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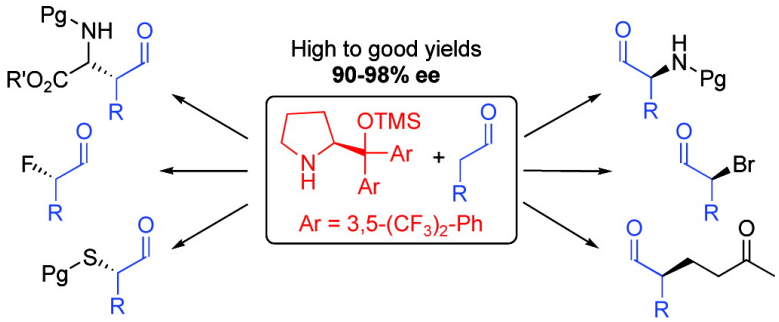

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A General Organocatalyst for Direct α-Functionalization of Aldehydes: Stereoselective C−C, C−N, C−F, C−Br, and C−S Bond-Forming Reactions. Scope and Mechanistic Insights

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Abstract: The development of a general organocatalyst for the α-functionalization of aldehydes, via an enamine intermediate, is presented. Based on optically active α,α-diarylprolinol silyl ethers, the scope and applications of this catalyst for the stereogenic formation of C−C, C−N, C−F, C−Br, and C−S bonds are outlined. The reactions all proceed in good to high yields and with excellent enantioselectivities. Furthermore, we will present mechanistic insight into the reaction course applying nonlinear effect studies, kinetic resolution, and computational investigations leading to an understanding of the properties of the α,α-diarylprolinol silyl ether catalysts.

Introduction

We are in "the golden age of organocatalysis", and organocatalytic reactions have in the past few years emerged as a powerful tool for the preparation of optically active compounds.[1]

The use of chiral secondary amines for the α-functionalization of aldehydes represents an important breakthrough in modern asymmetric synthesis and a large variety of functionalizations, such as C−C,[2] C−N,[3] C−X (X = halogen),[4] C−S,[5] C−O[6] bond-forming reactions among others, have been developed.

As a result of the thoroughly investigated α-functionalization of aldehydes, numerous different secondary amine-based catalysts have been developed. In many cases this leads to a very tedious screening of a large number of catalysts when developing new reactions because only a few organocatalysts stand out among the others for their application in a broad range of transformations.

Proline is certainly part of this noble club, and in the recent past, it has been defined as a "universal catalyst" because of its high utility especially in enantioselective aldol,[7] Mannich,[8] amination,[3] and α-aminoxylation reactions.[6a−e] The catalysts developed in the laboratories of MacMillan et al. also show an interesting generality and were found effective for chlorination,[4e]

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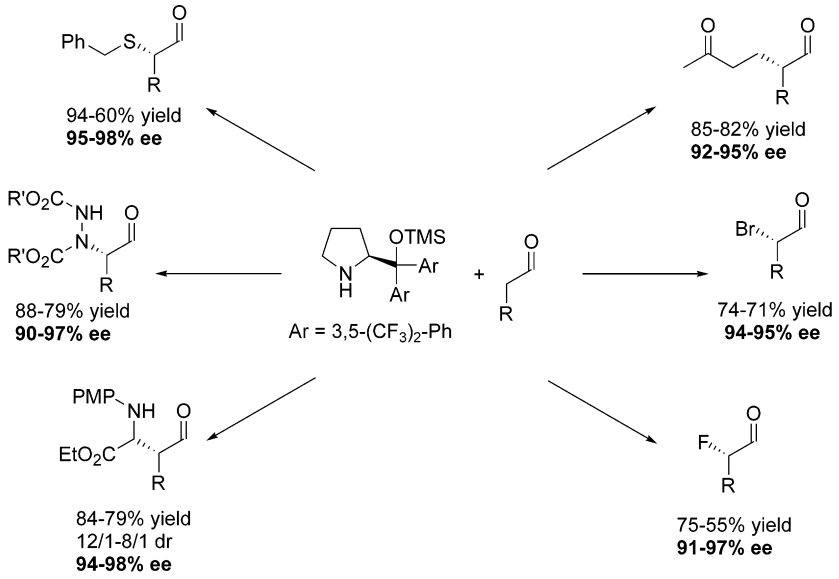
Scheme 1. Highly Enantioselective α-Functionalizations of Aldehydes Catalyzed by the α,α-Diarylprolinol Silyl Ether



fluorination,[4b] and aldol reactions of aldehydes.[9] However, for both proline and the MacMillan catalyst, good hydrogen-bonding properties of the electrophiles are in many cases proposed to be important to achieve high asymmetric induction.[10]

We therefore set out to develop an organocatalyst that could be suitable for a large variety of transformations as well as new enantioselective reactions that are not efficiently catalyzed by proline and other common organocatalysts. In this article we present the development of the α,α-diarylprolinol silyl ether as a general catalyst for α-functionalization of aldehydes. We have previously communicated the use of this catalyst for the stereogenic formation of C−F[4d] and C−S[5] bonds, and now we will demonstrate the generality of the catalyst to be also highly efficient for different asymmetric reactions, such as the stereogenic formation of C−C, C−N, and C−Br bonds, with good to high yields and with excellent enantioselectivities (Scheme 1). Furthermore, we will present mechanistic insight into the reaction course applying nonlinear effect studies, kinetic resolution, and computational studies leading to an understanding of the properties of the α,α-diarylprolinol silyl ether catalyst and to justify both the high enantioselectivity and the broad scope of the catalyst.

Results and Discussions

Catalyst Design. The high efficiency, in terms of both reactivity and enantioselectivity often observed with proline, is ascribed to the dual activation of both the nucleophilic aldehyde and the electrophile.[10] This means that the approach of the electrophile to the enamine intermediate is controlled by hydrogen bonding to the carboxylic acid function of proline and not by steric shielding. Consequently, proline is usually not an efficient catalyst in terms of enantioselectivity for reactions of aldehydes with electrophiles that are poor hydrogen-bond acceptors.

To overcome these limitations connected with the mechanism of chiral induction associated with proline, the strategy was to design a pyrrolidine derivative able to induce high enantioselectivities by controlling the geometry of the enamine and through efficient face shielding.

Our investigations started from a careful survey of a large set of experiments carried out by our and other groups involved in organocatalytic processes, and two related structures attracted our attention (Figure 1).

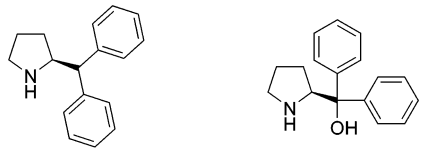


Figure 1.

