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Asymmetric Synthesis of Remote Quaternary Centers by Copper-Catalyzed Desymmetrization: An Enantioselective Total Synthesis of (+)-Mesembrine

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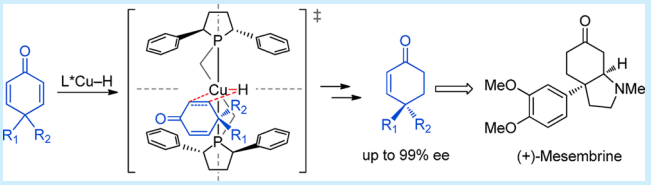
Supporting Information

ABSTRACT: Catalytic asymmetric syntheses of remote quaternary stereocenters have been developed by copper-catalyzed 1,4-hydrosilylation of γ,γ-disubstituted cyclohexadienones. A variety of cyclohexenones have been synthesized in good yield and excellent enantioselectivity. Versatile 2-silyloxy diene intermediates bearing γ,γ-disubstituted all carbon stereogenic centers can be isolated from the mild reaction conditions. The utility of this strategy is exemplified in a catalytic asymmetric total synthesis of (+)-mesembrine.



Cyclohexanones with remote quaternary stereogenic centers are useful moieties in bioactive natural products and pharmaceuticals (see Figure 1). Catalytic enantioselective

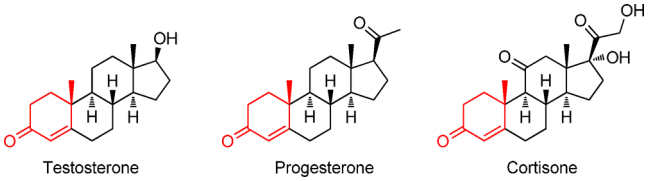
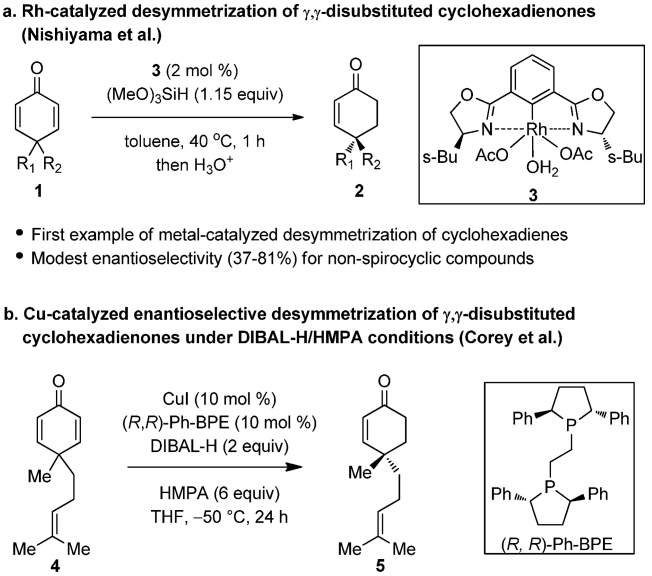


Figure 1. Examples of biomedically relevant molecules containing cyclohexanones with remote quaternary stereogenic centers.

synthesis of all-carbon quaternary stereocenters has been challenging in chemical synthesis.[1] Although transition-metal-catalyzed or organocatalytic α- or β-functionalization of cyclohexanones to construct α,α- or β,β-disubstituted all-carbon quaternary centers has been well-studied,[1b,2,3] establishing the remote γ,γ-all carbon quaternary centers in cyclohexanones in an enantioselective fashion remains less developed.

