Pergamon

Tetrahedron Letters 41 (2000) 6941–6944

TETRAHEDRON LETTERS

Lithium *N*-trityl-*N*-(*R*)-1-phenethylamide, a readily available and useful base for the enantioselective formation of chiral enolates from achiral ketones

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Received 14 July 2000; accepted 17 July 2000

Abstract

Lithium *N*-trityl-*N*-(*R*)-1-phenylethylamide (**6**) is a readily available and useful reagent for the enantioselective (20:1) conversion of 4-*t*-butylcyclohexanone to the corresponding (*S*)-enolate. This reaction provides access to numerous useful chiral compounds.

We recently reported a convenient one-step synthesis of trityl-*t*-butylamine (**1**) and the application of the corresponding lithium amide to highly stereoselective enolate formation from a variety of ketones.[1] The ease of preparation and recovery of **1** and the effectiveness of the lithio derivative as a superhindered base prompted us to investigate a chiral analog, *N*-trityl-*N*-(*R*)-1-phenylethyl amine (**2**), $[\alpha]_D^{23}$ +114 (*c* 1.0, in CH_2Cl_2), which is also available in one step by *N*-tritylation of commercial (*R*)-1-phenylethylamine (Aldrich).[1] In this note we describe a few illustrative applications of **2** in enantioselective synthesis which build on previous observations involving the chiral amines **3** (Koga[2]) and **4** (Simkins[3]).[4] The focus of the present study with **2** was on the substrate 4-*t*-butylcyclohexanone (**5**) since this is the most intensively studied reactant with respect to enantioselective enolate formation with bases such as **3** and **4**.[4]

After several screening experiments to determine optimum conditions for the enantioselective deprotonation of **5** by **6**, the *N*-lithio derivative of **2**, it was determined that excellent results could be obtained using 2 equivalents of lithium bromide, i.e. **6** and LiBr in a ratio of 1:2, in the presence of trimethylchlorosilane[5] in tetrahydrofuran (THF) as solvent at –100°C (liq. N_2–Et_2O bath). Removal of THF and evaporative distillation of the reaction mixture in vacuo afforded the trimethylsilyl enol ether **7** in 89% yield and 91% enantiomeric excess (ee).[6,7] Reaction of **7** with 1,4-benzoquinone in the presence of $Pd(OAc)_2$ in CH_3CN solution at 23°C afforded the chiral enone **8**, $[\alpha]_D^{23}$ +50.0 (*c* 0.02 in $CHCl_3$), of 91% enantiomeric purity in 83% isolated yield. The

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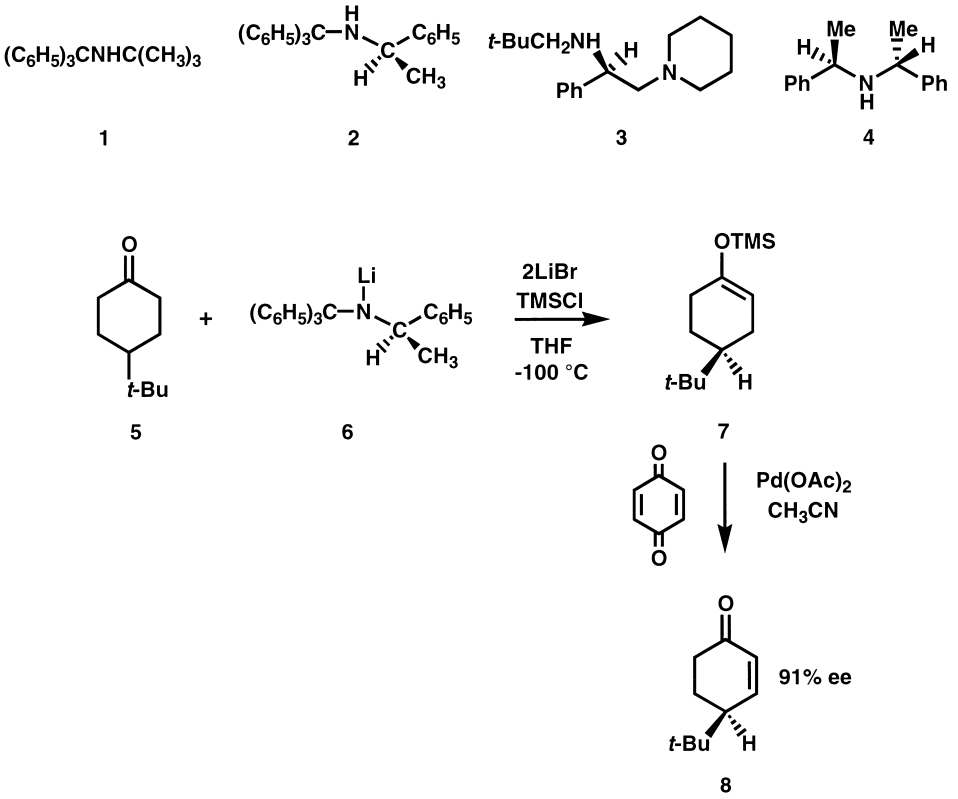
0040-4039/00/$ - see front matter
PII: S0040-4039(00)01185-0

conversion of **5** to **7** by **6** is considerably less enantioselective in the absence of LiBr or using **6** plus a coordinating diamine such as tetramethylethylenediamine (TMEDA) in THF (Scheme 1).

