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LETTERS

Tris(2,6-diphenylbenzyl)amine (TDA) and tris(2,6-diphenylbenzyl)phosphine (TDP) with unique bowl-shaped structures: synthetic application of functionalized TDA to chemoselective silylation of benzylic alcohols

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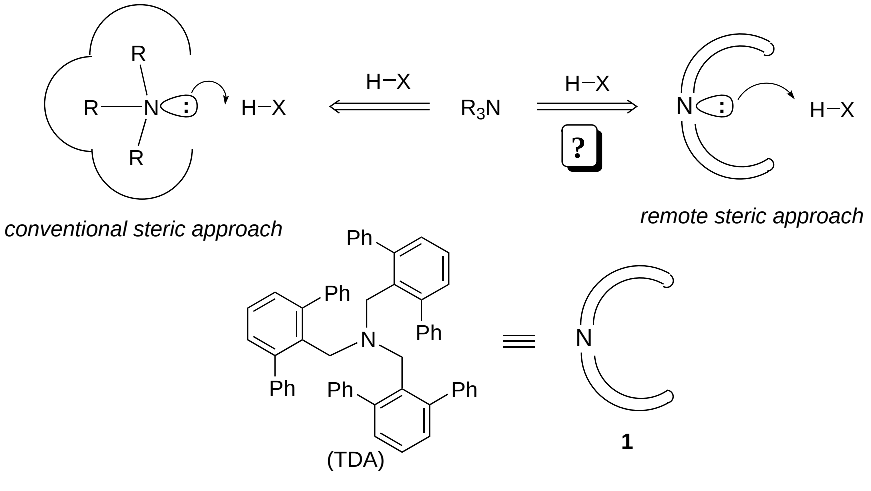
Abstract—A new strategy for obtaining the formal steric hindrance of tertiary amines by remote steric factors is described by designing the bowl-shaped, structurally unique tris(2,6-diphenylbenzyl)amine (TDA). In addition to its structural uniqueness, TDA possesses the rich electronic atmosphere derived from three 2,6-diphenylbenzyl moieties, thereby allowing the chemoselective silylation of benzylic alcohols preferentially over other alcohols based on the effective aromatic π,π interaction. This approach of preparing TDA is also applicable to the new synthesis of tris(2,6-diphenylbenzyl)phosphine (TDP). © 2001 Elsevier Science Ltd. All rights reserved.

Tertiary amines are known to abstract acidic protons from various organic substrates including acids, phenols, and carbonyl compounds possessing acidic α-protons. By combining use of trialkylsilyl halides or triflates, tertiary amines can also be utilized as bases for the silylation of alcohols, phenols, carbonyl compounds, etc. by abstracting these acidic α-protons.[1] Among various tertiary amines, triethylamine[2] is the most familiar. Sterically more hindered diisopropylethylamine[3] and 1,2,2,6,6-pentamethylpiperidine[4] might be useful for the selective silylation to protect several functional groups. However, preparation of more hindered tertiary amines seems troublesome due to the increasingly difficult introduction of bulky alkyl moieties on the nitrogen atom.[5] Accordingly, we are interested in the possibility of designing a bowl-shaped tertiary amine of type **1** to obtain formal steric hindrance by remote steric factors, as shown in Scheme 1. Reported herein is the design of



Scheme 1.

Keywords: tertiary amine; steric hindrance; chemoselectivity; silylation; phosphine.

