Review

Recent Progress in Lewis Base Activation and Control of Stereoselectivity in the Additions of Trimethylsilyl Nucleophiles

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Chem. Rev., **2008**, 108 (12), 5227-5252 • DOI: 10.1021/cr800421c • Publication Date (Web): 14 October 2008

Recent Progress in Lewis Base Activation and Control of Stereoselectivity in the Additions of Trimethylsilyl Nucleophiles

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Received June 26, 2008

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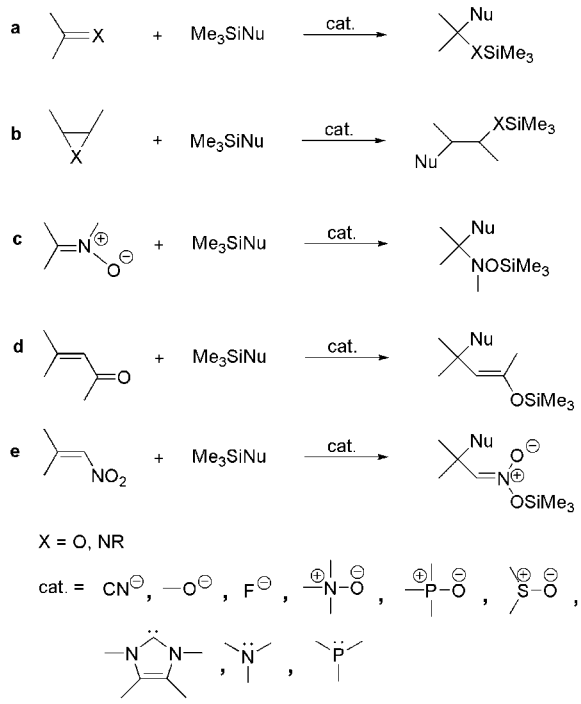
1. Introduction

Trimethylsilyl nucleophiles (Me_3SiNu), with silicon atoms attached to carbon, nitrogen, oxygen, or sulfur atoms, have long been recognized as effective alternatives for proton nucleophiles (HNu) in addition reactions to such electrophiles as aldehydes, ketones, imines, oxiranes, aziridines, nitrones, and polar conjugated systems.[1] The number of examples of such additions has been growing steadily over the past 40 years, while the availability of trimethylsilyl nucleophiles was on the rise and new methods of transformation of silylated pronucleophiles into active nucleophiles were emerging. The interest in Me_3SiNu additions was stimulated by the properties of the silicon atom, allowing the generation of active nucleophilic species ($Nu^{\ominus}$), under different conditions in comparison to HNu sources. Activation of Me_3SiNu by a Lewis base is primarily due to the affinity of silicon to fluorine or oxygen, facilitating the formation of a reactive pentacoordinate or hexacoordinate silicon intermediate, whereas HNu activation requires Brønsted or Lewis base-mediated proton abstraction. Although activation of Me_3SiNu and HNu may frequently be carried out with the same catalyst, deprotonation of weakly acidic carbon nucleophiles by strong bases in certain cases may be incompatible with the reaction conditions or with certain functional groups. Desilylative nucleophile activation occurs smoothly under catalytic conditions. Either 1,2-, 1,3-, or 1,4-additions can be carried out with trimethylsilyl nucleophiles, as shown in Scheme 1.

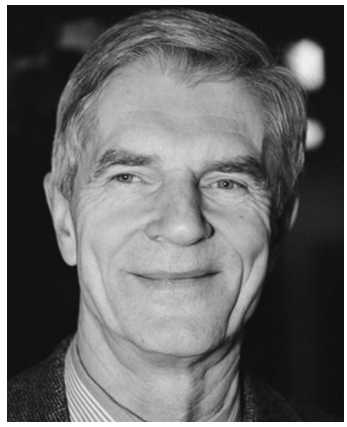
Scheme 1. Catalytic Nucleophilic 1,2-Additions of Me_3SiNu to Aldehydes, Ketones, and Imines (a) or to Epoxides and Aziridines (b), 1,3-Addition to Nitrones (c), and 1,4-Additions to α, β-Unsaturated Carbonyl Compounds (d) and Nitroalkenes (e)



The catalytic effect of the fluoride ion as well as polar *N*-oxide, *P*-oxide, and *S*-oxide bonds can be correlated with the dissociation energies of the Si−F and Si−O bonds (Figure 1), which are among the strongest single bonds and much stronger than the corresponding C−F and C−O bonds.

Either anionic or neutral Lewis bases are suitable for activation of silylated nucleophiles. Both inorganic (especially CsF) and organic fluorides (most frequently tetra-*n*-

10.1021/cr800421c CCC: $71.00
Published on Web 10/14/2008



Jacek Gawronski was educated and completed his Ph.D. and D.Sc. (1977) degrees in chemistry at Adam Mickiewicz University in Poznan, where he has held a position of research group leader since 1981. He did part of his predoctoral studies at the University of Kansas and later spent shorter or longer periods of time as a sabbatical fellow at the University of Nevada, Florida State University, Rijksuniversiteit Groningen, Universität Basel, and University of Gent. In 1990 he accepted a position of full professor at the Department of Chemistry, Adam Mickiewicz University, and head of the Laboratory of Organic Stereochemistry. His research interests range from organic stereochemistry, stereoselective synthesis, and macrocycle synthesis to optical activity and circular dichroism studies of chiral molecules.

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butylammonium fluoride, TBAF) are used as catalysts. In addition, alkali metal carboxylates, alkoxides, and phenoxides are useful as catalysts. Neutral Lewis bases, also called neutral coordinate organocatalysts (NCOs),[2] are of high interest in the context of asymmetric catalysis. *N*-Heterocyclic carbenes (NHCs),[3,4] amines, phosphines, and their derivatives are an emerging class of Me_3SiNu addition activators. Heteroaromatic and aliphatic *N*-oxides (e.g., *N*-methylmorpholine *N*-oxide, NMMO) are frequently used as organocatalysts for Me_3SiNu additions. In this respect, the additions of trimethylsilyl nucleophiles catalyzed by Lewis bases can be classified as organocatalytic. Following the general trend in organocatalysis,[5] we will emphasize in this review the control of enantio- and diastereoselectivity of these additions.

It is now accepted that the catalytic effect of the fluoride- or oxygen-containing ion ($Z^{\ominus}$) or polar oxide group (Y-Z) is due to its attack on one of the vacant 3d orbitals of silicon in the Me_3SiNu species (Scheme 2). A tight ion pair **A**, containing the hypervalent pentacoordinated silicon,[6] is the source of the anionic nucleophile (Nu), which reacts with the carbonyl or imine group (C═X) after its activation by association with the trimethylsilyl group (**B**). The product of nucleophile addition (**B**) is stabilized by silylation (**C**), and the catalyst Y-Z is released for further reaction. It is important to note that any chiral information from the Lewis base can be transferred to the newly formed chiral center if the intimate ion pair **B**, in which the Lewis base and the C═X group are held together by the silicon, corresponds to the transition structure of the reaction. Note that in bifunctional catalysis (see below) the pair Y-Z represents a Lewis acid−Lewis base system, not necessarily within one molecule of a catalyst. The reactive species in fluoride-catalyzed addition of an α-trimethylsilyl substituted benzylphenyl sulfide were recently investigated with the conclusion that the reaction is driven by a carbanion formation.[7]

Whereas Me_3SiNu activation remains an important issue in developing the most effective and selective methods of carrying out addition reactions, a new trend based on the simultaneous activation of the Me_3SiNu and the electrophile has been gaining importance. Electrophile activation requires the use of a Lewis acid, and this role is usually played by various transition metal salts and complexes. Dual activation can be performed by separate molecules of Lewis acid and Lewis base present in the system. However, far more effective, with respect to the stereochemical control of the reaction, appear to be bifunctional catalysts, combining the role of a Lewis base and a Lewis acid in one molecule.[8] In this review the coverage of the Lewis acid catalysts is arbitrarily limited to the main group metal salts and complexes (Mg, Al, Si, and Sn, and occasionally Zn).

A vast amount of information on the catalysis of Me_3SiNu additions has been recorded. The publications prior to 1988, dealing with nonenantioselective Me_3SiNu additions, have been reviewed.[1] The role of Lewis bases as promoters of addition reactions has only recently been fully recognized and reviewed.[9] Reviews of asymmetric reactions involving hypervalent silicate intermediates and catalyzed by Lewis bases have also appeared. They cover mainly the reactions of trialkoxysilyl and trichlorosilyl nucleophiles.[10,11] This present review is focused on organocatalytic additions of Me_3SiNu (including catalysis by main group metal derivatives of organocatalysts); stereoselective catalytic additions which are of current topical interest will be discussed in detail. The review embraces mainly a large number of relevant publications that have appeared since 1990. The following discussion is divided according to the type of Me_3SiNu used.

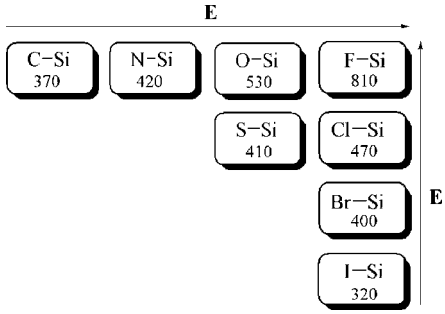
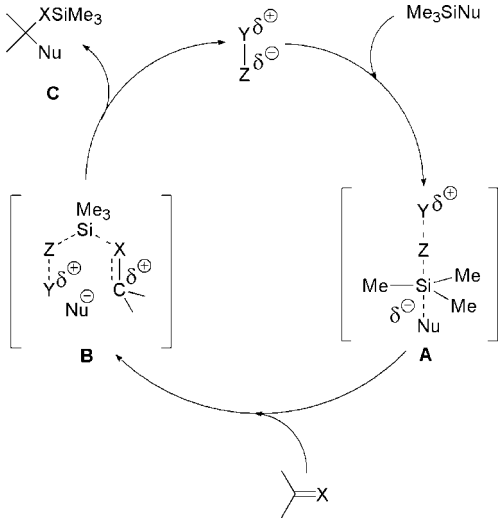


Figure 1. Average dissociation energies (kJ/mol) of synthetically important Si−carbon and Si−heteroatom bonds.

Scheme 2. Proposed Catalytic Cycle in the Addition of Me_3SiNu to a Carbonyl or Imine Group Mediated by an Electron-Rich Lewis Base Y-Z



2. Carbon Trimethylsilyl Nucleophiles

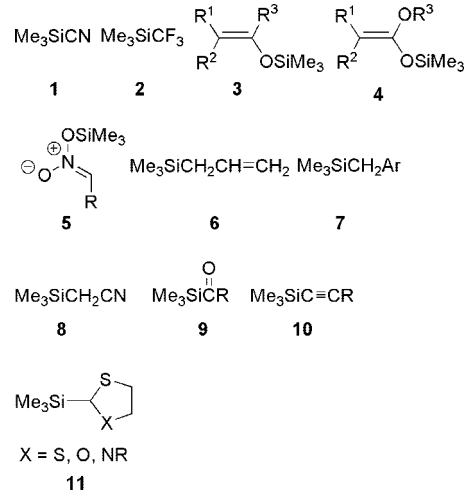
A wide range of carbon nucleophiles in which the trimethylsilyl group is attached to either a carbon or to an oxygen atom is available nowadays, either commercially or through well established procedures. These include trimethylsilyl cyanide (**1**), trifluoromethyltrimethylsilane (**2**), trimethylsilyl enol ethers (**3**), trimethylsilyl ketene acetals (**4**), and trimethylsilyl nitronates (**5**), as well as allyltrimethylsilane (**6**), arylmethyltrimethylsilanes (**7**), cyanomethylsilane (**8**), and acyltrimethylsilanes (**9**), alkynylsilanes (**10**), and various 2-trimethylsilyl-1,3-heterocycles (**11**). Despite the strength of the O−Si bond in **3**−**5**, these silylated nucleophiles can be activated in an organocatalytic cycle due to the transfer of the trimethylsilyl group from the oxygen atom of the nucleophile to the oxygen atom of the electrophile (Scheme 1), making the reaction thermodynamically feasible.

2.1. Trimethylsilyl Cyanide (Me_3SiCN)

2.1.1. Cyanosilylation of Aldehydes and Ketones

Cyanosilylation of aldehydes and ketones with Me_3SiCN (**1**)[12] is the most frequently studied silyl nucleophile addition, providing access to (chiral) α-hydroxy nitriles.[13] Uncatalyzed (thermal) addition of **1** to the carbonyl group of aldehydes or ketones has been reported[14,15] whereas the addition of **1** to enones and chalcones under microwave conditions has led to the products of conjugate hydrocyanation.[16] Reactive dicarbonyl compound, e.g. glyoxal or benzil, can add 2 equiv of **1** in an uncatalyzed reaction.[17] Uncatalyzed addition of **1**

Chart 1. Carbon Nucleophiles



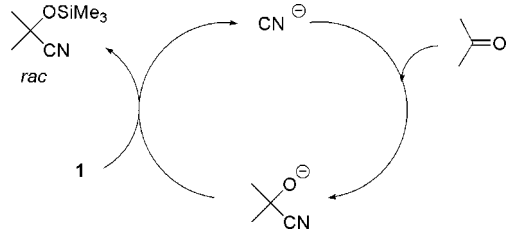
to acylphosphonates occurs at room temperature in toluene solution, probably due to the activating effect of the P═O group in the substrate.[18]

The cyanosilylation reaction proceeds efficiently either at or below room temperature under catalytic conditions and therefore can be adapted for enantioselective processes. The role of the cyanide ion as an initiator is of special interest, since its presence in the reaction medium promotes a nonstereoselective reaction path leading to a racemic product (Scheme 3). In fact, a recently reported procedure describes an efficient preparation of racemic silylated cyanohydrins of ketones by the action of NaCN and Me_3SiCl in DMSO.[19] The effect of *n*-tetrabutylammonium cyanide as an initiator has been well documented.[17,20−22]

Numerous salts, such as metal fluorides (e.g., CsF,[23a] KF,[23b] CuF_2[24]), lithium alkoxides,[25] and immobilized imidazolium hydroxide,[26] have been successfully used to catalyze nonstereoselective additions of **1**. Methyltriphenylphosphonium iodide has been reported to catalyze the addition of **1** to aldehydes;[27] however, the catalytic effect of the corresponding phosphonium cyanide generated in situ in this reaction cannot be excluded. Whereas quaternary ammonium bromides (e.g., nBu_2Me_2NBr) are ineffective as catalysts, their use in combination with *N*-oxides promotes the addition of **1** to ketones.[28] *N*-Methylmorpholine *N*-oxide alone is able to catalyze the addition of **1** to ketones under mild conditions (0.3 equiv catalyst load, room temperature, dichloromethane solution).[29] Other tertiary aliphatic *N*-oxides were found to be effective as catalysts for this addition reaction (0.05 equiv catalyst load, room temperature, diethyl ether solution).[30] Other than fluorides and oxygen bases, salts such as lithium chloride,[31] salts with nucleophilic oxygen atoms,[32−35] and elemental iodine[36] also can catalyze the addition of **1** to a carbonyl group. Salts such as lithium perchlorate,[37] magnesium bromide,[38,39] zinc bromide,[38] zinc iodide,[40,41b,42] aluminum trichloride,[17] bismuth tribromide,[43] indium tribromide and trichloride,[41] and diorganotin dichlorides[44] apparently act as Lewis acids, activating the carbonyl group for the addition of **1**, and not unexpectedly, enantioselective cyanosilylation reactions catalyzed by metal complexes have recently received in-depth coverage in the literature.[45b]

Salts and compounds with polar bonds, which do not have clear Lewis base or Lewis acid character, may in fact be treated as bipolar catalysts $Y^{\oplus}Z^{\ominus}$, activating both the electrophile and the nucleophile in a cyclic transition

Scheme 3. Reaction Cycle in the Addition of Me_3SiCN (1) to a Carbonyl Group Initiated by a Free Cyanide Anion

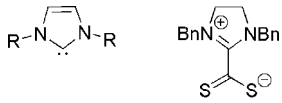


structure, incorporating the activator $Y^{\oplus}Z^{\ominus}$, the carbonyl group, and the silylated nucleophile, as shown in Scheme 2. An example of such a catalyst is imidazolinium-carbodithionate zwitterion **13**, which is known to effectively catalyze cyanosilylation of aldehydes at room temperature.[46]

It has been reported that tetracyanoethylene (TCNE) is an active catalyst for the cyanosilylation reaction, possibly operating through a single-electron transfer or by coordination of the electron-deficient double bond of TCNE to the carbonyl group.[47]

Cyanosilylation can be effectively catalyzed by such Lewis bases as amines, phosphines, and arsines.[48] The use of triethylamine as catalyst under solvent-free conditions has been described.[49] The reaction is also catalyzed by a diamino-functionalized mesoporous material.[50] Denmark and Chung reported that phosphines (nBu$_3$P), amines (NEt$_3$, DMAP, *N*-methylimidazole), hexamethylphosphoric triamide (HMPA), *N*,*N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), pyridine *N*-oxide, and triphenylphosphine oxide were among the active organocatalysts for the addition of **1** to benzaldehyde in acetonitrile. With the exception of HMPA, the catalytic activity of oxygen centered bases was found to be poor and the rate of reaction correlated well with the donor ability of the Lewis base.[51] Nonionic, strong bases of the phosphazene[52] and 1,1,3,3-tetramethylguanidine[53] type have been found to be effective as cyanosilylation catalysts.

