Silylation

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Catalytic Silylations of Alcohols: Turning Simple Protecting-Group Strategies into Powerful Enantioselective Synthetic Methods

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asymmetric catalysis · desymmetrization · enantioselectivity · kinetic resolution · silylation

In recent years, remarkable progress has been made in the enantioselective silylation of alcohols. Owing to the successful site- and stereoselective functionalization of hydroxy groups, silyl ether formations have evolved from being a simple reaction for functional-group protection into a powerful enantioselective process. In this Minireview, we highlight important recent findings in this emerging field.

1. Introduction

Protecting-group strategies[1] are of pivotal importance in organic synthesis. The temporary blockage of selected sites within a molecule with protecting groups allows for desired transformations to take place at other sites. Given the roles that a protecting group has to perform in a synthetic event, a good protecting group needs to be sufficiently stable while it can be readily installed and easily removed. Moreover, orthogonality is an extremely important factor to consider when the protection of multiple functional groups is required in a reaction system. Silyl ethers are arguably the most common hydroxy protecting groups, and the past few decades have witnessed their widespread use in organic synthesis.[2]

In modern organic chemistry, tremendous efforts have been devoted to the development of enantioselective synthetic methods.[3] Chiral alcohols are commonly present in numerous bioactive structures, and they are also valuable intermediates in organic synthesis.[4] In this context, the stereoselective functionalization of hydroxy groups represents an important approach to access optically enriched alcohols. Over the past decades, stereocontrolled acylation reactions of alcohols by activation through nucleophilic catalysis have received enormous attention, and intensive investigations in this area have led to a plethora of synthetic strategies for enantioselective acylation.[5] On the other hand, the silylation of alcohols was perceived only as an effective means of protection for a very long time. Following Corey and Venkateswarlu's initial introduction of the *tert*-butyldimethylsilyl (TBS) ether as an effective hydroxy protecting group in the early 1970s,[6] the subsequent three decades saw remarkable applications of silyl ethers as protecting groups in synthetic organic chemistry. A seminal report by Ishikawa and co-workers revealed exciting opportunities for achieving enantioselective functionalizations of alcohols by the formation of silyl ethers. In their 2001 report, Ishikawa et al. documented a silylation-based kinetic resolution strategy by the chiral-guanidine-promoted enantioselective silylation of secondary alcohols.[7] The reactions took up to 14 days to reach completion, and stoichiometric amounts of chiral guanidines had to be used to obtain the silylated secondary alcohols with poor to moderate enantioselectivity (Scheme 1). Despite all of these drawbacks, this report represents the first example of an enantioselective silylation of secondary alcohols. The implication of this study, namely that enantioselective functionalizations of alcohols could be realized through silyl ether formation, is particularly intriguing. Interestingly, the authors suggested that a silylguanidinium salt resulting from the reaction between the silyl chloride and the guanidine might be the real silylating agent, based on the examination of the ^{1}H NMR spectrum of an equimolar

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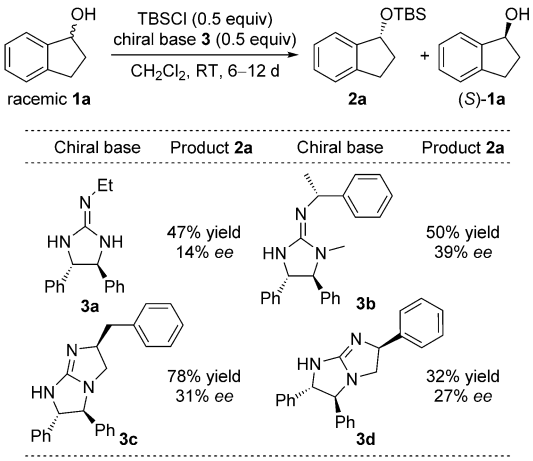


Scheme 1. Modified guanidines as chiral bases for the enantioselective silylation of secondary alcohols.

mixture of a guanidine and TBSCl. In spite of the importance of Ishikawa's disclosure, it was unclear for quite some time whether the silylation of hydroxy groups could be used as a practical method for the enantioselective functionalization of alcohols. From the mid-2000s onwards, a number of exciting reports on the enantioselective silylation of alcohols have appeared in the literature. These timely excellent studies not only changed the general perception of silyl ethers to be only excellent protecting groups, but also firmly established the concept that the silyl protection of alcohols could be utilized as an effective means for inducing asymmetry. In this Minireview, we highlight important contributions to this emerging area up to the end of 2014.[8]

Li-Wen Xu received his PhD degree from the Chinese Academy of Sciences (CAS) with Prof. Chun-Gu Xia in 2004, and was awarded the Presidential Award of the Chinese Academy of Sciences in the same year. He then worked as an Associate Research Professor at the Lanzhou Institute of Chemical Physics (CAS) and Hangzhou Normal University (HZNU), before he was appointed Full Professor at HZNU in 2009. His current scientific interests are focused on organosilicon chemistry, asymmetric catalysis, and organic synthesis.

Yun Chen was born in Shaanxi province and received her BS degree from Sichuan Normal University in 2014. Since then, she has been a master student at Shaanxi Normal University under the supervision of Prof. Li-Wen Xu. Her studies focus on selective silylation and asymmetric catalysis.

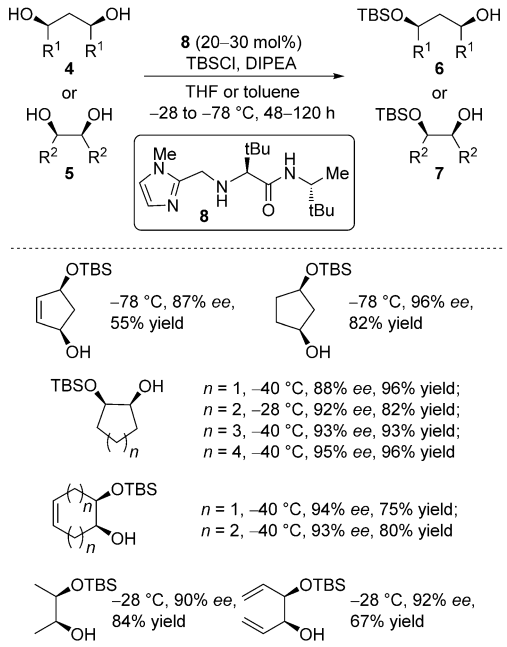
Yixin Lu received his B.Sc. from Fudan University, Shanghai, and subsequently obtained his Ph.D. in Organic Chemistry under the supervision of the Prof. George Just from McGill University, Canada in 2000. After postdoctoral appointments with Prof. Peter W. Schiller at the Clinical Research Institute of Montreal and with Prof. Ryoji Noyori at Nagoya University, he joined the National University of Singapore in 2003, where he now is a Professor. His key research interests include asymmetric catalysis and synthesis.

