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N-*TERT*-BUTYLDIMETHYLSILYL IMINES AS INTERMEDIATES FOR THE SYNTHESIS OF AMINES AND KETONES

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Abstract: *Grignard reagents add to benzonitrile at low temperature catalyzed by CuBr and TBSCl affording N-TBS ketimines, which were investigated as intermediaries for the synthesis of primary amines and ketones. N-silylimines were easily obtained by an organolithium addition to benzonitrile followed by a reaction with TBSCl in CH_2Cl_2. In situ reduction of these imines by BH_3 and 1,3,2-oxazaborolidines **1** or **2** as chiral templates afforded the corresponding amines with modest to good enantiomeric excess.*

Amines are established as useful synthetic precursors, as well as important intermediates for the synthesis of pharmacologically active compounds.[1] Although the asymmetric reduction of *N*-substituted imines has been successfully achieved using a variety of methods,[2] the facile preparation of optically active primary amines by the reduction of suitable imino analogs remains one of the most desired transformation.

As part of our research effort in developing new methods for the synthesis of chiral primary amines with biological activity, we became interested in the synthesis and reduction of *N*-trialkylsilyl arylalkylketimines. The well known *N*-trimethylsilylaldimines were first prepared by Rochow and coworkers,[3] and later by Hart *et al.*,[4] by reacting aldehydes with lithium bis(trimethylsilyl)amide. *N*-

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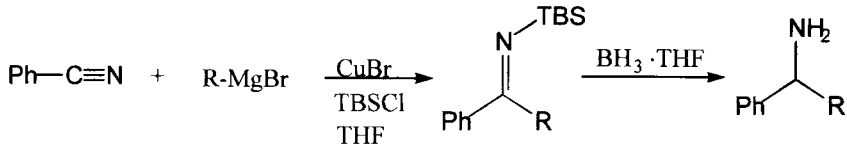
trimethylsilylaldimines have been widely used in the synthesis of primary amines,[5,6,7] β-aminoalcohols,[8] azetidinones, [9,10] and heterocyclic compounds. [11,12] However, the study of the corresponding *N*-trimetylsilylketimines as amine precursors, has been limited.[13]



Initially, it was our interest to investigate the preparation of *N*-silyl-substituted aromatic ketimines as intermediates in the synthesis of racemic phenylalkylamines. The reaction of ethyl magnesium bromide with benzonitrile in the presence of 1.8% molar CuBr[14,15] and one molar equivalent of trimethyl chlorosilane,[16] was studied at low temperature (-78→10°C) following the reaction progress by an infrared analysis. After two hours at -20°C, the C=N (silylimine) band appeared at 1640 cm^{-1}, and the C=C (N-silylenamine) band at 1610 cm^{-1} was also observed at 0°C. The *in situ* reduction of the *N*-silylimine-enamine mixture with two equivalents of BH_3•THF, afforded 18% yield of 1-phenylpropyl amine. Colvin and coworkers studied the effect of the bulkier *tert*-butyldimethylsilyl (TBS) group on the synthesis and stability of silylaldimines.[17] We observed a slower enamine formation with the TBS moiety, allowing a successful reduction of the imines of 1-phenylpropanone and 1-phenylpentanone, as shown in table 1. However, larger substituents on the imine carbon, such as isobutyl, favored the isomerization, and as a result, it decreased the primary amine yield.

A more effective approach for the phenylalkylamines synthesis, was the addition of an organolithium reagent to benzonitrile, and a subsequent reaction with a chlorosilane to produce the corresponding *N*-silylimines. Reduction of these intermediates gave the desired phenylalkylamines in good yield.

Our previous studies encouraged us to investigate the enantioselective reduction of the *N*-silylimines, using as chiral reagents the borane complex of 1,3,2-

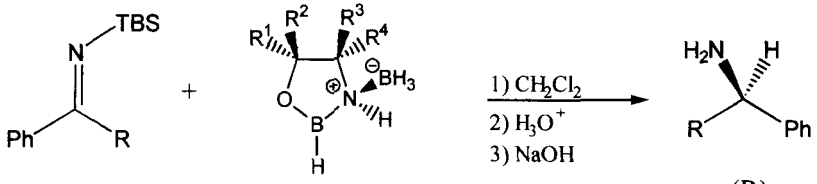
Table 1 Synthesis of Racemic Phenylalkylamines