Chart 2

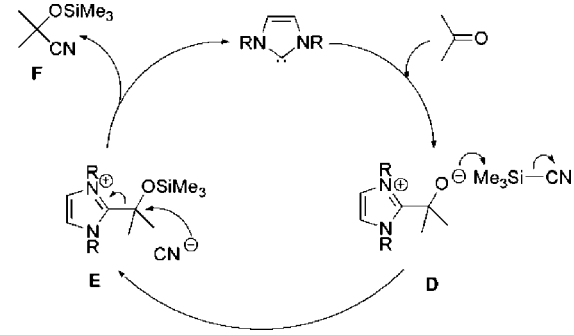


12 **13**

N-Heterocyclic carbenes (NHC, **12**), generated from the corresponding precatalyst salts, have recently been used to catalyze additions of Me_3SiCN to aldehydes and ketones. Although the reports of Aoyama,[54] Maruoka,[55] Suzuki,[56] and Song[57] differ in the type of NHC and reaction conditions used, the reaction proceeds rapidly in all cases. NHC **12** (RtBu), used by Song, was very effective and is notable for the very low catalyst load (0.005−0.0001 equiv). Suzuki et al. suggested a reaction pathway (Scheme 4), alternative to a general Me_3SiNu activation mechanism shown in Scheme 2, which operates through activation of the electrophile (the carbonyl group) to form an intermediate **D**, which is then silylated by the Me_3SiCN to give **E**. Subsequent substitution reaction with the participation of **E** and the cyanide anion produces the silylated cyanohydrin **F** and the NHC. Note that in this mechanism no pentavalent silicon intermediate is invoked.

The importance of cyanohydrins in nature and in organic syntheses as precursors of α-hydroxy acids and β-amino alcohols prompted the development of organocatalytic enan-

Scheme 4. Alternative Activation Pathway for the Cyanosilylation Reaction Catalyzed by NHC[56]



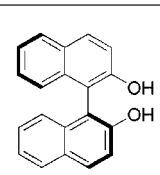
tioselective processes.[13,45] These are based primarily on the previously recognized catalytic effect of amines, amine oxides, and lithium phenoxides and carboxylates. Historically, the addition of **1** to aldehydes catalyzed by a chiral base has been reported in 2000 by Holmes and Kagan.[58] Using monolithium salts of either (*S*)-(−)-BINOL (Table 1, entry 1) or (*R*,*R*)-(−)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine (entry 2), generated in situ with the use of *n*-butyllithium, the silylated cyanohydrins were obtained in yields of up to 99% and with enantioselectivities of up to 97%, using as little as 1 mol % of the catalyst. A study of Ishihara et al. has shown a substantial effect of the lithium source on the yield and enantioselectivity of addition of **1** to aromatic aldehydes. When lithium hydroxide or lithium alkoxides were used instead of *n*-butyllithium, highly effective chiral lithium binaphtholate aqua or alcohol complexes were formed. Silylated cyanohydrins were obtained with excellent yields and enantioselectivities (Table 1, entry 3), providing a route for scaling-up the reaction.[59] Feng et al. reported on the use of sodium phenylglycinate as a catalyst for cyanosilylation of ketones, with enantioselectivities in the range of 55−97%. Although the catalyst load was rather high (0.3 equiv) (Table 1, entry 4), its easy availability and the simplicity of the procedure are encouraging for scaling-up the synthesis and for practical applications. Neither sodium nor potassium salts nor the salts of other amino or hydroxy acids were active as catalysts in this reaction.[60]

In addition to lithium phenoxides and carboxylates, enantioselective cyanosilylation of ketones with chiral Lewis bases has been reported. Deng et al. have shown that DABCO is efficient as a catalyst in cyanosilylations of ketones, including hindered ones.[61] Cinchona alkaloids, having a quinuclidine moiety embedded in a chiral skeleton, appeared to be good candidates as Lewis base chiral catalysts. Thus, α,α-dialkoxyketones were subjected to reaction with **1** in the presence of a dimeric alkaloid, such as $(DHQ)_2AQN$ or $(DHDQ)_2PHAL$, to give the adducts with high enantioselectivity (Table 1, entry 5).[61] In contrast, Denmark and Chung reported that addition of **1** to aldehydes, catalyzed by $(DHQ)_2PHAL$, gave products in moderate yields and with low enantioselectivities (Table 1, entry 6). The highest enantioselectivity was observed with the use of toluene as the solvent. Chiral amines, such as α-methylbenzylamine, *N*-methylephedrine, and strychnine gave only racemic products of cyanosilylation in acetonitrile solution. Likewise, addition of **1** to acetophenone, catalyzed by simple alkaloids, gave the product with low enantiomeric excess (below 10%).[75]

Chiral *N*-oxides play an increasingly important role in asymmetric catalysis.[76] *N*,*N*′-Dioxides with two proline-

Table 1. Reaction Conditions and Results of Enantioselective Catalysis of Me_3SiCN Additions to Aldehydes and Ketones

entry	carbonyl compound	catalyst (equiv)	solvent (temp, °C)	yield (%)	ee (%)	ref
1	aldehydes	**14** (0.01)	Et_2O (−78)	38−96	0−59	58a
2	aldehydes	**15** (0.01)	Et_2O (−78)	64−99	0−97	58b
3	aromatic aldehydes	**14** + LiO*i*Pr (0.01−0.10 each)	PhMe (−78)	83−99	81−98	59
4	ketones	**16** (0.3)	*i*PrOH/THF (−45)	75−97	55−97	60
5	α,α-dihydroxy ketones	**17** or **18** (0.02−0.1)	$CHCl_3$ (−30 or −50)	81−98	90−97	61
6	aldehydes	**18** (0.05)	various (20)	21−63	2−32	51
7	aryl aldehydes	**19a** (0.025)	CH_2Cl_2	57−92	53−73	62
8	α,α-dialkoxy ketones	**19b** (0.1) + *m*-CPBA (0.2)	$ClCH_2CH_2Cl$, *t*BuOMe (−45)	73−99	85−93	63
9	aldehyde	**20**	THF (−78)	82	22	56
10	aldehydes	**21** (0.1)	PhMe (−78)	quant	60−70	64
11	enones, aryl ketones	**22a** (0.05) + CF_3CH_2OH (1)	CH_2Cl_2 (−78)	81−98	89−98	65
12	aldehydes	**23** (0.1)	CH_2Cl_2 (20)	30−100	45−68	66
13	aliphatic aldehydes	**24** (0.3)	CH_2Cl_2 (−78)	49−89	72−90	67
14	aldehydes	**25a** (0.09) + $Bu_3P{=}O$ (0.36)	CH_2Cl_2 (−40)	91−100	83−98	68
15	aldehydes	**26** (0.05)	CH_2Cl_2 (−60)	82−98	70−80	69
16	aldehydes	**27a** (0.1) + $Ph_3P{=}O$ (0.4)	PhMe (−20)	70−99	70−98	70
17	aldehydes	**27b** (0.1) + HMPA (0.4)	Et_2O (−20)	65−92	92−99	71
18	aldehydes	**28** (0.01) + $Ph_3P{=}O$ (0.1)	CH_2Cl_2 (−40 to −50)	91−96	72−86	72
19	ketones	**28** (0.01) + $Ph_3P{=}O$ (0.3)	CH_2Cl_2 (20)	75−98	60−91	73
20	ketones	**29** (0.01) + $PhNMe_2$\?\O (0.005)	THF (−20)	80−99	79−94	74



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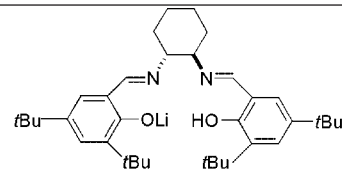

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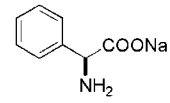

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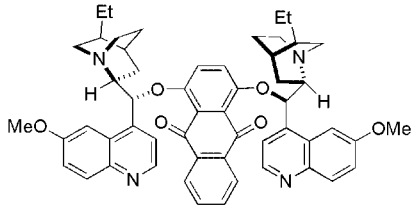

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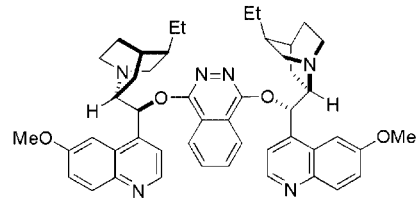

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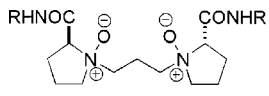
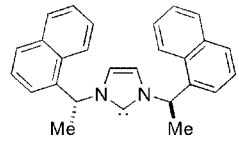


19a R = *c*-C_6H_{11}
19b R = *c*-C_5H_9



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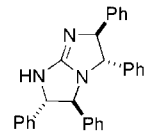

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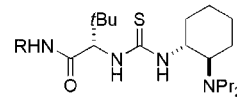
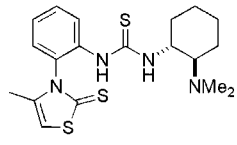


22a R = Me
22b R = *i*Pr
22c R = $CH(tBu)_2$
22d R = *i*Pr(*R*)CHCONMe$_2$



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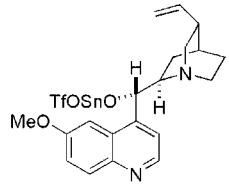

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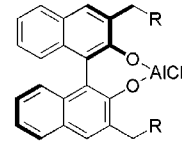
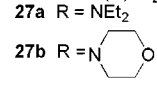
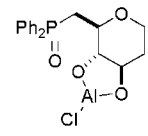


25a R = P(O)Ph_2
27a R = NEt_2



27b R =



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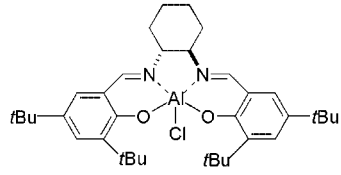

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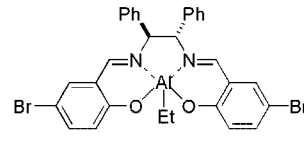

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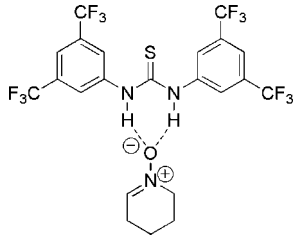


Figure 2. Proposed activation mechanism of a nitrone by a thiourea molecule substituted with electron-deficient groups.

based moieties represent yet another type of chiral organocatalyst for the addition of **1** to aldehydes. Enantioselectivities at the level of 53−73% were achieved with aromatic aldehydes, as shown in Table 1, entry 7.[62] Bisproline-type *N*,*N*′-dioxides can be generated in situ, using *m*-chloroperbenzoic acid (*m*-CPBA) as a source of oxygen. As shown in Table 1, entry 8, α,α-dialkoxyketones can be cyanosilylated in this way with good yields and excellent enantioselectivities.[63] It is important to note that the use of mono *N*-oxide (entries 7 or 8) led to a much lower yield and enantioselectivity of cyanosilylation. This indicates that two dipolar N−O bonds are more effective as activators of the silylated nucleophile, suggesting a hexacoordinated silicon species as an active intermediate.

Chiral NHC was applied by Suzuki et al. as an organocatalyst for cyanosilylation of 2-methoxy-1-naphthaldehyde (Table 1, entry 9). This first attempt to use NHC in an asymmetric cyanosilylation was only of limited success (ee 22%).[56]

Ishikawa and Isobe applied a C_2-symmetrical chiral guanine derivative for cyanosilylations of aldehydes (Table 1, entry 10). Quantitative yields and moderate enantioselectivities (60−70%) were achieved in these reactions.[64]

Bifunctional catalysis (dual activation)[8] has recently emerged as a promising method for improving the enantioselectivity of asymmetric additions. Both nucleophile and electrophile are activated by the catalyst molecule. The concept of electrophile activation by Lewis acid has long been the core of catalysis by transition metal complexes. In organocatalysis the role of the Lewis acid activator of the electrophilic group can be taken over by a urea or thiourea molecule substituted with an electron-withdrawing group, as a hydrogen-bond donor.[77] The N−H bonds of urea interact with the oxygen atom of a nitrone, increasing the reactivity of the C═N bond for nucleophile attack (Figure 2).[78]

Two chiral bifunctional thiourea catalysts have been used for the cyanosilylation reaction of aldehydes and ketones. Both have structures based on the *trans*-1,2-diaminocyclohexane (DACH) skeleton and have a thiourea moiety to activate the carbonyl group as well as an amine group to activate Me_3SiCN. Fuerst and Jacobsen used a structurally fine-tuned organocatalyst, combining DACH and *tert*-leucine molecules and two *n*-propyl substituents on the amine group (Table 1, entry 11). Cyanosilylations of ketones having one sp^2-hybridized substituent in the presence of **22** proceeded with high yields and enantioselectivities.[65] A subsequent mechanistic study of Zuend and Jacobsen, based on a kinetic analysis and DFT modeling of the transition state structures, confirmed the preferred mode of cooperative activation of the cyanosilylation reaction in which both the thiourea and the tertiary amine groups of the catalyst are involved in the rate-determining step. In this step, amine-bound HCN adds to the thiourea-bound ketone. Calculated transition structures

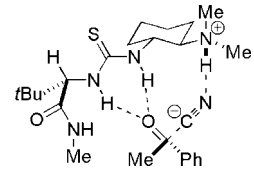
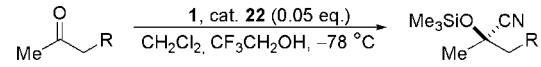


Figure 3. Proposed transition state for thiourea **22a**-catalyzed addition of cyanide to acetophenone.

Scheme 5. Enantioselective Additions of Me_3SiCN (1) to Alkyl Methyl Ketones[79]



	ee (%)	
R =	*n*Bu	Ph
cat. **22a**	11	8
22b	54	71
22c	63	84
22d	65	85

show that, with the use of catalyst **22a**, amine-bound HCN approaches the *re* face of the thiourea-bound acetophenone molecule (Figure 3).

On the basis of these findings, it was concluded that the structure of the amino acid portion of the catalyst is of high importance for the enantioselectivity of the addition. Indeed, structurally modified catalysts **22b**−**22d** displayed a much higher level of asymmetric induction in the demanding case of addition of **1** to alkyl methyl ketones (Scheme 5).[79]

Steele et al. introduced a tertiary amine−thiourea bifunctional chiral catalyst, as a mixture or individual thiazoline-2-thiourea derived atropisomers (Table 1, entry 12). Yields in the range 30−100% and moderate enantioselectivities (45−68%) were obtained in cyanosilylations of various aldehydes.[66]

Kobayashi et al. pioneered another method of bifunctional catalysis by combining the function of a tertiary amine (a Lewis base) and tin triflate (a metal-centered Lewis acid) in the derivative of a cinchona alkaloid **24** (Table 1, entry 13). The products of addition were obtained with good yields and enantioselectivities; however, the catalytic system produced such a reactivity profile toward aliphatic aldehydes only.[67]

The effect of simultaneous use of a bisoxazoline magnesium complex, acting as a chiral Lewis acid, and an uncomplexed bisoxazoline as a chiral Lewis base on the cyanosilylation of aldehydes was studied by Corey and Wang.[80] Their work indicated that mechanistically the role of the chiral Lewis base was to provide an equivalent of chiral cyanide ion for the addition reaction. The hydrogen cyanide could be produced by hydrolysis of **1**.

More recently, a different approach to bifunctional catalysis has been demonstrated by Shibasaki et al.[81] It combines a Lewis acid (aluminum phenoxide/chloride derived from BINOL) and a Lewis base (P═O group) action of bifunctional catalyst **25a** for a highly enantioselective cyanosilylation of various aldehydes (Table 1, entry 14).[68]

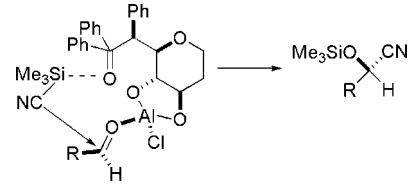
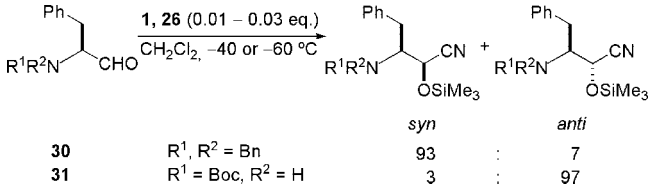


Figure 4. Proposed facial selectivity of cyanosilylation of aldehydes with bifunctional **26** catalyst.

