Recent Developments in Enantioselective Deprotonation Mediated by Sub-Stoichiometric Quantities of Chiral Bases

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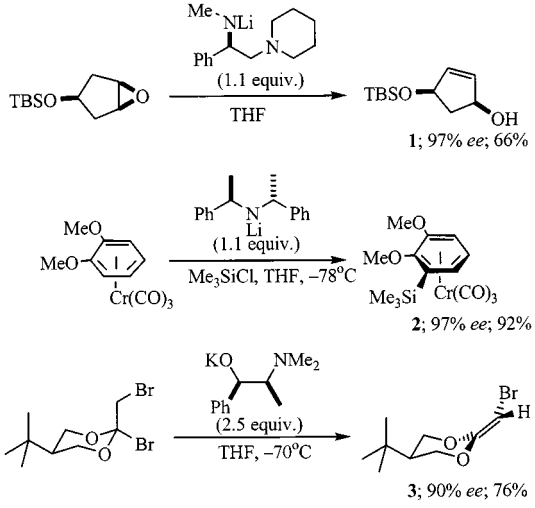
Recent developments in the enantioselective deprotonation of prostereogenic substrates by use of substoichiometric quantities of chiral bases are discussed. The effect that reaction parameters (such as solvent, temperature and additive) have on the stereoselectivity are outlined.

The enantioselective deprotonation of prochiral substrates is very well documented.[1] This reaction has been shown to be diverse, and has resulted in the development of efficient methodologies for the synthesis of a wide range of optically active substrates, such as allylic alcohol **1**,[2a] substituted silane **2**[2b] and vinyl bromide **3**[2c] (Scheme 1). The majority of reports have dealt with the use of a stoichiometric amount of a chiral base.[1,2] Despite the potential,[3] there are still very few examples of analogous substoichiometrically mediated processes.[4]

The concept of substoichiometrically mediated deprotonation is still in its infancy, whereas the related substoichiometrically mediated chiral protonation of prostereogenic substrates is much more mature.[5–7] This related methodology relies on the initial formation of the corresponding conjugate base, usually an enolate,[5] by MeLi addition to a silyl enol ether,[8a] SmI_2/allyl iodide addition to a ketene,[8b] or by simple deprotonation.[8c] Addition of a substoichiometric quantity of chiral acid **HA*** (typically 10 mol %) in the presence of a suitable stoichiometric quantity



Scheme 1. Enantioselective deprotonation mediated by a stoichiometric quantity of chiral base

of donor acid **HA** has resulted in the synthesis of optically active ketones **4** and **5** and amide **6** in good yield (Scheme 2). In many cases, the resulting stereocontrol has been shown to be superb and evidently illustrates the con-

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MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

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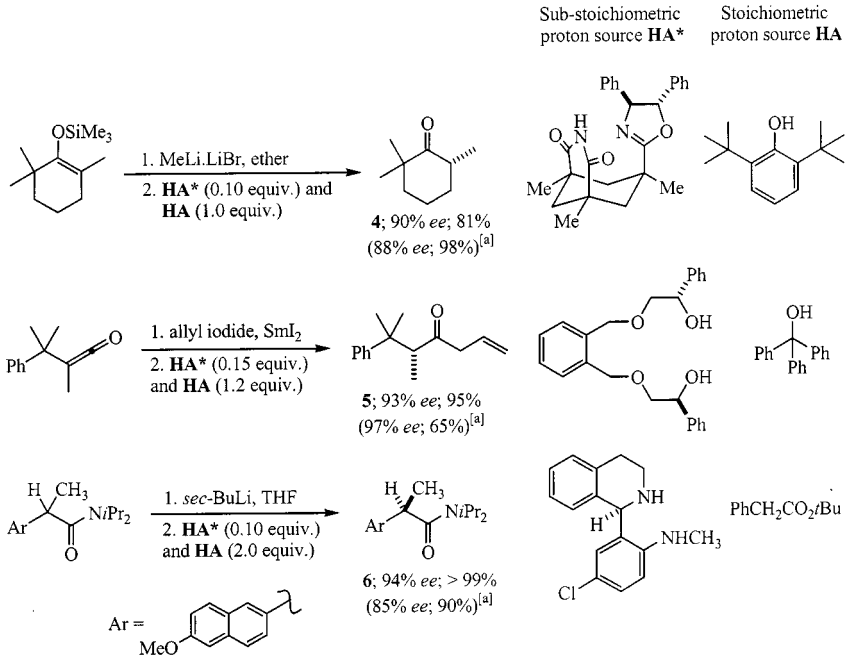


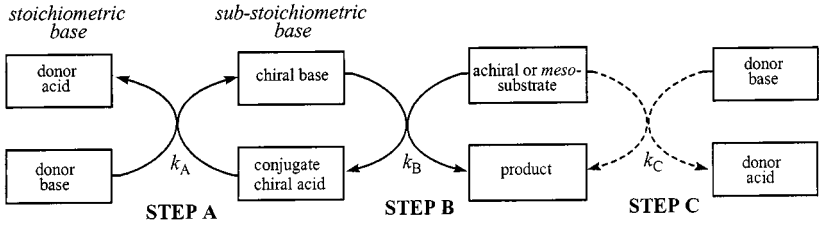
Scheme 2. Enantioselective protonation mediated by a substoichiometric quantity of a chiral proton source: [a] Reaction performed using a stoichiometric quantity of the chiral proton donor

cept of proton recycling. However, both of these related substoichiometric processes have experienced problems, most notably the use of a donor species that is kinetically basic/acidic enough to allow efficient recycling of the *active* chiral component, without itself participating in an analogous, competitive stereorandom process.