2. Desymmetrization of Diols through Enantioselective Silylation

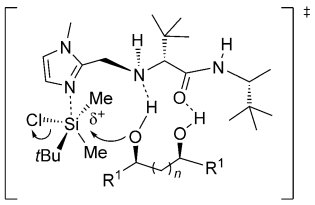
Alcohols are an important class of compounds in organic chemistry, and they are also valuable synthetic intermediates. The site-specific and enantioselective functionalization of polyhydroxy molecules is an area of great interest. Catalytic enantioselective desymmetrization[9] reactions of *meso* diols by acyl transfer reactions[10] have been intensively investigated; however, methods to desymmetrize *meso* diols by enantioselective silylation remain to be a great challenge.

In 2006, Hoveyda, Snapper, and co-workers disclosed their seminal work on the enantioselective silylation of *meso* diols catalyzed by amino acid derived small molecules.[11] The organic catalysts used in their study were carefully designed; both a Lewis basic moiety and a potential hydrogen-bonding site were incorporated in the catalyst structure, and the catalysts can be readily prepared from amino acids in a few trivial steps. Under the optimized reaction conditions, a number of 1,2- and 1,3-diols could be enantioselectively silylated. The substrate scope was quite broad, and different cyclic diols, including five-membered, six-membered, and medium-sized rings, could be silylated with high enantioselectivities (Scheme 2). The mechanistic insights gained in this study were intriguing, and the bifunctional nature of the catalyst was taken into consideration in the proposed transition state (Scheme 3). It was proposed that the hydrogen-bonding interactions between the substrate and the catalyst led to the silylation of one of the enantiotopic hydroxy groups. To explain the role of imidazole during silylation, Corey and Venkateswarlu had proposed that the *N*-dimethyl-*tert*-butylsilylimidazole intermediate that resulted from attack of the imidazole on the silyl chloride was the reactive silylating agent.[6] In the Hoveyda and Snapper report, the imidazole moiety was believed to bind to Si, leading to a polarization of the Si–Cl bond and thus promoting the re-distribution of electron density, which leads to enhanced electrophilicity at the hypervalent Si center.[12] To understand the importance of the different substructures in catalyst **8**, a number of structural analogues of catalyst **8** were prepared and used for the above-mentioned reaction. Although not conclusive, experimental findings indeed supported the proposed mode of action of the imidazole catalyst and agreed well with the proposed transition state.

The implication of the above report by Hoveyda, Snapper et al. is significant: The feasibility of enantioselective functionalizations of alcohols by the catalytic formation of silyl



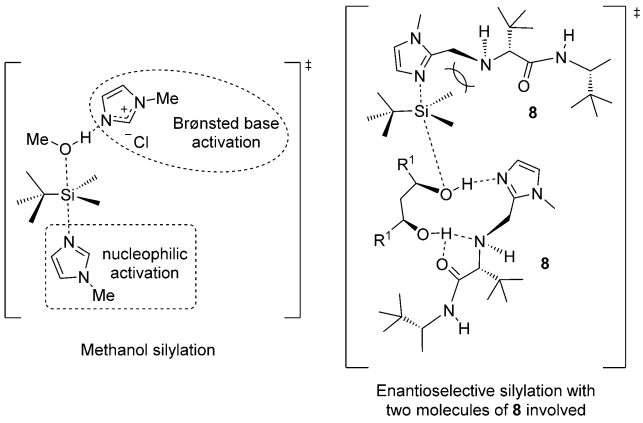
Scheme 2. Catalytic desymmetrization of various diols by enantioselective silylation. DIPEA = diisopropylethylamine.



Scheme 3. Proposed transition state for the enantioselective silylation of 1,2- and 1,3-diols.

ethers had been confirmed—a common protection strategy had excitingly been linked to a catalytic enantioselective process. However, the initially reported method suffered from severe drawbacks: High catalyst loadings (up to 30 mol%) and long reaction times of several days were required. To solve these problems, it was critical to improve the overall efficiency of the silylation catalyst.

In 2013, the same group disclosed a much improved catalytic system by combining chiral and achiral Lewis bases.[13] It is not uncommon to have a catalyst and a co-catalyst in one catalytic system, but catalyst and co-catalyst typically belong to two different molecule classes, and they perform independent roles during the reaction, rendering the catalytic process more efficient in a cooperative fashion. Therefore, at the outset, the idea of using two heterocyclic Lewis bases to effect enantioselective silylation seemed to be counterintuitive. This new strategy was based on a computational study of the silylation of methanol with TBSCl and imidazole. The calculations revealed that two imidazole molecules were involved in the silylation: One creates a highly electrophilic silyl intermediate, and the other one increases the nucleophilicity of methanol by acting as a Brønsted base

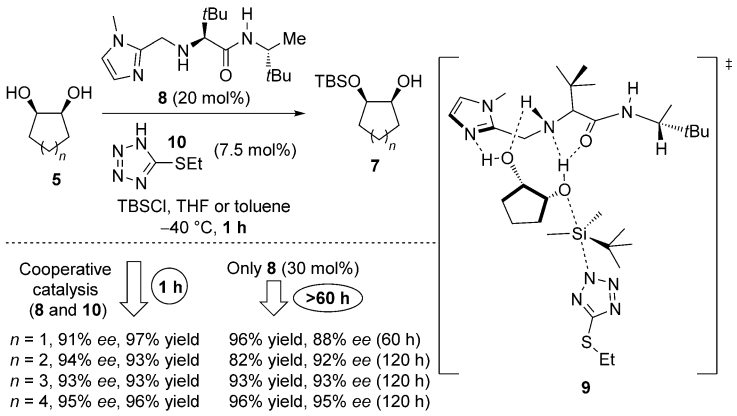


Scheme 4. A dual role for imidazole: Activation of the silane and enhancement of the substrate nucleophilicity.

