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Enantioselective Addition of Lithium Trimethylsilyl Acetylide to Substituted Cyclohexanones Synthesis of Optically Active Tertiary Cyclohexanols

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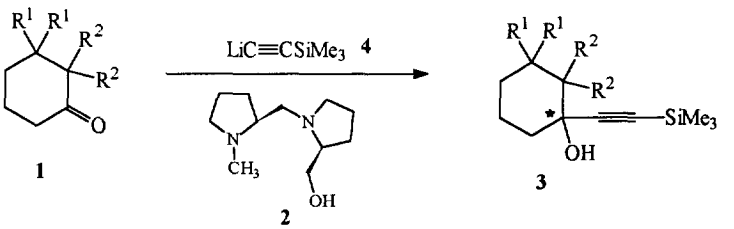
Abstract: Optically active tertiary alkynyl cyclohexanols were obtained by enantioselective addition of lithium trimethylsilylacetylide to cyclohexanones with different substituents in the α- and the β-position. (2*S*,2′*S*)-2-Hydroxymethyl-1-[(1-methylpyrrolidin-2-yl)methyl]pyrrolidine **2** proved to be an effective chiral ligand for the addition. Copyright © 1996 Elsevier Science Ltd

The addition of alkyllithium or Grignard reagents to aldehydes and ketones is a versatile and efficient method for the preparation of secondary and tertiary alcohols[1]. An enantioselective version of this reaction is possible by the use of metallorganic reagents modified by chiral ligands[2].

While a variety of ligands and methods for the enantioselective alkylation of aldehydes[2] are described, only a few are reported for the alkylation of acyclic ketones[3]. Concerning the addition of Grignard reagents to acetophenone the best results were obtained by Seebach[4] using a tartaric acid derivative (TADDOL) as the chiral catalyst. These conditions are very suitable for aromatic ketones whilst their transfer to aliphatic acyclic ketones leads to lower yields and enantiomeric excesses[3]. Up to now enantioselective additions to cyclic ketones are hardly known, one reported example is the alkylation of α-tetralone[4].

Looking for a short access to the Taxol A-ring, we were interested in the enantioselective addition of alkyllithiums to cyclohexanones **1** with different substituents at C-2 and C-3. The additions were performed in the presence of (2*S*,2′*S*)-2-hydroxymethyl-1-[(1-methylpyrrolidin-2-yl)methyl]pyrrolidine **2** as the chiral ligand[5] and lithium trimethylsilylacetylide **4** as metallorganic reagent (scheme 1).

Scheme 1



With ketone **5**[6] we observed a strong influence of the reaction conditions and of the substituents R^1 and R^2 on the yield and enantiomeric excess (Scheme 2, Table 1).

Scheme 2

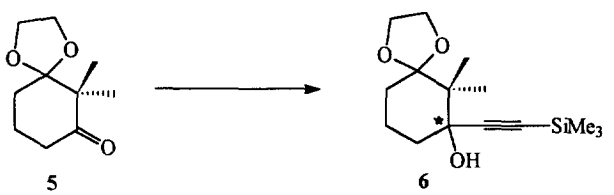


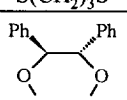
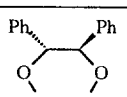
Table 1: Enantioselective additions of lithium trimethylsilylacetylide to ketone **5**[7]

entry	equiv. **2**	equiv. **4**	T (°C)	solvent	yield (%)	*ee* (%)[a]
1	4	5	-100	THF	0	0
2	4	2	-78	THF	15	71
3	4	5	-78	THF	50	78
4	4	2	-120	THF[b]	3	29
5	4	7	-78	THF	83	50
6	4	7	-100	THF	42	48
7	4	5	-30	THF	7	53
8	4	5	-120	THF	11	44
9	4	5	-78	DMM[c]	5	33
10	4	5	-78	Et_2O	33	46

a) ratios of enantiomers were determined by gaschromatography (β-cyclodextrin capillary column), b) 1 equiv. TMEDA, c) dimethoxymethane

The best result was obtained with 4 equivalents of ligand **2** and 5 equivalents of acetylide **4** at -78 °C in THF (entry 3). These conditions were transferred to cyclohexanones **1** with different substituents R^1 and R^2. Table 2 shows that the bulkiness of the groups R^1 and R^2 exerts a strong and inverse influence on yield and enantiomeric excess of **3**.

