DOI: 10.1002/ejoc.200901283

Aminal–Pyrrolidine Organocatalysts – Highly Efficient and Modular Catalysts for α-Functionalization of Carbonyl Compounds

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Keywords: Asymmetric catalysis / Organocatalysis / Michael addition / Enamine / Pyrrolidine

The substitution of the 4-position of hydroxyproline by a phenol group, together with an aminal on the 2-position, gave a synergistic effect leading to two powerful complementary organocatalysts. They show excellent enantiocontrol in the α-functionalization of a wide range of linear/branched aldehydes and ketones, including Michael additions to ethenediyl disulfones or nitrostyrene and α-amination. We obtained *ee*s up to 98.5 % with low catalyst loadings (down to 1 mol-%). As a proof of efficiency, TOFs of up to 1000 h^{-1} could be obtained.

Introduction

Enamine catalysis has recently emerged as a method of choice for the α-functionalization of carbonyl compounds.[1] An ever-increasing number of new reactions have been developed during the last decade, leading researchers to design more efficient catalysts. This is notably the case for the Michael addition, where the addition to nitro olefins has in particular been extensively studied. Rarely has a research area been so heavily investigated, leading to the design of powerful catalytic systems in such a short period.[2] This activity is mainly due to the novelty of the area, the opportunity to obtain useful synthons by new activation modes and in few steps, and mostly to the mild experimental conditions, which do not require particular equipment such as Schlenk tubes or a glove box. Among enamine catalysts, some of them have been found to be more general such as proline,[3] MacMillan's oxazolidinones,[4] or the widely used diarylprolinol silyl ethers.[5] These catalysts have shown widespread application but still need further development in order to obtain increased reactivity or lower catalyst loading, allowing organocatalysis to be a viable industrial process. This explains the need for a continuous effort towards the design of more efficient catalysts.

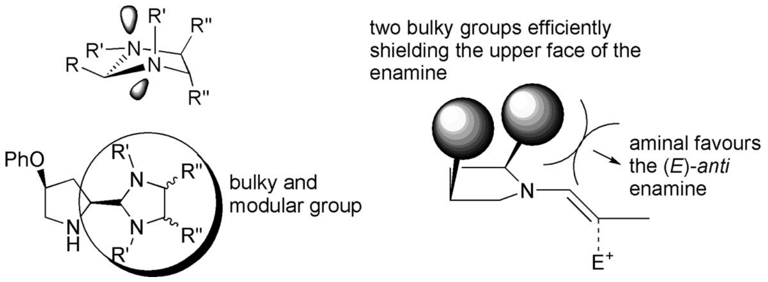

Figure 1. Aminal structure and proposed new aminal–pyrrolidine catalysts.

In order to imagine a new catalyst, many different parameters have to be taken into account, such as the basicity/acidity of the active site, the presence of a hydrogen donor, solubility, availability, and the possibility of recycling. Given these numerous factors, diarylprolinol silyl ethers have emerged as powerful catalysts for the α-functionalization of aldehydes. Designed on the basis of a strong steric hindrance on the 2-position of the pyrrolidine ring, they are able to promote high enantioselectivity in numerous reactions. Indeed, they favor the exclusive formation of the (*E*)-enamine, while totally shielding the upper face of the formed enamine.[6] Inspired by these results and by the fact that the presence of an extra amine on the pyrrolidine substituent led to high reactivity,[1m,2c] we recently briefly reported the design of a new catalyst incorporating an aminal on the pyrrolidine. The goal was to bring increased steric hindrance as close as possible to the catalytic site. Indeed, in the aminal structure, the nitrogen atoms are stereogenic (Figure 1).[7] The substituents on each nitrogen atom adopt

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.200901283.

a *trans* configuration relative to the substituent on the adjacent carbon atoms. Thus, the chiral information of the diamine backbone is transferred closer to the catalytic site. Furthermore, since various diamines can be incorporated at a late stage of the synthesis, these catalysts contain another interesting property. They are highly modular and tunable, and by just changing the diamine substituent, totally different properties can be obtained. These catalysts gave moderate to good results in the Michael addition to nitro olefins or ethenediyl disulfones.[8]

Herein, we wish to present further improvement of these catalysts by the introduction of a 4-phenoxy group on the pyrrolidine ring. The addition of a bulky substituent at the 4-position led to better control of the steric hindrance on the upper face of the enamine. Thus, the obtained catalysts gave impressive reactivity and selectivity for the α-functionalization of various carbonyl compounds, such as linear and α-branched aldehydes and cyclohexanone.

