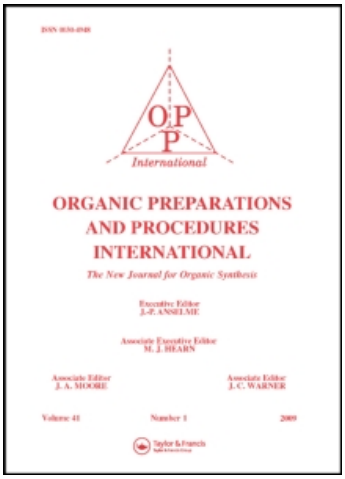

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SELECTED METHODS FOR THE REDUCTION OF THE AZIDO GROUP

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SELECTED METHODS FOR THE REDUCTION OF THE AZIDO GROUP

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INTRODUCTION

Organic azides have been known for more than 130 years[1] and their chemistry has been widely investigated because of their synthetic versatility and ease of preparation. The best known synthetic approaches to the azido functionality, the most commonly used azide reagents and some typical synthetic applications of azides are illustrated in *Schemes 1* and *2*. Azides should always be handled with caution because some members of this class are explosive. The great interest in these compounds and the chemical developments in this area, have resulted in more than a thousand papers and many reviews and books.[2] An excellent monograph, which focused on the literature that appeared from 1983-86, was published by Scriven and Turnbull in 1988.[2] Among the various azide reactions, reduction, particularly to amine, has received the greatest attention in recent years due to the development of organometallic catalysis. The aim of this review is to present the reduction methods of azides that have appeared in the literature in the last decade (1990-2000). The review is not meant to be encyclopedic. Rather the emphasis is on new procedures, particularly on catalyzed processes.

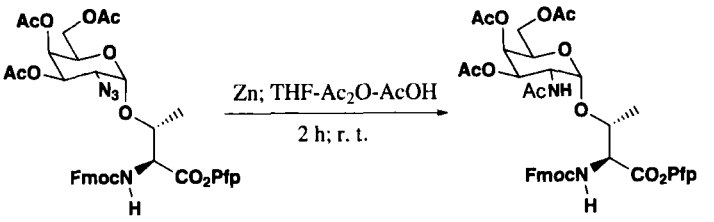
I. REDUCTION BY METALS

Palladium, platinum, nickel-Raney, Lindlar catalyst and zinc have been the most commonly used metals (0) for converting azides to amines. While these reductive processes are easy and generally inexpensive, they are poorly chemoselective[2, 14] and therefore incompatible with other functionalities and protecting groups. Mild and chemoselective methodologies, especially in view of a multistep synthesis of complex molecules, were recently proposed, which used either a metal (0) or a metal (0) assisted by a metal salt.

1. Metal (0)

In the course of a study on the specificity of a glycan interaction with a T-cell receptor,[15] a series of glycoacetamide precursors were suitably prepared by reducing the parent azido derivatives

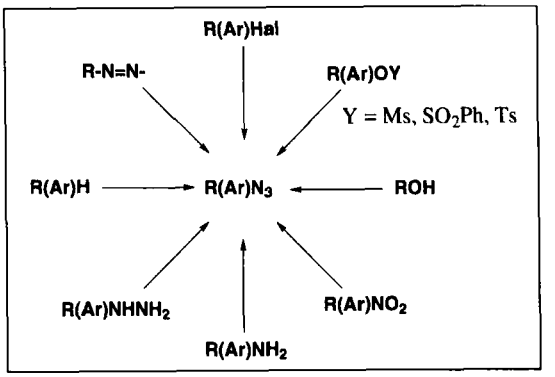
by Zn dust in THF-Ac_2O-AcOH. The reduction is mild and rapid; an example is reported in *Eq. 1.*

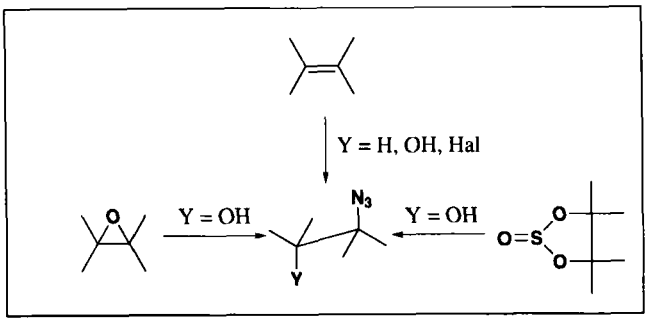


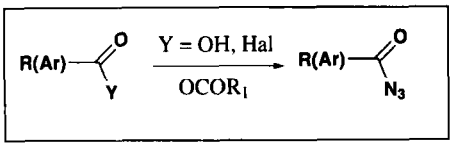
(1)

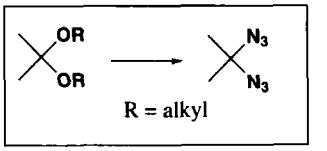
Fmoc = fluoren-9-yl-methoxycarbonyl
Pfp = pentafluorophenyl

Synthesis of Azides









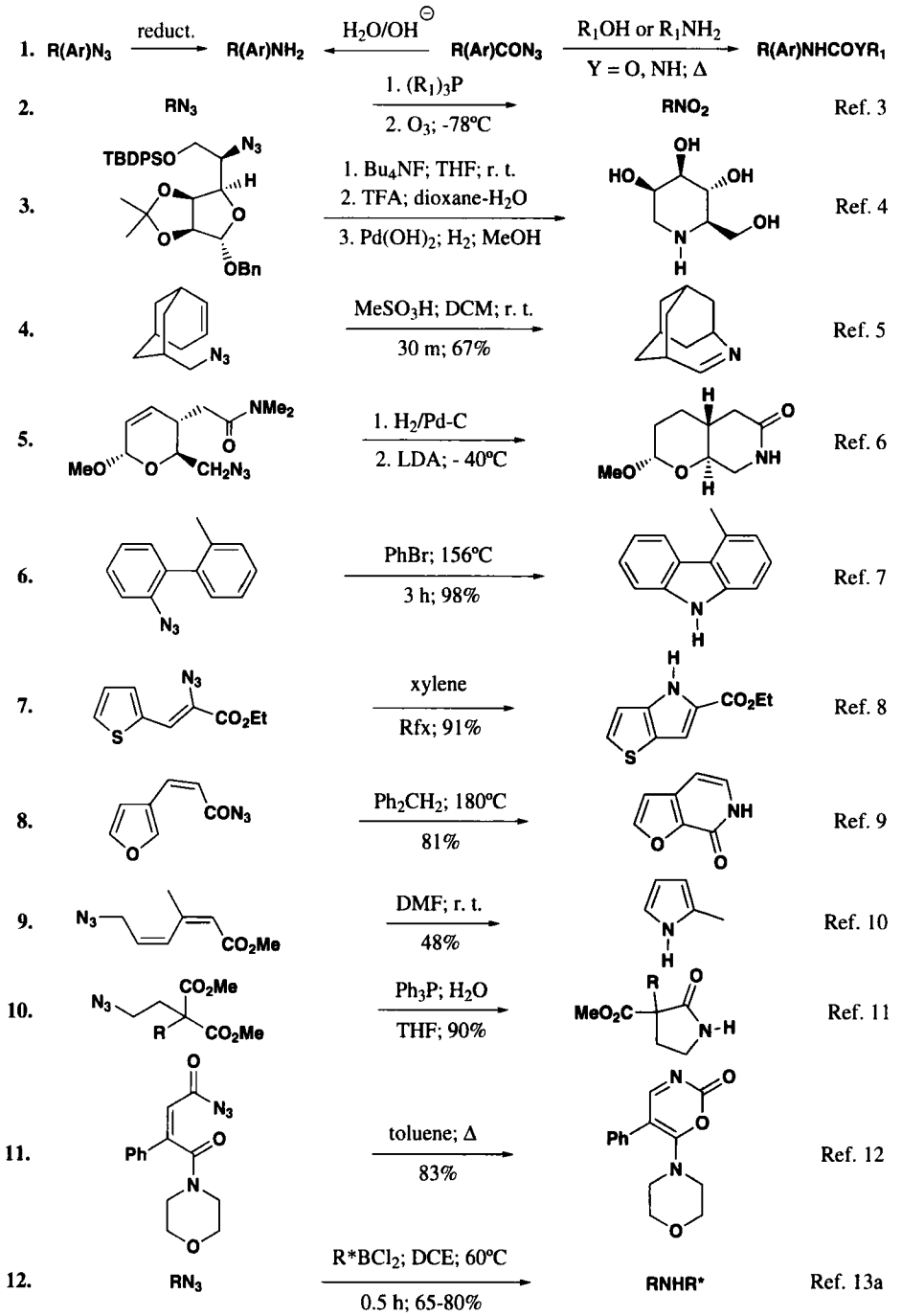
Azide Reagents

LiN_3, NaN_3*, KN_3, HN_3, BrN_3, IN_3, TsN_3*, $MeCON_3$, Me_3SiN_3* (TMSA), $(PhO)_2P(O)N_3$* (DPPA)

*commonly used

Synthesis of Azides and Azide Reagents

Scheme 1



Examples of Synthetic Applications of Azides

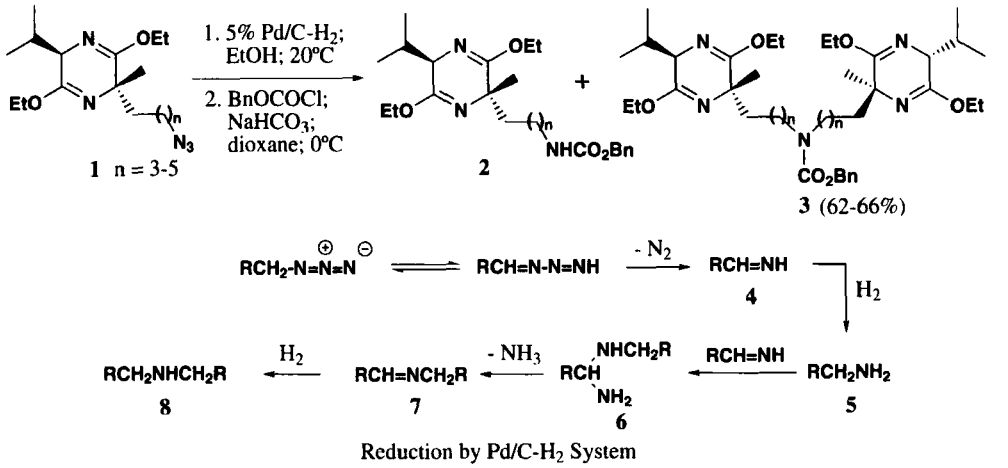
Scheme 2

Readily available and inexpensive alkaline earth metals, Mg and Ca, have been used, in combination with MeOH, as effective reducing agents of alkyl and aryl azides (*Eq. 2*). The reaction is complete in 15-20 min at 0° and can be further accelerated by a catalytic amount of iodine.[16]

$$RN_3 \xrightarrow[0°C;\ 15\text{-}20\ m;\ 94\text{-}98\%]{Mg\ or\ Ca;\ MeOH} RNH_2 \qquad (2)$$

R = Ph; Bn; Cy; PhCH=CH; C_7H_{15}; $C_{10}H_{21}$

Pd/C-H_2 in EtOH and in the presence of BnOCOCl was used[17] to reduce azidopyrazines **1**. Surprisingly the major reaction products were not the expected protected primary amides **2** but the secondary amides **3** (*Scheme 3*). It was suggested that the complexation of Pd with azides facilitates



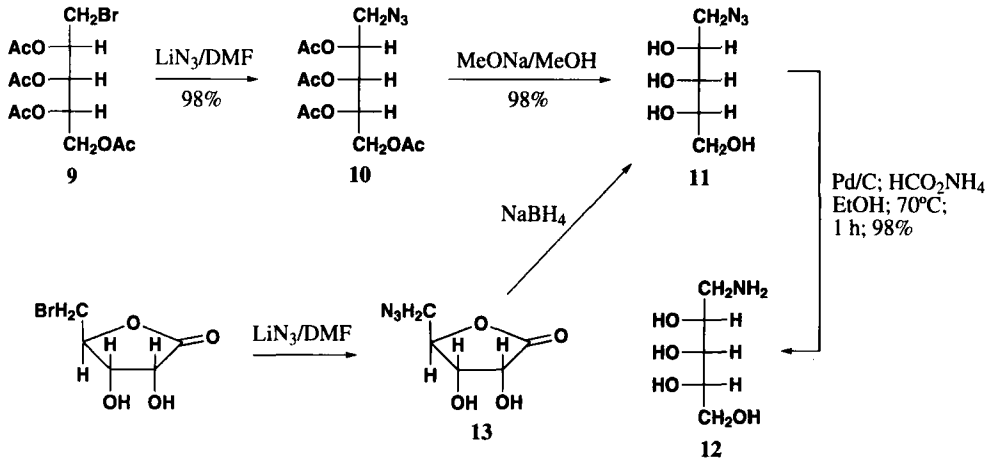
Reduction by Pd/C-H_2 System

Scheme 3

both the 1,4-shift of the hydrogen atom bound to the carbon bearing the azido group and the successive N_2- expulsion producing the imine **4**. The hydrogenation of **4** forms the primary amine **5** which adds a previously formed amine affording diamine **6**. The elimination of NH_3 from **6** gives imine **7** which adds hydrogen providing the secondary amine **8** which is then converted into the corresponding amide after reacting with the appropriate acyl chloride (*Scheme 3*).