Recently, Nishiyama and co-workers reported catalytic enantioselective desymmetrization of γ,γ-disubstituted cyclohexadienones with a [Rh(Phebox-^{s}Bu)] catalyst and trimethoxysilane to generate remote quaternary stereogenic centers at the γ-position (see Scheme 1a).[4] Although this is an important advance, this method uses a precious late-transition-metal catalyst, and excellent enantioselection was only observed in reactions with spirocarbocyclic cyclohexadienones. Alternatively, copper is an Earth-abundant transition metal that has received increased attention for organic syntheses. Consequently, there continues to be interest in the development of sustainable chemical catalysis through new asymmetric hydrosilylation strategies harnessing copper hydride.[5,6] In this direction, Corey and co-workers developed Cu-catalyzed enantioselective desymmetrization of γ,γ-disubstituted cyclohexadienones to construct remote γ,γ-disubstituted all carbon quaternary centers (see Scheme 1b).[7] Although this pioneering

Scheme 1. Enantioselective Desymmetrization of γ,γ-Disubstituted Cyclohexadienones



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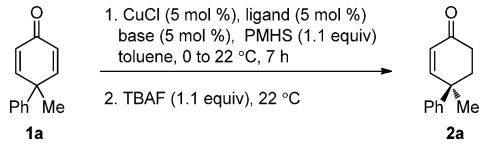
method deployed an inexpensive and readily available copper catalyst to deliver **5** with excellent enantioselectivity, it suffers with the use of excess strong reducing agent DIBAL-H and carcinogenic additive HMPA, which possibly limits the wide usability of this method, because of functional group compatibility.

In addressing the issues discussed above, we aimed to develop a mild catalytic method to produce enantio-enriched γ,γ-disubstituted cyclohexenones. Furthermore, we envisioned the potential to isolate 2-silyloxy diene intermediates bearing γ,γ-disubstituted all carbon stereogenic centers as being advantageous in a variety of succeeding transformations involving the accessible enolate or diene. Mechanistically, it was hypothesized that alkoxy copper species generated through enantioselective 1,4-hydrocupration of dienones could be intercepted with an appropriately substituted hydrosilane. Here, we report CuH-mediated enantioselective desymmetrization of γ,γ-disubstituted cyclohexadienones under mild reaction conditions. This strategy yielded both synthetically useful 2-silyloxy diene intermediates and cyclic enones upon desilylation, bearing all carbon quaternary stereocenters at the γ-position.

We commenced our investigation by exploring the reactivity and selectivity of 4-phenyl 4-methyl cyclohexadienone **1a** with chiral CuH generated in situ from CuCl, NaO^{t}Bu, PMHS [poly(methylhydrosiloxane)][8,9] and a chiral ligand screened from **L1** to **L10** (see Table 1). Cyclohexenone **2a** was formed

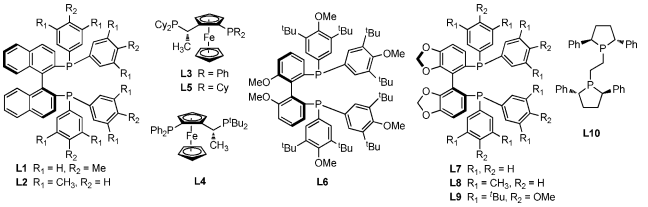
Table 1. Evaluation of Chiral Ligands[a]



entry	ligand	base	conversion[b] (%)	enantiomeric excess, ee[c] (%)
1	**L1**	NaO^{t}Bu	97	12
2	**L2**	NaO^{t}Bu	99	37
3	**L3**	NaO^{t}Bu	96	48
4	**L4**	NaO^{t}Bu	100	−4
5	**L5**	NaO^{t}Bu	96	38
6	**L6**	NaO^{t}Bu	84	58
7	**L7**	NaO^{t}Bu	5	
8	**L8**	NaO^{t}Bu	96	38
9	**L9**	NaO^{t}Bu	94	78
10	**L9**	KO^{t}Bu	93	74
11	**L9**	LiO^{t}Bu	51	73
12	**L9**	LiOMe	26	58
13	**L10**	NaO^{t}Bu	94	95

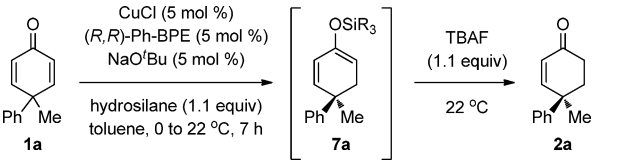
[a]Conditions: dienone **1a** (0.5 mmol), toluene (1.0 mL). [b]Monitored by HPLC analysis. [c]Determined by HPLC analysis on chiral stationary phases.