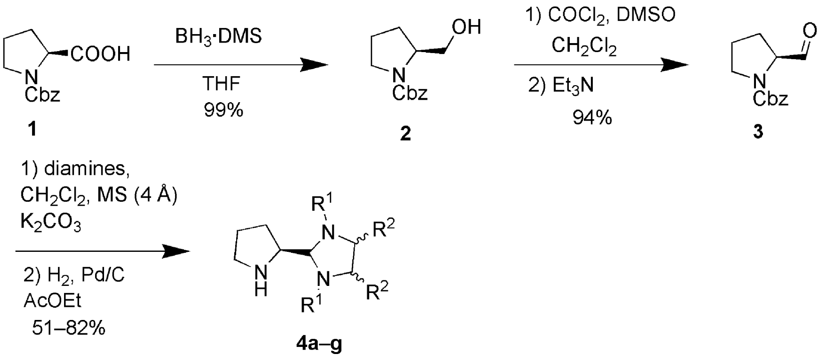
Results and Discussion

Preliminary Results Using Proline Derivatives

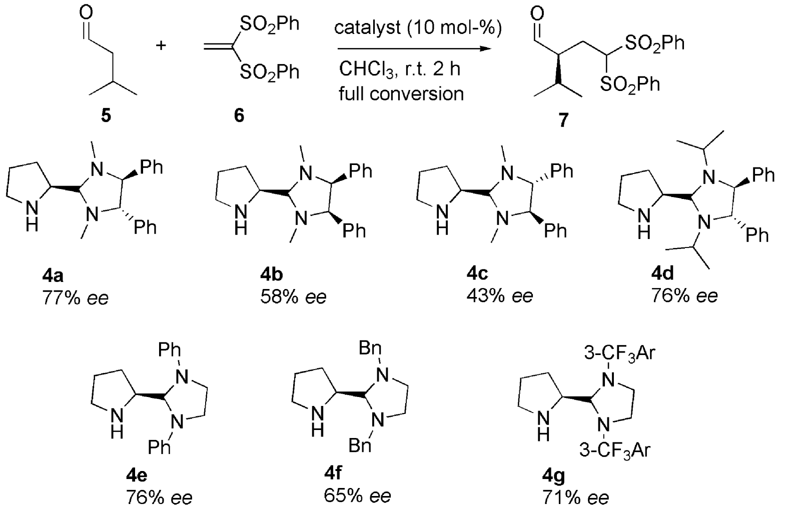
In a preliminary investigation,[8] we prepared catalysts **4a**–**g** in four steps from protected Cbz-L-proline (Scheme 1).[9] The protected Cbz-prolinal as well as the obtained catalysts were stable to prolonged storage without any loss of enantioselectivity. Boc-protected proline could not be a starting point due to the harsh acidic conditions needed for the deprotection, leading to aminal decomposition.

We then tested these seven catalysts in the Michael addition of isovaleraldehyde to an ethene-1,1-diyl disulfone (Scheme 2). This reaction, developed in our group, led to interesting gem-disulfone adducts.[10] The obtained Michael adducts are highly useful synthons due to the versatility of the sulfonyl group. This reaction can thus be considered as a formal alkylation of aldehydes. We previously achieved moderate yields and enantiocontrol using bipyrrolidine or bimorpholine derivatives.[11] Only recently did Palomo and co-workers, Lu and co-workers and our group report simultaneously the successful use of diarylprolinol silyl ethers in this reaction.[12]

All the aminals **4a**–**g** cleanly catalyzed the reaction in less than 2 h. As expected, the influence of the stereochemistry of the aminal was crucial in terms of selectivity. Impressively, the enantioselectivity varied from 77% *ee* to 43% *ee* from aminal diastereoisomers **4a** to **4c**, respectively. Replacing the methyl group by a bulkier isopropyl group on the nitrogen atoms in catalyst **4d** did not improve the selectivity



Scheme 1. Synthesis of proline-based aminal–pyrrolidine catalysts. MS = molecular sieves.



Scheme 2. Catalyst screening in the addition of isovaleraldehyde to ethenediyl disulfones.

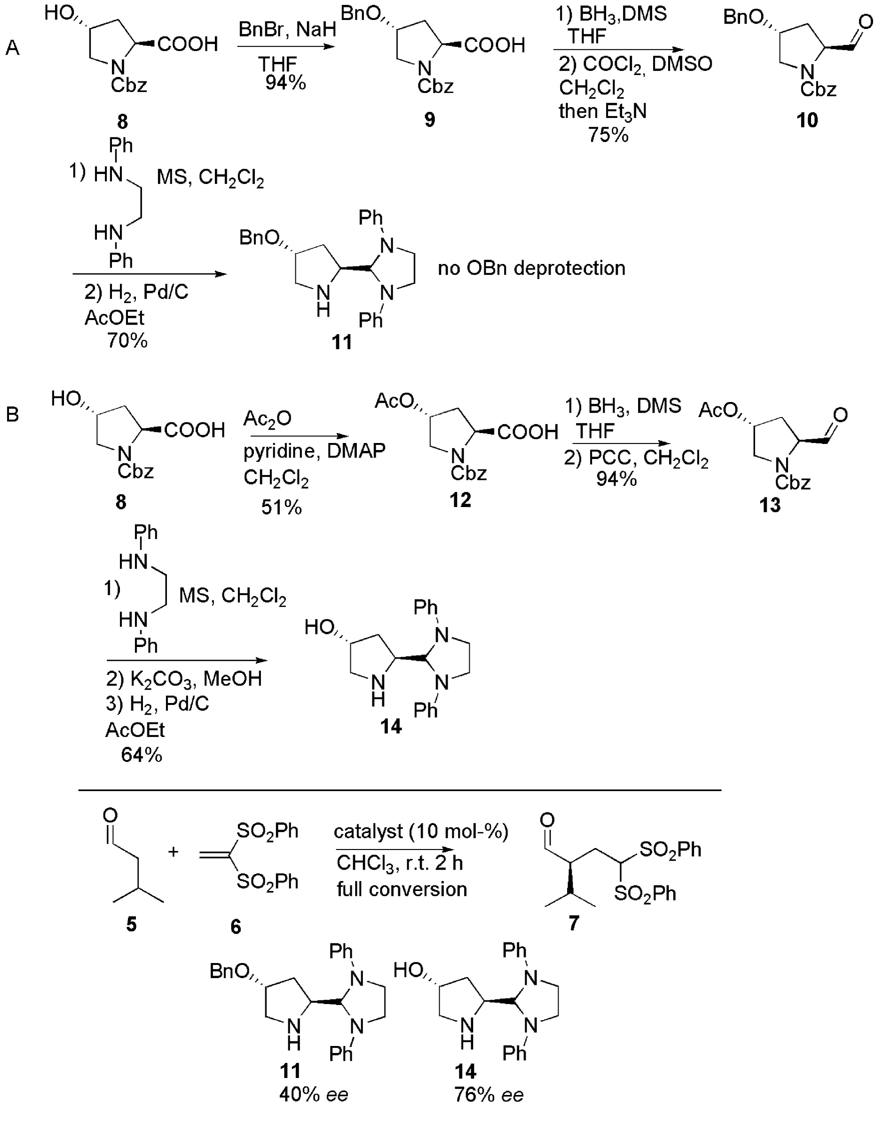
of the reaction (76% *ee*). These results suggest that it is not the substituent on the nitrogen atom but the phenyl group of the backbone that interacts in the transition state with catalyst **4a** or **4d**. This is consistent with the importance of the aminal configuration. Using an achiral diamine also gave good results. Catalyst **4e**, substituted by a phenyl group on the nitrogen atoms, gave the same enantioselectivity (76% *ee*) as that given by catalyst **4a**, whereas the addition of a benzyl or substituted aryl group lowers the enantioselectivity for catalysts **4f** and **4g**.

