Chiral base mediated transformation of cyclic 1,3-diketones

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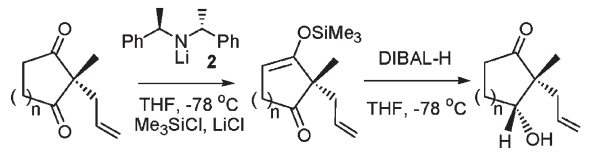
Treatment of certain 1,3-diketones with a chiral lithium amide base results in the formation of a non-racemic lithium mono-enolate; these intermediates can be transformed directly into chiral hydroxyketone products by reduction with DIBAL-H in high yield and with selectivities of up to 99% ee.

The enantioselective reduction of prochiral cyclic diketones to give chiral, non-racemic hydroxyketone derivatives is usually accomplished by Baker's yeast,[1,2] although other microorganisms have also been used,[3,4] and recently chiral oxazaborolidine catalysts have also been employed.[5]

Based on our recent results, which have demonstrated the utility of chiral lithium amide base enolisation for asymmetric transformation of cyclic imides,[6] we anticipated that a similar type of enolisation would be possible for cyclic diketones. We also expected that this type of enolisation would facilitate overall enantioselective reduction of a diketone, either directly or *via* enol silane intermediates. These ideas have proved to have some foundation, and we show herein that highly selective chiral base enolisation of cyclic diketones is indeed possible, and that this provides a new method of asymmetric diketone reduction.

In preliminary explorations, selective enolisation of a cyclopentanedione **1**, by addition of the chiral base **2**, using Me_3SiCl as the electrophilic trapping agent, gave mono-enol silane **3** in moderate yield (50%) and enantiomeric excess (65% ee), Scheme 1.

This initial enolisation–Me_3SiCl trapping process establishes a stereogenic centre at C-2 and sets the scene for subsequent diastereoselective reduction of the remaining carbonyl function. Thus, reduction of the ketone function of enol silane **3** using DIBAL-H, with concomitant enol silane hydrolysis on work-up, gave hydroxyketone **4**, with similar levels of enantiomeric enrichment to **3**. We then achieved similar results for the analogous cyclohexanedione **5**; correlation of products **4** and **7** with compounds described by Brooks and co-workers enabled the assignment of relative and absolute stereochemistry.[1]



1 n = 1
5 n = 2

3 n = 1, 50%, 65% ee
6 n = 2, 64%, 70% ee

4 n = 1, 55%
7 n = 2, 60%

Scheme 1

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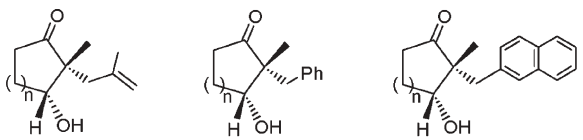
Although these preliminary findings validated our initial plan for accessing chiral cyclic hydroxyketones, we experienced significant problems in generalising the chemistry, due to the highly sensitive nature of the enol silane intermediates. Substantial improvement to the overall efficiency of the method could be achieved by the simple expedient of using the crude enol silanes (usually contaminated by 5–10% of starting diketone) in the reduction. Adopting this procedure enabled the enantioselective formation of the hydroxyketones **8–13** in overall yields of 69–79% from starting dione, and with promising levels of asymmetric induction.



8 n = 1, 69%, 68% ee
9 n = 2, 71%, 81% ee

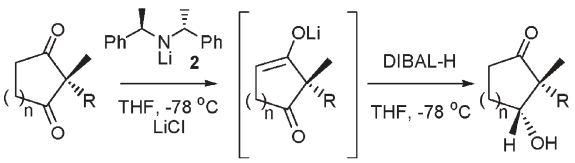
10 n = 1, 79%, 84% ee
11 n = 2, 74%, 91% ee

12 n = 1, 71%, 73% ee
13 n = 2, 72%, 79% ee

In these reductions high levels of diastereoselectivity were observed, with reduction occurring to give mainly the isomer shown (>95 : 5 dr), which results from hydride addition *syn* to the smaller C-2 substituent (*i.e.* the methyl group in each case). This is significant in that the aforementioned bio-transformation methods often give problematic mixtures of isomers.

