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# One-Pot Synthesis of Enantiomerically Enriched 2,3-Disubstituted Cyclopentanones via Copper-Catalyzed 1,4-Reduction and Alkylation

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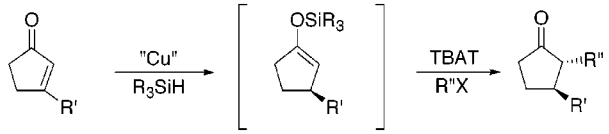
## ABSTRACT




**Enantiomerically enriched 2,3-disubstituted cyclopentanones were prepared via copper-catalyzed 1,4-reduction of 3-substituted cyclopentenones followed by alkylation of the resulting silyl enol ether. Using this procedure, *trans*-2,3-disubstituted cyclopentanones were produced in moderate to good overall yields (42–67%) and with excellent enantiomeric and diastereomeric excesses. The reduction and alkylation were performed in a single reaction vessel.**

The vicinal dialkylation of enones by conjugate addition of an organocopper reagent and alkylation of the resulting enolate is an important synthetic process to access 2,3-dialkylated cycloalkanones.[1] This method has been extensively utilized in the synthesis of natural products,[1] such as the *E* series of prostaglandins.[2] Catalysts for asymmetric conjugate addition have been used to make enantiomerically enriched 2,3-disubstituted cycloalkanones; these catalysts are not effective for cyclopentanone substrates due to the low enantioselectivity of the catalysts.[3] An equivalent transformation is the conjugate reduction of $\beta$-substituted enones followed by alkylation of the intermediate enol derivative.[4] Recently, we reported a highly enantioselective copper−hydride catalyst system for the reduction of $\alpha,\beta$-unsaturated esters[5a] and enones.[5b] This catalyst was particularly effective for asymmetric 1,4-reductions of $\beta$-substituted cyclopentenones. We now report a convenient one-pot procedure in

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(4) For a recent report on tandem copper hydride-catalyzed 1,4 reduction and aldol reaction/alkylation of cyclohexenones and acyclic enones, see: Lipshutz, B. H.; Chrisman, W.; Noson, K.; Papa, P.; Sclafani, J. A.; Vivian, R. W.; Keith, J. M. *Tetrahedron* **2000**, *56*, 2779.

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(8) Often, α-substituents have been employed to prevent equilibration. For the use of arylhetero α-substituents as substrate auxiliaries, see: (a) Fang, J.-M. *J. Org. Chem.* **1982**, *47*, 3464. (b) Liotta, D.; Saindane, M. T.; Barnum, C.; Zima, G. *Tetrahedron* **1985**, *41*, 4881. (c) Posner, G. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 2, Chapter 8.

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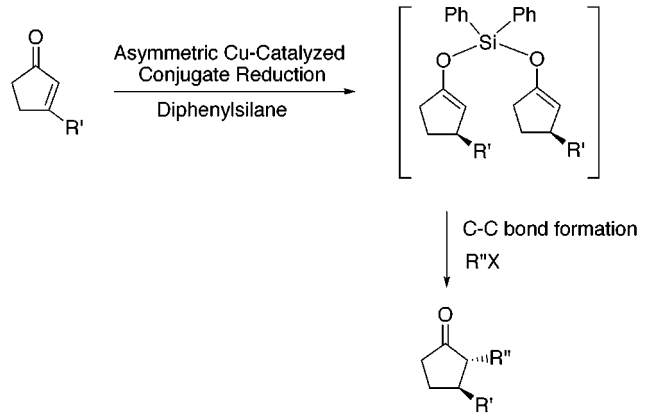
which asymmetric 1,4-reduction followed by regioselective alkylation yields enantiomerically enriched 2,3-disubstituted cyclopentanones (Scheme 1).

