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2-Nitromethylacrylates as Useful Dinucleophiles for the Enantioselective Organocatalytic Michael/Henry Cascade Reaction

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Abstract:

2-Nitromethylacrylates have proved to be suitable 1,3-dinucleophiles reacting with α,β-unsaturated aldehydes in the presence of a secondary-amine catalyst to furnish Michael/Henry cascade products in moderate yields and with high enantioselectivities although with moderate diastereoselectivities. The reaction proceeds by iminium ion activation of the enal, which reacts regioselectively with the γ-carbon of the nitronate anion formed *in situ*, furnishing the desired cyclohexenes with three new stereocenters. Furthermore, and trying to avoid the diastereoselectivity issue, an efficient sequential Michael/Henry/dehydration reaction has been developed leading to enantiopure cyclohexadienes in moderate yields and excellent enantioselectivities.

Keywords: Michael/Henry reaction; Enantioselective cascade reaction; Iminium catalysis

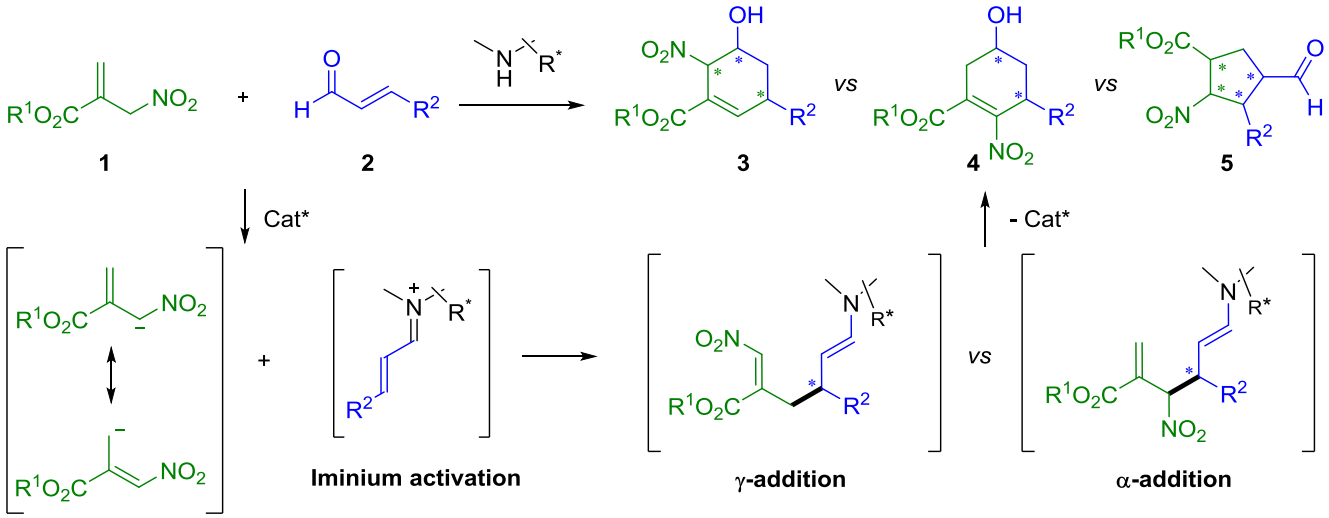
1. Introduction

The Henry reaction has been associated to the Michael addition in domino type transformations, since it is an useful tool to form C-C bonds and also allows the preparation of a wide range of structurally different compounds due to the ability of the nitro group to be transformed into other nitrogen and oxygen containing functionalities.[1] The application of this cascade reaction to the synthesis of optically active complex products is unquestionable and

the examples described in the literature show its remarkable applicability making it a highly efficient tool for obtaining functionalized products with total diastereo- and enantiocontrol employing different types of catalysts. In this sense, it should be highlighted the area of organocatalysis, where enamine and iminium activation together with H-bonding catalysis strategy enable to carry out Michael/Henry cascade reactions with high efficiency and an exceptional level of control of the stereocenters formed in most cases.[2]

In this context, and taking into account the experience acquired in our research group in the field of organocatalytic Michael/Henry reactions,[3] *we decided to focus our studies on developing a* ***Michael/Henry cascade process employing 2-nitromethylacrylates*** *as suitable functionalized Michael donors with α,β-unsaturated aldehydes under iminium activation* (Scheme 1).

