Efficient N-N Bond Cleavage of Chiral Trisubstituted Hydrazines with $BH_3 \cdot THF$

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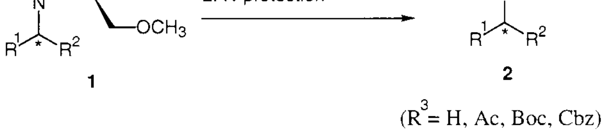
Abstract: Cleavage of the N-N bond of chiral trisubstituted hydrazines **1** with excess $BH_3 \cdot THF$ complex gives the corresponding optically active amines **2** in moderate to excellent yields and with high enantiomeric purity. This racemization and epimerization free cleavage procedure is compatible with functionalities sensitive to reductive cleavage conditions.

Enantiomerically-pure amines are fundamental structures and of great importance in organic synthesis. We have recently reported an efficient asymmetric synthesis of optically active amines based on the SAMP/RAMP-hydrazone methodology.[1] Conversion of aldehydes into SAMP/RAMP-hydrazones and subsequent 1,2-addition of organometallic compounds leads to the corresponding hydrazines **1**.[2] Alternatively, β-acceptor substituted hydrazine derivatives **1** can be synthesized diastereoselectively via conjugate addition of an enantiopure nitrogen nucleophile such as SAMP to enoates or 1-alkenyl sulphones. A key step in all these procedures to prepare optically active amines **2** is the cleavage of the hydrazine N-N bond.

We now wish to report an efficient method using $BH_3 \cdot THF$ as a cleavage reagent for trisubstituted hydrazines **1** in order to access the amines **2**, such as (1-ferrocenylalkyl)amines **3**, 1,1′-*bis*(1-amino-alkyl)-ferrocene derivatives **4**, 1,2-diamines **5**, β-amino sulphones **6** and BH_3-protected β-amino phosphines **7** (Scheme 1, Figure 1).



Scheme 1

Several methods for the cleavage of hydrazine N-N bonds have been reported in the literature. The reductive cleavage of heteroatom-heteroatom bonds using samarium (II) iodide is well known.[3] Lithium[4] and sodium[5] in ammonia has been used to cleave hydrazines, which have been activated by prior conversion to acetyl or benzoyl derivatives. However, this procedure suffers from occasional undesired cleavage of the C-N bond instead of the N-N bond. Several groups have also reported hydrogenolytic N-N bond cleavage methods using platinum dioxide,[6] palladium hydroxide[7] or palladium on carbon[8,3d] as catalysts. An additional well-known catalytic method is the *Raney*-nickel promoted hydrogenolysis of hydrazine N-N bonds.[9] In this case the cleavage reaction is dependent on the activity of the catalyst, which can be deactivated in several steps due to the preparation procedure.[10] Unfortunately, this N-N bond cleavage protocol suffers from harsh reaction conditions, a tedious preparation, competitive hydrogenation of aromatic residues and partial racemization and epimerization. Zinc in acetic acid[11] and formic acid[12] are other reagents to cleave hydrazine N-N bonds.

Feuer and *Brown*[13a] observed during their investigations to reduce the carbonyl groups of 1,2-dialkylperhydropyridazine-3,6-diones that a large excess of $BH_3 \cdot THF$ resulted in N-N bond cleavage. However, $BH_3 \cdot THF$ could only be applied to tetrasubstituted hydrazines, with the cleavage of trisubstituted hydrazines being unsuccessful. *Kibayashi et al.*[13b-e] have also published a similar method for the cleavage of tetrasubstituted hydrazines.

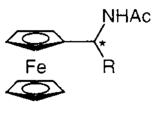
We now wish to report our method to cleave N-N bonds of a broad range of differently trisubstituted hydrazines **1** using $BH_3 \cdot THF$ as cleavage reagent and giving rise to the optically active amines **3**-**7** (Figure 1).

An efficient asymmetric synthesis of protected (1-ferrocenyl-alkyl)amines **3** starts from commercially available ferrocenylcarbaldehyde, which is converted into the SAMP-hydrazone.[14a,b] Nucleophilic 1,2-addition of organolithium compounds to the hydrazone C=N double bond leads to the corresponding hydrazines. Subsequent N-N bond cleavage of activated hydrazines using common methods such as lithium in liquid ammonia and samarium(II) iodide afforded ethylferrocene and vinylferrocene, respectively. Hydrogenolysis using platinum dioxide as catalyst gave low yields with significant loss of enantiomeric purity and large amounts of side-products. The *Raney*-nickel promoted hydrogenolysis afforded the protected amines **3**, but suffered from the disadvantages mentioned above. Partial epimerization or racemization could not be avoided even by varying the hydrogenolysis conditions. In order to cleave the N-N bond of the hydrazine we employed $BH_3 \cdot THF$ as reductive cleavage reagent, which led to amines **3** in good yields (80-89 %) and high enantiomeric excesses (93-95 %). In the same way 1,1′-*bis*(1-aminoalkyl)ferrocene derivatives **4** were synthesized.[14c] The N-N bond cleavage of the *bis*-hydrazines via *Raney*-nickel hydrogenolysis proceeded only in the methyl case **4a** with good yields and stereoselectivities. Accordingly, cleavage of the hydrazine N-N bond with $BH_3 \cdot THF$ afforded the protected amines **4** in good yields (53-69 %) and stereoselectivities (*de* = 80-90 %, *ee* = 90-98 %).

