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Organocatalytic enantioselective conjugate addition of nitromethane to alkylidenemalonates: asymmetric synthesis of pyrrolidine-3-carboxylic acid derivatives[†]

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A highly enantioselective nitromethane addition to alkylidene malonates catalyzed by cinchona-alkaloid derived thiourea based organocatalyst has been developed that offers a new route to the synthesis of substituted pyrrolidine-3-carboxylic acid derivatives and 3-arylpyrrolidines/pyrrolidones.

Pyrrolidine-3-carboxylic acids (PCA) and their derivatives are important structural motifs abundant in biologically active natural products and pharmaceuticals.^{1,2} A structure based search revealed that 2,4-disubstituted- and 4-substituted PCAs 1 and 2 are more abundant than trisubstituted- and other di- or monosubstituted isomeric PCAs (for details see ESI[†])³—among these, the 4-aryl PCAs outnumber the 4-alkyl ones. Some notable examples, which show promising bioactivity, are endothelin A antagonists ABT-627 and ABT 546, MK-0489, hKN1, CCR5 etc.² Other than PCA, 3-substituted pyrrolidines and 4-substituted-2pyrrolidones 3 are the third most abundant structural unit after PCAs 1 and 2. These compounds also show high enantiospecificity towards interaction with respective receptors. Thus development of a concise and general divergent method for enantioselective synthesis for these compounds is an attractive challenge to synthetic and medicinal chemists.

Retrosynthetic analyses divulge that α -acyl- β -aryl- γ -amino butyric acid derivatives 4, an important motif found in many natural products and pharmaceuticals,⁴ could be a common precursor to such pyrrolidine based molecules which in turn can be obtained by two different ways: conjugate addition of malonate to nitrostyrene (route 1), or nitromethane addition to alkylidene malonate (route 2, Scheme 1). Extensive research efforts have been dedicated to the former strategy accompanied with excellent success in terms of yields and stereoselectivity.^{5,6} General nitromethane addition to enone,⁷ chalcone,⁸ α , β -unsaturated acid derivatives⁹ are known in the literature, but addition of nitromethane to alkylidene malonates is still a formidable challenge.

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To the best of our knowledge, there are only two reports of nitroalkane addition to alkylidene malonates till date. First one is by Maruoka *et al.* under phase transfer condition by using a complex N-spiro C₂-symmetric chiral quaternary ammonium catalyst.¹⁰ Very recently during our study, Chiarucci *et al.* reported¹¹ the catalytic enantioselective addition of nitroalkane to alkylidene malonates. But surprisingly, other than only one example for nitromethane addition to benzylidene malonate (*ee* 88%),¹⁰ both reports are restricted to higher nitroalkanes and avoid the use of nitromethane. Moreover lack of C5-substitution of the pyrrolidine³ further underscores the drawback of the existing methodologies.

In recent years, organocatalytic conjugate addition reactions have emerged as an important weapon in the arsenal of the synthetic organic chemist.¹² For this particular study we decided to use thiourea based organocatalysts with tethered amine functionality as it is presumed that the unique structural feature of the catalyst enables it to act bifunctionally *via* activation of alkylidene and *in situ* enolate generation from nitromethane. We commenced our screening with chiral *trans*-cyclohexanediamine derived catalyst **A** and **B** for benzylidene malonate **5a** ($\mathbf{R} = \mathbf{OEt}$) under different conditions (Table 1). Initial results by using these catalysts were promising but still unsatisfactory as these showed moderate enantioselectivity 47% and 40%, respectively, with poor to moderate conversions (entries 2 and 3). It was therefore decided to turn our attention to naturally occurring chiral cinchona



Scheme 1 Divergent retrosynthetic route of PCAs 1, 2 and 3.

