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Communications

A New Convenient Method for the Monoprotection of α,ω-Alkanediamines

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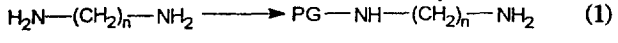
In the synthesis of biologically active peptides[1], synthesis of mono-*N*-protected alkanediamine **2, 3** from alkanediamine **1** is often required.

A considerable number of synthetic routes to effect this transformation had been reported previously.[2-6] However, these routes are somewhat inconvenient for a large scale reaction and are only of moderate efficiency. To overcome this problem, we developed a more practical method for the synthesis of multigram quantities of α,ω-alkanediamines protected at one end with *tert*-butoxycarbonyl (Boc) or benzyloxycarbonyl (Cbz) group which are the most widely used protecting groups for the amino function.

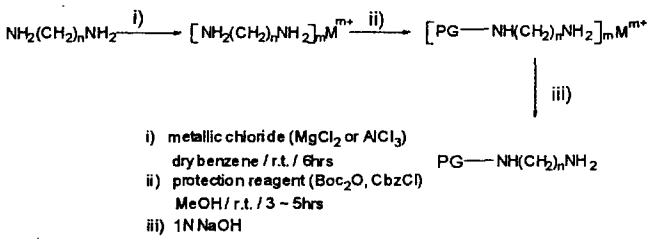
During an attempt to develop a convenient synthetic method, we have encountered a new mono amino protecting route of alkanediamines examplified in eq. 1 by using metallic (Mg(II), Al(III)) complexes of various α,ω-alkanediamines as the key step.



1	2,3	
	2	3
PG	Boc	Cbz

The usual procedure for the monoprotection of α,ω-alkanediamines is a three step process in the sequence shown in the following scheme.

The first step is the protection of one of the amino groups of α,ω-alkanediamines with a stoichiometric amount of metal ion [(a) 2 : 1 molar equivalent of alkanediamine to Mg^{2+}, (b) 3 : 1 molar equivalent of alkanediamine to Al^{3+}]. The second step is the addition of the protecting group to the free amino group position at the opposite from the metal. The final step in the sequence shown in the scheme is the liberation of the desired product, mono protected α,ω-alkanediamines, from the metallic complexes by a mild work up of alkali hydrolysis.

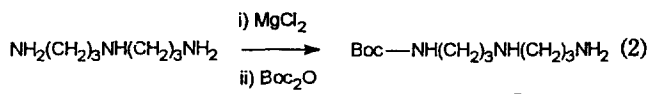


1~3 : a	b	c	d	e
n : 2	3	4	5	6

Scheme 1.

Treatment of α,ω-alkanediamine-metal complex with amino protection reagents (di-*tert*-butyldicarbonate, benzyloxycarbonyl chloride) in MeOH at room temperature affords the corresponding mono-*N*-protected alkanediamine after hydrolysis with 1 N NaOH and extraction from the aqueous phase with methylene choride. The desired *N*-Boc-alkanediamines and *N*-Cbz-alkanediamines were obtained in yields of up to 78% (depending on the class of diamine metal complex and diamine chain length). The results of this study were depicted in Table 1 and 2.

In a similar manner, when metal complex prepared from 1,7-diamino-4-azaheptane (**4**) with magnesium chloride was reacted with di-*tert*-butyldicarbonate as an amino protecting reagent in MeOH at room temperature, the corresponding desired product, *i.e.* *N*-Boc-1,7-diamino-4-azaheptane (**5**) was obtained in 65% yield[7] (eq. 2).



4 **5**

Table 1. *N*-(*tert*-Butoxycarbonyl)-α,ω-alkanediamine (**2a-e**)

Diamine	Used Metal	Product	Yield (%)[a]	R_f[b]	^{1}H NMR ($CDCl_3$), δ ppm
1a	Al^{3+}	**2a**	44	0.42	1.40 (s, 9H), 1.50 (s, 2H), 2.80 (t, 2H), 3.17 (q, 2H),
	Mg^{2+}		58		5.00 (br s, 1H)
1b	Al^{3+}	**2b**	55	0.40	1.30 (s, 2H), 1.45 (s, 9H), 1.50-1.70 (m, 2H), 2.75 (t, 2H),
	Mg^{2+}		78		3.20 (q, 2H), 4.70 (br s, 1H)
1c	Al^{3+}	**2c**	44	0.35	1.44 (s, 9H), 1.50-1.55 (m, 4H), 1.60 (s, 2H), 2.72 (t, 2H),
	Mg^{2+}		75		3.10 (q, 2H), 4.80 (br s, 1H)
1d	Al^{3+}	**2d**	36	0.32	1.25-1.60 (m, 6H), 1.44 (s, 9H), 2.16 (s, 2H), 2.72 (t, 2H),
	Mg^{2+}		64		3.10 (q, 2H), 4.65 (br s, 1H)
1e	Al^{3+}	**2e**	39	0.29	1.20-1.65 (m, 8H), 1.45 (s, 9H), 1.98 (s, 2H), 2.60 (t, 2H),
	Mg^{2+}		57		3.20 (q, 2H), 4.95 (br s, 1H)

[a]Yield of free amine **2** based on diamine **1**. [b]EtOH : CH_2Cl_2 : Acetone = 2 : 1 : 1.