**Scheme 1**

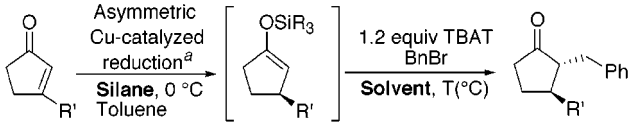



Highly regioselective alkylation of an enolate generated from the corresponding silyl enol ether is possible only when the enolate reacts with an alkylating agent prior to equilibration.[6] If equilibration occurs, polyalkylation and nonregioselective alkylation products are often formed along with the desired product. Lithium enolates derived from cyclopentanone are especially difficult to monoalkylate[7] because proton transfer is fast relative to that of cyclohexanones or other acyclic ketones.[8,9] When quaternary ammonium fluorides were used to activate silyl enol ethers derived from cyclic ketones, the regiospecificity of alkylation was reported to be higher than when lithium enolates were used in ethereal solvents.[10] However, even in these fluoride-mediated reactions, the TMS enol ether of cyclopentanone, unlike that of cyclohexanone, often gives substantial amounts of polyalkylated products.[10b,11]

Reaction conditions for the alkylation of cyclopentanone enolates were optimized using the diphenyl silyl enol ether obtained from an asymmetric conjugate reduction of 3-methylcyclopentenone (Table 1). DeShong's tetrabutylammonium triphenyldifluorosilicate (TBAT) was chosen as a fluoride source for the alkylation because it is an easily handled, nonhygroscopic solid that is commercially available.[12] After performing an asymmetric conjugate reduction in toluene by following our previously described procedures,[5b] the alkylation was carried out in the same reaction vessel by first removing the toluene in vacuo, followed by addition of $CH_2Cl_2$, an alkyl halide, and TBAT. Alternatively, an alkyl halide and a $CH_2Cl_2$ solution of TBAT were sequentially added directly to the toluene solution. In both procedures, the alkylation proceeded smoothly at room temperature (Table 1, entries 1 and 3). Methylene chloride was a better solvent than THF for the alkylation. When polymethylhydrosiloxane (PMHS) was used instead of diphenylsilane, the initial reduction step was much slower while the alkylation step proceeded as efficiently as when diphenylsilane was employed (entry 4). The alkylation process can be also conducted at higher temperatures (entry 5) with little effect. We also found that using an excess of the alkyl halide increased the yield slightly (entries 6−8). The 2,3-disubstituted cyclopentanone products (**3** or **4**)[13] were isolated as a mixture of cis and trans diastereomers, with only trace amounts of the 2,4-disubstituted regioisomers detected. The 2,3-disubstituted products were equilibrated in the presence of a catalytic amount of base (NaOMe in MeOH or NaOEt in EtOH) and yielded a high diastereomeric ratio.

Other reactive alkylating reagents were tested and furnished products in 60−65% yield (Table 2, entries 2−4). In each case, the trans diastereomer was obtained as the major

**Table 1.** Optimization of the α-Benzylation of Silyl Enol Ethers




**1** R' = $CH_3$ **1'** = 93% ee **3** R' = $CH_3$ dr = 92:8
**2** R' = $CH_2CH_2Ph$ **2'** = 95% ee **4** R' = $CH_2CH_2Ph$ dr = 94:6

| entry | enone | silane | BnBr (equiv) | solvent[b] | T (°C) | yield (%) |
|---|---|---|---|---|---|---|
| 1 | **1** | $Ph_2SiH_2$ | 2.0 | $CH_2Cl_2$ | rt | 62 |
| 2 | **1** | $Ph_2SiH_2$ | 2.0 | THF | rt | 53[c] |
| 3 | **1** | $Ph_2SiH_2$ | 2.0 | $CH_2Cl_2$:Tol = 1:1 | rt | 62 |
| 4[d] | **1** | PMHS | 2.0 | $CH_2Cl_2$:Tol = 1:1 | rt | 61 |
| 5 | **2** | $Ph_2SiH_2$ | 1.2 | $CH_2Cl_2$ | 50 | 60 |
| 6 | **2** | $Ph_2SiH_2$ | 1.4 | $CH_2Cl_2$:Tol = 1:1 | rt | 64 |
| 7 | **2** | $Ph_2SiH_2$ | 2.0 | $CH_2Cl_2$:Tol = 1:1 | rt | 67 |
| 8 | **2** | $Ph_2SiH_2$ | 3.0 | $CH_2Cl_2$:Tol = 1:1 | rt | 69 |

[a] Reductions were performed with 0.53 equiv of diphenylsilane, 5% CuCl, 5% NaO*t*-Bu, and 5% (*S*)-*p*-tol-BINAP (= 2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl) for 2−3 h until no enone was detected by TLC. [b] Solvent combination used for alkylation. [c] 4−9% regioisomers were formed. [d] 10% catalyst was used.

