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Organocatalytic Enantioselective Synthesis of Highly Functionalized Polysubstituted Pyrrolidines

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Abstract: The organocatalytic conjugate addition of different aldehydes to β-nitroacrolein dimethyl acetal, generating the corresponding highly functionalized nitroaldehydes in high yields and with high stereoselectivities, has been studied in detail. These transformations have been achieved by using both readily available starting materials in a 1:1 ratio as well as commercially available catalysts at a 10 mol% catalyst loading. Furthermore, a very short and efficient protocol has been devised for the preparation of highly enantioenriched pyrrolidines containing two or three contiguous stereocenters starting from the obtained Michael adducts. 3,4-Disubstituted pyrrolidines have been obtained in a single step by Zn-mediated chemoselective reduction of the nitro group followed by intramolecular reductive amination, and trisubstituted homoproline derivatives have been prepared by means of an olefination reaction and a cascade process involving chemoselective reduction of the nitro group followed by a fully diastereoselective intramolecular aza-Michael reaction.

Keywords: asymmetric synthesis · Michael addition · organocatalysis · pyrrolidines · stereoselective catalysis

Introduction

In recent years, organocatalysis has emerged as an excellent tool for the asymmetric synthesis of optically active compounds through operationally simple and environmentally friendly methodologies.[1] Many research groups worldwide have shown that one of the main advantages of this methodology is that relatively complex molecules can be easily prepared starting from readily available starting materials under efficient stereochemical control. The fact that most of the organocatalytic reactions reported tolerate the presence of water and oxygen, which allows them to be performed without having to use dried solvents or inert atmosphere, together with the commercial availability of many of the catalysts employed, has contributed to the rapid growth of this methodology in the field of organic synthesis.

A particular approach in this area involves the use of secondary amines as chiral catalysts. In this context, many methodologies have appeared for carrying out the α-functionalization, β-functionalization, and γ-functionalization of carbonyl compounds (aldehydes and/or ketones). As has been demonstrated, the catalytic systems necessary for the aforementioned transformations are generated through the activation of carbonyl compounds by the formation of an enamine,[2] iminium ion,[3] dienamine,[4] or iminium radical[5] intermediate. In these transformations, various types of new bonds can be formed, depending on both the nucleophile and electrophile components involved in the reaction. Thus, many successful methodologies have been reported for the stereocontrolled formation of C–C, C–N, C–O, C–S, C–Se, and C–halogen bonds. Furthermore, the possibility of utilizing differently substituted or conveniently functionalized starting materials has led to the synthesis of many optically active compounds with broad spectra of substitution patterns, increasing the interest of these adducts for further modification in so-called diversity-oriented synthesis (DOS).[6] Surprisingly, despite the already mentioned evident practical advantages of asymmetric organocatalysis, there have been relatively few literature reports concerning

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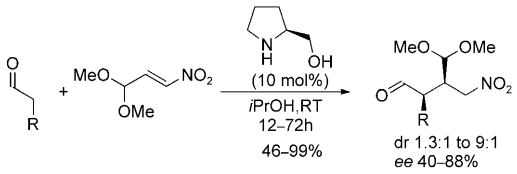
the direct application of this methodology to the synthesis of natural or pharmaceutically active products.[7]

In this context, the organocatalytic Michael reaction has become a powerful tool for the stereocontrolled synthesis of chiral compounds containing two or more stereogenic centers.[8] A particularly interesting variant of this transformation is the chiral amine-catalyzed conjugate addition of aldehydes to nitroalkenes,[9,10] in which the obtained adducts constitute versatile molecules that can be transformed into many useful chiral compounds by exploiting the intrinsic reactivity of the formyl moiety and, more especially, the nitro group.[11] However, although this transformation has been extensively studied by a number of research groups, the use of functionalized starting materials suitably predisposed for the preparation of polyfunctionalized compounds as intermediates for the synthesis of biologically relevant molecules still remains rather unexplored.[12]

Related to this topic, previous results obtained by our research group (Scheme 1) have demonstrated that commercially available L-prolinol can be used as an excellent organocatalyst in the conjugate addition of structurally diverse aldehydes to β-nitroacrolein dimethyl acetal (a functionalized nitroalkene).[13] The reactions proceed with good yields and enantioselectivities with a wide range of different aldehyde donors and, remarkably, require a 1:1 molar ratio of nucleophile/electrophile and a rather low substrate/catalyst ratio (up to 1 mol%). In this context, the use of β-nitroacrolein dimethyl acetal as a Michael acceptor represents a real advantage in this reaction because its high electrophilicity allows complete consumption of the starting aldehyde donor reagent in the presence of a small amount of catalyst. It has to be pointed out that in many of the examples described in the literature a large excess of the aldehyde along with a 20–30 mol% catalyst loading were necessary in order to obtain complete conversion in this type of transformation.[14]



Scheme 1. L-Prolinol-catalyzed Michael reaction of aldehydes and β-nitroacrolein dimethyl acetal developed by our group.

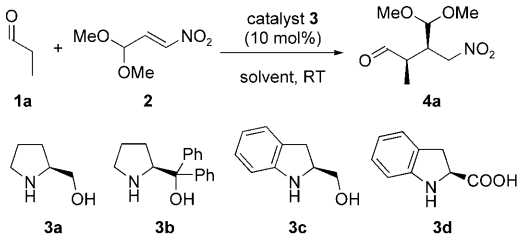
On the other hand, several limitations were reported in the preliminary studies, such as the long reaction times required to achieve synthetically useful yields and, more significantly, the low diastereoselectivity provided by the catalyst, which resulted in the final adducts being isolated as mixtures of *syn*/*anti* diastereoisomers in variable proportions. In this paper, we wish to present a detailed study aimed at improving this transformation, which has been especially directed towards overcoming the aforementioned limitations found in our first study. Furthermore, we have also explored the synthetic possibilities of the obtained polyfunctionalized adducts, which has led to a direct and efficient synthetic protocol for the stereocontrolled preparation of substituted pyrrolidines containing two or three contiguous stereogenic centers.

Abstract in Spanish: *Se ha estudiado detalladamente la reacción de adición conjugada organocatalítica enantioselectiva de distintos aldehídos con el dimetil acetal de β-nitroacroleína, obteniéndose los aductos correspondientes con excelente rendimiento y diastereo- y enantioselectividad. Esta transformación se lleva a cabo empleando cantidades equimolares de aldehído y nitroalqueno así como aminas secundarias quirales disponibles comercialmente como catalizadores en cantidad de 10% molar. Además, se ha puesto a punto un protocolo sencillo y eficaz para la síntesis de pirrolidinas enantioenriquecidas conteniendo dos o tres estereocentros contíguos partiendo de los aductos Michael obtenidos. Así, se han preparado pirrolidinas 3,4-disustituidas desde sus precursores nitroaldehídicos a través de un proceso en cascada consistente en la reducción quemoselectiva del grupo nitro seguido de una reacción de aminación reductora intramolecular. Del mismo modo, partiendo de los mismos precursores, se han preparado derivados de homoprolina con tres centros estereogénicos mediante una reacción de Wittig seguida de un proceso en cascada de reducción/reacción aza-Michael intramolecular, cursando esta última con total diastereoselectividad.*