Entry	RM/ Reaction Conditions	Red. Conditions	%Amine[a]
1	EtMgBr, Me_3SiCl/ CuBr/ THF/ -78°C → 0°C	0°C → 25°C	18%[b]
2	EtMgBr, t-BuMe_2SiCl/ CuBr, THF/ -78°C→25°C	0°C → 25°C	55%[b]
3	n-BuMgCl, t-BuMe_2SiCl/ CuBr/ THF/-78°C → 0°C	0°C →25°C	53%[c]
4	i-BuMgCl, t-BuMe_2SiCl/ CuBr, THF/-78°C → -5°C	0°C → 25°C	19%[c]
5	MeLi/ Hexane/-78°C → 25°C	-78°C → 25°C	60%[b]
6	n-BuLi/ Hexane/-78°C → 25°C	-78°C → 25°C	88%[b]
7	a) n-BuLi/-78°C →25°C b) t-BuMe_2SiCl/THF/-78°C →-10°C	-60°C → 25°C	73%[b]

[a] *Isolated and characterized by ^1H NMR, ^{13}C NMR, GC/MS and FT-IR.* [b] *Purified by distillation.* [c] *Purified by column chromatography.*

oxazaborolidines derived from (+) and (-) norephedrine, (**1**),[18] and (S)-2-amino-1,1,2-triphenylethanol, (**2**).[19] Table 2 summarize our preliminary results. In the first experiment, we added a THF solution of benzonitrile, TMSCl and a catalytic amount of CuBr to n-BuLi at low temperature, followed by the reduction of the *N*-TMS ketimine with **1** in THF. Although the chemical yield was high, the enantiomeric excess for the 1-phenylpentylamine was low. Using TBS as substituent, and the procedure for the preparation of **1** by Itsuno's method,[21] did not improve the enantioselectivity (entries 2-4) The method was additionally modified by adding TBSCl to the imine lithium salt at -10°C in dichloromethane, followed by reduction with the borane complex of 1,3,2-oxazaborolidines **1** and **2**, obtaining a moderate to good enantiomeric excess for the 1-phenylethylamine. Further studies are in progress, since we believe that this methodology is simple and valuable for the enantioselective synthesis of primary amines.

Addition of Grignard reagents to nitriles to form ketimines, followed by strong acid hydrolysis, has been an established method for the synthesis of ketones.[23]



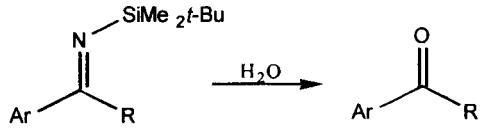
(-) **1**: $R^1 = H$, $R^2 = Ph$
$R^3 = H$, $R^4 = Me$
(S) **2**: $R^1 = R^2 = R^4 = Ph$
$R^3 = H$

Table 2 Synthesis of Chiral 1-Phenylalkylamines

Entry	R	Silylimine Method	Chiral Agent/ Reaction Conditions	Y[a] %	Ee %	Cof.
1	Bu	TMSCl, CuBr; THF; -78°C→-10°C, 3h	(+)-**1**[b] / THF, -78°C, 24 h	77	13[c]	S
2	Bu	TBSCl, CuBr, THF; -78°C→0°C, 1h	(+)-**1**[d]/THF, -78°C→25°C, 24 h	44	15[c]	S
3	Bu	TBSCl, CuBr, THF; -78°C, 2h	(+)-**1**[b] / THF, -78°C, 24 h	72	13[c]	S
4	Bu	TBSCl, CuBr, THF; -78°C→0°C, 1 h	(-)-**1**[b] / THF, -78°C→25°C, 48 h	78	16[c]	R
5	Me	a)-78°C→-10°C/ CH_2Cl_2 b)TBSCl, -10°C, 7 min	(-)-**1**[b] / CH_2Cl_2, -10°C, 5 h	37	39[e]	R
6	Me	a)-15°C→-10°C/ CH_2Cl_2 b)TBSCl/ -10°C, 7 min	(+)-**1**[b] / CH_2Cl_2, -10°C, 15 h	71[f]	50[e]	S
7	Me	a)-40°C→-10°C/ CH_2Cl_2 b)TBSCl /-10°C, 5 min	(S)-**2**[b] / CH_2Cl_2, -10°C, 15 h	33	79[e]	R

[a] *Isolated yield by column chromatography.* [b] *Prepared by Corey's Method.*[20] [c] *By GC using the α-methoxy phenylacetamide derivative.* [d] *Prepared by Itsuno's Method.*[21] [e] *By HPLC of the α-methoxyacetamide derivative.*[22] [f] *Purified by fractional distillation.*

However, the reaction is unsatisfactory because of the harsh conditions required, such as refluxing in high boiling solvents for long periods, and due to the formation of complex mixtures of cyclic triazines and polymeric materials.[24] Trace amounts of copper(I) salts were found to catalyze the otherwise sluggish alkylation of benzonitrile with a Grignard reagent,[14] improving substantially the yield of hindered ketones.[15]



The TBSCl promoted nucleofilic addition of ethylmagnesium bromide to benzonitrile in the presence of 1.8% molar CuBr at low temperature, and the high purity of propiophenone obtained *via* the *N*-silyl imine hydrolysis on silica gel, prompted us to investigate this metodology for the synthesis of aromatic ketones. Table 3 illustrates various examples in which aromatic ketones were prepared in quantitative yield.

