Enantioselective Enolborination

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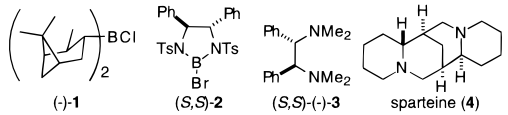
The development of new strategies and methodologies for asymmetric synthesis continues to attract considerable attention.[1] Although the majority of known methods involve transformation of an achiral substrate by enantioselective addition to a π-bond (i.e., an enantiotopic face selective reaction), the use of enantiotopic group selective reactions to effect desymmetrization of achiral C_s (or C_i) symmetric substrates or kinetic resolution of chiral substrates has recently emerged as a powerful strategy for asymmetric synthesis.[2] Few design elements are available to guide the development of new nonenzymatic enantiotopic group selective reactions, and many of the successful examples[2] involve application of previously established "reagent-controlled" enantioface selective reactions to chiral or C_s symmetric substrates that impart significant "substrate-controlled" selectivity.[3,4] In this paper, we report the use of "double stereodifferentiation"[5] to achieve highly enantioselective enolborination of both chiral and C_s symmetric ketones by reaction with chlorobis(isopinocampheyl)borane (**1**) (Ipc_2BCl or DIP-Chloride)[6] in the presence of a chiral diamine.



(-)-**1** (*S*,*S*)-**2** (*S*,*S*)-(-)-**3** sparteine (**4**)

We have been interested in processes for desymmetrization of C_s (or C_i) symmetric bifunctional substrates where enantiotopic groups can react sequentially.[7] In these cases, it becomes possible to obtain products with very high stereoisomeric purity from reactions with modest enantioselectivity[4] or even from mixtures of substrate stereoisomers.[8] Both the efficiency and efficacy of these processes are improved with recycling, especially if the enantioselectivity is not outstanding.[4,8] Because recycling requires that the product(s) (or byproducts) be efficiently converted back into the starting material(s), enantiotopic group selective reactions that are easily "reversed" are desirable.[4,8] Ketone enolization is an ideal reaction for application in these processes because it is both synthetically useful and easily "reversible" (e.g., by protonation). Enantioselective deprotonation of achiral C_s symmetric cyclic ketones by chiral lithium amide bases to form chiral lithium enolates has developed into a powerful tactic for asymmetric synthesis and several applications to natural product synthesis have appeared.[9] Although kinetic resolutions of racemic ketones by enantioselective deprotonation have been demonstrated,[10] the process in not particularly well suited to this application and various limitations are expected with *meso* bifunctional substrates (i.e. diketones).[11] Specifically, poor enantiotopic group selectivity is likely to result[3,4] in cases where deprotonation occurs with only modest levels of substrate-controlled regio- and/or stereoselectivity.[12] In searching for alternative methods to achieve enantioselective enolization, we considered enolborination.

Despite the widespread use of boron enolates for stereoselective synthesis,[13] to the best of our knowledge, enantioselective enolborination has not previously been reported. Indeed, in an early example Paterson et al.[14] inferred that the enantiotopic group selectivity (*E*) of enolborination of a racemic ketone with enantiopure Ipc_2BCl was less than ca. 2:1. To further investigate the potential of this process, we examined the enantioselectivity of enolborination of 4-*tert*-butylcyclohexanone (**5**) with Ipc_2BCl (**1**) under a variety of conditions (Scheme 1). Reaction of **5** with (−)-**1** (1.5 equiv) in the presence of Et_3N (1.5 equiv) at −78 °C in pentane gave **7** in 85% yield with modest selectivity (**7a**:**7b** = 1.7:1).[15,16] The selectivity was relatively insensitive (1.4−1.7:1) to changes in solvent (toluene, THF, CH_2Cl_2, ether), concentration (0.02−0.2 M), or order of addition of the reagents, but was modulated by temperature (1.1:1, 0 °C; 2.6:1, −131 °C) and the nature of the tertiary amine used (1.1−2.0:1; $^i Pr_2EtN$, $^i Pr_2MeN$, $^i PrMe_2N$, $EtMe_2N$, Pr_3N, TMEDA).[17] Similarly, poor enantioselectivity was observed for enolborination of **5** with (−)-Ipc_2BBr (1.5:1) or with **2**[18] (1.1:1).

The diastereoselectivity of *face selective* reactions can often be enhanced by exploiting the strategy of "double stereodifferentiation".[5] In principle, the enantioselectivity of *group selective*

(1) *Houben-Weyl, Stereoselective Synthesis*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, 1996.