Results and Discussion

We started by trying to improve our recently reported conditions for the Michael addition of aldehydes to β-nitroacrolein dimethyl acetal (**2**) using the reaction between propanal (**1a**) and **2** as a model system (Scheme 2). In our previous report, we had observed that prolinol (**3a**) was a very efficient catalyst for the reaction, but other simple amino alcohols such as α,α-diphenylprolinol (**3b**) and indolinemethanol (**3c**) as well as the α-amino acid 2-indolinecarboxylic acid (**3d**) were also able to promote the reaction, leading to higher enantioselectivities compared to those furnished by other commercially available chiral amines tested. We therefore decided to reinvestigate the use of these catalysts under different reaction conditions (Table 1), comparing the results with those obtained under the optimal conditions found in our preliminary report, which involved stirring a solution of the requisite aldehyde and β-nitroacrolein dimethyl acetal in *i*PrOH at RT using **3a** (10 mol%) as catalyst (entry 1). In all cases, we carried out the reaction using equimolar amounts of nitroalkene acceptor and aldehyde donor.

As can be seen in Table 1, when α-amino acid **3d** was employed as catalyst, a strong solvent effect was found. Thus, no reaction occurred in a protic solvent such as *i*PrOH (entry 2), while the use of THF furnished the Michael adduct **4a** in higher yield, and with higher diastereo- and



Scheme 2. Catalysts tested in the Michael reaction of propanal and β-nitroacrolein dimethyl acetal.

enantioselectivity, than was observed for the parent prolinol-catalyzed reaction (cf. entries 3 and 1), although a very long reaction time was required. Changing to the more polar solvent DMF (entry 4) resulted in a significant decrease in the enantioselectivity. No improvement was observed when we employed acid additives in the reaction, which are known to help in the formation of the intermediate enamine nucleophile in the catalytic cycle (entries 5 and 6). We next proceeded to evaluate indolinemethanol **3c** as catalyst, observing that this catalyst generally provided better yields and stereoselectivities than **3d**. The reaction in *i*PrOH afforded **4a** in modest yield (entry 7), and when THF was employed as solvent a very long time was required to attain a similar yield of the adduct (entry 8). Carrying out the reaction in DMF led to a moderate yield of the Michael adduct with good diastereo- and enantioselectivity (entry 9), and a noticeable increase in the yield was observed when the reaction was carried out in the presence of excess aldehyde (entry 10) or when a Brønsted acid additive was incorporated into the reaction design (entry 11). Interestingly, the addition of 2 equiv of water to the reaction mixture also resulted in a slight increase in the yield, without having any negative effect on the stereoselectivity (entry 12).[15] This might be attributed to the action of water in preventing the formation of stable oxazolidine by-products between either of the aldehydes present in the reaction medium (the starting material or the final adduct) and the amino alcohol catalyst that would eventually lead to catalyst consumption. Finally, we evaluated the use of α,α-diphenylprolinol **3b** as catalyst for this transformation, and again observed that very long reaction times were required in THF in order to achieve a modest yield of **4a** (entry 13), while the use of DMF as solvent (entry 14) allowed a similar yield of the Michael adduct to be obtained in a much shorter reaction time, as well as an improvement in the diastereoselectivity (*syn*/*anti* 9:1). As was observed with catalyst **3c**, the inclusion of 2 equiv of water as an additive (entry 15) resulted in a significant enhancement in the yield of the reaction (62% in just 24 h). In all cases, catalyst **3b** provided an excellent degree of enantioselection.

As a remarkable feature, it has to be pointed out that the use of indoline-containing catalysts **3c** and **3d** furnished the final adduct **4a** with opposite absolute configuration compared to the reaction catalyzed by **3a** or **3b**. This can be seen as another advantageous aspect of this methodology because all the catalysts employed in this study belong to the L-series of the corresponding α-amino acids from which they are obtained, which is the more abundant enantiomer usually present in natural sources.

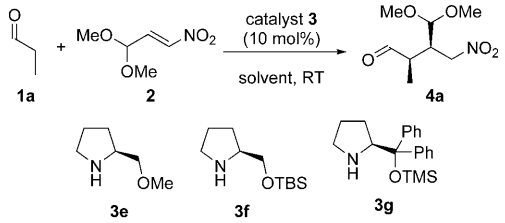
We anticipated that, as previously mentioned, the formation of inactive oxazolidine by-products could account for the lower activity and might therefore explain the long reaction times required to attain high yields of the Michael adduct, even in the presence of water as an additive. The possibility of oxazolidine formation no longer exists when the alcohol moiety is modified in the form of a silyl or alkyl ether and, moreover, the introduction of bulky trialkylsilyl substituents would result in additional steric requirements during the formation of the new stereocenters and therefore lead to an improvement in diastereo- and enantioselectivity. In addition, *O*-silylated derivatives would be expected to exhibit enhanced solubility in organic solvents as compared to their amino alcohol counterparts, which would also result in an improved catalyst performance. For these reasons, we decided to evaluate the use of prolinol ether derivatives **3e** and **3f** as potentially more active catalysts than the parent amino alcohol **3a** (Table 2). We also extended our study to diphenylprolinol silyl ether **3g**, which has been successfully

Table 1. Screening of the organocatalytic Michael reaction of propionaldehyde with nitroacrolein dimethyl acetal in the presence of amino acid **3d** or amino alcohols **3a**–**c**.[a]

Entry	Solvent	Catalyst	Additive	*t* [h]	Yield [%][b]	*syn*/*anti*[c]	*ee* [%][d]
1	*i*PrOH	**3a**	–	12	74	1.7:1	80
2	*i*PrOH	**3d**	–	168	<5	–	–
3	THF	**3d**	–	312	76	3.5:1	−85[e]
4	DMF	**3d**	–	72	19	2.2:1	−57[e]
5	DMF	**3d**	*p*-TsOH[f]	168	<5	–	–
6	DMF	**3d**	Ph_2CHCO_2H[f]	72	18	3.6:1	−52[e]
7	*i*PrOH	**3c**	–	72	20	20:1	−96[e]
8	THF	**3c**	–	312	21	3.3:1	−88[e]
9	DMF	**3c**	–	72	55	9.8:1	−91[e]
10	DMF[g]	**3c**	–	72	64	7.4:1	−93[e]
11	DMF	**3c**	Ph_2CHCO_2H[f]	72	66	8.2:1	−96[e]
12	DMF	**3c**	H_2O[h]	72	62	9.6:1	−98[e]
13	THF	**3b**	–	240	16	2.1:1	92
14	DMF	**3b**	–	168	35	9.0:1	98
15	DMF	**3b**	H_2O[h]	24	62	10:1	98

[a] Reaction carried out on a 1.00 mmol scale using 1 equiv each of **1a** and **2** with 10 mol% of catalyst in the specified solvent and at RT. [b] Isolated yield after flash column chromatography. [c] Determined by NMR analysis of the reaction mixture. [d] Calculated from chiral GC data after transformation to the corresponding acetal derived from propane-1,3-diol. [e] The opposite enantiomer was obtained. [f] 10 mol% of the additive was added to the reaction mixture. [g] Reaction carried out with 5 equiv of aldehyde. [h] Reaction carried out in the presence of 2 equiv of water.