(*S*)-2-(Diphenylmethyl)-pyrrolidine ((*S*)-**1**) is often found to be a very active catalyst for a variety of transformations, but only in few cases high enantioselectivities are obtained.[11] On the other hand, (*S*)-2-diphenyl-prolinol ((*S*)-**2a**) often promoted reactions with a good level of stereocontrol, but the processes are characterized by a low catalyst turnover.[12] This behavior has been partially attributed to the increased size of the substituent. Our working hypothesis was that the relatively small size of the hydroxyl group could not justify such a large decrease of reactivity. Instead, we ascribed the low catalyst turnovers observed for the pyrrolidine derivative (*S*)-**2a**, mainly to the formation of the relatively stable and unreactive hemiaminal species **A** and **B** that remove a significant amount of catalyst (*S*)-**2a** from the catalytic cycle (Scheme 2).[13]

To prevent the proposed hemiaminal formation, the hydroxyl group was protected with a TMS group [eq 1]. Among the many possible protecting groups, the TMS group was chosen because the TMS-protected catalyst can be prepared in one single step starting from the corresponding prolinol. This simple modification of (*S*)-**2** to (*S*)-**3** drastically increased the catalytic turnover in the α-functionalization of aldehydes (vide infra).

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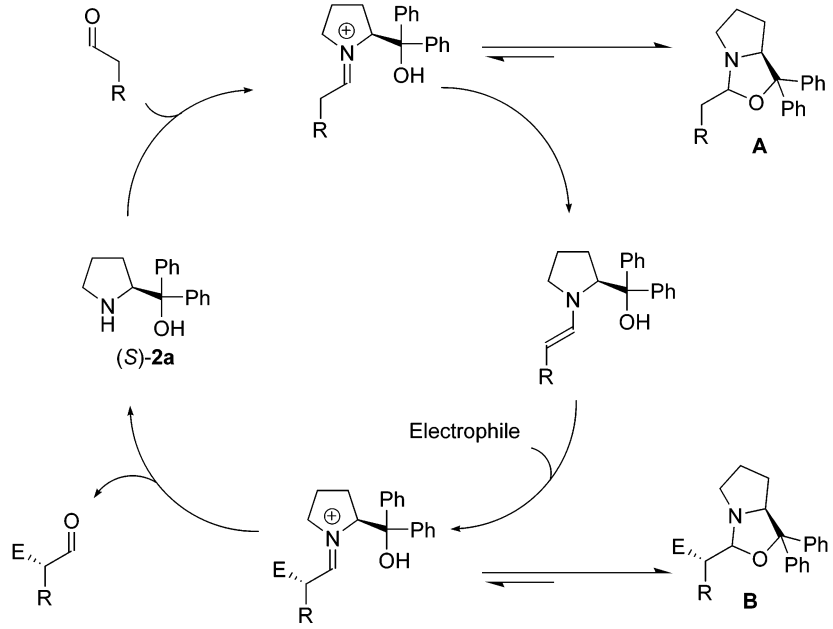
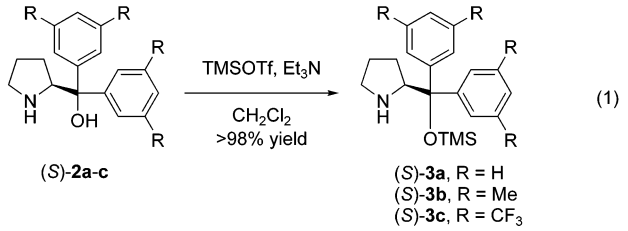
Scheme 2. Catalytic Cycle with Formation of Unreactive Hemiaminal Species **A** and **B** that Remove a Significant Amount of Catalyst (*S*)-**2a** from the Catalytic Cycle





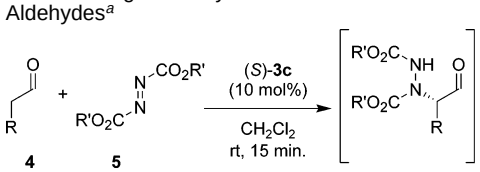
(1)

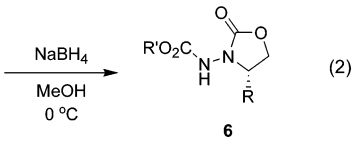
Further improvements in enantioselectivity were made through the variation of the aryl substituents in the catalyst structure, and the trifluoro derivative (*S*)-**3c** was identified as the best catalyst for a series of transformations (Scheme 1). It is important to note that the excellent results summarized in Scheme 1 are for both addition and substitution reactions and also for electrophiles not having hydrogen-bond capability.

Catalyst Survey. A. α-Amination of Aldehydes. The direct α-amination of aldehydes was independently developed by List[3b] and our group[3a] as an effective strategy for the formation of optically active amino alcohols and amino acid derivatives using L-proline as the catalyst. With the trifluoro substituted catalyst (*S*)-**3c** in hand we decided to investigate if this catalyst could match up with the high standards set by proline.

The results achieved with the α,α-diarylprolinol silyl ether (*S*)-**3c** matches those obtained with L-proline and smoothly catalyzed the reaction between aldehydes **4** and azodicarboxylates **5** in CH_2Cl_2 at room temperature [eq 2]. The α-aminated products **6a**−**e** were isolated in high yields and with 90−97% ee as the corresponding oxazolidinones after reduction of the aldehyde moiety and subsequent cyclization (Table 1). A comparison of the results obtained using the two alternative catalytic systems, reveals the following important differences: (*i*) the absolute configuration of the aminated product obtained with (*S*)-**3c** is opposite to the configuration obtained with L-proline, although the absolute configuration of the catalysts is the same (vide infra); (*ii*) some of the products are obtained with higher enantiomeric excess using catalyst (*S*)-**3c** (e.g., 97% ee vs 93% ee for **6b** and 97% ee vs 91% ee for **6d**); and (*iii*) reactions catalyzed by (*S*)-**3c** proceed faster.

Table 1. Organocatalyzed Enantioselective α-Amination of Aldehydes[a]





(2)

entry	aldehyde	R	R′	product	yield[b] [%]	ee[c] [%]
1	**4a**	Et	Et	**6a**	79	90
2	**4b**	*i*-Pr	Et	**6b**	88	97
3	**4b**	*i*-Pr	*i*-Pr	**6c**	73	92
4	**4c**	*t*-Bu	Et	**6d**	83	97
5[d]	**4d**	allyl	Et	**6e**	81	92

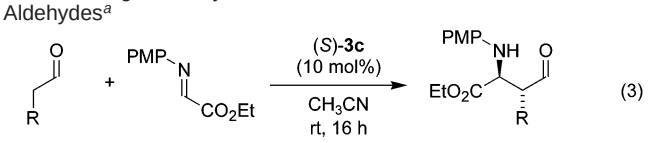
[a] Compound **5** (0.25 mmol) was added to **4** (0.30 mmol) and (*S*)-**3c** (0.025 mmol) in CH_2Cl_2 (0.5 mL) at room temperature. [b] Yield of isolated product. [c] The ee value was determined by chiral GC on the corresponding oxazolidinones. [d] Reaction performed at −15 °C.