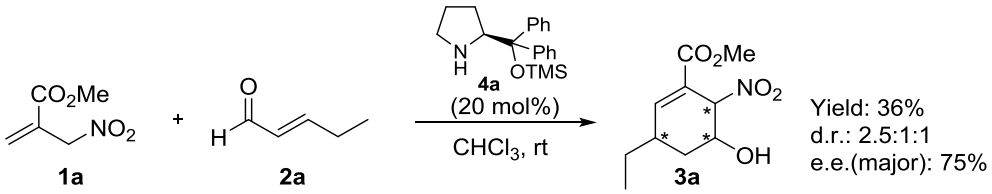
2-Nitromethylacrylates are expected to be active as carbon pronucleophiles in an initial Michael reaction because of the presence of two acidic protons in α position to the nitro group.[4] Moreover, the deprotonation of this compound **1** would lead to the generation of a resonance-stabilized allylic anion, with potential to react either at C-α or at C-γ position (Scheme 1). Assuming that the selected pronucleophile can undergo a conjugate addition to the iminium ion resulting from the condensation of the Michael acceptor –an α,β-unsaturated aldehyde **2**– and the aminocatalyst, the release of the catalyst after the initial Michael reaction would form a nitroaldehyde intermediate which is expected to undergo intramolecular Henry reaction in order to yield the desired product (compound **3** *vs* **4**). Nevertheless, we have to be aware of the fact that if the catalyst is not released from the resulting Michael addition product, another intramolecular conjugate addition can take place between the enamine and the remaining α,β-unsaturated ester moiety, leading to the formation of cyclopentanes **5** as shown in Scheme 1.



Scheme 1. Catalytic enantioselective Michael/Henry cascade reaction employing 2-nitromethylacrylates

2. Results and Discussion

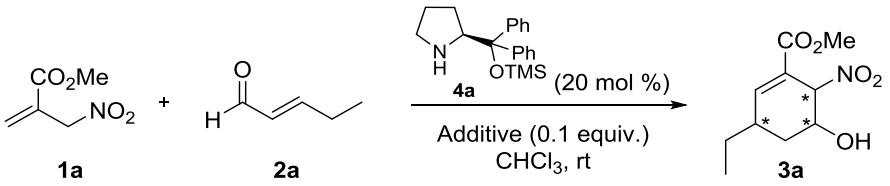
With this goal in mind, we surveyed the behavior of compound **1a** with *trans*-pentenal **2a** as model system in the presence of a chiral secondary amine catalyst. In a first attempt, we carried out the reaction using diphenylprolinoltrimethyl silyl ether **4a** as catalyst, in chloroform and at room temperature. When the compound **1a** was completely consumed, the ^{1}H-NMR of the crude reaction mixture revealed that the cyclohexene **3a** had been formed without observing other possible byproducts previously predicted (**4** or **5**). We concluded that the 2-nitromethylacrylate **1a** was behaving as a 1,3-dinucleophile, leading to the polysubstituted cyclohexene after performing the projected cascade reaction through initial selective γ-addition to the intermediate iminium ion derived from pentenal, followed by catalyst releasing and intramolecular Henry reaction. The compound **3a** was isolated by flash column chromatography in 36% yield as a mixture of three diastereoisomers (2.5:1:1), and with a 75% e.e. for the major diastereoisomer.

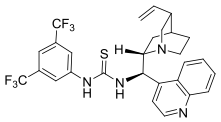
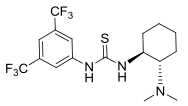


Scheme 2. Viability of the Michael/Henry reaction

These results made us explore the possibilities that this reaction could offer. The first parameter to study was the organocatalyst employed and therefore, we tested some different chiral secondary amines in the model reaction. Taking into account the high enantioselectivity achieved with prolinol derivative **4a**, we decided to use other diphenylprolinol derivatives with a bulkier *O*-protecting group and also diarylprolinol derivatives containing bulkier aryl substituents, but the reaction did not progress in any case and the starting materials were recovered in all cases. As the other catalysts tested did not show any activity, we decided to study the influence of the additive (Table 1). Some examples in the literature,[1a] made us think that Brønsted bases could be beneficial for the reaction, assuming that a base could help in the nucleophile formation by promoting the deprotonation of the substrate **1a**, and later on it could also assist the intramolecular Henry reaction. Fortunately, when bases such as DBU, 1,1,3,3-tetramethylguanidine, triethylamine and DMAP were used cyclohexene **3a** was selectively obtained (entries 2-5). The highest value regarding the yield was achieved with triethylamine but it showed poor diastereoselectivity (entry 4) and the best enantiocontrol was obtained employing DMAP although the yield was not good enough (entry 5).