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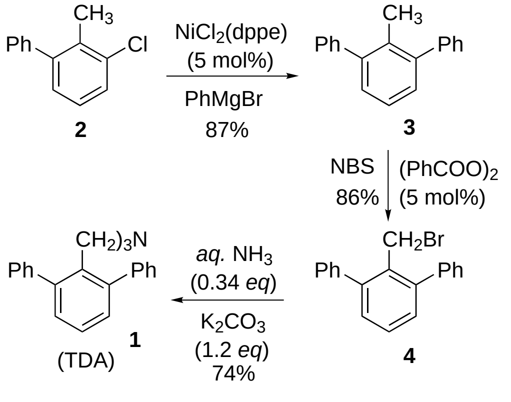
such a bowl-shaped, structurally unique tris(2,6-diphenylbenzyl)amine (TDA), which may also exhibit the eminent electronic effect by rich aromatic rings derived from three 2,6-diphenylbenzyl moieties.[6,7] This characteristic feature led us to illustrate the synthetic application to the chemoselective silylation of benzylic alcohols.

We conveniently synthesized TDA from commercially available 2-chloro-6-phenyltoluene (**2**) in the three-step sequence shown in Scheme 2. Thus, reaction of 2-chloro-6-phenyltoluene (**2**) in ether with an ethereal solution of PhMgBr (1.4 equiv.) in the presence of 5 mol% $NiCl_2$(dppe) under reflux for 16 h afforded 2,6-diphenyltoluene **3** in 87% yield,[8] which was then treated with NBS (1.2 equiv.) in cyclohexane under the influence of 5 mol% $(PhCOO)_2$ under reflux for 2 h to furnish 2,6-diphenylbenzyl bromide **4** in 86% yield.[9] This bromide **4** was heated with aqueous NH_3 (0.33 equiv.) in acetonitrile at 55°C for 16 h to give the desired TDA **1** in 74% yield [55% overall yield from 2-chloro-6-phenyltoluene].

The primary structure of TDA was determined by single-crystal X-ray diffraction analysis, as shown in Fig. 1,[10] suggesting the existence of an appropriate molecular pocket on the nitrogen atom.

The synthetic application of the bowl-shaped TDA is illustrated by the chemoselective silylation of benzylic alcohols in the presence of structurally similar alcohols.[1] Among various silyl ethers, the *tert*-butyldimethylsilyl ether has become one of the most popular silyl protective groups in organic synthesis,[11] because it is approximately ten^4 times more stable to basic hydrolysis than the trimethylsily groups. It is easily introduced by using a variety of reagents with the advantage of being quite stable to a variety of organic reactions, and is readily removed under conditions that do not attack other functional groups. Treatment of *tert*-$BuMe_2SiOTf$ in CH_2Cl_2 with Et_3N or pyridine at room temperature for 30 min, and subsequent exposure of a mixture of 1 equiv. each of 1-phenyl-1-pentanol (**5**) and 1-phenyl-3-heptanol (**6**) at −78°C for 1 h gave rise to two different *tert*-butyldimethylsilyl ethers **7** and **8** in a ratio of 34:66–44:56 (72–88% yields). Switching tertiary amine bases from NEt_3 or pyridine to sterically more hindered *i*-Pr_2NEt and 1,2,2,6,6-pentamethylpiperidine afforded silyl ethers **7** and **8** in a ratio of 43:57–42:58, respectively (86–89% yields). In marked contrast, however, use of bowl-shaped TDA as amine base for *tert*-butyldimethylsilylation produced a 78:22 mixture of **7** and **8** (73% yield), although structurally similar



Scheme 2.

