One-Pot, Three-Component, Highly Diastereoselective Metal-Free Synthesis of 2,3,4,5-Tetrasubstituted Pyrrolidines

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Abstract: An extremely efficient, highly diastereoselective, metalfree synthesis of 2,3,4,5-tetrasubstituted pyrrolidines is described. The three-component reaction between aldehydes, aminomalonates, and nitroalkenes proceeds with high diastereoselectivities and high yields.

Key words: metal-free, cycloaddition, three component, pyrrolidines, stereoselectivity

Multicomponent metal-free reactions are a very rapidly growing field of research. The operational and economic advantages associated with this methodology, together with the fact that metal-free reactions are environmentally friendly, robust, and very often the starting materials are commercially available, have led many research groups to engage in the development of new asymmetric or racemic multicomponent metal-free reactions.²

Pyrrolidine derivatives are an important class of organic compounds due to their frequent occurrence in nature and their use as intermediates in the synthesis of natural products and pharmaceuticals.³ Several polysubstituted pyrrolidines have shown very potent activities as enzyme inhibitors or as antagonists of receptors.⁴ Proline derivatives are also used to induce conformational constraints

into peptides.⁵ In addition to pharmaceuticals, the pyrrolidine moiety has also seen widespread use as a chiral auxiliary and catalyst for asymmetric synthesis.⁶

1,3-Dipolar cycloadditions are one of the simplest approaches for the construction of five-membered heterocyclic rings. The straightforward generation of 1,3-dipoles coupled with the often observed highly regio- and stereo-selective nature of their cycloaddition reactions have led to a number of syntheses which utilize such reactions as the key step.⁷

In organocatalysis, 1,3-dipolar reactions have been used extensively. In 2001, MacMillan⁸ and co-workers developed a 1,3-dipolar cycloaddition between α , β -unsaturated aldehydes and *N*-hydroxylamines, catalyzed by imidooxazolidine catalyst, obtaining the corresponding heterocycles with excellent enantioselectivities and diastereoselectivities. Following this concept, Cordova and co-workers developed a three-component version of this reaction using prolinol derivatives as catalyst.

In 2007, the research groups of Vicario⁹ and Cordova¹⁰ independently developed a very elegant approximation to the synthesis of pyrrolidines. They reacted preformed imines derived from 2-aminomalonates with α , β -unsaturated aldehydes, using diphenylprolinol derivatives as cat-



Scheme 1 Reaction proposal

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Table 1 Catalyst and Solvent Screening^a



Entry	Catalyst	Solvent ¹²	Time (h)	Yield (%) ^b	dr ^c
1	-	CHCl ₃	14	99	>25:1
2	5	CHCl ₃	14	80	1.2:1
3	6	CHCl ₃	14	15	1.1:1
4	7	CHCl ₃	14	30	1:1
5	-	МеОН	14	0	-
6	-	toluene	14	70	>25:1
7	-	DMSO	14	trace	n.d.

^a Experimental conditions: A mixture of **2a** (0.375 mmol) and benzaldehyde **3a** (0.375 mmol) in 0.5 mL of solvent was stirred at r.t. for 30 min. Then, nitrostyrene **1a** (0.25 mmol) and catalyst (20 mol%) were added.

^b Isolated yield of pure compound **4a**.

^c Determined by NMR analyses.

alyst. In both cases, the results were excellent, affording the pyrrolidine derivatives in almost enantiopure form.

With these ideas in mind, we envisioned an easy entry to pyrrolidines by reaction of imines derived from 2-aminomalonates and different nitroalkenes (Scheme 1).

Several reactions are known between iminoesters and nitroalkenes,¹¹ but these reactions are commonly catalyzed by metal salts or require high temperatures. To our knowledge, this is the first example of metal-free 1,3-dipolar cycloadditions between iminomalonates and nitroalkenes.

In an initial catalyst screening, we found that the reaction between 2-nitrostyrene 1a, aminomalonate 2a and benzaldehyde (3a) works best without any additive at room temperature, affording the corresponding pyrrolidine derivative in almost quantitative yield and excellent diastereoselectivity. The addition of different additives such as triethylamine or thiourea gave disordered reactions with low diastereoselectivities.

For instance, the additive-free reaction of **1a**, **2a**, and **3a** in CHCl₃ afforded the desired pyrrolidine **4a** in 99% yield in diastereopure form. Hence, we decided to investigate the scope of the metal-free reaction using the former reaction conditions and different aldehydes and nitrostyrenes.

The reactions between nitrostyrene, 2-aminomalonate, and different benzaldehydes were highly chemoselective and furnished the corresponding pyrrolidine derivatives in high yields and in high diastereoselectivities (Table 2). For example, 4-bromo-benzaldehyde (**3d**) reacts with diethyl 2-aminomalonate (**2a**) and nitrostyrene **1a** to afford the corresponding pyrrolidine **4d** in 95% yield and >25:1 diastereoselectivity.¹³

The relative configurations of the pyrrolidines **4** were established by nuclear Overhauser effect (NOE) experiments. This configuration could be explained by an *exo* approach in the 1,3-dipolar cycloaddition (Scheme 2).

