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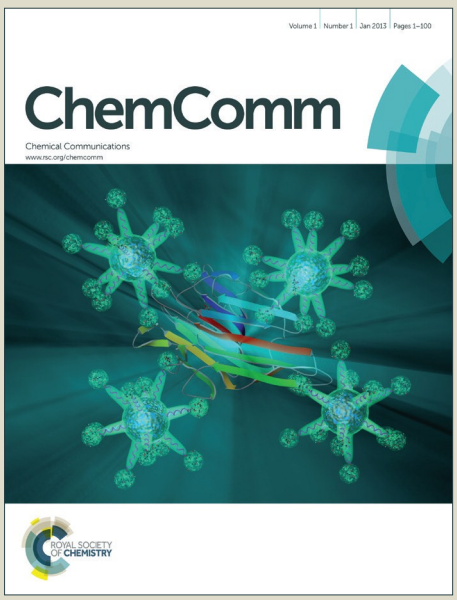

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ARTICLE TYPE

Organocatalytic Enantio- and Diastereoselective Synthesis of 3,5-Disubstituted Prolines†

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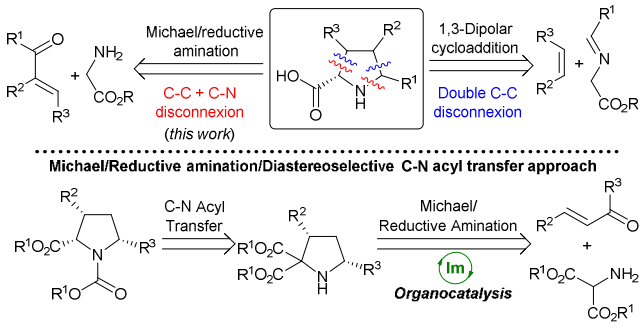
The asymmetric synthesis of substituted pyrrolidines has been accomplished using a novel organocatalytic cyclization reaction promoted by a *Cinchona* alkaloid base primary amine. The reaction proceeds smoothly yielding pyrrolidine-2,2-dicarboxylates after *in situ* diastereoselective reduction with high levels of enantioselection. Furthermore, these adducts could be easily transformed into *N*-protected disubstituted prolines through base-promoted diastereoselective C→N alkoxycarbonyl transfer reaction

Prolines and substituted prolines constitute essential chemical entities in organic synthesis and drug development.[1] This scaffold is the central unit of many bioactive natural or synthetic products and is also a privileged architecture for the preparation of chiral reagents used in the stereocontrolled versions of many organic transformations either as chiral ligands or organocatalysts.[2] As a result of their interest, developing new approaches for the stereocontrolled preparation of substituted prolines still remains as an active topic amongst synthetic organic chemists.[3] In general, the existing methodologies for the stereoselective preparation of this heterocyclic scaffold can be classified into two main groups. One is based on the chemical modification of proline or other commercially available proline derivatives and the second one relies on the *de novo* construction of the heterocyclic architecture through a ring closure process. Among these later strategies (see Scheme 1), the consecutive formation of two C-C bonds through enantioselective [3+2] cycloaddition has become a very powerful tool[4] but, on the contrary, methodologies involving an atypical simultaneous C-C and C-N disconnection are by far less explored.[5]



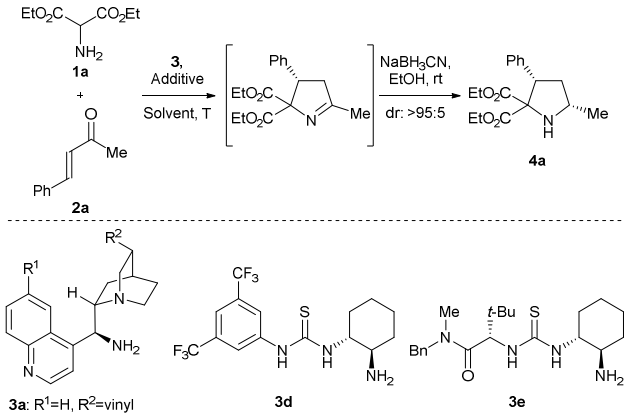
Scheme 1 Two different approaches to the proline scaffold and the access to enantiopure 3,5-disubstituted proline esters presented in this work