Table 2. *N*-(Benzyloxycarbonyl)-α,ω-alkanediamines (**3a-d**)

Diamine	Used Metal	Product	Yield (%)[a]	R_f[b]	^{1}H NMR ($CDCl_3$), δ ppm
1a	Al^{3+}	**3a**	21	0.43	2.64 (t, 2H), 2.76 (s, 2H), 3.07 (q, 2H), 4.98 (s, 2H),
	Mg^{2+}		42		6.93 (br s, 1H), 7.27 (s, 5H)
1b	Al^{3+}	**3b**	53	0.37	1.50-1.70 (m, 2H), 1.85 (s, 2H), 2.67 (t, 2H), 3.20 (q, 2H),
	Mg^{2+}		35		5.10 (s, 2H), 5.35 (br s, 1H), 7.33 (s, 5H)
1c	Al^{3+}	**3c**	73	0.35	1.30-1.50 (m, 4H), 2.42 (s, 2H), 2.58 (t, 2H), 3.04 (q, 2H),
	Mg^{2+}		68		4.96 (s, 2H), 6.57 (br s, 1H), 7.25 (m, 5H)
1d	Al^{3+}	**3d**	65	0.31	1.18-1.50 (m, 6H), 2.35 (s, 2H), 2.48 (t, 2H), 2.90 (q, 2H),
	Mg^{2+}		61		4.95 (s, 2H), 6.82 (br s, 1H), 7.28 (m, 5H)

[a]Yield of free amine **3** based on diamine **1**. [b]EtOH : CH_2Cl_2 : Acetone = 2 : 1 : 1.

All reaction products were homogeneous by TLC and have been fully characterized by ^{1}H NMR. *N*-Boc-α,ω-alkanediamines were identical in every respect with those recorded in references 4, 5, 6. *N*-Cbz-alkanediamines were characterized as their hydrochloride salts and compared with the data in reference 3.

A general procedure for the preparation of *N-tert*-butoxycarbonyl-1,2-ethanediamine (**2a**) is as follows; To a heterogeneous mixture of anhydrous magnesium chloride (9.5 g, 0.1 mol) in dry benzene (300 m*l*), 1,2-ethanediamine (12.0 g, 0.2 mol) was added. The mixture was allowed to stir 6 hrs and the solvent was removed using a rotatory evaporator. The resultant 1,2-ethanediamine magnesium complex was crystallized on standing, filtered and dried. The 1,2-ethanediamine magnesium complex was suspended in methanol (50 m*l*) and cooled in an ice bath. A solution of di-*tert*-butyldicarbonate (43.6 g, 0.2 mol) in MeOH was added to the magnesium complex mixture. After the addition was completed, stirring was continued for 5 hours at room temperature and the solvent was removed by evaporation. A solution of 1 N NaOH (100 m*l*) was added to the residue and the insoluble bis *N*-Boc-1,2-ethanediamine[9] and magnesium hydroxide were collected by filtration. The aqueous solution was extracted with CH_2Cl_2 (100 m*l*×3). The organic layer was dried (Na_2SO_4) and the resulting oil was purified by distillation under reduced pressure. The oil was gradually solidified to yield a white solid; mp. = 108-110 ℃ (lit.[4] 110-112 ℃); yield 9.3 g (58 %).

A general procedure of the preparation of *N*-benzyloxycarbonyl-1,2-ethanediamine (**3a**) is as follows; Using the procedure described for the preparation of **2a**, this compound was prepared using benzyloxycarbonyl chloride and triethylamine. The resulting viscous oil [yield: 8.2 g (42%)] was treated with acetone/hydrochloric acid and followed by crystallization of the precipitate from methanol/ethyl acetate to give the hydrochoride salt of the desired product; mp. = 158-159 ℃ (lit.[3] 157-159 ℃).

Our results provide the first examples of a mono amino protecting method employing metallic complexes of α,ω-alkanediamines. The advantages of this method are milder conditions, simpler manipulation, better yields and feasible on multigram quantities, compared with the previous methods. In addition, this methodology expected to provide a good access to obtain partially protected polyamines such as the biogenic amines cadaverine, spermine, spermidine, themospermine with different amino protecting groups.