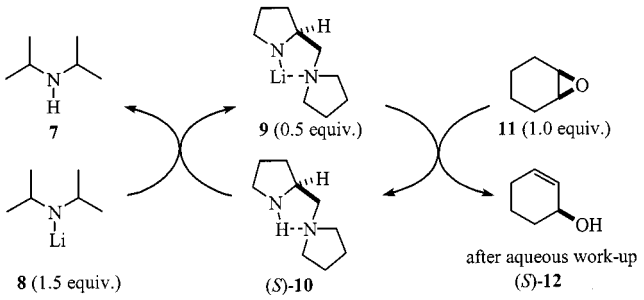
An idealised case is shown in Scheme 3. The rate of regeneration of the substoichiometric chiral base in step A, k_A, must be significantly faster than k_C (by at least two orders of magnitude) to prevent stereorandom deprotonation (occurring in step C) from reducing the overall enantiomeric excess obtained in step B. The rate of the stereoselective deprotonation of the substrate in step B, k_B, must also be greater than or equal to k_A, to ensure that the reaction pathway is controlled by this substoichiometric chiral base. However, this simple case does not exclude the possibility that proton transfer in step A could in principle be reversible. This is unimportant, provided that the rate at which this equilibrium is achieved is rapid. This model assumes that there are no competitive reactions involving crossed dimers of the chiral base/conjugate acid and the donor base/conjugate acid, which could result in variation of the stereocontrol. As long as the rate of deprotonation of the conjugate acid of the substoichiometric chiral base is fast enough, the stereochemical nature of the donor base will appear to be unimportant. However, all examples so far reported[4] deal exclusively with the use of achiral stoichiometric donor bases.

The first successful account of a substoichiometrically mediated enantioselective deprotonation process was reported by Asami in 1994.[4a] This seminal paper reported the discovery that a simple achiral lithium amide could be used as the stoichiometric base in the enantioselective deprotonation of *meso*-epoxides, with a proline-based lithium amide **9** as the substoichiometrically mediating base (Scheme 4).

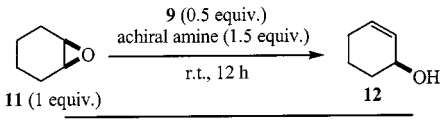
They first focused on reducing the amount of the chiral amide **9** from 1.65 equiv. to a substoichiometric amount (0.50 equiv.), whilst using an excess of a donor lithium amide (1.5 equiv.) (Schemes 4 and 5). The substructure of the lithium amide donor base was found to be surprisingly important for high stereocontrol. Moderate stereocontrol was obtained when lithium diisopropylamide (LDA) was used as the stoichiometric donor base (48% *ee*; Scheme 5: Entry 3). However, virtually no stereocontrol was shown when structurally related amides, such as dicyclohexylamide

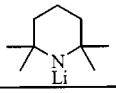


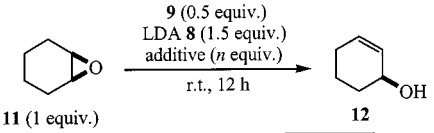
Scheme 3. A schematic mechanism for the enantioselective deprotonation mediated by a substoichiometric quantity of a chiral base



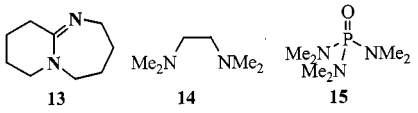
Scheme 4. The enantioselective deprotonation of cyclohexene oxide **11** with a substoichiometric quantity of amide **9**



Entry	achiral amine	% *ee* (% conv.)
1	Et_2NLi	37 (81)
2		37 (59)
3	LDA	48 (63)
4	$(cyclohexyl)_2NLi$	4 (38)
5		2 (72)



Entry	additive	*n*	% *ee* (% conv.)
6	–	0	48 (63)
7	DBU	2	61 (71)
8	DBU	4	68 (79)
9	DBU	6	72 (81)
10	DBU	10	74 (82)
11	TMEDA	2	43 (67)
12	HMPA	2	54 (63)



Scheme 5. The effect of different achiral amides and additives on the stereoselective synthesis of allylic alcohol **12**

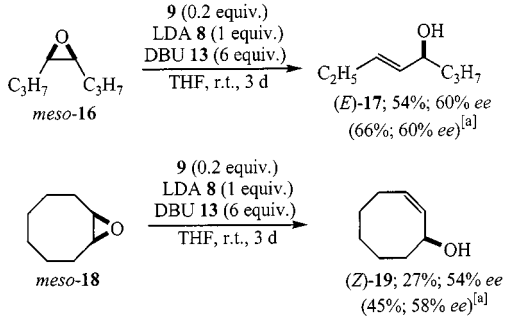
(4% *ee*; Scheme 5: Entry 4), were used. This lowering of the enantiomeric excess may indicate the different rates of proton transfer between the chiral amine (conjugate acid) and the achiral amide, which subsequently affects the efficiency of lithium recycling (Schemes 3 and 4). However, two additional effects complicate this further, the gradual increase in concentration of the Lewis basic achiral amine throughout the course of the reaction, together with the possibility of formation of heterochiral aggregates (involving both the donor amide and chiral amide), which may assist in promoting less stereoselective deprotonation processes.