The formation of secondary amines from azides can also be performed by using boranes and dichloroboranes;[13] optically active amines were obtained by using enantiopure organoboranes. Catalytic hydrogen transfer, using Pd/C as catalyst and ammonium formate as hydrogen donor, has also been used to synthesize 1-aminodeoxypentitols.[18a] The preparation of 1-amino-1-deoxy-L-ribitol **12** is illustrated in *Scheme 4*. The azido precursor **11** was obtained by treating bromo derivative **9** with LiN_3 in DMF with the subsequent deprotection of **10** or *via* azidolactone **13** that prevents the protection-deprotection steps.

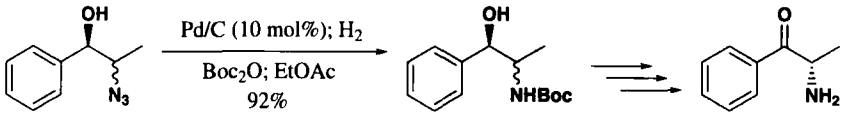
The azido group is converted directly into *N*-Boc amino group by treating it with *tert*-butyldicarbonate (Boc_2O) in a suspension of 10% Pd/C in ethyl acetate under a hydrogen



Preparation of 1-Amino-1-deoxy-L-ribitol (12)

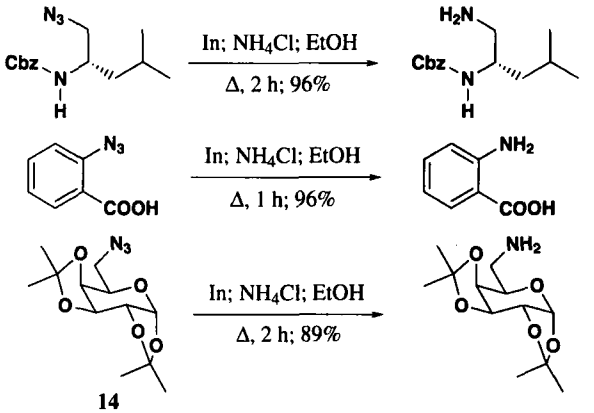
Scheme 4

atmosphere.[18b] This protocol was used to prepare a diasteromeric mixture of 2-(*N*-Boc-amino)-1-phenyl-1-propanols in the course of the synthesis of both enantiomers of cathinone (*Eq. 3*).[18c]



syn/anti 55:45 (-)-cathinone (3)

Indium in EtOH and in the presence of NH_4Cl has been used to convert azides into amines.[19] This protocol is mild, is applicable to both aromatic and aliphatic azides and is chemoselective towards a variety of functionalities and protecting groups such as CH=CH, COOH, COOR, $CR(OR)_2$, Cbz, Boc. Some examples are illustrated in *Scheme 5*.



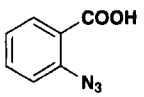
Reduction by In/NH_4Cl System in EtOH

Scheme 5

2. Metal (0) Assisted by a Metal Salt

The newest reduction systems of azides to amines or amides that use the combination metal (0)-metal salt are: Zn-$CoCl_2$ in THF,[20] Zn-$NiCl_2$ in THF,[21] Zn-$FeCl_3$ in EtOH,[22] Fe-$NiCl_2$ in THF,[23] Sm-$CoCl_2$ in THF,[24] and Sm-Cp_2TiCl_2/*t*-BuOH in THF.[25] Sm has also been used as a metal in combination with a catalytic amount of iodine.[26] This last reaction will be illustrated in Section III because of its similarity to the reduction using SmI_2. The results obtained by using the above-mentioned combination metal (0)-metal salt with a variety of azides are illustrated and compared in *Table 1*; further examples are the azides **14**,[22] **15**,[22] **16**,[21] **17**,[24, 25] **18**,[22] and **19**[22, 23] (Fig. 1) and *Scheme 5*.

Table 1. Reduction of Azides to Amines or Amides by a Metal(0) Assisted by a Metal Salt

Azide	Zn-$CoCl_2$[a]		Zn-$NiCl_2$[a]		Zn-$FeCl_3$[a]		Fe-$NiCl_2$[a]		Sm-$CoCl_2$[b]		Sm-Cp_2TiCl_2[c]	
	t (h)	Y (%)	t (h)	Y (%)	t (h)	Y (%)	t (h)	Y (%)	t (h)	Y (%)	t (h)	Y (%)
$C_6H_5N_3$	0.75	95	2	90	4	98	0.50	85	0.75	92	0.1	86
p-Cl-$C_6H_4N_3$	0.75	82	2.5	85	5	90	0.80	85	0.75	87	0.1	78
p-Br-$C_6H_4N_3$	0.80	83	2.5	92	4	90			0.75	85	0.1	81
p-I-$C_6H_4N_3$									0.75	88		
Me-$C_6H_4N_3$							1	80[d]	0.75	90[e]	0.1	75[e]
p-MeO-$C_6H_4N_3$	0.90	90	2	85	4	86	0.75	90				
p-Ac-$C_6H_4N_3$	0.50	80	2	80	5	83	0.80	80				
NO_2-$C_6H_4N_3$	0.50	80[f]	2.5	80[g]	4.5	80[f]	0.50	85[g]	1	90[f]		
m-Cl-$C_6H_4N_3$	0.75	85	2.5	78	4	87	0.75	82				
$C_6H_5CON_3$	1	80	2.5	82			0.40	90	0.75	84	0.1	87
Me-$C_6H_4CON_3$	0.75	86[e]	2	85[e]	4	80[e]			0.75	84[d]	0.1	75[d]
PhCH=CHCON$_3$	0.90	80	2.5	80	4.5	86			1	81		
$C_6H_5SO_2N_3$	0.50	82	2	85	4	82			0.75	83		
p-Me-$C_6H_4SO_2N_3$	0.67	85	2	90	4.5	81						
$C_nH_{(2n+1)}N_3$	0.50	66[h]	2	72[h]	4	80[h]			1	71[i]	0.1	76[i]
CyN_3	0.51	70	2.5	70	5	81						
					6	80						

a) 0°-r. t.; b) 40°; c) r. t.; d) *m*-Me; e) *p*-Me; f) *o*-NO_2; g) *p*-NO_2; h) C_6H_{13}; i) C_7H_{15}

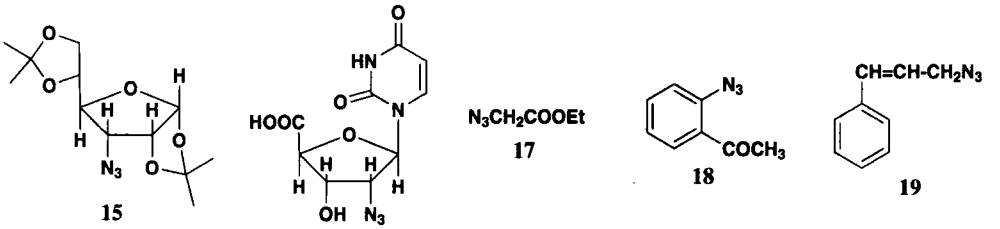


Fig. 1

All the procedures are efficient and reduce alkyl-, aryl-, aroyl- and arylsulfonyl azides with excellent yields. The azide functionality is selectively reduced in the presence of carbon-carbon double bond, nitro-, halo- and methoxy-aromatic groups and even the sensitive carbonyl and carboxyester groups remain intact. The metal (0)-metal salt combination is also efficient for the selective reduction of the acetonidoazides **14**[22] and **15**[22] and nucleosido-azide **16**.[21] The metal salt plays an important role. Thus $CoCl_2$ is more efficient than $NiCl_2$ and $FeCl_3$ when combined with Zn, while it affords the same results in combination with Sm and Zn. Cp_2TiCl_2 strongly increases the catalytic power with respect to $CoCl_2$ and $NiCl_2$ and the latter salt facilitates the reduction more when it assists Fe compared with Zn. Al-$NiCl_2$[23] and Mg-$CoCl_2$[20] are equally active, while Zn-$CeCl_3$ and Zn-$InCl_3$ did not give encouraging results.[21]

II. REDUCTION BY METAL SALTS

A protocol was recently used to carry out the reduction of azides to amines by samarium diiodide which is known to be a powerful electron-donor capable of promoting a wide range of reductions and coupling reactions.[25, 27-29] Independently, Benati[30] and Hesse[31] first reported the reduction of an azide functionality by using SmI_2 in THF at room temperature. The two compilations report a marked difference in the reactivities for *p*-chloro- and *p*-methoxyphenylazide (*Table 2*). This is probably ascribable to the origin of SmI_2 (commercial or prepared *in situ*) and/or the reaction medium and to its degree of dryness. The importance of the SmI_2 source, reaction medium and the water contained, are explained by Zhang [25, 26] and Beau.[32] Zhang suggests two protocols which use, one SmI_2 prepared *in situ*, in THF/*t*-BuOH and the other metallic samarium in MeOH with a catalytic amount of iodine (*Table 2*). Sm has a stronger reducing power than SmI_2, but in combination with I_2, the azides are reduced more slowly. Beau observes that the reduction of 3-azido-3-deoxy-D-glucopyranosides 20 and 21 to 22 and 23 respectively (*Fig. 2*), failed in dry THF at room temperature, while it proceeded with high yields if water (10 mol% v/v) was present in the initial solution of azide. SmI_2 transforms azido-aldehydes and –ketones to the corresponding amines,[30] despite the fact that (aromatic) aldehydes and ketones undergo rapid pinacol coupling in the presence of iodide.[33] The mechanism of azide reduction[32] presumably involves an initial electron transfer from SmI_2 to the azide group

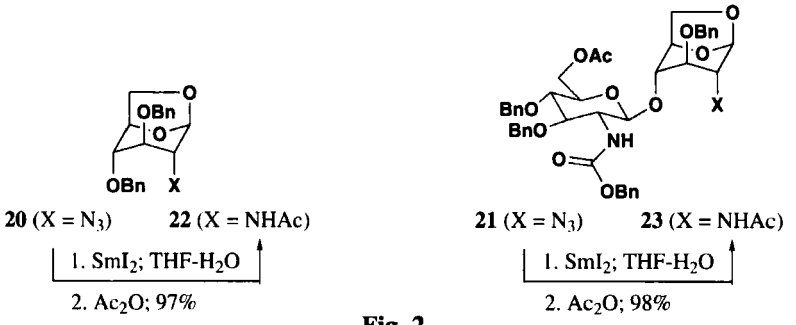
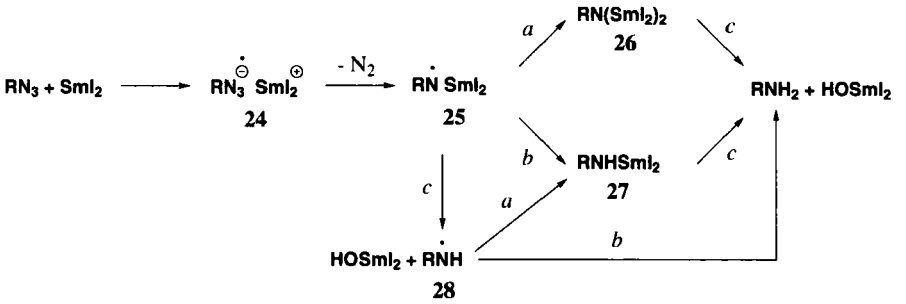


Fig. 2

(*Scheme 6*) giving a radical anion **24** which then leads to an aminyl radical **25** through the loss of N_2. The aminyl radical **25** give rise to **26** or **27** which in turn provides the amine by hydrolysis. In the presence of water the aminyl radical **25** gives the radical **28** which affords the amine *via* a direct hydrogen transfer or *via* reduction to **27** and successive hydrolysis.



a: SmI_2; *b*: hydrogen transfer; *c*: H_2O

Mechanism of the Azide Reduction by SmI_2

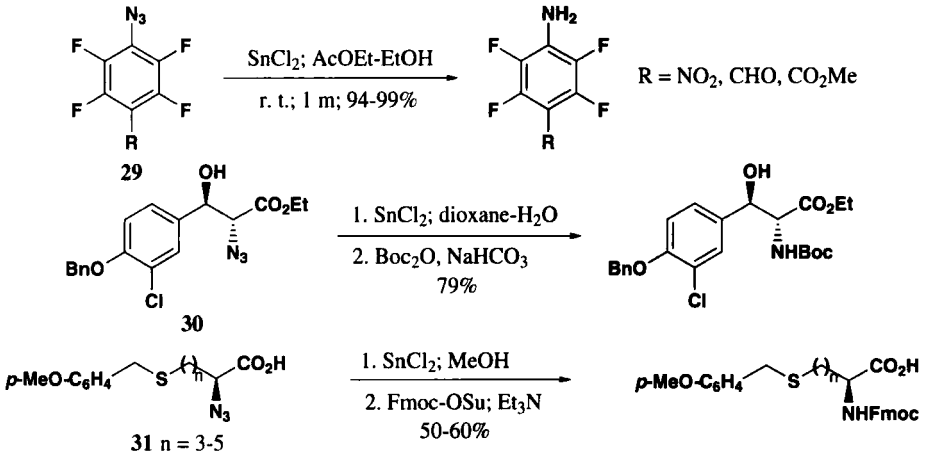
Scheme 6

Table 2. Reduction of Azides to Amines or Amides by SmI_2 and Sm in the Presence of a Catalytic Amount of I_2