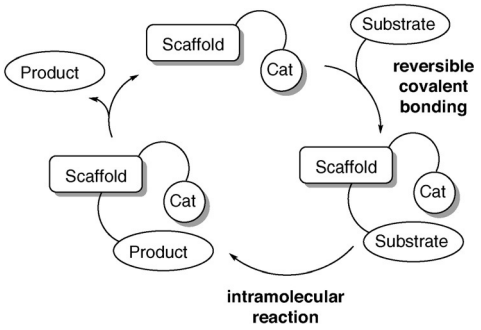
(Scheme 4). Moreover, the requirement for the two activating imidazole units to be situated *anti* to each other relative to the silicon center was inconsistent with the authors' previously suggested bifunctional interaction mode of **8** with the alcohol substrate. Therefore, two molecules of **8** should be involved in the diol silylation reaction. As nucleophilic catalysis is sensitive to steric hindrance, *N*-methylimidazole-derived **8** might be too hindered to be the most ideal nucleophilic activator. On the other hand, **8** was a good chiral Brønsted base. The high enantioselectivities and low silylation rates that were achieved with **8** as the sole catalyst support the above assumptions.

With all the above thoughts in mind, the authors then devised a catalytic system that is based on **8** as the chiral Brønsted base in combination with a structurally similar achiral co-catalyst as a strong nucleophilic activator. After examining a number of heterocyclic co-catalysts, 5-ethylthiotetrazole (**10**) was identified as the best co-catalyst for nucleophilic activation. Results of the enantioselective silylation of diols catalyzed by **8** with or without **10** as a co-catalyst are summarized in Scheme 5. The combination of **8** and **10** proved to be powerful, and the reaction went to completion within one hour even when the loading of **8** was reduced to 20 mol%. DFT calculations revealed that hydrogen-bonding interactions between **8** and the diol substrate were crucial in the transition state leading to the major enantiomer. The current catalyst loading of Brønsted basic **8** at 20 mol% is still quite high, and further reductions are needed in the future.

Enzymes are amazing biocatalysts that can enable organic reactions in biological systems with extremely high efficiency and precision, and they serve as great inspirations for synthetic chemists to design biomimetic approaches. The concept of "induced intramolecularity"[14] can be regarded as a biomimetic approach (Scheme 6). Through reversible covalent bonding interactions, the substrate binds to a chiral scaffold at a specific site that is capable of bringing the substrate and the catalyst into close proximity. Subsequently, a reaction takes place in an intramolecular fashion to afford the desired product. This strategy turns a bimolecular step



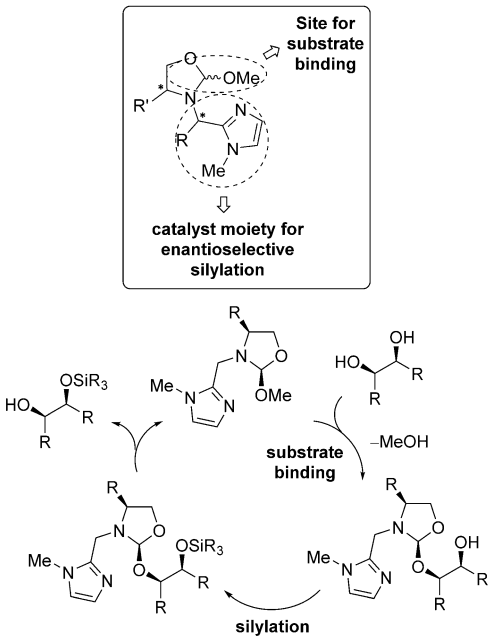
Scheme 5. Enantioselective silylation of diols catalyzed by imidazole **8** with and without 5-ethylthiotetrazole (**10**) as a co-catalyst.



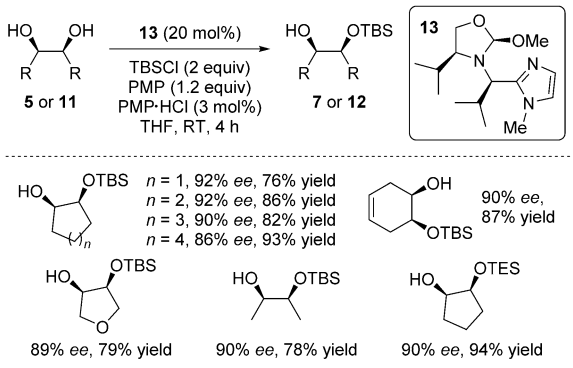
Scheme 6. The concept of induced intramolecularity.

into a unimolecular process, overcoming entropic penalties from which most intermolecular reactions suffer.

Based on the concept of intramolecularity, Tan and co-workers devised an efficient approach for the highly enantioselective desymmetrization of *meso* diols.[15] The catalyst motif contains a catalytic site adjacent to a covalent site for substrate binding. It was anticipated that the diol substrate would replace the OMe group and reversibly bind to the catalyst scaffold. Considering the close association between catalyst and substrate, the imidazole can efficiently promote the intramolecular silylation of the free hydroxy group. Upon release of the product, the catalyst is regenerated (Scheme 7). The newly designed catalysts indeed worked quite well for the enantioselective silylation of *meso* diols. In the presence of the best catalyst, **13**, the silylations of various diols proceeded smoothly, and the monosilylated products were obtained in good chemical yields and with excellent enantioselectivities (Scheme 8). It is noteworthy that the authors established TESCl (TES = triethylsilyl) as a practical reagent for the enantioselective silylation of diols. With the employment of TESCl, shorter reaction times were possible and less silyl chloride was needed. Moreover, the use of TESCl is also advantageous for difficult substrates that contain vinyl or aryl groups. Fundamental mechanistic insights were also gained and support the hypothesis that reversible covalent bonding, rather than hydrogen bonding, is responsible for substrate organization, and that stereoinduction is most likely enabled by the formation of the covalently bound catalyst–substrate intermediate.



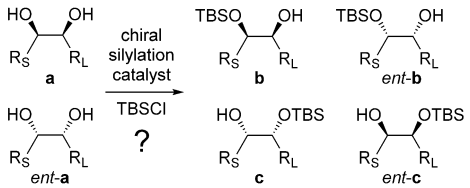
Scheme 7. Silylation enabled by induced intramolecularity.