with poor enantioselectivity with (*S*)-Tol-BINAP **L1** (entry 1 in Table 1), the enantioselectivity was slightly improved with (*S*)-DM-BINAP **L2** (entry 2 in Table 1). In the Josiphos series, **L3** further improved the enantioselectivity (entry 3 in Table 1), but other ligands (**L4** and **L5**) in that series were poorly selective (entries 4 and 5 in Table 1). The ligand (*S*)-DTBM-MeOBIPHEP (**L6**) resulted in moderate enantioselectivity (entry 6 in Table 1). While (*S*)-SegPhos **L7** gave a poor conversion to **2a** (entry 7 in Table 1), (*S*)-DM-SegPhos **L8** and (*S*)-DTBM-SegPhos **L9** notably improved conversion and enantioselectivity (entries 8 and 9 in Table 1). Encouraged by this initial result, we then studied the effect of base on Cu-catalyzed desymmetrization of **1a**. Changing the base from NaO^{t}Bu to KO^{t}Bu had little effect on both reactivity and enantioselectivity (entries 9 and 10 in Table 1). Diminished reactivity and enantioselectivity were observed with weaker bases (entries 11 and 12 in Table 1). To further improve the enantioselectivity, we turned our attention to the cyclic BPE phosphine, which has been recently applied to a variety of highly enantioselective Cu-catalyzed reactions.[10,11] We were pleased to find (*R,R*)-Ph-BPE **L10** gave good reactivity and excellent enantioselectivity (94% conversion, 95% ee; see entry 13 in Table 1).



Next, we studied the effect of hydrosilanes on reactivity and enantioselectivity (see Table 2). Initial success was achieved

Table 2. Evaluation of Hydrosilanes[a]



entry	silane	conversion[b,c] (%)	enantiomeric excess, ee[d] (%)
1	PMHS	95 (77)	95
2	$(MeO)_2MeSiH$	79	93
3	$(EtO)_2MeSiH$	87	93
4	$(TMSO)_3SiH$	65	92
5	Ph_2SiH_2	52	96
6	Et_2SiH_2	82	96
7[e]	Et_3SiH	100 (72)	96
8[f]	Et_3SiH	100 (87)	96

[a]Conditions: dienone **1a** (0.5 mmol), toluene (1.0 mL). [b]Monitored by HPLC analysis. [c]Value given in the parentheses is isolated yield for **2a**. [d]Determined by HPLC analysis on chiral stationary phases. [e]The reaction was performed at 40 °C. [f]The reaction was performed under the conditions of CuCl (2 mol %), NaO^{t}Bu (2 mol %), and (*R,R*)-Ph-BPE (2 mol %) at 40 °C.

with PMHS, which resulted in excellent selectivity and reactivity (entry 1 in Table 2), but it did not allow for isolation of the discrete 2-silyloxy diene intermediate **7a**, because of the polymeric nature of PMHS. Alkoxysilanes provided **2a** with good enantioselectivity, albeit diminished reactivity (entries 2−4 in Table 2). Dihydrosilanes (e.g., Ph_2SiH_2 and Et_2SiH_2) exhibited similar enantioselectivity, but the reactivity was modest (entries 5 and 6 in Table 2). Electron-rich triethylsilane afforded **2a** in complete conversion and excellent enantioselectivity at slightly elevated temperature (96% ee; see entry 7 in Table 2). However, under the reaction conditions with 5 mol % catalyst, 10%−15% of over-reduction product (i.e., cyclohexanone) was formed. By reducing the catalyst loading to 2 mol %, the over-reduction product was formed within <5% and the desired product **2a** was isolated in

