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CHIRAL PRODUCTS VIA ASYMMETRIC DEPROTONATION OF 4-*TERT*-BUTYLCYCLOHEXANONE USING CHIRAL LITHIUM AMIDE BASES

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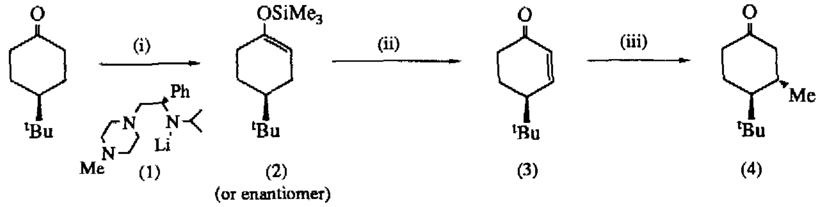
ABSTRACT: The asymmetric deprotonation of 4-*tert*-butylcyclohexanone using chiral lithium amide bases gives derived silyl enol ether products in up to 88% ee.

We recently described the first examples of asymmetric deprotonation reactions in which a prochiral ketone (*cis*-2,6-dimethylcyclohexanone) is converted directly to chiral products, including silyl enol ethers and *C*-alkylated ketones.[1] Since that report other significant developments have appeared in this new area of asymmetric synthesis;[2] perhaps the most successful and important of these being the report from Koga's group concerning the asymmetric deprotonation of 4-*tert*-butylcyclohexanone, using chiral bases having additional ligation sites. The best result was obtained using the base (**1**) in the presence of Me_3SiCl, at -105°C, to give the silyl enol ether (2) in 51% yield and 97% ee, Scheme 1.[3]



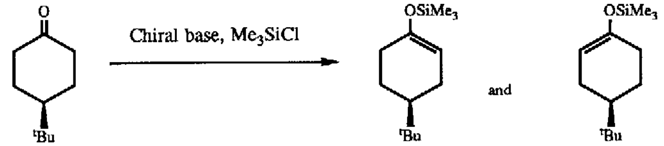
Reagents (i) (1), THF, Me_3SiCl. (ii) $Pd(OAc)_2$, diallylcarbonate, MeCN. (iii) Me_2CuLi.

Scheme 1

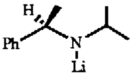
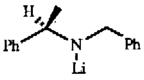
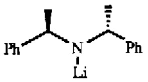
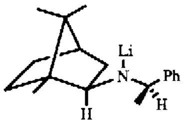
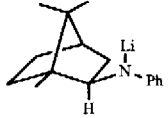
The ee and absolute configuration of the product were established by subsequent conversion through to the ketone (**4**).

We describe here our independent results concerning the deprotonation of 4-*tert*-butylcyclohexanone, which show that simple chiral bases (i.e. not having additional chelating heteroatom groups) are also highly effective for this asymmetric transformation. We have also converted optically active (**2**) into a variety of chiral products in order to illustrate the versatility of the method for the preparation of chiral building blocks, and also to unambiguously establish the ee in the initial deprotonation.

Thus when 4-*tert*-butylcyclohexanone was converted to the silyl enol ether (**2**) under our standard conditions using chiral bases (**5**) - (**9**) the results in the table were obtained.[4]



(*S*) -(-)-(**2**)   (*R*)-(+)-(**2**)

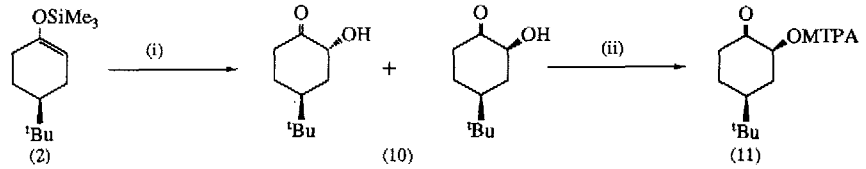
base	temp °C	yield %	$[\alpha]_D$°	$[\alpha]_{365}$°	ee %
 (5)	-78	82	-44.9	-	(57)
	-78	80	-36.2	-116	45^a
	-90	81	-51.0	-	(65)
 (6)	-78	71	-42.9	-133.9	51^a
 (7)	-78	73	-54.4	-171.5	(69)
	-90	66	-69.2	-218.6	88^b
 (8)	-78	80	-16.1	-	(20)
 (9)	-78	75	-23.5	-67.9	(27)

a - by conversion to (**4**), see ref. 5.
b - by conversion to (**11**), see text.
( )- by comparison with rotation data. All rotations in $CHCl_3$ (c, 1.5 - 1.7) at 20 - 21°C.