Aminal–Hydroxypyrrolidine Catalysts

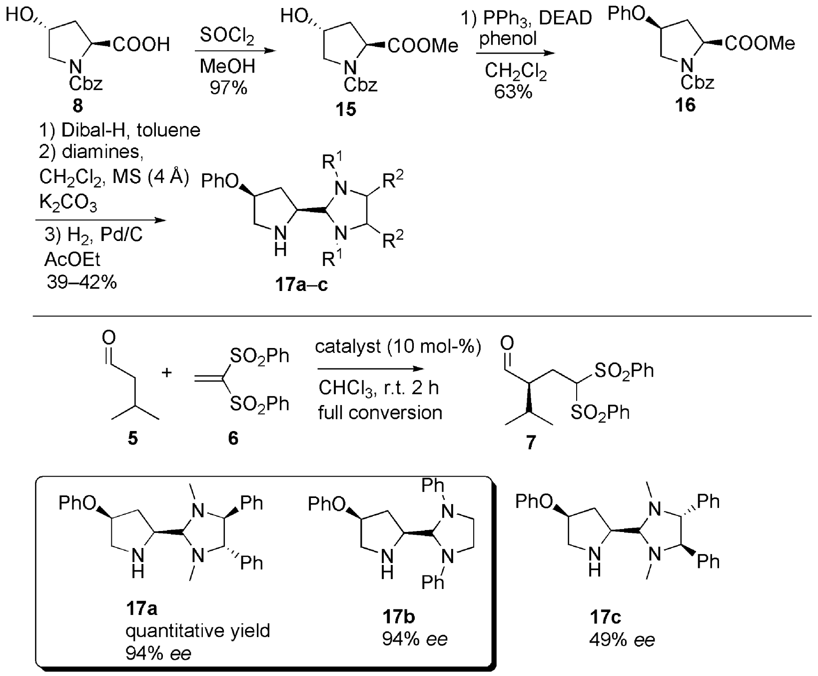
These good results in this challenging transformation motivated us to pursue catalyst improvements. We first thought to introduce a free hydroxy group on the pyrrolidine ring to activate the electrophile, as recently described by Palomo and co-workers.[2g] Starting from Cbz-protected hydroxyproline, we easily obtained OBn-protected **11** in five steps, but all attempts to deprotect the hydroxy group failed (Scheme 3A). Turning to the acetoxy protecting group allowed the synthesis of catalyst **14** by a six-step procedure (Scheme 3B). Unfortunately, when performing the catalytic test reaction, we observed no improvement of enantioselectivity, compared to that of proline catalyst **4e** (76% *ee*). This suggested that the free hydroxy group did not activate the electrophile at all.

By using benzyl-protected catalyst **11**, we observed a dramatic drop to 40% *ee*. This result was really important, since it showed that the 4-position substituent of the pyrrolidine ring interacted with the electrophile, lowering the enantioselectivity. This can be considered the mismatched case, since the two substituents of the pyrrolidine ring influenced the nucleophilic attack in a negative fashion.

We thus envisaged that changing the stereochemistry of this 4-pyrrolidine carbon center would create a synergistic effect leading to the matched case. Indeed, the aminal



Scheme 3. Synthesis and use of (4*R*)-hydroxypyrrolidine derivatives. MS = molecular sieves.



Scheme 4. Synthesis and use of 4-substituted aminal–pyrrolidine organocatalysts. MS = molecular sieves.

would favor the (*E*)-*anti* enamine, while the two bulky groups would interact together to force the electrophile to approach from the opposite face of the enamine (Figure 1). We easily synthesized this new family of 4-substituted aminal–pyrrolidine catalysts in five steps (Scheme 4). A Mitsunobu reaction using phenol allowed for the inversion of the configuration at C-4 of the pyrrolidine.[13]

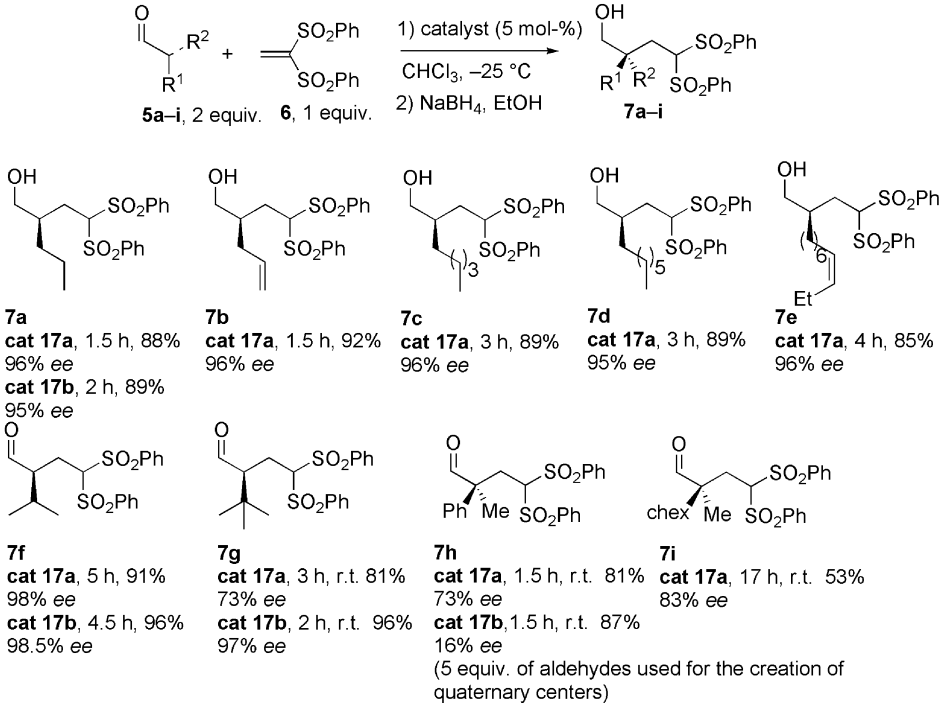
The first screening, by the addition to ethene-1,1-diyl disulfones, confirmed our hypothesis. We obtained impressively high enantioselectivity (94% *ee*) at room temperature using catalyst **17a** or **17b**, compared to the 77% *ee* obtained using the unsubstituted catalyst **4a**. This result clearly showed that the two bulky groups of the enamine interacted together to strongly enhance the enantioselectivity, while keeping high reactivity. We obtained a quantitative yield without any purification using catalyst **17a**, whereas catalyst **17b** gave a small amount (<10%) of the homo-aldol product. Diastereomeric **17c** did not give any increase in enantioselectivity compared to the unsubstituted **4c**. This clearly indicated that the addition of a bulky group at the 4-position was not sufficient to induce higher enantioselectivity. This had already been shown by List and coworkers, who had incorporated an OTBS group on the 4-position of a diarylprolinol silyl ether without any improvement in enantioselectivity.[14] Indeed, a synergistic effect between the two substituents is needed, indicating that the two bulky groups interact.