Table 2. Screening of the organocatalytic Michael reaction of propionaldehyde with nitroacrolein dimethyl acetal in the presence of catalysts **3e**–**g**.[a]



Entry	Solvent	Catalyst	Additive	*t* [h]	Yield [%][b]	*syn*/*anti*[c]	*ee* [%][d]
1	THF	**3e**	–	24	81	1.2:1	68
2	THF	**3f**	–	24	75	1:1.4	64
3	THF	**3g**	–	72	75	4.5:1	97
4	DMF	**3g**	–	72	79	5.8:1	98
5	DMF	**3g**	H_2O[e]	24	86	6.0:1	>99

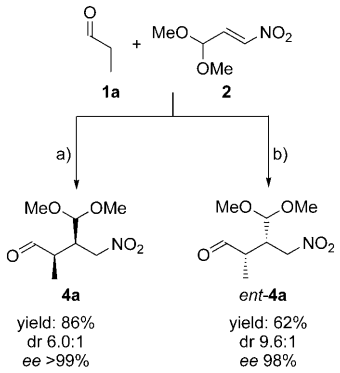
[a] Reaction performed on a 1.00 mmol scale using 1 equiv each of **1a** and **2** with 10 mol% of catalyst in the specified solvent and at RT. [b] Isolated yield after FC. [c] Determined by NMR spectrometric analysis of the reaction mixture. [d] Calculated from chiral GC data after transformation to the corresponding acetal derived from propane-1,3-diol. [e] Reaction performed in the presence of 2 equiv of water.

employed as a very efficient organocatalyst in other transformations.[16]

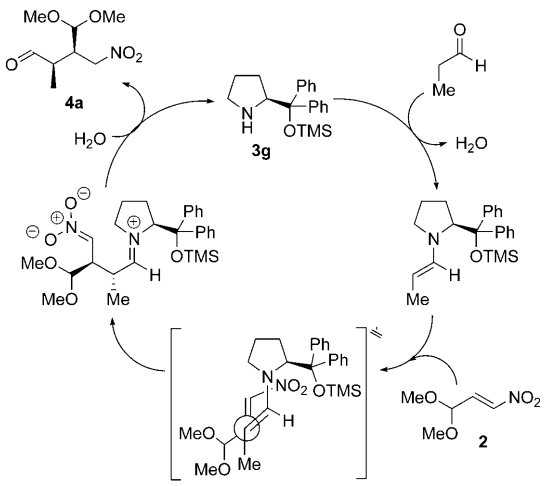
As can be seen in Table 2, modification of the free hydroxyl group in prolinol with a methyl or silyl ether led to a more active catalyst, as was expected, providing better yields of the Michael adduct in shorter reaction times (entries 1 and 2), although key parameters such as the diastereo- and enantioselectivity were adversely affected by these structural changes in the catalyst. On the other hand, the **3g**-catalyzed reaction (entry 3) proceeded much more rapidly than the parent reaction catalyzed by amino alcohol **3b** (cf. entry 3 in Table 2 with entry 13 in Table 1), while maintaining a high level of stereoselectivity, although the results were not much better than those obtained with simple L-prolinol **3a** in our preliminary study (see entry 1 in Table 1). Changing the solvent to DMF did not significantly improve the performance of this catalyst (entry 4 in Table 2), but, to our delight, when we carried out the reaction in the presence of 2 equivalents of water, a good yield of the desired Michael adduct **4a** was obtained in a much shorter time (24 h), while maintaining high diastereoselectivity and excellent enantioselectivity.

Therefore, after analyzing all of the results obtained during the catalyst screening process, it can be stated that we have found a suitable and improved synthetic protocol for carrying out the Michael reaction of propanal and β-nitroacrolein dimethyl acetal using small chiral organic molecules as catalysts. The optimal reaction conditions found for the synthesis of both enantiomers of Michael adduct **4a** are summarized in Scheme 3.

The observed absolute configuration of adduct **4a** obtained in the reaction catalyzed by the *O*-silyldiarylprolinol **3g** can be explained in terms of a mechanistic pathway such as that depicted in Scheme 4. In a first step, propanal and catalyst **3g** would condense to form a stereodefined nucleophilic enamine intermediate. This enamine would then react with the nitroalkene electrophile, and a final hydrolysis step should release the Michael adduct **4a** and the free catalyst **3g**, which would be ready to participate in a subsequent catalytic cycle. The key to the success of catalyst **3g** is the effect exerted by the bulky diphenyl(trimethylsilyloxy)methyl substituent at the pyrrolidine ring, which results in very efficient geometry control of the enamine intermediate together with an excellent ability to discriminate between its diastereotopic faces. The observed *syn*-diastereoselectivity may be rationalized in terms of an acyclic synclinal transition state, as proposed by Seebach and



Scheme 3. Optimal conditions found for the organocatalytic enantioselective Michael reaction between propanal and β-nitroacrolein dimethyl acetal. a) **3g** (10 mol%), H_2O (2 equiv), DMF, RT, 24 h. b) **3c** (10 mol%), H_2O (2 equiv), DMF, RT, 72 h.



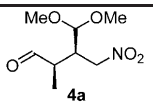
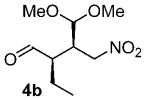
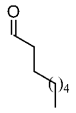
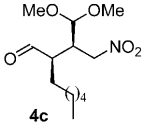
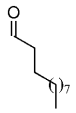
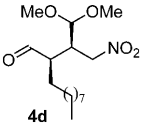
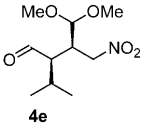
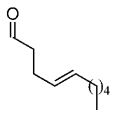
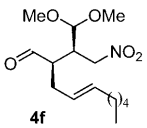
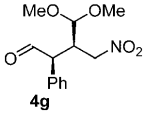
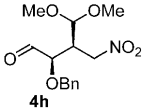
Scheme 4. Proposed catalytic cycle and transition state for the **3g**-catalyzed Michael reaction of propanal and **2**.

Golinski,[17] in which electrostatic interactions between the partially positive nitrogen of the enamine and the negatively charged oxygen atoms of the nitro group are invoked.

The difference in the sense of enantiodiscrimination exerted by indoline-derived catalysts **3c** and **3d** and the other proline-derived catalysts **3a**, **3b**, and **3e–g** can be easily explained in terms of the preferential formation of two differently arranged enamine intermediates during the activation of the aldehyde donor by the catalyst. It is well known that *O*-silylated diphenylprolinol-derived enamines adopt a preferential conformation in which the substituent at the pyrrolidine ring and the enamine substituent (Me in this case) remain as far as possible from each other in order to avoid steric crowding.[18] On the other hand, indolinecarboxylic acid-derived enamines adopt the opposite conformation in order to minimize steric interactions between the enamine substituent and the α-hydrogen of the aromatic ring (Figure 1).[19]

Having established an optimized protocol, we then proceeded to extend this methodology to other aldehyde donors with different substitution patterns in order to gain further insight into the scope and limitations of the method with regard to the aldehyde substrate (Scheme 5). It was envisaged that this would provide access to a wide range of differently substituted, highly functionalized, enantioenriched nitroalkanes of high synthetic potential due to the presence of the nitro group together with two chemically differentiated formyl groups. The results obtained are summarized in Table 3, together with a comparison with the previously reported reactions employing catalyst **3a**.