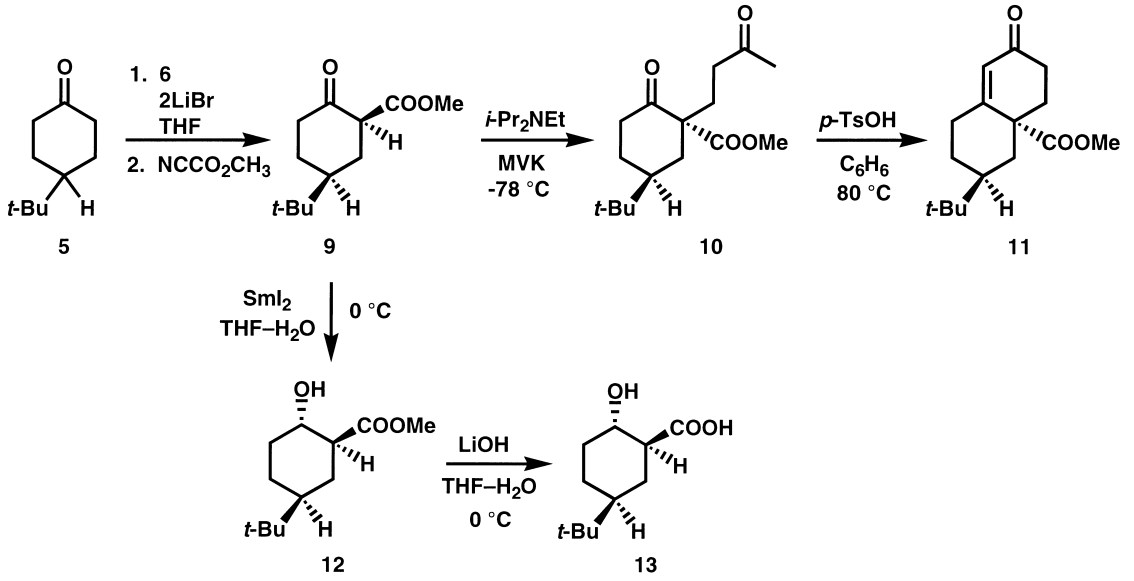


Scheme 1.

The enantioselectivity of the deprotonation of **5** by **6**–2LiBr to form the silyl enol ether **7** is comparable with the best results reported for the bases **3** and **4** which appear to be the most effective of those described in the literature.[4]

We have also examined the application of the hindered chiral base **6** to the enantioselective Robinson annulation of 4-*t*-butylcyclohexanone. Deprotonation of **5** by **6**–2LiBr, in the THF as described above, and subsequent reaction with methyl cyanoformate and 2 equivalents of TMEDA at –100°C for 2 h afforded the β-keto ester **9** in ca. 70% yield.[8,9] Treatment of **9** with diisopropylethylamine and methyl vinyl ketone (slow addition) in methanol at –78°C produced the Michael adduct **10** which upon heating with *p*-toluenesulfonic acid and 4 Å mol. sieves in benzene at reflux yielded the bicyclic α,β-enone **11** as a colorless oil in 69% overall yield after column chromatography on silica gel. The enantiomeric purity of **11**, $[\alpha]_D^{24}$ +74.1 (*c* 0.01 in $CHCl_3$), was determined to be 89% by HPLC analysis using a Chiralpak AD-RH column with 3:1 CH_3CN:H_2O for elution (retention times: major enantiomer, 6.6 min; minor enantiomer, 8.0 min) (Scheme 2).[10]

β-Keto ester **9** is a versatile intermediate for the synthesis of many other types of compounds. For example, in connection with a project on enantioselective hydroxylation by lead tetraacetate we needed a supply of the chiral ligand **13**. This chiral β-hydroxy acid was readily synthesized

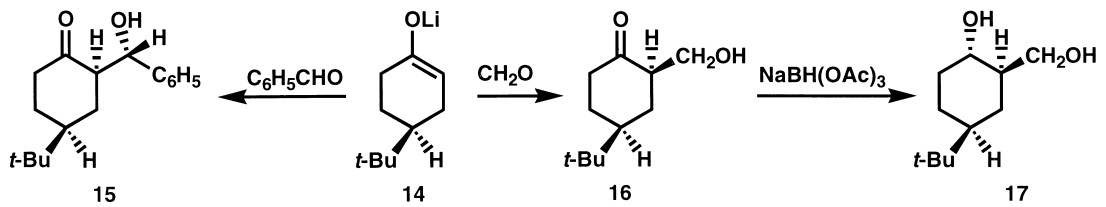


Scheme 2.

from **9** by a two-step sequence. Diastereoselective carbonyl reduction using 2.8 equivalents of SmI_2 in aqueous THF at 0°C,[11] and recrystallization from hexane afforded colorless crystals of **12**, mp 83°C, $[\alpha]_D^{24}$ +11.3 (*c* 0.015 in $CHCl_3$), of 92% ee by ^1H NMR analysis of the Mosher ester.[12] Saponification of hydroxy ester **12** using 1:1 THF:1N aqueous LiOH at 0°C for 2 h provided, after recrystallization from EtOAc, colorless crystals of hydroxy acid **13**, mp 161–162°C, $[\alpha]_D^{24}$ +21.6 (*c* 0.052 in EtOH), of ee >98% by ^1H NMR analysis of the Mosher ester.