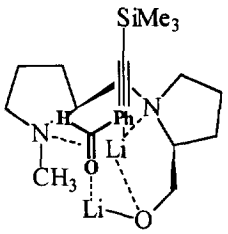
Table 2: Influence of R^1 and R^2 on chemical and enantiomeric excesses[8]

entry	R^1	R^2	yield (%)	*ee* (%)[a]
1	$-O(CH_2)_2O-$	$-CH_3$	50	78
2	-H	$-CH_3$	93	38
3	$-O(CH_2)_2O-$	-H	84	33
4	-H	$-CH_2Ph$	80	66
5	$-O(CH_2)_3O-$	$-CH_3$	43	86
6	$-S(CH_2)_3S-$	$-CH_3$	27	86
7[b]		$-CH_3$	70	82 (*de*)
8[b]		$-CH_3$	70	83 (*de*)

a) enantiomeric excesses were determined by gaschromatography (β-cyclodextrin capillary column) or by chiral shift-reagents, b) in entries 7 and 8 4 equiv. of **2** and 10 equiv. of **4** were used, for the preparation of the diols see reference [9]

The enantioselective addition of acetylide **4** to benzaldehyde led to the corresponding (*S*)-alcohols[10]. The formation of this excess enantiomer was explained by assuming a rigid complex of lithium acetylide **4** and chiral ligand **2** (Scheme 3).

Scheme 3



This complex is formed by coordination of the lithium atom of acetylide with both N-atoms and the O-atom of the chiral ligand **2**[11]. The O-atom of the carbonyl group coordinates with the lithiated hydroxygroup in **2**. The acetylide is transferred to the *re*-side of the carbonyl C-atom of benzaldehyde. The same arguments could also hold for the substituted cyclohexanones **3**.

In comparison with the unsubstituted acetal (entry 1, table 2) the (*R,R*)- and the (*S,S*)-1,2-diphenyl-1,2-ethanediol as acetal group (entries 7 and 8, table 2) increased the stereoselectivity (83 % *de*) as well as the chemical yield (70 %). Without the presence of **2** the acetals in entry 7 and 8 did not effect a diastereoselective addition of lithium trimethylsilylacetylide, therefore the slightly increased stereoselectivity cannot be explained by double stereodifferentiation. Presumably the higher enantiomeric excess is caused by the sterically more demanding phenyl groups.

In summary, a method for the synthesis of sterically hindered tertiary cyclohexanols in good chemical and enantiomeric excess was developed. The application of this versatile reaction to the synthesis of taxol intermediates is currently under study.

References and Notes

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6. Preparation of ketone **5**:
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7. All new compounds gave spectroscopic data in accord with their stucture. Representative data for compound **6**: ^{1}H NMR (300 MHz, $CDCl_3$): *d* 0.11 (s, 9 H, $Si(CH_3)_3$), 1.05 (s, 3 H, CH_3), 1.17 (s, 3 H, CH_3), 1.48-1.91 (m, 6 H, 3x CH_2), 3.85-3.98 (m, 4 H, 2x CH_2O), 4.10 (s, 1 H, OH, D_2O). ^{13}C NMR

(300 MHz, $CDCl_3$): *d* -0.1 (q), 16.8 (q), 17.8 (t), 22.7 (q), 29.8 (t), 34.9 (t), 45.4 (s), 64.3 (t), 65.6 (t), 75.7 (s), 87.5 (s), 107.6 (s), 112.8 (s). Anal. Calcd. for $C_{15}H_{26}O_3Si$: C, 63.78; H, 9.28. Found: C, 63.58; H, 9.30.

8. In a typical procedure 0.4 g (2 mmol) of **2** were dissolved in 10 ml THF under Argon and cooled to -35 °C. 0.38 mL (2.5 mmol) ethynyltrimethylsilane in 1 mL DMM and butyllithium (4.5 mmol) were added and the solution was stirred for 30 min at -35 °C. After cooling the reaction mixture to -78 °C 0.5 mmol of ketone were added in 1mL DMM and stirred for an additional hour. The solution was quenched with a saturated NH_4Cl-solution, extracted twice with ether (10 ml), dried over $MgSO_4$ and concentrated in vacuo. Purification followed by flash chromatography (petroleum/ether = 1:1).
9. The diols were prepared by asymmetric dihydroxylation of *trans*-stilbene: H. Kolb, M. VanNieuwenhze, K. Sharpless, *Chem. Rev.* **1994**, *94*, 2483-2547.
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