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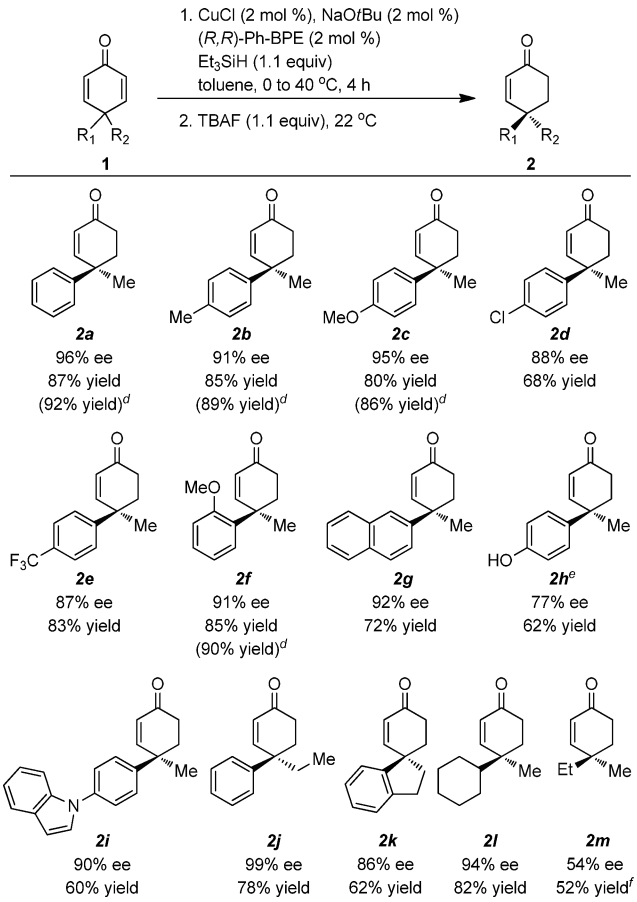
87% yield with identical enantioselectivity (entries 7 and 8 in Table 2), which indicates that there was no secondary resolution due to over-reduction. Notably, under the triethylsilane conditions, we were able to isolate the intermediate **7a**, which is a useful synthon for a variety of transformations.[12,13]

Having arrived at the optimal conditions to produce and isolate both synthetically useful γ,γ-disubstituted 2-silyloxy dienes **7** and cyclohexenone products **2** upon desilylation, we examined the scope of γ,γ-disubstituted cyclohexadienones, as presented in Scheme 2. The enantioselective desymmetrization

Scheme 2. Scope of the Desymmetrization Reaction[a,b,c]



[a]Conditions: Dienone (0.5 mmol), silane (0.55 mmol), toluene (1.0 mL). [b]Yields of isolated products. [c]The % *ee* values were determined by chiral HPLC analysis. The absolute configurations of **2a**, **2b**, **2c**, **2e**, **2g**, **2k**, and **2l** were determined by comparing the optical rotations with literature-reported values.[4] The configurations of other enones were assigned by analogy. [d]Yields of isolated 2-siloxy dienes (**7**). [e]TBS-protected phenol as substrate. [f]Low isolated yield due to product volatility.

of a variety of substrates, with various electronic and steric natures, generally gave **2** in good to excellent yield and with good to excellent enantioselectivity (77%−99% ee). A few representative siloxy dienes were isolated in high yields (86%−92%) and excellent enantioselectivities (91%−96% ee, **7a**, **7b**, **7c**, and **7f**; see the Supporting Information). Under these conditions, varying the electronic properties of the aryl group consistently gave good to excellent yields and enantioselectivities (**2a**−**2e**; see Scheme 2). Ortho-substitution in **1f** was compatible with the process. Reactions with 2-naphthyl, phenolic TBS ether, and N-substituted indole-containing substrates proceeded in good yield and high enantioselectivity (**2g**−**2i**). In the reaction of **1h**, the TBS group was tolerated during the desymmetrization and removed during the subsequent TBAF treatment. When the methyl group in substrate **1a** was replaced with ethyl, enantioselectivity was further improved (99% ee, **2j**). Note that 37% ee was observed for this substrate in Rh−H catalysis.[4] With recognition of biologically privileged all carbon spirocyclic scaffolds, cyclohexadienone **1k** was tested under the optimized reaction conditions. The product 5,6-spirocycle **2k** was obtained in 86% ee, which is an improvement over Nishiyama's catalyst system (78% ee).[4] Finally, we tested the cyclohexadienones with two alkyl substituents, the catalyst distinguishes cyclohexyl and methyl in **1l** well, and product **2l** formed in 94% ee and 82% yield. For one of the most challenging substrates **1m**, which has two minimally differentiated substituents Et and Me, the product **2m** was obtained in decent enantioselectivity (54% ee).