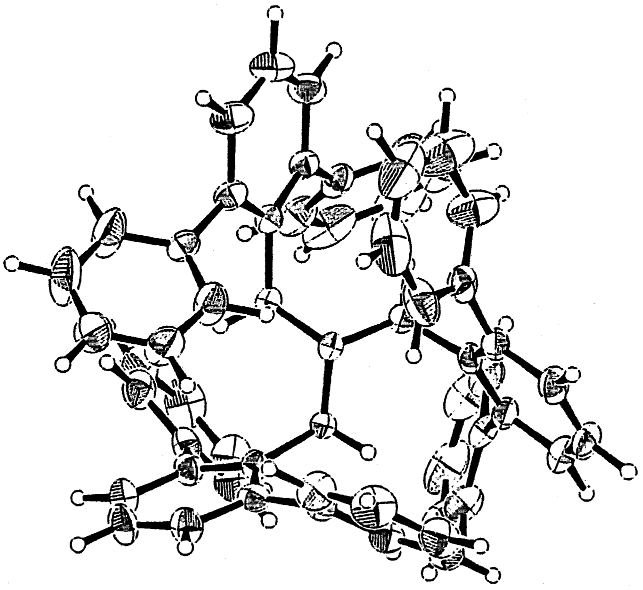
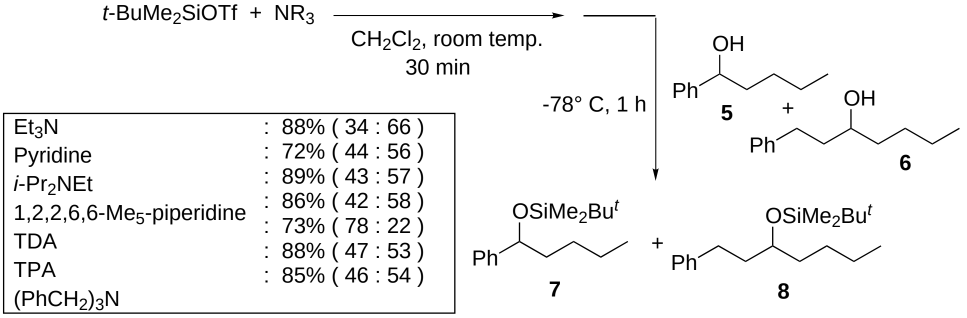


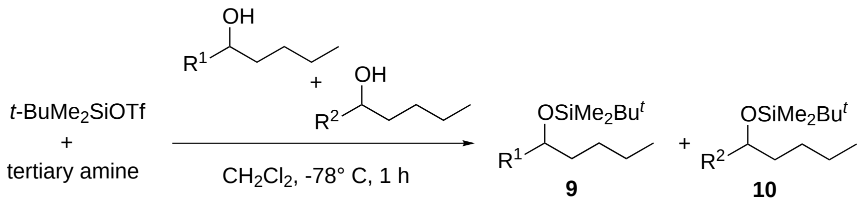
Figure 1. ORTEP diagram of TDA.



Et_3N	: 88% (34 : 66)
Pyridine	: 72% (44 : 56)
i-Pr_2NEt	: 89% (43 : 57)
1,2,2,6,6-Me_5-piperidine	: 86% (42 : 58)
TDA	: 73% (78 : 22)
TPA	: 88% (47 : 53)
$(PhCH_2)_3N$	: 85% (46 : 54)

Scheme 3.

Table 1. Chemoselective *tert*-butyldimethylsilylation of two different alcohols in the presence of several amine bases[a]



Entry	Amine	Alcohol		% Yield	Ratio[b]
		R^1	R^2		
1	TDA	Ph	CH_2CH_2Ph	73	78:22
2	TDA	Ph	Cyclo-C_6H_{11}	69	91:9
3	*i*-Pr_2NEt			90	47:53
4	TDA	β-Naphthyl	CH_2CH_2Ph	67	82:18
5	TPA			92	52:48
6	$(PhCH_2)_3N$			84	47:53
7	TDA	CH=CHPh	CH_2CH_2Ph	98	56:44

[a] The chemoselective *tert*-butyldimethylsilylation of two different alcohols was carried out in the presence of a mixture of *tert*-$BuMe_2SiOTf$ and amine (prepared by addition of *tert*-$BuMe_2SiOTf$ in CH_2Cl_2 to amine base at room temperature for 30 min) at −78°C for 1 h.

[b] The ratios of **9** and **10** were determined by GLC or ^1H NMR analyses.