Table 1. Influence of the additive in the cascade reaction.[a]



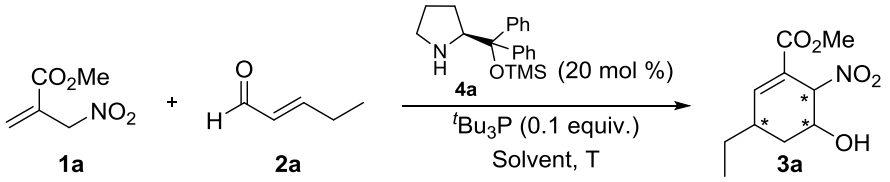
Entry	Additive	d.r.[b]	Yield (%)[c]	e.e. (%)[d]
1	-	2.5:1:1	36	36
2	DBU	2.5:1:1	34	86
3	1,1,3,3-Tetramethylguanidine	2.5:1:1	53	88
4	Et_3N	2:1.4:1	76	86
5	DMAP	2.4:1.2:1	43	90
6		5:2:1	40	88
7		3.3:1.7:1	29	79
8	Ph_3P	3.3:1:1.6	52	86
9	Bu_3P	2.5:1.7:1	33	90
10	$^tBu_3P$	2.5:1:1.5	74	88

[a] One equivalent of **1a** and two equivalents of aldehyde **2a** were used. [b] Determined by ^{1}H-NMR analysis for the mixture of diastereoisomers after flash column chromatography purification. [c] Referred to the mixture of diastereoisomers after flash column chromatography purification. [d] Calculated by HPLC for the major diastereoisomer.

Bifunctional Brønsted bases containing acidic H-donor sites were also tried as additives (entries 6-7) in order to evaluate their potential positive contribution to the reaction, but without giving better results than the ones obtained with triethylamine (entry 6). Finally, we decided to evaluate the use of phosphines as cocatalyst (entries 8- 10) and in this sense, the use of a bulky phosphine like $^tBu_3P$ gave the compound **3a** with good yield and an acceptable value of diastereomeric excess and the best enantioselectivity (entry 10). Moreover, it has to be pointed out that, in all cases the formation of other regioisomers was not detected by NMR analysis of the crude reaction mixture.

Selecting $^tBu_3P$ as the best additive, the optimization of the model reaction went on with the election of the most suitable solvent for the Michael/Henry transformation (Table 2). A battery of tests were run to evaluate the influence of different solvents, using polar as well as non-polar ones, and in a general view, the diastereo- and enantioselection of the cascade reaction was not influenced by the nature of the solvent (entries 1-7). The tests run revealed that chloroform (entry 1) remained being the most suitable solvent for the reaction in terms of overall yield and enantioselectivity. Finally, we tried to improve the diastereo- and enantiomeric ratio by lowering the temperature to -30ºC but the results previously obtained at rt could not be improved (entry 8).

