Asymmetric Catalysis

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Kinetic Resolution and Desymmetrization by Stereoselective Silylation of Alcohols**

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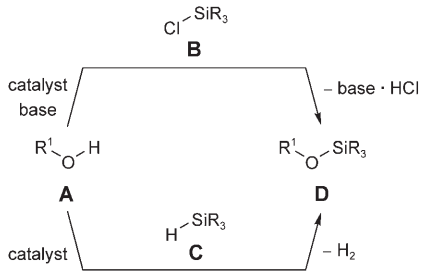
The importance of the silicon–oxygen linkage to temporarily protect a hydroxy group is reflected in its extensive use in the synthesis of complex molecules.[1] A relatively simple adjustment of the steric and electronic environment at the silicon atom accounts for literally dozens of common silicon-based proctective groups that are orthogonal in both the protection and deprotection steps. In the classic protocol for the formation of a silicon–oxygen bond,[2] a chlorosilane **B** is treated with an alcohol **A** in the presence of a nucleophilic catalyst and a stoichiometric amount of a base, often a pyridine derivative or tertiary amine (**A** + **B** → **D**, Scheme 1).

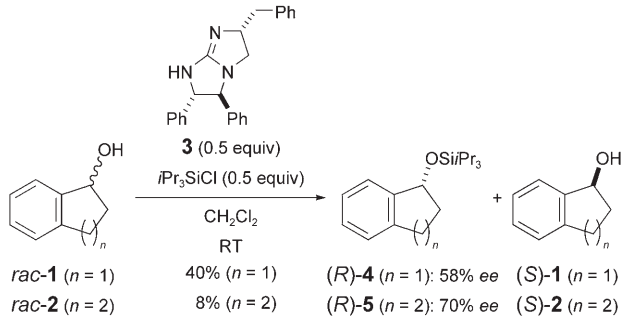


Scheme 1. Fundamental strategies for the formation of a silicon–oxygen bond.

Alternatively, but less-well established, the hydroxy group can be efficiently silylated by transition-metal-catalyzed dehydrogenative coupling of a hydrosilane **C** with **A** (**A** + **C** → **D**, Scheme 1); in this approach dihydrogen is generated as the sole by-product.[3]

Despite the ubiquity of the silicon–oxygen bond in synthetic intermediates, the stereoselective silylation of alcohols—as opposed to the related asymmetric acylation of alcohols[4]—is largely underdeveloped. This elusive methodology might be utilized in the desymmetrization of *meso* diols[5] as well as in the kinetic resolution[6] of racemic mixtures of alcohols.[7] A pivotal observation reported in the seminal paper by Corey and Venkateswarlu might even guide the design of nucleophilic catalysts for an asymmetric silicon–oxygen bond-forming process: imidazole was found to substantially enhance the reaction rates.[2] This reaction was believed to proceed with a silylated imidazole as the actual silylating reagent instead of the less-reactive corresponding chlorosilane.[8]

However, prior to the recent development of an imidazole-containing catalyst (see below), Ishikawa and co-workers employed enantiopure guanidine bases as chlorosilane activators in the, at that time unprecedented, enantioselective silylation reaction.[9] These authors reasoned that a combination of a chiral guanidine base and a chlorosilane would kinetically resolve racemic unfunctionalized alcohols (Scheme 2). Indeed, an equimolar mixture of activator **3**



Scheme 2. Enantioselective silylation of alcohols (2001).

and $i\mathrm{Pr}_3\mathrm{SiCl}$ was capable of discriminating between the enantiomers of 1-indanol (*rac*-**1**) and 1-tetralol (*rac*-**2**). The levels of enantioselection for ethers (*R*)-**4** (58% *ee*) and (*R*)-**5** (70% *ee*) remained modest and conversion was poor despite the use of a stochiometric amount of the chiral reagent.

To render this process catalytic in nucleophilic **3**, Ishikawa and co-workers also examined the activation of the chlorosilane by **3** in the presence of the achiral tertiary amine $\mathrm{Et}_3\mathrm{N}$, but no asymmetric induction at improved conversion was observed.[9] We also note that, based on an analysis of the acidities of the conjugate acids involved, catalytic turnover of the chiral activator might be difficult to achieve, since this

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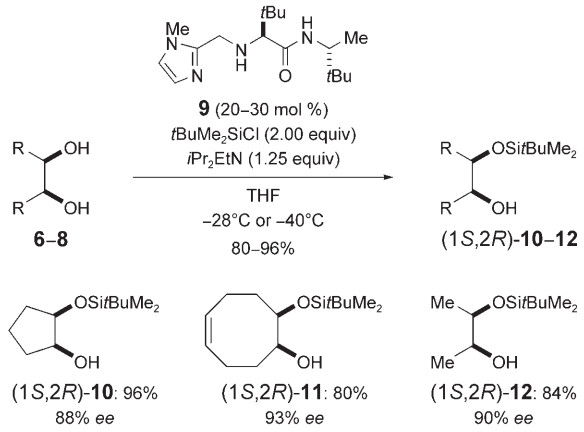
would require proton transfer from the protonated guanidine to the amine base with concomitant release of **3**. However, the pK_a values[10] for guanidinium (p$K_a \approx 13.5$) and ammonium ions (p$K_a \approx 10.0$) imply that this might be thermodynamically disfavored (ΔpK_a is more than three pK_a units).