Azide[a]	SmI_2[b]		SmI_2[c]		SmI_2[d]		SmI_2[e]	
	t (h)	Y (%)	t (h)	Y (%)	t (h)	Y (%)	t (h)	Y (%)
$C_6H_5N_3$			0.17	90	0.33	75	6[f]	87
p-Cl-$C_6H_4N_3$	1.25	92	0.17	88	0.33	71	6[f]	86
p-MeO-$C_6H_4N_3$	1.25	95	0.17	84				
p-Ac-$C_6H_4N_3$			0.17	79	0.17	83	6+2[g]	88
$C_7H_{15}N_3$			1	90	0.5	70	6+2[g]	76

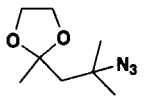
The reduction of alkyl- and arylazides to amines by $SnCl_2$ has been known for many years[34] but recently this salt has again attracted the attention of researchers. $SnCl_2$ was used to reduce perfluo-

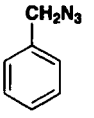
rinated aryl azides **29**,[35] the ethyl (2R,3R)-2-azido-3-(4-benzyloxy-3-chlorophenyl)-3-hydroxypropanoate **30**,[36] which is linked to *p*-hydroxy-α-phenylglycine in the antibiotic glycopeptide, Vancomycin,[37] and protected ω-mercapto-α-azido acids **31**[38] (n = 3) (*Scheme 7*).



Scheme 7

Sn (II) complexes prepared by treating $SnCl_2$ or $Sn(SR)_2$ with RSH and Et_3N react rapidly with azides to give amines and nitrogen.[39] In *Scheme 8*, the results related to 4-azido-4-methylpentan-2-one ethylene acetal (a tertiary azide) and benzyl azide are reported and the results were compared with those obtained by using other reducing species. The reducing agent apparently is $Sn(SR)_3^-$, which





Reducing System (20°C)	C[a] (%)	t (m)
1. Sn (II)/$(CH_2SH)_2$/Et_3N/MeCN	100	2
2. Sn (II)/$C_7H_8S_2$[b]/Et_3N/MeCN	100	3
3. Sn (II)/PhSH/Et_3N/MeCN	100	20
4. $CrCl_2$/HCl/MeCOMe-H_2O	100	40
5. H_2/Pd-C/MeOH	100	150
6. $LiAlH_4$/Et_2O	100	360

Reducing System (20°C)	C[a] (%)	t (h)
1. Sn (II)/Py-2-SH/Et_3N/MeCN	100	2
2. $SnCl_2$/MeOH	60	24
3. Na_2S/MeOH	70	24
4. PhSH/Et_3N/MeCN	45	24
5. $NaBH_4$/MeOH	20	24
6. $Pd(PPh_3)_4/C_6H_6$	0	24

a: Conversion Reaction; b: Me-C_6H_3-3,4-$(SH)_2$

Comparison of Reducing Power of Sn(II) Complexes with Other Reducing Systems

Scheme 8

reduces azides more rapidly than nitro compounds, and is inactive towards carbonyl groups, sulfoxides, sulfones, nitriles and esters. With respect to other standard reducing species, the complex $SnCl_2$/PhSH/Et_3N reduces sterically hindered azido groups as in nucleoside **32**[40] (X = N_3) and the azido group contained in substrates bearing a labile ester functionality such as **33** (X = N_3), (Fig. 3). These are intermediates in the synthesis of triply linked conjugated drugs.[41]

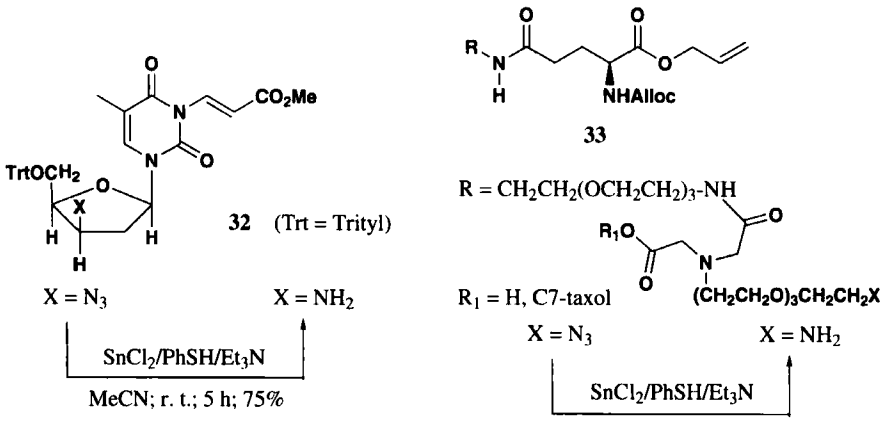
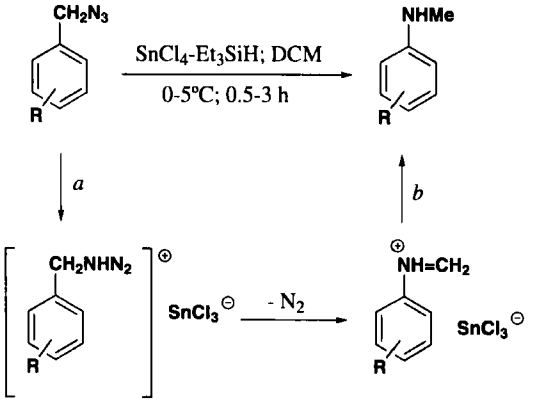


Fig. 3

$SnCl_4$ in combination with Et_3SiH transforms benzyl azides to *N*-methylanilines (*Scheme 9*).[42] Both reagents have to be present simultaneously; in the presence of $SnCl_4$ only, the reaction is very slow. $SnCl_4$ gives the best results with respect to other Lewis acids and the relative amounts of Et_3SiH and $SnCl_4$ (3.0-3.3 equiv. and 2.0 equiv. respectively) are crucial for achieving the best reaction



R	Yield (%)
p-*n*-Bu	91
p-Br	63
p-Ph	83[c]
m-Br	60
m-OMe	80
o-Me	91

a: $SnCl_4/Et_3SiH$ or $SnCl_2/HCl/Et_3SiH$; *b:* Et_3SiH; *c:* 20-25°C, 3 equiv. of $SnCl_4$

Reduction by $SnCl_4/Et_3SiH$

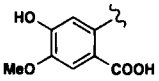
Scheme 9

yields. The success of the reaction depends on the nature and the position of the substituents on the phenyl ring: electron-withdrawing groups in the *meta* or *para* position and strong electron-donating groups in the *para* position prevent the reaction or give a mixture of products. The reaction appears to

proceed (*Scheme 9*) *via* an aminodiazonium trichlorostannate (II) which rearranges to give an iminium salt that is then reduced to the *N*-methylaniline derivative by Et_3SiH.

Iron, aluminum and molybdenum salts were recently used to transform azides into amines. Some data are reported in *Scheme 10*. $FeCl_3$ is used as catalyst (40 mol%) to reduce aryl- and alkyl azides with *N,N*-dimethylhydrazine (*Scheme 10, Table A*).[43] The procedure is mild and compatible

A. $RN_3 \xrightarrow[MeOH;\ r.\ t.]{H_2N\text{-}NMe_2/FeCl_3} RNH_2$

R	t (h)	Yield (%)
C_6H_5	0.5	82
o-CO_2H-C_6H_4	1	90
p-NO_2-C_6H_4	1.5	81
p-Cl-C_6H_4	1	78
o-CO_2Me-C_6H_4	1	80
$C_6H_5CH_2$	2.5	65
n-C_8H_{17}	2.5	60
	1	90

B. $RN_3 \xrightarrow[MeOH;\ r.\ t.]{FeSO_4/NH_3} RNH_2$

R	t (h)	Yield (%)
C_6H_5CO	1[a]	84
o-CO_2H-C_6H_4	2.5	96
p-Me-$C_6H_4SO_2$	3	90
p-Cl-C_6H_4	2.5	98
o-COMe-C_6H_4	2.5	96
$C_6H_5CH_2$	3	90
o-COPh-C_6H_4	2.5	94

a: under Rfx

C. $RN_3 \xrightarrow{AlI_3/PhH;\ Rfx} RNH_2$

R	t (h)	Yield (%)
C_6H_5	0.17	95
m-Cl-C_6H_4	0.17	89
m-NO_2-C_6H_4	0.25	95
m-MeO-C_6H_4	0.17	93
m-OH-C_6H_4	0.25	92
p-OH-C_6H_4	0.17	93
o-OH-C_6H_4	0.25	95
p-COOH-C_6H_4	0.17	92

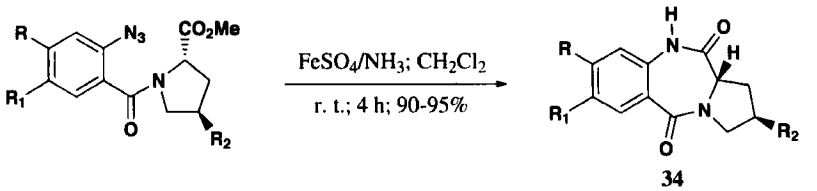
D. $RN_3 \xrightarrow[MeCN\text{-}H_2O;\ r.\ t.]{(BnNEt_3)_2MoS_4} RNH_2$

R	t (h)	Yield (%)
C_6H_5	6	75
p-Me-$C_6H_4SO_2$	0.1	96
p-NO_2-C_6H_4CO	1.5	95
p-CHO-C_6H_4CO	3	88
p-MeCO-C_6H_4	4	90
C_6H_5CO	0.5	90
$C_{15}H_{31}CO$	1	92
$C_{10}H_{15}SO_2$	0.1	96

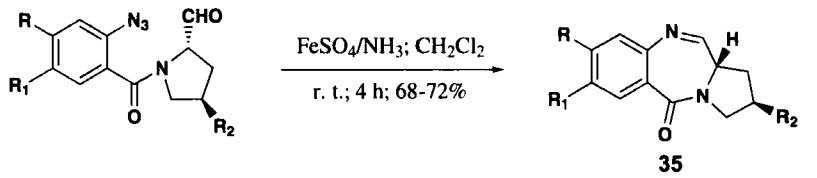
Reduction by Iron, Aluminum, and Molybdenum Salts

Scheme 10

with several organic functionalities but the high carcinogenicity of *N,N*-dimethylhydrazine is a drawback. $FeSO_4/NH_3$ is an excellent reducing system[44] (*Scheme 10, Table B*) that has also been used to prepare benzodiazepines **34** and **35** *via* azido reductive cyclization (*Eqs. 4 and 5*). AlI_3, prepared *in situ*, allows the reduction to be carried out in a very short time and, interestingly, is also effective with



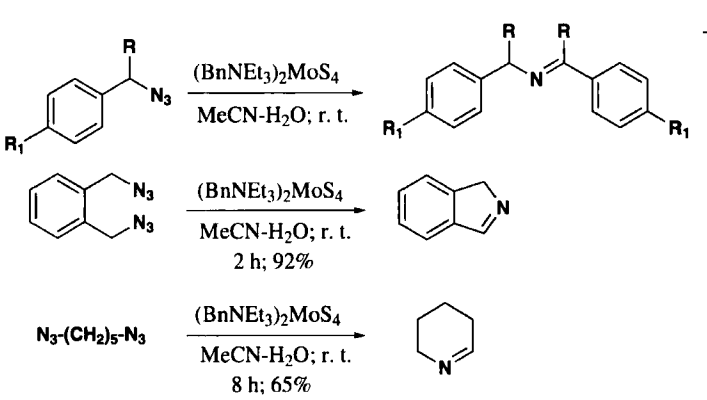
34 (4)



35 (5)

R = H, OH; R_1 = H, OMe, Me; R_2 = H, OH

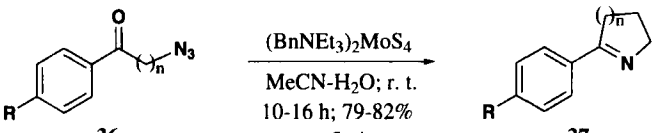
hydroxyphenyl azides (*Scheme 10, Table C*).[45] Benzyltriethylammonium tetrathiomolybdate $(BnNEt_{3)2}MoS_4$ reduces aryl azides as expected (*Scheme 10, Table D*), but with alkyl azides only imines, rather than primary amines, were obtained (*Scheme 11*)[46] while ω-azido carbonyl compounds **36** led to the formation of cyclic imines **37** (*Eq. 6*).[47]



R	R_1	t (h)	Yield (%)
H	H	3	82
H	OMe	20	80
Me	H	70	85

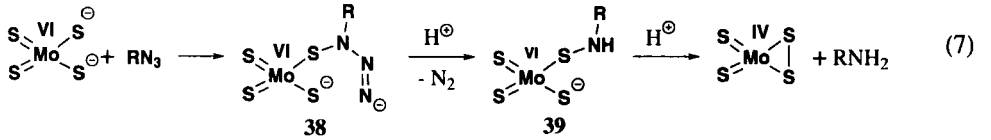
Reduction by $(BnNEt_3)_2MoS_4$ of Alkyl Azides to Imines

Scheme 11



36 37 (6)

The reduction of aryl azides by MoS_4^{2-} is, at first, surprising because molybdenum is in its highest oxidation state (VI). It has been suggested[46] (*Eq. 7*) that *N*-sulfinylamine **39,** produced by nitrogen extrusion from the intermediate **38,** undergoes an internal sulfur-sulfur electron transfer resulting in the breaking of the S-N bond and formation of the amine.



