Enantioselective intramolecular cyclizations of prochiral cyclohexanones using chiral lithium amide bases

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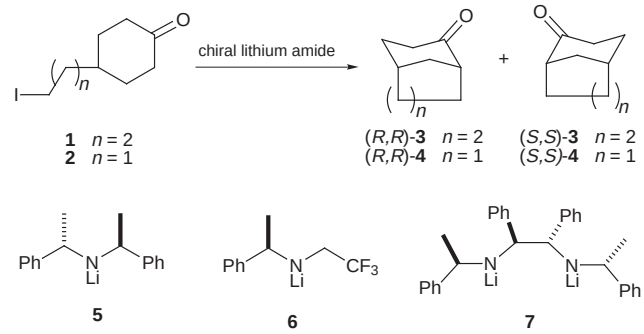
The first examples of intramolecular cyclizations of prochiral cyclohexanones with chiral lithium amide bases have been effected in good yields and enantiomeric ratios.

The use of an amide base and an electrophile to form a carbon–carbon bond at the α-position of a ketone is a fundamental method in organic chemistry. The enantioselective intermolecular version of this reaction, in which a chiral lithium amide base is used with a prochiral ketone, is becoming increasingly widespread.[1–3] As part of an ongoing project in natural product total synthesis, we were interested in applying an intramolecular variation of this chiral alkylation methodology to the preparation of a scalemic intermediate. To the best of our knowledge, this type of enantioselective cyclization has not been previously reported. Here we describe the first examples of the use of chiral lithium amide bases in the enantioselective *intramolecular* deprotonation–alkylation of two prochiral cyclohexanones.

The readily available iodo ketones **1**[7] and **2**[8] which were examined in this methodological study are shown in Scheme 1. The chiral lithium amides used are represented by structures **5**,[9] **6**[10] and **7**.[11] Using published work on intermolecular enantioselective deprotonations of cyclohexanones as a guide, experiments were conducted on cyclization of ketones **1** and **2** to bicyclic systems **3** and **4**, respectively, with amide bases **5**–**7**. Representative results are listed in Table 1.

Initial exploratory experiments were conducted with iodo ketone **1** and amide base **5**. This system leads preferentially to the (*R*,*R*)-enantiomer of **3**.[12,13] This absolute configuration is in accord with published results on deprotonation of simple 4-substituted cyclohexanones with base **5**.[14] Using HMPA as an additive in the intramolecular deprotonation–alkylation of **1** led to bridged ketone **3** in poor to moderate ers (enantiomeric ratios) (entries 1 and 2). These results are in accord with previously reported observations which suggest that HMPA is most effective in inducing high ers with a base that contains one or more internal ligation sites.[1b] However, LiCl has been shown to be a beneficial additive when employing bases either with or without internal ligation sites.[1f] In fact, the best yield and er of (*R*,*R*)-**3** (62% and 87:13, respectively) were achieved using amide **5** along with 2.5 equiv. of LiCl (entry 4).

Cyclization of ketone **1** with amide base **6** led preferentially to the (*S*,*S*)-enantiomer of **3**, whereas base **7** afforded the (*R*,*R*)-enantiomer, although ers were only moderate with both systems (73:27–80:20, entries 5–9). Unlike base **5**, amide base **6** gave



Scheme 1

Table 1 Enantioselective intramolecular cyclization of prochiral cyclohexanones with chiral lithium amides[a]