(9) For monoalkylation of the lithium enolate of cyclopentanone in THF−HMPA solution using additives, see: Morita, Y.; Suzuki, M.; Noyori, R. *J. Org. Chem.* **1989**, *54*, 1785, also see ref 7b.

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(11) Except these cases where tris(dialkylamino)sulfonium difluorotrimethylsilicate (TASF) was used as the fluoride source, see: (a) Noyori, R.; Nishida, I.; Sakata, J. *Tetrahedron Lett.* **1980**, *21*, 2085. (b) Noyori, R.; Nishida, I.; Sakata, J. *J. Am. Chem. Soc.* **1983**, *105*, 1598.

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(13) The ee of each product was determined by analyzing the ee of unalkylated 3-substituted cyclopentanone by HPLC or GC, and the absolute stereochemistry at the C-3 position of the product was assigned in accord with a previous report.[5b]

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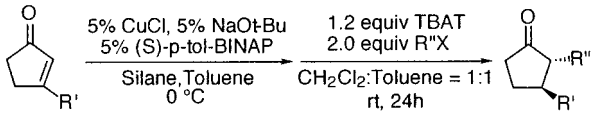
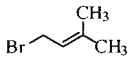
**Table 2.** One-Pot Synthesis of Chiral 2,3-Disubstituted Cyclopentanones




**1** R' = $CH_3$
**2** R' = $CH_2CH_2Ph$

| entry | enone | silane[a] | R"X | yield (%)[b] | dr[c] | equilibrated dr[d] | regio-isomer |
|---|---|---|---|---|---|---|---|
| 1 | **2** | $Ph_2SiH_2$ | BnBr | 67 | 94:6 | 97:3 | - |
| 2 | **2** | $Ph_2SiH_2$ | Allylbromide | 64 | 76:24 | 95:5 | - |
| 3[e] | **2** | PMHS | Allylbromide | 60 | 77:23 | " | - |
| 4 | **2** | $Ph_2SiH_2$ | MeI[f] | 65 | 73:27 | 94:6 | - |
| 5 | **1** | $Ph_2SiH_2$ | BnBr | 62 | 92:8 | 93:7 | - |
| 6 | **1** | $Ph_2SiH_2$ | $BrCH_2CO_2Et$ | 52 | 94:6[g] | 92:8 | - |
| 7 | **1** | $Ph_2SiH_2$ |  | 52 | 80:20 | 93:7 | 4% |
| 8 | **2** | $Ph_2SiH_2$ | *n*-BuI | 42 | 85:15 | 93:7 | 11% |

[a] 0.53 equiv of $Ph_2SiH_2$ or 1.15 equiv of PMHS was used. [b] Yields are the average of two or more isolated yields of >95% purity as determined by GC and $^1H$ NMR. [c] Diastereomeric ratio of the crude reaction mixture determined by GC. [d] Thermodynamically equilibrated diastereomeric ratio in the presence of catalytic NaOMe in MeOH or NaOEt in EtOH (entry 6). [e] 10% catalyst was used. [f] 1.4 equiv of MeI was used. [g] The major diastereomer of this reaction was determined to be trans (see Supporting Information). The relative stereochemistry of all other products was assigned by analogy.

product under the optimized reaction conditions. For example, ethyl bromoacetate reacted with the enolate derived from **1** to yield ethyl (*trans*-5-methyl-2-oxocyclopentyl)-acetate (entry 6).[14] Similarly, an allylic bromide, 4-bromo-2-methyl-2-butene, reacted to yield the desired product[15] in 52% yield contaminated with 4% of regioisomeric products (entry 7). Less reactive alkyl halides showed an increased tendency to form mixtures of alkylated products. For instance, treatment of the nascent silyl enol ether derived from **2** with *n*-butyl iodide produced a 42% yield of the desired product contaminated with 11% of regioisomers (entry 8).

In conclusion, we have developed a convenient one-pot procedure to prepare enantiomerically enriched 2,3-disubstituted cyclopentanones from $\beta$-substituted cyclopentenones via tandem asymmetric conjugate reduction and fluoride-promoted alkylation. The alkylation step proceeded with high regioselectivity and in good yield when reactive alkylating reagents were used. This methodology provides simple access to enantiomerically enriched 2,3-disubstituted cycloalkanones that are otherwise difficult to obtain.

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**Supporting Information Available:** Experimental procedures and characterization data of all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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