Asymmetric Deprotonation: A New Route to Chiral Compounds

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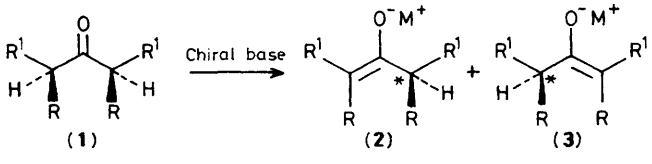
Enantioselective deprotonation of symmetrically substituted ketones under kinetically controlled conditions provides chiral products in up to 74% enantiomeric excess.

The ready availability of chiral starting materials is vital to modern organic synthesis and much effort has been expended in developing new asymmetric methodology to meet this requirement.[1] This communication reports a new asymmetric process which allows rapid, one-step preparation of chiral materials starting from symmetrically substituted ketones. This reaction relies on the enantioselective deprotonation of a symmetrical (*meso*) ketone (**1**) by a strong, hindered, chiral base under kinetically controlled conditions, thus providing chiral enolates (**2**) and (**3**) in unequal amounts,[2] Scheme 1.



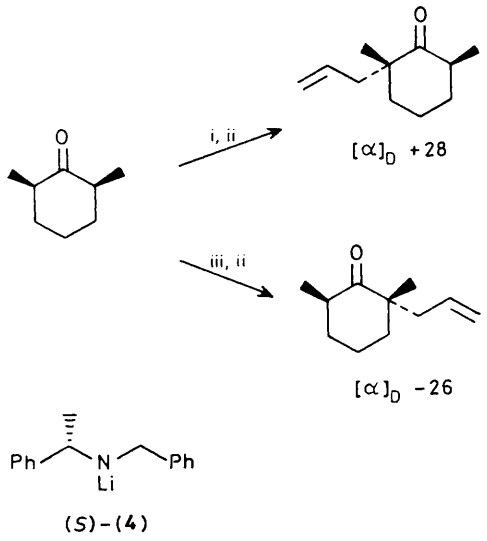
Scheme 1

Initially we examined the enantioselective deprotonation of *cis*-2,6-dimethylcyclohexanone using the lithium amide bases (**4**) derived from commercially available α-methylbenzylamines,[3] followed by quenching with allyl bromide, Scheme 2.

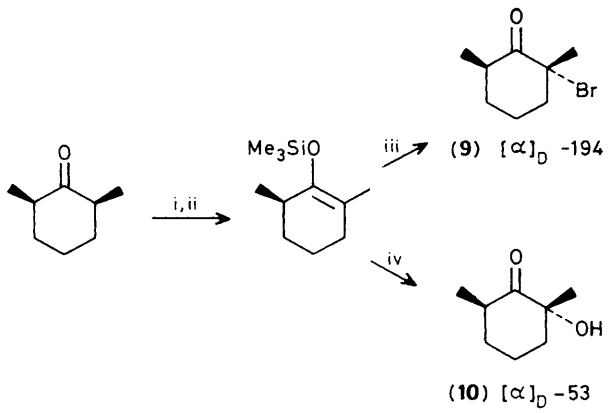
Examination of the ^{1}H n.m.r. spectra of the chiral products† in the presence of the chiral shift reagent Eu(tfc)$_3$ [tfc = 3-(trifluoromethylhydroxymethylene)-(−)-camphorato] indicated an enantiomeric excess (e.e.) of 25%. The relative stereochemistry indicated follows the assignment of Smith,[4] whereas the assignment of absolute stereochemistry was made on the basis of c.d. measurements.‡

† The diastereoisomer shown was the major product, but small amounts of the other diastereoisomer and dialkylated product were also obtained. All new compounds were fully characterized by spectroscopic, elemental analysis, and/or accurate mass methods.

‡ The ketone octant rule was used since the relative stereochemistry and conformation of this product appear unambiguous.

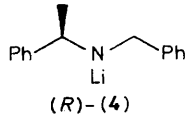
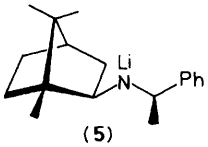
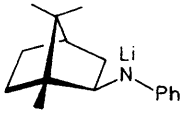
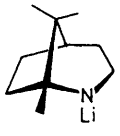
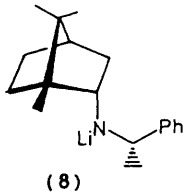


Scheme 2. *Reagents:* i, (*S*)-(**4**); ii, CH_2=$CHCH_2Br$, iii, (*R*)-(**4**). 65% yield, 25% e.e.



Scheme 3. *Reagents:* i, (**6**), THF; ii, Me_3SiCl; iii, *N*-Bromosuccinimide; iv, *m*-chloroperbenzoic acid. 70% e.e.

Table 1

	* *R* or *S*	e.e.
 (*R*)-(**4**)	*R*	29
 (**5**)	*S*	65
 (**6**)	*R*	74
 (**7**)	*R*	14
 (**8**)	*R*	5

That the asymmetric induction observed was due to a kinetically controlled deprotonation was shown by several results. Firstly deprotonation using (*R*)-(**4**) followed by addition of (*S*)-(**4**) prior to quenching with allyl bromide gave rise to chiral product with e.e. usually obtained using (*R*)-(**4**) alone. Furthermore reaction of *trans*-2,6-dimethylcyclohexanone under standard conditions resulted in totally racemic product.

The asymmetric deprotonation reaction was best carried out in tetrahydrofuran (THF). Substitution of either diethyl ether or dimethoxyethane resulted in lower e.e. However solvent additives such as hexamethylphosphoramide could be included immediately prior to quenching without detrimental effect.

Quenching of the chiral enolates on oxygen using acetic anhydride was found to be a more convenient procedure for later determination of e.e. using ^{1}H n.m.r. spectroscopy,§ and routinely provided enol acetate product in 75% yield. Table 1 shows results obtained in this way using the chiral bases (**4**)—(**8**).¶

Optimum results so far have been obtained using base (**6**) (enol acetate product has $[\alpha]_D$ + 50° ≡ 74% e.e.), and interestingly this base gives enantiocomplementary results to base (**5**).

We have also quenched the chiral enolate obtained using base (**6**) with Me_3SiCl, and subsequently converted the chiral trimethylsilyl enol ether into the optically active products (**9**) and (**10**), Scheme 3.

Enantioselective deprotonation using other ketone substrates is possible; for example with base (**6**) *cis*-2,6-dibenzylcyclohexanone gives the expected enol acetate in 72% e.e. Symmetrically substituted ketones without α-substituents also give chiral products, although so far with lower levels of induction.

§ The methyl signal due to the acetate group (δ 2.15) was split into two easily integrated signals on addition of chiral shift reagent.

¶ In a typical experiment the lithium amide base was formed by addition of Bu^{n}Li to a solution of the appropriate amine in THF under nitrogen at 0 °C. The mixture was warmed to room temperature over a period of of 2 h and then cooled to −78 °C before addition of the ketone in THF. This mixture was stirred at −78 °C for 3—8 h depending on the amine used, quenched with Ac_2O and worked up in the usual way. Flash chromatography gave the pure enol acetates in 70—80% yield with the optical purities indicated.

The ease of separation of chiral products from the amine reagents, and rapid recovery of the chiral amines in reusable form is a particularly attractive feature of this reaction.

Received, 27th September 1985; Com. 1403

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4 S. J. Branca and A. B. Smith, III, *J. Org. Chem.*, 1977, **42**, 1026.