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A KINETIC RESOLUTION OF RACEMIC EPOXIDES BY A CHIRAL LITHIUM AMIDE

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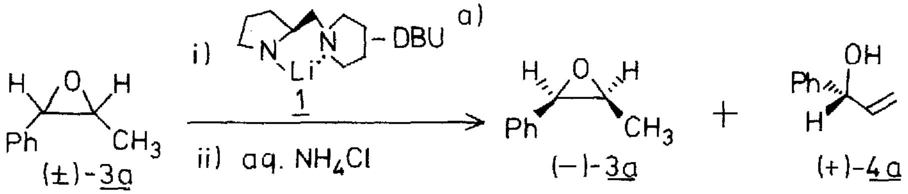
Summary: A kinetic resolution of cis-disubstituted epoxides was effectively achieved by a chiral lithium amide, prepared from (S)-2-(pyrrolidin-1-yl)-methylpyrrolidine.

In previous papers,1) we reported a highly enantioselective transformation of symmetrical epoxides to chiral allylic alcohols by the use of a chiral lithium amide (1), prepared from (S)-2-(pyrrolidin-1-yl)-methylpyrrolidine (2). In the reaction, a discrimination between two enantiotopic hydrogens in symmetrical epoxide is effectively achieved because of a difference of a steric interaction between chiral lithium amide 1 and epoxide in the transition state.1c) It was expected that the reaction can be applied to a kinetic resolution of racemic epoxides considering the similar transition state.

There have so far been reported only some methods for the kinetic resolution of epoxide, which include the enzymatic hydrolysis of epoxy esters,2a,b) enzymatic hydration of substituted cyclohexene oxide2c,d) or cis-2-ethyl-3-methyloxirane,2e) and enantioselective cyclization of a keto epoxide mediated by organoaluminium reagent.2f) In the present communication, we wish to report a new and efficient method for the kinetic resolution of racemic epoxides by the use of chiral lithium amide 1.

In the first place, we examined the kinetic resolution of (±)-cis-1-phenyl-1,2-epoxypropane (3a) with one-half molar equivalent of 1 in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in tetrahydrofuran (THF). (+)-(1S,2R)-3a reacted more rapidly to give (R)-1-phenyl-2-propen-1-ol (4a) in 70 % ee (38 % yield based on (±)-3a) and 52 % of (-)-(1R,2S)-3a was recovered in 62 % ee after work-up of the reaction. After the examination of molar ratio of reactants, (-)-(1R,2S)-3a was recovered in more than 95 % ee (1:(±)-3a=3:4) and (R)-4a was obtained in 72 % ee (1:(±)-3a=1:3). The results are summarized in Table 1.3)

Table 1. Kinetic Resolution of (±)-3a

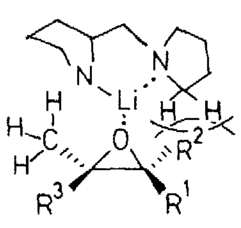


entry	1 : (±)-3a	(−)-3a		4a	
		%	ee/%[b)c)]	%[d)]	ee/%[e)]
1	3 : 4	31	>95	60	35
2	2 : 3	37	89	56	62
3	1 : 2	52	62	38	70
4	1 : 3	67	30	21	72

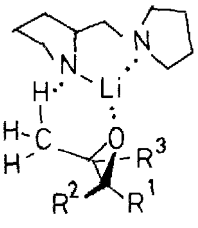
a) C_4H_9Li:2:DBU=1.0:1.1:1.1 b) The enantiomeric excess was determined by ^1H NMR taken in the presence of $Eu(hfbc)_3$. c) The absolute configuration was deduced from optical rotation ($[\alpha]_D^{26}$ −46.5 ° (c 1.70, $CHCl_3$) for entry 1; lit.[4)] $[\alpha]_D^{20}$ +47.5 ° (c 1.17, $CHCl_3$) for (+)-(1*S*,2*R*)-3a). d) The yield is based on (±)-3a. e) The enantiomeric excess and absolute configuration were determined after conversion to 1-phenyl-1-propanol by catalytic hydrogenation ($[\alpha]_D^{29}$ +32.8 ° (c 1.45, $CHCl_3$) for entry 4; lit.[5)] $[\alpha]_D$ −45.45 ° (c 5.15, $CHCl_3$) for (−)-(*S*)-1-phenyl-1-propanol).

Next, the reaction was applied to (±)-*trans*-1-phenyl-1,2-epoxypropane (3b), (±)-2-phenyl-1,2-epoxypropane (3c), and (±)-*cis*-2,3-epoxynonane (3d) using the molar ratio of 1:3=3:4 and 1:3=1:3, respectively. As shown in Table 2, chiral lithium amide 1 showed high enantiomer discrimination for *cis*-disubstituted epoxide, while moderate selectivity was observed for *trans*-disubstituted epoxide and terminal epoxide.