B. Mannich Reactions. The Mannich reaction is a classic method for the preparation of α-amino aldehydes.[2c] The L-proline catalyzed Mannich reaction of unmodified aldehydes with a *N*-PMP-protected α-imino ethyl glyoxylate to give direct access to highly functionalized α-amino acids has been thoroughly investigated mainly by Barbas et al.[8]

The application of catalyst (*S*)-**3c** (10 mol %) to this transformation (eq 3) turned out to be successful as reported in Table 2. Treatment of aldehydes **4a**,**b**,**d**−**f** with the *N*-PMP-

(11) Juhl, K.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1498.
(12) For some comparing studies on the reactivity between compound **1** and **2a** preformed within our group, see refs 4d, 4f, 5, 11, and 15d.
(13) (a) Zuo, G.; Zhang, Q.; Xu, J. *Heteroat. Chem.* **2003**, *14*, 42. (b) Okuyama, Y.; Nakano, H.; Hongo, H. *Tetrahedron: Asymmetry* **2000**, *11*, 1193.

Table 2. Organocatalyzed Enantioselective Mannich Reaction of Aldehydes[a]



(3)

entry[a]	aldehyde	R	product	yield[b] [%]	dr	ee [%]
1	**4a**	Et	**8a**	83	80:20	94[c]
2	**4b**	*i*-Pr	**8b**	79	92:8	98[c]
3	**4d**	allyl	**8c**	63[e]	90:10	98[d]
4	**4e**	Bn	**8d**	74	91:9	94[d]
5	**4f**	Me	**8e**	76	86:14	98[c]

[a] Compound **7** (0.25 mmol) was added to **4** (0.50 mmol) and (*S*)-**3c** (0.025 mmol) in CH_3CN (0.5 mL) at room temperature. [b] Yield of isolated product. [c] The ee value was determined by chiral HPLC. [d] The ee value was determined by chiral HPLC after $LiAlH_4$ reduction to the corresponding diol. [e] Yield of the corresponding diol after $LiAlH_4$ reduction.

protected α-imino ethyl glyoxylate **7** in the presences of catalyst (*S*)-**3c** at room temperature gave the Mannich adducts **8a**−**e** with very high enantioselectivies, 94−98% ee.

Investigation of the relative conformation between the two stereocenters in the Mannich adducts **8** revealed that the reaction proceeds with moderate to high *anti*-diastereoselectivity. It is worthwhile to emphasizing the fact that the use of L-proline leads to the opposite *syn*-diastereoisomer and this behavior is a direct consequence of the different structure and properties of the two catalysts leading to two different transition states (vide infra). Attempts have been performed previously to promote the *anti*-selective organocatalytic asymmetric Mannich reactions with the same reagents.[14] The application of (*S*)-2-methoxymethylpyrrolidine as the catalyst (20 mol %) gave the *anti*-diastereomer in moderate yields (44−68%) and enantioselectivities in the range of 74−82% ee. The use of catalyst (*S*)-**3c** leads to a significant improvement in terms of yield and enantioselectivity: for entries 1 and 2 in Table 2, the results with (*S*)-2-methoxymethylpyrrolidine were 44% yield, 1:1 dr, 75% ee and 52% yield, 10:1 dr, 82% ee, compared to 82% yield, 80:20 dr, 94% ee and 79% yield, 92:8 dr, 98% ee, respectively, with catalyst (*S*)-**3c**.

C. Conjugate Additions to Methylvinyl Ketone. Conjugate additions are reactions of fundamental importance in organic chemistry, and chiral secondary amines have been shown to catalyze the direct enantioselective Michael addition of aldehydes to vinyl ketones and nitrostyrene.[15] The additions of aldehydes to vinylmethyl ketone have previously been studied in our group.[15d] It was found that pyrrolidine derivative (*S*)-**1** was more reactive than prolinol (*S*)-**2a**; on the other hand, prolinol (*S*)-**2** provided considerably higher enantioselectivity in the reaction than (*S*)-**1**, which is in line with the earlier discussion (see above). Furthermore, in this reaction proline gave very low conversion and only 20% ee. We were pleased to find that aldehydes **4a**,**f**−**g** reacted with methylvinyl ketone **9** in a highly stereoselective manner and all products **10a**−**c** were obtained in high yields (80−83%) and excellent enantiomeric excesses (92−95% ee) using catalyst (*S*)-**3c** (eq 4 and Table 3). For this reaction the temperature had to be increased in order to obtain a shorter reaction time. It is important to point out that, even after these relatively long reaction times and the high reaction temperature, only minor amounts of homo-aldol product could be observed (<5%).

Table 3. Organocatalyzed Enantioselective Michael Addition of Aldehydes to Methylvinyl Ketone[a]

(4)

entry[a]	aldehyde	R	product	yield[b] [%]	ee[c] [%]
1	**4a**	Et	**10a**	83	93
2	**4f**	Me	**10b**	80	92
3	**4g**	*n*-Pr	**10c**	82	95

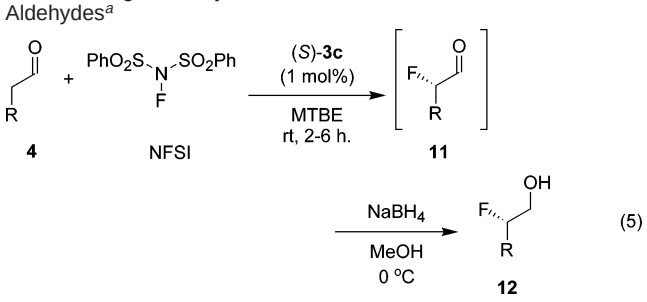
[a] Compound **9** (0.25 mmol) was added to **4** (0.50 mmol) and (*S*)-**3c** (0.025 mmol) in EtOH (0.5 mL) at 40 °C and stirred for 64 h. [b] Yield of isolated product. [c] The ee value was determined by chiral GC.

The (*S*)-**3c** catalyst improves the enantiomeric excess of the Michael adducts significantly compared to the catalyst (based on (*S*)-**1**) used in our initial study.[15d] For the Michael adducts **10a** and **10b**, we obtained 85% yield and 79% ee and 83% yield and 64% ee, respectively, in our initial study, while catalyst (*S*)-**3c** significantly improves the enantioselectivity to 93% and 92% ee, respectively, and with the same good yields (Table 3, entries 1, 2). Recently, after our first reports on the catalytic properties of *O*-protected diarylprolinol derivatives, Hayashi et al.[15b] and Gellman et al.[15a] independently reported the successful application of this type of catalysts in conjugated addition reactions. It should be noted that the work by Hayashi et al.[15b] extends the use of this class of catalysts to also include the addition of aldehydes to nitroalkenes using (*S*)-**3a**.