Organocatalytic Addition to Ethenediyl Disulfones

The good results obtained with catalyst **17a**,**b** led us to decrease the amount of catalyst to 5 mol-% and the number of equivalents of aldehyde to two. The temperature could even be lowered to –25 °C using catalyst **17a**. The results using a broad range of various linear and branched aldehydes are summarized in Scheme 5.

Satisfyingly, we obtained high yields and the same high enantioselectivities (95–96% *ee*) using different linear aldehydes **5a**–**e**. We directly reduced these product aldehydes to the corresponding alcohols to prevent any racemization during the purification process. More-substituted isovaleraldehyde led to the highest 98% *ee* using either catalyst **17a** or **17b**. We obtained the more-substituted adduct **7g** in only 73% *ee* using catalyst **17a**. But, due to the modularity of the catalysts, **17b** gave an encouraging 97% *ee* in this reaction. We obtained even more interesting results in the formation of quaternary carbon centers. Indeed, catalyst **17a** gave an impressive 73% or 83% *ee* in the formation of adduct **7h** or **7i**, respectively. These are the highest enantioselectivities reported to date for such a challenging reaction, much higher than the 47 and 64% *ee* observed with a diphenylprolinol silyl ether.[12a] In the case of **7h**, catalyst **17b** did efficiently catalyze the reaction but in very poor 16% *ee*. All these results on sulfone **6** are among the best reported to date in terms of catalyst loading and enantioselection. They highlight the great potential of aminal–pyrrolidine catalysts in the addition to ethene-1,1-diyl disulfones. Furthermore, they show substantial complementarity of the catalysts, confirming our hypothesis of catalysts modularity.

The introduction of the allyl moiety in substrate **7b** is highly interesting due to further possible derivatization of the C=C bond. To demonstrate the utility of this reaction, we cyclized adduct **7b** into its furan derivative using various activation modes (Scheme 6). Cyclization using PhSeCl gave a moderate yield and no diastereocontrol on the cyclized product. To overcome this problem, we decided to



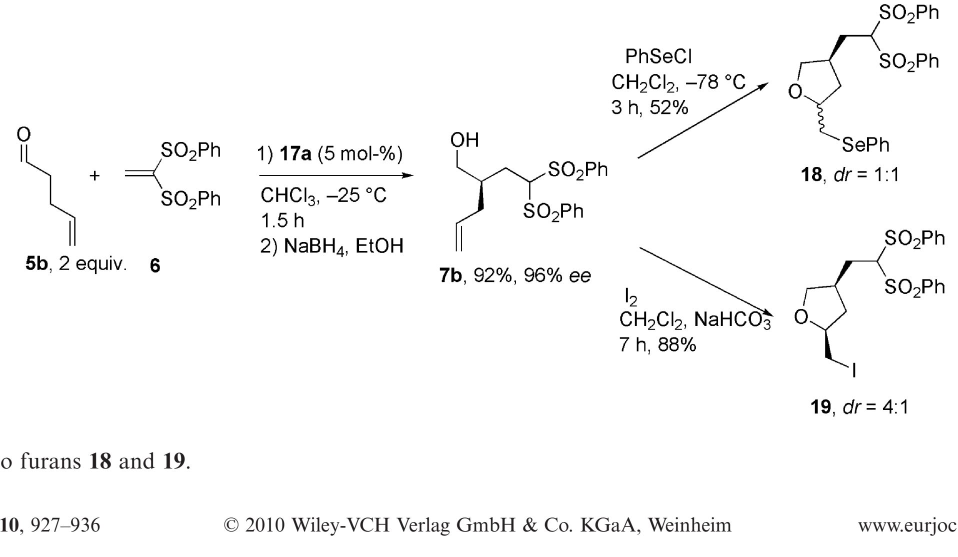
Scheme 5. Addition of linear and branched aldehydes to ethene-1,1-diyl disulfone catalysed by **17a** and **17b**. chex = cyclohexyl.

use cheaper iodine instead of selenium.[15] The iodocyclization proceeded satisfyingly, giving rise to adduct **19** in 88 % yield and 4:1 *syn* diastereoselectivity. This adduct, with its halogen atom and gem-disulfone moiety, seems a valuable synthon for further transformations.

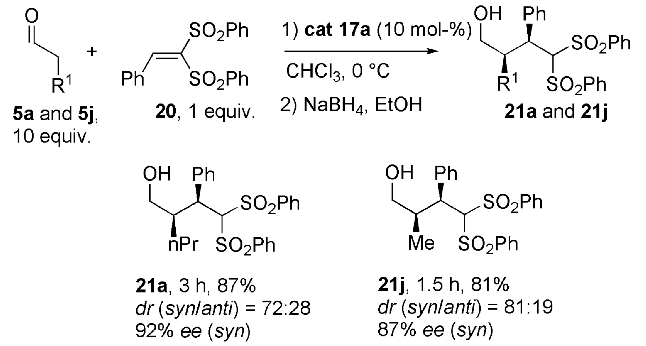
The good results obtained on sulfone **6** prompted us to turn our attention to other ethene-1,1-diyl disulfones, notably to the use of β-substituted disulfone **20** (Scheme 7). This sulfone had shown a tendency to easily decompose, thus lowering the yields, while the control of diastereoselectivity remained difficult.[12] Gratifyingly, catalyst **17a** gave impressively high yields and reactivities in this transformation, while maintaining good levels of diastereoselectivity. The observed *ee*s (87–92 %) were good but slightly lower than the one obtained using diphenylprolinol silyl ether; however, the reactivity of **17a** was much higher.

