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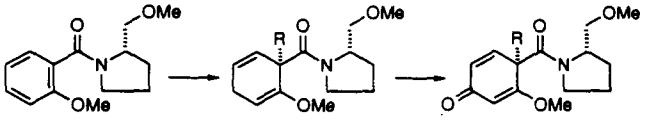
Asymmetric Synthesis of 4,4-Disubstituted-2-cyclohexen-1-ones from a Chiral 2-(Trimethylsilyl)benzamide

Arthur G. Schultz* and Liping Pettus

Department of Chemistry
Rensselaer Polytechnic Institute
Troy, NY 12180-3590

Abstract: Birch reduction-alkylation of the chiral 2-(trimethylsilyl)benzamide **4** provides 1,4-cyclohexadienes **5b-5e** with diastereomer ratios of >100:1. The conversions of **5b-5e** to the 4,4-disubstituted-2-cyclohexen-1-ones **8b-8e** are described. © 1997 Elsevier Science Ltd.

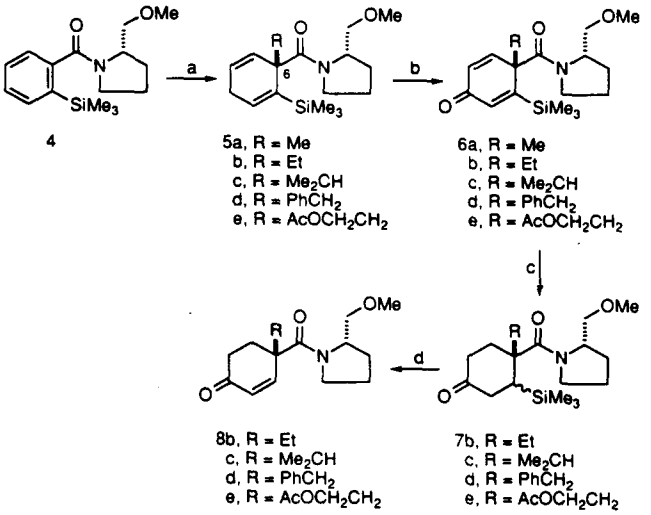
Chiral 4,4-disubstituted-2-cyclohexen-1-ones play an exceedingly important role in asymmetric organic synthesis.[1] Applications range from their use in conjugate addition reactions, Diels-Alder and dipolar cycloadditions to photochemical 2+2 cycloadditions, type A rearrangements and electron transfer processes. The Birch reduction-alkylation of chiral 2-(methoxy)benzamide **1** has provided a practical method for asymmetric synthesis of 3-methoxy-2,5-cyclohexadien-1-ones **3** by way of bis allylic oxidation of the intermediate 1,4-cyclohexadiene **2**.[2] Although the conversion of **2** or **3** to chiral 4,4-disubstituted-2-cyclohexen-1-ones might be possible, it seemed more economical to develop a synthesis of cyclohexenones from the 2-(trimethylsilyl)benzamide **4**. Herein, we report several examples of the highly diastereoselective Birch reduction-alkylation of **4** and attendant chemistry to prepare the 4,4-disubstituted-2-cyclohexen-1-ones **8b-8e**.



The Birch reduction of **4** [3] was carried out at -78 °C with potassium (> 2 equiv) in ammonia and THF solution in the presence of t-BuOH (1 equiv). After 10 min, lithium bromide (1.5 equiv) was added to the dark blue solution; after an additional 10 min, piperylene was added until the blue coloration disappeared. The alkylation reagent was added, stirring at -78 °C was continued for 2 h, and then solid NH_4Cl was added to the reaction mixture. The 1,4-cyclohexadienes **5a-5e** were immediately converted to the 2,5-cyclohexadien-1-ones **6a-6e** on oxidation with catalytic PDC and t-BuOOH in benzene in the presence of Celite.