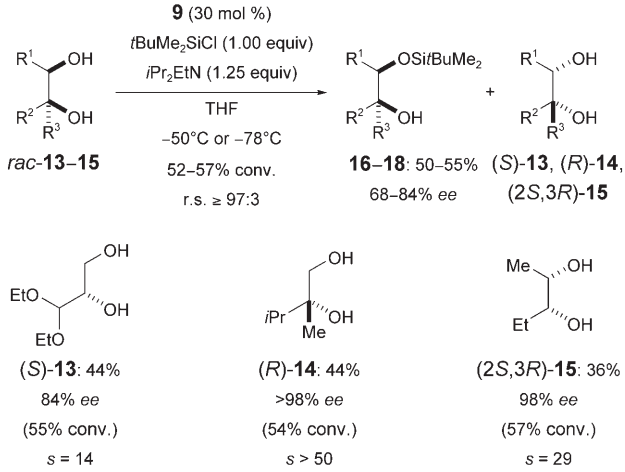
The inherent shortcomings connected with guanidine bases were recently overcome in a significant contribution by Hoveyda, Snapper, and co-workers, who described the enantioselective silylation of *meso* diols.[11] Firstly, and importantly, catalytic turnover was secured by exchanging the relatively basic guanidine entity for the weakly basic *N*-methylimidazole group (incorporated into **9**, Scheme 3), a



Scheme 3. Catalyst-controlled desymmetrization of *meso* 1,2-diols through enantioselective silylation (2006).

proven silaphilic activator of chlorosilanes.[2,8] The situation in regard to the pK_a values is now completely reversed: the intermediate imidazolium ion (p$K_a \approx 7.0$)[10] is three pK_a units more (not less) acidic than an ammonium ion. As a consequence of these factors, the catalyst–base combination **9**/*i*Pr$_2$EtN will permanently provide a free imidazole unit for catalytic turnover. Routinely used catalyst loadings (20–30 mol%) are, however, substoichiometric and leave room for improvement. Second, the peptide-like **9** possesses two further Lewis basic coordination sites, which are believed to act as acceptors for hydrogen bonds from the diol substrates **6**–**8**.[12] Organocatalyst **9** thus activates and preorganizes both the substrate and the reagent; in this way any competitive racemic background reaction might also be suppressed. A facile and enantioselective silylation of several cyclic as well as acylic *meso* diols was achieved using **9** (**6**–**8**→(1*S*,2*R*)-**10**–**12**, Scheme 3). Moreover, desymmetrization of selected *meso* 1,3-diols was also accomplished by using the same strategy.[11]

Impressively, the same team recently extended the substrate scope of this catalyst-controlled enantioselective silylation to unsymmetrically substituted 1,2-diols, thereby changing the desymmetrization into a kinetic resolution (Scheme 4).[13] In this latter scenario, bifunctional catalyst **9** will have to meet higher demands, as not only enantiomers but also regioisomers must be differentiated—one out of four, not one out of two substrates! Scheme 4 shows the resolution of the *syn* 1,2-diols *rac*-**13**–*rac*-**15** as representative examples of the skeletal motifs accepted by **9**. The high regioselectivities seen in the silylation of a primary alcohol over a tertiary or even secondary hydroxy group is not unusual[1] (regioselectivity > 98:2 in both cases) but the selectivity factors *s*[6b] are most remarkable for this novel process (*rac*-**13**→(*S*)-**13** and *rac*-**14**→(*R*)-**14**). We emphasize here that this kinetic resolution proceeds through the formation of a silicon–oxygen bond at a primary hydroxy group remote from the stereogenic carbon atom. The identical strategy also allows for the kinetic resolution of a variety of 1,2-disubstituted *syn* 1,2-diols. A striking example, which demonstrates the efficacy of this technique, is the enantioselective silylation of *rac*-**15**; the low-molecular-weight catalyst **9** is able to even differentiate small steric variations (Me versus Et in a vicinal diol) with useful site selectivity (regioselectivity 97:3) and, of course, high enantioselection (*rac*-**15**→(2*S*,3*R*)-**15**). The regioselectivity in all these reactions was independent of the temperature, while enantioselectivity was highly temperature dependent; this finding indicates a non-enantioselective background reaction.



Scheme 4. Regioselective kinetic resolution of unsymmetrically substituted *syn* 1,2-diols (2007).

