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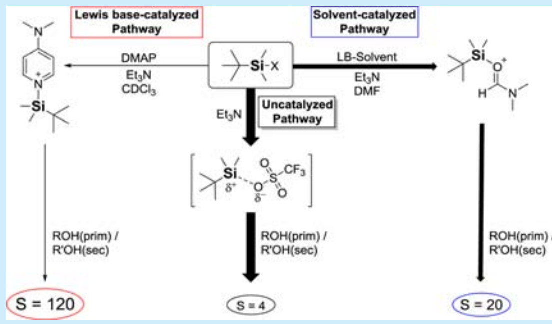
# Leaving Group Effects on the Selectivity of the Silylation of Alcohols: The Reactivity–Selectivity Principle Revisited

Pascal Patschinski* and Hendrik Zipse*

Department of Chemistry, Ludwig-Maximilians-Universität, Butenandtstrasse 5-13, 81377 München, Germany

Supporting Information

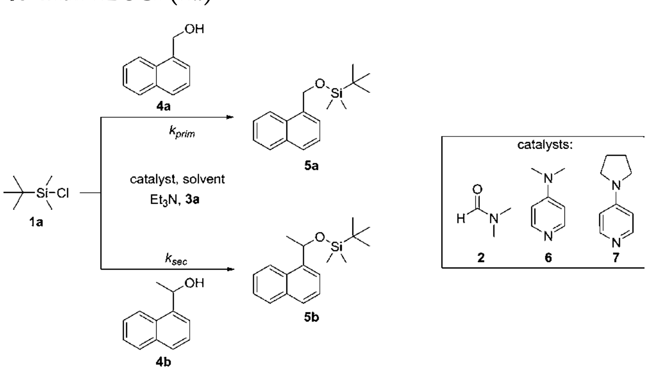
**ABSTRACT:** TBS protection of primary alcohol naphthalen-1-ylmethanol (**4a**) and secondary alcohol 1-(naphthalen-1-yl)ethanol (**4b**) has been studied under various reaction conditions. The primary/secondary selectivity is largest in the comparatively slow Lewis base catalyzed silylation in apolar solvents and systematically lower in DMF. Lowest selectivities (and fastest reaction rates) are found for TBS triflate **1b**, where only minor effects of solvent polarity or Lewis base catalysis can be observed.




The silylation of alcohols is one of the most important reactions in the chemo- and regioselective manipulation of complex organic molecules.[1−3] Its usefulness as a protecting group strategy derives, in part, from the ability to differentiate primary and secondary alcohols through the combined use of silylation reagents of different size and reactivity, catalysts, auxiliary bases, and solvents. The most frequently employed reagents such as *tert*-butyldimethylsilyl chloride (TBSCl, **1a**) combine a silyl group of intermediate size with a leaving group of moderate reactivity. The latter makes reagent **1a** compatible with a number of activation protocols, of which the "Corey procedure" involving DMF (**2**) as the solvent in combination with imidazole (**3a**) as base and the Lewis base catalyzed activation in apolar organic solvents with triethylamine ($Et_3N$, **3b**) are the most common ones.[4−6]

We have recently shown for the reaction of reagent **1a** with primary and secondary alcohols **4a** and **4b** that the selectivity (defined here as the ratio of reaction rates $S = k_{prim}/k_{sec}$) depends decisively on the catalysts and solvents used: while $S = 20.0$ using DMF, **2** as solvent, and Lewis base catalyst, significantly higher selectivities of 123 (DMAP, **6**) and 130 (PPY, **7**) have been obtained for electron-rich pyridines in $CDCl_3$. The enhanced selectivity observed in these latter cases is accompanied by a significant reduction in absolute reaction rates, which also implies that combinations of **6** or **7** with DMF as solvent provide effectively the same rate as obtained with DMF alone.[7] This result may be rationalized with the often invoked "reactivity–selectivity" principle,[8] and we therefore explore here the influence of other factors responsible for the reaction rates in silylation reactions. This particularly concerns the choice of the leaving groups present in the silylation reagents.