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 $\label{eq:table_1} \textbf{Table 1} Screening of organocatalysts for the conjugate addition of nitromethane to benzylidene malonates \textbf{5a}^a$



^a Reaction condition: 5a (0.40 mmol), catalyst (10 mol%) in nitromethane (1.0 ml) was stirred at room temperature (25 °C).
^b Isolated yields after column chromatography; 10–20% substrate 5a was recovered. ^c Enantioselectivity was determined by HPLC using chiral column.^d NR: no reaction.

alkaloids-derived catalysts C, D, E, F assuming that, presence of bulky aromatic rings and other pendant functionalities may provide more effective shielding to one enantioface leading to an increase in enantioselectivity. Indeed we are delighted to report better result in terms of selectivity and conversion. Cinchonine and cinchonidine based catalysts C and D showed similar, but opposite enantioselectivity and provided up to 72% selectivity for 5a (entries 4 and 5). Quinine based catalyst E provided lower yield as well as selectivity (entry 6); whereas the corresponding dihydro catalyst F proved to be better with 65% of enantioselectivity (entry 7), but lower than catalysts C and D. Modification of alcoholic counterpart of malonates provided some interesting resultsintroduction of bulkier ⁱPr and ^tBu groups saw a lowering of yields while introduction of the Bn group had no such effect. On the other hand, ⁱPr and Bn groups afforded slightly enhanced selectivities (entries 8 and 10), while selectivity suffered on modification to ^tBu group (entry 9).

An extensive solvent study was performed encompassing a wide range of solvents from polar, non-polar and mixed but the neat reaction condition turned out to be the best. Notably we

 $\begin{array}{l} \textbf{Table 2} \text{ Generalization of catalytic enantioselective conjugate addition of} \\ \textbf{nitromethane to alkylidene malonates 5} \end{array}$

	$\begin{array}{c} R \xrightarrow{CO_2Et} \\ CO_2Et \\ 5 \end{array}$	catalyst C (1 MeNO ₂ , 2	0 mol%) 25 °C, t	R CO ₂ Et	Ξt
Entry	R	Substrate 5	Time (d)	Yield (%) ^a	ee (%) ^b
1 2 3 4 5 6 7 8 8 9 10	$\begin{array}{c} Ph \\ 4\text{-}F\text{-}C_{6}H_{4} \\ 2\text{-}F\text{-}C_{6}H_{4} \\ 4\text{-}NO_{2}\text{-}C_{6}H_{4} \\ 2\text{-}Cl\text{-}C_{6}H_{4} \\ 4\text{-}Cl\text{-}C_{6}H_{4} \\ 4\text{-}Older\text{-}C_{6}H_{4} \\ 4\text{-}OMe\text{-}C_{6}H_{4} \\ 4\text{-}OMe\text{-}C_{6}H_{4} \\ 4\text{-}OMe\text{-}C_{6}H_{4} \\ \\ \mathcal{I}_{S} \\ \mathcal{I}_{c} \mathcal{I}_{s} \\ \mathcal{I}_{c} \mathcal{I}_{s} \end{array}$	5a 5b 5c 5d 5e 5f 5g 5h 5i 5j	4 4 3 5 5 4 5 4 4 4	67 70 68 76 69 67 64 65 64 65 64 62	72 98 76 97 76 80 70 68 59 66
11	N St	5k	5	58	63
12	Ns.	51	4	57	55

 a Isolated yields after column chromatography; 10–20% substrate 5 was recovered. b Enantioselectivity was determined by HPLC using chiral column.

found *ee* drops significantly (nearly 30%) in non-polar solvents like toluene. The effects of variation of catalyst loading and temperature were evaluated by using simplified neat condition. With increase in temperature *ee* drops down sharply along with yield. Variation of catalyst loading also has a considerable effect on yield and selectivity: decreasing the catalyst loading to 5 mol% resulted in a significant drop in *ee*, while increasing the catalyst loading (20 mol%) raised the yield minutely keeping selectivity same. Therefore we decided to pursue further investigations with 10 mol% catalyst loading and diethylalkylidene malonates to maintain an ideal compromise among yield, easy accessibility, cost and selectivity.

