ASYMMETRIC ADDITIONS OF ALKYLLITHIUM TO CHIRAL IMINES – α-NAPHTHYLETHYL GROUP AS A CHIRAL AUXILIARY –

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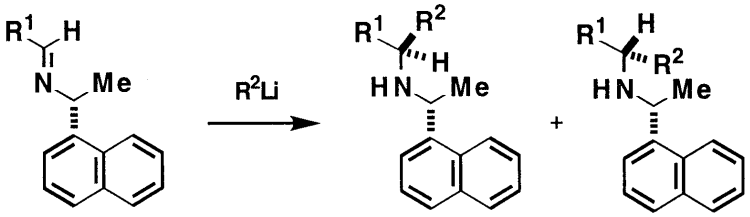
Asymmetric addition of alkyllithiums to *N*-alkylidene-α-naphthylethylamine was carried out. In the presence of BF_3•OEt_2, organolithiums reacted smoothly with the imine giving corresponding amines in high degrees of stereoselectivity (up to ~100% de).

KEY WORDS asymmetric alkylation; imine; α-naphthylethylamine; chiral auxiliary; optically active amines

The nucleophilic addition of organometallics to imines is one of the key methods of preparing various amines.[1] During our research on the synthesis of optically active amines from imines, we reported the asymmetric reduction of imines using newly developed chiral boranes.[2] In this paper, we would like to report our results on the asymmetric alkylation of imines with various organolithiums, in which chiral α-naphthylethyl group is used as a chiral auxiliary (Chart 1).

Chart 1



1: R^1=Ph
2: R^1=*t*-Bu

3: R^1=Ph, R^2=*n*-Bu, **4**: R^1=Ph, R^2=Me, **5**: R^1=Ph, R^2=*t*-Bu,
6: R^1=*t*-Bu, R^2=Me, **7**: R^1=*t*-Bu, R^2=*n*-Bu

The chiral *N*-alkylidenenaphthylethylimines, **1** and **2**, were easily prepared from (*R*)-α-naphthylethylamine and corresponding aldehydes.[3] The addition of *n*-BuLi (5 equivalents) to a toluene solution of **1** at -78°C gave a mixture of the alkylated amines, **3a** and **3b**, in a yield of only 30% (Table 1, entry 1). The diastereomeric excess was determined by ^{1}H-NMR analysis and found to be 50% de (**3a**:**3b**=75:25).[4] Tomioka and co-workers have reported the asymmetric alkylation of imine with MeLi in the presence of chiral ligands, in which coordinated Li cation acted as a chiral Lewis acid and activated the imines.[11-n] In our reactions, although addition of $MgBr_2$•OEt_2 or $Mg(OEt)_2$ did not improve the yield or selectivity, the reaction of **1** with *n*-BuLi in the presence of BF_3•OEt_2 proceeded at 0°C to give **3** at a yield of 64% with 42% de (entry 4). The higher selectivity was observed when the reaction was carried out at lower reaction temperature. The reaction

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Table 1. Alkylation of Imine 1 and 2 with Organolithiums

Entry	Imine	R^2Li (mol eq)	Additive (mol eq)	Solvent	Conditions (°C)	(h)	Result amine	%	a : b	(% de)
1	**1**	*n*-BuLi (5)	none	PhMe	-78	3	**3**	30	75 : 25	(50)
2	**1**	*n*-BuLi (2)	$MgBr_2$•OEt_2 (1.6)	PhMe	-78	3	NR			
3	**1**	*n*-BuLi (2)	$Mg(OEt)_2$ (2)	PhMe	-78	3	**3**	21	76 : 24	(52)
4	**1**	*n*-BuLi (2)	BF_3•OEt_2 (1.6)	PhMe	0	2	**3**	64	71 : 29	(42)
5	**1**	*n*-BuLi (2)	BF_3•OEt_2 (1.6)	PhMe	-20	2	**3**	80	79 : 21	(58)
6	**1**	*n*-BuLi (2)	BF_3•OEt_2 (1.6)	PhMe	-45	1	**3**	84	87 : 13	(74)
7	**1**	*n*-BuLi (2)	BF_3•OEt_2 (1.6)	PhMe	-78	1	**3**	76	93 : 7	(86)
8	**1**	*n*-BuLi (2)	BF_3•OEt_2 (1.6)	THF	-78	2	**3**	61	94 : 6	(88)
9	**1**	*n*-BuLi (2)	BF_3•OEt_2 (1.6)	Et_2O	-78	0.5	**3**	79	90 : 10	(80)
10	**1**	MeLi (2)	BF_3•OEt_2 (1.6)	PhMe	-78	2	**4**	81	92 : 8	(84)
11	**1**	MeLi (5)	BF_3•OEt_2 (1.6)	THF		a	**4**	55	90 : 10	(80)
12	**1**	*t*-BuLi (2)	BF_3•OEt_2 (1.6)	PhMe	-78	6	**5**	5	41 : 59	(18)
13	**1**	*t*-BuLi (2)	BF_3•OEt_2 (1.6)	THF	-78	1	**5**	99	63 : 37	(26)
14	**2**	MeLi (2)	BF_3•OEt_2 (1.6)	PhMe	-78	1.5	**6**	76	>99 : 1	(~100)
15	**2**	*n*-BuLi (2)	BF_3•OEt_2 (1.6)	PhMe	-78	1.5	**7**	93	85 : 15	(70)