Scheme 8. Enantioselective desymmetrization of *meso* diols catalyzed by scaffolding catalyst **13**. PMP = 1,2,2,6,6-pentamethylpiperidine.

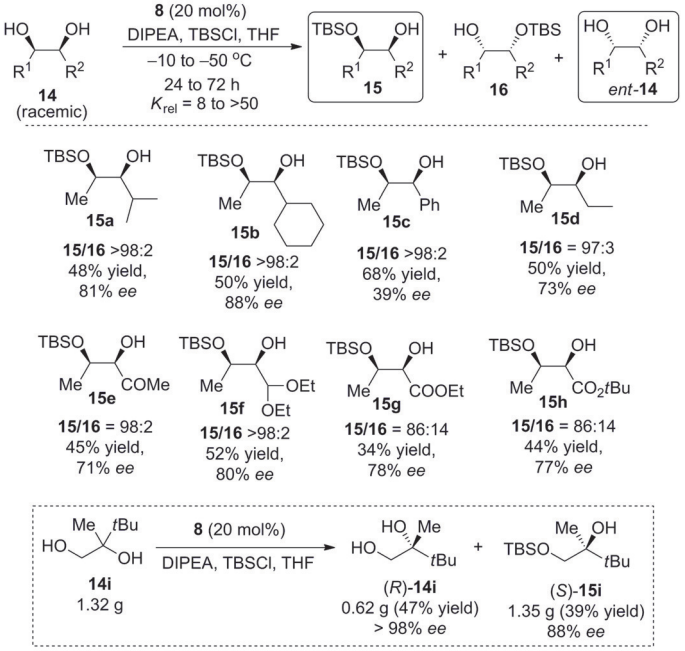
3. Silylation-Based Kinetic and Regiodivergent Resolution of Diols

Compared with *meso*-1,2-diols, racemic *syn*-1,2-diols are more difficult substrates to be functionalized in an enantioselective manner. To develop an effective kinetic resolution approach for 1,2-diols, one enantiomer needs to be more reactive than the other one to achieve an efficient kinetic resolution process, and regioselectivity could pose an extra problem, especially when the groups surrounding the two hydroxy groups are very similar in size (Scheme 9).



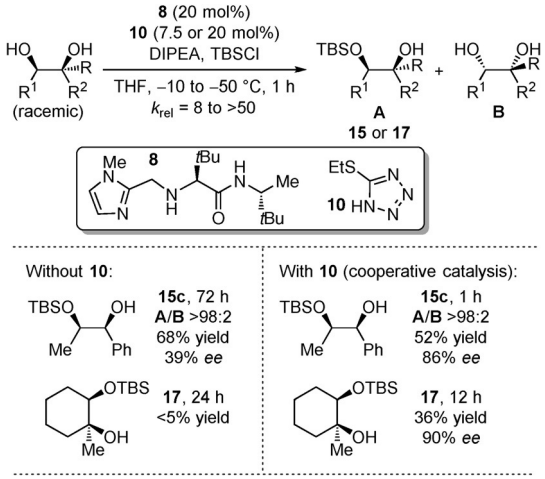
Scheme 9. Kinetic resolution of *syn* diols. R_S and R_L refer to small and large substituents, respectively.

Following their report on the silylation-based desymmetrization of *meso* diols,[13] the Hoveyda and Snapper groups then disclosed a kinetic resolution of 1,2-diols through a regioselective and enantioselective catalytic silylation.[16] The same catalyst **8** that was previously employed in the enantioselective silylation of *meso* diols was found to also be effective in the kinetic resolution of a range of racemic 1,2-diols. High enantioselectivities and regioselectivities were observed; both the monosilylated product **15** and the recovered diols (*ent*-**14**) were obtained in reasonable yields, and the diols (*ent*-**14**) were also obtained with high enantioselectivities. The resolution proceeded with poor site selectivity when one of the R groups was an ester (**15g** and **15h**), and it was proposed that intramolecular hydrogen-bonding interactions between the Lewis basic ester group and the neighboring hydroxy moiety enhanced the nucleophilicity of this α-hydroxy group. It is noteworthy that catalytic asymmetric silylation reactions of primary alcohols bearing an adjacent secondary or tertiary carbinol were also effective, and a gram-scale reaction provided both the recovered diol and the monosilylated product in useful yields and good to excellent enantioselectivities (Scheme 10).



Scheme 10. Kinetic resolution of *syn*-1,2-diols.

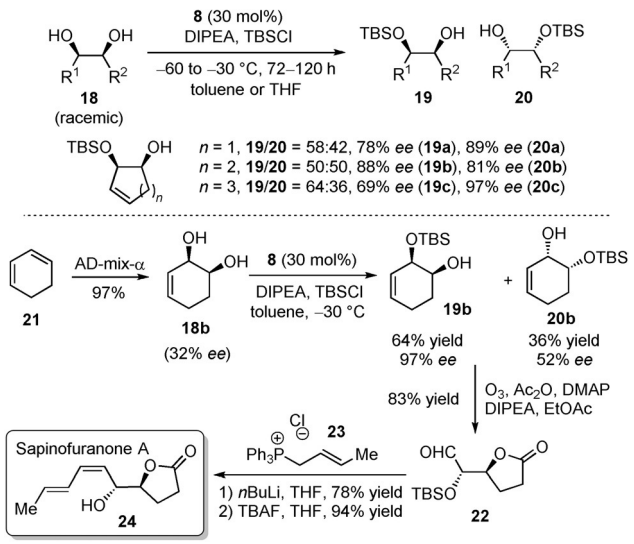
The new strategy of combining chiral and achiral Lewis basic catalysts was also applied to the kinetic resolution of diols by the same authors.[13] With amino acid derived imidazole **8** as the chiral Brønsted base and 5-ethylthiotetrazole (**10**) as the nucleophilic catalyst, catalytic kinetic resolution by enantioselective silylation proceeded smoothly. It is particularly noteworthy that the overall efficiency of the kinetic resolution was greatly enhanced with the introduction of achiral nucleophilic **10**; the reaction time for obtaining **15c** was reduced from 72 h to 1 h and a much higher enantioselectivity was achieved (Scheme 11).



