

Desymmetrization

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Asymmetric Induction at Remote Quaternary Centers of Cyclohexadienones by Rhodium-Catalyzed Conjugate Hydrosilylation

Yuki Naganawa,* Mayu Kawagishi, Jun-ichi Ito, and Hisao Nishiyama*

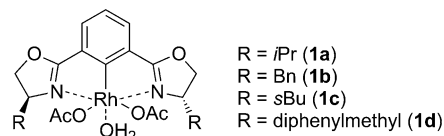
Abstract: The enantioselective desymmetrizing conjugate hydrosilylation of prochiral differently γ,γ -disubstituted cyclohexadienone derivatives **2** to furnish the corresponding cyclohexenones **4** with a remote chiral all-carbon quaternary center at the γ position is described. Chiral rhodium-bis(oxazolinyl)-phenyl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

The catalytic asymmetric construction of stereogenic all-carbon quaternary centers has been recognized to be particularly challenging.^[1] Cyclohexane rings containing stereogenic 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 of reactive cyclohexanones. Enantioselective C–C bond-forming processes for the α -functionalization of carbonyl groups are well-established.^[3,4] Furthermore, enantioselective conjugate addition reactions to β -substituted cyclohexenones are representative strategies for the synthesis of cyclohexanones with a stereogenic all-carbon quaternary center at the β -position.^[1d] Thus, the catalytic asymmetric preparation of cyclohexanones containing a stereogenic all-carbon quaternary center at the α - or β -position has been studied extensively.

One of the recent challenges in asymmetric synthesis is the construction of remote stereogenic quaternary centers distant from such reactive functionalities.^[5,6] We aim to develop general protocols to furnish optically active cyclohexenone derivatives with a stereogenic all-carbon quaternary center at the γ -position. The carbon atom at this position is inherently inert, and thus it is difficult to form new C–C bonds at this position by the use of common transformations. In this context, several research groups have demonstrated an interesting γ -asymmetric desymmetrization of achiral differently γ,γ -disubstituted cyclohexadienones to furnish the corresponding six-membered rings containing a stereogenic all-carbon quaternary center.^[7] Intramolecular desymmetri-

zation reactions have been performed successfully,^[7,8] whereas a few more challenging intermolecular variants with high enantioselectivity were developed with several organocatalysts.^[9] We anticipated that the simplest transformation, the desymmetrizing reduction of one C=C unsaturated bond within the γ,γ -disubstituted cyclohexadienones in an enantioselective manner, would furnish a cyclohexenone bearing a stereogenic all-carbon quaternary center at the γ -position. We addressed this issue by applying a transition-metal-catalyzed enantioselective conjugate hydrosilylation.^[10] Although the enantioselective conjugate hydrosilylation of α,β -unsaturated compounds is a well-studied reaction,^[11,12] the construction of remote all-carbon quaternary centers has rarely been investigated. The most challenging feature of this target transformation is that the metal catalyst must show discrimination in the steric environment of a quaternary carbon atom that has inherently no relationship to the reduction event.

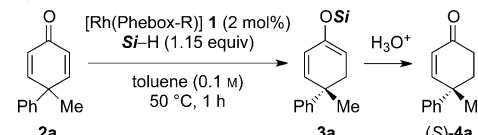
We applied chiral rhodium-bis(oxazolinyl)phenyl complexes [Rh(Phebox-R)] (**1a–d**; Bn = benzyl)^[13] as catalysts for



the enantioselective conjugate hydrosilylation of α,β -unsaturated compounds.^[14] As a model reaction, we stirred 4-methyl-4-phenylcyclohexadienone (**2a**) with triethoxysilane as a reductant in the presence of catalyst **1a** (2 mol %) in toluene at 50 °C (Table 1, entry 1). After 1 h, complete formation of the corresponding 2-silyloxy diene **3a** was observed. We did not use other reductants, such as hydrogen, as the formation of the electron-rich intermediate **3a** can suppress the undesirable reduction of the second C=C double bond. The subsequent treatment of **3a** under acidic conditions gave the desired cyclohexenone **4a** with an all-carbon quaternary center at the γ -position in 52 % yield (Table 1, entry 1). Gratifyingly, nonracemic **4a** was obtained with an enantiomeric ratio of 83.5 : 16.5. Next, we screened a series of hydrosilanes as reductants. Of the alkoxyhydrosilanes tested, the reaction with trimethoxysilane gave the best result (90 % yield, e.r. 86.5 : 13.5; Table 1, entries 2 and 3). On the other hand, the reaction with diphenylmethylsilane led to a decrease in chemical yield and enantioselectivity (Table 1, entry 4). The use of dihydrosilanes did not improve the result (Table 1, entry 5). Next, we examined the effect of the substituents on [Rh(Phebox-R)] (**1**; Table 1, entries 6–8). The use of [Rh(Phebox-sBu)] (**1c**) led to a slight improvement in enantioselectivity (Table 1, entry 7). Furthermore, a reaction