Entry	Ketone	Lithium amide (equiv.)	Additive (equiv.)	*T*/°C	Product	Yield (%)	Er[b] (*RR*:*SS*)
1	**1**	5 (1.3)	HMPA (2.4) + LiCl (1.3)[c]	−40→room temp.	(*R*,*R*)-**3**	58	59:41
2	**1**	5 (1.3)	HMPA (2.5) + LiCl (1.3)[c]	−50→−10	(*R*,*R*)-**3**	29	82:18
3	**1**	5 (1.3)	LiCl (1.3)[c]	−50→−10	(*R*,*R*)-**3**	44	87:13
4	**1**	5 (1.5)	LiCl (1.0) + LiCl (1.5)[c]	−60→−20	(*R*,*R*)-**3**	62	87:13
5	**1**	6 (1.5)	LiCl (2.0)	−60→−20	(*S*,*S*)-**3**	38	27:73
6	**1**	6 (1.5)	LiCl (1.0)	−60→−20	(*S*,*S*)-**3**	39	22:78
7	**1**	6 (1.5)	LiBr (1.0)	−60→−20	(*S*,*S*)-**3**	42	20:80
8	**1**	7 (1.5)	LiCl (2.0)	−60→−20	(*R*,*R*)-**3**	61	76:24
9	**1**	7 (1.1)	LiCl (1.0)	−60→−20	(*R*,*R*)-**3**	60	76:24
10	**2**	5 (1.5)	LiCl (1.0) + LiCl (1.5)[c]	−60→−20	(*R*,*R*)-**4**	53	79:21
11	**2**	5 (1.05)	LiCl (1.0) + LiCl (1.05)[c]	−80→−40	(*R*,*R*)-**4**	58	90:10
12	**2**	6 (1.5)	LiCl (1.0)	−60→−20	(*S*,*S*)-**4**	61	20:80
13	**2**	6 (1.05)	LiCl (1.0)	−80→−40	(*S*,*S*)-**4**	45	11:89
14	**2**	6 (1.5)	LiCl (1.0)	−80→−40	(*S*,*S*)-**4**	70	10:90
15	**2**	7 (1.1)	LiCl (1.0)	−60→−20	(*R*,*R*)-**4**	57	68:32
16	**2**	7 (1.05)	LiCl (1.0)	−80→−40	(*R*,*R*)-**4**	79	73:27

[a] The experimental procedure for entry 14 is typical: Under an argon atmosphere, a solution of BuLi in hexane (0.30 ml, 1.67 M, 0.502 mmol) was added to a solution of chiral amine (0.102 g, 0.502 mmol) and LiCl (0.014 g, 0.335 mol) in THF (13 ml) at −80 °C affording amide base **6**. The mixture was stirred for 30 min and ketone **2** in THF (0.5 ml) was then added *via* cannula. The solution was allowed to warm to −40 °C and was stirred for 18 h. The reaction mixture was quenched with saturated NH_4Cl (5 ml) and extracted with Et_2O (3 × 15 ml). The organic extracts were sequentially washed with brine (1 × 20 ml), 10% $Na_2S_2O_3$ (1 × 20 ml), 5% HCl (2 × 20 ml) and brine (1 × 20 ml). After drying with Na_2SO_4, and evaporation *in vacuo*, flash chromatography (SiO_2; pentane–Et_2O, 10:1) of the residue gave ketone **4** (0.029 g; 70%). [b] Ers (enantiomeric ratios) were determined by GLC using a chiral Supelco β-DEX 390 column. [c] Formed *in situ* from the hydrochloride salt.

the best results (39% yield and a 78:22 er) when using only 1.0 equiv. of LiCl (entry 6). These results could be improved slightly by substitution of LiBr as the additive in place of LiCl (entry 7). Amide base **7** gave a slightly higher chemical yield of **3** (61%, entry 8) than did amide **6**, but the er was not improved significantly. Thus, of the three bases tested, amide **5** provided the best overall results in cyclization of iodo ketone **1** (entry 4).

As was the case for cyclization of ketone **1**, iodo ketone **2** gave predominantly the (*R*,*R*)-enantiomer of bicyclic ketone **4** with bases **5** and **7**, and the (*S*,*S*)-enantiomer with **6**.[12] Interestingly, the results of the cyclization of ketone **2** were not optimal under the best reaction conditions determined for ketone **1** (*cf*. entries 10, 12 and 15). It was eventually found that of the three bases, lithium amide **6** gave the best results in cyclization of **2** with a 70% yield and a 90:10 er of (*S*,*S*)-**4** using the experimental conditions outlined in entry 14.