In summary, we have investigated new procedures for the synthesis of *N*-TBS ketimines from nitriles that we believe are useful for the preparation of aromatic ketones and primary phenylalkylamines. More important, we unfolded a new enantioselective procedure for the direct synthesis of chiral primary amines.

Experimental

General Procedure for Racemic Phenylalkylamines Synthesis using a Grignard Reagent, *1-Phenylpropylamine*: To a solution of ethyl magnesium bromide (45 mmol) in THF (40 mL) at -78 °C, prepared by the reaction of magnesium (1.22 g, 50 mmol) and ethyl bromide (3.35 mL, 45 mmol), a mixture of copper bromide (0.1g, 0.70 mmol), benzonitrile (4.08 mL, 40 mmol), and TBSCl (6.03 g, 40 mmol) in THF (20 mL) was added dropwise. The reaction mixture was allowed to warm at 0 °C and stirred until no nitrile was detected by infrared analysis. A borane·THF solution (40

Table 3 Synthesis of Aromatic Ketones

Entry	Ar	R	Yield(%)[a,b]
1	Ph	CH_3	90
2	Ph	CH_3-CH_2	82[c]
3	Ph	$CH_3(-CH_2)_3$	85
4	Ph	$(CH_3)_2CH$-CH_2	70
5	Ph	CH_3-CH_2-$CH(CH_3)$	80
6	Ph	Ph	97
7	$CH_3OC_6H_4$	CH_3-$(CH_2)_3$	84

[a] *Isolated yield of pure products obtained by column chromatography on silica using hexane-ethyl acetate.* [b] *All the ketones were fully characterized by ^1H NMR, ^{13}C NMR, GC/MS and FT-IR.*

mL, 2 M, 80 mmol) was then added to the reaction mixture at -10°C, and the resulting solution was stirred for 24 h at room temperature. Distilled water (10 mL) was cautiously added to the solution cooled at -20°C, followed by HCl (20 mL, 6 M). After the THF was rotoevaporated at 60°C, the aqueous phase was extracted with diethyl ether (two x 30 mL), and the ether extracts were washed with HCl (20 mL, 6 M). The combined aqueous phases were basified with NaOH (6 M), and extracted with ether (3 x 40 mL). The ether extracts were washed with brine, dried and concentrated *in vacuo* to leave *1-phenylpropylamine* as a light yellow oil. Purification by vacuum distillation at 40°C / 1.2 mm Hg gave a colorless oil (2.97 g, 55%): IR(neat/ cm^{-1}) 3363, 3288, 3025, 2961, 2873, 1602, 1491, 1452, 1373, 761, 700; MS (70 eV) m/z 130.15 (M^+-H, 4%), 106.25 (M^+-C_2H_5, 100%); ^{13}C NMR($CDCl_3$ / TMS / 300 MHz) δ ppm 10.21, 31.66, 57.03, 125.69, 126.08, 127.61, 127.73, 146.0; ^1H NMR δ: 7.01 (5H, m, Ph), 3.64 (1H, t, CHN), 1.78 (1H, s, NH_2), 1.56 (2H, m, CH_2), 1.30 (2H, m, CH_2), 0.68 (3H, s, Me).

General Procedure for Racemic Phenylalkylamines Synthesis using an Organolithium Reagent, *1-Phenylpentylamine*: To a solution of n-butyllithium (27 mL, 0.61 M, 16.5 mmol) in hexane at -78°C, benzonitrile (1.7 mL, 15 mmol) was