Scheme 11. Kinetic resolution of 1,2-diols using a combined chiral Lewis base/achiral Lewis base catalyst system.

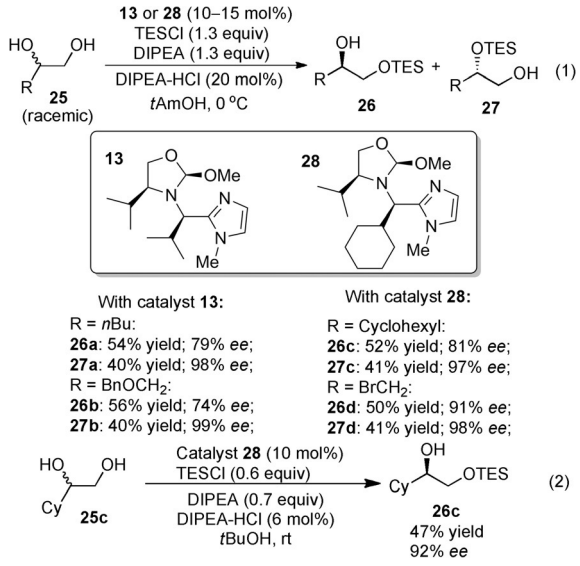
The catalytic enantioselective silylation of racemic 1,2-diols bearing two sterically and electronically similar groups is a challenging task. By employing their amino acid derived imidazole **8**, Hoveyda, Snapper, and co-workers developed regiodivergent reactions[17] of such diol substrates, which provide easy access to regioisomeric, enantiomerically enriched, monosilylated products.[18] Sapinofuranone A[19] (**24**) was efficiently synthesized by employing this regiodivergent reaction as a key step (Scheme 12).

The selective functionalization of one out of multiple functional groups within a molecular structure is extremely important in organic synthesis. In this context, the regioselective functionalization of a less reactive position over a more reactive one is a transformation of great synthetic value.[20] Further extending their strategy by making use of reversible covalent bonding interactions between substrate and catalyst, Tan et al. demonstrated that their scaffolding



Scheme 12. Regiodivergent resolution of diols and total synthesis of sapinofuranone A. DMAP = 4-dimethylaminopyridine, TBAF = tetrabutylammonium fluoride.

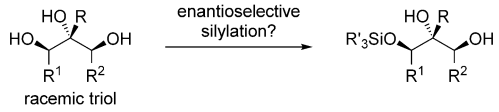
catalysts were effective for the regiodivergent resolution of 1,2-diols.[21] Diol substrates containing both a primary and a secondary hydroxy group were efficiently resolved, and the two different monosilylated products (**26** and **27**) were separable by column chromatography on silica gel. Remarkably, a secondary alcohol (**27**) could be enantioselectively functionalized in preference to a neighboring primary alcohol. Furthermore, the divergent resolution also enabled the enantioselective silylation of the primary alcohol (to yield products **26**). Interestingly, both the primary and secondary silylated products could be obtained in high enantiomeric purity by adjusting the amount of silylating agent (TESCl; Scheme 13).



Scheme 13. Regiodivergent resolution of 1,2-diols catalyzed by **13** or **28**.

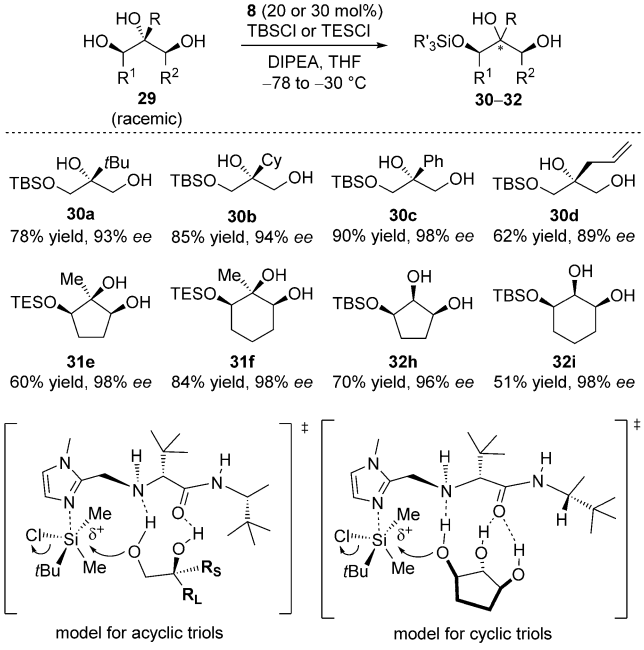
4. Enantioselective Silylation of Triols and Polyols

Structural motifs containing 1,2,3-triols are widely present in natural products and biologically important molecules,[22] and the selective functionalization of such structures is of significant synthetic value (Scheme 14). Having addressed the



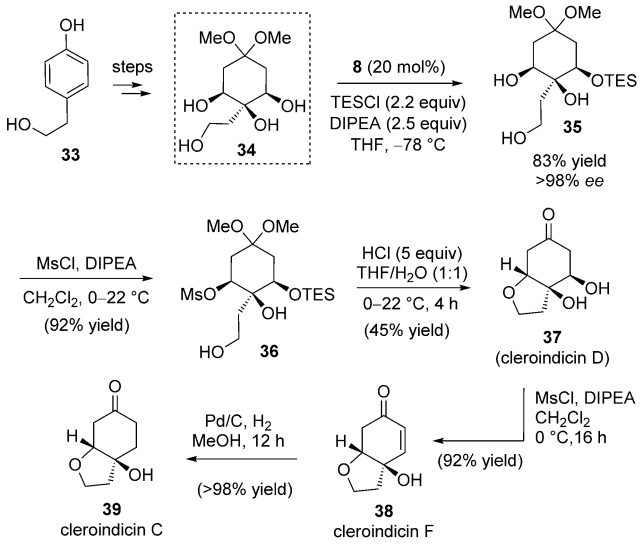
Scheme 14. Enantioselective silylation of triols.

enantioselective silylation of 1,2-diols, the Hoveyda and Snapper groups subsequently developed a catalytic enantioselective silylation of triols by employing their amino acid derived imidazole catalyst **8**.[23] The reaction was broadly applicable to different 1,2,3-triol substrates, including acyclic (**30**), cyclic (**31**), and secondary triols (**32**). Desymmetrization proceeded efficiently to yield monosilylated products in good yields and excellent enantioselectivities. The size of the central carbinol substituent had a great influence on the enantiomeric differentiation for acyclic substrates, but fortunately, the enantioselectivity was insensitive to the steric hindrance of the carbinol substituent in cyclic substrates. The above trends in enantioselectivity were rationalized by models postulated by the authors: The large substituent is positioned away from the amino acid unit in acyclic triols, whereas the silylation of cyclic triols was believed to be governed by the *exo* mode of substrate–catalyst association (Scheme 15). This method to access optically enriched 1,2,3-triols by enantioselective silylation was elegantly applied to



Scheme 15. Desymmetrization of triols by enantioselective silylation.