(2) For reviews, see: (a) Ward, R. S. *Chem. Soc. Rev.* **1990**, *19*, 1−19. (b) Gais, H.-J. In *Houben-Weyl, Stereoselective Synthesis*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, 1996; Vol. 1, pp 589−644.

(3) Heathcock, C. H.; Pirrung, M. C.; Lampe, L.; Buse, C. T.; Young, S. D. *J. Org. Chem.* **1981**, *46*, 2290−2300.

(4) Enantiotopic group selectivity (*E*) can be estimated from the following equation (r = reagent-controlled selectivity; s = substrate-controlled selectivity): $E = ((r)(s) + 1)/(r + s)$. For a discussion, see: Ward, D. E.; Liu, Y.; Rhee, C. K. *Can. J. Chem.* **1994**, *72*, 1429−1446.

(5) (a) Masamune, S.; Choy, W.; Pedersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1−76. (b) Nakayama, K. *J. Chem. Educ.* **1990**, *67*, 20−23. (c) Roush, W. R.; Hoong, L. H.; Palmer, M. A. J.; Straub, J. A.; Palkowitz, A. D. *J. Org. Chem.* **1990**, *55*, 4117−4126.

(6) For a review on uses of Ipc_2BCl, see: Dhar, R. K. *Aldrichimica Acta* **1994**, *27*, 43−51.

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(8) (a) Ward, D. E.; How, D.; Liu, Y. *J. Am. Chem. Soc.* **1997**, *100*, 1884−1894. (b) Ward, D. E.; Liu, Y.; How, D. *J. Am. Chem. Soc.* **1996**, *118*, 3025−3026.

(9) For a review, see: (a) Cox, P. J.; Simpkins, N. S. *Tetrahedron: Asymmetry* **1991**, *2*, 1−26. Also see ref 2b. (b) For a comprehensive list of references, see: Aoki, K.; Tomioka, K.; Noguchi, H.; Koga, K. *Tetrahedron* **1997**, *53*, 13641−13656.

(10) (a) Kim, H. D.; Kawasaki, H.; Nakajima, M.; Koga, K. *Tetrahedron Lett.* **1989**, *30*, 6537−6540. (b) Bambridge, K.; Simpkins, N. S. *Tetrahedron Lett.* **1992**, *33*, 8141−8144. (c) Bambridge, K.; Clark, B. P.; Simpkins, N. S. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2535−2541.

(11) For example: the requirement of inverse addition at low temperature; difficulty in controlling reaction conversion; potential for stereochemical "leakage" by inter- or intramolecular proton transfer between ketone and enolate.

(12) For example, the enantioselective deprotonation mediated kinetic resolution of 2-methylcyclohexanone[10a] is far more selective than that of 3-methylcyclohexanone[10c] because of poor substrate-controlled regioselectivity for the latter. Modest stereoselectivity in deprotonation of acyclic ketones would similarly limit group selective applications.

(13) For a review, see: Cowden, C. J.; Paterson, I. *Org. React.* **1997**, *51*, 1−200.

(14) Paterson, I.; McClure, C. K.; Schumann, R. C. *Tetrahedron Lett.* **1989**, *30*, 1293−1296.

(15) Selectivities and yields were measured by oxidation (i. O_3; ii. H_2CrO_4) of the enolborinates to the known diacids (**9**,[16a,b] **10**,[16c] **15**,[16d] and **18**[16e]) whose ee values were determined by ^{1}H NMR in the presence of (*R*)-1-phenylethylamine (for **9** and **15**) or (*R*)-1-(1-naphthyl)ethylamine (for **10** and **18**). The absolute configurations of the major enantiomers of **9**, **10**, and **18** were determined by optical rotation and that for **15** was assigned by analogy to the selectivity observed for **9**, **10**, and **18**.

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(18) Corey, E. J.; Yu, C. M.; Kim, S. S. *J. Am. Chem. Soc.* **1989**, *111*, 5495−5496.