38 39 (7)

The reduction of organic azides by catalytic hydrogenation was recently investigated using organouranium (IV) complexes and MCM-silylamine Pd (II)-complexes.[48] *bis*-Amide complex $(C_5Me_5)_2U(NHAd)_2$ [Ad = 1-adamantyl] converts 1-adamantyl azide to 1-adamantylamine[48a] that is dehydrogenated to $(C_5Me_5)_2U(=NAd)_2$ which, under an atmosphere of hydrogen, is again reduced to the starting complex. The result is that AdN_3 in the presence of $(C_5Me_5)_2U(NHAd)_2$, is catalytically hydrogenated to $AdNH_2$ in 16 h in THF at 65° with 76% yield.

A number of alkyl-, aryl- and arylsulfonyl azides were catalytically reduced to the corresponding amides in excellent yield by heterogeneous hydrogenation in MeOH at room temperature by mesoporous material MCM-41-silylamine Pd (II)-complexes.[48b] Carbonyl, sulfonyl, nitro and benzyl groups were not affected and no racemization was observed in the reduction of homochiral 3,4-diazido-1-benzylpyrrolidine. The catalyst was reused for five cycles with the same activity.

III. REDUCTION BY METAL AND NON-METAL HYDRIDES

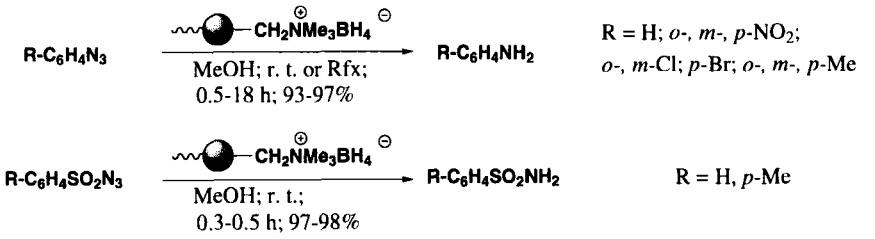
Classic hydrides such as $LiAlH_4$, $NaBH_4$ and BH_3 are limited in one or more ways with respect to the reduction of organic azides. $LiAlH_4$ is not tolerated by functionalities such as NO_2, CN, COR, COH, and CO_2R;[2] $NaBH_4$ reduces alkyl azides in low yields[2] and BH_3 cannot be used in the presence of double or triple carbon-carbon bonds or with acidic functionalities such as OH or COOH. Although $NaBH_4$ efficiently reduces arylsulfonyl azides to the amides,[49] aroyl azides surprisingly give mainly benzylic alcohols[50] (*Scheme 12*).

R	t (h)	40/41	Total Yield (%)
p-NO_2	0.08	100:0	98
p-Cl	0.5	98:2	98
H	1	90:10	90
p-Me	3	84:16	95
p-OMe	20	81:19	95

Reduction of Aroyl Azides to Benzylic Alcohols and Benzylamines by $NaBH_4$

Scheme 12

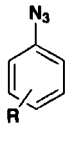
Recently several modified borohydride reagents, prepared from $NaBH_4$, have allowed efficient and selective reductions to be carried out. Borohydride-supported on an ion-exchange resin in MeOH reduces aryl azides and arylsulfonyl azides to amines and amides, respectively, in excellent yields (*Scheme 13*).[51]



Reduction of Aryl- and Arylsulfonyl Azides by Borohydride-supported Resin

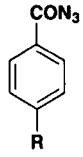
Scheme 13

Methyltriphenylphosphonium borohydride ($MePh_3P^+BH_4^-$), prepared by reaction of triphenylphosphonium iodide and $NaBH_4$, reduces aryl- and aroyl azides **42**, and **43** in dichloromethane at r. t. or under reflux to amines and amides respectively, easily and in high yields (*Scheme 14*).[52] Some



42

R	Yield (%)
p-NO_2	98
p-Cl	99
p-CO_2Et	94
p-Me	87
m-CN	98



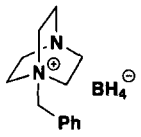
43

R	Yield (%)
MeO	95
Cl	88
Me	80

Reduction by ($MePh_3P^+BH_4^-$)

Scheme 14.

examples of reductions in the absence of solvent were also reported.[53] Aryl azides are similarly reduced to aryl amines by 1-benzyl-4-aza-1-azoniobicyclo[2.2.2]octane tetrahydroborate (BAAOTB) **44** and tetrabutylammonium tetrahydroborate (TBATB) **45** in *t*-BuOH at reflux temperature (*Scheme 15*).[54]



44

45

RN_3 —*t*-BuOH; Rfx, 2-10 h→ RNH_2

R	**44** Y (%)	**45** Y (%)
p-Me-C_6H_4	85	90
p-Cl-C_6H_4	90	90
p-Br-C_6H_4	90	85
p-NO_2-C_6H_4	92	90
o-NO_2-C_6H_4	90	85
1-Naphtyl	90	92
Bn	90	90

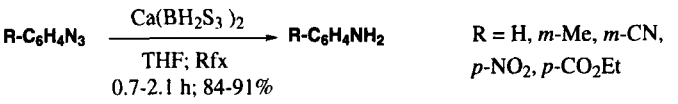
Reduction by (BAAOTB) **44** and (TBATB) **45**

Scheme 15

Sulfurated calcium borohydride $[Ca(BH_2S_3)_2]$ is a recently modified borohydride, prepared from $NaBH_4$, S and $CaCl_2$, that reduces aryl azides in good to excellent yields[55] (*Scheme 16*). Among the various boranes investigated, such as dialkyl-, alkoxy- and haloboranes, dichloroborane-dimethylsulfide $[BHCl_2 \cdot SMe_2]$ is very suitable for reducing organic azides. This reagent reduces a variety of

$$NaBH_4 + 3\,S \longrightarrow NaBH_2S_3 + H_2$$

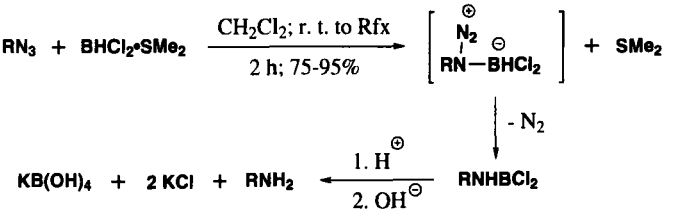
$$2\,NaBH_2S_3 + CaCl_2 \longrightarrow Ca(BH_2S_3)_2 + 2\,NaCl$$



Reduction by $[Ca(BH_2S_3)_2]$

Scheme 16

azides including tertiary, alkyl-, aryl- and benzyl azides while not affecting esters, nitriles, nitro, bromo and carbon-carbon double bond functionalities.[56] *Scheme 17* illustrates the reaction and gives some representative examples. The reduction is rapid, works with tertiary azides and is carried out in a non-aqueous medium which avoids eventual problems associated with easily enolizable functionalities.

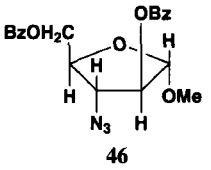


R = C_6H_{13}, $C_{12}H_{25}$, $C_{11}H_{23}$, Cy, C_7H_{13}, Ph, Bn, 1-adamantyl

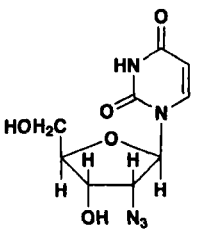
Reduction by $BHCl_2 \bullet SMe_2$

Scheme 17

Tributyltin hydride (Bu_3SnH), in the presence of azobis(isobutyronitrile) (AIBN), is also an efficient reducing agent for azides and was used in boiling dioxane[57] and in benzene/*N,N*-dimethylacetamide[58] to convert azidoarabinofuranoside **46** and azidonucleosides **47** and **48** into the corresponding amines (Fig. 4).



46



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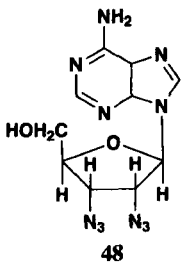
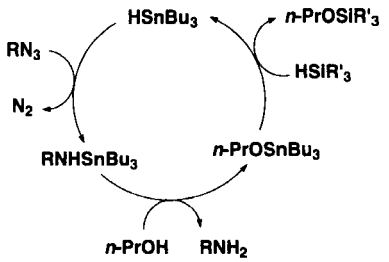


48

Fig. 4

An interesting Bu_3SnH-catalyzed, silicon hydride-mediated reduction process was recently discovered by Fu.[59] Bu_3SnH is utilized as a catalyst and a silicon hydride ($PhSiH_3$) fills the role of the stoichiometric reducing agent. The process (*Scheme 18*) requires an alcohol (*n*-Pr-OH was chosen for steric reasons) to transfer the Bu_3Sn group from the nitrogen of the reduction product $RNHSnBu_3$ to the oxygen of the alcohol; the resulting tin alkoxide is then reduced by silicon hydride to regenerate the catalyst Bu_3SnH. Polymethylhydrosiloxane [TMSO-$(SiHMeO)_n$-TMS] (PMHS) was also used with the same results. The reduction follows a radical pathway and AIBN was used as a radical initiator.



$$RN_3 \xrightarrow[PhH;\ Rfx;\ 1.5\text{-}2\ h]{Bu_3SnH\ (5\%)/AIBN,\ PhSiH_3;\ n\text{-}PrOH} RNH_2$$

R	$PhSiH_3$ Y (%)	PMHS Y (%)
$C_{12}H_{25}$	94	95
$C_{10}H_{21}-CH(CH_3)$	92	94
$C_5H_{11}-C(C_5H_{11})(C_4H_9)$	96	94
1-Adamantyl	99	96
p-$MeOC_6H_4$	94	91

Reduction by Silicon Hydride Catalyzed by Bu_3SnH

Scheme 18

$Zn(BH_4)_2$ is effective for many types of azides but is unstable at room temperature and must be freshly prepared for use. In addition, dry solvents are required for the reaction, because $Zn(BH_4)_2$ is hydrolyzed rapidly and vigorously with water. In order to overcome these problems, modified zinc borohydrides were prepared by complexation with 1,4-diazabicyclo[2.2.2]octane [$Zn(BH_4)_2$dabco], triphenylphosphine [$Zn(BH_4)_2(Ph_3P)$ and $Zn(BH_4)_2(Ph_3P)_2$] and poly-η-pyrazine [$Zn(BH_4)_2(PYZ)_n$]. *Charts 1-5* illustrate the azide reductions carried out by using $Zn(BH_4)_2$ and the cited complexes.

Lithium aminoborohydrides ($LiABH_3$) are a class of powerful selective reducing agents that can reduce a large variety of compounds.[65, 66] They are prepared from amine (A = piperidine and diethylamine for instance), borane dimethyl sulfide and *n*-butyllithium. Alkyl-, aryl azides, and 3-azidocholest-5-enes are converted to the corresponding amines in 1-3 h by $LiMe_2NBH_3$ in THF at 0° in quantitative yield and only 1.5 equiv. of $LiMe_2NBH_3$ were necessary, in contrast to 12-25 equiv. of $LiAlH_4$.[66]

Chart 1. Zinc Borohydride $Zn(BH_4)_2$

Preparation: $ZnCl_2 + NaBH_4$ in Et_2O[60] or DME[61]

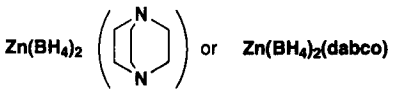
Azides checked[62]

$R\text{-}C_6H_4CON_3$	3.5-6 h, 92-95%	$R\text{-}C_6H_4CONH_2$	R = *p*-Me; *p*-MeO
$R\text{-}C_6H_4CON_3$	4-5.5 h, 92-96%	$R\text{-}C_6H_4CH_2OH$	R = *p*-NO_2; *p*-Cl; *m*-Cl
$R\text{-}CON_3$	0.5-2.5 h, 84-92%	$R\text{-}CONH_2$	R = Cy; oleoyl; lauroyl
$BnCON_3$	3 h, 85%	BnNHCHO	
$ArSO_2N_3$	3.5-4 h, 90-95%	$ArSO_2NH_2$	Ar = toluyl; 2-naphthyl
$Ar(R)N_3$	1-8 h; 65-94%, US or US + SiO_2	$Ar(R)NH_2$	Ar, R = variuos

Reaction Conditions: in DME at room temperature

Comments: The substituents in the aromatic ring of aroyl azides greatly influence the course of the reaction. Acyl azides give the corresponding amides, but phenylacetyl azide undergoes Curtius-type rearrangement followed by hydride attack to give *N*-benzylformamide. Alkyl and aryl azides require sonication (US) and in some cases US + SiO_2. Reaction mechanisms are illustrated. $Zn(BH_4)_2$ is unstable at room temperature and hydrolyzes vigorously on contact with water; hydride freshly prepared should be used. The reduction of the azido group is compatible with functional groups such as Cl, MeO, CO_2Me, and C=C.