Recently, we disclosed the use of the very inexpensive ethene-1,2-diyl disulfone **22** as an alternative to ethene-1,1-diyl disulfone **6**. This ethenediyl disulfone gave an unprecedented [1,2] sulfone shift, leading to the corresponding gem-disulfone. Most catalysts were inefficient in this reaction, and only aminal catalyst **4a** catalyzed the reaction in 82 % *ee* for the formation of adduct **7f** and 69 % *ee* for **23**.[16]

We were pleased to find that catalyst **17a** performed much better in this challenging transformation, giving the best results ever obtained (Scheme 8). In contrast, catalyst **17b** did not catalyze this particular transformation. Using catalyst **17a**, we observed a high 94 % *ee* and 88 % yield for the formation of **7f**, much higher than previously reported. More interestingly, catalyst **17a** also catalyzed the addition of cyclohexanone; we obtained 76 % *ee* of the clean adduct **23** with 91 % conversion after 6 h. This good result indi-

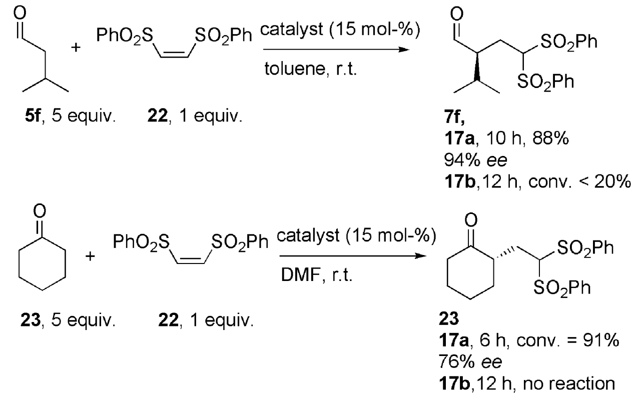


Scheme 6. Access to furans **18** and **19**.



Scheme 7. Addition of linear aldehydes to substituted ethenediyl disulfone **20** catalyzed by **17a**.

cated that the substitution on the pyrrolidine ring in catalyst **17a** did not block the formation of the more-substituted ketone enamine and still provided good enantioselectivity. This experiment extends the possible range of application of aminal–pyrrolidines from linear/β-branched aldehydes to ketones.



Scheme 8. Organocatalyzed addition to ethene-1,2-diyl disulfone **22** and subsequent [1,2] sulfone shift.

Organocatalytic Addition to Nitrostyrene

Besides ethenediyl disulfones, we were interested to know if our catalyst was also efficient in the benchmark reaction, that is the addition to nitro olefins (Table 1). As for ethenediyl disulfones, the introduction of a free hydroxy group on the pyrrolidine ring, as in catalyst **14**, did not activate the electrophile, giving rise to a poor 68% *ee* (Table 1, Entry 1). The results obtained using catalyst **17a** (Table 1, Entry 2) were quite disappointing. Indeed, the 4-phenoxy group did not seem to interact with the electrophile, giving only moderate enantiocontrol. Encouragingly, catalyst **17b** showed again a complementary reactivity to catalyst **17a**. It efficiently catalyzed the reaction of propionaldehyde or butyraldehyde with nitrostyrene with good diastereoselectivity and moderate to good enantioselectivity (Table 1, Entries 3 and 4). The less-hindered propionaldehyde gave rise to a good 91% *ee*, whereas bulkier butyraldehyde gave lower 85% *ee* for the same reaction.

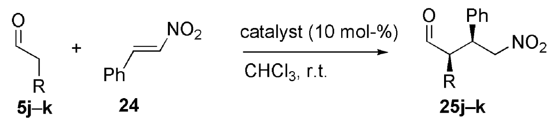
Organocatalytic C–N Bond Formation

Since our aminal–pyrrolidine catalysts were efficient in a wide range of conjugate additions, we wondered if they could be applied to other α-functionalizations of carbonyl groups, notably for the formation of C–heteroatom bonds. This would considerably enhance the scope of our catalyst and its potential as a general organocatalyst.

We thus focused our attention on the direct α-amination of aldehydes, creating a new C–N bond. This methodology, leading to interesting building blocks, had been reported separately by Jørgensen and co-workers and List using proline as the catalyst with good to excellent enantioselectivities.[17] Under the conditions developed using diphenylprolinol silyl ether, we were pleased to see that our catalyst performed well in this heterofunctionalization. The results are summarized in Table 2.

Using only 1 mol-% of catalyst **17a**, we obtained extremely high reactivities and good enantioselectivities (89–93% *ee*) with aldehydes **5f** and **5b** (Table 2, Entries 1 and 3). The obtained enantioselectivities were in the range of those obtained using L-proline or diphenylprolinol silyl ethers. In the case of pentenal **5b**, the reaction was complete after 4 min (as indicated by the disappearance of the DEAD yellow color)! This high reactivity and enantioselectivity, at such a low catalyst loading, constitutes a

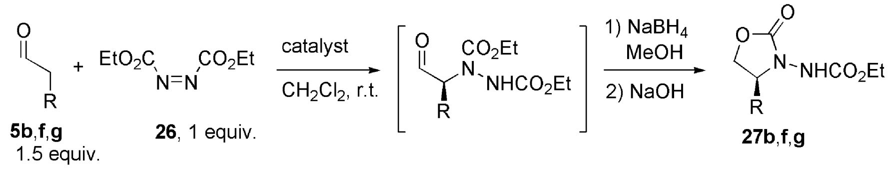
Table 1. Organocatalyzed addition to nitrostyrene.



Entry[a]	Catalyst	R (product)	*T* [h]	Conversion (yield) [%][b]	*dr* (*syn*/*anti*)[b]	*ee*[c] [%]
1	**14**	Et (**25k**)	7	100	73:23	68
2	**17a**	Et (**25k**)	36	100	78:22	75
3	**17b**	Et (**25k**)	22	100 (82)	88:12	85
4	**17b**	Me (**25j**)	22	100 (85)	91:9	91

[a] Reactions were performed on 0.2 mmol of nitrostyrene in 0.8 mL of $CHCl_3$ using 2 mmol of aldehyde. [b] Determined by ^1H NMR spectroscopy. Isolated yields shown in parentheses. [c] Determined by superfluid chromatography or chiral GC analysis.