Scheme 6. Diastereoselective Additions of Me_3SiCN (1) to *N*-Protected Amino Aldehydes[84]



The reaction is general, and both the yield and enantioselectivity could be significantly improved by the addition of $Bu_3P{=}O$. It was applied to an enantioselective total synthesis of epothilone A.[82]

The functionally similar catalyst **26**, based on a carbohydrate framework, has been designed by Shibasaki et al. Cyanosilylations of aldehydes with **26** as catalyst proceed with high yields and moderate enantioselectivities (Table 1, entry 15). A plausible stereochemical model accounting for the observed enantioselectivity during formation of the (*S*)-cyanohydrin product is shown in Figure 4.[69]

The bifunctional catalyst **27**, featuring a tertiary amine (Lewis base) and aluminum chloride (Lewis acid) embedded in the chiral BINOL skeleton, was used by the group of Najera and Saa (Table 1, entry 16). In the presence of triphenylphosphine oxide as an additive, aldehydes reacted with **1** with excellent yields and good to excellent enantioselectivities, and the catalyst could be recovered and reused.[70]

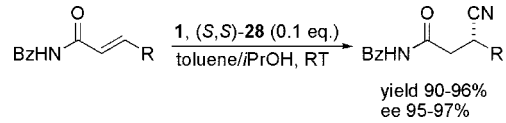
The readily prepared bifunctional catalyst **27b**, which is similar in its structure to **27a**, catalyzed the addition of **1** to aldehydes with over 92% enantioselectivity. The addition of HMPA greatly accelerated this reaction in diethyl ether as a solvent (Table 1, entry 17).[71]

In a number of recent reports it was demonstrated that bifunctional catalysis can be successfully achieved with two separate molecules, one acting as a Lewis base to activate the silylated nucleophile and the other—a Lewis acid—activating the carbonyl electrophile. Kim et al. used Al(salen) **28** and $Ph_3P{=}O$ as a pair of Lewis acid and Lewis base catalysts. Aromatic and aliphatic aldehydes and ketones afforded silylated cyanohydrins in high yields and with moderate enantioselectivities (Table 1, entries 18 and 19).[72,73] A 2-fold activation effect was also demonstrated by Feng et al., who used Al(salen) complexes and achiral *N*-oxides at low loads to catalyze the addition of **1** to ketones.[83] Good to high enantioselectivities of addition were achieved with the use of chiral Al(salen) complexes, such as **29** and achiral *N*,*N*-dimethylaniline *N*-oxide (Table 1, entry 20).[74]

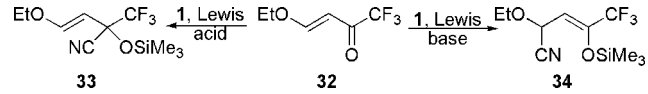
The bifunctional catalyst **26** was used for highly diastereoselective additions of **1** to chiral α-amino aldehydes. The *N*-protected amino aldehydes **30**, **31** derived from phenylalaninol showed an interesting dependence of diastereoselection on the nature of the protecting group. For example, with an NBn_2 group as in **30**, high *syn* selectivity of addition was observed, whereas the *N*-Boc protected aldehyde **31** gave predominantly the *anti* diastereomer (Scheme 6).

Amino aldehydes of **30** and *ent*-**30** or **31** and *ent*-**31** reacted with **1** in the presence of catalyst **26** with comparable diastereofacial selectivities: *ent*-**30**, 75% *syn*, 25% *anti*; *ent*-**31**, 4% *syn*, 96% *anti*. The reaction of *ent*-**30** is an example of the mismatched configuration of the substrate and the catalyst, as evidenced by the lower reaction rate and diastereoselectivity.[84]

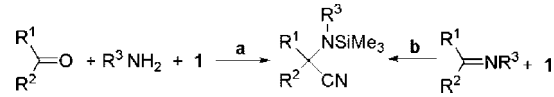
Scheme 7. Enantioselective Conjugate Additions of Me_3SiCN (1)[85]



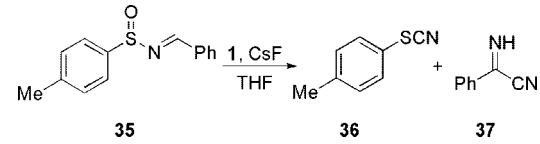
Scheme 8. Regioselective Additions of Me_3SiCN (1) to Enone 32[86]



Scheme 9. Three-Component Silylative Strecker Reaction (a) and Strecker-Type Cyanosilylation of Imines (b) as the Routes to Silylated α-Aminonitriles



Scheme 10. Unexpected Course of Addition of Me_3SiCN (1) to *N*-Sulfinylimine 35[105]



It is of interest to note that whereas all of the Lewis base induced cyanosilylation reactions discussed above are 1,2-additions, enantioselective catalysis with chiral Lewis acids such as **28** leads to 1,4-addition of **1** to α,β-unsaturated imides, with high yields and enantioselectivities (Scheme 7).[85]

The reaction is believed to proceed according to a dual activation mechanism involving the nucleophile bound to the Al complex and the electrophile (imide) activated by another molecule of the Al complex.

Significant effects of solvent, temperature, and catalyst on the regioselectivity of addition of **1** were observed in the case of *E*-1,1,1-trifluoro-4-ethoxybut-3-en-2-one (**32**). With a Lewis base catalyst (tertiary amine), the 1,2-addition product **33** was formed almost exclusively whereas, with Lewis acids (such as $BF_3{\cdot}Et_2O$, I_2, ZnI_2, $LiClO_4$, Me_3SiOTf), the 1,4-addition product **34** was the only product (Scheme 8).[86]

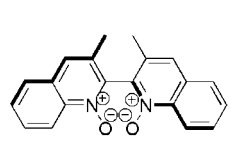
2.1.2. Addition to Imines (Strecker and Reissert Reactions)

The Strecker reaction with the use of Me_3SiCN (**1**) as a source of cyanide anion has received considerable attention as a method of synthesis of α-aminonitriles (Scheme 9).

A noncatalyzed three-component reaction between **1**, an aldehyde, and an amine in acetonitrile solution has been reported.[87,88] The authors suggest that the reaction may in fact be catalyzed by water generated in the reaction or accelerated by a pentacoordinate silicon species which is more nucleophilic than **1**. The use of a ketone as a component in Strecker reactions requires application of high pressure (0.6 GPa).[89] Direct, three-component Strecker reactions can be catalyzed by a variety of polar compounds, such as azaphosphatrane nitrate,[90] (bromodimethyl)sulfonium bromide,[91] ionic liquids ([bmim]BF_4 or [bmim]PF_6),[92] lithium perchlorate in diethyl ether,[93] or montmorillonite KSF clay.[94]

Table 2. Reaction Conditions and Results of Enantioselective Catalysis of Strecker-Type Additions of Me_3SiCN to Imines $R^1R^2C{=}NR^3$

	imine							
entry	R^1	R^2	R^3	catalyst (equiv)	solvent (temp, °C)	yield (%)	ee (%)	ref
1	Ar	H	$CHPh_2$	**38** (1)	CH_2Cl_2 (0)	30−95	12−95	108
2	Ar	alkyl	$P(O)Ph_2$	**39** (0.05) + *m*-CPBA (0.1)	PhMe (−20)	90−99	72−92	109
3	Ar, alkyl	H	9-fluorenyl	**25a** (0.09) + PhOH (0.2)	CH_2Cl_2(−40)	66−97	70−95	110a
4	Ar	H	9-fluorenyl	**40** (0.1) + *t*BuOH (1.1)	CH_2Cl_2(−50)	96−100	83−87	110b
5	Ar	Me	Ts	**41** (0.05) + DAHQ (0.2)	PhMe (−20)	90−99	61−91	111a
6	Ar	alkyl	Ts	**42** (0.02) + AdOH (1)	PhMe (0)	73−96	93−99	111b



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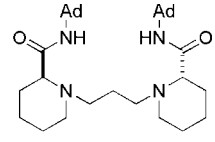
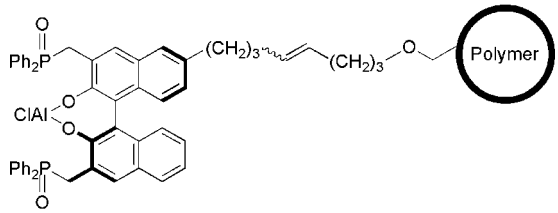


39 (Ad = 1-adamantyl)



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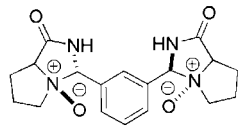

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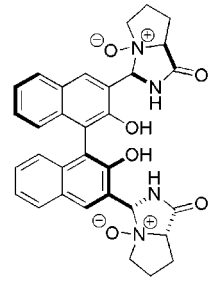


42

The reaction is known to be catalyzed also by protic (NH_2SO_3H[95]) or Lewis acids (bismuth trichloride[96]) or even iodine.[97]

Additions of **1** to aldimines or less reactive (less electrophilic) ketimines represent an indirect version (*Strecker-type*) of the reaction (Scheme 5). The reaction proceeds without a catalyst with highly reactive endocyclic imines, such as 3,4,5,6-tetrahydropyridines (Reissert reaction).[98] With *N*-tosyl-activated imines, catalysis with NHC[54,99] or with carboxylate salts[100] is effective. Addition of **1** to *N*-arylimines occurs in a mixture of polyethylene glycol and water as a solvent.[101] Lewis acid catalysis was reported for aldimines ($LiClO_4$ or $BF_3{\cdot}Et_2O$)[102] or for double addition of **1** to α,β-unsaturated aldimines ($AlCl_3$).[103] *N*-Acylhydrazones have been used as imine equivalents for the addition of **1** catalyzed by amines (NEt_3, DMAP, TMEDA, DABCO).[104] Unexpectedly, under CsF catalysis, the addition of **1** to *N*-sulfinylimine **35** caused breaking of the N−S bond to give *p*-toluenethiocyanate (**36**) and 2-imino-2-phenylacetonitrile (**37**) as the sole products (Scheme 10).[105]

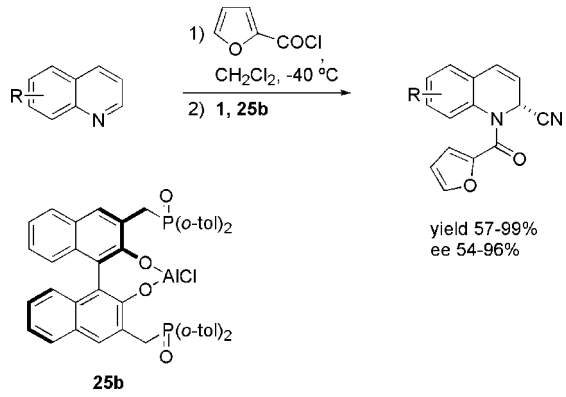
The developments concerning the enantioselective Strecker reaction have recently been reviewed.[106] Asymmetric organocatalysis of the Strecker reaction with the use of **1** is limited to its indirect variant. However, very recently, Feng et al. have disclosed a direct, one-pot, three-component asymmetric Strecker reaction of aldehydes, (1,1′-diphenyl) methylamine and **1**, catalyzed by chiral bisformamides, analogues of DMF. High enantioselectivities (up to 86% ee) were achieved with diamides of (*S,S*)-1,2-diphenyl-1,2-diaminoethane of *N*-formyl-L-proline.[107]

The described indirect methods include addition of **1** to imines catalyzed by either chiral *N*-oxides or chiral *P*-oxides. Feng et al. have studied the addition of **1** to aldimines, catalyzed by chiral bisquinoline *N,N*′-dioxides. The best results were obtained with the *N,N*′-dioxide **38**, used in equimolar amounts (Table 2, entry 1). Aryl substituents R^1 with electron-withdrawing groups appear to enhance the enantioselectivity of the catalyzed reaction. The authors suggest that the stereochemical outcome of the reaction is due to chelation of the silicon by both *N*-oxide groups.

Surprisingly, a chiral *N,N*′-dioxide catalyst prepared in situ from the diamine and *m*-CPBA can provide high enantioselectivity (up to 92% ee) in the addition of **1** to phosphinoylated ketimines (Table 2, entry 2). With only 0.05 equiv of the precatalyst **39** required and nondemanding conditions, the method appears suitable for practical use.[109]

The bifunctional catalyst **25a**, introduced by Shibasaki et al. for cyanosilylation of aldehydes, was successfully used for catalyzed asymmetric Strecker-type reactions. The catalyst molecule contains both Lewis base (P═O group) and Lewis acid (AlCl) centers. With the addition of phenol as a proton donor, enantioselectivities in the range 70−95% were achieved for the addition of **1** to a variety of alkyl and aryl imines, carrying an *N*-9-fluorenyl substituent (Table 2, entry 3).[110a] Phenol in this system protonates the negatively charged nitrogen atom that is generated by the addition of

Scheme 11. Enantioselective Reissert-Type Reaction of *N*-Acylquinolinium Derivatives[114,115]



$CN^{\ominus}$ to the imine, thus accelerating the formation of aminonitrile. It was found that Me_3SiCN is more reactive than HCN in the presence of phenol. Consequently, a catalytic amount of Me_3SiCN and a stoichiometric amount of HCN could be used in such a process.[112]

The bifunctional catalyst **40** supported on Janda/EL polymer (0.52 mmol/g loading) promoted Strecker-type reactions of aromatic and α,β-unsaturated imines in excellent yields and with good enantioselectivities (Table 2, entry 4).[110b]

The bifunctional catalyst, featuring both a Lewis base (*N*-oxide) and a Lewis acid (amide group), was introduced by Feng et al. The chiral part of the catalyst **41**, based on the L-proline skeleton, promoted moderate to high enantioselectivities of addition (Table 2, entry 5). Extremely sterically hindered phenolic additive, 2,5-di-(1-adamantyl)hydroquinone (DAHQ), proved to be superior for enhancing the reactivity and enantioselectivity of addition of **1**.[111a]

A polyfunctional organocatalyst **42**, bearing an *N*-oxide (Lewis base) and phenol/amide (acidic) functions embedded in the (*S*)-BINOL/L-proline skeleton, was developed by Feng et al. The catalyst showed outstanding performance in enantioselective Strecker reactions of ketimines at low catalyst loading, under mild reaction conditions (Table 2, entry 6).[111b]

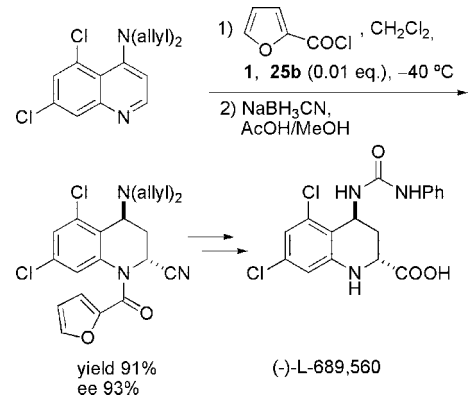
Quite recently, Kunz et al. reported enantioselective Strecker reactions of aldimines with **1** which employed 2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosylimines as organocatalysts. Despite the lack of any polar functional group in the catalyst molecule, enantioselectivities of Strecker reactions up to 96% were achieved.[113]

A catalyst similar to that used for cyanosilylation of aldehydes was used by Shibasaki's group for the asymmetric cyanosilylation of substituted quinolines (Reissert-type reaction) with good yields and enantioselectivities. Bifunctional catalyst **25b**, an analogue of **25a**, was found optimal for the addition of **1** to *N*-acyliminium ions, obtained in situ from the corresponding quinoline derivative and an acyl chloride (Scheme 11).[114,115]

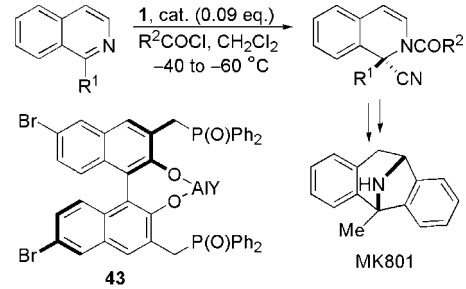
A transition structure accounting for the observed enantioselectivity of the addition has been proposed; however, the rate-determining step for the addition is the formation of an acyl quinolinium ion. The catalyst facilitates the second step, the addition of **1** to the acyl quinolinium ion.

Shibasaki's group developed a solid-supported catalyst, with the core structure of **25b**.[115] Catalyst **25b** was used for an asymmetric Reissert-type reaction, followed by stereoselective $NaBH_3CN$ reduction, as the key steps in the synthesis of NMDA receptor antagonist (−)-L-689,560 (Scheme 12).[115]

Scheme 12. Enantioselective Synthesis of NMDA Receptor Antagonist (−)-L-689,560[115]



Scheme 13. Enantioselective Reissert-Type Reactions of *N*-Acylisoquinolinium Derivatives[116]



cat.	Y	R^1	R^2	yield (%)	ee (%)
25a	–	Me	PhO	72	56
43	Cl	Me	PhO	93	88
43	Cl	2-BrC_6H_4	CH_2=CHO	53	73
43	OTf	2-BrC_6H_4	CH_2=CHO	63	98
43	OTf	Me	CH_2=CHO	88	89
43	OTf	Ph	CH_2=CHO	95	95

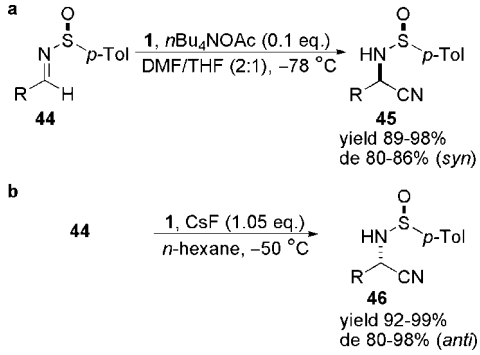
In a systematic study of Reissert-type reactions, Shibasaki et al. used a series of bifunctional catalysts **43**, electronically tuned by substitution of BINOL at the 6,6′-positions with halogen atoms. Compared to **25a**, the catalyst with two bromine substituents gave the best results in enantioselective addition of **1** to isoquinolines, with the formation of a quaternary stereocenter. Changing the counterion at the Al from Cl to OTf additionally improved the enantioselectivity of the addition (Scheme 13).