Chart 2. Zinc Borohydride-(1,4-diazabicyclo[2.2.2]octane)



Preparation[52]: $ZnBH_4$ + dabco in Et_2O

Azides checked[52]

$R\text{-}C_6H_4N_3$	0.85-12 h, 92-97%	$R\text{-}C_6H_4NH_2$	R = *p*-NO_2; *p*-Cl; *p*-CO_2Et; *p*-Me; *m*-CN
$R\text{-}C_6H_4CON_3$	3-48 h, 88-97%	$R\text{-}C_6H_4CONH_2$	R = *p*-OMe; *p*-Cl; *p*-Me; *p*-NO_2
RN_3	0.25-0.34 h, 95-100%	RNH_2	R = C_4H_9; 2-OH-C_6H_{10}; $PhCH(OH)CH_2$

Reaction Conditions: in THF at room temperature

Comments: $Zn(BH_4)_2$dabco is highly stable in protic solvents and, on contact with water, liberates hydrogen gas slowly. Functionalities such as NO_2, Cl, CO_2Et, CN, and COMe are preserved. The OH group does not prevent the reaction.

Chart 3. Zinc Borohydride(triphenylphosphine) $Zn(BH_4)_2(Ph_3P)$

Preparation[63] $ZnBH_4 + Ph_3P$ (1 equiv) in Et_2O-THF

Azides checked[63]

R-$C_6H_4N_3$	immediate-1 h, 90-100%	**R-$C_6H_4NH_2$**	R = *p*-NO_2; *m*-CN; *p*-CO_2Et; *p*-Cl; *p*-Me
R-$C_6H_4CON_3$	0.16-2.5 h, 65-99%	**R-$C_6H_4CONH_2$**	R = *p*-Me; *p*-MeO; *p*-NO_2; H
$ArSO_2N_3$	1.5-2.2 h, 76-86%	**$ArSO_2NH_2$**	Ar = toluyl; 2-naphthyl
RN_3	1-3 h, 100%	**RNH_2**	R = Bn; PhCH(OH)CH_2

Reaction Conditions: in THF at room temperature or reflux or under neat conditions at room temperature

Comments: Functionalities such as CN, CO_2Et, Cl and OMe are preserved and the OH group does not prevent the reaction.

Chart 4. Zinc Borohydride *bis*-(Triphenylphosphine) $Zn(BH_4)_2(Ph_3P)_2$

Preparation[63] $ZnBH_4 + Ph_3P$ (2 equiv) in Et_2O-THF

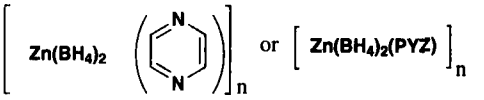
Azides checked[63]

R-$C_6H_4N_3$	0.08-0.30 h, 85-99%	**R-$C_6H_4NH_2$**	R = *m*-CN; *p*-CO_2Et; *p*-Cl; *p*-Me
R-$C_6H_4CON_3$	immediate-2 h, 50-95%	**R-$C_6H_4CONH_2$**	R = *p*-Cl; *p*-MeO; *p*-NO_2
$ArSO_2N_3$	0.17-0.5 h, 85-93%	**$ArSO_2NH_2$**	Ar = toluyl; 2-naphthyl
RN_3	immediate-0.25 h, 100%	**RNH_2**	R = Bn; PhCH(OH)CH_2

Reaction Conditions: in THF at room temperature or reflux or under neat conditions at room temperature, 30 and 60°C.

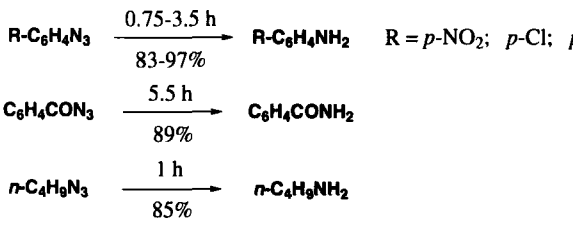
Comments: This reducing agent reacts vigorously with acids and slowly with water and is soluble in THF, MeCN, DCM, and $CHCl_3$. Functionalities such as CN, CO_2Et, Cl, and OMe are preserved. The OH group does not prevent the reduction.

Chart 5. Poly-η-(pyrazine)-zinc Borohydride



Preparation[64] $ZnBH_4$ + pyrazine in Et_2O

Azides checked[64]

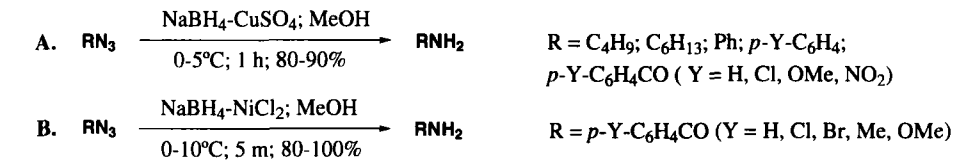


Reaction Conditions: in THF or Et_2O at room temperature

Comments: $Zn(BH_4)_2(PYZ)$ can be stored for months, does not reduce nitriles, oxiranes, oximes, esters, amides, halo- and nitro-compounds but reduces ketones, aldehydes, and acyl chlorides.

IV. REDUCTION BY HYDRIDES CATALYZED OR ASSISTED BY A METAL SALT

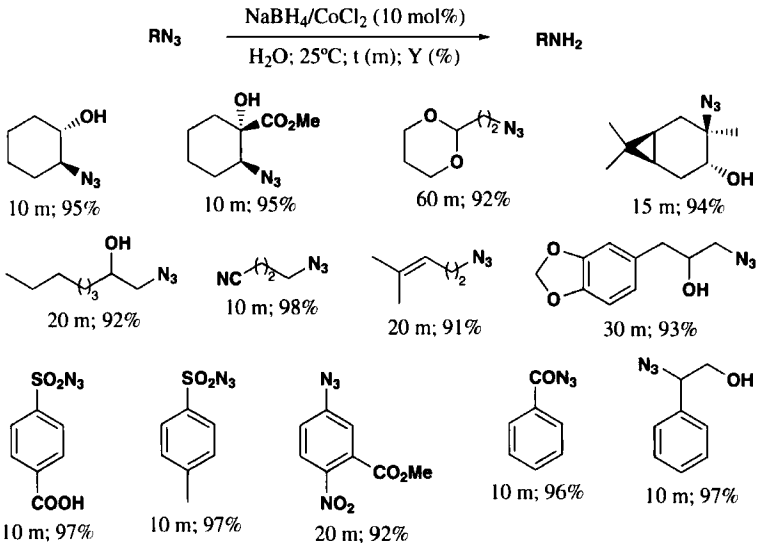
The reducing ability of $NaBH_4$ towards the azido groups is strongly increased when used in the presence of a salt such as $CuSO_4$, $NiCl_2$, $CoCl_2$, $Sn(1,2\text{-}S_2\text{-}C_6H_4)_2$ or $Ni(OAc)_2$. $NaBH_4$ with a catalytic amount of $CuSO_4$ (10 mol%) quickly and selectively reduces alkyl-, aryl-, and aroyl azides to amines and amides (*Scheme 19, A*).[67] $NiCl_2$ was, on the contrary, used in large excess (200 mol%) to reduce aroyl azides[68] (*Scheme 19, B*) giving benzamides, while by using only $NaBH_4$, benzyl alcohols were the major products.[50]



Reduction by $NaBH_4$ Catalyzed by $CuSO_4$ or $NiCl_2$

Scheme 19

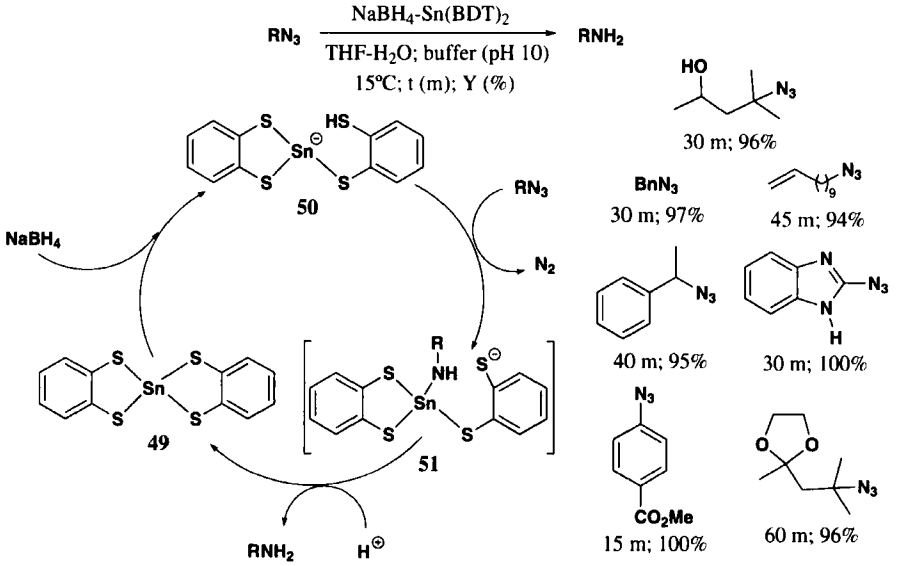
p-Nitrobenzoyl azide was barely reduced under these conditions, but by using a large excess of $NaBH_4$-$NiCl_2$ and sonication, methyl *p*-aminobenzoate was isolated in 72% yield. $NaBH_4$ in the presence of a catalytic amount of $CoCl_2$ (10 mol%), in aqueous medium only allows the N_3 group to be reduced to NH_2 in a large variety of aliphatic-, cycloaliphatic-, aryl-, aroyl-, and arylsulfonyl azides (*Scheme 20*).[69] When the azide is highly hydrophobic, the best results were achieved by carrying out the reaction in the presence of 10 mol% of cetyltrimethylammonium bromide (CTABr). This reducing system tolerates functionalities such as CO_2H, CO_2Me, OH, NO_2, CN, C=C and, after removing the reaction product by diethyl ether extraction of the aqueous reaction mixture, the mother liquors can be



Reduction by $NaBH_4$ Catalyzed by $CoCl_2$

Scheme 20

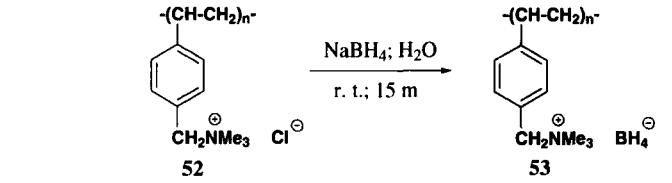
re-used at least five times. Tin (IV) *bis*-(1,2-benzenedithiolate) **49** [Sn(1,2-S_2-$C_6H_4)_2$; $Sn(BDT)_2$] in a catalytic amount (5-10 mol%) and $NaBH_4$ (0.67, 1.0 or 1.5 mol/eq) convert primary, secondary, tertiary, aromatic and heteroaromatic azides, in THF-H_2O solution, to amines in excellent yields under mild conditions (*Scheme 21*).[70] The control of the pH is important to achieve the best results. The reducing agent transfers a hydride ion to **49** producing the active species **50** which reduces the azide with extrusion of N_2. The intermediate **51** gives the amine and regenerates the catalyst **49** by protonation. At the end the catalyst can be recovered.



Reduction by $NaBH_4$ Catalyzed by $Sn(BDT)_2$

Scheme 21

Borohydride exchange resin (BER) **53** is an ammonium borohydride prepared by treating a chloride anion exchange resin **52** with aqueous $NaBH_4$. While $NaBH_4$ in MeOH rapidly decomposes in the presence of transition metal salts, BER **53** is much more stable.[71] BER **53** in the presence of a catalytic amount of $Ni(OAc)_2$ (10 mol%) [72] or $CuSO_4$ (10 mol%)[71] in methanol solution readily reduces aliphatic and aromatic azides at room temperature (*Scheme 22*). These reducing systems tolerate esters, chloro, acetal, nitrile, aliphatic oxiranes and tosylate functionalities whereas carbon-carbon multiple bonds, ketone and iodo groups were reduced.