Product yields and diastereomeric composition for the two-step conversion **4** → **5** → **6** are shown in Table I. Diastereomeric compositions of **6a-6e** were determined by direct GC comparison to 1:1 mixtures of diastereomers prepared by reductive alkylation of methyl 2-(trimethylsilyl)benzoate, saponification, coupling of the resulting carboxylic acids to (S)-prolinol (methyl ether) and oxidation to the dienones.[4] Although MeI gave only moderate stereoselectivity in the enolate alkylation step, all more sterically demanding alkyl halides afforded outstanding stereocontrol.

Hydrogenation of **6b-6e** with 10% Pd/C in EtOAc gave cyclohexanones **7b-7e** as mixtures of diastereomers at C(3). A modification[5] of the procedure for oxidative elimination of β-trimethylsilyl ketones described by Fleming and co-workers[6] enabled the conversion of **7b-7e** to the 4,4-disubstituted-2-cyclohexen-1-ones **8b-8e**, with yields as indicated in Table I.



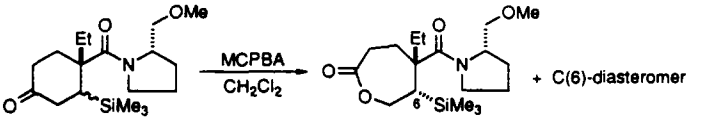
Reaction conditions: (a) K, NH_3, t-BuOH, THF, -78 °C; LiBr; piperylene; RX, -78 °C; (b) PDC (cat), Celite, t-BuOOH, PhH; (c) H_2 (63 psi), 10% Pd/C, EtOAc; (d) $CuCl_2$, DMF, 60 °C.

Table I. Conversions of 2-(Trimethylsilyl)benzamide **4** to cyclohexadienones **6a-6e** and cyclohexenones **8b-8e**

entry	RX	Cyclohexadienones **6** yield (%)[a]	ratio[b]	Cyclohexenones **8** yield (%)[c]
1	MeI	92	3.2:1	---
2	EtI	87	>100:1	87
3	Me_2CHI	86	>100:1	88
4	$PhCH_2Br$	80	>100:1	82
5	$AcOCH_2CH_2Br$	85	>100:1	83

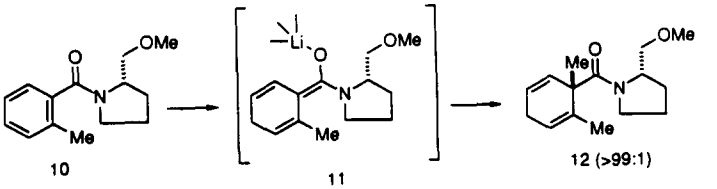
[a]Isolated yields for the reaction sequence **4** → **5** → **6** after flash chromatography on silica gel; diastereomers were not separated. [b]Diastereomer ratio determined by GC analysis; see ref. 4. [c]Isolated yields for the reaction sequence **6** → **7** → **8** after flash chromatography on silica gel.

The stereochemical sense of enolate alkylation was determined for **7b** by utilization of the silicon-directed Baeyer-Villiger oxidation[7] to give caprolactone **9** and its C(6) diastereomer. A single crystal X-ray structure determination for **9** provided the molecular structure shown in Figure 1.[8] The absolute configuration at C(6) for the series **5a-5e** was assigned by consideration of the molecular structure of **9** and trends observed for the ^{1}H NMR chemical shifts and GC retention times[4] for **6a-6e** and their minor diastereomers.



7b 9

The sense of stereoselectivity for alkylation of the enolate generated from the 2-(methoxy)benzamide **1** has been explained by a mechanism that involves internal chelation control.[9] In contrast to **1**, the 2-(methyl)benzamide **10**, in which chelation control cannot operate, gives opposite stereoselectivity; alkylation occurs from the least hindered face of the intermediate enolate **11**, away from the methoxymethyl group on the chiral auxiliary, to give **12**.[9]



10 11 12 (>99:1)

It is interesting that the bulky trimethylsilyl substituent in **4** affords the same sense of stereoselection for enolate alkylation as that for primary 2-alkyl substituents in **10** and related benzamides.[10] Additional characterization of the enolate generated from Birch reduction of **4** and synthetic applications of the 1-trimethylsilyl-1,4-cyclohexadienes **5** will be reported in the near future.

