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Novel guanidinyl pyrrolidine salt-based bifunctional organocatalysts: application in asymmetric conjugate addition of malonates to enones

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ABSTRACT

Novel guanidinyl pyrrolidine salts are useful bifunctional organocatalysts for the asymmetric addition of malonates to enones. These organocatalysts are effective under a wide range of reaction conditions and afford products in high yield and enantioselectivity.

Nowadays, asymmetric organocatalysis is recognised as a valuable addition and/or as an alternative methodology to more established metal-based procedures.[1] Since the two seminal reports by List, Lerner and Barbas[2] and MacMillan and co-workers,[3] two modes of aminocatalysis, namely enamine activation[4] and iminium activation,[5] have been extensively exploited in asymmetric organocatalysis. The iminium activation strategy has been used in a wide range of organocatalytic processes including cycloaddition,[5] transfer hydrogenation[6] and 1,4-addition.[7] In the latter case, the conjugate addition of malonates to enones has attracted specific attention in synthetic organic chemistry. Pioneering work, introduced proline rubidium salts to catalyse the addition of di-*iso*-propyl and di-*tert*-butyl malonates to both acyclic and cyclic enones. Products were obtained with low to good enantioselectivities (35–88% ee).[8,9] Ten years later, a highly efficient methodology was reported using an imidazolidine catalyst. High yields (up to 99%) and good to excellent enantioselectivities (84–99% ee) were obtained.[10] However, when the more synthetically useful dimethylmalonate was used ee's were moderate. Long reaction times as well as a large excess of malonate were required. Recently Ley and co-workers introduced a new methodology based on the use of proline tetrazole catalyst and a stoichiometric amount of base. In this case only 1.5 equiv of malonate was used and the reaction time was reduced to 3 days. Moreover, good to high enantioselectivities were obtained when both dimethylmalonate and diethylmalonate were used.[11,12] Only very recently, Zhao and Yang reported a highly efficient strategy using primary–secondary diamine catalysts.[13] Indeed the use of 20 mol % of catalyst gave the desired products in a relatively short reaction time (24 h) in excellent yields (up to 99%) and enantioselectivities (up to 99% ee) for a wide range of acyclic enones. When cyclohexenone was used, reaction times increased considerably (150 h) and products were obtained in moderate yield but still with good enantioselectivity (90% ee). It is noteworthy, that strategies based on other activation modes have recently led to efficient organocatalytic enantioselective malonate addition to enones,[14,15]albeit sometimes less efficient with cyclic enones.[14]

The results reported herein concern the application of new organocatalysts **I** containing a pyrrolidine ring and an acyclic guanidine moiety (Fig. 1).

The initial hypothesis was that the pK_a of guanidine would be well suited for deprotonation of the malonate. Moreover, the presumed ability of guanidinium ion to efficiently complex a malonate by both electrostatic interaction and two-directional hydrogen bonds would be suitable for the efficient orientation of nucleophilic attack of malonate. Consequently, the attack of the nucleophile could occur *syn* with respect to the pyrrolidine substituent,

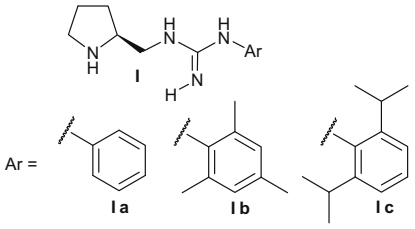

Figure 1. Organocatalysts with pyrrolidine guanidine scaffold.

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which is in contrast to the steric hindrance (compare Refs. 10,12). During the final course of this work, the report of Pansare and Lingampally[16] based on a similar working hypothesis[17] was published and it prompted us to report our preliminary results. It should be noted that the use of acyclic guanidine catalysts is rare compared to that of their cyclic or bicyclic counterparts.[18] It was decided to evaluate type **I** catalysts that contain aromatic ring moiety on the guanidine (Fig. 1). The appropriate choice of substituents on this ring could efficiently modulate the pK_a, steric and electronic properties of guanidine. In this work we describe the catalytic activities of compounds **Ia**, **Ib** and **Ic** which essentially differ in the steric hindrance of the guanidine moiety.

Compounds **Ia**, **Ib** and **Ic** were efficiently synthesised in three steps according to slightly modified literature procedure starting from *(S)-N*-Boc-aminomethylpyrrolidine (see ESI for Supplementary data).[19]