D. α-Fluorination of Aldehydes. Several groups have recently investigated the asymmetric α-halogenation of aldehydes, and MacMillan et al.[4e] and our group[4f] independently reported the direct enantioselective α-chlorination of aldehydes. This was shortly followed by the independent development of enantioselective α-flourination of aldehydes by Barbas et al.,[4a] MacMillan et al.,[4b] Enders et al.,[4c] and us.[4d] Our approach to the asymmetric α-fluorination of aldehydes relied on *N*-fluorobenzensulfonimide (NFSI) as the fluorination agent and the disubstituted-diphenylprolinol silyl ether (*S*)-**3c** as the catalyst,[4d] since the use of L-proline, L-proline amide, and (*R*,*R*)-2,5-diphenylpyrrolidine all gave poor yields and enantioselectivity. A screening showed that, with catalyst (*S*)-**3c**, high asymmetric induction was obtained, and the choice of solvent had only a minor effect on the selectivity. However, reactions in CH_2Cl_2 and CH_3CN gave only moderate conversions of, e.g., 3-phenyl butanal **4b** in the presence of 10 mol % of catalyst (*S*)-**3c** and 1.2 equiv of NFSI. This was the result of the desilylation of (*S*)-**3c** to give (*S*)-**2c** in the presence of NSFI. We have found that (*S*)-**2c** shows very low catalytic activity, and the low conversion was caused by inactivation of the catalyst, in line with earlier discussions. However, an improvement in stability of catalyst (*S*)-**3c** was observed in methyl-*tert*-butyl ether (MTBE). Complete conversion of NFSI was obtained, along with significant amounts of difluorinated

(14) Córdova, A.; Barbas, C. F., III. *Tetrahedron Lett.* **2002**, *43*, 7749.
(15) (a) Chi, Y.; Gellman, S. H. *Org. Lett.* **2005**, *7*, 4253. (b) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212. (c) Wang, W.; Wang, J.; Li, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 1369. (d) Melchiorre, P.; Jørgensen, K. A. *J. Org. Chem.* **2003**, *68*, 4151. (e) Betancort, J. M.; Barbas, C. F., III. *Org. Lett.* **2001**, *3*, 3737. (f) Mase, N.; Thayumanavan, R.; Tanaka, F.; Barbas, C. F., III. *Org. Lett.* **2004**, *6*, 2527. (g) Betancort, J. M.; Sakthivel, K.; Thayumanavan, R.; Tanaka, F.; Barbas, C. F., III. *Synthesis* **2004**, 1509. (h) Hechavarria Fonseca, M. T.; List, B. *Angew. Chem., Int. Ed.* **2004**, *43*, 3958. (i) Peelen, T. J.; Chi, Y.; Gellman, S. H. *J. Am. Chem. Soc.* **2005**, *127*, 11598.

Table 4. Organocatalyzed Enantioselective α-Fluorination of Aldehydes[a]



(5)

entry	aldehyde	R	conv to **11**[b] [%]	product	yield[c] [%]	ee[d] [%]
1	**4c**	*t*-Bu	>95	**12a**		97
2	**4e**	Bn	>90	**12b**	74	93
3	**4g**	*n*-Pr	>95	**12c**		96
4	**4h**	*n*-Bu	>90	**12d**		91
5[e]	**4i**	*n*-Hex		**12e**	55	96
6	**4j**	1-Ad		**12f**	75	96
7	**4k**	Cy		**12g**	69	96
8	**4l**	$(CH_2)_3OBn$		**12h**	64	91

[a] NFSI (0.25 mmol) was added to **4** (0.375 mmol) and (*S*)-**3c** (0.0025 mmol) in TBME (0.5 mL) at room temperature. [b] Conversion determined by GC. [c] Yield of the respective alcohol obtained by reduction with $NaBH_4$. [d] The ee value was determined by CP-GS on the aldehydes or by chiral HPLC on the alcohol or alcohol derivative. [e] 1.1. equiv of NFSI; 1 equiv of aldehyde.

aldehydes. Further optimization of the reaction conditions revealed that decreasing the catalyst amount to only 1 mol % and using a slight excess of aldehyde gave higher yields maintaining the high enantiomeric excess. The corresponding optically active fluoro alcohols **12a**−**h** could be isolated in moderate to high yields and excellent enantioselectivity (91−97% ee) after $NaBH_4$ reduction (eq 5 and Table 4).

As mentioned above several papers were published within a few weeks describing the organocatalyzed enantioselective α-fluorination of aldehydes.[4a−d] A comparison of the properties of catalyst (*S*)-**3c** with the imidazolidinone catalyst used by both Barbas et al.[4c] and MacMillan et al.[4b] shows that both systems give excellent enantioselectivity. However, higher catalytic activity of (*S*)-**3c** leads to shorter reaction times. The higher reaction rate observed using (*S*)-**3c** allows a lower catalytic loading (0.25 to 1 mol %), while the imidazolidinone system required 2.5 to 100 mol %.

E. α-Bromination of Aldehydes. The direct α-halogenation reactions developed by our group have been further advanced to include also the enantioselective α-bromination of aldehydes using the C_2-symmetric (*R*,*R*)-2,5-diphenylpyrrolidine as the catalyst.[4g] We were pleased to find that when a selection of aldehydes **4b**,**c**,**j** were treated with 4,4-dibromo-2,6-di-*tert*-butylcyclohexa-2,5-dienone **13** in the presence of catalyst (*S*)-**3c** in CH_2Cl_2 at −24 °C, a smooth α-bromination occurred with excellent asymmetric induction (eq 6 and Table 5). The corresponding optically active bromo alcohols **14a**−**c** could be isolated after $NaBH_4$ reduction in high yields.

The low temperature was necessary only to prevent undesired side reactions such as bromination of the catalyst. At 0 °C the corresponding reaction stopped after 30% conversion, whereas at −24 °C full conversion was obtained after 90 min with the same enantiomeric excess for the optically active α-bromo alcohol. Compared to the use of (*R*,*R*)-2,5-diphenylpyrrolidine[4g] as the catalyst for the α-bromination, catalyst (*S*)-**3c** has several advantages, such as easier synthesis of the catalyst and no need for mixed solvents and additives such as benzoic acid and water. Furthermore, (*S*)-**3c** uniformly gives excellent enantioselectivities of the optically active α-bromo alcohols **14a**−**c**, while (*R*,*R*)-2,5-diphenylpyrrolidine[4g] gave enantioselectivies from 65% ee and up.