Hoveyda, Snapper, and co-workers proposed a transition state that rationalizes the reactivity of the catalytic system and suggests the origin of stereoinduction (**E**, Figure 1).[11,13] On the one hand, two-point binding of the substrate through hydrogen bonds is the key to success. The difunctional catalyst **9** offers two Lewis basic binding sites, a secondary amine and an amide oxygen atom, thus allowing for preferential recognition of one enantiomer over the other in a defined geometry and thereby minimizing steric interactions with the

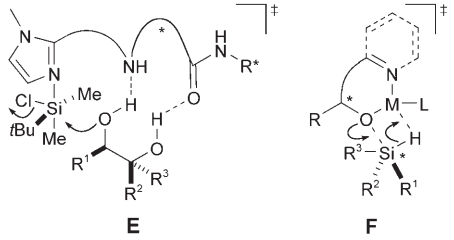
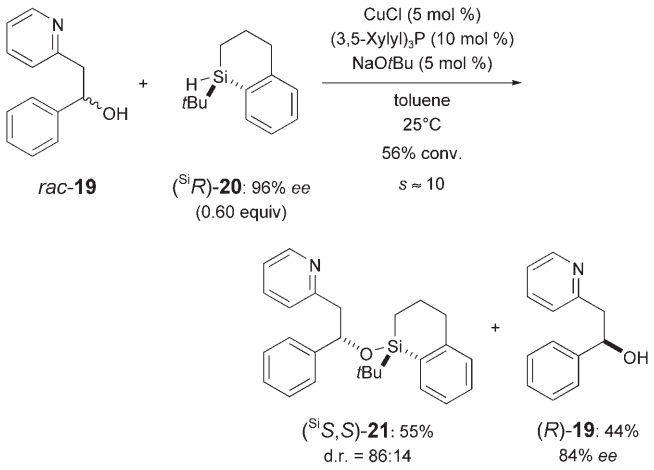


Figure 1. Two-point binding in the stereoselective silylation of diols and the dehydrogenative coupling of donor-functionalized alcohols.

catalyst backbone. On the other hand, the *N*-methylimidazole unit enables hypervalent activation[14] of the chlorosilane, *t*BuMe$_2$SiCl, which facilitates quasi-intramolecular transfer of the electrophilic silicon moiety to the proximal hydroxy group. Overall, this catalyst-controlled enantioselective silylation is based on enantiodiscrimination of a racemic or *meso*-configured starting material through the formation of hydrogen bonds with the chiral template.[12] Such an activation mode is less common in the non-enzymatic kinetic resolution of alcohols; a few examples exploiting this strategy[15] as well as related concepts based on coordination to chiral metal complexes[16] have been reported in acylation processes in recent years.

The aforementioned alternative formation of a silicon–oxygen bond through dehydrogenative coupling (**A** + **C** → **D**, Scheme 1) is also applicable to the kinetic resolution of racemic mixtures of alcohols (Scheme 5).[17] In this approach



Scheme 5. Reagent-controlled kinetic resolution of a donor-functionalized alcohol by dehydrogenative silicon–oxygen coupling with a silicon-stereogenic silane (2005).

by our research group, asymmetric induction originates from the the silicon-stereogenic silane (^{Si}R)-**20**. This virtually enantiopure reagent undergoes preferential σ-bond metathesis with one of the enantiomeric copper(I)–alkoxide chelates through the tentative transition state **F** (Figure 1). The geometry at the silicon atom in this transition state is currently unclear; racemization of this hypercoordinate silicon species is not observed. Again, two-point binding of the donor-functionalized secondary alcohol is essential to secure good stereoselectivity. This reagent-controlled kinetic resolution produced the ether (^{Si}S,*S*)-**21** with promising diastereoselectivity (d.r. = 86:14 at 56% conversion), which, in turn, corresponded to an enantiomeric excess of 84% *ee* for the slow-reacting substrate (*R*)-**19** (*rac*-**19** → (^{Si}S,*S*)-**21**, Scheme 5). Furthermore, the chiral-resolving reagent (^{Si}R)-**20** as well as the fast-reacting ether (*S*)-**19** were recovered racemization-free by reductive cleavage of the ether (^{Si}S,*S*)-**21**. A markedly improved protocol in which the same concept is applied will be reported shortly.[18]

The recent findings by Hoveyda, Snapper, and co-workers have rapidly advanced the area of asymmetric silylation[11,13] so that it almost matches the ability of non-enzymatic asymmetric acylation.[4] In particular, the results obtained in the kinetic resolution of vicinal diols compare well (if not better) with the dihydroxylation of alkenes.[19] It must be noted, however, that stereoinduction has relied on the desymmetrization or resolution of bidentate alcohols.[11,13,17,18] A challenging perspective is the extension of this methodology to simple alcohols not having a pendant donor (hydroxy or pyridyl) group that procurs rigidity to the stereoselectivity-determining transition state. With only a handful of reports published, stereoselective silylation can likely expect a bright future.

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