The procedure was applied to the synthesis of biologically active compounds, such as the potent anticonvulsant MK801.[116]

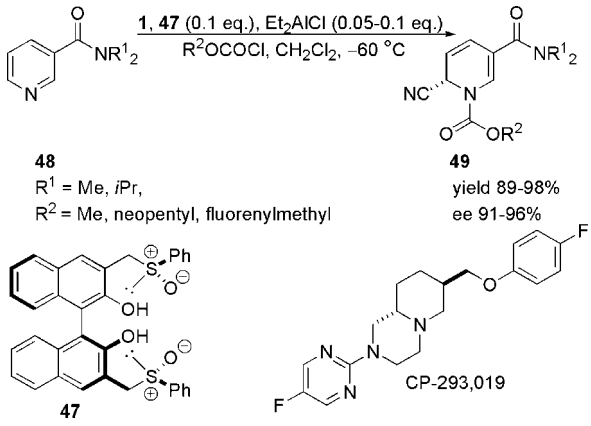
Mukaiyama et al. reported diastereoselective Strecker-type additions of **1** to chiral sulfinimines, catalyzed by simple carboxylate salts, such as acetates and benzoates. With tetra-*n*-butylammonium acetate as catalyst, sulfinimines derived from aliphatic aldehydes (**44**) gave products **45** in nearly quantitative yields and with significant *syn* diastereoselectivities (Scheme 14a).[117] Hou et al. have found that the addition of **1** to enolizable sulfinimines **44** is promoted by CsF in equimolar amounts, leading to *anti* products **46** with high yields and diastereoselectivities (Scheme 14b).[118]

The reaction is also diastereoselective when R in **44** is an *N*-benzylaziridine ring. Enantioselective Reissert-type reactions of pyridine derivatives were reported for the first time by Shibasaki et al. with the use of bifunctional catalyst (**47** + Et_2AlCl) in which the chiral sulfoxide moieties provided

Scheme 14. Diastereoselective Strecker-Type Reactions of *N*-Sulfinylimine 44[117,118]



Scheme 15. Enantioselective Reissert-Type Reactions of *N*-Acylpyridinium Derivatives[119]



the necessary Lewis base activity for cyanosilylation with **1**. Several nicotinic acid amides **48** were transformed to chiral dihydropyridines **49** with high yields and enantioselectivities. The synthetic utility of such a reaction was demonstrated in a formal synthesis of the dopamine D_4 receptor-selective antagonist, CP-293,019 (Scheme 15).[119]

Diastereoselective reactions, either Strecker or Reissert-type, are useful for the synthesis of various chiral amino acids. Antagonists of metabotropic glutamate receptors, (*S*)-αM4CPG, (*S*)-MPPG, (*S*)-AIDA, and (*S*)-APICA, were synthesized from aryl ketones using (*R*)-phenylglycinol as chiral auxiliary (Scheme 16).[120]

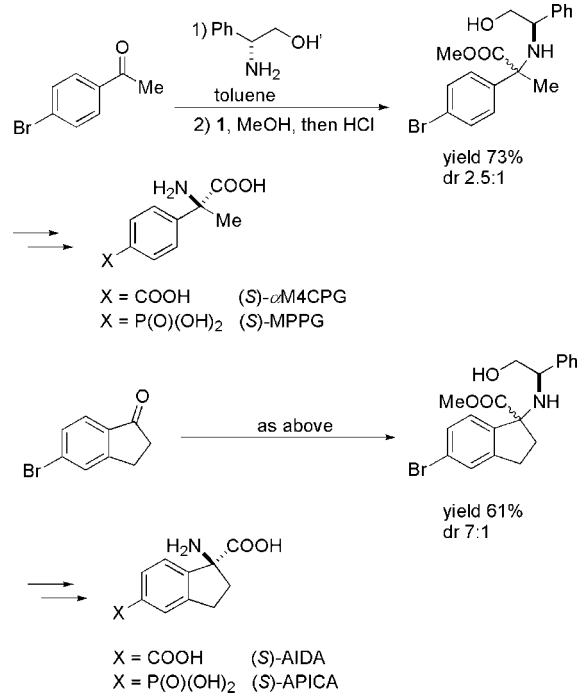
Cyanosilylation of chiral didehydropyrrolidines **50a**,**b** (derived from D-mannitol) catalyzed by the Lewis acid $ZnCl_2$ afforded nitriles **51a**,**b** in high yields. It was found that the configuration of the cyano-substituted carbon atom depends on the thermodynamic stability of the product. Whereas **51a** epimerizes readily at room temperature to a 1:1 mixture of epimers, **51b** is the stable diastereoisomer (Scheme 17).[121]

2.1.3. Addition to Aziridines

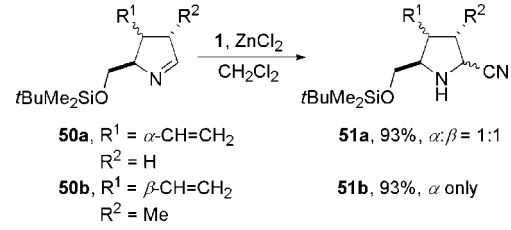
Nucleophilic ring opening of aziridines is a valuable synthetic transformation.[122] With Me_3SiCN (**1**) it leads regioselectively to substituted *trans*-β-amino nitriles (Scheme 18). The cyanide anion adds preferentially to the less substituted carbon atom.

The reaction proceeds with good yields when electron-withdrawing groups (R = Ts, Bz) are present in the aziridine ring. The catalysts reported include nBu_4NF[123] and tertiary amines, such as NEt_3 and TMEDA, as well as diphosphine $Me_2PCH_2CH_2PMe_2$.[124] To date, no enantioselective organocatalytic reactions of aziridines with Me_3SiCN were reported

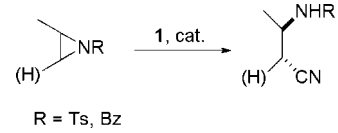
Scheme 16. Diastereoselective Syntheses of Various Unnatural α-Amino Acids[120]



Scheme 17. Diastereoselective Cyanosilylation of Dehydropyrrolidines[121]



Scheme 18. Addition of Me_3SiCN (1) to Activated Aziridines



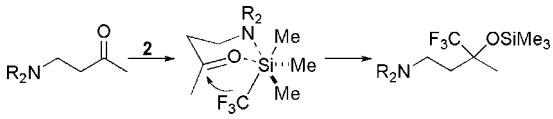
(see, however, the seminal work of Shibasaki et al. on enantioselective desymmetrization of activated aziridines with Gd bifunctional catalysts[125]).

2.2. Trifluoromethyltrimethylsilane (Me_3SiCF_3)

2.2.1. Trifluoromethylation of Aldehydes and Ketones

Trifluoromethyltrimethylsilane (Me_3SiCF_3, Ruppert's reagent,[126] **2**) has recently been intensively used as the reagent of choice for nucleophilic addition of the CF_3 group to aldehydes, ketones, and imines.[126c] A convenient procedure for the synthesis of **2** from bromotrifluoromethane has been reported by Prakash et al.[127a] Prakash, Hu, and Olah have recently reported a procedure for the preparation of **2** from nonozone depleting trifluoromethane via phenyl trifluoromethyl sulfide.[127b] Introduction of trifluoromethyl groups into organic compounds is of interest for the pharmaceutical industry,[128] since enantiomerically pure compounds of this type include an anti-HIV agent efavirenz,[129] befloxatone,[130] and a modulator of the androgen receptor.[131] Since a number of review papers on the synthesis of fluorinated organic

Scheme 19. Autocatalysis of the Addition of Me_3SiCF_3 (2) to β-Amino Ketones



compounds appeared in recent years,[132−134] this section will focus on very recent results of catalyzed additions of **2** to carbonyl compounds, including enantioselective addition reactions.

The Si−CF_3 bond in **2** is longer and weaker compared to that of the CF_3SiH_3 analogue, due to the repulsion between the positively charged carbon atom of the CF_3 group and the silicon center.[132a] This allows ready activation of **2** by the action of fluorides, such as nBu$_4$NF,[126c,132a,135] CsF,[136] KF,[137] KF·tBuOK,[138] Ph$_3$SnF·KF,[139] other salts (acetates,[140] phosphates, carbonates[141]), and phenoxide in DMF solution,[142] amines (Et$_3$N, pyridine), and phosphines (Ph$_3$P, tBu$_3$P)[143−145] as well as amine oxides (Me$_3$NO)[141,146] and phosphine oxides (Ph$_3$P═O).[144] Polar solvents, such as DMSO and DMF, in the presence of molecular sieves 4 Å, also catalyze the addition of **2** to carbonyl compounds;[147] however, it should be noted that **2** adds to DMSO in the presence of nBu$_4$NF as a catalyst.[148] **2**/CsF reagent is efficient for substitution of the alkoxy group by the CF_3 group in simple esters.[136,149,150] Catalysis with tetra-n-butylammonium fluoride appears to be more selective, since **2** reacts only with the keto group of α-ketoesters.[151]

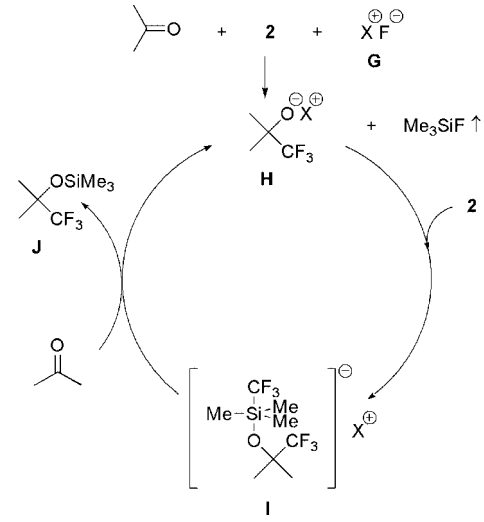
The catalytic action of the amine group in the addition of **2** to ketones was convincingly demonstrated for compounds combining both functionalities. For β-amino ketones, the reaction mechanism involves a cyclic transition structure in which the amino and the carbonyl groups coordinate to the silicon atom (Scheme 19).

Recently, a systematic study of Mukaiyama et al. has shown that trifluoromethylation of carbonyl compounds can be efficiently catalyzed by numerous nitrogen- or oxygen-containing anions generated from amides, imides, and carboxylic acids. Whereas lithium acetate worked well as a catalyst (0.05 equiv) in polar solvents (DMF, DMSO), n-tetrabutylammonium acetate was active also in nonpolar solvents, such as toluene, CH_2Cl_2, AcOEt, and THF.[152]

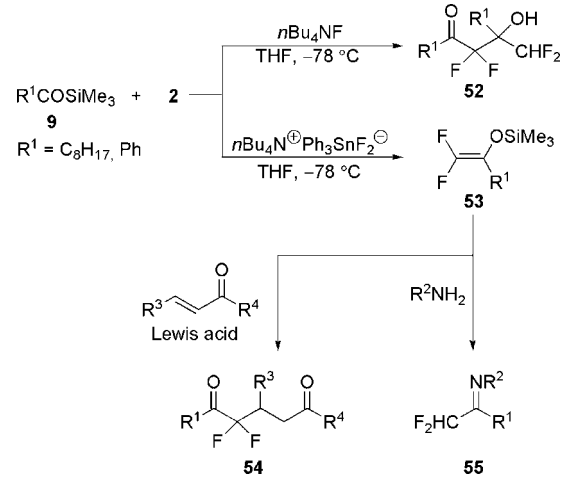
In general, the reaction cycle for the addition of **2** to carbonyl compounds initiated by a fluoride ion may differ from the general mechanism suggested in Scheme 2. The reaction is initiated by fluoride **G** with the formation of alkoxide **H** and volatile Me_3SiF, which may leave the reaction medium. In the catalytic cycle, the chiral alkoxide may act as an activator of **2** to form transient complex **I**, from which the CF_3 group is transferred to the carbonyl compound. The addition product **J** originates either from the first cycle, in which fluoride XF is the initiator, or from subsequent cycles, in which the alkoxide product **H** acts as the catalyst. If this mechanism is operative, it should have a significant impact on the overall enantioselectivity of the addition, due to catalysis by two different chiral species, i.e. ammonium fluoride (XF) and alkoxide product **H** (Scheme 20).

Addition of **2** to aldehydes can also be catalyzed by an NHC such as **12** (R = 1-adamantyl) in DMF solution at 0.005 equiv catalyst load.[153] With all the catalysts mentioned, 1,2-addition of **2** to α,β-unsaturated aldehydes takes place preferentially.[135,154] However, 1,4-addition of the CF_3 group catalyzed by a fluoride ion was observed in the case of

Scheme 20. Reaction Cycle of Silylative Trifluoromethylation with Me_3SiCF_3 (2) and Metal or Ammonium Fluorides (XF) as Initiators



Scheme 21. 2,2-Diflouro-1,5-diketones (54) and α,α-Difluoroimines (55) from Acylsilanes 9 and Me_3SiCF_3 (2)[158]



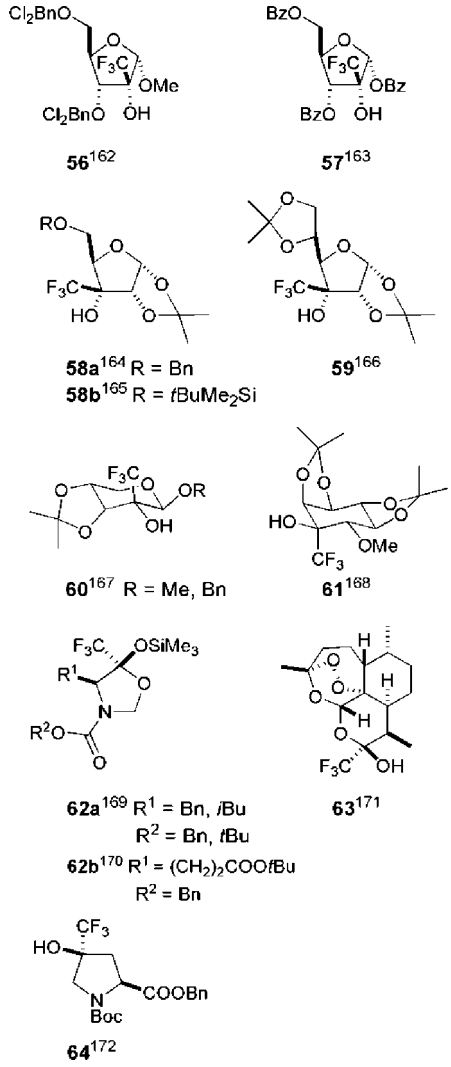
substituted chromones and 4-quinolones.[155] Recently, Lewis acid-catalyzed trifluoromethylation of aldehydes has been described.[156]

A dramatic effect of the catalytic fluoride source has been shown by Portella et al. in the reaction of **2** with acylsilanes. Whereas nBu$_4$NF catalysis leads to an aldol product without participation of $TMSCF_3$, the use of less nucleophilic tetrabutylammonium difluorophenyl stannate (nBu$_4$N$^{\oplus}$-Ph$_3$SnF$_2^{\ominus}$) as catalyst leads clearly to difluoroenoxysilanes, useful difluoroenolate equivalents (Scheme 21). [157]

Difluoroenoxysilanes **53** can undergo a 1,4-addition to enones upon catalysis with a Lewis acid to give 2,2-difluoro-1,5-diketones **54**.[158] On the other hand, difluoroenoxysilanes can act as electrophiles in the reaction with amines to give difluoroimines **55**, useful intermediates for the synthesis of α-difluoromethyl amines and amino acids, including optically active ones.[159]

Chiral aldehydes and ketones react with **2** under catalytic conditions with moderate to high diastereoselectivities. A number of syntheses of trifluoromethyl-substituted amino acids, sugars, steroids, and amines have been discussed.[160,161] The diastereoselectivities of these reactions depend on both the structure of the substrate and the catalyst used. In some

Scheme 22. Products of Highly Diastereoselective (dr ≥20:1) Additions of Me_3SiCF_3 (2) to Carbonyl Compounds (All Reactions Catalyzed by nBu_4NF)

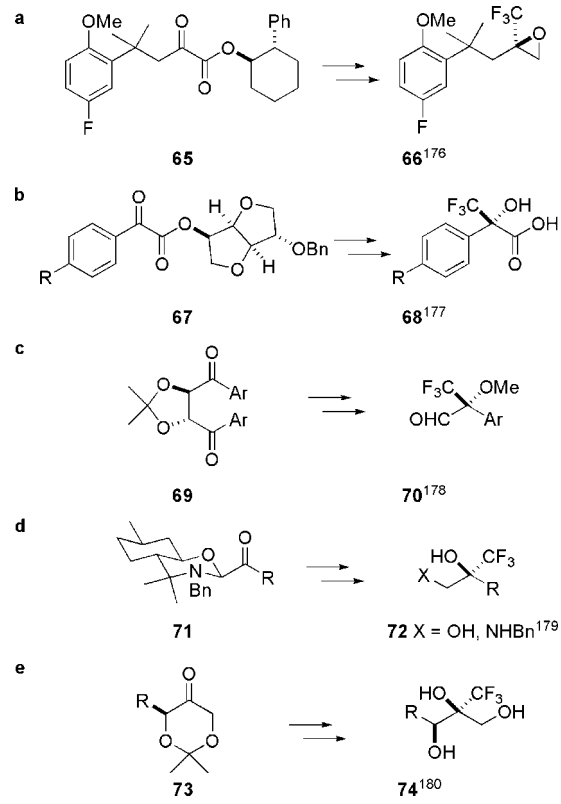


cases, high levels of diastereoselectivity (dr ≥20:1) have been achieved with nBu_4NF as the catalyst (Scheme 22).