Protected C_2-symmetrical 1,2-diamines **5** can be prepared in high diastereo- and enantiomeric excesses by nucleophilic 1,2-addition of organocerium reagents to the C=N double bond of *bis*-SAMP-hydrazones and subsequent reductive N-N bond cleavage of the corresponding hydrazines.[15] Attempts to introduce an activating group into the 1,2-*bis*-hydrazines in order to cleave the N-N bond with lithium in ammonia failed. The cleavage of the N-N bond with *Raney*-nickel as well as with platinum dioxide as hydrogenation catalysts was unsuccesful. In both cases the generated diamines might serve as chelating ligands for the released heavy metal cations. Consequently, $BH_3 \cdot THF$ was used as cleaving reagent which afforded the protected 1,2-diamines **5** in moderate to good yields (22-58 %) and high diastereomeric and enantiomeric purity (*de* = 86-96 %, *ee* = 96-≥98 %).

Optically active β-amino sulphones **6** can be prepared by conjugate addition of the chiral nitrogen nucleophile SAMP to 1-alkenyl sulphones.[16] Subsequent N-N bond cleavage of the resulting β-hydrazino sulphones **1** leads to enantiomerically pure protected amines **6**. The employment of *Raney*-nickel is not feasible, since the C-S bond is cleaved under these reaction conditions. Since samarium(II) iodide and platinum dioxide failed to cleave the N-N bond, $BH_3 \cdot THF$ was the cleaving reagent of choice. The protected amines **6** were obtained in good yields (58-82 %) and excellent enantiomeric excesses (≥96 %). In this case the chiral auxiliary (SMP) was recycled as the Boc-protected derivative.

The BH_3·THF N-N bond cleavage of trisubstituted hydrazines **1**, prepared by 1,2-addition of organometallic reagents to α-phosphinylated SAMP-hydrazones, afforded the BH_3-protected β-amino phosphines **7** in good yields (81-83 %) and diastereoselectivities (75-78 %).[17]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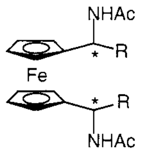
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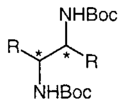
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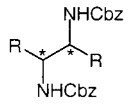
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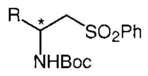
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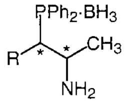
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Figure 1

Table 1. Reductive N-N bond cleavage of hydrazines **1** with exc. BH_3·THF to the corresponding amines **3**-**7**.

3-7	R	time [h]	equiv. BH_3·THF	yield[a] [%]	*de*[b] [%]	*ee*[b] [%]	confg.
3a	Me	5	10	89	-	95	(*R*)
3b	*n*-Bu	5	20	82	-	95	(*R*)
3c	*n*-Hex	5	20	80	-	93	(*R*)
4a	Me	5	20	69	84	96	(*R*)
4b	*n*-Bu	5	20	53	80	98	(*R*,*R*)
4c	*n*-Hex	5	20	53	80	90	(*R*,*R*)
5a	*n*-Bu	70	20	58	86	≥98	(*R*,*R*)
5b	Ph	70	20	22	96	≥96	(*R*,*R*)
6a	Et	5	10	60	-	≥96	(*R*)
6b	*c*-Hex	5	10	58	-	≥96	(*R*)
6c	BOM[c]	5	10	82	-	≥96	(*R*)
7a	*n*-Pr	19	10	81	75	[d]	(*R*,*R*)[e]
7b	*i*-Pr	19	10	83	78	[d]	(*R*,*R*)[e]

[a] **3**-**6**: yield of two steps (cleavage and protection), **7**: yield is based only on cleavage step. [b] Determined by NMR spectroscopy (standard shift experiments or on MTPA amides of the amines), GC or HPLC employing chiral stationary phases. [c] Benzyloxymethyl-. [d] The *ee*-value was not determined. [c] The configuration given is based on previous results.[9a,18]

In conclusion, an efficient method to cleave N-N bonds of trisubstituted hydrazines has been reported. The employment of the BH_3·THF complex as reductive cleaving reagent gives the corresponding amines in good yields and without racemization or epimerization. Further advantages of this cleavage protocol are the simplicity, generality and the compatability with reducible functional groups, such as aryl groups, in the starting hydrazine.

General Procedure for the N-N bond cleavage with BH_3·THF:[19]

The hydrazines **1** were dissolved in dry THF (20-50 mL/mmol) and refluxed with 10 or 20 equivalents of BH_3·THF (1.0 m in THF) for 5 to 70 h. The reaction was cooled to -5 °C (**3** and **4**) or to room temperature (**5**-**7**), acidified with aqueous hydrochloric acid and stirred for 2 h. The THF was evaporated under reduced pressure and the aqueous solution was basified with solid KOH (**3** and **4**) or saturated $NaHCO_3$-solution (**5**-**7**) and extracted with methylene chloride or diethyl ether. The crude amine was usually protected by reaction with Boc_2O, benzyl chloro formate or acetyl chloride before isolation and characterization.

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