In this sense, and as a part of our ongoing project focussed on the stereocontrolled synthesis of complex heterocycles through organocatalytic cascade reactions,[6] we envisaged a possible synthetic approach to enantiopure highly substituted proline derivatives such as the one shown in Scheme 1. According to our plans, the target highly functionalized prolines would be accessed from pyrrolidine-2,2-dicarboxylates by means of our recently developed intramolecular base promoted C-N acyl transfer reaction which has to proceed with good diastereoselection.[7] The access to the key pyrrolidine-2,2-dicarboxylates in an enantiopure form was designed to be carried out through a sequence of organocatalytic enantioselective one pot/cascade reactions[8] relying on a cascade Michael reaction/intramolecular condensation process between aminomalonates and α,β-unsaturated ketones, followed by the diastereoselective reduction of the resulting pyrroline in a one-pot fashion. In view of this reaction design, asymmetric organocatalysis through iminium ion activation of the enone shows up as a very reliable methodological approach to render the initial Michael reaction enantioselective.[9] This approach has been employed in several examples of Michael/condensation cascades but in all cases using α,β-unsaturated aldehydes as substrates, which in case of being afterwards subjected to reduction of the azomethine moiety generated on the condensation step do not lead to the formation of an additional stereocenter.[10]

We started our investigations using diethyl aminomalonate **1a** and *trans*-4-phenylbut-3-en-2-one **2a** as model substrates for performing the aforementioned cascade Michael/condensation reaction using diverse primary amines **3a-e** as catalysts and under various reaction conditions (Table 1). We initially surveyed the use of primary amine catalysts derived from cinchona alkaloids, as it has been demonstrated that these are a privileged class of organocatalysts in the activation of enones *via* iminium ion formation.[11] In this sense, the reaction using catalyst **3a** in the presence of TFA as cocatalyst in THF proceeded smoothly forming the expected pyrroline, which was subsequently subjected to *in situ* reduction with $NaBH_3CN$, leading to **4a** in good yield, high enantioselectivity and as a single diastereoisomer (entry 1). This later finding indicated that the stereocenter generated at the Michael reaction step was able to exert a very efficient asymmetric induction on the reduction of the imine moiety. Remarkably, the reaction was also found to be fully regioselective, without any evidence on the presence of the possible byproduct arising from a competitive aza-

Michael/intramolecular aldol reaction that could eventually occur due to the ambident nature of the aminomalonate nucleophile. Changing the acidic additive to $MeSO_3H$ improved the enantioselectivity (entry 2) and these conditions were tested with other related cinchona-based primary amine catalysts, but none of them performed better than **3a** (entries 3 and 4). The same applies to other bifunctional primary amine/thiourea catalysts such as **3d**[12] and **3e**[13] that are also known to be effective promoters of Michael-type reactions with enones under iminium activation (entries 5 and 6). Other solvents were also surveyed but none performed better than THF (entries 7-9). Finally, we also carried out the reaction at lower temperature, which furnished **4a** in slightly better enantioselectivity but a very prolonged reaction time was necessary to reach to a comparable yield to that obtained in entry 2.

Table 1 Optimization of the reaction conditions.[a]

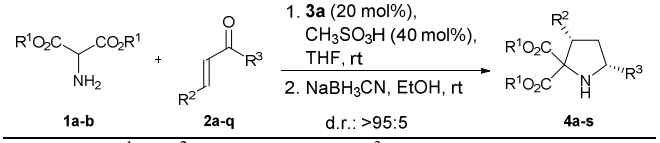


Entry	3	Additive	Solvent	Temp	Yield (%)[b]	ee (%)
1	**3a**	TFA	THF	rt	92	82
2	**3a**	$MeSO_3H$	THF	rt	89	89
3	**3b**	$MeSO_3H$	THF	rt	93	83
4	**3c**	$MeSO_3H$	THF	rt	79	73
5	**3d**	-	THF	rt	54	81[c]
6	**3e**	-	THF	rt	62	36[c]
7	**3a**	$MeSO_3H$	$CHCl_3$	rt	80	83
8	**3a**	$MeSO_3H$	EtOAc	rt	81	80
9	**3a**	$MeSO_3H$	Toluene	rt	88	82
10	**3a**	$MeSO_3H$	THF	4ºC	83	90