The use of nitrogen-based additives to increase the efficiency of this *catalytic* cycle was found to be essential. A cyclic amidine, DBU, gave better stereoselectivity than either TMEDA or HMPA. It was shown to behave similarly to the stoichiometric case, giving an enantiomeric excess of up to 48% (yield 63%) (Scheme 5: Entry 6). Both the turnover and the enantiomeric excess were further increased to 82% and 74%, respectively, when a large excess of the DBU additive was used (10 equiv.) (Scheme 5: Entry 10). However, the obvious disadvantages of these early studies were the large amount of substoichiometric chiral lithium amide **9** required (0.5 equiv.). On probing this reaction with a variety of different quantities of LDA and amide **9**, there appeared to be a small dependence on both reagents for optimum yield and enantiomeric excess (Table 1). The relative concentrations of these reagents (LDA/**9**) were also found to be important; comparable ratios of LDA/**9** (Table 1: Entry 2 and 6 versus 3 and 7) gave closely matched stereocontrol over a range of different reagent quantities. In general, the larger the quantity of the chiral amide **9**, the better the enantiomeric excess. Nevertheless, good stereoselectivity was still achievable at levels around 10 mol % (68% *ee*; Table 1: Entry 4), whereas a slightly higher amount (20 mol %) was found to be the optimum, giving the allylic alcohol **12** in 75% *ee* (Table 1: Entry 6).

Table 1. The effect of the relative ratio of LDA/amide **9** on the stereoselective deprotonation of epoxide *meso*-**11**

Entry	**9**	LDA	% *ee* (% conv.)	ratio LDA/**9**
1	0.50	1.50	72 (81)	3
2	0.33	1.67	73 (83)	5
3	0.20	1.80	68 (69)	9
4	0.10	1.90	68 (76)	19
5	0.05	1.95	59 (65)	39
6	0.20	1.00	75 (71)	5
7	0.12	1.08	69 (75)	9
8	0.06	1.14	59 (61)	19

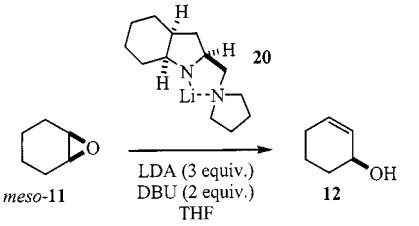
Under these optimised conditions, both (*Z*)-4-octene oxide *meso*-**16** and cyclooctene oxide *meso*-**18** eliminated efficiently to give the corresponding allylic alcohols (*E*)-**17** and (*Z*)-**19** in moderate yield and enantiomeric excess (Scheme 6). It is worthy of note that eliminations involving



Scheme 6. Desymmetrisation of *meso*-epoxides **16** and **18**: [a] Yield and enantiomeric excess obtained when the reaction was performed under stoichiometric conditions (**9**, 1 equiv. and 1.65 equiv. DBU)

either the larger carbocyclic ring, cyclooctene oxide *meso*-**18**, or the conformationally flexible, acyclic (*Z*)-4-octene oxide *meso*-**16**, were less stereoselective than that involving cyclohexene oxide *meso*-**11** itself. However, the levels of stereocontrol under both stoichiometric and substoichiometric conditions do appear to be comparable.

Asami has further developed[4d] a second-generation chiral amide **20**, based on his original proline-based amide **9** (Scheme 7). This more substituted chiral amide contained two further stereogenic centres within the carbon skeleton of the bicyclic pyrrolidine ring and was found to give higher yields and enantiomeric excesses than obtained in the stoichiometric case (89% *ee*; 86%).



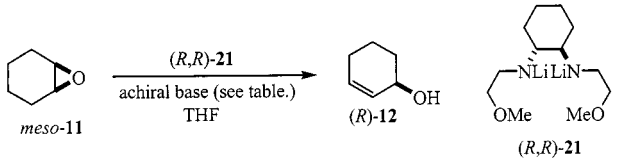
Entry	20	% *ee* (% conv.)
1	0.20 equiv.	88 (95)
2	0.10 equiv.	88 (93)
3	0.05 equiv.	85 (93)
4	0.03 equiv.	79 (92)
5	0.01 equiv.	60 (74)

Entry	temp	% *ee* (% conv.)[a]
6	r.t.	88 (95)
7	0 °C	94 (89)
8	−5 °C	94 (84)
9	−15 °C	93 (73)

Scheme 7. Investigations into the substoichiometric effect of chiral amide **20**: [a] Reactions performed with amide **20** (20 mol %)

The amount of the chiral amide **20** could be reduced further, to 3 mol %, before the stereoselectivity was significantly lowered (Scheme 7: Entries 1−5). Additionally, there appears to be a temperature threshold between 0 °C and −5 °C; a slight increase or decrease in temperature around this range caused the stereocontrol to be reduced, whereas a lower temperature (e.g., −15 °C) was required before the yield was similarly affected.