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Scheme 1

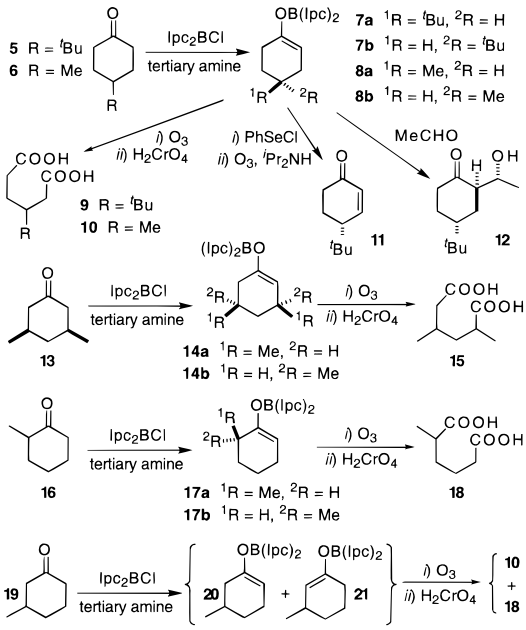

Table 1. Selectivity of Enolborination of Cyclohexanones[a]

			selectivity[b] (yield[b], rxn time)	
ketone	amine	R_2BCl	at −78 °C	at −131 °C[c]
			7a:**7b**	
5	Et_3N[d]	(−)-**1**[d]	1.7:1 (85%, 4 h)	2.6:1 (75%, 6 h)
	(−)-**3**	Chx_2BCl	1:2.4 (60%, 6 h)	
		(−)-**1**	1:2.8 (40%, 6 h)	
		(+)-**1**	1:4 (55%, 6 h)	1:16 (75%, 24 h)
	4	Chx_2BCl	2.8:1 (80%, 6 h)	
		(−)-**1**	5:1 (80%, 6 h)	19:1 (80%, 10 h)
		(+)-**1**	2:1 (65%, 6 h)	
			8a:**8b**	
6	(+)-**3**	(−)-**1**	9:1 (80%, 10 h)	23:1 (80%, 15 h)
	4	(−)-**1**	17:1 (80%, 4 h)	26:1 (80%, 10 h)
			14a:**14b**	
13	(+)-**3**	(−)-**1**	3:1 (60%, 10 h)	8:1 (60%, 10 h)
	4	(−)-**1**	12:1 (75%, 10 h)	23:1 (65%, 10 h)
			17a:**17b**	
(±)-**16**[e]	(+)-**3**	(−)-**1**	15:1 (15%, 4 h)	>30:1 (15%, 6 h)
	4	(−)-**1**	>30:1 (15%, 4 h)	>30:1 (15%, 4 h)
			(*S*)-**20**:(*R*)-**20**:**21**	
(±)-**19**[e]	(+)-**3**	(−)-**1**	89:11:4.5 (15%, 4 h)	>97:3:4.5 (15%, 6 h)
	4	(−)-**1**	95:5:2 (15%, 4 h)	>97:3:<2 (15%, 4 h)

[a] Reaction in pentane (**4** and Et_3N) or 2:1 ether pentane (**3**) (0.06 M in ketone), R_2BCl (2 equiv), diamine (1 equiv). [b] See footnote 15. [c] Pentane/$N_{2(l)}$ slush bath. [d] 1.5 equivalents. [e] 0.30 M in ketone, 0.4 equiv of boron reagent and 0.2 equiv of diamine.

reactions should be modulated by the same effect; however, there are few literature precedents for such applications.[19] We screened a number of enantiopure tertiary amines in an effort to improve the enantioselectivity of enolborination of **5**. The monoamines tested[20] had only a modest effect on the selectivity of enolborination of **5** (i.e., **7a**:**7b** <2.6:1); better results were obtained with the diamines **3** and sparteine (**4**) (Table 1). The selectivity observed under conditions of "double stereodifferentiation" roughly followed the multiplicativity rule[21] for most of the amines. The selectivity of enolborination of **5** with Ipc_2BCl and **3** or **4** was particularly sensitive to temperature and reached 89% diastereomeric excess (de) at −131 °C. Enantioselective enolborinations of 4-methylcyclohexanone (**9**) and *cis*-3,5-dimethylcyclohexanone (**13**) with Ipc_2BCl and **3** or **4** also proceeded with excellent selectivities (Table 1).[15] In addition to oxidation, the product enolborinates undergo the expected transformations. For example, reaction of **7b** (89% de)[22] with PhSeCl followed by oxidation gave **11** (51% yield, 89% enantiomeric excess (ee));[23] alternatively, reaction with acetaldehyde gave the aldol **12** (56%, 90% ee).[24,25]