Table

Several important features of the results are worth noting. Firstly, all of the bases tried gave predominantly (*S*)-(-)-(**2**) in good yield. Results with some bases, e.g. (**5**), were more variable than in our previous experiments with *cis*-2,6-dimethylcyclohexanone, and sensitive to minor variation in the reaction temperature. The camphor derived bases which had proved quite successful in our previous work gave rather disappointing results,[6] whilst the base (**7**) gave material of high optical purity. On carrying out the conversion of two of our samples of (**2**) to (**4**) we obtained estimates of their ee as shown in the table.[5] By extrapolation using this correlation our best result represented about 85% ee. Note that our results are somewhat in conflict with the previous report,[3] in that the measured optical rotation of our product ($[\alpha]_{365}^{22}$ -218.6°, c, 1.5, $CHCl_3$) is *higher than any obtained earlier*, but the ee is apparently lower.[7] In view of this problem we decided to prepare other products which would allow confirmation of our initial results.

Firstly (**2**) was oxidised using mCPBA to the α-hydroxyketone (**10**) (as a 10:1 mixture of isomers), the ee of which was determined by conversion to the corresponding MTPA ester (**11**), (>97% yield). Comparison of the ^1H nmr spectrum of this compound with that of a sample prepared using racemic (**10**) clearly indicated a de of 88% for this sample of (**11**), and therefore an ee of 88% for (**2**), Scheme 2.

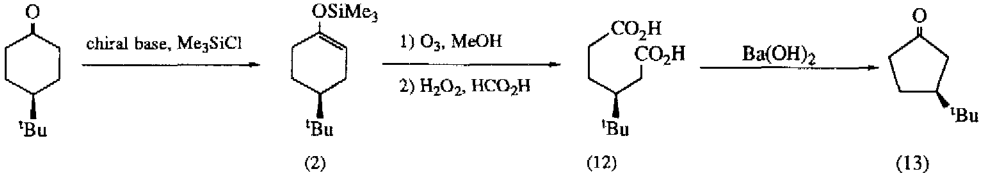


Reagents

(i) mCPBA. (ii) Separate major isomer. MTPACl.

Scheme 2

We next carried out ozonolytic cleavage of the same silyl enol ether, and used an oxidative work-up to obtain the known diacid (**12**), lit. $[\alpha]_D$ +17.2° (c 1, acetone).[8] Our optical rotation of this product also indicated 88% optical purity, and therefore further reinforces the two previous estimates, Scheme 3.



yield %	$[\alpha]_D$°, c, °C	ee^a%	yield %	$[\alpha]_D$°, c, °C	ee^b%	yield %	$[\alpha]_D$°, c, °C	ee^c%
84	-12.7, 1.63, 24	16	62	+2.80, 1.03, 22	16	-	-	-
44	-48.8, 1.60, 27	63	60	+11.4, 1.03, 22	66	66	-106.7, 1.06, 27	66
89	-56.9, 1.55, 24	73	58	+13.2, 1.00, 24	76	63	-121.5, 1.03, 25	75
70	-67.2, 1.53, 24	86	60	+15.2, 1.00, 24	88	62	-140.4, 0.93, 25	87

a - by comparison with material of $[\alpha]_D^{22}$ -69.2° (c, 1.5, $CHCl_3$), shown to be 88% ee by Mosher derivative, rotations in $CHCl_3$.
b - by comparison with the literature rotation of the diacid (12) in acetone.
c - by comparison with the literature rotation of (13) in MeOH.

Scheme 3

As can be seen, other batches of (**2**) of lower optical purity were also converted to the diacid (**12**) with entirely consistent results. Finally, we were pleased to find that the optically active diacid (**12**) could be directly converted to (*S*)-3-*tert*-butylcyclopentanone (**13**), lit. $[\alpha]_D$ -161.9° (c 0.86, MeOH),[8] by simply heating with $Ba(OH)_2$ and distilling off the product as it is formed. Again, the optical rotation of the obtained (**13**) is totally consistent with our earlier results.

The best result from the previous work[3] gave (*R*)-(+)-(**2**) having $[\alpha]_{365}^{25}$ +210°, measured in benzene. Enantiomeric product (*S*)-(-)-(**2**) of lower optical purity ($[\alpha]_{365}$ -120°) was actually converted to (**4**), establishing an ee of 56%. The ee of other samples of higher optical purity was then presumably determined by extrapolation of this result, giving the optimum value of 97% ee.

By contrast, in our work, we have checked the ee of (**2**) obtained of ***highest optical purity***. Estimates of the ee of (**2**) obtained by correlation with (**4**), (**12**) and (**13**), or by formation of the Mosher derivative (**11**), match within ± 2-3%. As can be seen from the figures in Scheme 3 correlations at different ee levels also give consistent results.

We believe we have thereby firmly established that the simple lithium amide base (**7**) gives a higher level of asymmetric induction in deprotonations of 4-*tert*-butylcyclohexanone than the base (**1**), and that the level of induction in the previous work is probably lower than at first thought.