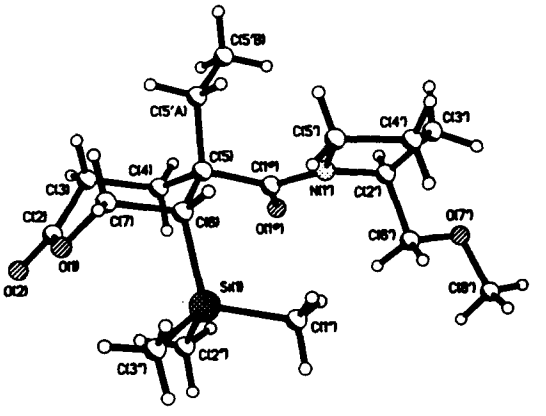


Figure 1. Molecular structure of **9**

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References and Notes

1. For example, see: Devine, P. N.; Meyers, A. I. *J. Am. Chem. Soc.* **1994**, *116*, 2633-2634.
2. For examples of the conversion of **1** and substituted analogues **1** to 2,5-cyclohexadien-1-ones, see: (a) Schultz, A. G.; Malachowski, W. P.; Pan, Y. *J. Org. Chem.* **1997**, *62*, 1223-1229. (b) Schultz, A. G.; Taveras, A. G.; Taylor, R. E.; Tham, F. S.; Kullnig, R. K. *J. Am. Chem. Soc.* **1992**, *114*, 8725-8727. (c) Schultz, A. G.; Taveras, A. G.; Harrington, R. E. *Tetrahedron Lett.* **1988**, *29*, 3907-3910. (d) Schultz, A. G.; Plummer, M.; Taveras, A. G.; Kullnig, R. K. *J. Am. Chem. Soc.* **1988**, *110*, 5547-5555.
3. The 2-(trimethylsilyl)benzamide **4** was prepared from 2-(trimethylsilyl)benzoic acid and (S)-prolinol in 88% yield. For the preparation of 2-(trimethylsilyl)benzoic acid, see: Schultz, A. G.; Antoulinakis, E. G. *J. Org. Chem.* **1996**, *61*, 4555-4559.
4. GC analyses were performed on a Hewlett Packard 5710A gas chromatograph with a flame ionization detector (300 °C) fitted with a 6 ft x 1/8" stainless steel column filled with 3% OV-17 on chromosorb-whp 80/100 mesh (gas pressure: N_2 40 psi; air 24 psi; H_2 40 psi). Peak areas were measured with a HP-3380A integrator. Analysis information: **6a** (column temperature 200 to 250 °C, 1 °C/min) 17.3 min, minor diastereomer 20.3 min; **6b** (200 to 250 °C, 1 °C/min) 16.7 min, minor diastereomer 19.9 min; **6c** (180 to 240 °C, 1 °C/min) 22.8 min, minor diastereomer 26.0 min; **6d** (200 to 250 °C, 1 °C/min) 17.0 min, minor diastereomer 20.3 min; **6e** (200 to 260 °C, 1 °C/min) 28.8 min, minor diastereomer 31.2 min. New compounds were characterized by ^1H and ^{13}C NMR, IR, low resolution MS and combustion analyses.
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8. Crystals of **9** (mp 168-170 °C) were obtained from a solution of **9** in EtOAc/hexane under diffusion control (isothermal distillation occurred at room temperature); $[\alpha]^{23}_D$ -82.0 ° (c 0.5, $CHCl_3$).
9. (a) Schultz, A. G.; Macielag, M.; Sundararaman, P.; Taveras, A. G.; Welch, M. *J. Am. Chem. Soc.* **1988**, *110*, 7828-7841. (b) Schultz, A. G. *Chinese Chem. Soc. (Taiwan)* **1994**, *41*, 487-495.
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