Alexakis has also investigated[4c] the enantioselective deprotonation of cyclohexene oxide *meso*-**11** with a C_2-symmetric diamide, (*R*,*R*)-**21** (Scheme 8). By use of traditional stoichiometric methodology, this chiral diamide gave the allylic alcohol (*R*)-**12** in good yield (68%), with an enantiomeric excess of 76% (Scheme 8: Entry 1). Attempts to regenerate the original lithium diamide (*R*,*R*)-**21** by the Asami lithium amide donor base (LDA)/additive (DBU) strategy[4a,4d] proved unsuccessful and gave the allylic alcohol (*R*)-**12** in a significantly reduced enantiomeric excess (Scheme 8: Entry 4; from 32 to 13% *ee*). This presumably indicates that stereorandom deprotonation of cyclohexene oxide with LDA has a rate comparable to that of deprotonation of the conjugate acid to regenerate the highly basic chiral lithium diamide (*R*,*R*)-**21**. However, more efficient recycling could only be achieved when a particularly strong carbon base such as *n*BuLi was used (Scheme 8: Entry 2). The background stereorandom elimination of cyclohexene oxide *meso*-**11** with *n*BuLi appears to be particularly slow, and this is presumably due to the slower proton transfer between a *C*-based acid (cyclohexene oxide) and base (*n*BuLi) in comparison with that with the related *N*-based acids and *C*-based bases.[9] In all cases so far discussed, the additive DBU noticeably enhanced the stereocontrol in the deprotonation step, whereas with this particular lithium diamide it was lowered from 32 to 13% *ee* (Scheme 8: Entries 3 and 4). A possible explanation is that the more reactive diamide (*R*,*R*)-**21** aggregates differently from related monoanionic amides in the presence of the DBU additive.



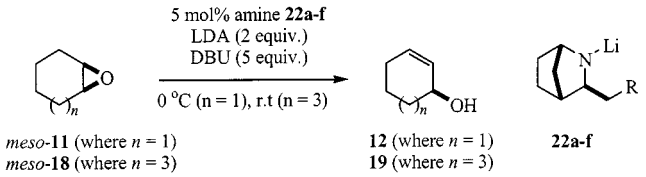
Entry	(*R*,*R*)-21	achiral base	additive	% *ee* (% conv.)
1	1.0 equiv.	—	—	76 (68)
2	0.2 equiv.	*n*BuLi (1 equiv.)[a]	—	67 (47)
3	0.2 equiv.	LDA (1.5 equiv.)	—	32 (66)
4	0.2 equiv.	LDA (1.5 equiv.)	DBU (6 equiv.)	13 (35)

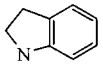
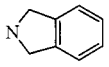
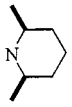
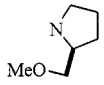
Scheme 8. The use of diamide (*R*,*R*)-**21** as a substoichiometric chiral base: [a] Reaction performed in benzene at 5 °C

Andersson has further probed this reaction by using a series of generic azabicyclo[2.2.1]heptane amide bases **22a**−**f** (Scheme 9).[4f,4g] These amides were initially screened against both cyclohexene oxide and cyclooctene oxide, with LDA (2 equiv.) used as the stoichiometric base. The pyrrolidine-based amide **22a** gave the highest reported enantiomeric excess for the deprotonation of cyclohexene oxide, affording the allylic alcohol **12** with near perfect enantiomeric excess (96%) (Scheme 9: Entry 1). The homologous piperidine-based amide behaved similarly (Scheme 9: Entry 2), but further attempts at modifying this substructure gave a noticeable reduction in stereocontrol (Scheme 9: Entry 3−6). The presence of an additive such as DBU (5 equiv.) was similarly found to be essential for efficient recycling of the chiral amide; without it the stereoselectivity was substantially reduced from 78 to 44% *ee* (Scheme 10: Entry 1 versus 9). Similarly, the polarity and the structural nature of the solvent were also important; THF was found to be better than both diethyl ether and dioxane (Scheme 10: Entry 9 versus 10 and 11), whereas a nonpolar noncoordinating solvent such as benzene gave lower stereocontrol (Scheme 10: Entry 12).

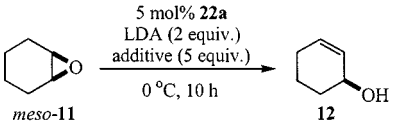
Under these optimised conditions, other unsubstituted cyclic epoxides eliminated efficiently; six- and seven-membered rings, for example, gave better stereocontrol than related five- and eight-membered rings (Scheme 11: Entries 6 and 10 versus 1 and 11). The effect of additional substituents within these carbocyclic frameworks could also alter the stereocontrol by affecting the conformation required for this *syn*-stereospecific β-elimination process.