F. α-Sulfenylation of Aldehydes. Catalyst (*S*)-**3c** is also a very effective catalyst for the direct asymmetric α-sulfenylation,[5] and before our report, all practical methods for preparation of chiral α-sulfenylated aldehydes have been multistep procedures that involve chiral auxiliaries.[16] According to our knowledge, no catalytic processes are available for the preparation of these optically active sulfur compounds. For the direct α-sulfenylation of aldehydes, several challenges emerged with regard to sulfenylating reagent, such as the sulfur protecting and leaving groups. A careful screening showed that compound **15**, having triazole as the leaving group, gives access to the benzyl protected thiol functionality and fulfilled the requirement for being the optimal sulfenylating agent.[5]

In analogy to other reactions previously studied, catalyst (*S*)-**2a** was completely inactive while catalyst (*S*)-**1** promoted the formation of the desired product in good yield, but with low enantiomeric excess due also to the racemization of the optically active sulfenylated aldehydes in the reaction mixture. The α,α-diarylprolinol silyl ether (*S*)-**3c** turned out to be an effective catalyst for the α-sulfenylation of simple aldehydes (eq 7), and the results are summarized in Table 6.

Substrates having a small (Me) or bulky (*t*-Bu) substituent were consistently converted into products **17** with 95−98% ee. The newly functionalized aldehydes racemize on silica, and the products were isolated after in situ reduction with $NaBH_4$ to the corresponding optically active alcohol **17a**−**f**. Very recently, several attempts were carried out to perform direct organocatalytic enantioselective α-sulfenylation and selenenylation reactions of adehydes.[17] For the direct α-sulfenylation, a large number of organocatalysts, such as L-proline, L-proline amide, and pyrrolidine trifluoromethanesulfonamide, as well as other chiral amines, were tested using *N*-(phenylthio)phthalimide as the sulfenylating reagent. However, no enantiomeric excess was reported. The related α-selenenylation of both aldehydes and ketones were also studied with L-proline amide and pyrrolidine trifluoromethanesulfonamide as the catalysts and *N*-(phenylseleno)phthalimide as the selenenylation reagent, and low enantioselectivity was reported for this transformation.

Mechanistic Insights

Control of Enantioselectivity through Control of Enamine Geometry. In the transition state, the conjugation of the lone-pair electrons of the nitrogen atom with the double bond restricts the number of possible conformations of the reactive enamine intermediate (Scheme 3).

(16) For examples: (a) Youn, J.-H.; Herrmann, R.; Ugi, I. *Synthesis* **1987**, 158. (b) Poli, G.; Belvisi, L.; Manzoni, L.; Scolastico, C. *J. Org. Chem.* **1993**, *58*, 3165. (c) Enders, D.; Schäfer, T.; Piva, O.; Zamponi, A. *Tetrahedron* **1994**, *50*, 3349. (d) Chibale, K.; Warren, S. *Tetrahedron Lett.* **1994**, *35*, 3991. (e) Enders, D.; Schäfer, T.; Mies, W. *Tetrahedron* **1998**, *54*, 10239. (f) Evans, D. A.; Campos, K. R.; Tedrow, J. S.; Michael, F. E.; Gagné, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 7905. See also: (g) Jereb, M.; Togni, A. *Org. Lett.* **2005**, *7*, 4041.

(17) (a) Wenig, W.; Li, H.; Wang, J.; Liao, L. *Tetrahedron Lett.* **2004**, *45*, 8229. (b) Wang, W.; Wang, J.; Li, H. *Org. Lett.* **2004**, *6*, 2817. (c) Wang, J.; Li, H.; Mei, Y.; Lou, B.; Xu, D.; Xie, D.; Guo, H.; Wang, W. *J. Org. Chem.* **2005**, *70*, 5678.

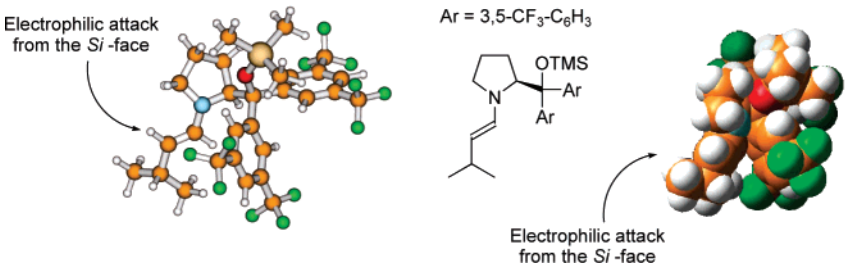
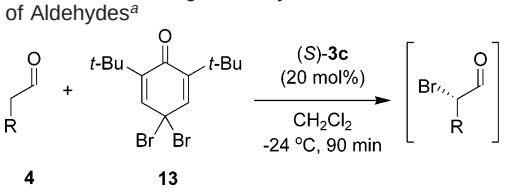
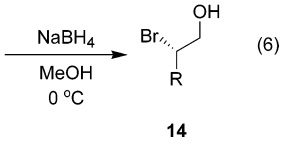


Figure 2. DFT-optimized structure of the enamine formed by 3-methyl butanal (**4b**) and catalyst (*S*)-**3c**.

Table 5. Direct Organocatalyzed Enantioselective α-Bromination of Aldehydes[a]



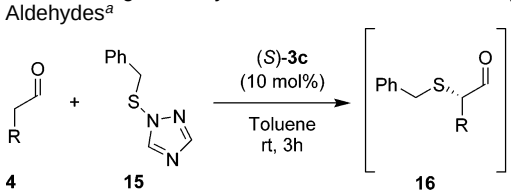


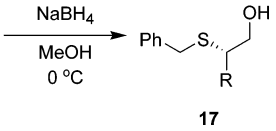
(6)

entry	aldehyde	R	product	yield[b] [%]	ee[c] [%]
1	**4b**	*i*-Pr	**14a**	74	94
2	**4c**	*t*-Bu	**14b**	71	95
3	**4j**	Adm	**14c**	74	95

[a] Compound **13** (0.37 mmol) was added to **4** (0.25 mmol) and (*S*)-**3c** (0.025 mmol) in CH_2Cl_2 (0.5 mL) at −24 °C and stirred for 90 min. [b] Isolated yield. [c] The ee value was determined by chiral GC. [d] The ee value was determined by chiral HPLC after *m*-nitrobenzoylation of **14c**.

Table 6. Organocatalyzed Enantioselective α-Sulfenylation of Aldehydes[a]





(7)

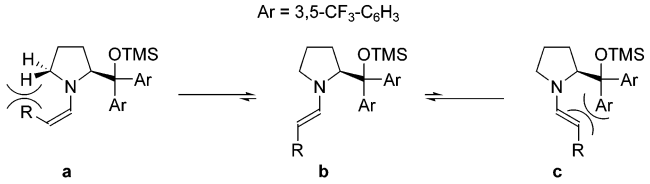
entry	aldehyde	R	product	yield[b] [%]	ee[c] [%]
1	**4a**	Et	**17a**	85	96
2	**4b**	*i*-Pr	**17b**	81	98
3	**4c**	*t*-Bu	**17c**	83	97
4	**4d**	Allyl	**17d**	64	96
5	**4e**	Bn	**17e**	94	97
6	**4f**	Me	**17f**	60	95

[a] Compound **15** (0.33 mmol) was added to **4** (0.25 mmol) and (*S*)-**3c** (0.025 mmol) in toluene (0.5 mL) at room temperature. [b] Yield of the respective alcohol obtained by reduction with $NaBH_4$. [c] The ee value was determined by chiral HPLC on the alcohol or other derivatives.