High levels of face diastereoselectivity in the addition of **2** to ketofuranoses **56**, **57**, **58a**, **58b**, and **59** can be accounted for by the effect of α-oxygen substituent(s), directing the attack of the nucleophile toward the opposite face of the carbonyl group.[162−166] In contrast, chiral aldehydes react with **2** with lower selectivities. Examples include an *O*-protected acyclic derivative of D-lyxose (dr 1:1),[173] a protected derivative of L-erythrose (dr 1.2:1),[174] and a protected derivative of D-erythrose (dr 1.5:1).[175] Sugar lactones react with **2** to give, after removal of the trimethylsilyl protecting group, an equilibrium mixture of hemiacetals.[175] However, prior to deprotection in some instances (e.g., **62a**), high diastereoselectivities of addition were achieved.[169] Hemiacetal **63** was found to be configurationally homogeneous after the deprotection step.[171]

Some of these reactions are of practical importance and illustrate a strategy combining the effect of chirality of the substrate or auxiliary and the effect of the organocatalyst used. Thus, the Boehringer Ingelheim group used a chiral auxiliary, *trans*-2-phenylcyclohexanol, to obtain the chiral α-ketoester **65**. The chiral auxiliary controls the trifluoromethylation reaction, providing a diastereoisomer ratio of 84:16 in the reaction in toluene solution. The diastereoselectivity is lower in polar solvents such as DMF. The main diastereoisomer could readily be converted to a pharmaceutical intermediate **66** (ee 99%) on a kilogram scale (Scheme 23a).[176]

Scheme 23. Generation of Synthetically Useful Compounds with Quaternary Chiral Centers by Addition of Me_3SiCF_3 to Chiral Ketones



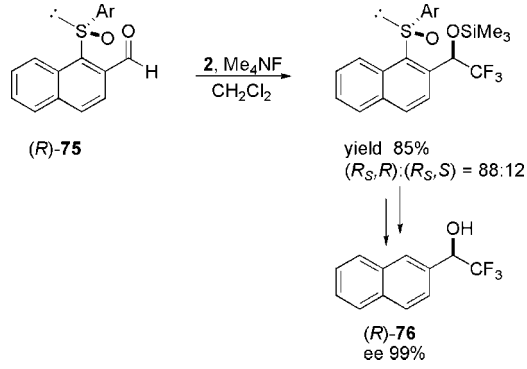
A diastereoselective addition of **2** to a chiral keto ester was applied for the preparation of Mosher's acid analogues **68**. Carbohydrate derived alcohols were used as chiral auxiliaries; the highest level of diastereoselectivity (up to 92:8) was achieved with isosorbide derivatives **67** (Scheme 23b).[177]

Chiral aryl ketones **69**, derived from tartaric acid, undergo monotrifluoromethylation with **2**/nBu_4NF with dr of up to 99:1 (Ar = Ph). According to the authors, the addition of **2** to the carbonyl group occurs in agreement with the Felkin−Anh model. Cleavage of the C−C bond with periodic acid afforded the aldehyde **70**, a precursor of Mosher's acid (Ar = Ph) (Scheme 23c).[178] The Felkin−Anh model can also be used to rationalize the results of the highly diastereoselective addition (dr in excess of 50:1) of **2** to 2-acyl-1,3-perhydrobenzoxazines **71**, derived from (−)-8-benzylaminomenthol. These products can easily be converted to trifluoromethylated 1,2-diols and 1,2-amino alcohols **72** (Scheme 23d).[179]

Chiral 2-trifluoromethyl-1,2,3-triols **74** were synthesized by Enders and Herriger from α-alkylated dioxanones **73** using the **2**/nBu_4NF methodology. The diastereoselectivity of the addition was over 96%, with the addition occurring preferentially to the face of the C=O group not shielded by the substituent R (Scheme 23e).[180]

A chiral aryl sulfinyl group attached to the substrate molecule can effectively discriminate the addition of **2** to the carbonyl group. Toru et al. have reported the synthesis

Scheme 24. Diastereoselective Synthesis of Enantiopure (*R*)-1-(2-Naphtyl)-2,2,2- trifluoroethanol (76)[181]



of enantiopure 1-(2-naphthyl)-2,2,2-trifluoroethanol **76**, based on highly face-selective addition of **2** to the aldehyde **75**. The addition occurs from the less hindered carbonyl face, *anti* to the Ar group (Scheme 24).[181]

The enantioselective introduction of a trifluoromethyl group into molecules of medicinal, agrochemical, and chemical interest has recently been studied intensely. The Ruppert−Prakash reagent **2** appears well-suited to serve the purpose according to the mechanism shown in Scheme 20. The asymmetric induction in the addition of **2** to aldehydes or ketones originates from the presence of chiral ammonium ion in the fluoride catalyst. Since the ammonium cation should be closely associated with the alkoxy intermediates **H** or **I**, in order to act enantioselectively in the addition reaction, the use of nonpolar solvents such as toluene or dichloromethane and low reaction temperatures appear to be imperative. Recent results of enantioselective catalysis in the synthesis of trifluoromethyl alcohols are summarized in Table 3.

Whereas *Cinchona* alkaloids are poor catalysts for the addition of **2**,[143] ammonium fluorides, derived from *Cinchona* alkaloids, are at present the best choice for organocatalytic trifluoromethylation of aldehydes and ketones. Prakash et al. reported a highly enantioselective addition of **2** to 9-anthraldehyde, catalyzed by *N*-benzylquininium fluoride **77a** (entry 1).[182] Iseki et al. used 4-trifluoromethyl-substituted benzylammonium salts of cinchonine **77b**. Whereas the yields were high, the enantioselectivities of these reactions were low to moderate (entry 2).[183] The same catalyst was used by Caron et al. to synthesize enantiomerically enriched diol **82** from the corresponding ketone **83**. With the use of a 2,4-dimethoxybenzoate protection for the primary hydroxyl group, a high enantioselectivity of the addition was achieved (entry 3).[184] Catalysts based on cinchonine quaternized with arylmethyl fluorides other than 3,5-dimethoxybenzyl or 1-naphthylmethyl gave inferior results. Recently, Shibata, Toru, et al. introduced an operationally simple catalytic system based on the bis-cinchoninium dibromide salt **78** and commercial tetramethylammonium fluoride as a source of fluoride ion. The procedure avoids a direct preparation of chiral ammonium fluorides, which are difficult to purify and obtain in dry form (entry 4).[185a] Lower enantioselectivities (up to 40%) were achieved in the system comprising of chiral quaternary halide and KF.[185b] Mukaiyama and co-workers demonstrated that cinchonidine-derived quaternary ammonium phenoxides **79** are alternative effective catalysts for trifluoromethylation of aryl methyl ketones. Yields were excellent; however, enantioselectivities were only moderate (entry 5).[186] Very recently, a catalyst combining the chirality of alkaloid quaternary ammonium bromide and disodium binaphthalate has been described by Feng et al.[187] A combination of disodium (*R*)-binaphtholate and a derivative of quinine (**80**) afforded the products of trifluoromethylation of aromatic aldehydes with moderate enantioselectivities (entry 6). It was suggested that the binaphtholate salt activates the molecule of **2** through hexacoordinate silicon species.

Nonalkaloid derived chiral salts were found less effective as catalysts for the trifluoromethylation of aldehydes. Kuroki and Iseki synthesized a chiral tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF) analogue **81**. Excellent yields of the trifluoromethyl alcohols were obtained; however, low enantioselectivities were observed (up to 52% for benzaldehyde). See entry 7.[188]

It is obvious that, despite recent progress, the enantioselectivity of addition of **2** to aldehydes and ketones is far from satisfactory for general use. Only in rare cases (Table 3) were enantioselectivities of over 90% reported for specific catalytic systems.

2.2.2. Trifluoromethylation of Imines

Trifluoromethylated amines, valuable building blocks for the pharmaceutical industry, can be obtained by the addition of **2** to *N*-aryl- and *N*-sulfonylimines or azirines, catalyzed (promoted) by CsF,[189] nBu$_4^+$Ph$_3$SiF$_2^-$ (TBAT),[190] tetraalkylammonium fluorides,[191,192] or P(tBu)$_3$,[144] in THF or DMF as solvents. It has been claimed that the reactivity of the **2**/CsF system toward an imine electrophile may be enhanced by the addition of an auxiliary silylating agent, Me$_3$Si-imidazole.[193] Lithium, sodium, and *n*-tetrabutylammonium carboxylates (0.1 equiv) also catalyze the addition of **2** to *N*-sulfonylimines efficiently.[193,194] More electrophilic are nitrones, which react with **2** to give *O*-trimethylsilyl ethers of hydroxylamines under catalysis with potassium *tert*-butoxide.[195]

The directing power of the chiral *tert*-butanesulfinyl substituent on the imine nitrogen atom was used by Prakash, Mandal, and Olah for the preparation of highly diastereomerically enriched *N*-sulfinamines **84**, from which enantiomerically enriched trifluoromethylated amines **85** could be obtained by acid-catalyzed hydrolysis. The reaction is best catalyzed by nBu$_4^+$Ph$_3$SiF$_2^-$, and the direction of asymmetric induction can be described as the approach of the "CF$_3$" group from the less hindered C=N *re* face, to give a Cram-type product (Scheme 25).[196]

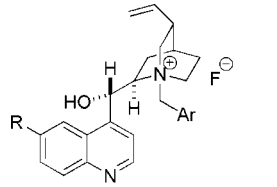
A similar methodology has been applied by Kawano and Mukaiyama to chiral *N*-(tolylsulfinyl)imines **86**. Trifluoromethylated amines **87** were obtained with high diastereomer ratio in favor of the S_S,*R* diastereoisomer, using nBu$_4$NOAc or nBu$_4$NOPh as a catalyst. From **87**, R = 2-furyl, enantiomerically pure (*R*)-3,3,3-trifluoroalanine (**88**) was obtained in just one step (Scheme 26).[197]

α-Amino aldehydes **89**, derived from enantiomerically pure α-amino acids, were similarly converted to diamines **92**, using the sulfinimine derivatization and diastereoselective Me$_3$SiCF$_3$ addition methodology (Scheme 27).[198]

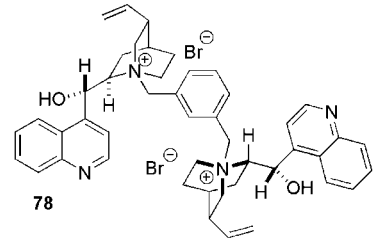
Very high matched double diastereoselectivity of addition of **2** to **90** (>99:1 ratio of diastereoisomers **91**) was observed for the *S*,R_S diastereoisomer of the imine **90**. Mismatched asymmetric induction with much lower diastereoselectivity of addition was found for the *R*,R_S configured imine **90**.

Table 3. Reaction Conditions and Results of Enantioselective Catalysis of Addition of Me_3SiCF_3 to Aldehydes and Ketones

entry	carbonyl compound	catalyst (equiv)	solvent (temp, °C)	yield (%)	ee (%)	ref
1	9-anthraldehyde	**77a** (−)	PhMe (−78)	(−)	95	182
2	aldehydes, aryl ketones	**77b** (0.1−0.2)	PhMe (−78)	87−99	15−51	183
3	ketone **83**	**77b** (0.04)	CH_2Cl_2 (−78)	97	92	184
4	aryl ketones	**78** + Me_3NF (0.1 each)	PhMe/CH_2Cl_2 (−60 to −50)	34−97	52−93	185
5	aryl methyl ketones	**79** (0.1)	PhMe/CH_2Cl_2 (−78)	90−99	44−87	186
6	aryl aldehydes	**80** (0.1)	Et_2O, 4 Å MS (−15)	68−95	41−71	187
7	aldehydes	**81** (0.1)	Et_2O (−78)	71−99	10−52	188



77a R = OMe, Ar = Ph
77b R = H, Ar = 4-$CF_3C_6H_4$



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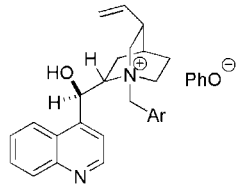
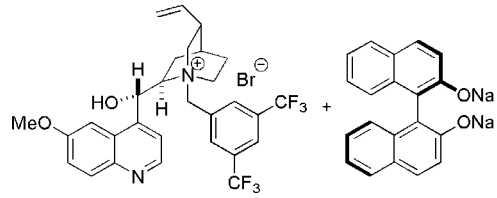


79 Ar = 3,5-[3,5-$(CF_3)_2C_6H_3$]$_2C_6H_3$



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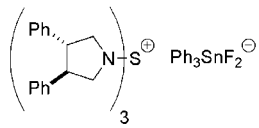

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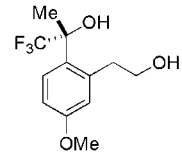

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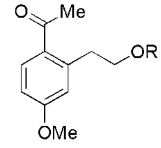
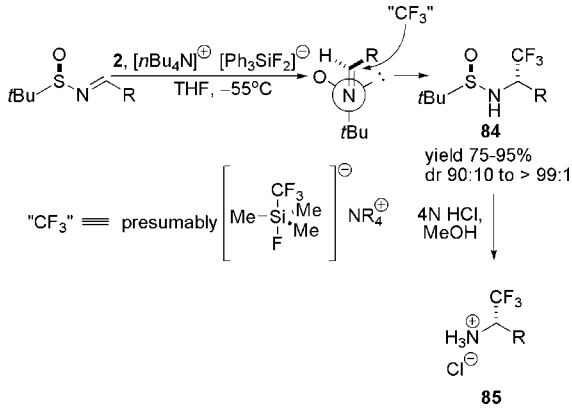
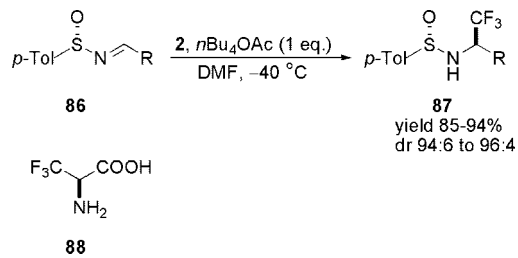


83

Scheme 25. Diastereoselective Route to Enantiomerically Enriched α-Trifluoromethyl Amines 85[196]

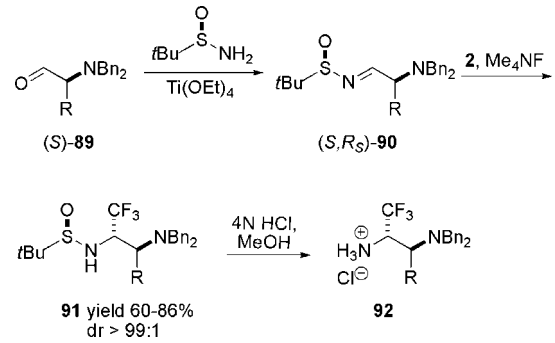


Scheme 26. Diastereoselective Additions of Me_3SiCF_3 to Chiral *N*-(Tosylsulfinyl)imines[197]



Diastereoselective 1,2-addition of **2** to chiral α,β-unsaturated imines **93** was developed by the group of Prakash. Either $nBu_4^+Ph_3SiF_2^-$ or Me_3SiF activate the reagent when used in stoichiometric amounts to give the products **94** with good to excellent diastereoselectivities (Scheme 28).[199]

Scheme 27. Diastereoselective Synthesis of α-Trifluoromethyl-*vic*-diamines[198]

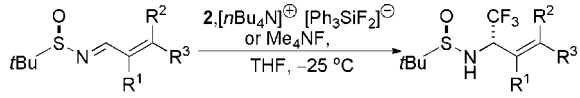


2.3. Trimethylsilyl Enol Ethers and Trimethylsilyl Ketene Acetals

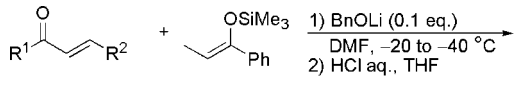
2.3.1. Mukaiyama−Aldol and Mukaiyama−Michael Additions

Mukaiyama-type aldol reactions (1,2-addition) and Mukaiyama−Michael reactions (1,4-addition) are among the most useful methods of carbon−carbon bond formation. Originally, the discovery of Mukaiyama et al. of $TiCl_4$-catalyzed aldol reaction of silyl enol ethers[200] later evolved into base-promoted aldol reactions. The effect of chiral bases (phosphoramides) on the stereochemical course of aldol reactions

Scheme 28. Regio- and Diastereoselective Additions of Me_3SiCF_3 to *N*-Sulfinyl-α,β- unsaturated Imines[199]



Scheme 29. Diastereoselective Mukaiyama−Michael Additions of Trimethylsilyl Enol Ethers[220]



R^1	R^2	yield (%)	*anti*:*syn*
Ph	Ph	93	92:8
Ph	Me	75	75:25
Me	Ph	92	96:4
*t*Bu	Ph	70	96:4

of trichlorosilyl enolates was disclosed by Denmark et al. in the 1990s.[201]

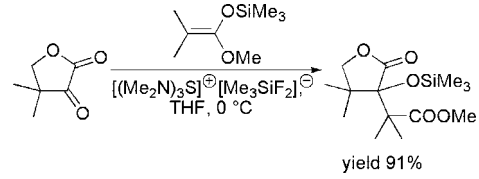
In these reactions, an enolate anion is formed in situ from an appropriate precursor such as trimethylsilyl enol ether (**3**) or trimethylsilyl ketene acetal (**4**), using catalytic activity of the fluoride anion (nBu$_4$N, tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF), CsF)[202−206] or lithium carboxylates.[152] Lithium acetate is of special interest as a catalyst, due to its low cost and low toxicity and the possibility to run the reactions at temperatures below 0 °C in DMF or in DMF/H_2O.[207] Other catalysts include lithium benzamide, lithium succinimide,[208] and potassium phthalimide,[209] as well as lithium 2-pyrrolidone[210] or lithium diphenylamide in DMF at low temperature (−45 °C).[211] The reaction can be self-promoted by polar Lewis base moieties (carboxylate salts, sodium amides) attached to the aldehyde substrate.[212] Alkali metal alkoxides catalyze the Mukaiyama−aldol reaction in the initial stage; further propagation of the reaction is believed to proceed by the aldolate anion (reaction product) catalysis.[213] Trimethylsilyl enol ethers can also be activated by the action of TCNE[47] or NHC.[214] While the trimethylsilyl ketene acetal of methyl isobutyrate, activated by NHC (**12**, R = 1-adamantyl), adds smoothly to aldehydes at room temperature,[214] it reacts differently with enolizable ketones, producing their silyl enol ether derivatives with high yields.[215] Other Lewis base catalysts for the Mukaiyama-type aldol reaction of aldehydes include phosphines, e.g. tris(2,4,6-trimethoxyphenyl)phosphine,[216] pyridine *N*-oxide/LiCl,[217] and *N*-methylimidazole/LiCl.[218]

Mukaiyama−Michael additions of trimethylsilyl enol ethers to α,β-unsaturated carbonyl compounds can be promoted by KH in DMF or by 50% aqueous NaOH under phase transfer conditions[219] or by lithium alkoxides.[220] In the latter case, the reaction is *anti* selective, as shown in Scheme 29.

