-arylcyclohexadienone **2**.[a]



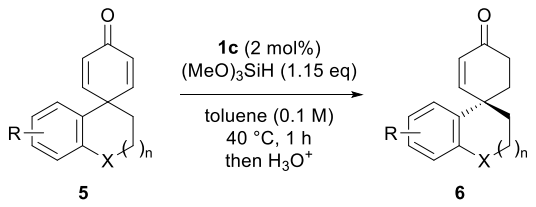
Entry	R	R'	Yield [%][b]	*e.r.* [%]
1	Ph	Me (**2a**)	82 (**4a**)	88.5:11.5
2	*p*-tolyl	Me (**2b**)	95 (**4b**)	88.5:11.5
3	*m*-tolyl	Me (**2c**)	95 (**4c**)	85.5:14.5
4	*o*-tolyl	Me (**2d**)	99 (**4d**)	85:15
5	p-$MeOC_6H_4$	Me (**2e**)	92 (**4e**)	90.5:9.5
6	p-$F_3CC_6H_4$	Me (**2f**)	92 (**4f**)	82.5:17.5
7	2-Np	Me (**2g**)	53 (**4g**)	88:12
8	Ph	Et (**2h**)	99 (**4h**)	68.5:31.5
9	cyclohexyl	Me (**2i**)	89 (**4i**)	84:16

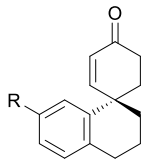
[a] Reaction conditions: **2** (0.1 mmol), trimethoxysilane (0.115 mmol), **1c** (2 mol%), toluene (1 mL), 40 °C, 1 h. [b] Isolated yield.

To further broaden the utility of this protocol, we focused on cyclohexadienone **5** incorporating spirocarbocycle backbones (Table 3). Spiro-containing chiral compounds are unique motifs found in natural compounds isolated from a wide range of biological sources.[16] We initially performed the reaction of spiro-containing cyclohexadienone **5a** to provide the corresponding product **6a** in 89% yield with 96.5:3.5 er. Concerning the substituent at the tetrahydronaphthalene core, the reactions of **5b-g** with electron-donating or -withdrawing substituents at various positions of the aromatic ring were carried out. The ers of desired products **6b-g** were uniformly high in the range of 92:8 to 96.5:3.5 er. Since spirocarbocycles containing heteroatoms are ubiquitous structures in nature, we also employed the spiro-fused heterocyclic compounds **5h-n**.[16] The enantioselective conjugate hydrosilylation proceeded smoothly to furnish the desired products **6h-n** in good yields and with good ers. Finally, we determined that the ring size of **5** had a significant impact on the enantioselectivity. For example, the reaction of **5o** having a five-membered ring provided the product **6o** with a slightly lower enantioselectivity (89:11 er). In contrast, the reaction of **5p** having a seven-membered ring resulted in a dramatic decrease of enantioselectivity (61.5:38.5 er).

To enhance the synthetic utility of the present protocols, we moved on to the derivatization of the obtained compounds **6a** (Scheme 1A). α-Iodination of **6a** by Johnson's procedure[17] was accomplished to give α-iodocyclohexenone **7** which could be a versatile building block. As an example, we demonstrated the Suzuki-Miyaura cross coupling of **7** to furnish the corresponding product **8** in 85% yield and without loss of er.

Table 3. Reaction of cyclohexadienone **5** having a spirocycle.



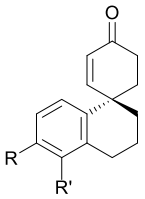


6a (R = H) : 89% yield, 96.5:3.5 er

6b (R = OMe) : 88% yield, 96.5:3.5 er [a]