Table 3. Organocatalytic enantioselective Michael reaction of **2** and different aldehydes catalyzed by **3g** and **3a**.[a]

Entry	Aldehyde	Product	Catalyst	*t* [h]	Yield [%][b]	*syn*/*anti*[c]	*ee* [%][d]
1		 **4a**	**3g**	24	86	6.0:1	>99
			3a	12	74	1.7:1	80
2		 **4b**	**3g**	48	63	11:1	>99
			3a	48	75	3.7:1	80
3		 **4c**	**3g**	72	85	>20:1	>99
			3a	72	65	1.7:1	80
4		 **4d**	**3g**	72	61	>20:1	92
			3a	72	63	2:1	83
5		 **4e**	**3g**	72	75	>20:1	>99
			3a	70	46	9:1	88
6		 **4f**	**3g**	72	81	3:1	>99
			3a	72	63	1.3:1	82
7		 **4g**	**3g**	48	85	1.5:1	>99
			3a	36	99	1.3:	40
8		 **4h**	**3g**	72	<5	n.d.[e]	n.d.[e]
			3a	48	99	1.5:1	97

[a] Reaction performed on a 1.00 mmol scale using 1 equiv each of **1** and **2** with 10 mol% of catalyst in the specified solvent and at RT. For data concerning the use of catalyst **3a** in this reaction, see ref.[13] [b] Isolated yield after FC. [c] Determined by NMR spectrometric analysis of the reaction mixture. [d] Calculated from chiral GC or HPLC data (see the Supporting Information). [e] n.d. = Not determined.

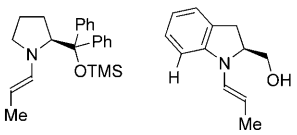
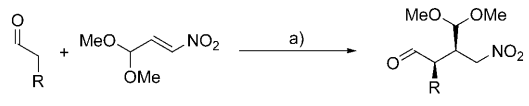


Figure 1. Conformations of the most favored enamines formed with catalysts **3g** and **c**, respectively.

As Table 3 shows, a broad range of differently substituted aldehydes could be used in the conjugate addition reaction, affording the desired polyfunctionalized products. As can be seen, the yields obtained in all the reactions ranged from good to excellent, and in almost all cases the use of catalyst **3g** improved the conversion of the reaction or allowed it to be carried out in a shorter time compared to when catalyst

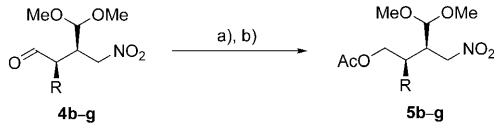


1a–h **2** **4a–h**

Scheme 5. Organocatalytic enantioselective Michael reaction between aldehydes and β-nitroacrolein dimethyl acetal catalyzed by **3g** or **3a**. a) **3g** (10 mol%), H_2O (2 equiv), DMF, RT, or **3a** (10 mol%), *i*PrOH, RT.

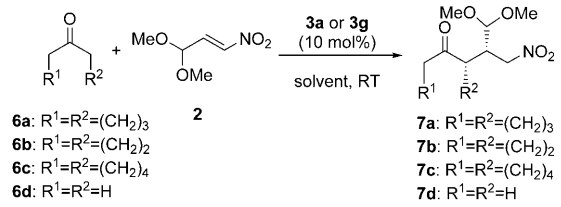
3a was used. For example, the **3a**-catalyzed reaction of **1e** and **2** (R = *i*Pr) furnished **4e** in 46% yield, while when catalyst **3g** was employed the yield was increased to 75% (entry 5). However, the most important advantage associated with the use of catalyst **3g** was found in the diastereo- and enantioselectivities of the reactions, which were significantly improved in all cases, with the adducts **4a–g** being obtained in *syn*/*anti* ratios of up to >20:1 with 92% *ee* or higher. The only exceptions were found for the reaction with phenylacetaldehyde (entry 7), which furnished the Michael adduct **4g** as a 1.5:1 mixture of diastereoisomers, albeit with excellent enantioselectivity, and in the case of benzyloxyacetaldehyde (entry 8), in which case the **3g**-mediated reaction furnished only traces of the conjugate addition product **4h** whereas the use of L-prolinol **3a** allowed the preparation of functionalized nitroalkane **4g** in excellent yield and with moderate diastereoselectivity.

γ-Nitroaldehydes **4b–g** were found to be somewhat unstable compounds and therefore, for better characterization and handling purposes, we decided to transform these adducts into the corresponding more stable acetates **5b–g** through a reduction/esterification procedure (Scheme 6). Thus, nitroaldehydes **4** were subjected to reduction of the formyl group with $NaBH_4$ in MeOH, and then the obtained alcohols were directly esterified with acetic anhydride in the presence of a catalytic amount of DMAP. The obtained esters could be conveniently characterized, and we also employed these acetate derivatives to determine the enantioselectivity of the Michael reaction because in this form the two enantiomers could be easily separated by chiral GC, which could not be accomplished with their γ-nitroaldehyde precursors **4b–g** under all conditions examined.



Scheme 6. Transformation of γ-nitroaldehydes **4** into esters **5**. a) $NaBH_4$, MeOH, RT. b) Ac_2O, DMAP, CH_2Cl_2, RT. DMAP = 4-dimethylaminopyridine.

We also investigated the possibility of carrying out the Michael reaction using ketones as Michael donors (Scheme 7). It has to be pointed out that the amine-catalyzed enantioselective Michael reaction of ketones with nitroalkenes is a rather undeveloped transformation compared with the parent reaction using aldehydes as donors.[20] Moreover, it is very often found in this case that the catalysts that perform well in the addition of ketones to nitroalkenes usually give poor results when the same reaction is carried out using aldehydes.



Scheme 7. Organocatalytic enantioselective Michael reaction of ketones and β-nitroacrolein dimethyl acetal.[21]

In the present case, catalyst **3g** proved to be completely inactive in this transformation when we attempted the reactions of β-nitroacrolein dimethyl acetal **2** with cyclohexanone **6a** and acetone **6d**, but, on the other hand, L-prolinol (**3a**) turned out to be an effective catalyst for this transformation (Table 4).[22] In fact, when we examined the reaction of cyclohexanone (**6a**) and **2** catalyzed by **3a** under the optimal conditions that we had established when employing aldehydes as donors, the Michael adduct **7a** was obtained in moderate yield but with excellent diastereo- and enantioselectivities (entry 1). We also surveyed other solvents with a view to improving the yield of the reaction (entries 2–5), observing that it could be improved by using polar aprotic solvents such as THF (entry 2) or DMF (entry 3) without significantly affecting the stereoselectivity. We extended these reaction conditions to other cyclic ketones such as cyclopentanone (**6b**) (entry 6) and cycloheptanone (**6c**) (entry 7), observing that the reactions became very slow and furnished only low yields of the Michael adducts, which were accompanied by large amounts of the starting materials. Acetone was also tested as a Michael donor but, in this case, the enantioselectivity of the reaction was significantly lower (entries 8 and 9).