To assess the potential of this process for kinetic resolution, enantioselective enolborinations of (±)-**16** and of (±)-**19** with (−)-**1** and (+)-**3** or **4** were examined (Table 1). The reactions were run to low conversions so that the product ratios would closely approximate the relative reactivity of the substrate enantiomers. Enolborinations of (±)-**16** were completely regioselective and occurred with excellent enantiomer selectivity in favor of the (2*R*)-isomer. Similar reactions of (±)-**19** were highly regioselective and gave preferential enolborination of the (3*S*)-isomer. For example, reaction of excess (±)-**19** with (−)-**1** and **4** at −78 °C followed by oxidation gave an ca. 50:1 mixture of diacids (3*S*)-**10** (90% ee)[15] and **18** (ee not determined) in 15% combined yield consistent with an enantiotopic group selectivity of at least 13:1 in favor of enolborination of (3*S*)-**19**.[26] Outstanding selectivity was observed at −131 °C. These results are particularly significant as the kinetic resolution of **19** by enantioselective deprotonation proceeds poorly.[10c] The difference in group selectivity between the two methods is undoubtedly due to the much higher substrate-controlled[4] regioselectivity of enolization of **19** with boron halides (>30:1 with chlorodicyclohexylborane (Chx_2BCl))[27] compared to lithium amides (3:1 with lithium diisopropylamide).[10c]

In conclusion, we have demonstrated highly enantioselective enolborination of both achiral and chiral substituted cyclohexanones. The method relies on double stereodifferentiation[5] to achieve efficient group selectivity. There is considerable potential to improve the enantioselectivity by screening various available or designed amines and boron reagents. The current methodology complements the previously developed enolizations using chiral lithium amides[9] and gives comparable selectivities. Considering the already established utility of boron enolates in stereoselective synthesis,[13] enantioselective enolborination should develop into a powerful tool for asymmetric synthesis.

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Supporting Information Available: Experimental procedures (8 pages). See any current masthead page for ordering information and Web access information.

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(19) For an example, see: (a) Lattanzi, A.; Bonadies, F.; Scettri, A. *Tetrahedron: Asymmetry* **1997**, *8*, 2141−2151. (b) Lattanzi, A.; Bonadies, F.; Senatore, A.; Soriente, A.; Scettri, A. *Tetrahedron: Asymmetry* **1997**, *8*, 2473−2478.

(20) (*R*)-*N*,*N*-Dimethyl-1-(1-naphthyl)ethylamine, (*S*)-*N*,*N*-dimethyl-1-(phenyl)ethylamine, (2*S*,5*S*)-*N*,2,5-trimethylpyrrolidine, and (*S*,*S*)-*N*-methylbis[1-(phenyl)ethyl]amine were examined.

(21) That is, given the enolborination selectivities attributable solely to **1** (i.e., the selectivity with Et_3N) and to the chiral amine (i.e., the selectivity with Chx_2BCl), under double stereodifferentiation, the matched selectivity is approximated by the product of those selectivities and the mismatched selectivity by their ratio.[5]

(22) Prepared by reaction of **5** with (+)-**1** and (−)-**3** at −131 °C for 24 h. NMR analysis of the derived diacid **9** (75% yield) indicated a 16:1 mixture of enantiomers.

(23) The ee was determined by optical rotation: Aoki, K.; Nakajima, M.; Tomioka, K.; Koga, K. *Chem. Pharm. Bull.* **1993**, *41*, 994−996.

(24) Other diastereomers were not detected; however, the diol resulting from in situ reduction of the ketone in **12** was isolated (15%). Reaction with C_6H_5CHO, ChxCHO, or tBuCHO gave diol products nearly exclusively. For intramolecular reduction of the intermediate 3-oxoalkyl diisopinocampheylborinates, see: Ramachandran, P. V.; Lu, Z.-H.; Brown, H. C. *Tetrahedron Lett.* **1997**, *38*, 761−764.

(25) The ee was determined by ^1H NMR analysis of the derived Mosher's ester.

(26) If **10** is 90% ee (*S* enantiomer) and if **18** is 100% ee (*R* enantiomer), then at least 93% (i.e.13: 1) of the mixture of diacids is derived from (*S*)-**19**. Assuming that $r = 20$ and $s = 30$,[27] the group selectivity is predicted[4] to be 12:1.

(27) Brown, H. C.; Dhar, R. K.; Ganesan, K.; Singaram, B. *J. Org. Chem.* **1992**, *57*, 2716−2721.