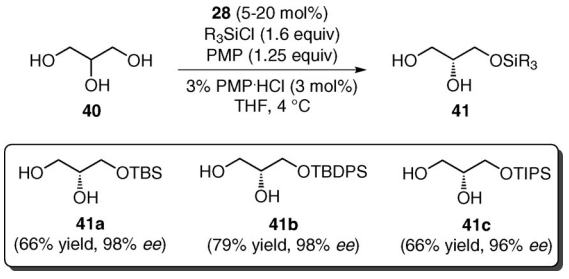
the total synthesis of cleroindicins D, F, and C. The key enantioselective silylation step afforded advanced intermediate **35** in good yield and very high enantioselectivity; this valuable synthetic intermediate cannot easily accessed by other synthetic methods (Scheme 16).



Scheme 16. Total synthesis of cleroindicins D, F, and C with an enantioselective silylation as the key step. Ms = methylsulfonyl.

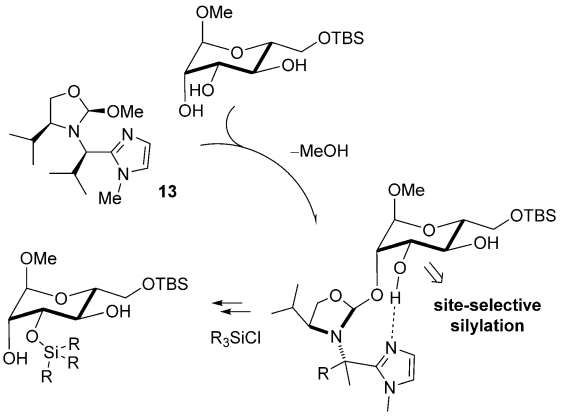
Tan and co-workers achieved the highly enantioselective desymmetrization of glycerol again by applying the concept of reversible covalent bonding.[24] With catalyst **28**, which is capable of engaging in efficient substrate binding, the desymmetrization of glycerol was very efficient (Scheme 17).

There are a vast number of natural products and bioactive molecules that contain multiple hydroxy groups, for example, carbohydrates. Given their importance in the biological sciences and pharmaceutical industry, it is highly desirable to develop strategies for the site-selective functionalization of carbohydrates. The challenge is intrinsic: One has to differentiate between multiple hydroxy groups of great similarity with high precision. Recently, Tan et al. successfully developed an efficient approach to site-selectively functionalize complex molecules containing multiple hydroxy groups.[25] The scaffold catalysts that are capable of substrate–catalyst interactions through the reversible formation of covalent

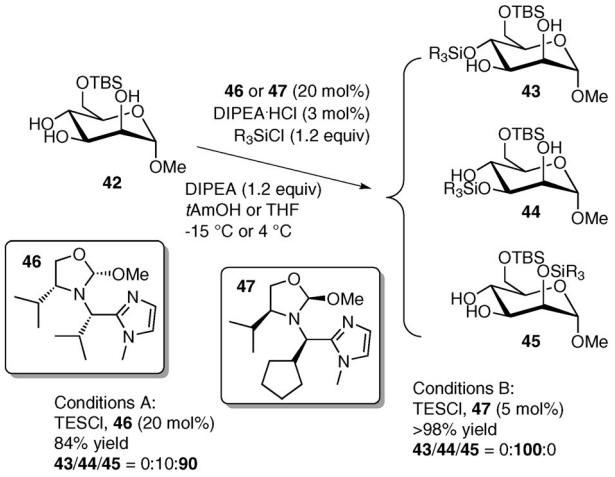


Scheme 17. Desymmetrization of glycerol. TBDPS = *tert*-butyldiphenylsilyl.

bonds were again utilized in this study. It was envisaged that a *cis*-1,2-diol structural motif within a complex molecule could bind to the catalyst, which would bring the adjacent hydroxy group into close proximity of the imidazole moiety for the subsequent silylation reaction (Scheme 18). Some representative results are illustrated in Scheme 19. When a methyl-α-D-mannose derivative was subjected to silylation reactions in the presence of catalyst **46** or **47**, site-selective silylation was observed.



Scheme 18. Site-selective functionalization of mannose.



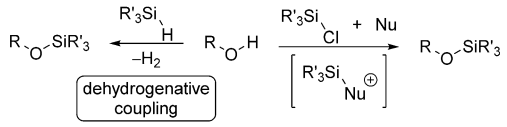
Scheme 19. Functionalization of mannose derivatives.

The inherent preference for C3 silylation could be turned over by catalyst control. Employment of **46** resulted in selective silylation of the C2 hydroxy group, whereas highly C3-selective silylation was observed when **47** was used as the catalyst. The site-selective silylation of the mannose derivative can be ascribed to the unique recognition of a *cis*-1,2-diol moiety within a complex structure in the presence of scaffolding catalysts. Impressively, the authors also described site-selective functionalizations of methyl-α-L-rhamnose, methyl-β-D-arabinose, galactose derivatives, 1,6-anhydro-β-D-galactose, as well as other therapeutically important agents containing *cis*-1,2-diols. Notably, the man-made catalytic

system enabled modifications of the less reactive axial positions of monosaccharides and natural products. Extending the same concept, Tan et al. also developed a site-selective silylation of the ribonucleosides.[26] Although these site-selective silylations of polyols were not really enantioselective processes, such approaches are highly interesting as they offer wonderful opportunities for synthetic chemists to site-selectively manipulate complex molecules.