Synthesis of trisubstituted pyrrolidines: The pyrrolidine ring is a ubiquitous structural feature shared by many natural products and drugs. As a consequence, the development of short, versatile, and efficient procedures for the stereocontrolled preparation of pyrrolidines represents a very important field of research for organic chemists.[23] Enantiomeri-

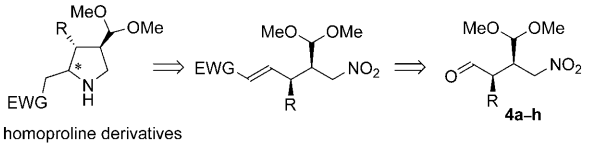
Table 4. Screening of the **3a**-catalyzed Michael reaction of ketones with **2**.[a]

Entry	Ketone	Product	Solvent	Yield [%][b]	*syn*/*anti*[c]	*ee* [%][d]
1	**6a**	**7a**	*i*PrOH	27	>20:1	96
2	**6a**	**7a**	THF	51	>20:1	97
3	**6a**	**7a**	DMF	44	>20:1	91
4	**6a**	**7a**	toluene	16	>20:1	95
5	**6a**	**7a**	$CHCl_3$	20	>20:1	87
6	**6b**	**7b**	THF	30	>20:1	87
7	**6c**	**7c**	THF	10	>20:1	n.d.
8	**6d**	**7d**	THF	20	–	43
9	**6d**	**7d**	acetone	40	–	43
10	**6d**	**7d**	*i*PrOH	56	–	70

[a] Reaction carried out on a 1.00 mmol scale using 1 equiv each of **6** and **2** with 10 mol% of catalyst in the specified solvent and at RT. [b] Isolated yield after FC. [c] Determined by NMR spectrometric analysis of the reaction mixture. [d] Calculated from chiral GC data.

cally pure pyrrolidines and derivatives are compounds of great interest, which have found application as chiral reagents or catalysts for use in the field of organic synthesis, and are also very important biologically active compounds with potential therapeutic applications in medicine.

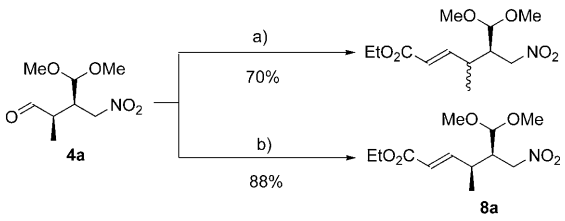
Taking into account the importance of providing new methodologies for the synthesis of enantioenriched polysubstituted pyrrolidines bearing different functional groups, we decided to prepare a variety of different derivatives with a homoproline general structure using our newly developed methodology. Thus, a short retrosynthetic analysis, as shown in Scheme 8, shows that pyrrolidines can be obtained after



Scheme 8. Retrosynthetic analysis for the synthesis of homoproline derivatives.

an intramolecular aza-Michael reaction of a conveniently substituted ω-amino-α,β-unsaturated ester intermediate, the amino group in which can be formed from the corresponding nitro derivative by chemoselective reduction. This ω-nitro-α,β-unsaturated ester derivative should be easily accessible from our adducts **4a**–**g** by a simple olefination procedure. It has to be pointed out that a key step in this synthesis relies upon the intramolecular aza-Michael addition, in which a third new stereogenic center is created. In this context, it is expected that the chiral information already present in the aminoenoate precursor should exert effective asymmetric induction in the formation of this new stereocenter, although special attention would have to be paid to the experimental conditions for carrying out this transformation in order to obtain the final compounds as single diastereoisomers.

We proceeded to carry out the synthesis according to the proposed synthetic plan using adduct **4a** as a model substrate, and therefore we started with the projected olefination reaction in order to obtain the ω-nitro-α,β-unsaturated ester **8a** (Scheme 9). We first explored the use of a Horner–Wadsworth–Emmons olefination procedure under conditions previously found to be appropriate in a similar context[24] and, in fact, when we carried out the reaction between **4a** and ethyl 2-(diethoxyphosphoryl)acetate in the presence of DBU, we obtained the expected ω-nitro-α,β-unsaturated ester **8a** in excellent yield but as a disappointing 1:1 mixture of diastereoisomers due to epimerization of the stereocenter at the α-position of the starting aldehyde. This epimerization process could not be avoided by changing the solvent, the base, or the temperature. We attributed the epimerization of the α-stereocenter of the starting material to the acidity of the proton at this position, which could undergo a fast deprotonation/protonation process under the basic conditions required for the HWE olefination reaction. For

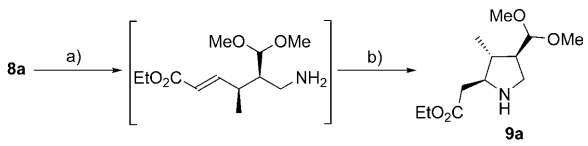


Scheme 9. Olefination of adduct **4a**. a) $(EtO)_2P(O)CH_2CO_2Et$, DBU, CH_2Cl_2, RT. b) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, RT.

this reason, we decided to switch to a Wittig reaction as an alternative protocol for the preparation of adduct **8a** under neutral reaction conditions. Thus, when we stirred a solution of Michael adduct **4a** and ethoxycarbonylmethylenetriphenylphosphorane in CH_2Cl_2 at room temperature, we were able to isolate the α,β-unsaturated ester **8a** in good yield (88%) and without epimerization at the α-stereocenter.

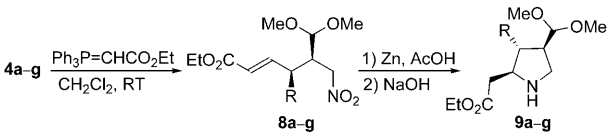
We next proceeded to carry out chemoselective reduction of the nitro group in the presence of the α,β-unsaturated ester moiety, which was accomplished by treating adduct **8a** with Zn in AcOH followed by basification, standard work-up, and final purification by flash chromatography. To our delight, the reaction proceeded in a very clean way, directly furnishing pyrrolidine **9a** (Scheme 10). This indicates that a clean and selective reduction of the nitro group occurred, followed by an intramolecular aza-Michael reaction, which most probably occurred after basifying the reaction mixture and during work-up. In addition, we also found that the cyclization step proceeded with complete diastereoselectivity, furnishing a single diastereoisomer, as indicated by NMR analysis of the crude reaction mixture. This also indicates that the chirality present in the ω-amino-α,β-unsaturated ester precursor was able to exert very effective asymmetric induction during the aza-Michael reaction step. The configuration of the newly created stereogenic center was determined by NOE experiments, which showed a 1,2-*trans* relationship with the methyl substituent at the adjacent stereocenter and a 1,3-*cis* relationship with the dimethoxymethyl substituent (Scheme 10).