To probe this conformational effect, a variety of substituted cyclopentene and cyclohexene oxides *meso*-**24**−**28** were screened to find the acceptable substitution pattern for good stereocontrol (Scheme 11). Virtually all of the epoxides tested eliminated with superb stereocontrol (typically

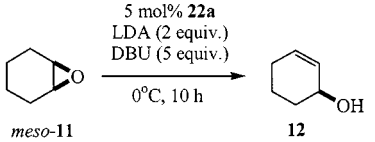


Entry		R=	n = 1 % *ee* (% conv.)	n = 3 % *ee* (% conv.)
1	**22a**		96 (51)	63 (70)
2	**22b**		95 (50)	59 (65)
3	**22c**		73 (38)	54 (43)
4	**22d**		75 (46)	37 (40)
5	**22e**		46 (22)	35 (25)
6	**22f**		84 (24)	43 (22)

Scheme 9. The structural effect of the chiral amide **22a**–**f** on overall stereocontrol



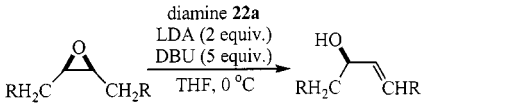
Entry	additive	solvent	% *ee* (% conv.)
1	none	THF	44 (40)
2	DBU	THF	96 (51)
3	DBN	THF	67 (81)
4	DABCO	THF	41 (36)
5	DMPU	THF	44 (49)
6	TMEDA	THF	40 (67)
7	pyridine	THF	69 (80)
8	DMAP	THF	22 (30)

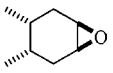
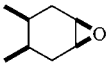
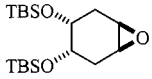
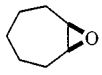
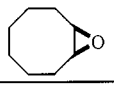


Entry	solvent	% *ee* (% conv.)
9	THF	78 (92)[a]
10	ether	38 (63)
11	1,4-dioxane	65 (70)
12	PhH	35 (58)

Scheme 10. The effect of additives and solvent on the desymmetrisation of epoxide *meso*-**11**: [a] 1 mol % **22a** used

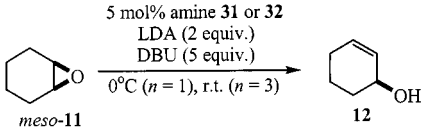
94–97% *ee*). The only noticeable exception was the *syn*-stereoisomeric cyclopentene oxide *meso*-**24** (c.f. Scheme 11: Entry 3; 5 mol %, 67% *ee*); however, under traditional stoichiometric conditions, excellent stereocontrol returned (95% *ee*; Scheme 11: Entry 4).

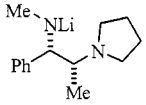
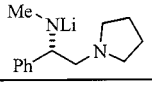


Entry	epoxide		22a (mol %)	% *ee* (% conv.)
1		*meso*-**23**	20[a]	(*R*); 49 (67)
2			120[a]	(*R*); 95 (78)
3		*meso*-**24**	5	(*R*); 67 (60)
4			120	(*R*); 95 (85)
5		*meso*-**25**	20[a]	(*R*); 95 (42)
6		*meso*-**11**	5	(*R*); 96 (91)
7		*meso*-**26**	5	(*R*); 94 (95)
8		*meso*-**27**	5	(*R*); 97 (95)
9		*meso*-**28**	5	(*R*); 97 (60)
10		*meso*-**29**	5	(*R*); 96 (89)
11		*meso*-**18**	5	(*R*); 78 (81)

Scheme 11. Enantioselective desymmetrisation of *meso*-epoxides **11**, **18** and **23**–**29**: [a] Reaction performed at room temperature

Andersson has also reported the use of norephedrine-based lithium amides **31** and **32**,[4g] which gave excellent stereocontrol with the cyclohexene oxide *meso*-**11** (up to 90% *ee*) (Scheme 12). The presence of the additional methyl substituent at C(2) was found to be particularly important; the stereoselectivity without it was reduced to 64% *ee*

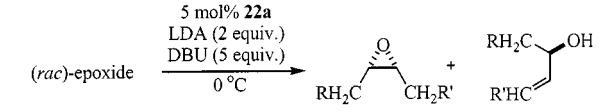


Entry			% *ee* (% conv.)
1		**31**	90 (4)
2			*rac* (3)[a]
3		**32**	64 (5)
4			*rac* (3)[a]

Scheme 12. The effect of additive concentration on the enantiomeric excess: [a] Reaction run in the absence of LDA, with Li-**31** or Li-**32** (2.0 equiv.), respectively

(Scheme 12: Entry 1 versus 3). However, when 2 equiv. of lithium amides **31** and **32** were used in the absence of any donor base, all the stereocontrol was surprisingly lost (Scheme 12: Entries 2 and 4). The fact that the stoichiometric reaction gave no stereocontrol suggests that two competing pathways exist.

Kinetic resolution of racemic epoxides through the use of a stoichiometric quantity of chiral amide has also been reported (Scheme 13).[1a,10] High levels of stereocontrol are rare, and the conversion yield is typically less than 30%. However, this problem has been partially solved by use of Andersson's amide **22a** under substoichiometric control conditions.[4g] This resolution procedure was shown to be efficient, giving both the allylic alcohol and the recovered epoxide in high yield and with good stereocontrol (up to 96% *ee*). It is worth noting that the unsymmetrical epoxide (*rac*)-**33** eliminates to give the tertiary allylic alcohol by removing the less hindered proton, whereas the epoxide (*rac*)-**34** can only undergo β-elimination via the neighbouring methyl group (Scheme 13).