52 **53**

RN_3 — $NaBH_4$-$Ni(OAc)_2$; MeOH; r. t.; 30 m; 92-96% → RNH_2 ; R = C_8H_{17}; Bn; $Me(CH_2)_4CHMe$; Cy; Et_2OCCH_2; $MeCOCH_2CMe_2$; EtO_2CCHMe; $Cl(CH_2)_3$; PhCHEt; Ph; *p*-Me-C_6H_4

RN_3 — BER **53**-$CuSO_4$; MeOH; 0-5°C; 1-6 h; 74-99% → RNH_2 ; R = C_8H_{17}; Bn; $Me(CH_2)_7CH{=}CH$; *p*-Cl-$C_6H_4CH_2$; Ph

Reduction by BER **53** Catalyzed by $Ni(OAc)_2$ or $CuSO_4$

Scheme 22

Tributyltin hydride in the presence of a catalytic amount of Ni-diphenylphosphinoethane dichloride (Ni-dppeCl_2) (2.5 mol%) reduces a variety of azides[73] (*Eq. 8*). Primary and secondary azides are reduced in good yields with the exception of alkylaryl azides. Tertiary azides are not affected. A three-step mechanism was proposed.

RN_3 — Bu_3SnH-(Ni-dppeCl_2); THF; 0°C; 16-95% → RNH_2 ; R = C_8H_{17}; $C_{10}H_{21}$; Cy; $PhCHCH_2Me$; $PhC(CH_2)_2$; 2-Th$(CH_2)_2$; Bn; *p*-tolyl (8)

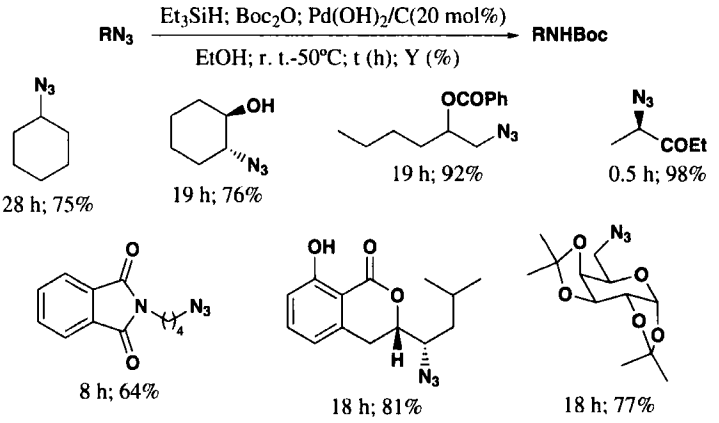
V. REDUCTION BY NON-METAL CONTAINING COMPOUNDS

Before the nineties, phosphorus- and sulfur-containing compounds, especially Ph_3P and H_2S-dithiol, were the non-hydrides and non-metal reducing agents commonly used to convert azides to amines.[2] Recently, phosphorus- and sulfur-modified compounds and silicon- and selenium-containing compounds have significantly improved this type of reduction.

1. Silicon Compounds

The reducing abilities of Et_3SiH, $PhSiH_3$ and polymethylhydrosilane were illustrated above (Section III, $SnCl_4/Et_3SiH$, Sn-Et_3SiH; Section IV, $Bu_3SnH/PhSiH_3$ or Bu_3SnH/PMHS). The combination of azide reduction and *N*-Boc-protection offers an efficient route to prepare *N*-protected amines. This strategy was investigated by Saito[18b] and Afonso[74] who used Pd/C-H_2O in the presence of di-*tert*-

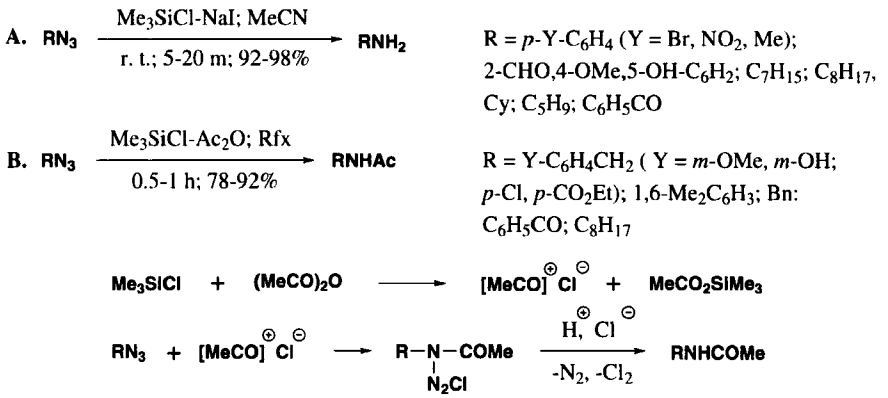
butyldicarbonate (Boc_2O) and n-Bu_3P with Boc_2O, respectively. More recently, Kotsuki[75] carried out the reductive transformation of azides to the corresponding *N*-Boc derivatives in the presence of a catalytic amount (20%) of $Pd(OH)_2$ on carbon, Degussa type, using Et_3SiH as reducing agent . The reaction proceeds chemoselectively at room temperature or 50° in EtOH. Some representative examples are illustrated in *Scheme 23.*



Reduction by Et_3SiH/Boc_2O with 20 mol% of Degussa $Pd(OH)_2/C$

Scheme 23

Iodotrimethylsilane, generated *in situ* from chlorotrimethylsilane and sodium iodide in MeCN, is an efficient reducing agent of alkyl-, aryl- and aroyl azides to give the corresponding primary amines and amides (*Scheme 24, A*).[76] The reaction is complete in a few minutes and aldehydes, nitro and halo functionalities are not affected and secondary alkyl azides are reduced in good yields.



Reduction by Me_3SiI or Me_3SiCl

Scheme 24

Chlorotrimethylsilylane combined with acetic anhydride is also an excellent reducing system for azides which are converted directly to *N*-acetylated amines (*Scheme 24, B*).[77] The proposed

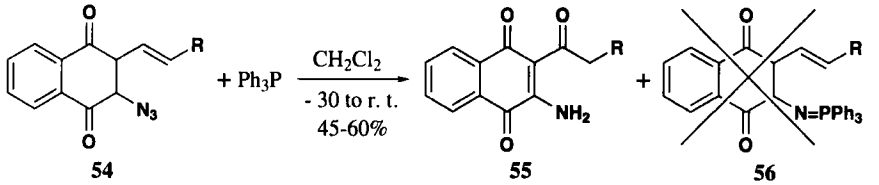
mechanism involves attack of acylonium ion on the electron rich nitrogen atom of the azide and N_2 and Cl_2 extrusion, proton and chloride assisted, from the intermediate diazochloride.

2. Phosphorus Compounds

The Staudinger reaction[2] is a mild, selective route to convert azides into amines that involves the use of triphenylphosphine. The iminophosphorane intermediate is then converted to amine by hydrolysis (*Eq. 9*). Various modifications have been reported and some unusual behavior

$$RN_3 + Ph_3P \longrightarrow RN{=}N{-}N{=}PPh_3 \xrightarrow{-N_2} RN{=}PPh_3 \xrightarrow{H_2O} RNH_2 + Ph_3PO \qquad (9)$$

observed. Thus when the 2-azido-3-vinyl-1,4-naphthoquinones **54** were treated with Ph_3P at -30° for 6 h and at room temperature for 12 h, 3-acyl-2-amino-1,4-naphthoquinones **55** were isolated instead of the expected iminophosphoranes **56** (*Eq. 10*).[78]



54 **55** **56** (10)

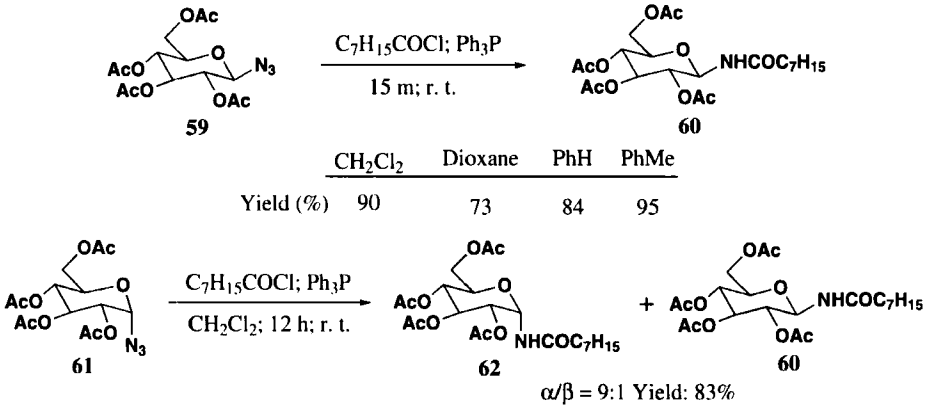
R = Me; Pr; Bn; Ph

The reaction of azides with trimethyl phosphite at room temperature in THF gives the iminophosphoranes **57** (*Eq. 11*) which in the presence of one equivalent of water give the phosphoramidates **58**.[79] The reaction is compatible with several functionalities including esters, thioesters and

$$RN_3 + (MeO)_3P \xrightarrow[12\ h;\ -N_2]{THF;\ r.\ t.} \underset{\mathbf{57}}{RN{=}P(OMe)_3} \xrightarrow[81\text{-}94\%]{H_2O} \underset{\mathbf{58}}{RNHP(O)(OMe)_2} + MeOH \qquad (11)$$

R = CH_2CO_2Me; $(CH_2)_2CO_2Et$; $(CH_2)_2SPh$; CH_2SMe; CH_2SPh; CH_2CN; $CH_2{=}CCO_2Me$; CH_2COMe; CH_2COPh

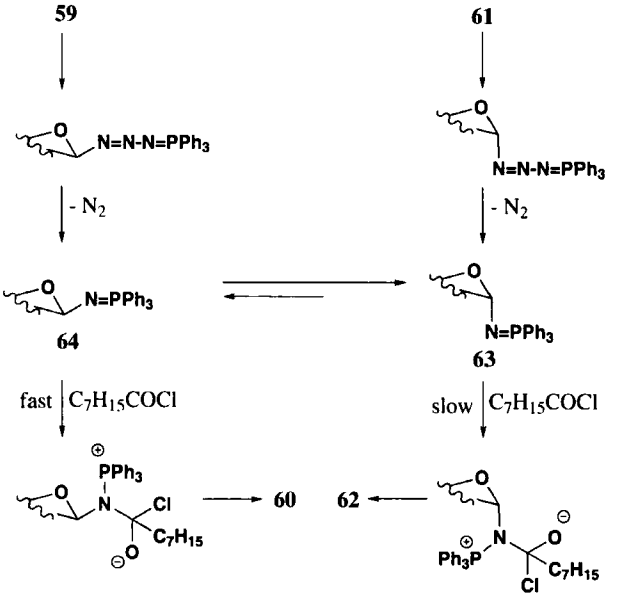
nitriles. The procedure allows methylthio- and phenylthiomethylamines protected as phosphoramidates to be prepared. A modified Staudinger reaction uses acyl chlorides and Ph_3P to synthesize amphiphilic glycosylamides from glycosyl azides without transient reduction to glycosylamines.[80] β-glycosyl azide **59** reacts with octanoyl chloride (2 equiv.) and Ph_3P (1.3 equiv.) stereoselectively affording β-glycosyl amide **60** at room temperature in high yield. The reaction is immediate as indicated by an instantaneous N_2 evolution and concomitant appearance of Ph_3PO; the yield depends on the solvent (*Scheme 25*). The reaction was extended to other acyl chlorides and β-glycosyl azides. α-Glycosyl azides react more slowly than the corresponding β-anomers and give mixtures of α- and β-glycosylamides. Thus the α-anomer **61** affords a 9:1 α/β mixture of glycosylamides **62** and **60**. A



Reduction of β-Glycosyl Azides **59** and **61** by Ph_3P and Octanoyl Chloride.

Scheme 25

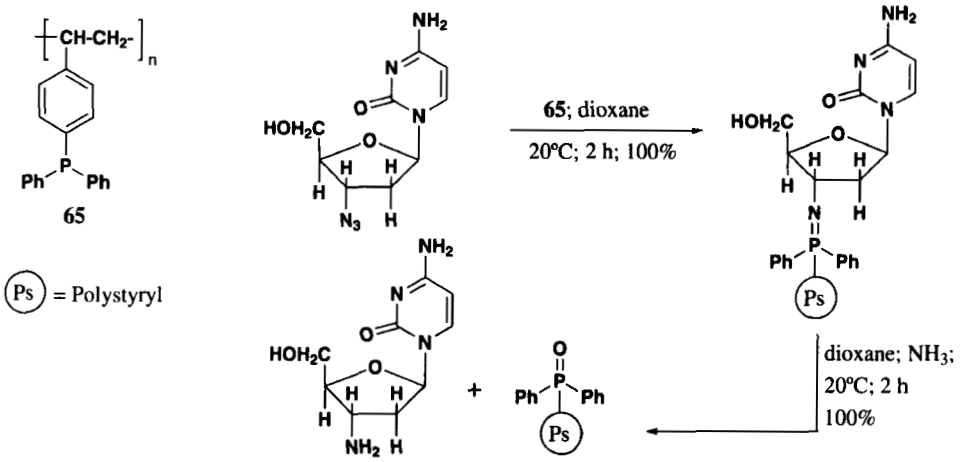
tentative explanation is illustrated in *Scheme 26*.[80] The α-phosphazene **63** is the thermodynamically favored anomer but the β-anomer **64** reacts faster.