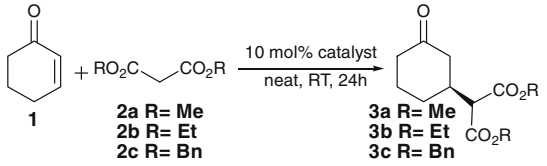
The investigation was started by evaluating the catalysts ability to promote conjugate addition of malonates to cyclohexenone **1** under neat conditions at room temperature. As shown in Table 1 the use of 10 mol % of free base catalysts **Ia**, **Ib** and **Ic** and dimethylmalonate as the nucleophile led to a total conversion but afforded a racemic product. These results probably reflect a simple base catalysis[20] and the absence of iminium formation. At this point it seemed clear that the use of free base catalysts was not appropriate to allow concomitant iminium formation and guanidine activation.[21] Consequently, the use of carboxylic acid salts of the catalysts was explored with the idea that faster iminium formation would occur. A subsequent dual activation by the guanidinium carboxylate ion pair could then take place (carboxylate assisted deprotonation of malonate and complexation of the resulting specie by guanidinium). First, it was observed that trifluoroacetic acid salts **Ia**$(CF_3CO_2H)_2$, **Ib**$(CF_3CO_2H)_2$ and **Ic**$(CF_3CO_2H)_2$ were completely inert. No formation of the expected product was observed by TLC analysis even after a prolonged reaction time. This can be explained by the experimental conditions which are favourable for the formation of the iminium ion but unfavourable for the deprotonation of the malonate. Consequently, catalyst salts with a more basic counteranion were investigated. Pleasingly, pivalic acid salts **Ia**$(tBuCO_2H)_2$, **Ib**$(tBuCO_2H)_2$ and **Ic**$(tBuCO_2H)_2$ efficiently catalysed the asymmetric addition of malonates **2a**, **2b** and **2c** to cyclohexenone **1** using 10 mol % of catalyst and 1.5 equiv of malonate.[22] As shown in Table 1, after a reaction time of 24 h high isolated yield and good enantioselectivity (73–82%) were observed with all three malonates. The *S* configuration of products is in agreement with nucleophile attack occurring *syn* with respect to the pyrrolidine substituent. Comparable isolated yields (85–95%) were obtained in all reactions whatever catalysts or malonates were used.

Enantioselectivity varied however according to the catalysts and malonates. Slightly better enantioselectivity was observed for more hindered substituents on the guanidine moiety. This trend was clearer when dimethylmalonate was used, 73%, 76% and 82% ee's were obtained when catalysts **Ia**$(tBuCO_2H)_2$, **Ib**$(tBuCO_2H)_2$ and **Ic**$(tBuCO_2H)_2$ were used, respectively, (entries 4–6). Moreover, in contrast with most of the previous reports, the same or better enantioselectivities were obtained when dimethylmalonate was used. This is particularly interesting with regard to its higher reactivity for further synthetic applications.

It was next demonstrated that enantioselectivity could be improved when the reaction was performed in various solvents (Table 2). Using dimethylmalonate and catalyst **Ic**$(tBuCO_2H)_2$ the enantioselectivity was maintained (84% ee) or slightly decreased (78% ee) when toluene or isopropanol was used (entries 2 and 8), but enantioselectivity increased significantly with both acetonitrile and chloroform (93% ee and 91% ee) (entries 4 and 6). Nevertheless, yields were moderate with these last two solvents (51% after 48 h). Fortunately, good yields can be obtained (80%) at higher concentrations without affecting enantioselectivity (entries 5 and 7).

The effect of temperature was next investigated. In spite of the high catalyst loading and long reaction times which are often required in organocatalysis to achieve good conversion, attempts to carry out reactions at higher temperatures are rarely reported. This could be explained by the assumption that heating has a negative impact on enantioselectivity. Nevertheless some examples with an opposite trend have been reported.[24] In asymmetric organocatalysis, Kappe and co-workers clearly demonstrated that heating can significantly enhance the reaction rate without affecting

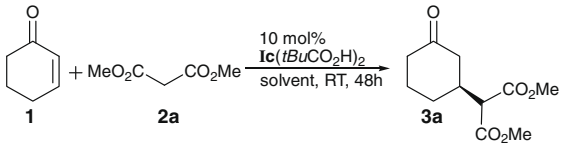
Table 1
Addition of malonates to cyclohexenone[a]



Entry	Catalyst	Malonate	Product	Yield[b] (%)	ee[c,d] (%)
1	**Ia**	**2a**	**3a**	nd[e]	rac[f]
2	**Ib**	**2a**	**3a**	nd[e]	rac[f]
3	**Ic**	**2a**	**3a**	nd[e]	rac[f]
4	**Ia** $(tBuCO_2H)_2$	**2a**	**3a**	90	73
5	**Ib** $(tBuCO_2H)_2$	**2a**	**3a**	87	76
6	**Ic** $(tBuCO_2H)_2$	**2a**	**3a**	91	82
7	**Ia** $(tBuCO_2H)_2$	**2b**	**3b**	81	69
8	**Ib** $(tBuCO_2H)_2$	**2b**	**3b**	85	73
9	**Ic** $(tBuCO_2H)_2$	**2b**	**3b**	88	75
10	**Ia** $(tBuCO_2H)_2$	**2c**	**3c**	95	77
11	**Ib** $(tBuCO_2H)_2$	**2c**	**3c**	97	78
12	**Ic** $(tBuCO_2H)_2$	**2c**	**3c**	94	81

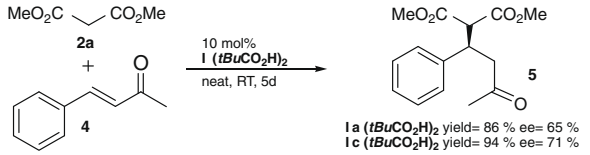
[a] Reaction conditions: 2-cyclohexenone **1** (0.5 mmol), malonates **2** (0.75 mmol), catalyst **I** (10 mol %), 24 h, rt.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis (Chiralpak IC), average of two runs.
[d] Absolute configuration determined from Refs. 12,23.
[e] nd: not determined.
[f] rac: racemic.