a. -78°C for 8 h, then rt for 3 h.

at -78°C showed 86% de (entries 5-7). Tetrahydrofuran and ether were also suitable solvents in this alkylation (entries 8-9). Among alkyllithiums screened, MeLi gave the best result (~100% de, Entry 14), whereas bulky *t*-BuLi gave poor selectivity (Entries 12 and 13).

The absolute configuration of the new stereocenter was determined as follows: the chiral auxiliary was removed from **6a** by hydrogenolysis [H_2, $Pd(OH)_2$/C] and the resulting chiral amine was converted to known *N*-tosyl-3,3-dimethyl-2-butylamine (**8**). Comparison of the specific rotation of **8**, $[\alpha]_D^{15}$ +39.3 (*c* 1.05, EtOH), with the reported value[5] showed the absolute configuration of **8** to be *R*, hence the absolute configuration of **6a** to be 1*R*,1'*R*. The crystallographic structure of **4a** also showed that the absolute configuration of the new stereogenic center is *R* (Figure 1).

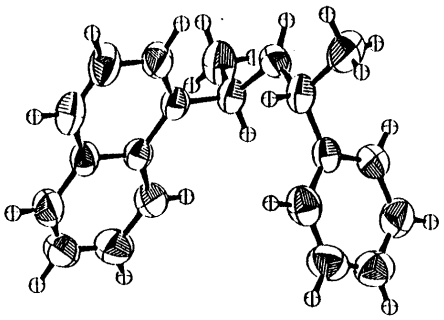

Fig. 1. Crystal Structure of 4a

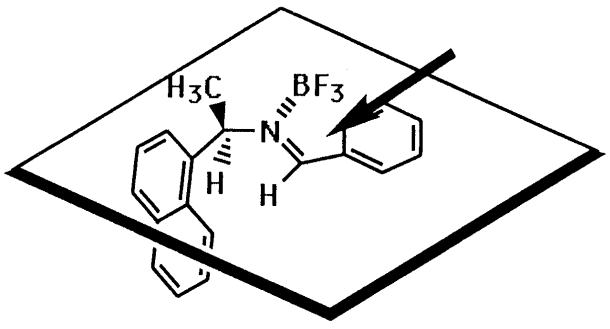

Fig. 2. Transition State Model for 1

The lowest energy conformation of BF_3-complexed **1**, which was obtained by a semi-empirical molecular orbital calculation (MOPAC, AM1), is shown in Figure 2. In this conformation, the naphthyl group was almost perpendicular to the π-plane which consisted of C=N double bond and the phenyl group. Therefore, the alkyl lithium reagent should attack from the top of the π-plane and give the observed diastereomer predominantly. The methylation of the chiral imine, which was prepared from (*R*)-α-methylbenzylamine and benzaldehyde, showed very poor asymmetric induction (4% de). This result is also explained by the transition model. Different from the naphthyl group, the phenyl group in the chiral auxiliary could not fulfill a spatial requirement to shield the π-plane.

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3) All new compounds are characterized spectroscopically (nmr, ir, low mass, high mass and/or elemental analysis).

4) Characteristic ^{1}H-NMR data (δ_H) of alkylation products used for calculation of diastereomer ratio:

PhC<u>H</u>N	**3a**	3.35	**3b**	3.76	**4a**	3.58	**4b**	3.89	**5a** 3.07	**5b**	3.61
NC<u>H</u>Me		4.36		4.48		4.39		4.58			
*t*BuC<u>H</u>N	**6a**	2.43	**6b**	3.83	**7a**	3.17	**7b**	3.63			
NC<u>H</u>Me		4.64		5.22							

5) M. Raban, C. P. Moulin, S. K. Lauderback, and B. Swilley, *Tetrahedron Lett.*, **1984**, *25*, 3419; for 59% ee of (*S*)-**8**: $[\alpha]_D$ -12.85 (EtOH).

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