The availability of diverse products such as the six-membered ring keto-alcohol (**10**), enone (**3**), five-membered ring ketone (**13**), and the acyclic diacid (**12**) from a chiral silyl enol ether further indicates the potential applications of chiral base chemistry for the preparation of optically active building blocks. The flexibility arises from the multitude of reactions available to silyl enol ethers, which are here generated directly in chiral form using very cheap and easily prepared secondary amines.

Acknowledgement

We thank the SERC for a research fellowship to R. P. C. C.

References and Notes

1. N. S. Simpkins, J. Chem. Soc., Chem. Commun., 1986, 88.
2. N. S. Simpkins, Chem. Ind., 1988, 387.
3. R. Shirai, M. Tanaka, and K. Koga, J. Am. Chem. Soc., 1986, 108, 543.
4. We initially followed the published procedure for the preparation of (**2**) as closely as possible. In a typical run chiral base was generated by the addition of butyllithium (0.9 ml, 2.4 mmol) to the corresponding amine (2.6 mmol) at -78°C in THF (40 ml). After 5 min the mixture was allowed to warm to room temperature, and then recooled to -78°C. Me_3SiCl (1.3 ml) was then added, and after 2 min 4-*tert*-butylcyclohexanone (0.308g, 2.0 mmol) was added dropwise in THF (10 ml) over a period of 5 min. The mixture was stirred for a further 10 min at -78°C before the addition of Et_3N (4 ml) followed by saturated $NaHCO_3$ (10 ml).The product was extracted into petroleum spirit (2 x 20 ml), the organic layer separated, and then washed with saturated NH_4Cl (2 x 20 ml), saturated $NaHCO_3$ (2 x 20 ml), dried ($MgSO_4$), and the solvent removed under reduced pressure. The residue was then subjected to chromatography (silica), and then distilled (Kugelrohr) to give (**2**) as a colourless oil, b.p. 66-67°C (0.44 mm Hg); $\nu_{max.}$ 3040, 2960, 2870 and 1675 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 0.18 (9H, s), 0.87 (9H, s), 1.12-1.34 (2H, m), 1.73-1.88 (2H, m), 1.95-2.25 (3H, m) and 4.84 (1H, m); δ_C (63 MHz; $CDCl_3$) 0.44, 24.5, 25.2, 27.5, 31.1, 32.2, 44.1, 104.1 and 150.4; *m/z* 226.2 (M^+), 211.2 (M-Me), 169.1, 142.1 and 127.1 (Found: M^+ 226.1752. $C_{13}H_{26}OSi$ requires M, 226.17529); yields and optical data as shown in the table. We later used rather more concentrated conditions for the deprotonation and obtained comparable results.
5. Two samples of (**2**) were independently taken through to (**4**), as indicated in the table. Material having $[\alpha]_{365}$ -116° was converted as in Scheme 1 to give (**4**) having $[\alpha]_D^{20}$ -111.5° (c, 1.1 $CHCl_3$) = 45% ee. Another batch of (**2**) with $[\alpha]_{365}$ -133.9° was reacted with PhSeCl, and then with H_2O_2 to give the enone (**3**), which was then reacted with Me_2CuLi as before. The product (**4**) had $[\alpha]_D^{20}$ -126.8° (c, 1.1 $CHCl_3$) = 51% ee.
6. We have since applied the in-situ Me_3SiCl quench technique to the deprotonation of *cis*-2,6-dimethylcyclohexanone using base (**8**) and obtained improved levels of asymmetric induction - 83% as opposed to 68% using an external quench.
7. Our value of $[\alpha]_{365}$ -218.6° in $CHCl_3$ for (**2**) obtained using base (**7**) is actually ***higher than the theoretical maximum*** for this compound calculated by Koga. Note that we prefer to measure $[\alpha]_D$ and $[\alpha]_{365}$ values in $CHCl_3$ and that we find a linear relationship between the $[\alpha]_D$ and $[\alpha]_{365}$ values. Values of $[\alpha]_D$ or $[\alpha]_{365}$ measured in benzene are ***even higher*** than those measured in $CHCl_3$. Thus a sample of (**2**) having $[\alpha]_{365}$ in $CHCl_3$ of -163.9° has a corresponding $[\alpha]_{365}$ in benzene of -207.3°. According to reference 3 this sample should therefore have an optical purity of 96%, in actual fact conversion to diacid (**12**) gives an estimate of ee of 72%, in line with our other results. We would like to thank Dr A. Drake, Department of Chemistry, University College, London, for measurements of $[\alpha]_{365}$.
8. M. Tichy, P. Malon, I. Fric, and K. Blaha, Collect. Czech. Chem. Commun., 1977, 42, 3591.

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