6c (R = F) : 99% yield, 94.5:5.5 er

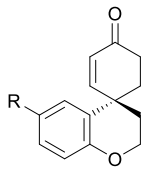
6d (R = Cl) : 82% yield, 92:8 er



6e (R = OMe, R' = H) : 62% yield, 95:5 er

6f (R = Cl, R' = H) : 95% yield, 94.5:5.5 er

6g (R = H, R' = OMe) : 95% yield, 95.5:4.5 er

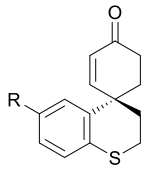


6h (R = H) : 89% yield, 94:6 er

6i (R = Me) : 93% yield, 94:6 er

6j (R = F) : 97% yield, 92.5:7.5 er

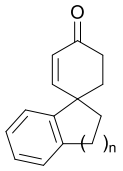
6k (R = Cl) : 88% yield, 92:8 er



6l (R = H) : 94% yield, 91:9 er

6m (R = Me) : 91% yield, 90.5:9.5 er

6n (R = Cl) : 90% yield, 85:15 er

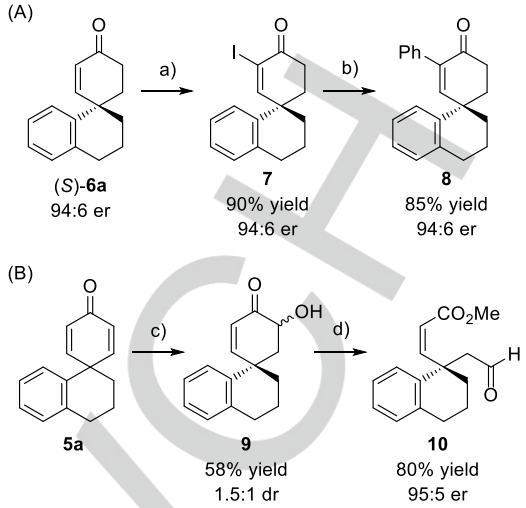


6o (n = 1) : 90% yield, 89:11 er

6p (n = 3) : 95% yield, 61.5:38.5 er

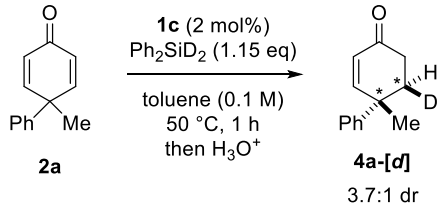
[a] Catalyst loading: 6 mol%.

Since the present protocol proceeds through the generation of 2-silyloxy dienes such as **3a**, we next performed an enantioselective desymmetrizing conjugate hydroslylation and subsequent Rubottom oxidation[18] sequence (Scheme 1B). The corresponding α-hydroxycyclohexenone **9** was obtained albeit with low diastereoselectivity. Oxidative cleavage of **9** by the treatment of $Pb(OAc)_4$ in methanol provided functionalized compound **10** having α,β-unsaturated ester and aldehyde moieties in 80% yield with 95:5 er.[18]



Scheme 1. Derivatization of chiral spirocyclic compounds. Reagents and Conditions: a) I_2 (3 equiv), DMAP (10 mol%), CCl_4/pyridine (1:1), 50 ºC, 24 h. b) $PhB(OH)_2$ (2 equiv), 10% Pd/C, K_3PO_4 c) Rh(Phebox-sBu) **1c** (2 mol%), $(MeO)_3SiH$ (1.15 equiv), toluene (0.1 M), 40 ºC, 1 h, then *m*CPBA (1.5 equiv), $NaHCO_3$, toluene/H_2O, 0 ºC, 1.5 h. d) $Pb(OAc)_4$ (2 equiv), MeOH/benzene (1:1), 0 ºC, 10 min.

To determine which hydrogen of products was transferred from hydrosilanes, we conducted the reaction of **2a** with Ph_2SiD_2 (Scheme 2). This deuterium incorporation experiment revealed that deuterium was selectively introduced at the β-carbon of **4a-[*d*]** in cis orientation with methyl group.[19]



Scheme 2. Deuterium incorporation experiment.

As for stereochemical analysis, the olefinic groups of **2a** are enantiotopic, whereas the two faces of each olefin are diastereotopic. Therefore, both group and face selection must be controlled for high enantioselectivity. On the basis of the deuterium incorporation experiment, plausible models of an asymmetric induction are illustrated in Figure 2.[14] Cyclohexadienone **2a** coordinates to a vacant site of the Rh complex which would have hydride in the equatorial position.[14c] The Rh-H species attacks from the *Re*-face of the unsaturated bond due to the steric repulsion between the bulky *sec*-butyl group and **2a** as shown in intermediates **I-1A** and **I-2A**, and thus the group selection was realized. At the same time, the steric environment of two substituents (Ph and Me) at γ-position of **2a** can be differentiated due to the steric hindrance of bulky *sec*-butyl group of **1c** and trimethoxysilyl substituent on the Rh center as shown in intermediates **I-1A** and **I-3A**, and thus the face selection was realized. As a result, the C_2 symmetry of **1c** plays an important role, and hence the desired product (*S*)-**4a** is obtained in an enantioselective fashion.