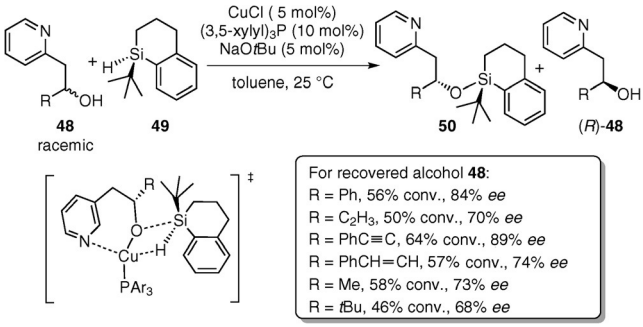
5. Kinetic Resolution with Chiral Silanes and Kinetic Resolution of Simple Alcohols

The impressive advances in enantioselective silylation that have been discussed up to now deal with substrates that contain multiple hydroxy groups. On the other hand, simple alcohol substrates, that is, molecules that contain one hydroxy moiety as the only functional group, are also compounds of great synthetic and therapeutic significance. However, despite their importance, the resolution of simple alcohols by silylation remains to be a difficult task. In enantioselective silylation reactions, most approaches employ bifunctional chiral catalysts with a nucleophilic moiety (e.g., an imidazole) together with a suitable silylating agent (e.g., a silyl chloride). Attack of the nucleophile on the silicon atom results in the formation of a hypervalent silyl species, which not only serves as an activated silylating agent, but also controls the enantioselectivity of the reaction. In an attractive alternative approach, the desired Si–O bond is formed by a transition-metal-catalyzed dehydrogenative coupling reaction (Scheme 20).[27,2b]



Scheme 20. Two silylation strategies.

In 2005, the Oestreich group reported a kinetic resolution of chiral secondary alcohols[28] with silicon-stereogenic silanes.[29] In their reaction system, a copper(I) precatalyst[30] was chosen to promote the dehydrogenative coupling between chiral silanes and alcohols. It was found that virtually no stereoselectivity was attainable for simple unfunctionalized secondary alcohols. Two-point substrate binding, for example, with 2-pyridyl-substituted alcohols, to the copper center was shown to be crucial. By employing silicon-stereogenic silane **49**, the kinetic resolution by a diastereoselective dehydrogenative coupling proceeded efficiently, affording the recovered alcohols in 68–89% *ee* (Scheme 21). The chiral silane was recovered and recycled without racemization at the silicon atom. Full studies of this Cu–H catalyzed reagent-controlled kinetic resolution process were also carried out by the same authors.[31] Investigations of potential donor groups other than the 2-pyridyl unit are particularly interesting. Different pendant donors were attached to the alcohol substrates, and the structure of the



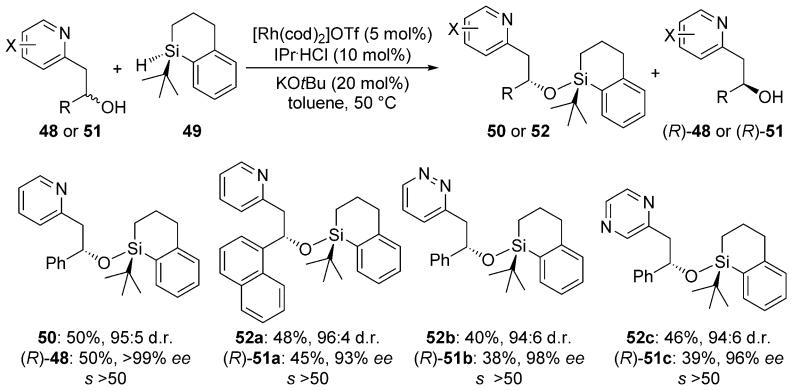
Scheme 21. Stereoselective silylation of 2-pyridyl alcohols by a dehydrogenative Si–O coupling with silicon-stereogenic silane **49**.

pendant heterocyclic moiety was found to be crucial. Whereas pyridine-type and oxazole subunits were effective donor moieties, benzothiazole- or thiophene-functionalized alcohols were unsuitable. Oestreich and co-workers also applied this elegant concept to the kinetic resolution of challenging alcohol structures, including propargylic tertiary alcohols[32] and trifluoromethyl-substituted carbinols.[33] Furthermore, azine[33] and oxime ether[34] donors could also be used for these functional-group-directed stereoselective Si–O coupling reactions.

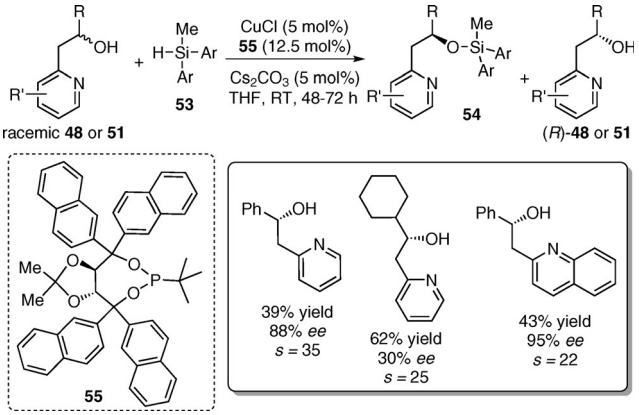
To render the reagent-controlled kinetic resolution of alcohols more effective, Oestreich et al. next focused on the screening of various transition metal/ligand combinations, aiming for much improved selectivity factors.[35] They found that the employment of a cationic rhodium(I) precursor, $[Rh(cod)_2]OTf$, and an N-heterocyclic carbene ligand led to a highly efficient kinetic resolution of donor-functionalized alcohols, affording both the silylated products and the recovered alcohols with excellent *ee* values (Scheme 22). It is noteworthy that the selectivity factors that were reported for these reactions were extremely high, far beyond the values commonly reported for kinetic resolutions.

The employment of chiral silanes as a reagent for a resolution process is certainly not ideal. A dehydrogenative Si–O coupling reaction that relies on an achiral silane in combination with a chiral ligand would certainly be a more attractive and practical option. In 2010, Oestreich and co-workers accomplished the kinetic resolution of 2-pyridyl-substituted alcohols in the presence of monodentate phosphonite ligand **55**.[36] After an extensive screen of phosphine ligands, achiral triorganosilanes, and alcohols with different donor subunits, an optimized procedure was established for the kinetic resolution of alcohols by an enantioselective dehydrogenative Si–O coupling reaction. The process was effective for 2-pyridyl alcohols containing an aryl moiety, whereas substrates with only alkyl moieties were found to be less suitable (Scheme 23). Notably, mechanistic studies supported the hypothesis that only one single chiral monodentate ligand is involved in the crucial asymmetry-inducing σ-bond metathesis.