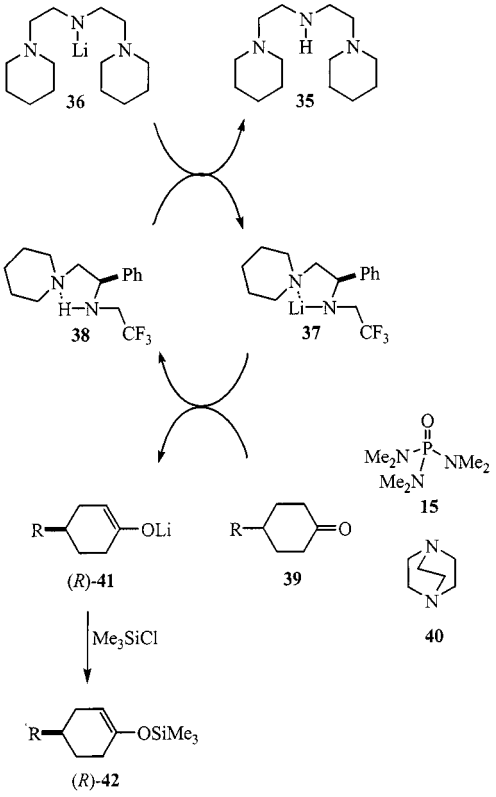


Entry	epoxide	epoxide % *ee* (%conv.)	allylic alcohol % *ee* (% conv.)
1	(*rac*)-**33**	(*S*)- 78% *ee*; 40%	(*R*)- 96% *ee*; 44%
2		(*S*)- 87% *ee*; 32%	(*R*)- 94% *ee*; 20%
3	(*rac*)-**34**	(*S*)- 77% *ee*; 44%	(*R*)- 88% *ee*; 37%
4		(*S*)- 94% *ee*; 45%	(*R*)- 84% *ee*; 43%

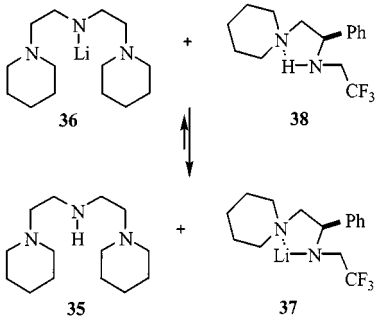
Scheme 13. The kinetic resolution of epoxides (*rac*)-**33** and -**34** by use of a substoichiometric quantity of amide **22a**

Andersson et al. have also investigated[4g] the use of Lewis basic additives (such as DBU), and the effect they have on the overall stereoselectivity. It was concluded that such additives enhanced the proportion of more stereoselective monomeric basic chiral species, by inhibiting the formation of unselective aggregates. There was also found to be a linear relationship between the enantiomeric purity of the chiral lithium amide **22a** and the product at a sufficiently high DBU concentration (6 equiv.). A negative nonlinear effect was observed at lower concentrations of DBU (0−3 equiv.), in which the overall stereocontrol was presumably more influenced by the presence of more reactive heterochiral *meso* aggregates.

Koga et al. have extended this substoichiometric chiral amide methodology[4b] to the synthesis of enantiomerically pure carbonyl derivatives by desymmetrisation of achiral ketones such as **39** (Scheme 14). Instead of using a simple achiral lithium amide, such as LDA, as the stoichiometric donor base,[4a] they developed a stoichiometric tridentate amide **36** for recycling their chiral amide **37** through deprotonation of the corresponding amine **38** (Scheme 15). This strategy was based on the assumption that the less Lewis acidic lithium amide **36** would be kinetically less basic than the related chiral amide **37**. This would allow rapid and efficient proton transfer between the donor base **35** and the conjugate *N*-based acid **38** without stereorandomly deprotonating the carbonyl substrate. Through systematic screening, they discovered that the trifluoroethyl-substituted amine **38** was an excellent substrate that allowed efficient amide formation **37** through deprotonation by the donor base **36** (Scheme 15). The combination of two additives [HMPA (**15**) and DABCO (**40**)] was shown to be important for the stereoselective outcome of this reaction (Table 2). It appears that HMPA is the more dominant additive, increasing both yield and enantiomeric excess through an improvement in turnover. The use of DABCO (1.5 equiv.) was



Scheme 14. The enantioselective deprotonation of 4-substituted cyclohexanone **39** by use of a substoichiometric quantity of amide **37**



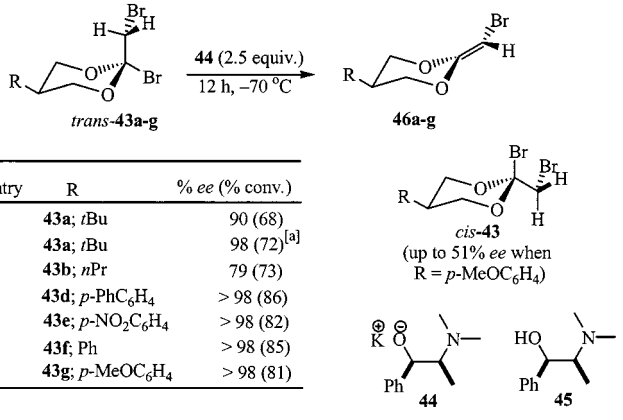
Scheme 15. The relative basicity of the donor amide **36** favours exclusive formation of the chiral amide **37**

Table 2. The yield and enantiomeric excess in the synthesis of the silyl enol ether **42**