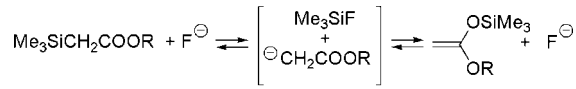
Similarly, Mukaiyama−Michael additions of trimethylsilyl ketene acetals are catalyzed by lithium amides, lithium imides, or lithium acetate in DMF solution.[221] The addition can also be carried out by activating the nucleophile with anhydrous DMSO solvent[222] or with a 2:1 complex of benzoic acid and tetra-*n*-butylammonium hydroxide.[223]

The electrophiles showing reactivity toward **3** or **4** include aldehydes, ketones, imines, and lactones; the latter are less reactive than ketones, allowing for chemoselective group transformation, as shown in Scheme 30.[205]

Scheme 30. Chemoselective Mukaiyama−Aldol Reaction[205]



Scheme 31. Observed NMR Chemical Shifts Due to ^{29}Si in the Process of Generation of Ketene Silyl Acetals 4[205]



4

$R^1 = R^2 = H$ in Chart 1

^{29}Si(C)	^{29}Si(F)	^{29}Si(O)
δ 2.7	δ 32.2	δ 15.3

The case of **4** with $R^1 = R^2 = H$ is of special interest, since its precursor is alkyl trimethylsilylacetate, Me_3SiCH_2COOR. The ketene silyl acetal **4** appears to be formed under fluoride ion catalysis during the reaction, based on an analysis of the NMR chemical shift of the ^{29}Si signal (Scheme 31). Further activation of **4** proceeds through a penta- or hexacoordinated silicon species, eventually yielding the enolate−metal or the enolate−organic cation pair.[205]

Interestingly, ethyl 2-trimethylsilyl acetate was found to add under fluoride ion initiation to less common electrophiles, such as perfluoroketene dithioacetals[224a] of *N*-methylquinolinium iodides.[224b]

The regioselectivity of the addition of enolate nucleophiles, generated from their trimethylsilyl precursors, to α,β-unsaturated carbonyl electrophiles appears to be dependent on the nature of the catalyst used.[225] While metal ion (Lewis acid) assisted catalysis leads to 1,2-addition (Mukaiyama−aldol), organocatalysis favors 1,4-addition (Mukaiyama−Michael). This is illustrated by the results of Zhang and Corey concerning the addition of silyl enol ethers **96** to chalcones **95**, catalyzed by *N*-(9-anthracenylmethyl)dihydrocinchoninium hydroxide, generated in situ from the bromide **97** (Scheme 32a).[226]

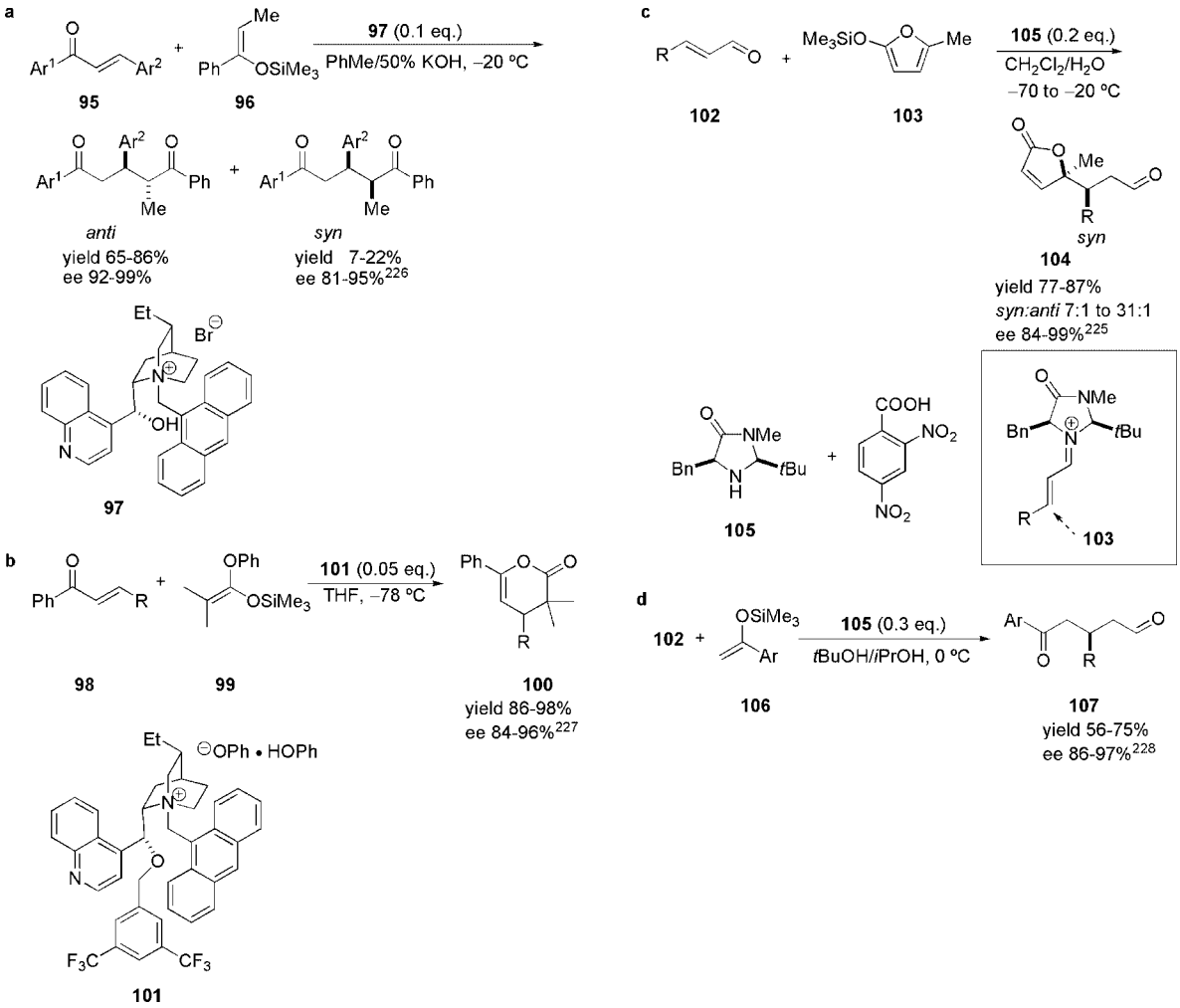
The reaction is *anti* selective (*anti*:*syn* = 3:1 to 20:1), and the products are obtained in highly enantioenriched form.

Sequential Mukaiyama−Michael addition of trimethylsilyl ketene acetal **99** to chalcones **98**, catalyzed by structurally related cinchona alkaloid-derived quaternary ammonium phenoxide−phenol complex **101** and subsequent lactonization, provides access to 3,4-dihydropyran-2-ones **100** with high yields and enantioselectivities (Scheme 32b).[227]

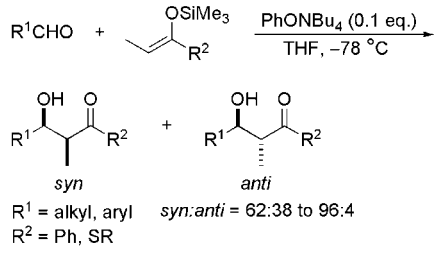
MacMillan et al. developed a different approach to organocatalytic Mukaiyama−Michael addition. The use of the imidazolidinone catalyst **105** allows one to obtain chiral enantioenriched γ-butenolide products **104**, having broad applications in the synthesis of natural products. The reaction presumably proceeds through an iminium ion activation of enal **102**, to which the silyloxy furan **103** adds preferentially from the *si* face, since the *re* face is blocked by the bulky *tert*-butyl group (Scheme 32c).[225]

Further examples of Mukaiyama−Michael additions of trimethylsilyl enol ethers **106** to enals **102** are shown in Scheme 32d. Catalysis by MacMillan's imidazolidinone **105** afforded 1,5-dicarbonyl compounds **107** in good yields and with high enantiomer excesses, despite a greater susceptibility of enals toward 1,2-addition.[228]

Scheme 32. Organocatalytic Enantioselective Mukaiyama−Michael Additions of Trimethylsilyl Enol Ethers and Trimethylsilyl Ketene Acetals



Scheme 33. *syn* Diastereoselective Mukaiyama−Aldol Reactions[229]



Lewis base-catalyzed Mukaiyama−aldol reactions of trimethylsilyl enolates with aldehydes show preference toward *syn* aldol formation. Thus, ammonium phenoxide catalysis affords *syn* aldols with moderate to high diastereoselectivities; *syn* diastereoselectivity is observed regardless of the configuration (*Z* or *E*) of the trimethylsilyl ketene thioacetals used for the addition (Scheme 33).[229]

Mukaiyama−aldol reactions of saturated aldehydes with trimethylsilyl enol ethers[230] and trimethylsilyl ketene acetals[231] can be catalyzed by *N*-benzylcinchoninium fluoride (**108**) or *N*-benzylcinchonidinium fluoride (**109**) (Scheme 34a).

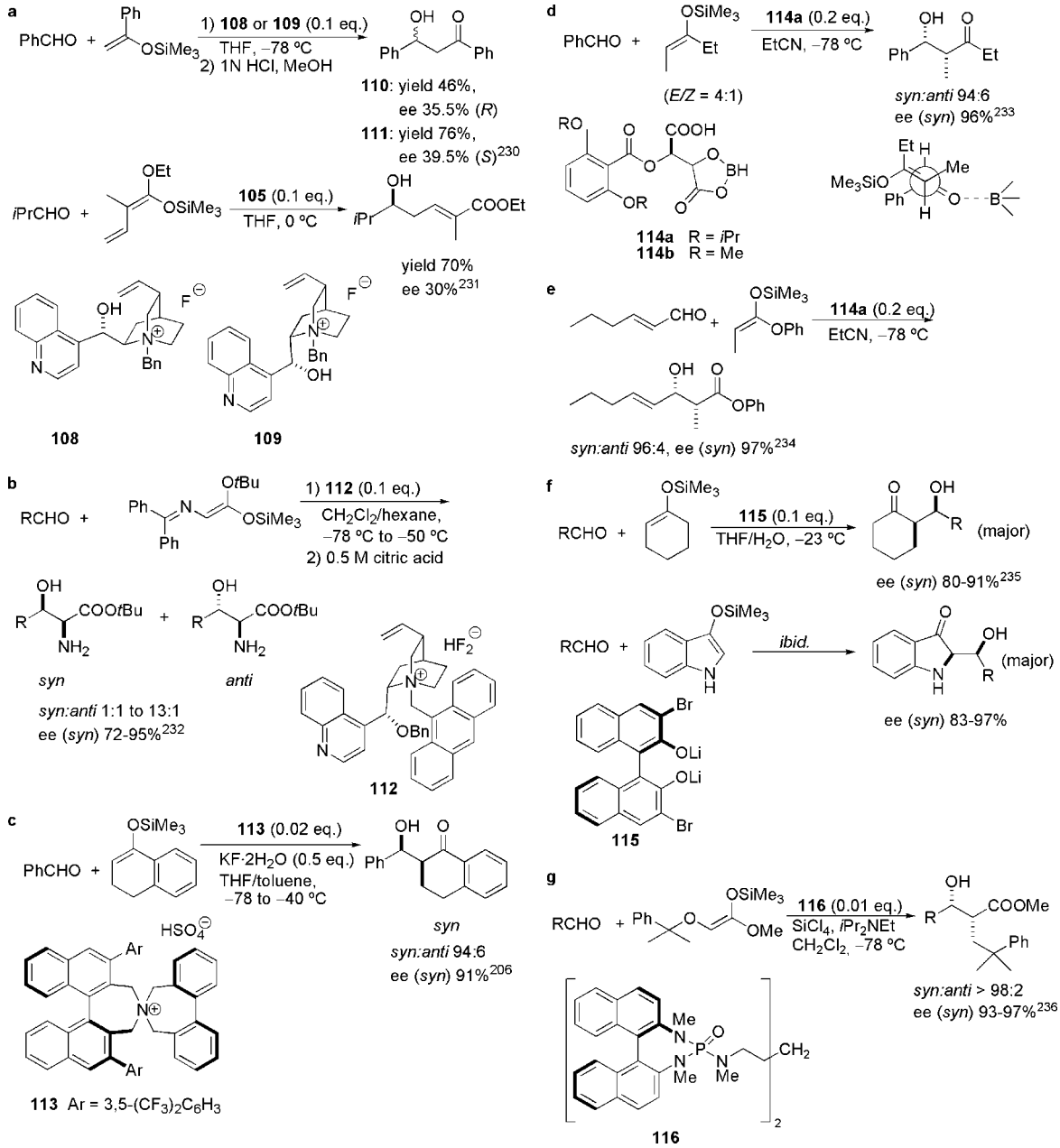
The enantioselectivities of these reactions are low, however, pseudoenantiomeric organocatalysts **108** and **109** allow one to obtain the aldol products of the opposite configuration.

N-Methylanthracenyl-*O*-benzyl cinchonidinium bifluoride **112**, introduced by Corey et al., is apparently a highly efficient catalyst for Mukaiyama−aldol reactions of aldehydes with ketene trimethylsilyl acetals. The addition yields α-amino *β*-hydroxy esters of preferentially *syn* configuration and with a good enantiomer excess (Scheme 34b).[232] Maruoka et al. introduced a useful and efficient chiral catalyst, based on a structurally rigid, C_2-symmetric quaternary ammonium fluoride molecule, generated in situ from the hydrogen sulfate precursor and $KF \cdot 2H_2O$. They also observed beneficial effects of the CF_3 substituents in the catalyst molecule **113**, as well as toluene as the cosolvent, for improving the stereoselectivity of the aldol reaction (Scheme 34c).[206]

Interestingly, Yamamoto's acyloxyborane **114a**, derived from tartaric acid, can efficiently catalyze Mukaiyama−aldol reactions with high diastereo- and enantioselectivities (Scheme 34d).[233] The Brønsted acid-type catalyst effectively shields one of the faces of the aldehyde while activating it through coordination to the boron atom. A similar aldol-type reaction with the use of ketene silyl acetals has also been reported by Yamamoto et al.; see the example in Scheme 34e.[234]

The catalysis of Mukaiyama-type aldol reactions by the chiral base lithium binaphtholate **115** has been reported by Nakajima et al.[235] Under aqueous conditions, *syn* adducts were obtained as the major diastereoisomers, with enantioselectivities of up to 97% (Scheme 34f).