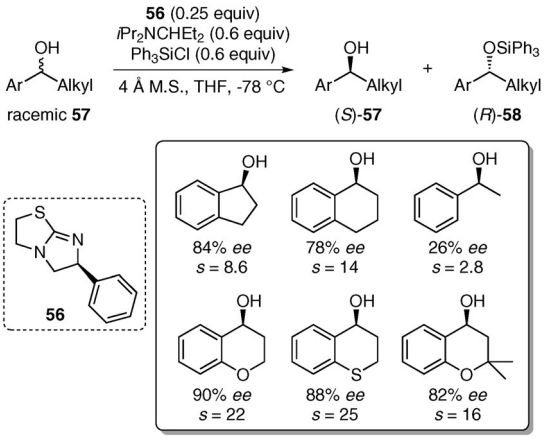
The idea of performing kinetic resolutions of alcohols by transition-metal-catalyzed dehydrogenative Si–O couplings as developed by the Oestreich group is conceptually interesting. The substrates, however, were limited to alcohols with



Scheme 22. Rhodium-catalyzed kinetic resolution of donor-functionalized alcohols by dehydrogenative Si–O coupling. cod = cycloocta-l,5-diene, IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene.



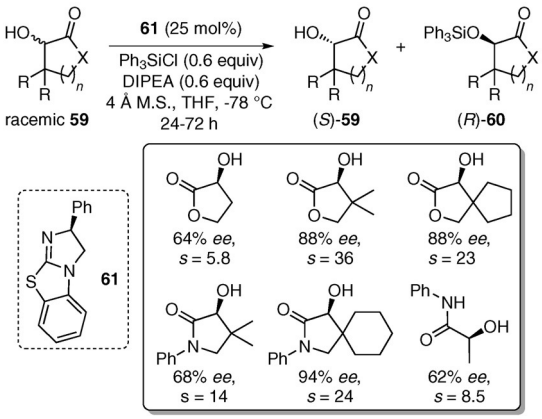
Scheme 23. Enantioselective dehydrogenative Si–O coupling with achiral silanes and chiral ligand **55**.



Scheme 24. Enantioselective silylation of monofunctionalized alcohols catalyzed by isothiourea (−)-tetramisole (**56**). M.S. = molecular sieves.

a pendant neighboring donor group as their coordination to the metal center was always required. The efficient resolution of monofunctionalized secondary alcohols remained to be a challenging task. In 2011, the Wiskur group disclosed a kinetic resolution of monofunctionalized secondary alcohols by enantioselective silylation.[37] The chiral isothiourea (−)-tetramisole (**56**), which was initially introduced by the Birman group[38] as an acylation catalyst, was found to be a good catalyst for the kinetic resolution process. Under the optimized conditions, which involved the use of triphenylsilyl chloride as the silylating agent and THF as the solvent, benzylic alcohols with benzo-fused five- or six-membered ring structures were well resolved. However, simple acyclic alcohols could not be efficiently resolved, and low selectivity factors and poor *ee* values were obtained (Scheme 24).

Recently, Wiskur and co-workers successfully accomplished a kinetic resolution of α-hydroxylactones and -lactams by enantioselective silylation.[39] In the presence of triphenylsilyl chloride and Hünig's base (DIPEA) in THF, (−)-benzotetramisole **61** was an effective catalyst of this process. Impressively, good to excellent selectivity factors and high *ee* values were achieved for a broad range of substrates (Scheme 25). However, the reaction worked less satisfactorily for acyclic esters and amides. Very recently, the same group



Scheme 25. Kinetic resolution of α-hydroxylactones and -lactams by enantioselective silylation with (−)-benzotetramisole (BTM, **61**) as the catalyst. X = O, NAr; *n* = 1, 2.

performed mechanistic studies by employing differently *para*-substituted triarylsilyl chloride reagents in the silylation, and it was postulated that an S_N2-like transition state with a pentavalent silicon center with tetramisole as the leaving

group and the alcohol as the incoming nucleophile was involved in the rate-determining step.[40]

6. Conclusion and Outlook

The recent impressive advances in the asymmetric silylation of alcohols have firmly established silylation reactions as a powerful synthetic strategy to enantioselectively functionalize hydroxy-containing molecules. The implications of this conceptual development are truly exciting, particularly when considering the extraordinary roles that silyl ethers have played in protecting-group chemistry. The functionalization of alcohols by silylation is still at its early stage, and many innovative enantioselective silylation methods are expected to emerge in the near future.[41] Fully realizing the potential of regioselective and enantioselective silylation reactions of alcohols will have an enormous impact on asymmetric synthesis and catalysis.

The pioneering studies on enantioselective silylation that were described in this Minireview have opened up a new fascinating research field. However, many challenging problems remain to be solved, for example, for many types of alcohol substrates, efficient enantioselective silylation conditions have not been developed thus far. Currently, excellent silylation methods are available mainly for cyclic and acyclic 1,2-diols and 1,2,3-triols, carbohydrates, as well as simple alcohols with a neighboring donor group. It is imperative to develop highly enantioselective silylation approaches for difficult substrates, such as acyclic 1,3-diols or simple monofunctionalized alcohols. From a synthetic viewpoint, it would be highly desirable to be able to stereo- and site-selectively functionalize hydroxy groups in complex molecular architectures. Efforts towards silylation reactions applicable to a broad scope of substrates will definitely trigger the development of more powerful catalytic systems. It is envisioned that new catalytic systems, for example, non-imidazole-based organocatalysts or well-designed chiral ligands for metal catalysis, will have to be developed to enable more enantioselective silylation processes. We anticipate that this emerging field will continue to evolve and grow. Making synthetic chemists aware of the power of enantioselective silylation will ensure that many more innovative silyl ether based functionalization reactions and powerful catalytic systems will be developed in the near future to fully address all the currently unsolved problems.

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