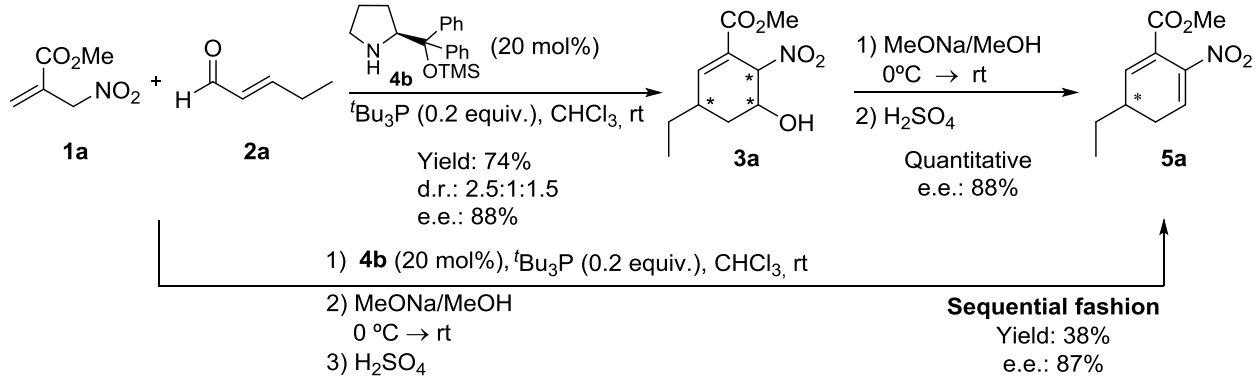
Table 2. Influence of the solvent and temperature in the cascade reaction.[a]



Entry	Solvent	T (ºC)	d.r.[b]	Yield (%)[c]	e.e. (%)[d]
1	$CHCl_3$	rt	2.5:1:1.5	74	88
2	Hexane	rt	2.5:1:1.5	58	86
3	Toluene	rt	2:1.8:1	36	88
4	THF	rt	10:0.7:1	40	87
5	AcOEt	rt	10:7:1	28	88
6	MeOH	rt	1.7:1.3:1	57	83
7	DMF	rt	2.5:1:1	40	87
8	$CHCl_3$	-30	2.5:1.5:1	30	86

[a] One equivalent of **1a** and two equivalents of aldehyde **2a** were used. [b] Determined by ^{1}H-NMR analysis for the mixture of diastereoisomers after flash column chromatography purification. [c] Referred to the mixture of diastereoisomers after flash column chromatography purification. [d] Calculated by HPLC for the major diastereoisomer.

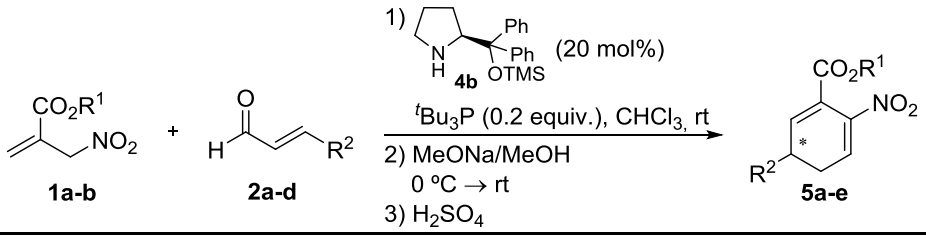
The poor diastereoselectivity achieved in all reactions might lay in the second step of the cascade reaction. Taking into account that the C-3 stereocenter that comes from the Michael addition of the nucleophile to the iminium ion is expected to be efficiently controlled by the catalyst, it seems sensible to think that the lack of stereogenic control derives from the intramolecular Henry reaction in which the stereocenters C-5 and C-6 are created, after the release of the organocatalyst. Aware of this diastereoselection problem, we thought about possible transformations that could lead to a convenient process in which all diastereoisomers would converge into a single product. The dehydration of the cyclohexene **3a**, obtaining cyclohexadiene **5a** seemed a promising way to eliminate two sterocenters and to simplify the structure of the compound, maintaining the stereocenter created at the initial Michael reaction step. Therefore, a dehydration reaction was carried out, employing sodium methoxyde in methanol observing that the reaction took place in a quantitative way, and fortunately, being possible to carry out in a sequential fashion in an efficient manner (Scheme 3).



Scheme 3. Chemical manipulation of adduct **3a**

With those results in our hands we decided to evaluate the importance of the substitution of the enals used as Michael acceptors and the substitution of the acrylate **1**, in order to see the influence of this substitution, in the sequential Michael/Henry/dehydration reaction. As it can be seen in Table 3, overall yields obtained were around 30-40% in all cases in which linear aliphatic substituents were present at the β-position of the enal regardless the length of the chain. On the other hand, the enantiomeric excesses increased when longer chains were introduced (entries 1-3). In contrast, when a bulkier element, such as an ^{i}Pr group, was placed at the β position of the α,β-unsaturated aldehyde (entry 4) the yield decreased drastically although the enantioselection was very high. Similarly when the bulkier acrylate **1b** was employed a poor yield of compound **5e** was achieved although in very good enantiomeric excess.