Table 2. Organocatalyzed α-amination of aldehydes.



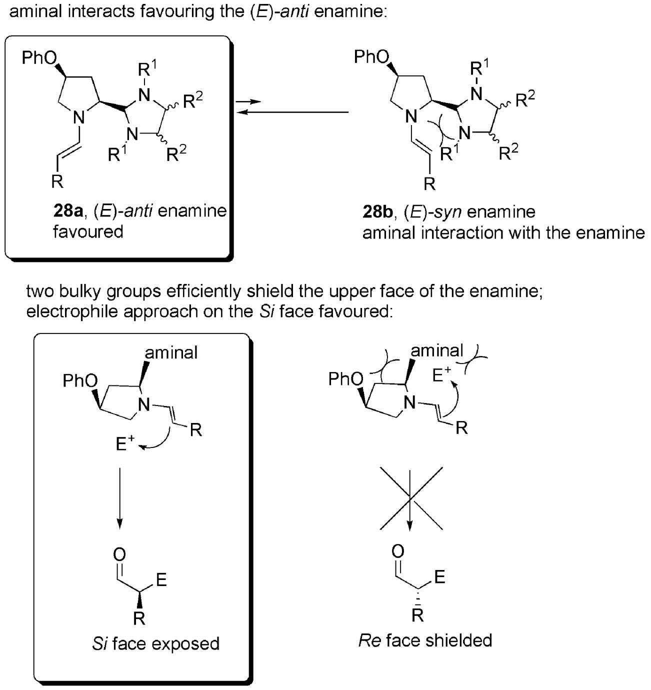
Entry[a]	Catalyst (mol-%)	R (product)	T [min]	Yield [%]	*ee* [%][b]
1	**17a** (1)	*i*Pr (**27f**)	10	83	93
2	**17b** (1)	*i*Pr (**27f**)	16	76	89
3	**17a** (1)	allyl (**25b**)	4	75	89
4	**17b** (1)	allyl (**25b**)	25	68	81
5	**17a** (0.5)	allyl (**25b**)	45	50[c]	n.d.
			60	61[c]	–
6	**17a** (10)	*t*Bu (**25g**)	240	90[c]	38
7	**17b** (10)	*t*Bu (**25g**)	80	67	96

[a] Reactions were performed on 0.25 mmol of DEAD in 0.25 mL of CH_2Cl_2 using 1.5 equiv. of aldehyde. [b] Determined by chiral GC analysis. [c] Conversions.

unique example of high turnover frequency (TOF) in enamine catalysis (TOF > 600–1000 h^{-1}). A high TOF and turnover number (TON) are crucial characteristics for the future development of enamine catalysis from an industrial point of view. When we further decreased the catalyst loading to 0.5 mol-%, we obtained a partial conversion, indicating that further reaction condition optimization is necessary (Table 2, Entry 5). Catalyst **17b** also gave good reactivities but slightly lower enantioselectivities on aldehydes **5f** and **5b** (Table 2, Entries 2 and 4). In contrast, using highly hindered aldehyde **5g**, catalyst **17b** gave much better results than **17a** (Table 2, Entries 6 and 7). We obtained an impressive 96% *ee* in this transformation, but full conversion required 10 mol-% of catalyst.

Stereochemical Outcome

The transition state in the various organocatalytic reactions of aldehydes using either **17a** or **17b** can be rationalized by analogy to diphenylprolinol silyl ethers.[6] The absolute configuration of the adducts obtained led us to postulate that high enantioselectivity came from steric control in the transition state (Scheme 9). Among the two possible (*E*) enamines, the (*E*)-*anti* one is favored due to the bulkiness of the aminal moiety. The presence of the two bulky groups at the 2- and 4-position of the pyrrolidine ring creates a strong steric hindrance on the upper face of the enamine, thus avoiding the attack of the electrophile from this *Re* face. With the lower face being less exposed, the electrophile can approach from this *Si* face affording the observed enantiomer. The same analysis can be performed on cyclohexanone, where the (*E*)-*syn* enamine is favored. This steric interaction is strong enough to allow good enantioselectivity, regardless of the nature of the electrophile.



Scheme 9. Proposed transition state using aminal–pyrrolidine catalysts.

Conclusions

We have disclosed the synthesis and use of highly efficient aminal–pyrrolidine organocatalysts. A careful design of the pyrrolidine substituents led to a considerable increase in enantioselectivity. A cooperative effect between the bulky aminal on the 2-position of the pyrrolidine ring and a phenoxy group on the 4-position led to two different catalysts, giving high reactivity and some of the highest enantioselectivities ever observed in the α-functionalization of a wide range of carbonyl compounds. We obtained *ee*s up to 98.5% in the addition of linear and branched aldehydes or a ketone to ethene-1,1- or -1,2-diyl disulfone, nitrostyrene, and diethyl azodicarboxylate. The modularity of the catalyst, introduced by the aminal portion, induces totally different properties in the new catalysts, giving rise to two complementary catalysts (**17a** and **17b**) and to a broad applicability. Furthermore, low catalyst loadings and some of the highest TOFs ever obtained in enamine catalysis were observed with high enantioselectivities. This last factor is highly important, and further developments are necessary before these enamine catalysis reactions can be applied on an industrial scale. This substitution on the 4-position can also be considered as the starting point for an efficient solid-phase version of these catalysts.[18]

Experimental Section

General Remarks: ^{1}H (400 MHz or 300 MHz) and ^{13}C (100 MHz) NMR spectra were recorded with a Bruker 400 FT or a Bruker 300 FT NMR spectrometer in $CDCl_3$, and chemical shifts (δ) are given in ppm relative to residual $CHCl_3$. Multiplicity is indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), dt (doublet of triplet), ddd (doublet of doublet of doublet), and br. s (broad singlet). Coupling constants are reported in Hertz [Hz]. Mass spectra (MS) were obtained by ESI and HRMS-ESI. Optical rotations were recorded with a Perkin–Elmer 241 polarimeter at 20 °C in a 10 cm cell in $CHCl_3$. $[\alpha]_D^{29}$ values are given in 10^{-1} deg cm^2 g^{-1} (c is given in g/100 mL). IR spectra were recorded in an NaCl cell with a Perkin–Elmer Spectrum One IR spectrometer. The *ee* values were determined by chiral-SFC measurements with a Berger SFC instrument with the stated column or chiral GC analysis. Gradient programs are described as follows: initial methanol concentration (%) – initial time [min] – percent gradient of methanol (%/min) – final methanol concentration (%); retention times (t_R) are given in min. Flash chromatography was performed using silica gel 60 Å. If needed, THF and CH_2Cl_2 were dried by filtration through alumina (activated at 350 °C under nitrogen for 12 h). All the organocatalyzed reactions were conducted in nondried solvents. Unless otherwise specified, products were purchased directly from commercial sources.