[*] Dr. Y. Naganawa, M. Kawagishi, Dr. J.-i. Ito, Prof. Dr. H. Nishiyama
Department of Applied Chemistry, Graduate School of Engineering
Nagoya University
Chikusa, Nagoya 464-8603 (Japan)
E-mail: yuki.n@apchem.nagoya-u.ac.jp
hnishi@apchem.nagoya-u.ac.jp

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Table 1: Optimization of reaction conditions.^[a]


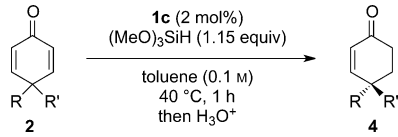
Entry	1	Si-H	Yield [%] ^[b]	e.r.
1	1a	(EtO) ₃ SiH	52	83.5 : 16.5
2	1a	(EtO) ₂ MeSiH	87	77.5 : 22.5
3	1a	(MeO) ₃ SiH	90	86.5 : 13.5
4	1a	PhMe ₂ SiH	13	72.5 : 27.5
5	1a	Ph ₂ SiH ₂	57	81.5 : 18.5
6	1b	(MeO) ₃ SiH	99	85.5 : 14.5
7	1c	(MeO) ₃ SiH	97	87 : 13
8	1d	(MeO) ₃ SiH	91	75.5 : 24.5
9 ^[c]	1c	(MeO)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

[a] Reaction conditions: **2a** (0.1 mmol), hydrosilane (0.115 mmol), **1** (2 mol%), toluene (1 mL), 50 °C, 1 h. [b] Yield of the isolated product.

[c] The reaction was carried out at 40 °C. [d] The reaction was carried out at room temperature.

performed at a lower temperature of 40 °C gave **4a** with the highest enantiomeric ratio (e.r. 88.5:11.5; Table 1, entry 9), whereas a reaction attempted at room temperature did not proceed at all (entry 10). The absolute configuration of **4a** was determined as *S* by comparison with reported compounds.^[15]

Next, we examined the generality of the reaction of 4-aryl 4-methylcyclohexadienone substrates **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-aryl 4-methylcyclohexadienones **2b–g** bearing various substituents on the phenyl ring to increase steric bulkiness. The introduction of *meta* or *ortho* substituents tended to slightly diminish the enantioselectivity, contrary to expectations (Table 2, entries 2–4). To examine the electronic effect of the substituents, we conducted the reaction with compounds **2e** and **2f** (Table 2, entries 5 and 6). The introduction of an electron-donating group improved the enantioselectivity of the

Table 2: Reaction of 4-alkyl 4-aryl cyclohexadienones **2**.^[a]


Entry	R	R'	Yield [%] ^[b]	e.r.
1	Ph	Me (2a)	82 (4a)	88.5 : 11.5
2	<i>p</i> -tolyl	Me (2b)	95 (4b)	88.5 : 11.5
3	<i>m</i> -tolyl	Me (2c)	95 (4c)	85.5 : 14.5
4	<i>o</i> -tolyl	Me (2d)	99 (4d)	85 : 15
5	<i>p</i> -MeOC ₆ H ₄	Me (2e)	92 (4e)	90.5 : 9.5
6	<i>p</i> -F ₃ CC ₆ H 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] Yield of the isolated product. Np = naphthyl.