A theoretical calculation at the DFT level was performed by using simplified model structures **I-1B**, **2B** and **3B** containing a methyl substituted Phebox ligand and a trihydroxysilyl substituent on the Rh center.[19] Among them, the stationary point of **I-1B** was obtained, while geometry optimization of **I-2B** and **I-3B** was not successful. This result is supporting that the intermediate **I-1A** effectively decreases the steric repulsion between **2a** and **1c**.

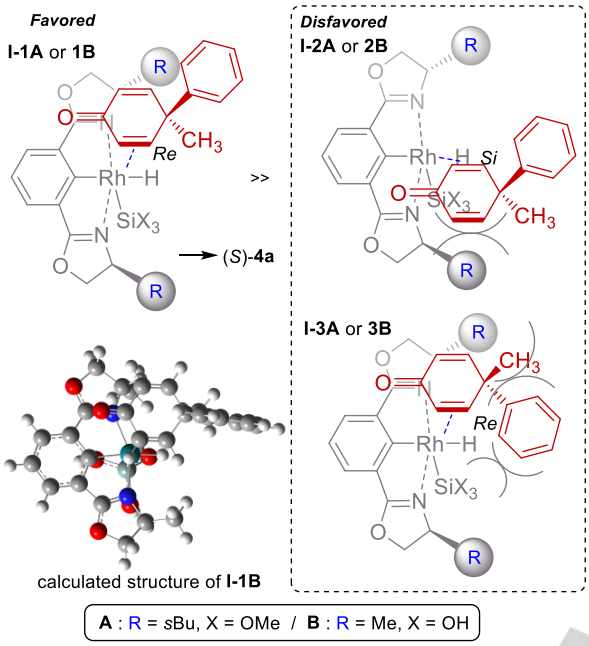


Figure 2. Plausible models of asymmetric induction and an optimized structure of **I-1B**.

In summary, we developed general protocols to provide cyclohexenone derivatives having remote chiral all-carbon quaternary centers, one of the most challenging targets in asymmetric synthesis. Enantioselective desymmetrization of γ,γ-differently disubsituted cyclohexadienones **2** catalyzed by [Rh(Phebox-*s*Bu)] **1c** proceeded well to furnish chiral cyclohexenone derivatives **4**. The Rh-H species generated from **1c** can recognize not only the enantiotopic face of unsaturated bonds of **2** but also the remote steric environment of a quaternary carbon at the γ-position. This catalytic system was extended to the asymmetric transformation of cyclohexadienones **5** bearing spirocarbocycles to give the corresponding products **6** with enantiomeric ratios of up to 96.5:3.5.

Keywords: Asymmetric Synthesis • Quaternary Center • Rhodium • Hydrosilylation • Desymmetrization

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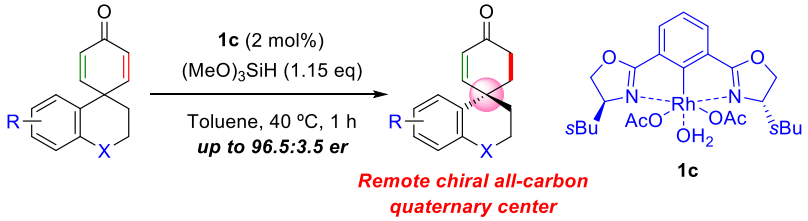

The catalytic asymmetric construction of chiral all-carbon quaternary centers is one of the most challenging issues in synthetic organic chemistry. This paper describes the Rh-catalyzed enantioselective desymmetrizing conjugate hydrosilylation of prochiral γ,γ-differently disubstituted cyclohexadienone derivatives to furnish the corresponding cyclohexenones having a remote chiral all-carbon quaternary center at the γ-position.

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