Mechanism for the formation of the β-anomer **60** from α-anomer **61**

Scheme 26

Holletz and Cech[81] modified the classic Staudinger procedure by replacing Ph_3P with a polymer-supported triarylphosphine. The commercial polystyryl diphenylphosphine resin **65** was used to reduce azidonucleosides to amines. An example is illustrated in *Scheme 27*. The most important feature of this procedure is that only filtration and evaporation are required to isolate the product.

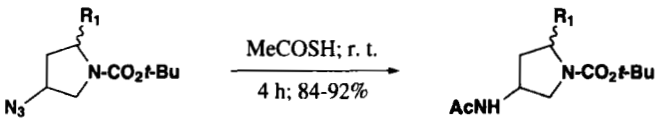


Reduction of Nucleosylazides by Phosphine-Supported Resin **65**

Scheme 27

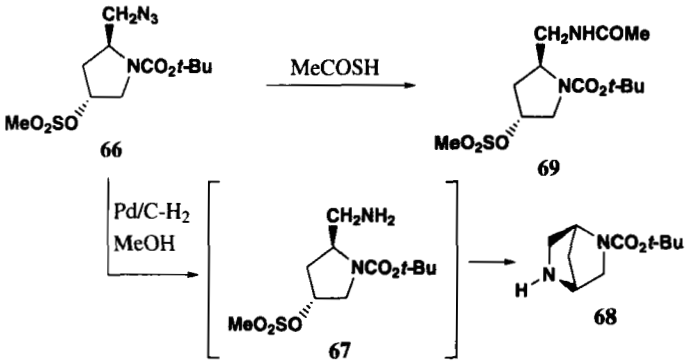
3. Sulfur Compounds

Reductive acetylation of azides was performed by using thiolacetic acid at room temperature.[82] Several functional groups are stable under the conditions required for this protocol. The procedure is particularly useful when the incipient amine, derived from the reduction process, can react inter- or intramolecularly with another functional group (*Eq. 12*).



R_1 = H, Me, CO_2Me (12)

Thiolacetic acid acetylates the amino group very rapidly, preventing undesired reactions. This is the case with azide **66**. When it is reduced by Pd/C-H_2, it gives the bicyclic secondary amine product **68** as a result of the intramolecular cyclization of the incipient primary amine **67**, whereas the thiolacetic acid treatment affords the acetamido mesylate **69** (*Scheme 28*). The process is probably

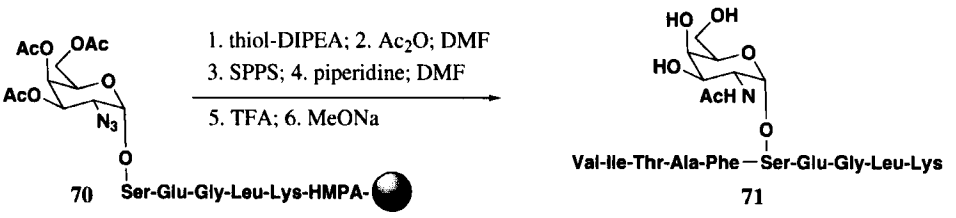


Reduction of Azide **66** by Treatment with MeCOSH and Pd/C-H_2

Scheme 28

initiated by traces of H_2S present in thioacetic acid (H_2S is known to reduce azides[2, 83]) and then the necessary H_2S is generated by the acetylation process.

Various thiolytic reagents with diisopropylethylamine (DIPEA) as catalyst have been investigated for the reduction of azidoglycopeptide **70** with subsequent acetylation in the solid phase peptide synthesis (SPPS) of **71** (*Scheme 29*).[15]



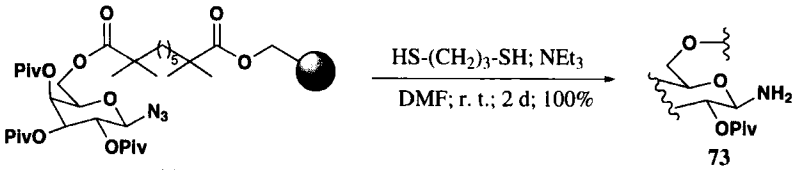
thiol	DTT	MCA	BME	PDT
Yield (%)	99	98	65	15

DTT = dithiothreitol; BME = β-mercaptoethanol; MCA = *N*-methyl-α-mercaptoacetamide; PDT = propane-1,3-dithiol

Reduction of Azidoglycopeptide **70** by Various Thiolytic Reagents

Scheme 29

Another example of solid-phase thiolytic reduction of the azido group is the conversion of polymer-linked galactosyl azide **72** to the corresponding amine **73** by using propane-1,3-dithiol and triethylamine in DMF (*Eq. 13*).[84] The reduction is quantitative and proceeds without anomerization.

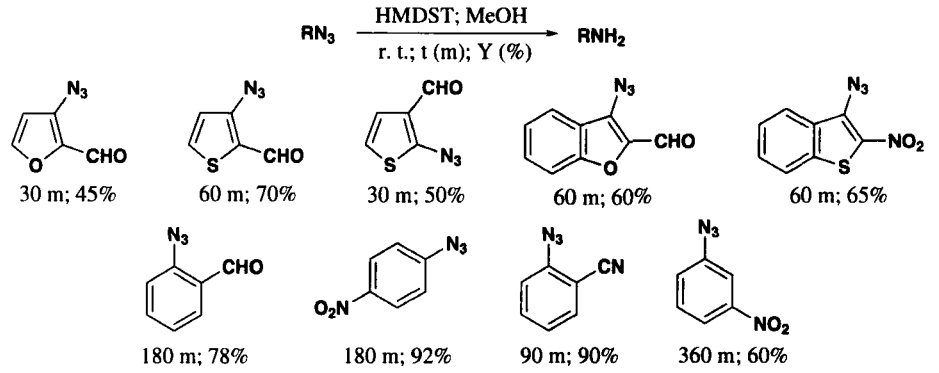


72 **73** (13)

Piv = Pivaloyl

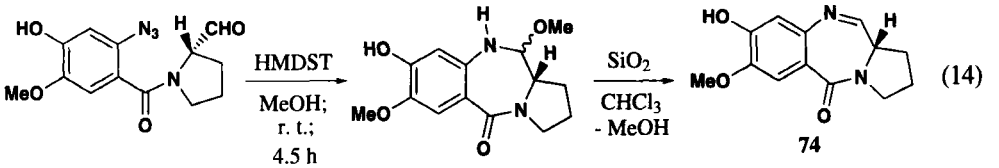
The reduction with complex hydrides was not successful and under Staudinger conditions extended anomerization was observed. Hexamethyldisilathiane ($Me_3SiS_2SiMe_3$; HMDST) reduces aryl- and heteroaryl azides provided that the azido group is properly activated.[85] *Scheme 30* illustrates some examples.

HMDST has also been successfully used for the formation of a seven-membered ring through an azido reduction cyclization process to synthesize the pyrrolo[2,1-c][1,4]benzodiazepine ring system.[86] An example is the synthesis of the natural product DC-81 (**74**) (*Eq. 14*). Interestingly, the cyclization step of the diazepine ring formation occurs with retention of configuration of the stereogenic center, whereas epimerization was found[87] when the reaction was performed under acidic conditions.



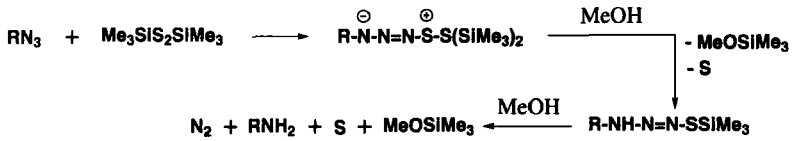
Reduction of Aryl- and Heteroaryl Azides by HMDST

Scheme 30



(14)

The HMDST azide-reduction process is formally equivalent to the Staudinger reaction. The nucleophilic attack of the HMDST sulfur atom at the terminal azido nitrogen is followed by desilylation by methanol and sulfur and nitrogen extrusion (*Eq. 15*).[85] The formation of an imino sulfurane with nitrogen extrusion before the desilylation cannot be excluded.[88] The possibility that the reducing species is H_2S, generated by HMDST, was experimentally excluded.[86]

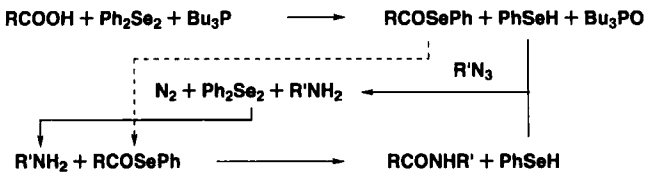


(15)

4. Selenium Compounds

As mentioned above, the reduction of azide in the presence of an activated carboxylic component results in the formation of an amide. If the reducing agent is continuously regenerated, the process is catalytic and if *N*-protected carboxy activated amino acids are used, a *one-pot* approach to peptide synthesis can be developed.

Mamdapur,[89] Ghosh[90] et al. developed this strategy to synthesize amides and peptides by activating the carboxy function with Ph_2Se_2/Bu_3P and generating the selenophenyl ester and selenophenol at r. t. (*Eq. 16*). The azido group is reduced by PhSeH to amine which condenses with the active selenophenyl ester to give the desired amide or peptide and selenophenol which reacts again with azide repeating the sequence. This *one-pot* peptide synthesis is regulated by two redox reactions.



(16)

Using this methodology various peptides were synthesized with high yields and high optical purities. *Table 3* illustrates some examples.

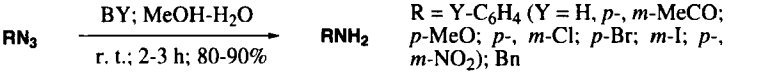
Table 3. *One-pot* Synthesis *via* a Double Redox Reduction Cycle

RCOOH	$R'N_3$	Solvent	Peptide	Yield (%)
Bz-Leu	$N_3CH_2CO_2Et$	CH_2Cl_2	Bz-Leu-Gly-OEt	93
Z-Gly-Phe	$N_3CH_2CO_2Et$	CH_2Cl_2	Z-Gly-Phe-Gly-OEt	91
Ac-Phe	(L)-$N_3CH(Me)CO_2Et$	CH_2Cl_2	Ac-Phe-Ala-OEt	80
Boc-Tyr	N_3CH_2CO-Gly-Phe-Met-OMe	MeCN	Boc-Tyr-Gly-Gly-Phe-Met-OMe	88

VI. BIOCATALYTIC REDUCTION

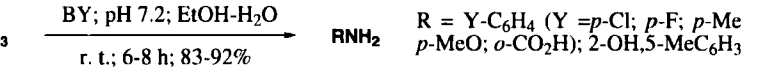
In recent years there has been a growing interest in biocatalytic processes, particularly those devoted to transformations mediated by Baker's yeast.[91] This catalytic reductive methodology is exceptionally mild and is a convenient route to convert azides to amines.

The first example of a Baker's yeast (BY)-mediated reduction of organic azides was reported by Sandhu in 1996.[92] Some representative examples are given in *Eq. 17* and additional ones



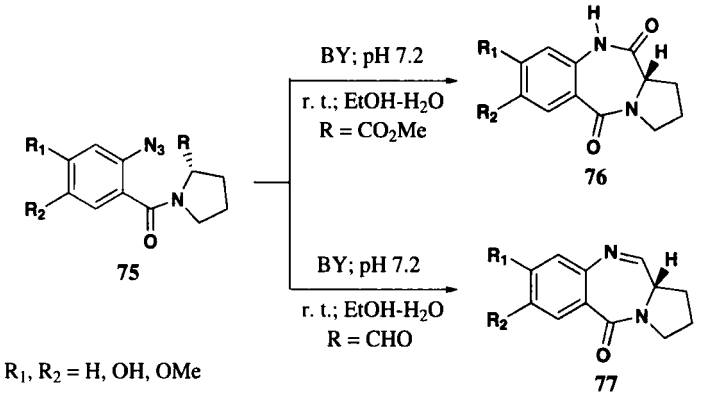
(17)

were described at almost the same time by Kamal[93] (*Eq. 18*). The Baker's yeast reduction is chemoselective towards the azido group in the presence of aromatic halides, methoxy, carboxylic, nitro and aryl acetyl groups, however the phenolic functionality interferes.[92, 93]



(18)

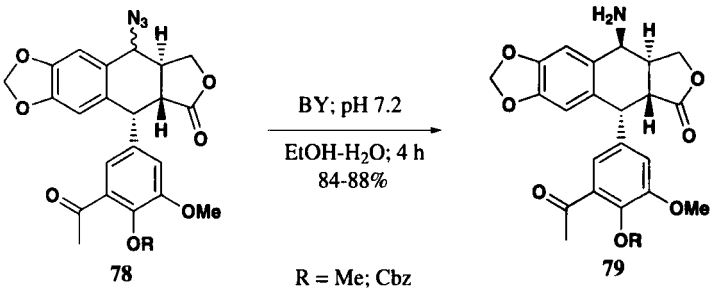
A synthetic application of this protocol is the reductive cyclization of azidoaldehydes and azidocarboxylates in the course of chemoenzymatic synthesis of DNA-binding pyrrolo[2,1-c][1,4]benzodiazepine (PBD) (*Scheme 31*).[93] The azido derivatives **75** by reduction with Baker's yeast gave quantitatively PBD **76** and **77**.