The *E*-conformation (**b**) is energetically favored over the *Z*-conformation (**a**), and the bulky substituent on the α-position of the pyrrolidine ring raises the energy of the conformation (**c**). The large aryl and silyl substituents of the catalyst (*S*)-**3c** can efficiently shield the *Re*-face of the favored *E*-configuration of the enamine.

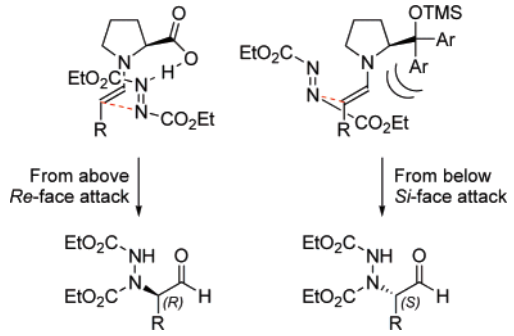
This hypothesis is confirmed by a model based on DFT calculations of the optimized enamine intermediate using a 6-31G* basis set.[18] The energetically lowest intermediate structure shows that one of the 3,5-trifluoromethyl phenyl groups efficiently covers the *Re*-face of the enamine (Figure 1). As a consequence, the electrophilic attack must occur from the *Si*-face providing the excellent enantioselectivities (Figure 2).

Scheme 3. Enamine Intermediate Conformations



The absolute configuration of the products has been found to be identical for all the products and in agreement with the model proposed.[19] It is interesting to note that catalyst (*S*)-**3c** and L-proline that have identical absolute configurations, however, due to the different nature of the transition state, in the case of amination reaction and Mannich reaction, promote the formation of products with the opposite absolute configuration at the α-carbon stereocenter (Scheme 4).

Scheme 4. Transition-State Models for L-Proline and α,α-Diarylprolinol Silyl Ether (*S*)-**3c** Catalyzed α-Amination of Aldehydes



Effect of Catalyst Structure on the Enantioselectivity of the Reactions. The effect of the structure of the aromatic groups of the prolinol derivative on the enantiomeric excess of the product has been investigated for the α-sulfenylation of 3-methyl butanal. The experiments were carried out varying the R-substituent on the aromatic groups in the catalyst (see eq 1). The enantiomeric excess was found to be increasing when moving from the simple diphenyl-prolinol ((*S*)-**3a**) to 3,5-dimethyl ((*S*)-**3b**) and 3,5-ditrifluoromethyl ((*S*)-**3c**) substitution

(18) (a) Frisch, M. J. et al. *Gaussian 98*, revision A.7; Gaussian, Inc.: Pittsburgh, PA, 1998. (b) Frisch, M. J. et al. *Gaussian 03*, revision B.05; Gaussian, Inc.: Pittsburgh, PA, 2003.
(19) The absolute configuration was determined by comparison of optical rotation with literature data. See Supporting Information for references.

Scheme 5. Explanation to the Configurative Stability of α-Functionalized Aldehydes

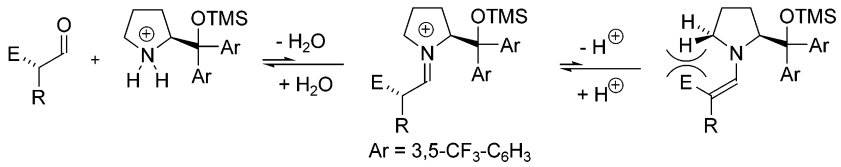
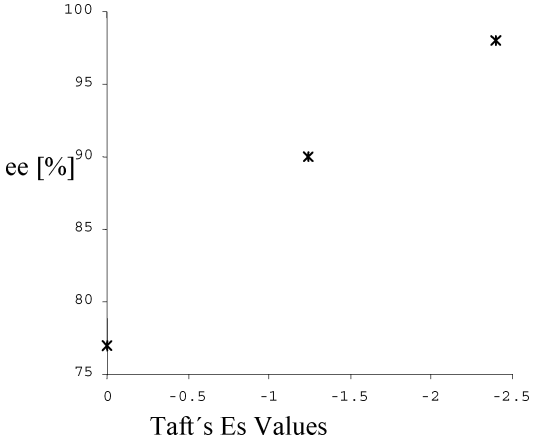


Table 7. Relation between Taft's E_s Values of the Aromatic Substituents of (*S*)-**3** and Enantioselectivity in the α-Sulfenylation of 3-Methyl Butanal[a]



entry	R	Taft's E_s values	ee[b] [%]
1	H	0	77
2	CH_3	−1.24	90
3	CF_3	−2.40	98

[a] Compound **15** (0.27 mmol) was added to **4b** (0.25 mmol) and (*S*)-**3c** (0.025 mmol) in toluene (0.5 mL) at ambient temperature for 3 h. [b] The ee value was determined by chiral GC.

(Table 7), indicating that the electronic properties of the R-group in the catalyst have no effect on the enantiomeric excess.

Taft's E_s values,[20] which are steric substituent constants, are in approximately linear correlation with the optical activity of the products (Table 7). The size of CF_3 is relatively large, in the order of Me < *i*-Pr < CF_3 < *t*-Bu and, hence, in sharp contrast to the small van der Waal radius of fluorine.[21] This supports that the asymmetric induction observed with catalyst (*S*)-**3c** completely relies on selective enamine conformation and steric shielding.

Conformational Stability of the Products (Thermodynamic and Kinetic). The stability of the chiral center of the product is as important as its enantioselective formation, and the structure of the catalyst (*S*)-**3c** is also suited to prevent this undesired path.

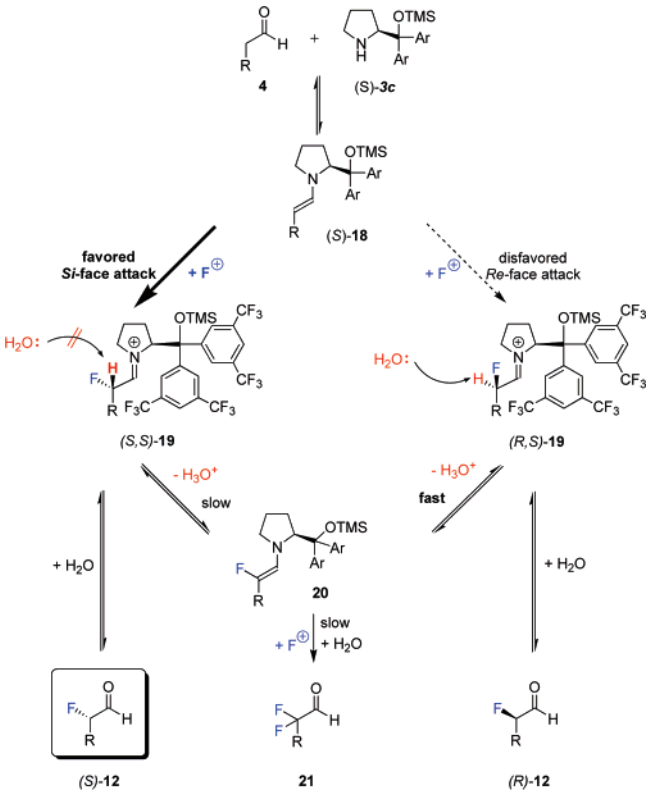
The racemization of the α-functionalized aldehydes is in general prevented because of the higher energy of the enamine species with the more sterically demanding disubstitued aldehyde, thus leading in preference to iminium-ion hydrolysis and release of the product (Scheme 5).