To gain further insight into the enantio-determining step of the desymmetrization process (see Figure 2a), we performed density functional theory (DFT) calculations for the hydrocupration of **1a** with the presumed catalyst (**L10**CuH). Our computational studies predict that, during the hydrocupration, **1a** can approach two sterically accessible quadrants (II and IV) in the C2 symmetric catalyst, where four diastereotopic olefin faces of two enantiotopic olefins were differentiated within the asymmetric environment of **L10**CuH via TS1 to TS4. Among them, TS3 avoids the most severe steric interactions of the unreacted olefin moiety and two substituents (i.e., Ph and Me) at the γ-position of **1a** with the phenyl substituents (quadrants I and III) on the phospholane moieties in the CuH/Ph-BPE catalyst, leading to the preferential formation of the hydrocupration intermediate shown in TS3 with an activation free energy of 18.4 kcal/mol, which is 2.7 kcal/mol lower than that from the second lowest barrier shown in TS1 (Figures 2b and 2c). Additions of **L10**CuH to two other diastereotopic faces of two olefins through TS2 and TS4 experiences the unfavorable steric repulsions of the olefin moiety and substituents at the γ-position of **1a** with two quadrants in the catalyst, with the formation of relevant reacting complexes disfavored by 3.8 and 3.3 kcal/mol relative to TS3, respectively (Figure 2c). These calculated results offer a plausible mechanistic basis for the CuH/Ph-BPE catalyst to induce enantioselective desymmetrization of the remotely substituted cyclohexadienones.

Since mesembrine was first isolated in 1957,[14] this alkaloid has attracted a great deal of interest from chemists,[15] because of its interesting biological activity.[16] We were interested in demonstrating the versatility of the Cu-catalyzed enantioselective desymmetrization strategy to access the octahydroindole skeleton core bearing an all-carbon quaternary center (see Scheme 3). Pd-catalyzed α-arylation of Boc-protected amino aldehyde **9** with 3,4-dimethoxy-1-bromobenzene **10** provided aldehyde **11** in 52% yield.[17] Base-catalyzed Robinson annulation[18] of **11**, followed by DDQ-mediated dehydrogenation[19] afforded dienone **12** in 56% yield (two steps). The key Cu-catalyzed desymmetrization of **12** delivered enone **13** (82% yield, 97% ee). The completion of this synthesis was achieved by removal of the Boc group, followed by concomitant amine conjugate addition under the acidic conditions to furnish (+)-mesembrine **8** in 81% yield and 97% ee.

In summary, we have developed a protocol involving Cu-catalyzed enantioselective desymmetrization of γ,γ-disubsti-