Entry	39	amide (equiv.)	36 (equiv.)	HMPA	DABCO	% *ee* (% conv.)
1	**39a**; R = *t*Bu	**37** (1.24)	0.0	2.4	0.0	**42a**; 81% (85%)
2	**39b**; R = Ph	**37** (1.24)	0.0	2.4	0.0	**42b**; 80% (77%)
3	**39c**; R = *i*Pr	**37** (1.24)	0.0	2.4	0.0	**42c**; 79% (75%)
4	**39d**; R = Me	**37** (1.24)	0.0	2.4	0.0	**42d**; 78% (82%)
5	**39a**; R = *t*Bu	**37** (0.30)	3.6	—	—	**42a**; 31% (57%)
6	**39a**; R = *t*Bu	**37** (0.30)	2.4	2.4	0.0	**42a**; 70% (75%)
7	**39a**; R = *t*Bu	**37** (0.30)	2.4	2.4	1.5	**42a**; 79% (83%)
8	**39b**; R = Ph	**37** (0.30)	2.4	2.4	1.5	**42b**; 76% (77%)
9	**39c**; R = *i*Pr	**37** (0.30)	2.4	2.4	1.5	**42c**; 76% (80%)
10	**39d**; R = Me	**37** (0.30)	2.4	2.4	1.5	**42d**; 75% (70%)

found to give a marginal increase in the enantiomeric excess. These results were similar to the stoichiometric cases with 1.24 equiv. of chiral amide **37** and a trimethylsilyl chloride (Me_3SiCl) quench strategy.

The use of substoichiometric chiral base mediated reactions have not been restricted to the use of lithium amides. Plaquevent has recently readdressed the balance with a new complementary class of basic auxiliaries, namely chiral alkoxides such as **44** (Scheme 16).[4e] These had previously been shown to be efficient bases in the HBr elimination of diastereoisomeric dibromides *cis*- and *trans*-**43a**−**g** to give the vinyl bromides (*R*)-**46a**−**g** with superb enantiomeric excesses (from 79 to > 98% *ee*).[11] The transfer of this stoichiometric approach to a substoichiometrically mediated process was based on the observation that potassium hydride (KH) does not significantly promote dehydrobromination of the dibromide **43** (Table 3). Additionally, with potassium hydride as the donor base, no reaction occurred at low temperature (−70 to −20 °C; Table 3: Entry 2), while an excess of alkoxide **44** gave a similar selectivity. This shows that, at a low temperature (−70 °C), potassium hydride surprisingly does not react with either **43** or **44**. On increasing the reaction temperature to 25 °C, both stoichiometric and substoichiometric reactions gave identical stereocontrol (60% *ee*; Table 3: Entries 3 and 4), which illustrates the potential of this in situ formation of alkoxide **44** from the conjugated acid and potassium hydride (Scheme 17). However, the enantiomeric excess was slightly lower than that at −70 °C, but was increased to 68% *ee* by increasing the reaction time at a slightly higher temperature (−17 °C). The choice of a metal counterion is important, a potassium counterion behaved better than either a sodium or lithium counterion and consequently gave better turnover.



Entry	R	% *ee* (% conv.)
1	**43a**; *t*Bu	90 (68)
2	**43a**; *t*Bu	98 (72)[a]
3	**43b**; *n*Pr	79 (73)
4	**43d**; *p*-PhC_6H_4	> 98 (86)
5	**43e**; *p*-$NO_2C_6H_4$	> 98 (82)
6	**43f**; Ph	> 98 (85)
7	**43g**; *p*-$MeOC_6H_4$	> 98 (81)

Scheme 16. The enantioselective dehydrobromination of *trans*-**43a**−**g** by use of a stoichiometric quantity of base: [a] After one crystallisation of the crude material

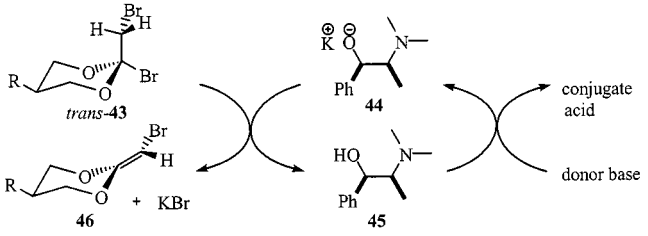
Table 3. The yields and enantiomeric excesses obtained involving a substoichiometric quantity of alkoxide **44**

Entry	44 (equiv.)[a]	R	time	temp. [°C]	% *ee*[b]
1	2.50	**43a**; *t*Bu	12 h	−70	90
2	0.25	**43a**; *t*Bu	12 h	−70 < *T* < −20	no reaction
3	2.50	**43a**; *t*Bu	15 min	25	61
4	0.25	**43a**; *t*Bu	15 min	25	60
5	0.25	**43a**; *t*Bu	20 min	−17	68
6	0.25	**43a**; *t*Bu	90 min	−18	67

Entry	donor base	R	% *ee* (% conv.)
7	MeOK	**43a**; *t*Bu	61 (66)
8	EtOK	**43a**; *t*Bu	28 (65)
9	*i*PrOK	**43a**; *t*Bu	11 (60)
10	*t*BuOK	**43a**; *t*Bu	0 (100)