Table 2. Substituent effect on the chemoselective *tert*-butyldimethylsilylation of two different alcohols **11** and **6** in the presence of bowl-shaped TDA or *i*-Pr_2NEt[a]

Entry	*p*-Substituent (X)	% Yield (ratio)[b] with TDA	% Yield (ratio)[b] with *i*-Pr_2NEt
1	NMe_2	86 (49:51)	
2	CH_3	73 (73:27)	88 (48:52)
3	H	73 (78:22)	89 (43:57)
4	Br	72 (85:15)	89 (40:60)
5	CF_3	78 (88:12)	90 (28:72)
6	CN	79 (91:9)	

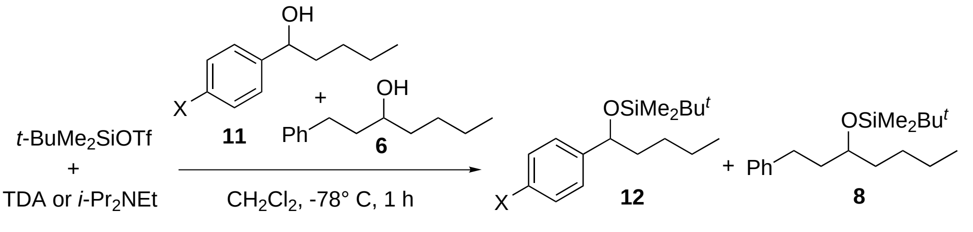
[a] The chemoselective *tert*-butyldimethylsilylation of two different alcohols **11** and **6** was carried out in the presence of a mixture of *tert*-$BuMe_2SiOTf$ and amine (prepared by addition of *tert*-$BuMe_2SiOTf$ in CH_2Cl_2 to TDA or *i*-Pr_2NEt at room temperature for 30 min) at −78°C for 1 h.

[b] The ratios of **12** and **8** were determined by GLC analysis.

tris(2-phenylbenzyl)amine (TPA) and tribenzylamine resulted in low chemoselectivity (46:54–47:53 in 85–88% yields) (Scheme 3).

Other selected examples included in Table 1 clearly demonstrate the effectiveness of bowl-shaped TDA in the recognition and discrimination of benzylic alcohols preferentially based on the aromatic π,π stabilization between these alcohols and benzene rings of TDA, thereby allowing the chemoselective functionalization of benzylic alcohols. Discrimination of structurally similar 1-phenylpentanol and 1-cyclohexylpentanol appears feasible (entry 2). 1-β-Naphthylpentanol exhibits better discrimination ability than 1-phenyl-1-pentanol (entries 4–6). However, the *trans*-2-phenylethenyl group is less effective (entry 7).

The existence of hypothetical aromatic π,π interaction between benzylic alcohols and benzene rings of TDA was verified by examining the *para*-substituent effect on the benzylic portions of alcohol **11** for the chemoselective *tert*-butyldimethylsilylation of two different alcohols **11** and **6**, as shown in Table 2. Namely, by plotting the logarithm of the observed discrimination ratios of silyl ethers **12** and **8**, obtained by chemoselective silylation, versus the Hammett substituent constant (σ) for the particular *para*-substituent in **11**, we successfully observed a linear relationship as illustrated in Fig. 2.[12]