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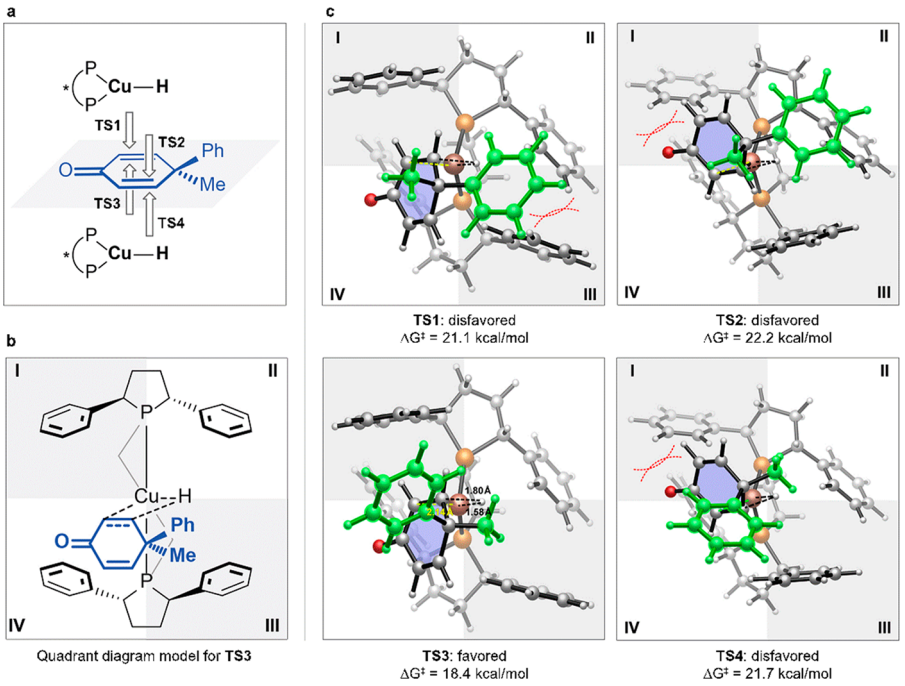
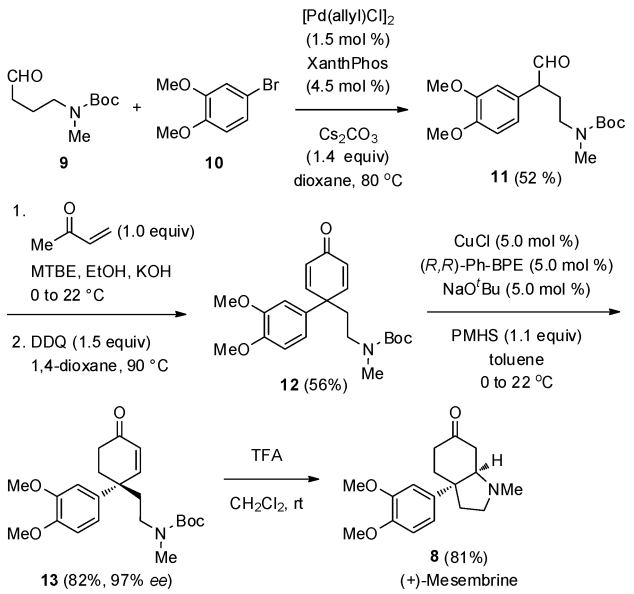


Figure 2. (a) Approaches of CuH to four diastereotopic faces of two enantiotopic olefins. (b) Quadrant diagram model for the hydrocupration of **L10**CuH with cyclohexadienones **1a** in TS3. (c) DFT calculations of transition states of hydrocupration of **1a** with **L10**CuH catalyst. Energies were calculated at the M06/SDD−def2TZVP/SMD(toluene) level of theory with geometries optimized at the B3LYP-D3(BJ)/SDD−6-31G(d) level (see the Supporting Information for more details and references).

Scheme 3. Total Synthesis of (+)-Mesembrine[a]



[a]Data taken from ref 20.

tuted cyclohexadienones to provide chiral cyclohexenones bearing remote all carbon quaternary stereogenic centers at a γ-position. Under the mild catalytic conditions, reactions with chiral CuH complex generated in situ from CuCl, NaO^{t}Bu, (*R*,*R*)-Ph-BPE, and Et_3SiH exhibited a relatively broad scope with good to excellent enantioselectivity. In addition, the use of Et_3SiH allowed for the isolation of synthetically useful 2-siloxy dienes which can be utilized for further transformations. Finally, the utility of this approach was exemplified in an asymmetric total synthesis of (+)-mesembrine.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02084.

Detailed experimental procedures, ^{1}H and ^{13}C NMR spectra of all new compounds, and HPLC trace analysis of enantio-enriched compounds (PDF)

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Notes

The authors declare no competing financial interest.

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