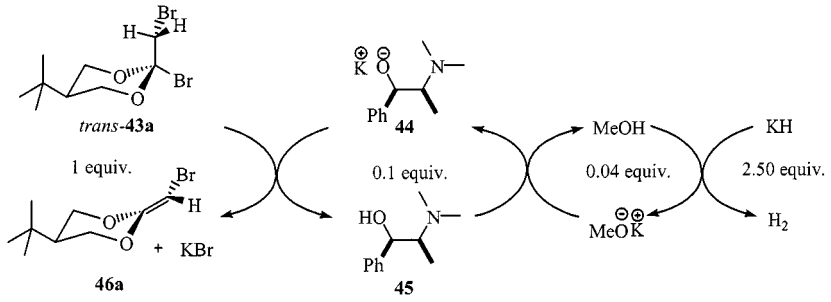
Entry	MeOH equiv.	R	% *ee* (% conv.)[c]
11	0.40	**43a**; *t*Bu	68 (90)
12	0.20	**43a**; *t*Bu	83 (90)
13	0.05	**43a**; *t*Bu	86 (90)
14	0.04	**43a**; *t*Bu	90 (90)
15	0.04	**43a**; *t*Bu	> 98 (> 98)
16	0.04	**43b**; *n*Pr	77 (79)
17	0.04	**43c**; *i*Pr	65 (65)
18	0.04	**43d**; *p*-PhC_6H_4	96 (> 98)
19	0.04	**43e**; *p*-$O_2NC_6H_4$	> 98 (> 98)
20	0.04	**43f**; Ph	> 98 (> 98)
21	0.04	**43g**; *p*-$MeOC_6H_4$	> 98 (> 98)

[a] KH/**43a** = 2.5:1. [b] Conversions > 95%, except Entry 2. [c] Reaction time 72 h; temperature −80 °C, KH/MeOH/**45**/*trans*-**43** = 2.50:0.04:0.1:1.

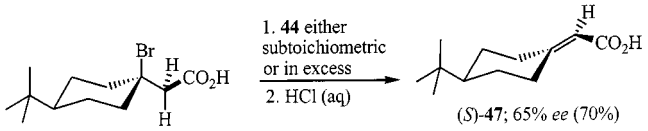


Scheme 17. Enantioselective dehydrobromination of *trans*-**43** by use of a substoichiometric amount of alkoxide **44**

In an attempt to increase the enantioselectivity, Plaquevent et al. performed this elimination reaction at a lower temperature with a series of achiral alkoxide donor bases (Table 3: Entries 7−10). Unsurprisingly, they found that the more basic the alkoxide, the lower the stereoselectivity (MeOK > EtOK > *i*PrOK > *t*BuOK), due to compet-



Scheme 18. Enantioselective dehydrobromination by use of a combination of two donor bases



Scheme 19. Synthesis of a dissymmetric carboxylic acid (*S*)-**47**

itive stereorandom deprotonation. However, it does seem surprising that the related chiral alkoxide **44** (derived from *N*-methylephedrine) does not simply protonate in the presence of MeOH. This may not be an issue if proton transfer between MeOK and *N*-methylephedrine **45** is rapid and reversible to allow the chiral alkoxide **44** to deprotonate the dibromide *trans*-**43** at a faster rate.

The breakthrough needed to improve this stereoselectivity came by marriage of these two strategies, namely the use of KH in excess as the donor base in the presence of MeOH(K) as the transfer reagent within the cycle (Scheme 18). This process does rely on the fact that MeOH appears to be kinetically more acidic than *N*-methylephedrine at a lower temperature. Regeneration of the chiral alkoxide was clearly influenced by the presence of a small quantity of MeOH (4 mol %), giving the vinyl bromide (*R*)-**46a** in 90% *ee*, nearly identical to that found in the stoichiometric case. The optimum conditions were found to require 2.50 equiv. of KH, 0.04 equiv. of MeOH and 0.1 equiv. of chiral amine **45**. These conditions were screened against a series of other prostereogenic substrates **43b**−**g** (Table 3: Entries 11−21). Very high enantioselectivities were obtained, especially for aromatic derivatives **43d**−**g** (*ee* values typically from 94 to > 98%). The versatility of this methodology was further illustrated by the synthesis of an axially dissymmetric carbocyclic carboxylic acid **47** with an enantiomeric excess of 65% (Scheme 19). Similar levels of stereocontrol were achieved using traditional stoichiometric methodology.

Conclusion

In conclusion, enantioselective deprotonation of prostereogenic substrates mediated by substoichiometric amounts of chiral bases has been shown to be an efficient route for the synthesis of optically active allylic alcohols,[4a,4c,4d,4f,4g] silyl enol ethers[4b] and vinyl bromides.[4e] There is currently only a limited number of applications of this methodology, due primarily to the infancy of this strategy. For this area to develop, there is a need for the gathering of more mechanistic information about the role that these additives and stoichiometric donor bases play. This should aid the understanding of aggregate formation and their associated stereoselectivity. Such developments should assist the discovery of a general method that might easily be tailored for particular functionality and substrates.

Acknowledgments

I would like to thank Dr. Mike Watkinson (Queen Mary, University of London) for his useful comments.

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[9] The relative rate of proton transfer between highly electronegative atoms (such as O and N) is at least three orders of magnitude faster than the related process between a highly electronegative atom and a carbon atom. This is primarily due to H-bonding, preordering the transition state for proton transfer. By analogy, it can be assumed that proton transfer between an electronegative atom and a carbon atom is significantly faster than proton transfer between two carbon donors which are devoid of classical H-bonding effects. For additional information regarding rates of proton transfer, see: M. Eigen, *Angew. Chem. Int. Ed. Engl.* **1964**, *3*, 1−19 and references therein.

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