This explanation is not sufficient in the case of α-fluorinated aldehydes because of the small steric interaction of the fluorine atom. The van der Waal radius of the fluorine atom (1.35 Å) is

(20) (a) Taft, R. W., Jr. *J. Am. Chem. Soc.* **1952**, *74*, 2729. (b) Taft, R. W., Jr. *J. Am. Chem. Soc.* **1952**, *74*, 3120. (c) Taft, R. W., Jr. *J. Am. Chem. Soc.* **1953**, *75*, 4231.

(21) (a) de Riggi, I.; Virgili, A.; de Moragas, M.; Jaime, C. *J. Org. Chem.* **1995**, *60*, 27. (b) Wolf, C.; König, W. A.; Roussel, C. *Liebigs Ann.* **1995**, 781.

Scheme 6. Explanation to the Configurative Stability of α-Fluorinated Aldehydes



in fact not much larger than the van der Waal radius of the hydrogen atom (1.20 Å). The configurational stability is even more surprising because a significant amount of difluorinated product has been observed. In fact, both processes, racemization and difluorination, pass through the same enamine intermediate.

The complex system that leads to the formation of highly optically active products in the fluorination reaction is shown in Scheme 6.

In the preferably formed (*S*,*S*)-**19** iminium ion, the remaining α-hydrogen atom (shown in bold red) is covered by the shielding substituents on the catalyst. The geminal fluorine atom and the substituents on the pyrrolidine ring are presumably forming a hydrophobic pocket that protects the remaining acidic α-proton from abstraction by water and prevents racemization through enamine formation. For that reason, the nucleophilic attack of water will more easily take place at the carbon atom of the iminium ion releasing the α-fluorinated aldehyde and thereby closing the catalytic cycle. The opposite situation is presumed in the formation of the disfavored iminium-ion intermediate (*R*,*S*)-**19** where the remaining α-hydrogen atom is not shielded, consequently resulting in a fast enamine formation and subsequent racemisation or difluorination.

In Figure 3 is reported the calculated structure for the iminium-ion intermediate formed after α-fluorination, (*S*,*S*)-**19** and (*R*,*S*)-**19**.

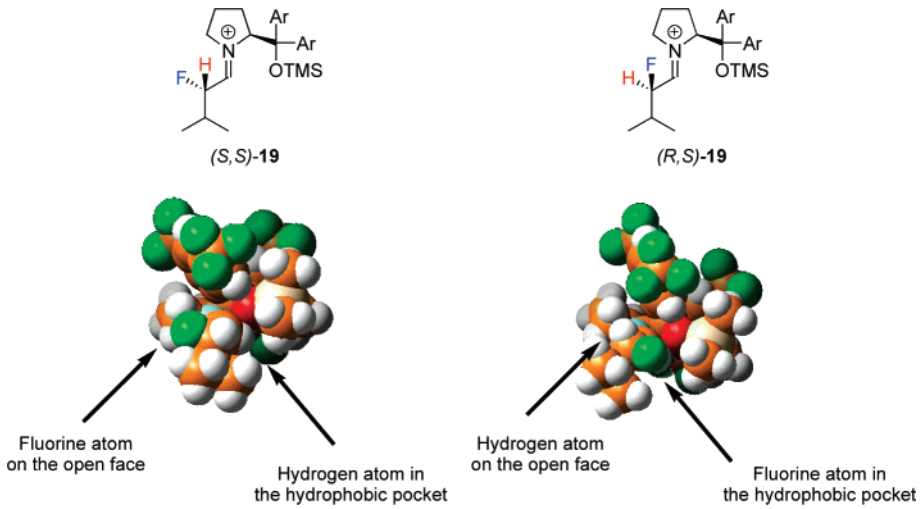


Figure 3. DFT-optimized structures of the iminium-ion intermediate (*S*,*S*)-**19** and (*R*,*S*)-**19**.

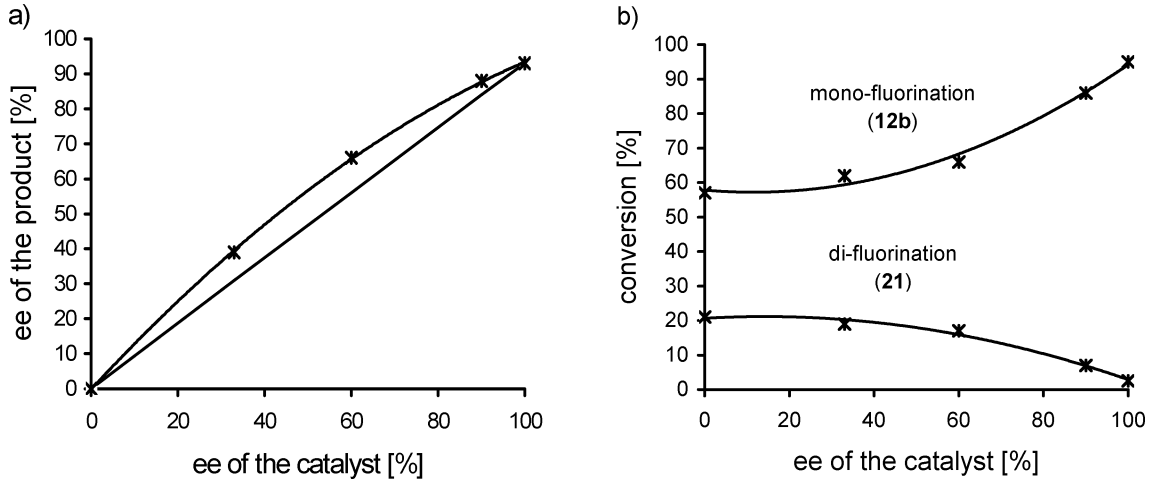
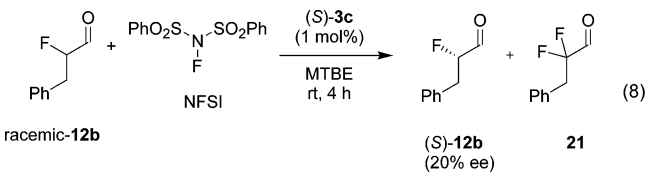


Figure 4. NFSI (0.27 mmol) was added to **4e** (0.25 mmol) and the appropriate mixture of (*S*)-**3c** and (*R*)-**3c** (0.025 mmol) in MTBE (0.5 mL) at ambient temperature and enantiomeric excess, and conversion was determined by GP-GC.