Scheme 34. Organocatalytic Enantioselective Mukaiyama−Aldol Reactions of Trimethylsilyl Enol Ethers and Trimethylsilyl Ketene Acetals

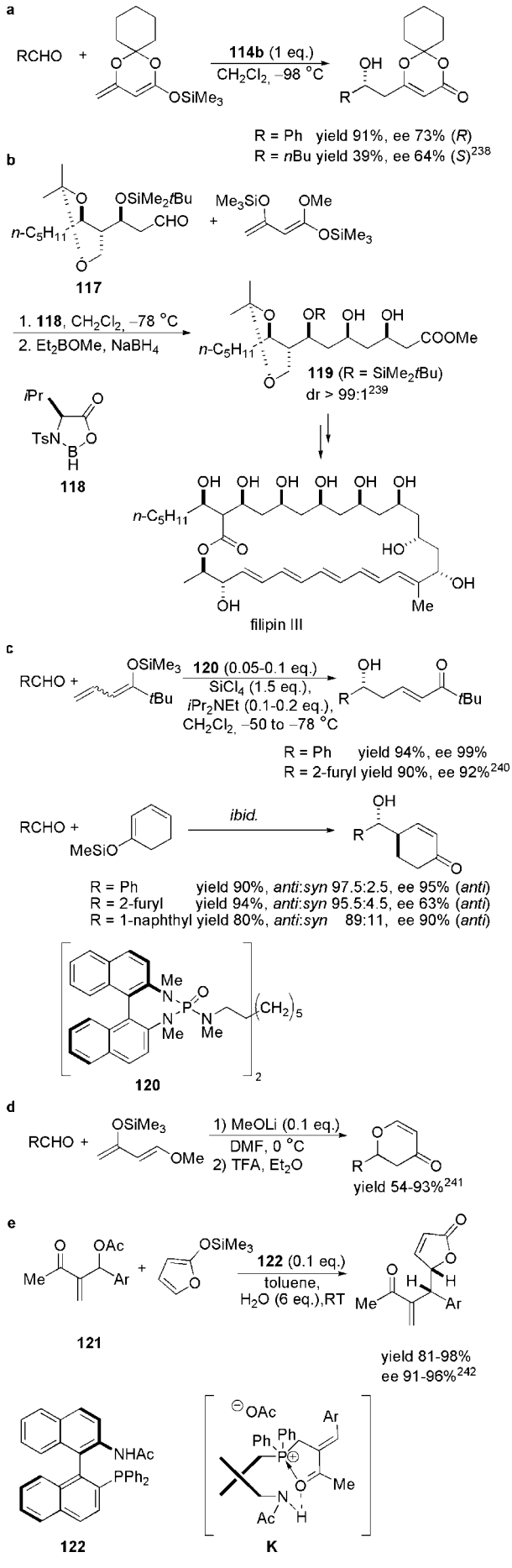


Denmark et al. developed a Lewis base-catalyzed, Lewis acid-mediated enantioselective Mukaiyama-type aldol reaction employing the bisphosphoramide catalyst **116** and $SiCl_4$. Additions of silyl ketene acetals to aldehydes could thus be performed highly *enantio* and *syn* diastereoselectively, when a large amyl protecting group was attached to the α-oxygen atom of the glycolate silyl acetal (Scheme 34g). Interestingly, highly *anti* selective glycolate aldol reactions were achieved simply by manipulating the pattern and the size of the silyl ketene acetal substituents.[236]

Vinylogous aldol reactions[237] of trimethylsilyl dienol ethers catalyzed by acyloxyboranes are useful in the synthesis of complex polyol molecules. Catalysis by acyloxyborane **114b** was moderately enantioselective, even at high catalyst load[238] (Scheme 35a). Kiyooka et al. used vinylogous aldol reactions for the synthesis of the polyol fragment of filipin III. This reaction employed the chiral aldehyde **117** and the acyloxyborane **118** to produce the aldol, which was further reduced with Et_2BOMe and $NaBH_4$ under substrate-controlled *syn* selectivity to yield the protected polyol **119** (Scheme 35b).[239] Denmark and Heemstra recently reported that ketone-derived vinylogous trimethylsilyl dienol ethers undergo highly enantioselective aldol reactions with aldehydes catalyzed by bisphosphoramide **120** (Lewis base) and $SiCl_4$ (Lewis acid); see Scheme 35c.[240] Mukaiyama−aldol reactions of Danishefsky's diene with aldehydes, catalyzed by alkoxides, lead to the products, which further cyclize under acidic conditions to 2,3-dihydropyran-4-ones. Formally, the process corresponds to a hetero Diels−Alder reaction[241] (Scheme 35d).

Morita−Baylis−Hillman acetates **121** undergo enantioselective reaction with 2-trimethylsilyloxy furan, catalyzed by BINOL-based diphenylphosphines, to give γ-butenolides (Scheme 35e). High enantioselectivities were obtained in the presence of chiral phosphine **122**, bearing an acetamide substituent which acts as a Bronsted acid to activate the carbonyl group in the substrate. The role of the phosphine group is to form the intermediate enone dienofile **K** (ac-

Scheme 35. Vinylogous Mukaiyama−Aldol Reactions



Scheme 36. Mukaiyama−Mannich-Type Additions to Aldimines

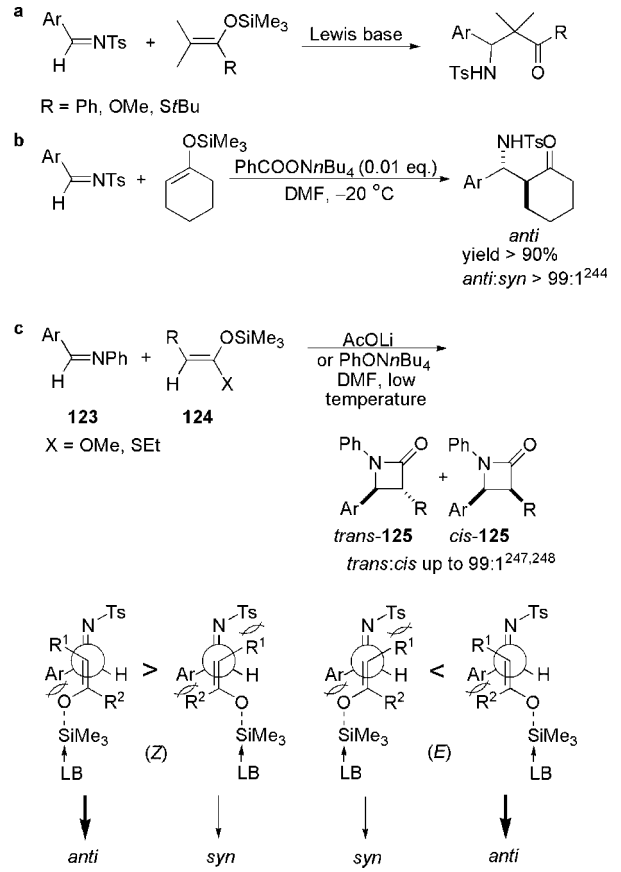


Figure 5. Rationalization of *anti* selectivity in Mukaiyama−Mannich-type additions.[251]

cording to the Kirsche mechanism). Water additive helps to activate the silyloxy group through a pentacoordinated silicon intermediate. In addition, the water possibly assists the Grob-type fragmentation, which follows the Diels−Alder cycloaddition step.[242]

2.3.2. Mukaiyama−Mannich-Type Additions

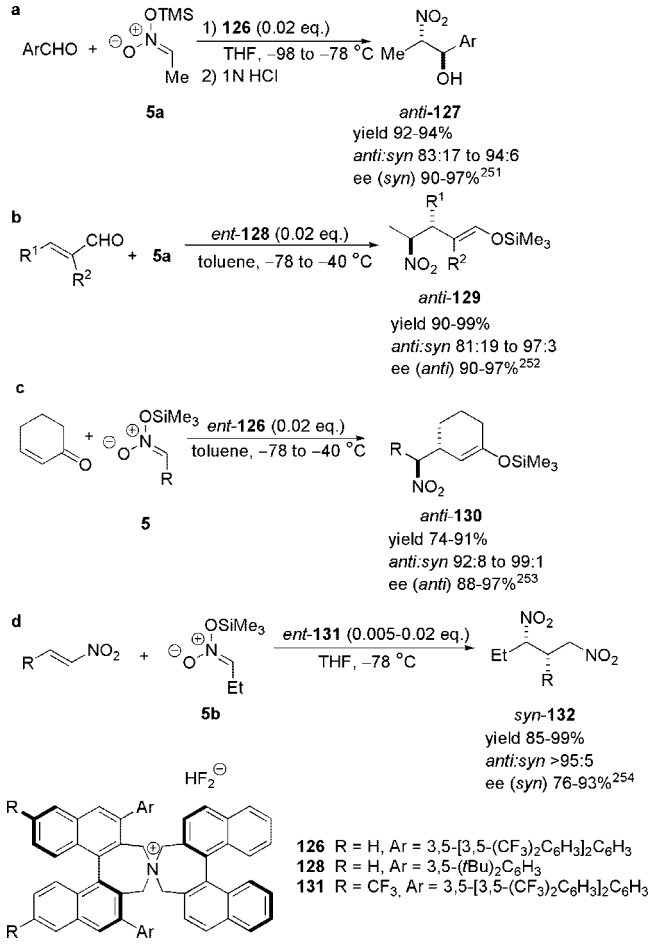
Mukaiyama et al. studied Mannich-type additions of ketone silyl enol ethers and ketene silyl (thio)acetals to activated aldimines; see Scheme 36a.

It has been found that the addition can be catalyzed by lithium benzamide or potassium phthalimide in DMF solution,[243] lithium acetate,[244a] lithium acetate in DMF−H_2O (50:1),[244b] lithium alkoxide or an *N*-lithium derivative of the Mannich product in DMF,[245] and ammonium or potassium carboxylates.[244c] With ketone silyl enol ethers, the reaction is *anti* selective;[242,243,245] an example is shown in Scheme 36b.

This *anti* selectivity of addition is remarkable, since it is independent of the configuration of the silyl enol ether. It is plausibly explained with the steric interaction between the Ts group of the imine and the R^1 substituent of the enolate in the transition state leading to the *syn* product. This interaction is apparently stronger than that between R^2 and Ar groups in the transition state leading to the *anti* stereoisomer (Figure 5).

High diastereoselectivity was observed in the addition of a ketene silyl acetal to chiral sulfinylimines, catalyzed by tetra-*n*-butylammonium carboxylates.[246]

Scheme 37. Oragnocatalytic Enantioselective Additions of Trimethylsilyl Nitronates



N-Arylaldimines **123** react with silyl ketene acetals **124** (X = OMe) under catalysis with lithium acetate to give the products of a Mukaiyama−Michael-type addition, which further cyclize to β-lactams **125**, having preferentially *trans* configuration, regardless of the configuration of the acetal **124**.[247] Even higher *trans* diastereoselectivity (up to >99:1) was achieved with silyl ketene thioacetals **124** (X = SEt) and catalysis with tetra-*n*-butylammonium or lithium phenoxide[248] (Scheme 36c).

2.4. Trimethylsilyl Nitronates

Nitroalkanes are a valuable source of stabilized carbanions which undergo conjugate addition to electron-deficient alkenes as electrophiles, with the formation of a C−C bond.[249] Trimethylsilyl nitronates **5** are readily available precursors of carbanions which can be released by a fluoride-catalyzed desilylation of **5**. Either aldehydes, enals, enones, or nitroalkenes can be used as electrophiles. Given the possibility of reducing the nitro into an amino group, transforming it into a carbonyl group (Nef reaction), or eliminating it, the addition reaction provides access to a wide variety of functionalized chiral products. The enantioselective version of addition of **5** owes its success to Maruoka et al., who have developed *N*-spiro C_2-symmetric chiral quaternary ammonium bifluorides **126**, **128**, and **131** as efficient catalysts; see Scheme 37.[250]

The enantioselective nitroaldol (Henry) reaction (a) with the use of nitronate **5a** provides access to a range of nitroalcohols **127** of preferred *anti* configuration, with high yields and enantioselectivities.[251] This *anti* stereoselectivity of the nitroaldol reaction can be rationalized with a model of the transition state (Figure 6) in which the arrangement of both the electrophile and the nucleophile leading to the *syn* stereoisomer is destabilized by steric repulsion of the R^1 and R^2 groups.

Maruoka's catalyst can also effectively catalyze 1,4-additions of **5** to α,β-usaturated aldehydes (b),[252] enones (c),[253] and nitroalkenes (d).[254] Such reactions are otherwise difficult to be carried out, particularly in the case of α,β-unsaturated aldehydes, and they are important due to the possibility of establishing up to three consecutive stereocenters in an acyclic system. In addition, the catalyst load is remarkably low (0.02 equiv or less) in all the reactions listed in Scheme 37.

2.5. Miscellaneous Carbon Trimethylsilyl Nucleophiles

A number of trimethylsilyl carbon nucleophiles which upon desilylation can generate weakly stabilized carbanions have been used in organic synthesis. These include allyl (**6**), benzyl (**7**), cyanomethyl (**8**), acyl (**9**), alkynyl (**10**), and 1,3-heterocyclic (**11**) trimethylsilyl nucleophiles.

The reports published after 1988[1] focus on the activation of these nucleophiles for the addition to carbonyl and imine nucleophiles. Thus, allyltrimethylsilane (**6**) can be organocatalytically activated with TCNE in refluxing acetonitrile for the addition to aldehydes, ketones, and acetals.[47] Allyltrimethylsilane adds to aldehydes[255] or in situ formed imines[256] in acetonitrile solution under catalysis with iodine. The strong nonionic base P(*i*PrNCH$_2$CH$_2$)$_3$N of Verade et al. catalyzes the addition of **6** to aromatic aldehydes.[257] Tetra-*n*-butylammonium triphenyldifluorosilicate (TBAT) is another catalyst for the cleavage of Si−C bonds in allyl-, benzyl-, alkynyl-, and dithianylsilanes, allowing high-yield additions to aldehydes and ketones.[258] Similarly to the procedure of Sakurai for the addition of allylsilanes to aldehydes and ketones,[259] the addition of **6** to imines is catalyzed by tetra-*n*-butylammonium fluoride (TBAF) at low catalyst load (0.01 equiv).[260] The same catalyst is ineffective for the catalysis of addition of allylsilanes to sulfines, providing access to allyl sulfoxides in moderate to good yield.[261] An interesting regioselectivity of addition of allyl or benzyl trimethylsilanes to thioketones or dithioesters was observed by Degl'Innocenti et al. Whereas allyl lithium or magnesium reagents add at the carbon, TMS reagents add at the sulfur under TBAF or TASF catalysis, to give allyl or benzyl thioethers or dithioacetals.[262]

Intramolecular Michael-type addition of allyl silanes **133**, mediated by TBAT, is a route to diasteroisomerically pure 2,3-dihydro-4-pyridones **134** (Scheme 38).[263]

Cyanomethylation of carbonyl compounds with trimethylsilylacetonitrile (**8**), an equivalent of an aldol reaction, can

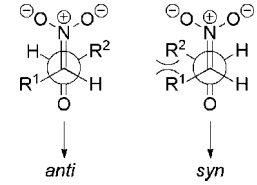
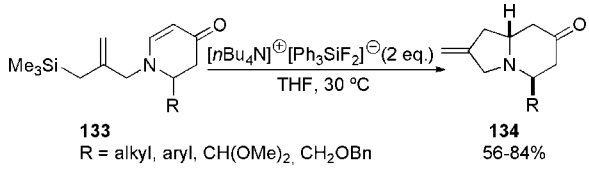
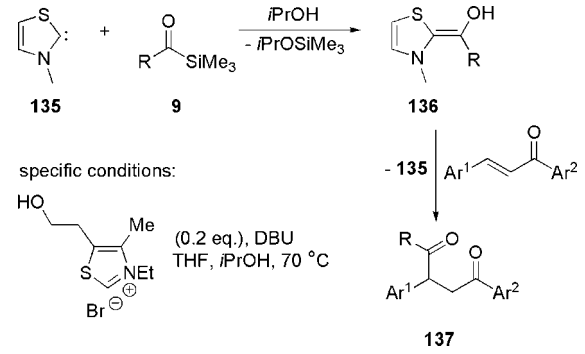


Figure 6. Transition state models for nitroaldol reaction leading to a preferred *anti* configured product.

Scheme 38. Intramolecular Michael-Type Addition of Allylsilanes[263]



Scheme 39. Route to 1,4-Dicarbonyl Compounds from Acylsilanes 9[267]



be catalyzed by tris(diethylamino)sulfonium fluoride (TASF) or NaOMe in THF or CH_2Cl_2.[264] Other ionic Lewis bases, such as lithium acetate or benzoate, are effective in catalyzing the addition of **8** to aromatic aldehydes and ketones[265] as well as to imines[266] in DMF solution.

Acyltrimethylsilanes (**9**) can be activated for sila-Stetter reactions by in situ generated NHCs.[4] The activation proceeds through addition of the carbene catalyst, such as **135**, to **9** and subsequent 1,2-silyl migration to produce a Breslow-type intermediate **136**, after desilylation with *i*PrOH. Deprotonated **136** adds preferentially in a conjugated fashion to chalcones, producing 1,4-dicarbonyl products **137** (Scheme 39).[267]

These products can be further transformed to furans or pyrroles. The reaction can also be carried out under neutral aqueous conditions.[268]

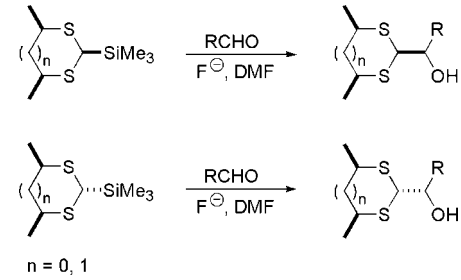
Acetal-protected sugar lactones react with 2-(trimethylsilyl)thiazole, adding diastereoselectively to the carbonyl group, under catalysis with TASF.[205]

Perfluoroketene dithioacetals undergo a coupling reaction with silyl alkynes **10,** induced by *N*-tetramethylammonium fluoride (TMAF)—a rare example of a nontransition metal catatyzed carbon−carbon forming reaction with alkenyl fluoride as a substrate.[269]

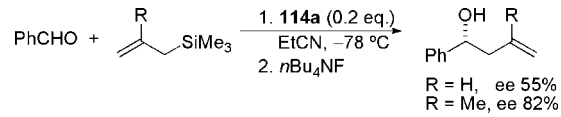
Silylated dithiolane (**11**, X = S), oxathiolane (**11**, X = O), and thiazolidine (**11**, X = NR) can be regarded as formyl or acyl anion equivalents. The masked formyl anion can be activated by the action of fluoride ion on the silyl precursors with the participation of hypervalent silicon species, as shown by recent studies of Degl'Innocenti et al.[270] The reaction of silylated dithiolanes with electrophiles in the presence of fluoride ions leads to the products with retention of configuration of the original carbon−silicon bond. Examples of such processes are shown in Scheme 40.[271]

To date, none of the additions of trimethylsilyl carbon nucleophiles mentioned in this section have been carried out under strictly asymmetric organocatalysis conditions. However, electrophile activation employing the chiral (acyloxy)borane complex **114a** introduced by Yamamoto et al. enables allylation of benzaldehyde with moderate to good

Scheme 40. Stereospecificity of Addition of Silylated Dithioacetals to Aldehydes[271]



Scheme 41. Enantioselective Addition of Allylsilanes to Benzaldehyde[208]



enantiomer excesses of the products (Scheme 41, see also section 2.3).[208]

3. Heteroatom Trimethylsilyl Nucleophiles

Compared to carbon trimethylsilyl nucleophiles, their heteroatom analogues have not yet received as much attention in organocatalytic additions. However, transition metal complex-catalyzed additions of trimethylsilyl azide were studied inter alia by the groups of Jacobsen and Shibasaki. Thus, Me_3SiN_3 (**138**) was extensively used in the process of asymmetric opening of epoxides[272] and aziridines[273] catalyzed by chromium salen complexes, and a yttrium complex-catalyzed addition of **138** to *meso*-aziridines was applied to the synthesis of Tamiflu.[274] In this review, the discussion will be limited to the use of **138** for conjugate addition to α,β-unsaturated carbonyl compounds and for ring-opening reactions of aziridines, although less common additions, except hexamethyldisilothiane **140**.