**Scheme 1. Silylation of Primary and Secondary Alcohols 4a/4b with TBSCl (1a)**




The reactivity of TBSCl **1a** toward alcohols **4a** and **4b** was characterized already under a variety of reaction conditions before.[7] We reiterate here that the rate of reaction of **4b** in DMF-$d_7$ does not depend on the type or amount of the auxiliary base added, as long as there is sufficient base present to neutralize the HCl byproduct. In the complete absence of auxiliary base, initial rates are practically identical to those using 1.2 equiv of $Et_3N$ **3b**, but the reaction eventually comes to a halt at just below 80% conversion. Addition of 1.2 equiv of $Et_3N$ **3b** to the reaction mixture at that point neutralizes the HCl byproduct and allows the reaction to go to completion. The reaction rates show little variation with the particular type of auxiliary base, as is demonstrated by reaction half-lives of 7.4 ± 0.6 min for $Et_3N$ **3b** and 7.5 ± 0.2 min for imidazole **3a**. Even increasing the concentration of imidazole **3a** to 1.8 equiv does not influence the reaction rate ($t_{1/2} = 7.4 \pm 0.4$ min) (Figure 1). These results are, together with those for pyridines **6** and **7**, most easily rationalized by assuming that DMF-$d_7$ is the only catalytically active Lewis

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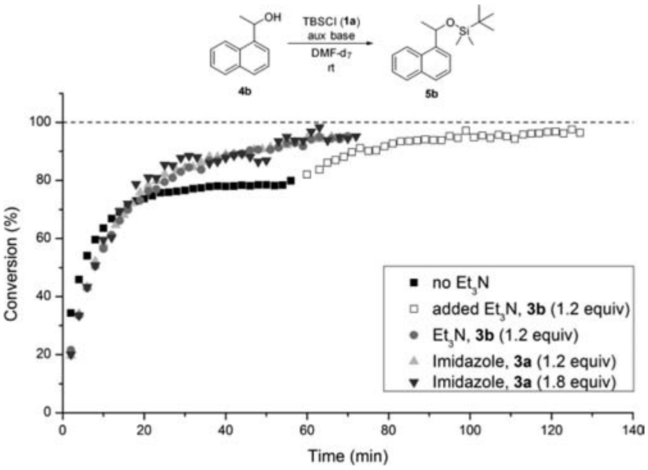
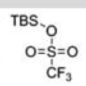
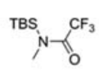
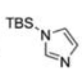



**Figure 1.** Comparison of auxiliary bases in DMF-$d_7$ for the silylation of **4b** with **1a**.

base present under these conditions, while all other bases (**3a**, **3b**, **6**, **7**) merely act as auxiliary bases. This is distinctly different from the alternative mechanism involving imidazole as the catalytically active Lewis base.[4,9]

The influence of the leaving group on the reaction rate was first explored for reagents containing the TBS protecting group such as *tert*-butyldimethylsilyl chloride (TBSCl, **1a**), *tert*-butyldimethylsilyl triflate (TBSOTf, **1b**),[10] *tert*-butydimethylsilyl cyanide (TBSCN, **1c**),[11] *tert*-butyldimethylsilyl imidazole (TBSImi, **1d**),[12] and *tert*-butyldimethylsilyl-*N*-methyltrifluoroacetamide (MTBSTFA, **1e**).[13] These measurements were performed using the previously developed procedure for secondary alcohol **4b** using 30 mol % of DMAP and Et$_3$N (1.2 equiv) in CDCl$_3$ (Table 1).[7]

**Table 1. Reaction Half-Lives for the Silylation of 4b with 30 mol % of DMAP Catalyst for Various Leaving Groups in CDCl$_3$ and DMF-$d_7$**

| reagent | $k_{eff}$[a] CDCl$_3$ | $t_{1/2}$[b] CDCl$_3$ | $k_{eff}$[a] DMF | $t_{1/2}$[b] DMF |
|---|---|---|---|---|
| **1b**,  | 5.1 | 0.15 ± 0.01 | 4.1 | 0.2 ± 0.1 |
| **1a**, TBS–Cl | $1.6 \cdot 10^{-3}$ | 471.1 ± 10 | $1.1 \cdot 10^{-1}$ | 7.1 ± 0.2 |
| **1c**, TBS–CN | $8.7 \cdot 10^{-5}$ | 8855 ± 23 | $4.9 \cdot 10^{-2}$ | 19.4 ± 2.9 |
| **1e**,  | $4.9 \cdot 10^{-5}$ | 15682 ± 45 | $1.1 \cdot 10^{-2}$ | 72.6 ± 20 |
| **1d**[c,d],  | $4.1 \cdot 10^{-6}$ | $1.84 \cdot 10^{6}$ | $1.1 \cdot 10^{-3}$ | 833.8 |

[a]$k_{eff}$ in l·mol$^{-1}$·s$^{-1}$. [b]Half-life in min. [c]Based on 4.4% conversion after 10 d in CDCl$_3$. [d]Based on 6.4% conversion after 120 min in DMF-$d_7$.