[a] Reaction conditions: 2-aminomalonate (**1a**) (0.86 mmol), enone (**2a**) (0.62 mmol), catalyst (**3**) (20 mol%), additive (40 mol%) in 3 mL of solvent at rt for 24h; then $NaBH_3CN$ (1 mmol) in EtOH (25 mL), 10 min. [b] Yield of isolated pyrrolidine **4a** as a single diastereoisomer (d.r.: >95:5) as ^{1}H-NMR analysis of crude reaction mixture indicated. [c] The opposite enantiomer was obtained. [d] Reaction was stirred for 96h

Having established a good protocol for the reaction, we proceeded to extend these conditions to other dialkyl aminomalonates **1a-b** and enones **2a-n** (Table 2). The reaction performed excellently when a variety of β-aryl and heteroaryl-substituted enones were employed, regardless the electronic nature of the aryl substituent, leading to the expected pyrrolidines in high yields and as single diastereoisomers of very high enantiomeric purity after *in situ* reduction (entries 1-2). These reactions needed from 20 to 168 h to reach to completion, observing that those enones incorporating electron-donating groups at the aryl substituent required for longer reaction times than those with electron-withdrawing groups (compare entries 5, 10 and 12). The position of the substituent at the aryl moiety had a moderate influence in the rate of the reaction (entries 3-5, 6-7 and 8-9). Heteroaryl substituted enones were also studied, although in this case it was found that running the reaction in $CHCl_3$ and using TFA (40 mol%) as co-catalyst resulted in a higher enantioselectivity (entries 13-14 *vs* 15-16). A bulkier ethyl substituent at the α'-position of the enone reagent was also well tolerated (entry 17), but when α'-aryl-substituted enones were surveyed, the reaction did not perform satisfactorily (entries 18 and 19). For instance, the reaction between **1a** and 1,3-diphenyl-2-propen-1-one **2p** furnished the intermediate pyrroline after the initial cascade Michael/condensation process in low yield and moderate enantioselectivity.[14] This intermediate was unreactive towards reduction under our optimized conditions, presumably because of the conjugated nature of the azomethine moiety. When 1-phenyl-2-buten-1-one **2q** was employed, the formation of a complex mixture of products was observed. On the other hand, the reaction performed well when a different aminomalonate such as **1b** was used (entries 20 and 21), yielding the desired heterocycles with good yields and enantioselectivities.

Table 2 Scope of the reaction. Enantioselective synthesis of pyrrolidines.[a]



Entry	4	R^1	R^2	R^3	Time (h)	Yield (%)[b]	ee (%)[c]
1	**4a**	Et	Ph	Me	42	89	89
2	**4b**	Et	4-MeC_6H_4	Me	41	70	90
3	**4c**	Et	2-$MeOC_6H_4$	Me	119	67	89
4	**4d**	Et	3-$MeOC_6H_4$	Me	68	77	89
5	**4e**	Et	4-$MeOC_6H_4$	Me	41	79	89
6	**4f**	Et	2,6-$(MeO)_2C_6H_3$	Me	97	63	77
7	**4g**	Et	3,5-$(MeO)_2C_6H_3$	Me	29	67	87
8	**4h**	Et	2-FC_6H_4	Me	42	78	89
9	**4i**	Et	4-FC_6H_4	Me	26	74	89
10	**4j**	Et	4-ClC_6H_4	Me	27	78	89
11	**4k**	Et	4-$CF_3C_6H_4$	Me	23	53	87
12	**4l**	Et	4-$NO_2C_6H_4$	Me	20	70	86
13	**4m**	Et	2-Furyl	Me	72	73	76
14	**4n**	Et	2-Thienyl	Me	96	72	78
15[c]	**4m**	Et	2-Furyl	Me	120	80	86
16[c]	**4n**	Et	2-Thienyl	Me	120	81	87
17	**4o**	Et	4-$MeOC_6H_4$	Et	168	65	89
18	**4p**	Et	Ph	Ph	192[d]	31	58
19	**4q**	Et	Me	Ph	120	<5	n.d.[e]
20	**4r**	Me	Ph	Me	41	91	90
21	**4s**	Me	2,6-$(MeO)_2C_6H_3$	Me	72	67	80

[a] Reaction conditions: See ESI for each case. [b] Yield of isolated product **4** as a single diastereoisomer (d.r.: >95:5) as ^{1}H-NMR analysis of crude reaction mixture indicated. [c] Reaction carried out using TFA as additive and $CHCl_3$ as solvent. [d] The intermediate pyrroline was isolated. [e] n.d. = not determined.