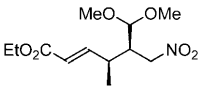
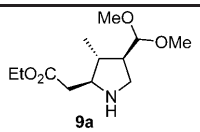
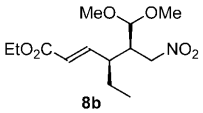
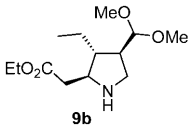
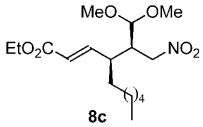
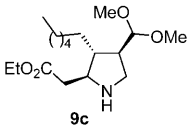
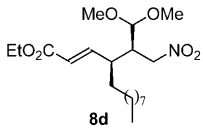
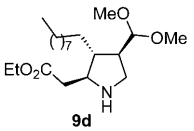
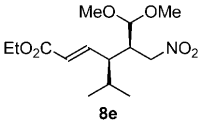
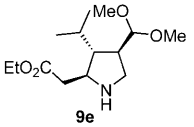
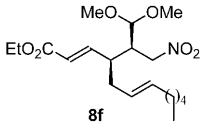
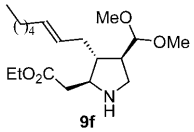
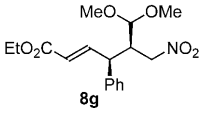
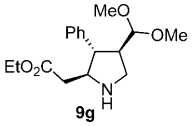
These conditions were extended to the rest of the nitroaldehydes **4b**–**g**, showing that this reaction sequence could be easily performed in all cases, furnishing the target trisubstituted homoproline products **9b**–**g** in only two steps (Table 5). The olefination step proceeded in good yield in each case[25] and without any appreciable epimerization at the stereogenic centers created during the organocatalytic enantioselective Michael reaction step. Moreover, the final reduction/cyclization step also took place with complete dia-



Scheme 10. Synthesis of homoproline derivative **9a**. a) Zn, AcOH, RT. b) NaOH (pH 12)

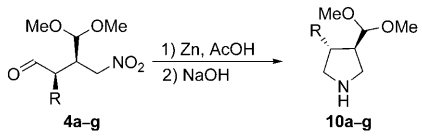
Table 5. Synthesis of the α,β-unsaturated esters **8** and pyrrolidines **9**.

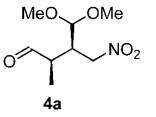
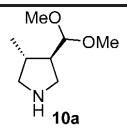
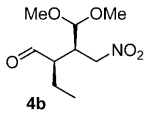
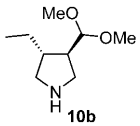
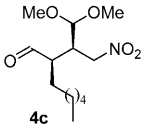
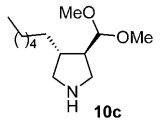
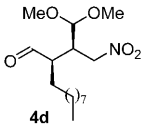
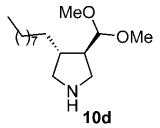
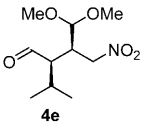
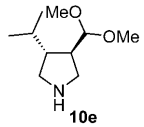
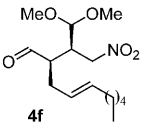
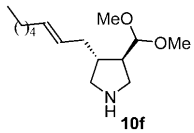
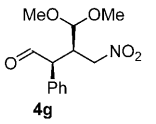
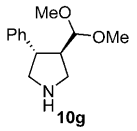


Entry	Substrate	Product	Yield [%][a]	Product	Yield [%][a]
1	**4a**	 **8a**	88	 **9a**	68
2	**4b**	 **8b**	85	 **9b**	64
3	**4c**	 **8c**	78	 **9c**	66
4	**4d**	 **8d**	74	 **9d**	44
5	**4e**	 **8e**	73	 **9e**	71
6	**4f**	 **8f**	45	 **9f**	84
7	**4g**	 **8g**	69	 **9g**	51

[a] Isolated yield after flash column chromatography.

Table 6. Synthesis 3,4-disubstituted pyrrolidines **10**.



Entry	Substrate	Product	Yield [%][a]
1	 **4a**	 **10a**	51[b]
2	 **4b**	 **10b**	74
3	 **4c**	 **10c**	75
4	 **4d**	 **10d**	81
5	 **4e**	 **10e**	79
6	 **4f**	 **10f**	75
7	 **4g**	 **10g**	80

[a] Isolated yield after flash column chromatography. [b] The reaction was carried out at −15 °C (see ref. [26]).

stereoselectivity regarding the generation of the third stereocenter, thus cleanly furnishing the target pyrrolidines **9b–g** as single diastereoisomers of high enantiomeric purity.

Synthesis of disubstituted pyrrolidines: A direct access to chiral 3,4-disubstituted pyrrolidines using Michael adducts **4a–g** was also envisaged by carrying out a cascade process consisting of chemoselective reduction of the nitro group followed by intramolecular reductive amination (Table 6). To our delight, when we treated γ-nitroaldehyde **4d** with Zn in AcOH, a clean reaction occurred and we were able to isolate pyrrolidine **10d** in excellent yield as a single diastereoisomer. This shows that the reduction/reductive amination cascade process also proceeded without epimerization at the α-stereocenter of the starting material, which was expected to be fairly prone to racemization during the reductive amination step through imine/enamine tautomerization. These conditions were extended to all of the Michael adducts **4**, furnishing pyrrolidines **10a–g** in excellent yields and as single diastereoisomers in all cases.[26]

Conclusion

We have improved our recently developed protocol for carrying out the organocatalytic conjugate addition of differently substituted aldehydes to β-nitroacrolein dimethyl acetal (a functionalized nitroalkene). The use of commercially available (*S*)-2-(trimethylsilyloxydiphenylmethyl)pyrrolidine (**3g**) as catalyst provided the final adducts in good yields, in shorter reaction times, and with higher enantio- and diastereoselectivities than those provided by L-prolinol, which was found to be the most efficient catalyst in our previous study. Moreover, the corresponding Michael adducts could be

easily transformed into highly functionalized enantioenriched pyrrolidines by two different methodologies. Pyrrolidines containing three stereogenic centers were obtained by a new protocol relying on a Wittig olefination reaction followed by a cascade process consisting of chemoselective reduction of the nitro group followed by a base-promoted fully diastereoselective intramolecular aza-Michael reaction. Alternatively, 3,4-disubstituted pyrrolidines were obtained in a single step from the Michael adducts by another cascade process consisting of chemoselective reduction followed by intramolecular reductive amination. The methodology presented herein constitutes a very efficient, short (three steps from nitroacrolein dimethyl acetal for the synthesis of trisubstituted pyrrolidines and only two steps for the 3,4-disubstituted derivatives), and modular approach for the construction of differently substituted stereodefined proline derivatives, which are molecules of interest due to their substitution pattern involving well differentiated functionalities suitable for further modifications.