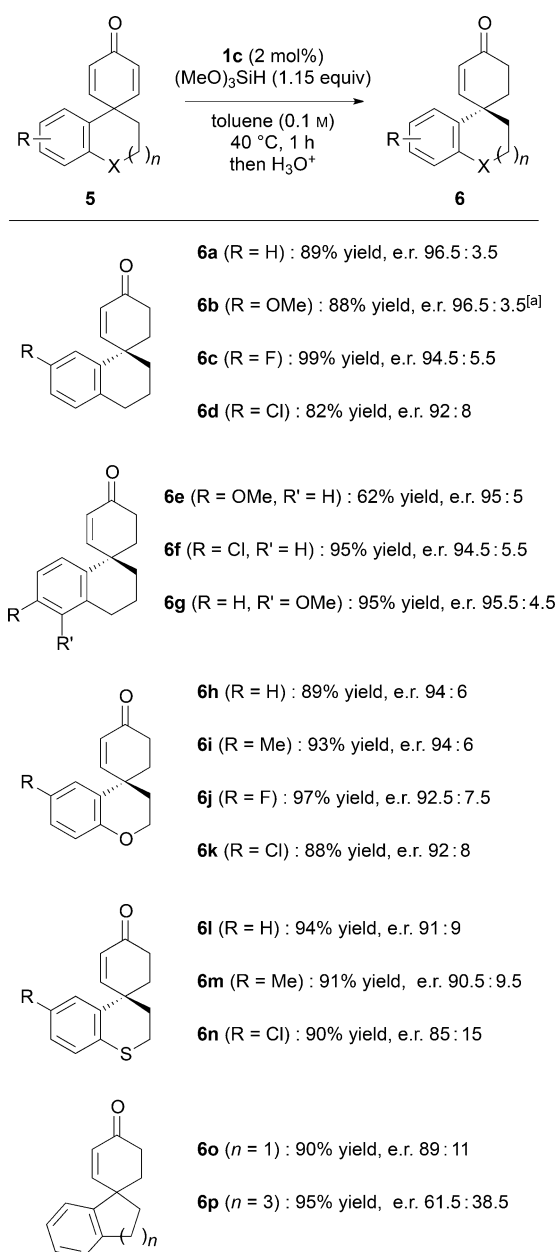
reaction, whereas the introduction of an electron-withdrawing group resulted in lower enantioselectivity. The reaction of compound **2g** with a larger aromatic substituent gave the desired product with a similar enantiomeric ratio to that observed for the standard product **4a** (Table 2, entry 7). We next performed the reaction of 4-ethyl-4-phenylcyclohexadienone (**2h**) to investigate the steric importance of the alkyl side chain of **2a** (Table 2, entry 8). The enantiomeric ratio of **4h** was dramatically decreased to 68.5:31.5. Finally, the reaction of **2i**, with two different alkyl groups (cyclohexyl and Me), gave product **4i** with moderate enantioselectivity (Table 2, entry 9). The absolute configuration of the product **4e** was determined as *S* by comparison with reported compounds.^[15] For unreported compounds **4**, the absolute configuration was tentatively assigned by analogy.

To further broaden the utility of this protocol, we focused on cyclohexadienones **5** incorporating a spirocarbocyclic backbone (Scheme 1). Spiro-containing chiral compounds are unique motifs found in natural compounds isolated from a wide range of biological sources.^[16] Cyclohexadienone **5a** was converted into the corresponding product **6a** in 89% yield with e.r. 96.5:3.5. Reactions of **5b–g**, with electron-donating or -withdrawing substituents at various positions of the aromatic ring of the tetrahydronaphthalene core gave the desired products **6b–g** with uniformly high e.r. values in the range of 92:8 to 96.5:3.5. 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 enantioselectivity. Finally, we determined that the ring size of **5** had a significant impact on the enantioselectivity. For example, the reaction of **5o** containing a five-membered ring provided the product **6o** with slightly lower enantioselectivity (e.r. 89:11). In contrast, a dramatic decrease in enantioselectivity was observed for the reaction of **5p**, with a seven-membered ring (e.r. 61.5:38.5).

To enhance the synthetic utility of the present protocols, we examined the derivatization of product **6a** (Scheme 2A). α -Iodination of **6a** by the procedure described by Johnson et al.^[17] gave α -iodocyclohexenone **7**, which could be a versatile building block. For example, the Suzuki–Miyaura cross-coupling of **7** furnished the corresponding product **8** in 85% yield and without loss of enantiomeric purity.

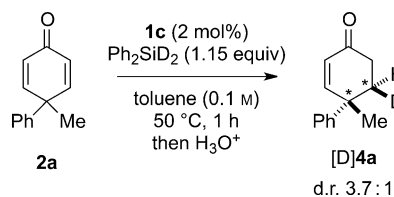
Since the present transformation proceeds through the generation of 2-silyloxy dienes, such as **3a**, we next performed an enantioselective desymmetrizing conjugate hydrosilylation and Rubottom oxidation^[18] sequence (Scheme 2B). The corresponding α -hydroxycyclohexenone **9** was obtained, albeit with low diastereoselectivity. Oxidative cleavage of **9** by treatment with Pb(OAc)₄ in methanol provided the functionalized compound **10** with α,β -unsaturated-ester and aldehyde moieties in 80% yield with e.r. 95:5.^[18]

To determine which hydrogen atom of the products was transferred from the hydrosilane, we investigated the reaction of **2a** with Ph₂SiD₂ (Scheme 3). In this deuterium-incorporation experiment, deuterium was selectively introduced at the β -carbon atom of [**D**]**4a** in a *cis* orientation to the methyl group.^[19]

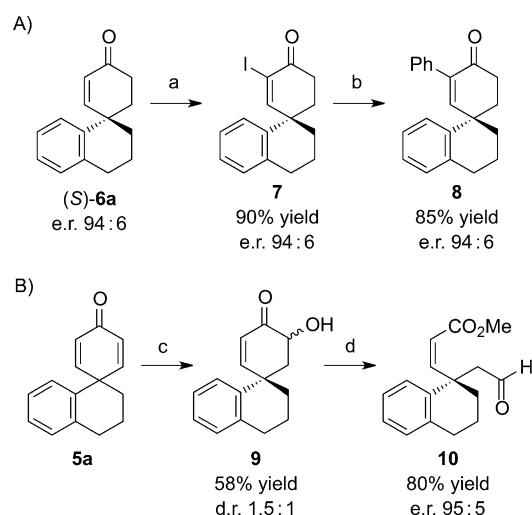


Scheme 1. Reaction of spirocyclic cyclohexadienones **5**. [a] Catalyst loading: 6 mol%.