General Procedure for the Michael Addition to Ethene-1,1-diyl Disulfones or Ethene-1,2-diyl Disulfones: To a solution of the aminal–pyrrolidine catalyst in the solvent (0.4 mL, $CHCl_3$ for **6** and **20**, toluene or DMF for **22**), at the appropriate temperature, were added successively the carbonyl compound (0.4 mmol, 2 equiv. for linear aldehydes and **6**, 5 equiv. for α-branched aldehydes and cyclohexanone, and 10 equiv. for the addition to **20**) and the ethenediyl disulfone (0.2 mmol, 1 equiv.). The mixture was stirred at the indicated temperature. Reactions were monitored by TLC. When the reaction was complete, the reaction mixture was brought to 0 °C, ethanol (1.5 mL) was added, followed by the slow addition of $NaBH_4$ (1.5 equiv. per aldehyde equivalent). The mixture was stirred at 0 °C for 30 min. Aqueous HCl (1 M, 3 mL) was then added, the organic layer was extracted with CH_2Cl_2 (3 × 4 mL) and dried with sodium sulfate, and the solvent was evaporated. Purification by flash chromatography using a cyclohexane/ethyl acetate mixture afforded the corresponding Michael adduct. In the case of disulfone **20**, the excess aldehyde was removed by evaporation prior to reduction. In the case of aldehydes **5f**–**i** and cyclohexanone, the compounds were not reduced to the alcohols. To these reaction mixtures was added saturated aqueous NH_4Cl (2 mL), and the mixture was extracted with CH_2Cl_2 (3 × 3 mL), the combined organic layers were dried with Na_2SO_4, and evaporation of the solvent led to the crude compound. If needed, purification by flash chromatography using a cyclohexane/ethyl acetate mixture afforded the corresponding Michael adduct.

(*R*)-2-[2,2-Bis(phenylsulfonyl)ethyl]pent-4-enal (7e): 181 mg from 0.5 mmol of starting sulfone. Yield 92%. The *ee* was determined by SFC (Chiralcel OJ column, 2 mL/min, 200 bar, MeOH 5%–2–2–25%, 30 °C), t_R = 8.6 and 9.5 min. $[\alpha]_D^{20}$ = –25.3 ($CHCl_3$, c = 1.1, 96% *ee*). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.92–2.21 (m, 6 H, alkyl), 3.37–3.43 (m, 1 H, CH_2O), 3.61–3.66 (m, 1 H, CH_2O), 4.96–5.12 (m, 3 H, CH=CH), 5.58–5.67 (m, 1 H, $CHSO_2$), 7.51–7.69 (m, 6 H, Ph), 7.90–7.96 (m, 4 H, Ph) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.9 (CH_2), 36.2 (CH_2), 38.5 (CH), 65.5 (CH_2), 81.3 (CH), 117.5 (CH_2), 129.1 (CH), 129.6 (CH), 134.6 (CH), 135.5 (CH), 137.6 ($C_{quat.}$) ppm. MS ESI: m/z = 395.0 $[M + H]^+$. HRMS ESI $[M + H]^+$ calcd. for $C_{19}H_{22}O_5S_2$ 395.0981; found 395.0996.

(*S*)-2-Isopropyl-4,4-bis(phenylsulfonyl)butanal (7f): 76 mg. Yield 96%. The *ee* was determined by chiral SFC (Chiralcel OJ column, 2 mL/min, 200 bar, MeOH 10%–2–1–25%, 30 °C, t_R = 4.5 and 6.20 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.94 (d, J = 6.8 Hz, 3 H, Me), 0.99 (d, J = 7.1 Hz, 3 H, Me), 2.11–2.17 (m, 2 H, CH_2), 2.47–2.54 (m, 1 H, OH), 2.90–2.94 (m, 1 H, CHCO), 4.68–4.71 (dd, J = 9.1, 3.1 Hz, 1 H, $CHSO_2$), 7.53–7.60 (m, 4 H, Ph), 7.67–7.73 (m, 2 H, Ph), 7.88–7.96 (m, 4 H, Ph), 9.59 (s, 1 H, CHO) ppm. Spectroscopic data are in agreement with those in the literature.[11a]

(2*R*,3*S*)-2-Methyl-3-phenyl-4,4-bis(phenylsulfonyl)butanal (21j): 36 mg from 0.1 mmol of starting material. Yield 81%. The *ee* was determined by SFC on the isolated major diastereomer (Chiralcel IC column, 2 mL/min, 200 bar, MeOH 10%–2–2–25%, 30 °C), t_R = 15.7 and 16.4 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.75 (d, J = 6.6 Hz, 3 H, Me), 2.22–2.25 (m, 1 H, OH), 3.13–3.18 (m, 1 H, CHMe), 3.60–3.68 (m, 1 H, CHPh), 3.86 (dd, J = 9.2, 1.6 Hz, CH_2OH), 4.14–4.19 (m, 1 H, CH_2OH), 5.76 (s, 1 H, $CHSO_2$), 7.26–7.55 (m, 15 H, Ph) ppm. Spectroscopic data are in agreement with those in the literature.[12c]