With these optimized conditions in hand we performed an extensive screening of various aromatic and heterocyclic alkylidene malonates (Table 2). All substrates underwent smooth reaction and provided moderate to good yields in spite of incomplete conversion. The electron withdrawing groups at *para*-position (*p*-F and *p*-NO₂) gave excellent enantioselectivities (*ee* 98% and 97%) as well as good conversion (entries 2 and 4). *o*-Fluoro substrate **5b** also afforded good yield, but enantioselectivity decreased to 76% (entry 2). *p*-Cl, *o*-Cl– and *o*-Br-phenyl alkylidenes **5e**, **5f** and **5g** gave good yields (64–69%) with high enantioselectivities (*ee* 80%, 76% and 70%; entries 5–7). The enantioselectivity suffered for the electron donating substrates, *p*-methyl- and *p*-methoxy substrates



Scheme 2 Nitromethane addition to benzylidene acetylacetate 7.

5h and **5i** showed moderate ee (entries 8 and 9). This asymmetric protocol has also been successfully applied to the heteroaromatic substrates. Their reaction profiles are similar to electron-rich aromatic alkylidenes, provided good yield of addition products, but with moderate enantioselectivities (entries 10–12). The absolute stereochemistry of the adduct **6a** was determined to be "S" by comparing the optical rotation $\{[\alpha]_D^{25} = +6.12 \text{ (c, } 1.30, \text{ CHCl}_3)\}$ with the literature^{5b,6c} data $\{[\alpha]_D^{25} = +7.30 \text{ (c, } 1.07, \text{ CHCl}_3)\}$ and by analogy stereochemistry of other adducts **6** produced by cinchonine mediated catalyst **C** was assigned.

This nitromethane addition was also explored to 2-benzylidene acetylacetate 7, generating an additional chiral center. Under the same reaction conditions this provided good yield of addition products **8** with moderate diastereo- and enantioselectivity (Scheme 2).

The nitromethane adduct **6** could be the key intermediate for the synthesis of a variety of PCAs by simple chemical modifications. As an example, the adduct **6a** is transformed to 4-phenylpyrrolidine-3-carboxylic acid ester **10a** following literature procedure¹³ in three steps *via* semi-one-pot method (Scheme 3). For this purpose, the compound **6a** was treated with NaBH₄ and NiCl₂·6H₂O in MeOH to afford the lactam **9a** *via* reduction and subsequent cyclization. Lactam **9a** on treatment with Et₃O⁺BF₄⁻ followed by reduction with NaBH₃CN provided the 4-phenylpyrrolidene-3-carboxylic acid ester **10a**.

In conclusion, we report the first catalytic and enantioselective conjugate addition of nitromethane to alkylidene malonates. Cinchonidine and cinchonine derived thiourea catalysts were found to provide good to excellent enantioselectivity with opposite selectivity. The reaction was explored with a variety of substrates with good to excellent enantioselectivities (ee 55% to 98%) in moderate to good yields. Electron-rich benzylidene- and hetereoarylidene malonates showed lower ee, whereas electron-deficient benzylidene malonates, particular *p*-fluoro and *p*-nitro substrates gave excellent enantioselectivities (ee 98% and 97%). Addition to the alkylidene acetylacetate has also been explored,



Reagents: a) NiCl₂ .6H₂O (1 equiv), NaBH₄ (8 equiv), MeOH, 0 °Crt, 4 h; b) (i) Et₃O⁺BF₄⁻ CH₂Cl₂, rt, 14 h; (ii) NaBH₃CN, HCl (cat.), MeOH; 57% overall yield

Scheme 3 Synthesis of 4-phenylpyrrolidine-3-carboxylic acid ester.

which showed moderate diastereo- and enantioselectivity. The method is exemplified with the efficient synthesis of 4-phenyl-pyrrolidine-3-carboxylic acid ester. Further investigation towards a more efficient catalyst system and more extensive applications of this protocol is currently in progress.

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