Synthesis of PBD *via* Baker's Yeast Reduction

Scheme 31

The biocatalytic reduction of azides **78** employing Baker's yeast, was also used to synthesize 4β-aminopodophyllotoxin congeners **79** (*Eq. 19*).[94] The process is highly stereoselective affording 4β-aminocompounds **79** either from α- or β-azides **78**. This may result from the isomerization of the amine functionality *via* Schiff's base formation in the presence of oxido-reductase in the yeast.



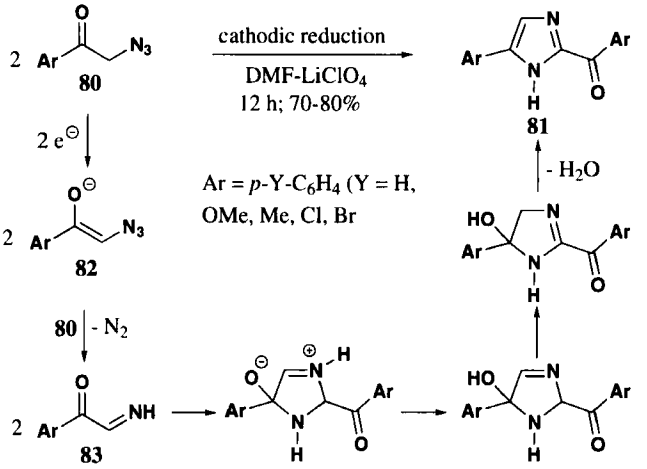
(19)

The azido group of various organic azides, e.g. α-ketoazides, is resistant to biocatalytic reduction while the keto function is more reactive. This allows optically active *syn* and *anti* α-hydroxyazides to be prepared by using reducing biocatalysts.[18c, 95] Recently the same reaction was successfully performed in THF *via in situ* generated oxazaborolidine-borane complex.[96]

VII. ELECTROCHEMICAL REDUCTION

As part of a study of carbene and nitrene anion radicals, the preparation of an arylnitrene anion radical in the condensed phase was investigated by electrochemical reduction of *p*-nitrophenyl azide in DMF, MeCN and *n*-PrCN.[97] The transformation begins with a one-electron transfer process that affords p–NO_2-$C_6H_4N_3^{\bullet-}$ which is too short-lived to be observed and decomposes, with nitrogen extrusion, giving the nitrene anion radical p-NO_2-$C_6H_4N^{\bullet-}$ which rapidly dimerizes to 4,4'[O_2N-C_6H_4N=NC_6H_4-NO_2]$^{2-}$. The electrochemical reduction of p-NO_2-$C_6H_4N_3$ in the presence of $(CF_3)_2CHOH$ is a two-electron process that produces N_2 and p-NO_2-$C_6H_4NH_2$ while the diazoalkane $(EtO_2C)_2C{=}N_2$ is produced in high yield, when the process is carried out in the presence of diethyl malonate.

The electrochemical reduction of phenacyl azides **80** (*Scheme 32*) in a DMF-$LiClO_4$ medium at a mercury cathode in a divided cell under controlled potential, gives 2-aroyl-4(5-)arylimidazoles **81** in 70-80% yield.[98] The fundamental steps of these processes are the formation of enolates **82**, the self-condensation of aryl glyoxaldimines **83**, and subsequent dehydration.



Electrochemical Reduction of Aroyl Azides

Scheme 32

VIII. CONCLUSION

The stability of the azido group under oxidative conditions makes it a good, versatile candidate as an amino protective group for a multi-step synthetic sequence, particularly for peptide synthesis. Therefore, interest in new procedures for azide synthesis and for reactions of the azido group is not surprising. The reduction of azides is of particular interest because it is an important chemical process from a synthetic point of view. New reagents, new protocols, the improvement of existing procedures and the development of solid-phase azide chemistry are expected in the future.

IX. SELECTED EXPERIMENTAL PROCEDURES

CAUTION: ***All azides are potentially explosive and extreme caution must be exercized in their handling.***

Reduction with In/NH_4Cl[19].- Indium powder (1.0 mmol) and NH_4Cl (1.0 mmol) were added to a solution of (S)-1-azido-2-*N*-*t*-butoxycarbonylamino-4-methyl-pentane (1.0 mmol) in ethanol (3 mL). The resulting reaction mixture was heated at reflux with constant stirring (1 h). The final mixture was cooled to room temperature, diluted with ethyl acetate (5 mL), stirred for 10 min and passed through a short pad of celite to give a clear solution. Removal of solvent under reduced pressure gave the (S)-1-amino-2-*N*-*t*-butoxycarbonylamino-4-methyl-pentane in pure form with 96% yield.

Reduction with Zn-$FeCl_3$[22].- To a mixture of ferric chloride (1.0 mmol) and zinc powder (1.0 mmol) in a round bottom flask was added a solution of cinnamoyl azide (1.0 mmol) in ethanol (25 mL) drop-

wise with constant stirring at 0°. The reaction mixture was brought to room temperature and stirring was continued for 4.5 h. The metal was filtered off and the filtrate was concentrated and extracted with chloroform (2 x 30 mL). The extract was washed with water and brine and dried over Na_2SO_4. The organic layers were distilled off under reduced pressure to get the crude amide which was further purified by column chromatography using chloroform as eluent. The pure cinnamamide was obtained in 86% yield.

Reduction with SmI_2[30].- A carefully degassed solution of *p*-methoxyphenyl azide (1.0 mmol) in anhydrous THF (10 mL) was treated, under nitrogen, with 30 mL of a commercial 0.1 M solution of SmI_2 in THF. The resulting mixture was stirred at room temperature for 1.66 h, and then was hydrolyzed with water and some 5% aqueous sodium carbonate. Extraction with diethyl ether, removal of the solvent and column chromatography gave pure *p*-methoxyaniline in 95% yield.

Reduction with Sn(S-2-Py)$_3^-$ Complex[39].- To a stirred solution of anhydrous $SnCl_2$ (1.5 mmol), in 10 mL of acetonitrile at room temperature, 2-mercaptopyridine (6 mmol), Et_3N (4.5 mmol) and benzyl azide (1.0 mmol) were added in sequence. After 2 h the solvent is evaporated under reduced pressure and then 25 mL of 2 N NaOH and 25 mL of dichloromethane are added. Separation of the two phases, extraction of the aqueous layer twice more with dichloromethane, drying of the organic solutions, and evaporation of the solvent afforded benzylamine nearly quantitatively.

Reduction with $FeSO_4$•$7H_2O$/NH_3[44].- To a stirred solution of toluensulphonyl azide (1.0 mmol) in dichloromethane (10 mL), $FeSO_4 \cdot 7H_2O$ (5 mmol) and 25% ammonia solution (1 mL) were added. The reaction mixture was stirred at room temperature for 3 h. The final mixture was diluted with dichloromethane and filtered through a pad of celite. The filtrate was washed with water. The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel to afford pure toluenesulfonamide in 90% yield.

Reduction with $Ca(BH_2S_3)_2$[55].- To a suspension of $Ca(BH_2S_3)_2$ (1.5 mmol) in dry THF (10 mL) was added *p*-nitrophenyl azide (1.0 mmol) in THF (5 mL) and the mixture was stirred under reflux conditions for 0.7 h. The solvent was evaporated under reduced pressure at room temperature. The residue was then treated with a 10% ethereal solution of HCl (15 mL) to pH 1. The precipitate sulfur was filtered off and the filtrate was extracted repeatedly with diethyl ether (15 mL) and the combined extracts were dried over anhydrous Na_2SO_4 and evaporated to give the corresponding crude *p*-nitroaniline in 86% yield.

Reduction with $BHCl_2$•SMe_2[56].- A dry 5-mL flask equipped with a magnetic stirring bar, septum inlet and reflux condenser was charged with 1.5 mL (1.5 mmol) of a one molar dichloromethane solution of $BHCl_2$•SMe_2. The reaction flask was connected to a gas buret through a dry ice-acetone trap to measure the evolved nitrogen. To this, 1-azidoadamantane (1.0 mmol) was added in 7-8 min at room temperature. The reaction was monitored by the nitrogen evolved in the reduction (no hydrogen is evolved). In this time the reaction is ~75% complete as indicated by the nitrogen evolved. The reaction mixture was then refluxed for one hour in order to achieve a complete reduction in a reasonably short period of time. The solvent was removed from the reaction mixture under vacuum and the inter-

mediate was hydrolyzed with conc. hydrochloric acid by heating at 80° for 0.6 h. The reaction mixture was then cooled to room temperature, made strongly alkaline with aqueous potassium hydroxide and was extracted with diethyl ether (3 x 15 mL). The combined organic extracts were washed with water, brine, and dried over anhydrous magnesium sulfate. Removal of the solvent gave the 1-adamantanamine in 75% isolated yield.

Reduction with $NaBH_4/CoCl_2{\cdot}6H_2O$[69].- To a mixture of *trans*-2-azidocyclohexanol (1.0 mmol) and $CoCl_2{\cdot}6H_2O$ (0.1 mmol) at 25° was added dropwise under stirring a solution of $NaBH_4$ (2.0 mmol) in water (2 mL). The formation of a black precipitate indicated the formation of a cobalt boride species. The final mixture was stirred at 25° for 10 min and then extracted with diethyl ether (5 x 10 mL). The organic phase, dried (Na_2SO_4) and concentrated under reduced pressure, gave the pure *trans*-2-aminocyclohexanol with 95% yield.

Re-use of Cobalt Boride.- The pH of remaining mother liquors (ca. 2 mL) was adjusted to 8.0 by adding a few drops of concentrated HCl. *trans*-2-Azidocyclohexanol (1.0 mmol) was then added, followed by powdered $NaBH_4$ (2.0 mmol) in small doses. The mixture was stirred at 25° for 10 min. and then extracted with diethyl ether. The mother liquors could continue to be reused.

Reduction with Me_3SiI[76].- To a solution of 1-heptyl azide (1.0 mmol) in acetonitrile (10 mL), sodium iodide (1.5 mmol) was added and the resulting mixture was stirred for 5 minutes, then a solution of chlorotrimethylsilane (1.5 mmol) in acetonitrile (2 mL) was added dropwise and stirring continued for another 10 minutes. The reaction mixture was quenched with 10% sodium thiosulphate solution and it was extracted with ethyl acetate (20 mL). The organic layer was washed with brine solution, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue purified by column chromatography afforded the corresponding pure 1-heptylamine in 92% yield.

Reduction with polymer bound triphenylphosphine[81].- Polystyryl diphenylphosphine resin (0.33 g, loaded with ca. 3.0 mmol PPh_3/g resin) was suspended in anhydrous dioxane (5 mL) and 1-[*trans*-3'-azido-2'-hydroxymethyl-tetrahydrofuran-5'-yl]-2,4-(1*H*,3*H*)-pyrimidinedione (200 μmol) was added. The suspension was slightly shaken for 2 h at room temperature. After that time concentrated ammonia (4 mL, 32 %) was added. After shaking for another 2 h, the suspension was filtered and the residual solid was washed with H_2O (3 x 10 mL). The solution was filtered and lyophilised to give 1-[*trans*-3'-amino-2'-hydroxymethyltetrahydrofuran-5'-yl]-2,4-(1H,3H)-pyrimidinedione as a white powder in almost quantitative yield.

Reduction with HMDST[85].- A solution of 3-azido-2-formylthiophene (1 mmol) in methanol (10 mL) was treated with hexamethyldisilathiane (2.0 mmol) and then stirred at room temperature for 1 h. The mixture was diluted with dichloromethane, washed with saturated $NaHCO_3$, dried, and evaporated. Purification of the residue by column chromatography on silica gel gave the pure 3-amino-2-formylthiophene in 70% yield.

Reduction with Baker's yeast[92].- To a suspension of commercial baker's yeast (5 g) in water (15 mL), vigorously stirred at room temperature, a solution of *p*-chlorophenyl azide (1.0 mmol) in methanol (6 mL) was added. This reaction mixture was further stirred for 3 h and dichloromethane

(7.5 mL) was added. After the phases were separated, the organic layer was filtered through a celite pad, washed, dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give pure *p*-chloroaniline in 90% yield.

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