added dropwise. After 1 h the solution was allowed to warm at room temperature and an IR analysis showed the absence of the nitrile band. To the solution cooled at -10°C was added TBSCl (2.3 g, 15 mmol) in THF (10 mL). The reaction mixture was stirred until a strong silylimine band was detected at 1649 cm^{-1} by infrared analysis. A borane·THF solution (30 mL, 2 M, 60 mmol) was then added to the reaction mixture at -60°C, and the resulting solution was stirred for 4 h and allowed to warm at room temperature overnight. Distilled water (10 mL) was cautiously added to the solution cooled at -20°C, followed by HCl (10 mL, 12 M). After the THF was rotoevaporated at 60°C, the aqueous phase was extracted with diethyl ether (3 x 20 mL), and the organic phase was washed with HCl (20 mL, 6 M). The combined aqueous phases were strongly basified with NaOH (6 M), and extracted with diethylether (4 x 20 mL). The organic extract was washed with brine, dried over $MgSO_4$ and then concentrated *in vacuo* to leave *1-phenylpentylamine* as a light yellow oil. Purification by vacuum distillation at 80°C / 0.9 mm Hg gave a colorless oil (1.91 g, 78%): IR(neat/ cm^{-1}) 3362, 3327 (NH_2), 1602 (NH_2); MS (70 eV) m/z 162 (M^+-H), 106 (M^+-C_4H_9, 100%); ^{13}C NMR ($CDCl_3$ / TMS / 300 MHz) δ ppm 13.91, 22.58, 28.67, 39.13, 56.24, 126.28, 126.82, 128.36, 146.40. ^1H NMR δ: 7.31 (5H, m, Ph), 3.87 (1H, t, CHN), 2.0 (1H, s, NH_2), 1.60 (2H, m, CH_2), 1.30 (2H, m, CH_2), 0.89 (3H, s, Me).

General Procedure for Enantioselective Reduction of *N*-Silylimines. *1-Phenylethylamine:* The *N*-TBS-phenylmethylimine was prepared by the addition of benzonitrile (0.84 mL, 8.25 mmol) in CH_2Cl_2 (20 mL) to methyl lithium (11 mL, 1.5 M, 16 mmol) in ether at -15°C, and stirred until all the nitrile had reacted, followed by the subsequent addition of TBSCl (1.24 g, 8.25 mmol) in CH_2Cl_2 (15 mL). After the brown-reddish solution was allowed to stir at -10°C for 7 min, a mixture of BH_3·SMe_2 complex (9 mL, 2 M, 18.1 mmol) and 1,3,2-oxazaborolidine **1** in dichloromethane (20 mL) was added. Compound **1** was, prepared by Corey's method[20] from (1S, 2R)-(+)-norephedrine (2.49 g, 16.5 mmol), and BH_3·SMe_2 (18 mL, 2 M, 36 mmol). The reaction mixture was then stirred over night at the same temperature. The yellow clear solution obtained from the reduction was carefully

treated at 0°C with distilled water to hydrolyze the excess hydride, and then with 6 M HCl until the mixture was strongly acidic. After the mixture was stirred for 16 h at room temperature, the CH_2Cl_2 was removed under reduced pressure and the residue was extracted with ether (2 x 25 mL). The aqueous phase was cooled at 0°C, basified with 6 M NaOH, and extracted with ether (5 x 50 mL). Combined extracts were washed with brine, dried over anhydrous K_2CO_3, and rotoevaporated to give a light yellow oil. Fractional distillation provided the 1-*phenylethylamine* (0.71 g, 71%) as a clear liquid, characterized by IR, NMR, MS and comparison with an authentic sample. The amine (17 mg) in THF (1 mL) was converted into (R)-α-methoxyphenylacetamide by treatment with (R)-*N*-succinimidyl-α-methoxyphenylacetate (SMPA) (42 mg) in a sealed ampule at 100°C. HPLC analysis of the diastereoisomeric mixture showed 50% ee,[22] of the S enantiomer as compared with the standard.

General Procedure for Ketone Synthesis. ***Acetophenone:*** To a solution of methyl magnesium chloride (4.2 mL, 3 M, 12.6 mmol) in THF at -70°C was added a mixture of copper bromide (0.035 g, 0.24 mmol), benzonitrile (0.8 mL, 7.8 mmol), and TBSCl (1.37 g, 9.1 mmol) in THF (10 mL) during a 5 min period. The resulting mixture was stirred for 10 min, allowed to warm at room temperature over a period of 2 h. Distilled water was added to the ice cooled solution, and the aqueous phase extracted with diethyl ether (3 x 15 mL). After the ethereal solution was dried ($MgSO_4$), and rotoevaporated, the oily residue was purified by column chromatography on silica gel (ethyl acetate) to give *acetophenone* (0.91 g, 90% yield, 96.5% purity). IR (neat)/cm^{-1}: 1684 (C=O); ^{1}H NMR δ: 7.65 (5H, m, Ar), 2.55 (3H, s, Me); ^{13}C NMR δ 197.88 (C=O), 136.93, 132.88, 128.36, 128.34, 26.34 (Me); MS (70 eV) m/z: 120 (M^+), 105 (M-Me), 77 (Ph).

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