The energetically lowest intermediate structures show that the 3,5-trifluoromethyl phenyl groups and the TMS group efficiently shield the α-proton in (*S*,*S*)-**19**, thereby protecting it from abstraction preventing enamine formation. On the other hand, for the diastereoisomer (*R*,*S*)-**19**, the α-proton is placed in the open face and is more accessible toward abstraction.

A direct implication of our hypothesis is that the catalytic system developed should be able to differentiate between the two enantiomers of the monofluorinated product and promote the kinetic resolution of racemic α-fluoro aldehydes.

In fact, a racemic mixture of α-fluoro aldehyde **12b** was slowly converted to the difluorinated product **21** in the presence of 0.5 equiv of NFSI and 1 mol % of catalyst (*S*)-**3c** (eq 8). After 20% conversion to **21** (4 h reaction time), 20% ee of α-fluoro aldehyde (*S*)-**12b** was found. The experiment clearly revealed that (*R*)-**12b** was consumed faster than (*S*)-**12b**.



(8)

To have an enhanced understanding of the process under study, we planned a new set of experiments. The aldehyde **4e** was subjected to the standard reaction conditions, and in Figure 4a is shown the relation between the enantiomeric excess of the monofluorinated product and the enantiomeric excess. The nonlinear effect observed is in agreement with a postulated hydrophobic pocket and with the described kinetic resolution of **12b**. When catalyst (*S*)-**3c** is used in excess, relative to (*R*)-**3c**, the minor amount of (*R*)-**12b** formed is quickly difluorinated to give **21** in the presence of the relatively large amount of (*S*)-**3c**. At the same time, the difluorination of (*S*)-**12b** proceeds at a much lower rate, because it can be catalyzed only by the small amount of (*R*)-**3c** present in the reaction mixture. Therefore the enantiomeric excess of (*R*)-**12b** over (*S*)-**12b** is higher than expected.

The effect of the optical purity of the catalyst on the conversion of the aldehyde **4e** to the mono- (**12b**) and difluorinated (**21**) products in the presence of NFSI and catalyst (*S*)-**3c** was also studied (Figure 4b). It was observed that when the enantiomeric excess of the catalyst was increased the amount of difluorination product decreased. This is another conformation of our hypothesis since catalyst (*S*)-**3c** mainly promotes the difluorination of the optically active product obtained in the presence of catalyst (*R*)-**3c** and vice versa, and it was reasonable to expect the largest amount of difluorinated product **21** when racemic **3c** is used.

Table 8. Effect of Solvent and Temperature on Enantioselctivity and Conversion in the Michael Addition of Butanal **4a** to Methylviny Ketone **9** Catalyzed by (*S*)-**3c** after 48 h Reaction Time[a]

entry	solvent	temp [°C]	conversion to **10a**[b] [%]	ee[c] [%]
1	DCE	40	17	96
2	TBME	40	11	97
3	CH_3CN	40	6	95
4	EtOH	40	72	96
5	EtOH	20	30	96
6	EtOH[d]	60	58	93
7	EtOH	60	90	88

[a] Compound **9** (0.25 mmol) was added to **4a** (0.50 mmol) and (*S*)-**3c** (0.025 mmol) in the appropriate solvent (0.5 mL) and at the appropriate temperature for 44 h. [b] Conversion determined by ^{1}H NMR experiments. [c] The ee value was determined by chiral GC. [d] 20 h reaction time.

Solvent and Temperature Effect. A large advantage of the use of the newly developed α,α-diarylprolinol silyl ether (*S*)-**3c** is that the high enantioselectivities are the result of efficient shielding and the fixed geometry of the enamine intermediate. A consequence of this fact is that the choice of the solvent and temperature can be used to modulate the reactivity but has only a minor effect on the enantioselectivity. For example, the Michael addition of butanal **4a** to methylvinyl ketone **9** catalyzed by (*S*)-**3c** was screened (eq 4) for a series of solvents and conversion and enantioselectivity were determined after 48 h at 40 °C (Table 8). It was found that EtOH gave the highest conversion, although, for the four solvents compared, there is no effect on the stereoselectivity of the reaction.

The stability of the system was further demonstrated by increasing the temperature further, and at 60 °C for 24 h 60% conversion and 93% ee were obtained. After 48 h at 60 °C almost full conversion was observed together with a decrease of enantiomeric excess to 88%, most likely due to racemisation of the product. However, for very reactive electrophiles, i.e., diethyl azodicarboxylates, an increase in enantiomeric excess (from 86% to 92% ee) was observed when decreasing the temperature from 20 to −15 °C for the amination of 4-pentenal (Table 1, entry 5). It is also important to point out for the Michael addition reaction that, even at 60 °C for 48 h, only a minor amount of homo-aldol product could be observed (<10%). Furthermore, in contradiction to proline, the pyrrolidine derivative is soluble in all the common solvents but only partially soluble in the more polar EtOH, DMF, and DMSO.

Catalyst (*S*)-**3c** has been mixed with 3-methyl butanal under standard reaction conditions (0.5 M and ambient temperature). Experiments in CD_3OD, CD_3CN, $CDCl_3$, CD_2Cl_2, and $CD_3S(O)CD_3$ revealed that between 55% and 70% of the catalyst has reacted with the aldehyde to form the enamine species.

Conclusions

We have demonstrated that the α,α-diarylprolinol silyl ether (*S*)-**3c** is able to catalyze α-amination, fluorination, bromination, and sulfenylation of aldehydes, as well as Mannich and Michael addition reactions, and herein we present the preparation of 30 different compounds with 90−98% ee from achiral precursors. It has also been shown by interpretation of experimental data, calculations, and kinetic studies that the high asymmetric induction obtained with catalyst (*S*)-**3c** is an effect of highly efficient face-shielding and a fixed geometry of the reactive enamine intermediate. Furthermore, when using catalyst (*S*)-**3c** a high conformational stability of the products is observed as a result of the proposed hydrophobic pocket that protects the product from racemisation. This catalytic system is extremely flexible, since solvents and temperature influence only the yields and not the enantioselectivities of the reactions. Recently, we also demonstrated that catalyst (*S*)-**3c** was capable of iminium-ion activation with high stereoselectivity.[22] Further investigations of the capacity of this catalyst toward new reactions are currently under investigation in our laboratory and results from these studies will be presented in the future.

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Supporting Information Available: Complete experimental procedures and computational methods. Enantiomeric separation conditions, spectral data, and optical rotation for all new compounds. Complete ref 18. This material is available free of charge via the Internet at http://pubs.acs.org.

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