In conclusion, we have demonstrated that intramolecular enantioselective cyclizations of prochiral ketones using chiral lithium amide bases are feasible, and can be effected with good ers. The cyclization of ketone **1** was best accomplished to give (*R*,*R*)-**3** in 62% yield and an 87:13 er using lithium amide base **5**, while the cyclization of homologous ketone **2** was effected to afford (*S*,*S*)-**4** in 70% yield and a 90:10 er with amide base **6**. It appears that the chemical yields and ers in these intramolecular cyclizations are highly dependent upon the reaction conditions, base, additive and substrate used, and no obvious trends are evident at this very early stage of development. We are hopeful, however, that with additional work some empirical rules can be devised for this type of enantioselective cyclization.

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Notes and references

1 (*a*) For reviews, see: K. Koga, *J. Synth. Org. Chem. Jpn*., 1990, **48**, 463; (*b*) P. J. Cox and N. S. Simpkins, *Tetrahedron*: *Asymmetry*, 1991, **2**, 1; (*c*) K. Koga, *Pure Appl. Chem*., 1994, **66**, 1487; (*d*) K. Koga and M. Shindo, *J. Synth. Org. Chem. Jpn*., 1995, **53**, 1021; (*e*) N. S. Simpkins, *Pure Appl. Chem*., 1996, **68**, 691; (*f*) P. O'Brien, *J. Chem. Soc*., *Perkin Trans. 1*, 1998, 1439.

2 The large majority of the work on enantioselective deprotonation of prochiral ketones using chiral lithium amide bases involves trapping the resulting enolates as silyl enol ethers: K. Aoki and K. Koga, *Tetrahedron Lett*., 1997, **38**, 2505; R. Shirai, D. Sato, K. Aoki, M. Tanaka, H. Kawasaki and K. Koga, *Tetrahedron*, 1997, **53**, 5963; H. Chatani, M. Nakajima, H. Kawasaki and K. Koga, *Heterocycles*, 1997, **46**, 53; K. Aoki, K. Tomioka, H. Noguchi and K. Koga, *Tetrahedron*, 1997, **53**, 13 641.

3 In addition, chiral lithium amide bases have beeen successfully used for the enantioselective rearrangement of epoxides (ref. 4), aromatic and benzylic functionalization of aryl chromium complexes (ref. 5), as well as the asymmetric [2,3]-Wittig rearrangement (ref. 6).

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7 Iodo ketone **1** was synthesized from 4-(3-chloropropyl)cyclohexanone (*cf*. A. G. Schultz and J. P. Dittami, *J. Org. Chem*., 1984, **49**, 2615) by a Finkelstein reaction (NaI, acetone, 90%).

8 Iodo ketone **2** was prepared from 4-(2-hydroxyethyl)cyclohexanone (M. A. Ciufolini and N. E. Byrne, *J. Am. Chem. Soc*., 1991, **113**, 8016) using PPh_3 and I_2 (60%).

9 The amine is available commercially as the hydrochloride salt.

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11 K. Bambridge, M. J. Begley and N. S. Simpkins, *Tetrahedron Lett*., 1994, **35**, 3391.

12 The absolute stereochemistry of bicyclic ketones **3** and **4** was determined using the CD Octant rule. For a good discussion, see: E. L. Eliel and S. H. Wilen, *Stereochemistry of Organic Compounds*, Wiley, New York, 1994, p. 1022.

13 Racemic ketone **3** is commercially available. Racemic **4**: E. N. Marvell, D. Sturmer and C. Rowell, *Tetrahedron*, 1966, **22**, 861.

14 K. Sugasawa, M. Shindo, H. Noguchi and K. Koga, *Tetrahedron Lett*., 1996, **37**, 7377.

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