Although we were encouraged by the new results described above, two steps (pots) are required to accomplish a single selective reduction process. The formation of an intermediate enol silane acts as a device for selectively protecting one of the ketone functions present in the starting dione. We proposed that a one-pot variant might be possible if, instead of preparing intermediate enol silanes, we simply utilised the initially formed chiral lithium mono-enolate **14** as the reduction substrate, Scheme 2.

The use of a derived metal enolate to protect a ketone function in a molecule, whilst another carbonyl is reduced, is an established (although not widely used) strategy for regio- or chemoselective reduction,[7] but the idea has not been explored before in conjunction with a chiral base process. When applied to our diketone substrates we obtained the results shown in Table 1.†



14

Scheme 2

Table 1 Synthesis of **8–13** according to Scheme 2

Entry	Product	Yield (%)	Product de (%)[a]	Product ee (%)[b]
1	**8**	69	31	77
2	**9**	69	99	99
3	**10**	71	58	74
4	**11**	77	95	99
5	**12**	81	35	67
6	**13**	70	98	88

[a] Determined by ^{1}H NMR spectroscopy and cross-checked with data from [b]. [b] Determined by HPLC using either a Chiralcel OD or OJ column except for **8**—by GC using a 2,3-di-*O*-pentyl-γ-CD column. Diastereomer ratios were also evident from these analyses.

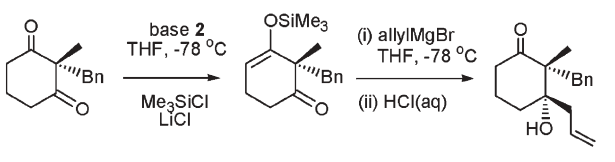
Two key differences were observed in the results obtained this way, compared to the reductions involving the enol silane intermediates. Firstly, for the five-membered systems (odd-numbered entries) the moderate levels of asymmetric induction are maintained, whilst the almost complete diastereoselectivity seen before is seriously eroded. More significantly, for the six-membered systems (even-numbered entries) the diastereoselectivity of the reduction is maintained, and the overall enantioselectivity is significantly enhanced—hydroxyketones **9** and **11** being formed in essentially enantiomerically pure form.

The erosion of diastereoselectivity in the reduction of the five-membered lithium enolates, but not for the six-membered cases, is not straightforward to explain. In the reduction of lithium enolates **14**, issues of enolate aggregation, and/or the formation of (chiral) intermediate aluminium 'ate'-complexes, could be responsible for the observed effects.

In terms of enantiomeric excess, the intrinsic enantioselectivity of the chiral base in the deprotonation step appears to be more effectively translated into the ee of the hydroxyketone using the 'enolate protecting group' method. When using the enol silanes, high selectivity is probably undermined by the extreme sensitivity of these intermediates, which results in varying degrees of hydrolysis (on handling or *in situ*) that leads ultimately to racemic hydroxyketone.

Our success in achieving hydride addition to the non-racemic enol silanes and the mono-lithium enolate intermediates **14** prompted us to attempt an analogous Grignard addition. Initially we tested this idea using allylmagnesium bromide, *e.g.* Scheme 3.

Thus, generation of the chiral enol silane **16**, starting from dione **15**, followed by Grignard addition, gave the hydroxyketone **17** in good yield and ee, and as a single diastereoisomer. The alternative, direct, method, involving addition of the Grignard reagent to the chiral base reaction mixture, gave the same level of induction, **17** being isolated in slightly lower yield (74%). So far this chemistry



15 **16** **17** 80%, 83% ee

Scheme 3

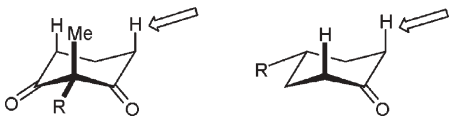


Fig. 1 Sense of enolisation using base **2**.

has not been explored in detail and at this stage it is not possible to make generalisations concerning the scope, yields and selectivities of the process.