The enantioselective generation of the chiral enolate **14** from **5** by asymmetric deprotonation using **6**–2LiBr can also obviously be applied to aldol coupling reactions. Treatment of the chiral enolate thus formed with benzaldehyde at –100°C in THF produced after chromatography on silica gel the major product **15** (58% yield, 89% ee by HPLC analysis using a Chiralpak AD-RH with 3:1 acetonitrile:water for elution[13]).[14] Recrystallization of **15** from EtOAc–heptane gave **15** of 98.5% ee, $[\alpha]_D^{24}$ –49.7 (*c* 0.05 in EtOH), mp 74–74.5°C (Scheme 3).

Reaction of the chiral enolate **14** in THF solution at –100°C with a solution of monomeric formaldehyde in THF[15] afforded, as major product after silica gel chromatography, the hydroxy ketone **16** as a colorless oil (ca. 50% yield); 89% ee by ^1H NMR analysis of the Mosher ester. Reduction of **16** with sodium triacetoxyborohydride in CH_3CN–HOAc at 23°C for 6 h produced the *trans* diol **17** cleanly as a colorless solid (from heptane), mp 86–87°C.[16]



Scheme 3.

The basis of the observed ca. 20:1 enantioselectivity of deprotonation of **5** by **6** and LiBr to form the (*S*)-enolate **14** is a matter of conjecture at this time. One reasonable transition state model involves an eight-membered transition state with the ring members: α-H (axial), C(α), C=O, Li–Br and $LiNR_2$ with the lone pair on nitrogen attacking α-H (axial).

In summary, the chiral amine **2**, which is readily available in one step from inexpensive commercial precursors, and the *N*-lithio derivative **6** are promising synthetic reagents. The utility of **6** in enantioselective enolate formation has been demonstrated by the conversion of 4-*t*-butylcyclohexanone (**5**) via the chiral enolate **14** to several interesting transformation products.

Acknowledgements

This work was supported by grants from the National Science Foundation and the National Institutes of Health.

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6. Enantiomeric excess of **7** was determined by transformation to **8** and analysis of **8** by HPLC using a Chiral Technologies Inc. Chiralpak AD column with 5% isopropyl alcohol in hexane for elution; retention times: minor enantiomer 6.3 min, major enantiomer **8**, 7.3 min; flow rate, 1 mL/min at 23°C.
7. Extractive work-up of the residue remaining from the distillation of silyl enol ether **7** allowed efficient recovery of the chiral amine **2**.
8. (a) Crabtree, S. R.; Mander, L. N.; Sethi, S. *Org. Synth*. **1991**, *70*, 256. (b) Mander, L. N.; Sethi, P. *Tetrahedron Lett*. **1983**, *24*, 5425.
9. The enol methoxycarboxyl ester of **5** was produced as a byproduct of the conversion **5**→**9** in ca. 7% yield under these conditions; in the absence of TMEDA more of this byproduct was formed.
10. The relative stereochemistry of **11** follows from previously known diastereoselective Robinson annulations. See, for example: Turner, R. B.; Lee Jr., R. E.; Hildenbrand, E. G. *J. Org. Chem*. **1961**, *26*, 4800.
11. (a) Singh, A. K.; Bakshi, R. K.; Corey, E. J. *J. Am. Chem. Soc*. **1987**, *109*, 6187. (b) See also: Beeson, C.; Pham, N.; Dix, T. A. *Tetrahedron Lett*. **1992**, *33*, 2925.
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13. Retention times: minor enantiomer, 7.1 min; major enantiomer, 8.3 min.
14. The assignment of absolute configuration of **15** follows from data reported above for the enolate **14**. The equatorial arrangement of the α-hydroxybenzyl substituent is indicated by the 500 MHz ^{1}H NMR spectrum of **15** which shows an 8.9 Hz coupling constant between the α-methine proton and one of the β-methylene protons. Finally, the configuration at the α-hydroxybenzyl stereocenter follows from the pericyclic chair ring transition state preference for the lithium enolate aldol reaction with aldehydes; see: House, H. O.; Crumrine, D. S.; Teranishi, A. Y.; Olmstead, H. D. *J. Am. Chem. Soc*. **1973**, *95*, 3310.
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16. Compounds **7**–**9**, **11**–**13**, and **15**–**17** described above were characterized by infrared, ^{1}H NMR, ^{13}C NMR and high resolution mass spectra using chromatographically purified or recrystallized samples.