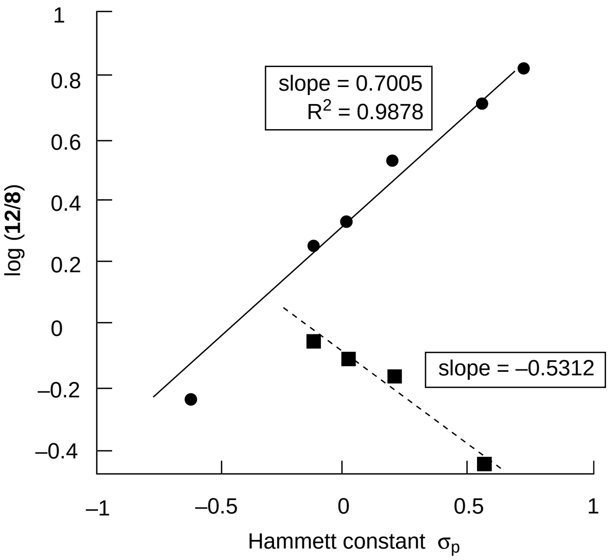
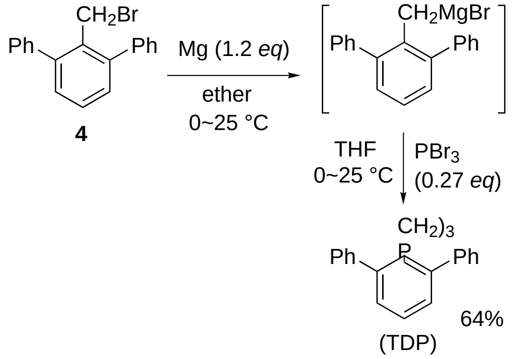


Figure 2. Plot of chemoselectivity versus Hammett constant σ_p. Plots (●) and (■) were obtained with TDA and *i*-Pr_2NEt, respectively.



Scheme 4.

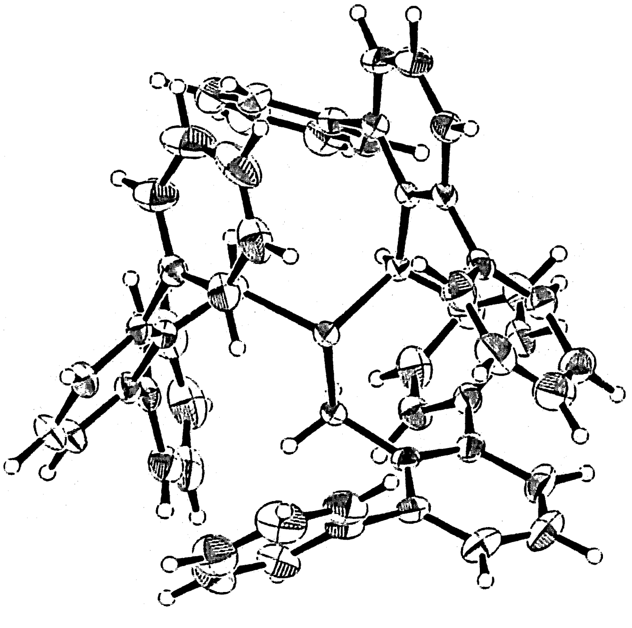


Figure 3. ORTEP diagram of TDP.

It should be noted that the direction of slopes derived from TDA and *i*-Pr_2NEt are totally opposite, as indicated in Fig. 2.

It seems clear that our approach for designing the bowl-shaped tertiary amine TDA is also applicable to the new synthesis of a phosphino analogue, tris(2,6-diphenylbenzyl)phosphine (TDP), as shown in Scheme 4. Since tertiary phosphines play an important role as phosphine ligands in the synthesis of transition-metal catalysts,[13] the structurally unique, bowl-shaped TDP has potential for numerous synthetic applications in transition-metal chemistry (Fig. 3).

Acknowledgements

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10. *Crystal data*: $C_{57}H_{45}N{\cdot}CH_2Cl_2$, $M=828.92$, orthorhombic, $a=36.763(4)$, $b=11.129(3)$, $c=21.394(5)$ Å^3, $U=8753(2)$ Å, $T=293$ K, space group *Pbcn* (no. 60), $Z=8$, $\mu(\mathrm{Mo\ K}_\alpha)=1.89\ \mathrm{cm}^{-1}$, 10974 reflections measured, 10970 unique ($R_{\mathrm{int}}=0.363$), 10049 reflections were used for calculation. Refinement converged with $R_1=0.056$ and $R_w=0.064$ [$w=1/\sigma^2(F_o)$]. The crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (e-mail: deposit@ccdc.cam.ac.uk) as CCDC 152190.

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