Experimental Section

General procedure for the organocatalytic Michael reaction of aldehydes 1a–h and β-nitroacrolein dimethyl acetal 2; enantioselective synthesis of nitroaldehydes 4a–g and nitroesters 5b–g: An ordinary vial equipped with a magnetic stirring bar was charged with catalyst **3g** (0.10 mmol, 10 mol%), DMF (2.0 mL), and the appropriate aldehyde **1a–g** (1.0 mmol), and stirring was maintained at RT for 5 min. Nitroalkene **2** (1.0 mmol) and H_2O (2.0 mmol) were then added and the mixture was stirred at RT until completion of the reaction. The crude reaction mixture was then directly applied to a column of silica gel and subjected to flash chromatography (*n*-hexane/AcOEt 8:2), yielding the target γ-nitroaldehydes **4a–g** as colorless oils. For the purposes of better characterization and *ee* determination, aldehydes **4b–g** were transformed into the corresponding acetates by reduction/esterification. This was carried out by dissolving the respective aldehydes **4b–g** in MeOH (2 mL), cooling the solution to 0°C, and then adding $NaBH_4$ (10.0 mmol) in small portions. Each reaction mixture was stirred at RT until full conversion was observed by TLC, whereupon saturated aqueous NH_4Cl solution (2 mL) and CH_2Cl_2 (10 mL) were carefully added and the resulting mixture was stirred for a further 30 min. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3×3 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed in vacuo. The obtained yellowish oil was redissolved in CH_2Cl_2 (2 mL), and then DMAP (0.1 mmol) and acetic anhydride (1.0 mmol) were added at RT. The reaction mixture was stirred for 30 min and was then directly applied to a column of silica gel and subjected to flash chromatography (*n*-hexane/AcOEt 7:3) to yield the desired esters **5b–g** as colorless oils.

(2*R*,3*R*)-4,4-Dimethoxy-2-methyl-3-(nitromethyl)butanal (4a): Nitroaldehyde **4a** (0.17 g, 0.86 mmol) was obtained according to the general procedure starting from propanal (60 mg, 1.00 mmol) and β-nitroacrolein dimethyl acetal (0.15 g, 1.00 mmol) in the presence of catalyst **3g** (32 mg, 0.10 mmol) and water (36 mg, 2.00 mmol). Yield: 0.17 g, 0.86 mmol, 86%; $[\alpha]_D^{20}=-12.4$ ($c=1.0$, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz, TMS): $\delta=$ 1.13 (d, 3H, $J=7.3$ Hz), 2.55 (m, 1H), 3.11 (m, 1H), 3.32 (s, 3H), 3.34 (s, 3H), 4.30 (d, 1H, $J=6.5$ Hz), 4.35 (dd, 1H, $J=13.5$, 7.0 Hz), 4.57 (dd, 1H, $J=13.5$, 6.2 Hz), 9.56 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=$ 9.8, 41.4, 44.6, 54.6, 55.7, 73.7, 103.8, 201.7 ppm; IR: $\tilde{\nu}=1558$ (NO_2), 1724 cm^{-1} (C=O); MS (EI): *m*/*z* (%): 204 (2) [M^+], 174 (13), 142 (8), 127 (42), 113 (26) 99 (100), 84 (32), 75 (90); HRMS: *m*/*z*: calcd for $[C_8H_{14}NO_5]^+$: 204.0872; found: 204.0872. The *ee* (>99%) was determined by chiral GC-MS using a CP-Chirasil-Dex CB column after transformation to the acetal derived from propane-1,3-diol;[27] $T_{inj}=250$°C, $T_{det}=280$°C, constant pressure flow = 7 psi, $T_i=70$°C (2 min), $T_{f1}=100$°C (20°C min^{-1}, hold 30 min), $T_{f2}=210$°C (0.1°C min^{-1}): (minor *anti*-isomer) major enantiomer: $t_R=167.85$ min; minor enantiomer: $t_R=169.36$ min; (major *syn*-isomer) major enantiomer: $t_R=176.16$ min; minor enantiomer: $t_R=178.49$ min.

(2*R*,3*R*)-2-Ethyl-4,4-dimethoxy-3-(nitromethyl)butanal (4b): Nitroaldehyde **4b** (0.14 g, 0.63 mmol) was obtained according to the general procedure starting from butanal (72 mg, 1.00 mmol) and β-nitroacrolein dimethyl acetal (0.15 g, 1.00 mmol) in the presence of catalyst **3g** (32 mg, 0.10 mmol) and water (36 mg, 2.00 mmol). Yield: 0.14 g, 0.63 mmol, 63%; $[\alpha]_D^{20}=+12.9$ ($c=1.0$, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=1.01$ (t, 3H, $J=7.3$ Hz), 1.46 (m, 1H), 1.80 (m, 1H), 2.52 (m, 1H), 3.01 (m, 1H), 3.33 (s, 3H), 3.35 (s, 3H), 4.34 (m, 2H), 4.59 (dd, 1H, $J=13.6$, 7.1 Hz), 9.61 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=12.4$, 19.5, 41.1, 51.3, 55.2, 55.3, 73.3, 104.4, 202.7 ppm; IR: $\tilde{\nu}=1555$ (NO_2), 1718 cm^{-1} (C=O); MS (EI): *m*/*z* (%) 218 (1) [M^+], 141 (38), 127 (21), 113 (78), 97 (33), 81 (60), 75 (100); HRMS: *m*/*z*: calcd for $[C_9H_{17}NO_5]^+$: 219.1107; found: 219.1109. The *ee* was determined after transformation to **5b** (see below).

(2*R*,3*R*)-2-Ethyl-4,4-dimethoxy-3-(nitromethyl)butyl acetate (5b): The ester **5b** was obtained by reduction/esterification of **4b** (0.14 g, 0.64 mmol) following the general experimental procedure using $NaBH_4$ (0.22 g, 6.00 mmol), Ac_2O (0.05 mL, 0.60 mmol), and DMAP (7 mg, 0.06 mmol). Yield: 0.16 g, 0.60 mmol, 90%; $[\alpha]_D^{20}=-2.9$ ($c=0.45$, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=0.98$ (t, 3H, $J=7.1$ Hz), 1.42 (m, 2H), 1.91 (m, 1H), 2.06 (s, 3H), 2.86 (m, 1H), 3.35 (s, 6H), 4.08 (d, 2H, $J=5.1$ Hz), 4.35 (m, 2H), 4.51 ppm (dd, 1H, $J=12.9$, 6.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=11.9$, 20.9, 22.0, 38.0, 41.2, 54.2, 55.2, 64.3, 73.7, 104.9, 171.8 ppm; MS (EI): *m*/*z* (%): 185 (2) {M^+-78}, 111 (21), 93 (4), 75 (100), 55 (4); HRMS: *m*/*z*: calcd for $[C_{11}H_{21}NO_6]^+$: 263.1369; found: 263.1377; IR: $\tilde{\nu}=1555$ (NO_2), 1740 cm^{-1} (C=O). The *ee* (>99%) was determined by chiral GC-MS using a CP-Chirasil-Dex CB column; $T_{inj}=250$°C, $T_{det}=280$°C, constant flow = 1.0 mL min^{-1}, $T_i=$ 70°C (3 min), $T_{f1}=100$°C (30°C min^{-1}, hold 30 min), $T_{f2}=210$°C (0.5°C min^{-1}): minor *anti*-isomer: first enantiomer: $t_R=81.17$ min; second enantiomer: $t_R=81.42$ min, major *syn*-isomer: minor enantiomer: $t_R=$ 83.61 min; major enantiomer: $t_R=86.06$ min.