It is worth noting that the observed sense of enantioselectivity seen in the enolisation of these diketones is that expected based on precedent for simple cyclic ketones—nicely illustrated by comparing the site of proton abstraction in dione **15** with that in 4-alkylcyclohexanones, Fig. 1.

Therefore it is possible to use the new chemistry in a predictive sense to synthesise useful chiral ketone building blocks.

In conclusion, we have described a new variant of the chiral base enantioselective enolisation, applicable to cyclic diones, which enables either one-pot or two-pot overall asymmetric reduction. As shown in Scheme 3, there is also potential for a powerful desymmetrisation involving C–C bond formation, and we expect that this aspect can be developed by correct choice of nucleophilic organometallic.

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Notes and references

† Typical procedure *e.g.* preparation of (−)-**11**: the chiral amine hydrochloride salt (73 mg, 0.28 mmol) was suspended in dry THF (2 ml), cooled to −78 °C, and a solution of *n*-butyllithium in hexane (2.11 M, 0.26 ml) was added. The mixture was stirred at room temperature for 10 min. 2-Benzyl-2-methylcyclohexane-1,3-dione **15** (50 mg, 0.23 mmol) was dissolved in dry THF (2 ml) and cooled to −78 °C. The base was cooled to −78 °C and added to the diketone *via* transfer cannula. The mixture was stirred at −78 °C for 1 h, before a solution of DIBAL-H in THF (1.7 M, 0.45 ml) was added. The mixture was stirred at −78 °C for 4 h, before the reaction was quenched by the addition of HCl (1 M, 2 ml). The reaction mixture was diluted with ethyl acetate (20 ml) and water (3 ml), and the organic phase was separated. The aqueous phase was extracted with ethyl acetate (3 × 5 ml) and the combined organic phases were washed with HCl (1 M, 3 × 3 ml), brine (3 × 3 ml) and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (silica, EtOAc–petroleum ether, 1 : 3, R_f = 0.23) giving the desired ketoalcohol **11** as a white solid, mp 78–79 °C, (39 mg, 0.18 mmol, 77%), $[\alpha]_D$ −25 (*c* 0.5 in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): 1.08 (3H, s, CH_3), 1.72–1.91 (2H, m, CH_2), 1.98–2.19 (2H, m, CH_2), 2.51–2.59 (2H, m, CH_2), 2.97 (1H, d, *J* 14, C*H*HPh), 3.11 (1H, d, *J* 14, CH*H*Ph), 3.77 (1H, dd, *J* 7, 3, C*H*OH), 7.14–7.33 (5H, m, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) 20.4 (CH_3), 20.7 (CH_2), 28.5 (CH_2), 37.3 (CH_2), 37.7 (CH_2), 54.5 (C), 75.7 (CH), 126.3 (CH), 128.0 (CH), 130.6 (CH), 137.5 (C), 213.8 (C). IR (solution in CH_2Cl_2): 3687, 3603, 2942, 2685, 2410, 2302, 1705, 1604, 1516, 1494, 1373, 1065, 992, 969 cm^{-1}. MS (EI, 180 °C) *m/z* (%): 218 (62), 159 (14), 147 (19), 127 (16), 117 (12), 99 (11), 91 (100), 71 (8). HR-MS (EI, 180 °C): Calc. for $C_{14}H_{18}O_2$: 218.1307. Found: 218.1307. HPLC: (Chiralcel OD, hexane–IPA, 95 : 5, 0.5 ml min^{-1}): 41.6 min (major), 54.9 min (minor); 27.0 min and 38.1 min (minor diastereomer); 99% ee, 95% de.

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