The absolute configuration was determined by X-ray analysis of compound **4q** (Figure 1) that showed a *3S,5S* configuration at the two stereogenic centers created during the Michael/condensation/reduction process.[15] This was extended to the other pyrrolidines **4a-s** based on mechanistic analogy. The configuration of the stereocentre generated in the initial Michael reaction catalyzed by **3a** is in agreement with the stereochemical outcome of other Michael additions to enones mediated by this catalyst.[11a] The *5S* configuration is also in agreement with a diastereoselective reduction under substrate control with the hydride reagent approaching from the less hindered face of the intermediate pyrroline leading to the diastereoselective formation of a 3,5-*cis* relative arrangement.

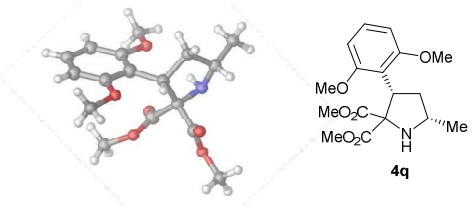
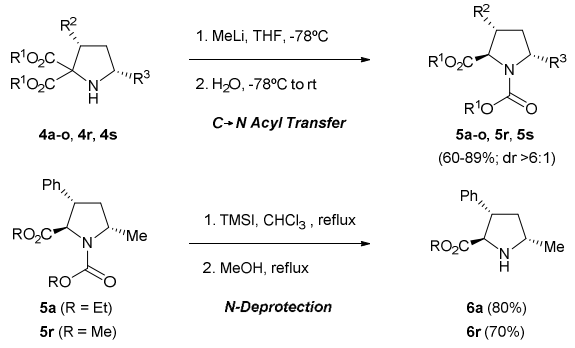


Figure 1. X-ray structure of compound **4q**

Finally, and in order to access to the proline scaffold, we next proceeded to subject to all obtained pyrrolidine adducts **4** to the base-promoted intramolecular C→N acyl transfer reaction that has been recently developed in our group.[7] In this sense, when compounds **4a-o** and **4r-s** were treated with one equivalent of MeLi in THF at low temperature a fast reaction took place, isolating proline ester derivatives **5a-o** and **5r-s** as the corresponding ethyl or methyl carbamates respectively after aqueous work-up. The rearrangement took place with high diastereoselectivity with respect to the generation of the new stereocenter at C-2. We also proceeded to carry out the *N*-deprotection of some representative derivatives in order to demonstrate the synthetic potential of this methodology to access to structurally complex chiral proline ester derivatives. The deprotection also took place smoothly without epimerization of any of the stereocenters present at the starting materials.



Scheme 2 Synthesis of proline ester derivatives through intramolecular diastereoselective C→N acyl rearrangement.

Conclusions

We have demonstrated that densely substituted proline esters can be obtained in good yields, complete diastereoselection and high enantioselectivities directly from aminomalonates and α,β-unsaturated ketones through a one-pot Michael reaction/intramolecular condensation/diastereoselective reduction sequence followed by base-promoted diastereoselective intramolecular C→N acyl transfer reaction. The key process for the installation of the initial stereocenter relies on the capacity of a readily available primary amine catalyst derived from cinchonine to promote the initial Michael reaction under iminium ion activation of the enone and all the subsequent steps rely on diastereoselective reactions proceeding under complete substrate control using simple experimental protocols. This method shows up as an excellent and direct synthetic approach to stereodefined *N*-protected and unprotected 3,5-disubstituted proline esters from very simple and cheap starting materials.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Detailed experimental procedures, NMR data and chiral HPLC traces of racemic and enantiomerically enriched pyrrolidines. See DOI: 10.1039/b000000x/

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15 CCDC 957613 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.