Table 3. Sequential Michael/Henry/dehydration reaction.[a]



Entry	R^1	Acrylate	R^2	Enal	Product	Yield (%)	e.e. (%)[b]
1	Me	**1a**	Et	**2a**	**5a**	38	87
2	Me	**1a**	Me	**2b**	**5b**	32	85
3	Me	**1a**	^{n}Bu	**2c**	**5c**	33	92
4	Me	**1a**	^{i}Pr	**2d**	**5d**	17	93
5	^{i}Bu	**1b**	Et	**2e**	**5e**	12	88

[a] One equivalent of **1a-b** and two equivalents of aldehyde **2a-d** were used. [b] Calculated by HPLC after flash column chromatography purification.

In a plausible mechanism proposed, a Michael addition of the deprotonated 2-nitromethylacrylate **1** to the iminium ion resulting from the fusion between the aminocatalyst **4a** and the α,β-unsaturated aldehyde **2**, would take place. After the catalyst

is released, an intramolecular Henry cyclization occurs, achieving the cyclohexenes **3** which would undergo a sequential dehydration step to provide the corresponding cyclohexadienes **5**.

3. Materials and Methods

General procedure for the Michael/Henry cascade reaction: The α,β-unsaturated aldehyde **2a** (0.50 mmol) was added to a solution of (*S*)-α,α-diphenyl-2-pyrrolidinemethanol trimethylsilyl ether **4a** (0.05 mmol), tri-tertbutylphosphine (0.05 mmol) and acrylate **1a** (0.25 mmol) in chloroform (2 mL). The reaction was stirred at room temperature until full conversion. Afterwards the reaction mixture was diluted in diethyl ether (10 mL) and washed with $NaHCO_3$ (1 × 8 mL), brine (2 × 8 mL) and H_2O (2 × 8 mL). The organic extracts were dried over anhydrous Na_2SO_4 and the solvent was evaporated under vacuum. The crude was charged onto silica gel and subjected to flash column chromatography to obtain the cyclohexenes **3a**.

General procedure for the Sequential Michael/Henry/dehydration reaction: The α,β-unsaturated aldehyde **2a-d** (0.50 mmol) was added to a solution of (*S*)-α,α-diphenyl-2-pyrrolidinemethanol trimethylsilyl ether **4a** (0.05 mmol), tri-*tert*butylphosphine (0.05 mmol) and the acrylate **1a-b** (0.25 mmol) in chloroform (2 mL). The reaction was stirred at room temperature until full conversion. The solvent was evaporated under reduced pressure and after dissolving the reaction crude in dry MeOH (2 mL) it was added *via* canula to a solution of metallic sodium (2 mmol) in MeOH (4 mL) at 0 ºC. The reaction mixture was allowed to reach room temperature and stirred it for 1 hour. Then a solution of H_2SO_4/MeOH (1:5) was added until pH≈5 was achieved and the solvent was evaporated under vacuum. H_2O (20 mL) and CH_2Cl_2 (20 mL) were added and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The organic extracts were dried over anhydrous Na_2SO_4 and the solvent was evaporated under vacuum. The crude was charged onto silica gel and subjected to flash column chromatography in order to achieve compound **5a-e**.

4. Conclusions

To sum up, we have developed a methodology that involves an organocatalytic Michael/Henry cascade reaction under iminium activation between enals and 2-nitromethylacrylates **1a-c**. The selected Michael donor, 2-nitromethylacrylate, has proved to be a suitable starting material for the reaction, acting as an appropriate 1,3-dinucleophile and has reacted with α,β-unsaturated aldehydes stereocontrolled by α,α-diphenylprolinol *O*-silylated catalyst, but showing poor diastereoselectivity.

In order to avoid this problem, we have designed a methodology involving Michael/Henry cascade reaction followed by a sequential dehydration leading to the enantiopure cyclohexadienes **5a-e** in a moderate yield but good enantioselectivity.

Acknowledgments

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Conflicts of Interest

The authors declare no conflict of interest.

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