Table 2
Optimisation studies with catalyst **Ic**$(tBuCO_2H)_2$[a]

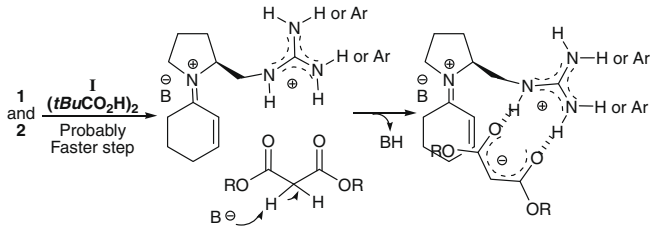


Entry	Solvent	Yield[b] (%)	ee (%)
1	None	91	82[c]
2	*i*PrOH (1 mL)	68	78[c]
3	*i*PrOH (0.5 mL)	82	79[c,d]
4	CH_3CN (1 mL)	51	93[c]
5	CH_3CN (0.5 mL)	76	91[c,d]
6	$CHCl_3$ (1 mL)	51	91[c]
7	$CHCl_3$ (0.5 mL)	80	92[c,d]
8	Toluene (1 mL)	76	84[c]
9	Toluene (0.5 mL)	89	84[c,d]
10	$CHCl_3$ (0.5 mL)[e]	89	90[d]

[a] Reaction conditions: 2-cyclohexenone **1** (0.5 mmol), malonates **2** (0.75 mmol), catalyst **Ic**$(tBuCO_2H)_2$ (10 mol %), solvents (1 mL or 0.5 mL), 48 h, rt.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis (Chiralpak IC).
[d] ^{13}C NMR of ketal with (2*R*,3*R*)-2,3-butanediol.
[e] Reflux, reaction time 12 h.



Scheme 1.



Scheme 2.

enantioselectivity for proline-catalysed Mannich and Aldol reactions.[25] Consequently, we decided to conduct the addition of dimethylmalonate to cyclohexenone catalysed with 10 mol % of **Ic**(tBuCO$_2$H)$_2$ at reflux in chloroform. Pleasingly, the expected product could be obtained in a high isolated yield (89%) after a relatively short reaction time (12 h) and with no decrease in enantioselectivity (90% ee) (entry 10).

The ability of **I**(tBuCO$_2$H)$_2$ to catalyse the addition of malonate to a less reactive Michael acceptor was then tested by the addition of dimethylmalonate **2a** to 4-phenyl-3-buten-2-one **4** in the presence of **Ia**(tBuCO$_2$H)$_2$ and **Ic**(tBuCO$_2$H)$_2$ (Scheme 1). A reaction time of 5 days was necessary to obtain the expected product **5** in good to high isolated yields (86% and 94%). Unfortunately the reaction proceeded with lower enantioselectivity (65% and 71%).

A detailed mechanism for these reactions is difficult to be established only on the basis of the results described above. Nevertheless, some reasonable assumptions can be made (Scheme 2).The formation of iminium intermediate can be postulated based on the fact that the use of polar solvents and higher temperature had only a slight effect on enantioselectivity obtained. When the trifluoroacetate salt of the catalyst was used, formation of iminium intermediate probably occurred, but the trifluoroacetate was not basic enough to deprotonate the malonate. In contrast, when a pivalate salt was used, pivalate with its guanidinium counteranion was probably basic enough for deprotonation. The guanidinium then acts as a complexing agent and controls the approach of malonate from the *si* face of the iminium double bond (attack *syn* with respect to the pyrrolidine substituent).

In summary, a new class of bifunctional organocatalysts based on guanidinyl pyrrolidine scaffold was developed. First investigations show that such compounds were able to catalyse conjugate addition of malonate to enone in a relatively short reaction time and in a wide range of experimental conditions including solvent-free and high temperature conditions. High yield and good enantioselectivities were obtained using only 1.5 equiv of dimethylmalonate. The bifunctional character of the catalyst is highlighted by the stereo direction of malonate addition. Fine tuning of the steric and electronic properties of guanidine as well as varying the nature of the basic counteranion would lead to more effective catalysts. Detailed mechanistic studies as well as the application of type **I** catalysts to more challenging reactions are currently under investigation.

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Supplementary data

Supplementary data (experimental details and characterisation data for all new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.05.011.

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