In terms of the stereochemical nature of the transformation, 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 for asymmetric induction



Scheme 3. Deuterium-incorporation experiment.



Scheme 2. Derivatization of chiral spirocyclic compounds. Reagents and conditions: a) I₂ (3 equiv), DMAP (10 mol%), CCl₄/pyridine (1:1), 50 °C, 24 h; b) PhB(OH)₂ (2 equiv), 10% Pd/C, K₃PO₄; c) [Rh(Phebox-sBu)] (**1c**; 2 mol%), (MeO)₃SiH (1.15 equiv), toluene (0.1 M), 40 °C, 1 h, then *m*CPBA (1.5 equiv), NaHCO₃, toluene/H₂O, 0 °C, 1.5 h; d) Pb(OAc)₄ (2 equiv), MeOH/benzene (1:1), 0 °C, 10 min. DMAP = 4-dimethylaminopyridine, *m*CPBA = *m*-chloroperbenzoic acid.

are illustrated in Figure 1.^[14] Cyclohexadienone **2a** coordinates to a vacant site of the Rh complex, which would have the hydride in the equatorial position.^[14c] The Rh–H species attacks the *Re* face of the unsaturated bond owing to steric repulsion between the bulky *sec*-butyl group and **2a**, as shown in intermediates **I-1A** and **I-2A**, thus leading to the required group selectivity. At the same time, the steric environment of the two substituents (Ph and Me) at the γ-position of **2a** can be differentiated owing to the steric repulsion of the bulky *sec*-butyl group of **1c** and the trimethoxysilyl substituent on

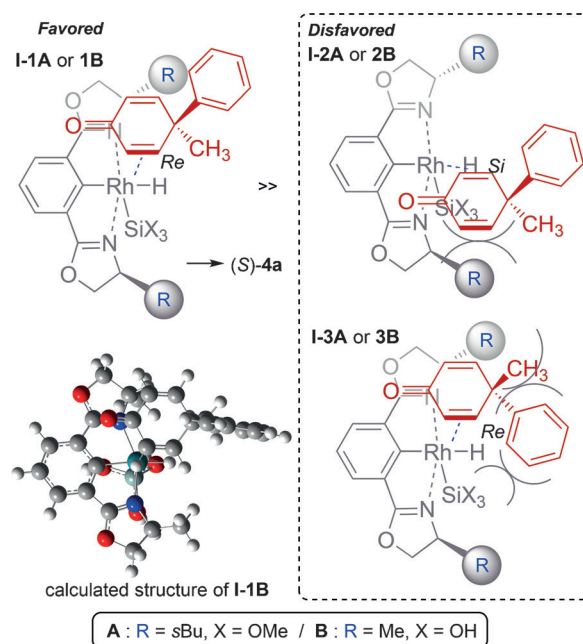


Figure 1. Plausible models of asymmetric induction and an optimized structure of **I-1B**.

the Rh center, as shown in intermediates **I-1A** and **I-3A**, thus leading to the required face selectivity. In this way, 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**, **I-2B**, and **I-3B** containing a methyl-substituted Phebox ligand and a trihydroxysilyl substituent on the Rh center.^[19] The stationary point of **I-1B** was obtained, whereas geometry optimization of **I-2B** and **I-3B** was not successful. This result supports the hypothesis that intermediate **I-1A** effectively decreases the steric repulsion between **2a** and **1c**.

In summary, we have developed general protocols for the synthesis of cyclohexenone derivatives with remote stereogenic all-carbon quaternary centers, which are among the most challenging targets in asymmetric synthesis. The enantioselective desymmetrization of differently γ,γ -disubstituted cyclohexadienones **2** under the catalysis of [Rh(Phebox-*s*Bu)] (**1c**) proceeded well to furnish chiral cyclohexenone derivatives **4**. The Rh–H species generated from **1c** could recognize not only the enantiotopic face of the double bonds of **2** but also the remote steric environment of a quaternary carbon center at the γ -position. This catalytic system was extended to the asymmetric transformation of spirocarbocyclic cyclohexadienones **5** to give the corresponding products **6** with enantiomeric ratios of up to 96.5:3.5.

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Keywords: asymmetric synthesis · desymmetrization · hydrosilylation · quaternary centers · rhodium

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