General procedure for the synthesis of α,β-unsaturated esters 8a–g: (Ethoxycarbonylmethylidene)triphenylphosphorane (5.0 mmol) was added to a solution of the appropriate aldehyde **4** (1.0 mmol) in dry CH_2Cl_2 (30 mL) at 0°C. Stirring was maintained at this temperature until completion of the reaction, as monitored by TLC analysis. A saturated aqueous solution of NH_4Cl (10 mL) and H_2O (10 mL) were then added and the aqueous layer was separated and extracted with CH_2Cl_2 (3× 10 mL). The combined organic fractions were collected, dried over Na_2SO_4, and the solvent was removed in vacuo. The crude reaction mixture was then subjected to purification by flash column chromatography (*n*-hexane/AcOEt 7:3).

Ethyl (4*S*,5*R*,2*E*)-6,6-dimethoxy-4-methyl-5-(nitromethyl)hex-2-enoate (8a): ω-Nitroester **8a** (0.17 g, 0.61 mmol) was obtained according to the general procedure starting from **4a** (0.14 g, 0.69 mmol) and Ph_3P=$CHCO_2Et$ (1.26 g, 3.45 mmol). Yield: 0.17 g, 0.61 mmol 88%; $[\alpha]_D^{20}=-15.2$ ($c=1.0$, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=1.12$ (d, 3H, $J=$ 6.7 Hz), 1.25 (t, 3H, $J=7.1$ Hz), 2.66 (m, 2H), 3.33 (s, 3H), 3.34 (s, 3H), 4.22 (m, 4H), 4.52 (dd, 1H, $J=12.6$, 6.8 Hz), 5.81 (d, 1H, $J=15.6$ Hz), 6.80 ppm (dd, 1H, $J=15.6$, 7.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=14.2$, 16.8, 34.9, 44.4, 54.7, 55.1, 60.4, 73.1, 104.5, 122.4, 149.2, 166.2 ppm; IR: $\tilde{\nu}=1555$ (NO_2), 1716 cm^{-1} (C=O); MS (EI): *m*/*z* (%) 229 (M^+-46), 197 (16), 183 (18), 137 (4), 131 (12), 123 (19), 99 (16), 81 (9), 75 (100), 54 (2); HRMS: calcd for $[C_{11}H_{17}O_3]^+$ (M^+-78): 197.1178; found: 197.1168.

General procedure for the cascade reduction/cyclization reaction: **synthesis of pyrrolidines 9a–g and 10a–g**: Zn (25.0 mmol) was added in small portions over a period of 10 min to a solution of the unsaturated nitroester **8** (for the synthesis of **9**) or the γ-nitroaldehyde **4** (for the synthesis of **10**) (1.0 mmol) in H_2O/AcOH (1:1; 20 mL) at 0°C. The reaction mixture was stirred for 2 h at RT, then filtered, and the filtrate was adjusted to pH 12 with 4 M NaOH. The aqueous layer was extracted with CH_2Cl_2 (3× 10 mL). The organic fractions were combined, dried over Na_2SO_4, and the solvent was removed in vacuo. Pyrrolidines **9a–g** and **10a–g** were iso-

lated after purification by flash column chromatography (AcOEt/MeOH 10:3).

Ethyl (2*S*,3*R*,4*R*)-[4-(dimethoxymethyl)-3-methylpyrrolidin-2-yl]acetate (9a): Pyrrolidine **9a** (76 mg, 0.31 mmol) was obtained according to the general procedure starting from **8a** (0.12 g, 0.45 mmol) and Zn (0.75 g, 11.32 mmol). Yield: 76 mg, 0.31 mmol, 68%; $[\alpha]_D^{20} = -12.7$ ($c = 0.7$, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 1.05$ (d, 3H, $J = 6.7$ Hz), 1.23 (t, 3H, $J = 7.1$ Hz), 1.51 (m, 1H), 2.01 (m, 1H), 2.33 (m, 2H), 2.59 (dd, 1H, $J = 15.6$, 3.6 Hz), 2.97 (m, 2H), 3.32 (s, 3H), 3.34 (s, 3H), 4.12 (q, 2H, $J = 7.1$ Hz), 4.23 ppm (d, 1H, $J = 7.1$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 14.2$, 17.3, 38.9, 41.6, 46.9, 48.7, 53.7, 54.0, 60.5, 63.0, 107.5, 172.6 ppm; IR: $\tilde{\nu} = 1733$ (C=O), 3418 cm^{-1} (NH); MS (EI): *m*/*z* (%) 246 (1) [M^++1], 215 (33), 198 (81), 182 (51), 170 (24), 168 (15), 158 (100), 129 (32), 126 (52), 108 (13), 97 (15), 94 (97), 85 (34), 75 (42), 56 (20); HRMS: *m*/*z*: calcd for $[C_7H_{12}NO]^+$: 126.0919; found: 126.0923 [M^+ −119].

(3*R*,4*R*)-3-(Dimethoxymethyl)-4-methylpyrrolidine (10a): Pyrrolidine **10a** (72 mg, 0.45 mmol) was obtained according to the general procedure starting from **4a** (184 mg, 0.89 mmol) and Zn (1.45 g, 22.25 mmol) and carrying out the reaction at −15 °C (see ref. [26]). The solvents had to be removed especially carefully because pyrrolidine **10a** was found to be volatile. Yield: 72 mg, 0.45 mmol, 51%; $[\alpha]_D^{20} = +10.0$ ($c = 0.6$, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 1.09$ (d, 3H, $J = 6.5$ Hz), 2.11 (m, 1H), 2.53 (m, 1H), 2.97 (m + brs, 3H), 2.04 (m, 1H), 3.19 (m, 1H), 3.33 (s, 3H), 3.35 (s, 3H); 4.31 ppm (d, 1H, $J = 6.9$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 18.9$, 36.6, 49.0, 49.3, 53.5, 53.8, 55.5, 107.3 ppm; IR: $\tilde{\nu} =$ 3414 cm^{-1} (NH); MS (EI): *m*/*z* (%) 129 (M^+−30, 14), 127 (17), 112 (21), 96 (72), 85 (100), 75 (38), 71 (19), 67 (18); HRMS: *m*/*z*: calcd for $[C_6H_{10}]^+$: 96.0813; found: 96.0814 [M^+−63].

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[22] Literature examples show that diarylprolinol silyl ethers are not active in organocatalytic reactions with ketones that rely on enamine catalysis (see ref. [16]). A test reaction in which cyclohexanone and **3g** were mixed in $CDCl_3$ in an NMR tube indicated that no enamine was formed even after 4 days, probably because enamine formation was hampered by steric overcrowding. Other catalysts, such as **3b**, **3c**, and **3d**, were also tested, but no Michael addition product was obtained after a reaction time of 4 d.
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[26] Reaction of nitroaldehyde **4a** with Zn at RT furnished pyrrolidine **10a** as a 4:1 mixture of diastereoisomers as a result of partial epimerization at C4. This side reaction was avoided by carrying out the reaction at −15 °C, thereby obtaining **10a** as a single diastereoisomer. We also found this compound to be fairly volatile, which is the most probable reason for the lower yield obtained compared to those of the other pyrrolidines **10**.
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