Very little conversion can be observed under these basic conditions for silyl imidazole **1d**, which is estimated to react 1 order of magnitude slower than **1e**. For the more reactive reagents **1a**, **1c**, and **1e**, the rate in DMF-$d_7$ is increased by 2 orders of magnitude compared to that in CDCl$_3$, while for triflate **1b** reaction rates are quite comparable in both solvents. Additional experiments in CDCl$_3$ demonstrate that the rate of reaction of silyl triflate **1b** is independent of catalyst concentration, in significant contrast to the first-order dependence observed for reagents **1a** and **1c** (Figure 2). This implies that the strongly activated reagent **1b** undergoes a direct (that is, uncatalyzed) reaction with substrate alcohol **4b**.

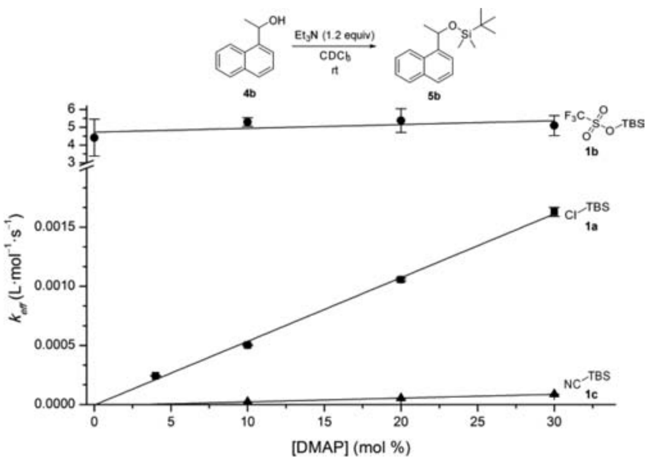



**Figure 2.** Influence of catalyst concentration for various silylation reagents in CDCl$_3$.

An analogous set of measurements has been performed in DMF-$d_7$ as the solvent and Et$_3$N **3b** as the auxiliary base. This leads to practically the same absolute rates as compared to CDCl$_3$ for silyl triflate **1b** that hardly depend on DMAP concentration. This is also true for silyl chloride **1a**, silyl cyanide **1c**, and silyl amide **1e** whose respective reaction rates remain practically unchanged after addition of 30 mol % DMAP (Figure 3). It

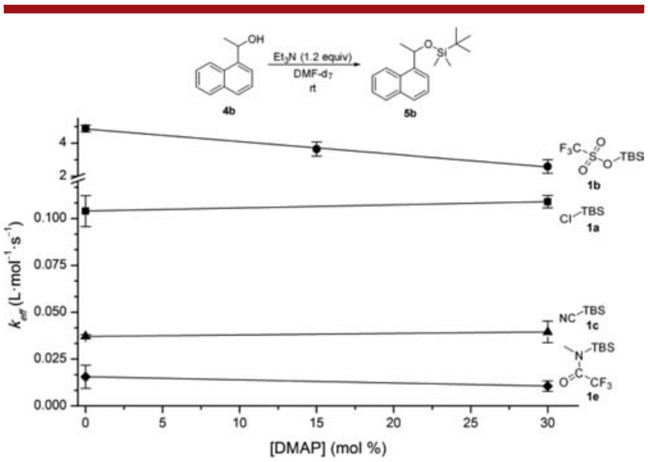



**Figure 3.** Influence of catalyst concentration for various silylation reagents in DMF-$d_7$.

should be added here that turnover curves for **1c** deviate from the second-order behavior observed for all other reagents such as to indicate (partial) autocatalysis through product cyanide (see the Supporting Information). Even under these conditions, very little turnover can be detected for silyl imidazole **1d**. Because of the higher reactivity of primary alcohol **4a**, absolute reaction rates could only be determined for the reagents **1a** and **1c** in CDCl$_3$. When a catalyst loading of 4 mol % of DMAP is used, silyl chloride **1a** is approximately 1 order of magnitude faster than silyl cyanide **1c**. For both reagents, the rate of reaction depends linearly on the catalyst concentration (see the Supporting Information for details).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Reactions in DMF-$d_7$ were found to be too fast for accurate direct rate measurements for all reagents **1a–e**, and the reactivity of primary alcohol **4a** was therefore quantified through competition experiments with secondary alcohol **4b**. These experiments employ equimolar mixtures of alcohols **4a** and **4b**, and the underlying reaction kinetics are thus directly comparable to those of kinetic resolution experiments.[14] Turnover curves in these experiments measure the chemoselectivity (expressed as $C$ = ([**5a**] − [**5b**])/([**5a**] + [**5b**]) as a function of turnover (of both substrate alcohols **4a** and **4b**). For the highly selective silylation in $CDCl_3$ using silyl chloride **1a** with 4 mol % of DMAP (**6**) as catalyst and $Et_3N$ (**3b**, 1.2 equiv) as the auxiliary base, we find that primary alcohol **4a** turns over almost completely before that of secondary alcohol **4b** commences at conversions >50% (Figure 4). The corresponding turnover curve is characterized by