The next step was the evaluation of different nitroalkenes. To our delight, the reaction worked well with any kind of nitroalkene, however, the reaction with aliphatic nitroalkenes rendered pyrrolidines with lower yields (Table 3). For example, the three-component reaction of **3a**, aminomalonate **2a**, and nitrostyrene **1b** afforded pyrrolidine derivative **4f** in 97% yield and in diastereopure form.

In summary, we have reported a highly diastereoselective synthesis of polysubstituted pyrrolidines, which are formed in high yields and diastereopure form. Moreover, the metal-free tandem reaction represents a versatile asymmetric entry to different proline derivatives. Mechanistic studies, synthetic applications, and the development of a chiral version are ongoing in our laboratory.



Scheme 2 The *exo* approximation in cycloaddition

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^a Experimental conditions: A mixture of 2a (0.375 mmol) and aldehyde 3a-e (0.375 mmol) in 0.5 mL of solvent was stirred at r.t. for 30 min. Then, nitrostyrene 1a (0.25 mmol) was added.

^b Isolated yield of pure compound **4**.

^c Determined by NMR analyses.

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References and Notes

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$R \xrightarrow{\text{NO}_2 + H_2N} \xrightarrow{\text{CO}_2\text{Et}}_{\text{CO}_2\text{Et}} + \underbrace{Ph}_{\text{H}} \xrightarrow{\text{CHCl}_3, \text{ r.t., 14 h}}_{\text{CHCl}_3, \text{ r.t., 14 h}} \xrightarrow{\text{O}_2N} \xrightarrow{\text{R}}_{\text{CO}_2\text{Et}}_{\text{CO}_2\text{Et}}$									
1 Entry	2a R	3a	4 Product	Yield (%) ^b	dr ^c				
1	Br	1 ³ 2	O_2N Ph^{V} H H CO_2Et CO_2Et CO_2Et CO_2Et	97	>25:1				
2	O ₂ N	34	O_2N O_2N Ph^{V} H H H CO_2Et CO_2Et CO_2Et CO_2Et	96	>25:1				
3	Cl		O_2N O_2N Ph H CO_2Et CO_2Et CO_2Et CO_2Et	95	>25:1				
4	Br		$ \begin{array}{c} Br \\ O_2N \\ Ph^{V} \\ H \end{array} $ $ \begin{array}{c} CO_2Et \\ CO_2Et \\ CO_2Et \end{array} $ $ \begin{array}{c} 4i \end{array} $	94	>25:1				
5	Ũ	No the second se	O ₂ N PH ^V N H 4j	76	>25:1				

Table 3 Reactions with Different Nitro Olefins^a

^a Experimental conditions: A mixture of 2a (0.375 mmol) and aldehyde 3a (0.375 mmol) in 0.5 mL of solvent was stirred at r.t. for 30 min. Then, nitrostyrene 1 (0.25 mmol) was added.

^b Isolated yield of pure compound **4**.

^c Determined by NMR analyses.

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- (13) Typical Experimental Procedure for the Three-Component Synthesis of Pyrrolidine Derivatives To a stirred solution of aldehyde 3 (0.375 mmol, 1.5 equiv)

in CHCl₃ (0.5 mL) at r.t., diethyl 2-aminomalonate (2a, 0.375 mmol, 1.5 equiv) was added. The reaction was stirred at r.t. for 30 min and then nitroalkene **1** was added. The reaction was then stirred at r.t. overnight. Next the crude was purified by silica gel column chromatography to afford the pyrrolidine derivative **4**.

Compound **4d**: colorless oil. ¹H NMR (400 MHz, CDCl₃): $\delta = 7.48-7.44$ (m, 2 H), 7.33–7.28 (m, 7 H), 5.58 (dd, J = 6.8, 8.0 Hz, 1 H), 5.46 (d, J = 8.4 Hz, 1 H), 5.12 (d, J = 7.2 Hz, 1 H), 4.42–4.21 (m, 2 H), 3.91 (q, J = 7.6 Hz, 1 H), 3.46 (q, J = 7.6 Hz, 1 H), 1.29 (t, J = 7.6 Hz, 3 H), 0.78 (t, J = 7.6 Hz, 3 H). ¹³C NMR (100 MHz, CDCl₃): $\delta = 171.1$, 168.4, 135.7, 134.9, 132.4, 131.6, 130.9, 128.9, 128.7, 128.6, 128.3, 122.9, 93.5, 75.9, 63.8, 62.2, 62.0, 51.9, 14.0, 13.3. Copyright of Synlett is the property of Georg Thieme Verlag Stuttgart and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.