The stereochemistry is understandable in terms of the cyclic transition states for both enantiomers. Clearly, transition state T_1 experiences substantial nonbonded interaction involving the side chain R^2 and chiral diamine 1. This is not the case with transition state T_2. Therefore, (+)-(1*S*,2*R*)-3a, (+)-(1*R*,2*R*)-3b, (−)-(*S*)-3c, and (+)-(2*R*,3*S*)-3d, which take the transition state T_2, react more

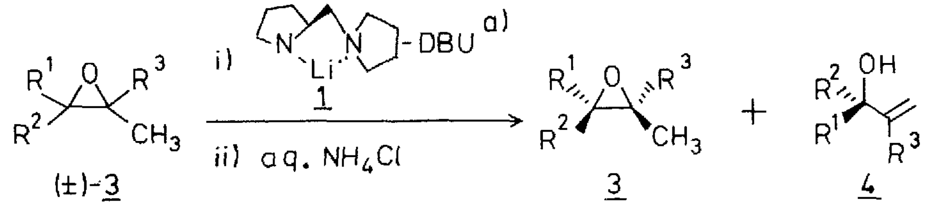


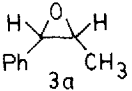
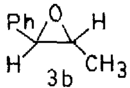
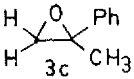
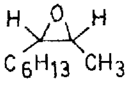
T_1



T_2

Table 2. Kinetic Resolution of Epoxides by Chiral Lithium Amide 1



entry	epoxide	1 : (±)-3	3		4	
			%	ee/%[b]	%[c]	ee/%
1	 3a	3 : 4	31	>95(1S,2R)[d]	60	35[d](R)[d]
2		1 : 3	67	30(1S,2R)[d]	21	72[d](R)[d]
3	 3b	3 : 4	27	45(1S,2S)[e]	63	15[f](S)[f]
4		1 : 3	67	11(1S,2S)[e]	20	34[f](S)[f]
5	 3c	3 : 4	11	39(R)[g]	69	-
6	 3d	3 : 4	29	>95(2S,3R)[h]	63	55[i](S)[j]
7		1 : 3	66	25(2S,3R)[h]	22	77[i](S)[j]

a) C_4H_9Li:2:DBU=1.0:1.1:1.1 b) The enantiomeric excess was determined by ^{1}H NMR taken in the presence of Eu(hfbc)$_3$. c) The yield is based on (±)-3. d) See Table 1. e) The absolute configuration was deduced from optical rotation ($[\alpha]^{28}_D$ -25.3 ° (c 0.8, CHCl$_3$) for entry 3; lit.[4] $[\alpha]^{20}_D$ +50.0 ° (c 1.17, CHCl$_3$) for (1R,2R)-3b). f) The enantiomeric excess and absolute configuration were determined after conversion to 1-phenyl-1-propanol by catalytic hydrogenation ($[\alpha]^{26}_D$ -15.6 ° (c 0.86, CHCl$_3$) for entry 4; lit.[5] $[\alpha]_D$ -45.45 ° (c 5.15, CHCl$_3$) for (+)-(S)-1-phenyl-1-propanol). g) The absolute configuration assignment is tentative.[6] h) The absolute configuration was assigned to be (2S,3R) because (+)-(S)-4d was obtained predominantly. i) The enantiomeric excess was determined by ^{1}H NMR taken in the presence of Eu(tfc)$_3$ after conversion to corresponding acetate. j) The absolute configuration was deduced from optical rotation ($[\alpha]^{30}_D$ +11.6 ° (c 1.12, EtOH) for entry 7; lit.[7] $[\alpha]^{25}_D$ -19.1 ° (c 6.7, EtOH) for (-)-(R)-1-nonen-3-ol).

rapidly to yield allylic alcohol 4, and (-)-(1R,2S)-3a, (-)-(1S,2S)-3b, (+)-(R)-3c, and (-)-(2S,3R)-3d are recovered after the reaction. The effect is most prominent with cis-disubstituted epoxide for which high selectivity has been actually achieved. The selectivity decreases in the cases of trans-disubstituted epoxide or terminal epoxide because R^2 is H.

As mentioned above, efficient chemical kinetic resolution of nonfunctionalized epoxide has been first achieved by the use of chiral lithium amide 1. The present method would provide an useful method for the preparation of chiral cis-disubstituted epoxide as well as chiral allylic alcohol.

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3) A typical experimental procedure is described for entry 3: To a THF solution of 2 (1.01 mmol) was added a hexane solution of butyllithium (0.90 mmol) and a THF solution of DBU (1.00 mmol) at 0 °C. After 30 min, a THF solution of (±)-3a (1.80 mmol) was added and the reaction mixture was stirred for overnight at room temperature. After usual work-up, the residue was separated by TLC (silica gel) to give (-)-(1R,2S)-3a in 62 % ee (0.94 mmol, 52 % recovery) and (R)-4a in 70 % ee (0.68 mmol, 38 %).

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