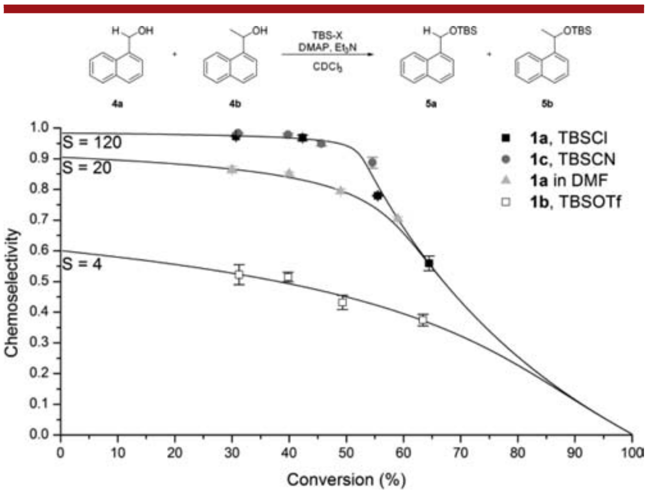


**Figure 4.** Competition experiments performed for **1a**, **1b**, and **1c** in $CDCl_3$ with 4 mol % of DMAP **6**.

chemoselectivities $C$ just below 1.0 for the first 50% turnover and a subsequent systematic decline to $C$ = 0.0 afterward. The data points located in the critical region between 30 and 70% turnover can nicely be fitted with a selectivity value $S$ = 120 obtained from previous direct kinetic measurements for alcohols **4a** and **4b**,[7] thus confirming the validity of the relative rate measurements obtained here. The same high selectivity $S$ was measured under these conditions for silyl cyanide **1c**, while that for silyl triflate **1b** is much lower at $S$ = 4. Changing to the Lewis basic solvent DMF-$d_7$, the reaction of silyl chloride **1a** becomes significantly less selective with $S$ = 20, again in line with previous observations.[7] In conclusion, these results show that the most reactive reagent (triflate **1b**) is the least selective in differentiating between primary and secondary alcohols **4a** and **4b**. Comparatively low selectivities are also found when the (catalytically active) Lewis base solvent DMF-$d_7$ is employed.

Whether the selectivity of the highly reactive silyl triflate **1b** can be increased through moving to lower reaction temperatures was finally addressed in competition experiments using 1:1 mixtures of alcohols **4a** and **4b** in $CD_2Cl_2$ at +20, 0, and −78 °C (Figure 5). This change in solvent away from $CDCl_3$ is expected to have only a minor influence on reaction rates[7] but allows reliable selectivity measurements at much lower temperatures. A small increase in selectivity was observed when lowering the reaction temperature from 20 °C ($S$ = 4) to 0 °C ($S$ = 6). Lowering the reaction temperature further to −78 °C leads to $S$ = 15. It can thus be concluded that only moderately selective

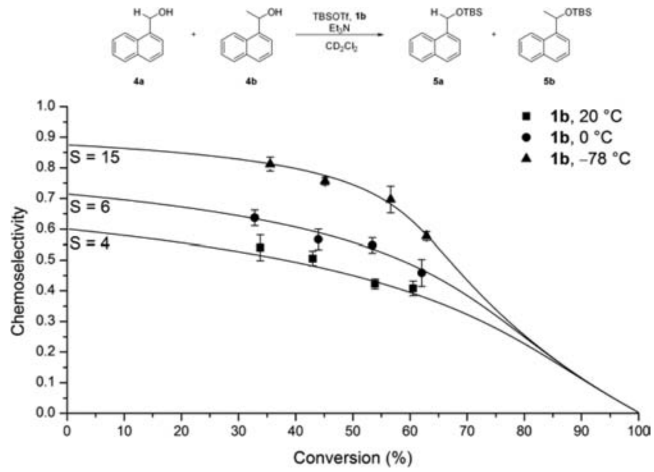


**Figure 5.** Temperature-dependent competition experiments with silyl triflate **1b** in $CD_2Cl_2$.

transformations can be achieved by highly reactive reagents even at low temperature.