(*S*)-2-[2,2-Bis(phenylsulfonyl)ethyl]cyclohexanone (23): The *ee* was determined by SFC (Chiralcel OJ column, 2 mL/min, 200 bar, MeOH 5%–2–2–25%, 30 °C), t_R = 8.55 and 12.37 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25–1.30 (m, 1 H, cyclohexanone), 1.62–2.10 (m, 8 H, cyclohexanone), 2.28–2.57 [m, 4 H, CH_2CO and $CH_2(CHSO_2)$], 3.03–3.09 (m, 1 H, CHCO), 4.97 (dd, J = 9.3, 3.6 Hz, 1 H, $CHSO_2$), 7.53–7.69 (m, 6 H, Ph), 7.87–7.96 (m, 4 H, Ph) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.0 (CH_2), 26.5 (CH_2), 27.8 (CH_2), 34.8 (CH_2), 42.9 (CH_2), 47.3 (CH), 80.7 (CH), 129.0 (CH), 129.3 (CH), 129.7 (CH), 134.4 ($C_{quat.}$) ppm. Spectroscopic data are in agreement with those in the literature.[12d]

Procedure for Iodocyclization. Synthesis of (2*S*,4*R*)-4-[2,2-Bis(phenylsulfonyl)ethyl]-2-(iodomethyl)tetrahydrofuran (19): Adapted from a known procedure.[15] To a solution of the alcohol (58 mg, 0.15 mmol) in CH_2Cl_2/saturated aqueous $NaHCO_3$ (1:1, 1.5 mL) in a round-bottomed flask protected from light, was added iodine (89 mg, 0.35 mmol). The solution was then stirred at room temperature for 7 h, and aqueous $Na_2S_2O_5$ (3 mL) was slowly added. The aqueous layer was extracted with CH_2Cl_2 (3 × 4 mL), the combined organic layers were dried with $MgSO_4$ and filtered, and the solvent was evaporated. The expected compound (69 mg, 0.13 mmol) was obtained as a 4:1 mixture of diastereoisomers after simple filtration through a small plug of silica using diethyl ether as the eluent. Yield 88%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.06–1.11 [m, 1 H (major diastereomer, alkyl)], 1.79–1.81 (m, 1 H, minor diastereomer, alkyl), 2.19–2.26 (m, 3 H, alkyl), 2.63–2.79 (m, 1 H, alkyl), 3.11–3.21 (m, 2 H, CH_2I), 3.35 (dd, CHO, J = 6.0, 2.8 Hz, 1 H, minor diastereomer), 3.43 (t, CHO, J = 7.6 Hz, 1 H, major diastereomer), 3.87–4.01 (m, 2 H, CH_2O), 4.32 (t, J = 6 Hz, 1 H, $CHSO_2$), 7.56–7.73 (m, 6 H, Ph), 7.92–7.95 (m, 4 H, Ph) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.8 (CH_2), 29.2 (CH_2), 37.9 (CH), 38.5 (CH_2), 73.0 (CH_2), 78.7 (CH), 82.5 (CH), 129.3 (CH), 129.7 (CH), 134.9 (CH), 137.5 ($C_{quat.}$) ppm. MS ESI: m/z = 521.3 $[M + H]^+$. HRMS calcd. for $C_{19}H_{22}N_3O_5S_2I$ 520.9947; found 520.9965.

General Procedure for the Michael Addition to Nitrostyrene: To a solution of the aldehyde (2 mmol) and nitrostyrene (0.2 mmol) in $CHCl_3$ (0.8 mL) was added the appropriate amount of catalyst, and the reaction mixture was stirred at room temperature. The reaction was monitored by TLC. After the reaction was complete, aqueous NH_4Cl (2 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic layers were dried with Na_2SO_4 and filtered, and the solvents were evaporated. The crude material was purified by chromatography on silica gel using cyclohexane/ethyl acetate (8:2) as the eluent.

(2*R*)-2-Methyl-4-nitro-3-phenylbutanal (25j): 35 mg, yield 85 %. The *ee* was determined by SFC [Chiralpak OD-H, 2 mL/min, 200 bar, MeOH 2%–6–1–15%, 30 °C, t_R = 7.1 (2*S*,3*R*) and 7.6 (2*R*,3*S*) min]. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.02 (d, J = 7.2 Hz, 3 H, Me), 2.75–2.84 (m, 1 H, CHMe), 3.83 (dt, J = 9.4, 5.6 Hz, 1 H, CHPh), 4.70 (dd, J = 12.8, 9.4 Hz, 1 H, CH_2NO_2), 4.82 (dd, J = 12.8, 5.4 Hz, 1 H, CH_2NO_2), 7.17–7.21 (m, 2 H, Ph), 7.28–7.40 (m, 3 H, Ph), 9.73 (s, 1 H, CHO) ppm. Spectroscopic data are in agreement with those in the literature.[19]

General Procedure for the α-Amination of Aldehydes: To a stirred solution of diethyl azodicarboxylate (0.25 mmol) and the corresponding aldehyde (0.375 mmol) in CH_2Cl_2 (0.25 mL) was added the aminal–pyrrolidine catalyst, and the solution was stirred at room temperature until the yellow color disappeared. MeOH (0.6 mL) was then added, followed by the slow addition (exothermic) of $NaBH_4$ (3 equiv.). The reaction mixture was then stirred at room temperature for 30 min before aqueous NaOH (0.5 M, 2.5 mL) was added. After 2 h of stirring at room temperature, the solvent was evaporated. The residue was suspended in water (3 mL), and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were then dried with Na_2SO_4 and filtered, and the solvent was evaporated. In most cases, the products were of sufficient purity without further silica gel chromatography.

Ethyl (*S*)-4-Isopropyl-2-oxooxazolidin-3-ylcarbamate (27f): 45 mg, yield 83 %. The *ee* was determined by GC [Chirasil Dex Cβ column, 150 °C for 30 min, 1 °C/min to 170 °C, then holding for 5 min, t_R = 43.2 (*S*) and 45.3 (*R*) min]. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.93 (t, J = 2.4 Hz, 6 H, CH_3), 1.28 (t, J = 6.8 Hz, 3 H, CH_3), 2.02–2.06 (m, 1 H, CHMe), 3.91–4.09 (m, 2 H, CH_2CO_2), 4.18–4.24 (m, 3 H, CH_2O and CHN), 4.38–4.41 (m, 1 H, CH_2O), 6.77 (br. s, 1 H, NH) ppm. Spectroscopic data are in agreement with those in the literature.[17]

Supporting Information (see footnote on the first page of this article): Full experimental procedures and catalyst synthesis.

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Received: November 9, 2009