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7. Our procedure gave only a small amount of the side products (a mixture of the tri- and di-protected amines). Using the procedure described for the preparation of **2a**, pure *N*-Boc-1,7-diamino-4-azaheptane (**5**) was easily obtained by vacuum distillation. ^{1}H NMR ($CDCl_3$) 1.25 (s, 2H), 1.32 (br s, 1H), 1.44 (s, 9H), 1.65 (m, 4H), 2.68 (dt, 4H), 2.77 (t, 2H), 3.25 (q, 2H), 5.62 (br s, 1H) (Lit. reference 4).
8. This bis-substituted *N,N'-tert*-butoxycarbonyl-1,2-ethanediamine was formed (10% yield) and could be easily removed by taking advantage of its water solubility.

Influence of Different Classes of Boranes and Solvents on Asymmetric Induction in Enantioselective Borane Reduction of Prochiral Ketones Catalyzed by a Chiral Oxazaborolidine

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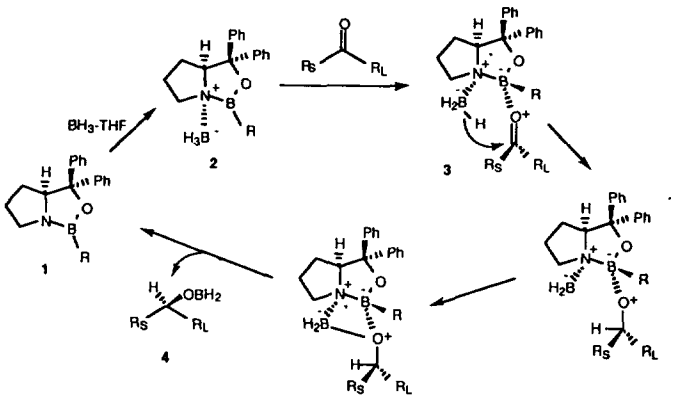
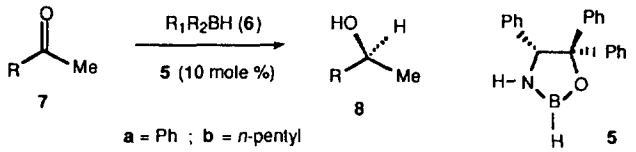
The discovery of chiral oxazaborolidines as catalytic reagents for the enantioselective borane reduction of prochiral ketones has been an important milestone in organic synthesis.[1] As a reasonable reaction mechanism for the catalysts, it has been suggested that Lewis acid-base adducts (**2**) formed by reaction of **1** with BH_3-THF serve as effective reagents for the reduction which occur by coordination of the electrophilic boron of the oxazaborolidine on carbonyl oxygen and then intramolecular hydrogen transfer from the NBH_3 moiety to the activated carbonyl *via* a six-membered ring transition state (**3**), followed by regeneration of **2** by the subsequent ligand exchange with borane to form the alkoxyborane **4** (Scheme 1).[2] Accordingly, it is expected that nature of borane used as a hydride donor plays an important role for the enantioselective reduction. It has been reported that borane-THF, borane dimethylsulfide (BMS), or catecholborane as a source of hydride proves to be successful in achieving high enantioselectivities for the reduction.[1c-d] However, the



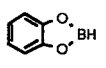
Scheme 1.

direct comparison on the asymmetric inducing effect by different classes of boranes for the reduction has not been accomplished.

On the other hand, the oxazaborolidine system (R=H in **1**) has been suggested to exist normally as a dimer but to decompose to the corresponding monomer in the presence of a Lewis basic solvent like THF.[2] Recently, Nevalanien reported that solvents played important roles not only in the behavior of a free oxazaborolidine but in the stabilization of reactive intermediates involved in the catalytic cycle on the basis of *ab initio* molecular orbital calculations.[3] However, no data for the influence of solvents in providing the enantioselectivities have been available. Hereby we report the comparison study for the influence of boranes as a source of hydride and solvents on the asymmetric induction in the catalytic enantioselective borane reduction of prochiral ketones.



6 R_1R_2BH = BH_3-THF (**a**) ; BH_3-SMe_2 (**b**) ; 9-BBN (**c**) ; Br_2BH (**d**) ;



e

We first chose oxazaborolidine **5** and different classes of boranes **6**, such as borane-THF (**a**), BMS (**b**), 9-BBN (**c**), dibromoborane (**d**) and catecholborane (**e**),[4] as representatives. And then we examined the influence of boranes **6** as a hydride donor on the asymmetric induction in the reduction of acetophenone **7a** and 2-heptanone **7b** selected as representative aromatic and aliphatic ketones, respectively, with each of **6** catalyzed by **5**. Thus, **5** was prepared from (R)-2-amino-1,1,2-triphenylethanol[5] and BMS in THF at 65 ℃. The reduction was performed by adding a solution of ketone to a solution of each of **6** in the presence of 10 mole% of **5** in THF at room temperature (*ca.* 25 ℃) over 1 h period under a positive nitrogen atmosphere. In this reaction, the stoichiometric ratio of ketone : **5** : hydride was 1 : 0.1 : 2. The