In order to rationalize the influence of the leaving groups on relative reaction rates, reaction enthalpies ($\Delta H_{Rxn}$) for the silylation of secondary alcohol **4b** have been calculated at the MP2/G3MP2large//MPW1K/6-31+G(d) level of theory in combination with the SMD continuum solvation model in chloroform. For the sake of brevity, trimethylamine was used as auxiliary base in the calculation. For all reagents **1a–e** a satisfactory correlation can be found between reaction rates in $CDCl_3$ ($k_{eff}$) against the reaction enthalpy ($\Delta H_{Rxn}$). This correlation can be used to predict reaction rates for other reagents such as TBS perchlorate and azide (Figure 6).

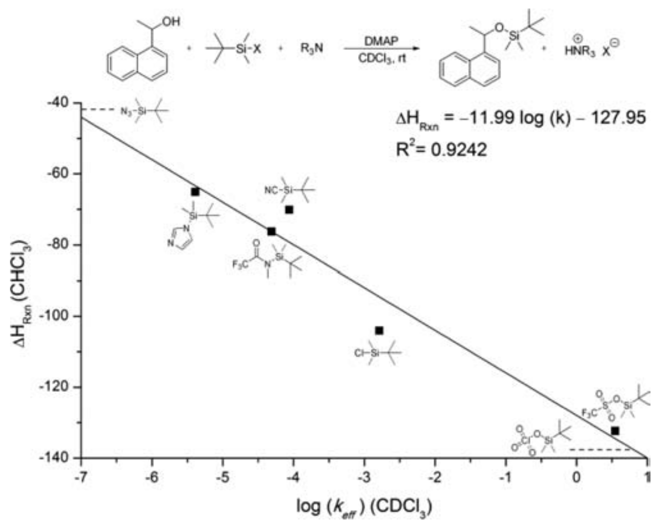


**Figure 6.** Correlation of reaction enthalpy $\Delta H_{Rxn}$ vs log($k_{eff}$) with **4b** and DMAP (30 mol %) in $CDCl_3$.

Three different mechanistic scenarios for the silylation of alcohols emerge from the current results as a function of leaving groups, solvents, and Lewis bases (Figure 7). The fastest and least selective reactions are observed for TBS triflate **1b**. Reactions show only small solvent effects in this case and hardly respond to Lewis base catalysis. This can best be rationalized through direct (that is uncatalyzed) reaction of alcohols with **1b**, whose properties may approximately be understood as those of a



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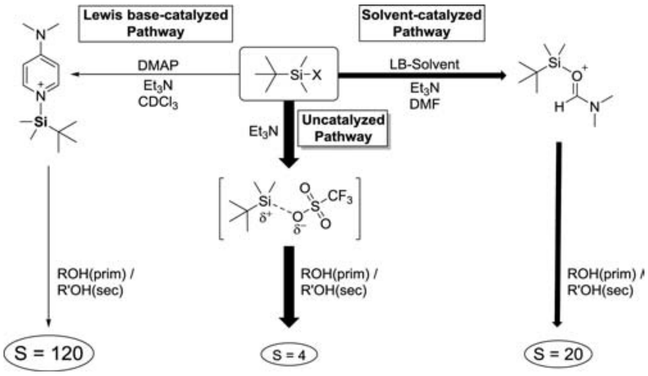


**Figure 7.** Overview of various pathways for the silylation reaction depending on the choice of solvent and leaving group.

contact ion pair. Better selectivities at somewhat slower rates are obtained in DMF as a Lewis basic solvent for the less reactive reagents **1a**, **1c**, and **1e**. These reactions are likely to involve silylated DMF as transient intermediates of the catalytic cycle. Best selectivities and slowest rates are obtained in apolar organic solvents such as $CDCl_3$ and $CD_2Cl_2$ for the Lewis base catalyzed reaction of reagents **1a**, **1c**, and **1e**. That reaction rates correlate so systematically with selectivities is likely due to the steric demands of the respective transition states: while the uncatalyzed reaction of alcohols with triflate **1b** proceeds through transition states composed only of these two reactants, the Lewis base catalyzed pathways have to accommodate the presence of either a small (such as DMF) or a larger (e.g., DMAP) Lewis base.[15] This qualitative rationale also implies that the development of sterically more encumbered Lewis bases may lead to still larger selectivities for the Lewis base catalyzed processes.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental details, explanation of methods, theoretical calculations, and time conversion plots. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01536.

## ■ AUTHOR INFORMATION

### Corresponding Authors

*patch@cup.lmu.de.
*zipse@cup.lmu.de.

### Notes

The authors declare no competing financial interest.

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