Trimethylsilyl halides (**139**) are widely used as reagents for the protection of hydroxyl, sulfhydryl, and amino groups. They are also useful for ring-opening reactions of aziridines. Trimethylsilyl sulfur-centered nucleophiles **141** have not yet attracted wide interest as nucleophiles for organocatalytic additions.

Chart 3. Heteroatom Nucleophiles

Me_3SiN_3	Me_3SiX (X = Cl, Br, I)
138	**139**
$(Me_3Si)_2S$	Me_3SiR (R = NCS, SPh, OC(=S)Me)
140	**141**

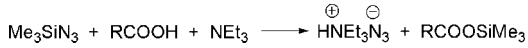
3.1. Trimethylsilyl Azide (Me_3SiN_3) and Trimethylsilyl Halides (Me_3SiX)

3.1.1. Conjugate Addition of Me_3SiN_3 to α,β-Unsaturated Carbonyl Compounds

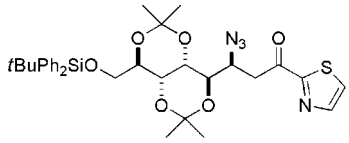
Organocatalysis of this reaction is generally performed with the use of tertiary amines, such as NEt_3, in the presence of a stoichiometric amount of acetic or pivalic acid.[275,276] No reaction occurs in the absence of the carboxylic acid, which apparently promotes generation of the azide ion (Scheme 42).

Another source of acid can be a concentrated solution of HCl. The use of a mixture of Me_3SiN_3 and an acid allows one to avoid 1,2-addition of **138** to the aldehyde group.[277]

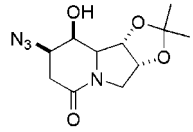
Scheme 42. Organocatalytic Activation of Trimethylsilyl Azide



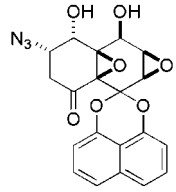
Scheme 43. Products of Diastereoselective 1,4-Additions of Me_3SiN_3 (138) to α,β- Unsaturated Carbonyl Compounds.



*n*Bu$_4$NF, 94%
(*syn*:*anti* 3:1)[279]



DBU, AcOH, 84%[280]



MeOH, DMF, 70 °C, 67%[281]

Amberlite IRA900F$_3$, a polystyrene-bound quaternary 4-trimethylbenzylammonium fluoride, is a practical organocatalyst for conjugate addition of **138** to unsaturated carbonyl compounds under solvent-free conditions.[278] The electrophiles for this reaction include enals, enones, and α,β-unsaturated esters, nitriles, or nitro compounds.

Substrate-controlled diastereoselective additions of **138** to α,β-unsaturated carbonyl compounds, structurally related to natural products, have been reported (Scheme 43).

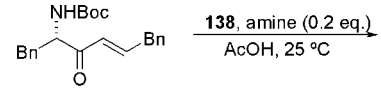
These reactions are moderately diastereoselective and show a striking preference toward C−N bond formation *syn* to the vicinal C−O bond of the substrate. Note that in the last example shown in Scheme 43 the reaction was carried out without the use of a typical catalyst, albeit with a large excess of **138** and at elevated temperature.

Diastereoselective enone hydroazidation was used in the synthesis of **143**, a mimic of the Phe-Phe dipeptide and a structural element of two potent inhibitors of HIV-PR, Ritonavir, and Lopinavir. Addition of **138** to the amino-substituted enone **142** showed remarkable dependence on the structure of the amine catalyst used. The reaction proceeded essentially with quantitative yield, and the desired *syn* stereoisomer was obtained with a diastereomer ratio of up to 7:1 with the use of a chiral amine, an L-proline methyl ester (Scheme 44).[282]

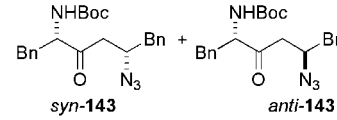
Enantioselective catalysis of conjugate addition of **138** to α,β-unsaturated *N*-acylpyrrolidinones **144** has been reported by Miller et al.[283] This reaction was catalyzed by tripeptides **146a** and **146b**. With as little as 0.0025 equiv of the catalyst load, products **145**, the precursors of β-amino acids, were obtained with high yields and enantiomer excesses (Scheme 45).

With the nonmethylated *N*-terminal histidine residue in **146b**, slightly lower enantioselectivity of the addition was observed, presumably due to a higher conformational diversity of the catalyst.

Scheme 44. Diastereoselective Additions of Me_3SiN_3 to Enone 142[282]



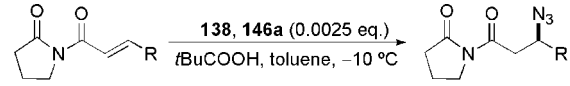
142



syn-**143** *anti*-**143**

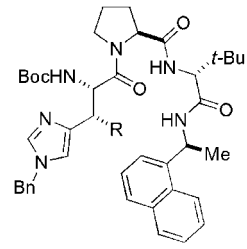
amine:	*syn*-**143**	:	*anti*-**143**
NEt_3	1	:	1
DBU	1	:	1
imidazole	2	:	1
NMM	5	:	1
L-proline methylester	5	:	1
	7	:	1 (at −18 °C)

Scheme 45. Enantioselective Conjugate Additions of Me_3SiN_3 (138)[283]



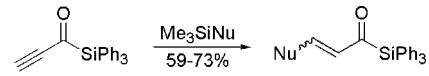
144

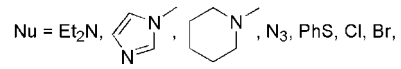
145
R = Me, Et, *i*Pr, Cy
yield 65-90%
ee 85-92%



146a R = Me
146b R = H

Scheme 46. Addition of Heteroatom Trimethylsilyl Nucleophiles to Acetylenic Silyl Ketenes[284]





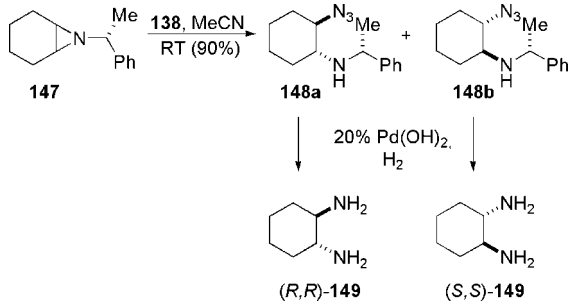
Various heteroatom trimethylsilyl nucleophiles undergo spontaneous addition to acetylenic silyl ketones to give cleanly α,β-unsaturated acyl silanes with moderate yields (Scheme 46).[284]

The diastereoselectivity of this reaction is dependent on the nature of the silicon substituent. Whereas in most cases the *trans*-configured product was obtained, the *cis* addition product was observed in the addition of Me_3SiNH_2, $Me_3SiNHMe$, and Me_3SiPh.

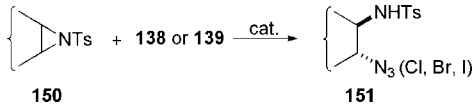
3.1.2. Additions to Aziridines

The reactivity of trimethylsilyl nucleophiles toward aziridines depends on both the nature of the nucleophile and the substituent on the nitrogen atom. Aziridines bearing no electron-withdrawing substituent apparently are unreactive toward Me_3SiCN (see section 1.1.3), but with the more reactive Me_3SiN_3 (**138**), the reaction proceeds at room temperature to give the ring-opening products in high yields.[285] It is quite obvious that the reaction is autocatalyzed by either the substrate or the amine product acting as a Lewis base. Addition of a Lewis acid catalyst, such as Sn(OTf)$_2$, in fact leads to a lower yield of the addition product in many cases.[286]

Scheme 47. Diastereoselective Synthesis of Enantiomers of 1,2-*trans*-Diaminocyclohexane from Chiral Aziridine 147[286]



Scheme 48. Stereoselective Ring Opening of Activated Aziridines with Trimethylsilyl Azide (138) and Trimetylsilyl Halides (139)



The addition of **138** or trimethylsilyl halides to *N*-tosylated aziridines is efficiently catalyzed by NHCs.[287]

With a chiral substituent at the nitrogen atom of the aziridine, addition of **138** is diastereoselective. Thus, with **147** as a substrate, the two diastereomeric adducts **148a** and **148b** are formed in a ratio of 4:1. These products after chromatographic separation can be hydrogenated to enantiomers of *trans*-1,2-diaminocyclohexane (**149**) in high yield (Scheme 47).[286]

N-Tosyl- or *N*-benzoyl-substituted aziridines **150** react with **138** or **139** only under catalysis, to give *trans*-configured 2-sulfonamido azides or halides **151** (Scheme 48).

The reaction is not only stereoselective but also regioselective: the nucleophile attacks the less substituted (less hindered) carbon atom. Effective catalysts include nBu$_4$NF,[123,288] TMEDA,[124] NHCs,[287] or even DMF at 40 °C[289] and β-cyclodextrin in a water/acetone mixture.[290]

An enantioselective desymmetrization of *meso*-aziridines with **138** catalyzed by a chiral Brønsted acid has recently been reported. The aziridines were activated by 4-nitrobenzoyl or 3,5-dinitrobenzoyl groups; however, the best enantioselectivity was achieved with the *N*-3,5-di(trifluoromethyl)benzoyl substituent, as in **152**. The chiral acid was a derivative of phosphoric acid (VAPOL PA-1, Scheme 49).[291]

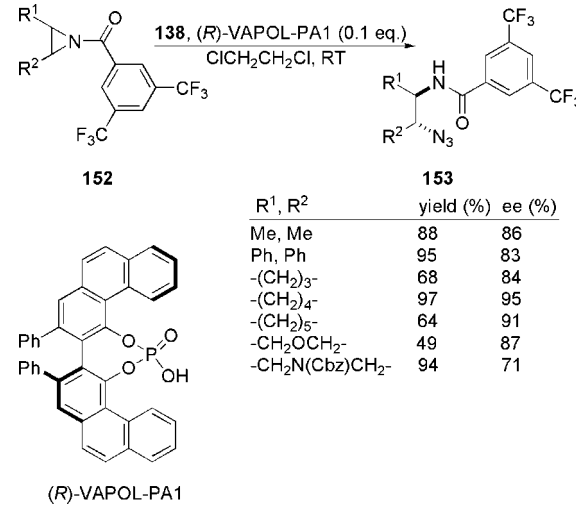
Chiral azido-amides **153** were obtained with good yield and with enantiomer excess in the range of 71−95%. This remarkable azidation works presumably through the formation of an active catalyst species, by trimethylsilyl group transfer from **138** to VAPOL PA-1. The silylated catalyst activates the aziridine group by Si···O association of the active catalyst with the carbonyl group of the benzoylated aziridine.

3.2. Trimethylsilyl Sulfur Nucleophiles

Among trimethylsilyl sulfur nucleophiles, hexamethyldisilothiane (HMDST, **140**) reactivity was most intensely studied.[270a,292]

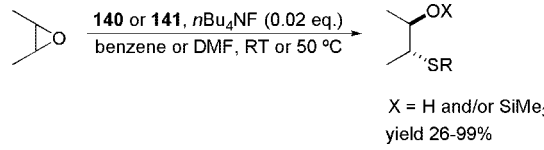
Only a few examples of fluoride ion-catalyzed additions of trimethylsilyl sulfur nucleophiles have been reported in the literature. Various epoxides were subjected to reactions with either HMDST (**140**), trimethylsilyl isothiocyanate (**141**, R = N═C═S), trimethylsilyl thiophenolate (**141**, R = SPh), or *O*-trimethylsilyl thioacetate (**141**, R = OC(═S)Me), using nBu$_4$NF as a catalyst (Scheme 50).[293,294]

Scheme 49. Enantioselective Ring Opening of Aziridines 152 with Me_3SiN_3 (138)[291]



R^1, R^2	yield (%)	ee (%)
Me, Me	88	86
Ph, Ph	95	83
-$(CH_2)_3$-	68	84
-$(CH_2)_4$-	97	95
-$(CH_2)_5$-	64	91
-CH_2OCH_2-	49	87
-$CH_2N(Cbz)CH_2$-	94	71

Scheme 50. Stereoselective Ring Opening of Epoxides with Trimethylsilyl Sulfur Nucleophiles 140 or 141[293,294]



The reaction obeyed the usual regioselectivity pattern. Moreover, ambiphilic reagents (**141**, R = N═C═S or OC(═S)Me) behaved exclusively as sulfur-centered nucleophiles. Partial desilylation of the products was observed in these reactions; however, the products did not undergo either decyanation (when R = NCS) or deacetylation (when R = OC(═S)Me).

It should be mentioned here that reagents of the structure Me_3SiSR under anionic catalysis (*n*-tetrabutylammonium fluoride or cyanide) exclusively undergo 1,4-additions to α,β-unsaturated aldehydes and ketones. This is in sharp contrast to the analogous reaction of **1**, which results in selective 1,2-addition (cyanohydrination).[295]

4. Conclusion and Perspectives

Catalytic additions of trimethylsilyl nucleophiles offer a number of advantages compared to additions of ionic metal nucleophiles. Me_3SiNu are stable and commercially available compounds in a number of structural variations. They are soluble in nonpolar solvents, offering the possibility of activation by a catalyst in a low polarity environment and at low temperatures. These features are desired for effective asymmetric induction in the additions to prochiral substrates.

Despite the large number of published reports on the use of silylated nucleophiles in stereoselective synthesis and many successful applications, there are still unsolved or partially solved issues that deserve to be mentioned at the conclusion of this review. Up to now the widespread use of Me_3SiNu centered around just a few nucleophiles. These include Me_3SiCN, since its addition to aldehydes, ketones, and imines leads to highly desirable derivatives of α-functionalized carboxylic acids. Very high levels of asymmetric induction have been reached in numerous versions of this reaction. The addition of Me_3SiCF_3 to carbonyl and imine electrophiles has been intensely studied due to the importance of chiral quaternary trifluoromethyl derivatives in pharma-

ceutical applications. Despite the efforts, organocatalysis of the reaction has not yet provided consistent, high levels of enantioselectivity of the addition. Mukaiyama-type aldol and Michael reactions, fundamental for the stereoselective construction of complex natural products, utilize trimethylsilyl enol ethers and trimethylsilyl ketene acetals. Reported enantioselective reactions vary in their efficiency, indicating that there is need for the improvement of organocatalytic control of the reaction.

In contrast to the wide use of trimethylsilyl−carbon nucleophiles, trimethylsilyl−heteroatom (N, S, halogen) addition reactions are still awaiting new methodologies, particularly for making these reactions enantioselectively viable. In fact, higher reactivity of trimethylsilyl−heteroatom nucleophiles compared to trimethylsilyl−carbon nucleophiles makes the control of such reactions a highly challenging goal.

For numerous reasons, some of which are mentioned above, 1,2-additions to carbonyl and imine electrophiles are most frequently studied. Organocatalyzed conjugate addition reactions and ring opening reactions of oxiranes and aziridines are much less frequently encountered.

The question of the role of Lewis base as an initiator or a true catalyst is central to understanding the stereochemical consequences of additions of silylated nucleophiles. This issue has been thoroughly discussed in a recent excellent review of Denmark.[236] There is the possibility of two competing processes, one truly catalyzed by a (chiral) Lewis base (cf. Scheme 2) and the second autocatalyzed by a chiral alkoxide product (cf. Scheme 20). The second process may be particularly important in the case of fluoride ion catalysis, since the formation of volatile Me_3SiF, having a strong Si−F bond, may lead to depletion of the catalyst in the reaction medium. As a result, the stereochemical outcome of a nucleophile addition reaction may depend on the structure of the alkoxide product, which is chiral but not necessarily homochiral. This may lend an explanation of the difficulties in reaching consistently very high levels of enantioselection in the Lewis base, organocatalytic addition reactions of silylated nucleophiles (see for example Tables 1−3).

Mimicking the multicenter structure and synergistic cooperation of Lewis base−Lewis acid centers of enzymes, bifunctional catalysis has the potential to control enantioselection of asymmetric additions of silylated nucleophiles at the highest levels. The success of several catalytic systems and procedures will stimulate new developments and improvements aimed at future industrial applications. Among the issues that should be addressed is catalyst recovery. Although catalyst loads vary from less than 0.01 to 1 equiv, the amount most frequently used is 0.1 equiv. Unless the catalyst is an inexpensive commercial substance (and this is usually not the case with chiral catalysts), its recovery (immobilization) should be considered. Alternatively, development of more accessible (chiral) catalysts, used at lower molar loads, could significantly improve perspectives for industrial applications.

5. Acknowledgments

We thank Professor Armin de Meijere for critical remarks concerning the manuscript. This work was supported by Grant No. PBZ-KBN-118/T09/10 from the Committee for Scientific Research.

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