Highly enantioselective organocatalytic Michael addition of nitroalkanes to 4-oxo-enoates†

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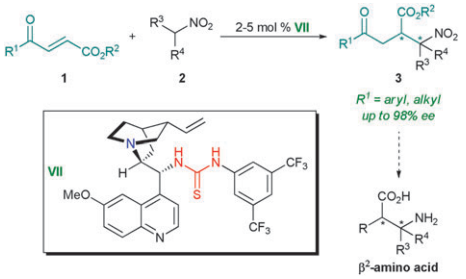
A useful Michael addition reaction using nitroalkanes as the nucleophile and 4-oxo-enoates as the Michael acceptor has been disclosed, and the reaction allows expedient access to functionalized chiral γ-keto esters in high yields and excellent enantioselectivities (up to 98% ee), with a low catalyst loading.

The conjugate addition of carbon nucleophiles to activated unsaturated systems has become a classic and fundamental bond-forming reaction in organic synthesis since its discovery in 1887.[1] The broad spectrum of potential donors and acceptors makes this reaction exceptionally versatile and a wide range of synthetically useful adducts bearing various functional groups can be generated. In this context, the employment of nitroalkanes as a nucleophilic donor has drawn enormous attention from the chemical community[2] because of the easy manipulation of the nitro functionality into amines (reduction), hydrides (radical denitration), aldehydes, ketones (Nef reaction), and other valuable building blocks.[3] While numerous efficient nitro-Michael reactions have been developed and widely applied in the synthesis of complex targets, developing catalytic asymmetric variants continues to be an important challenge.

Recently, highly enantioselective nitro-Michael additions with enones,[4] enals,[5] nitroalkenes,[6] and α,β-unsaturated amides[7] and esters,[8] were accomplished by either metallic catalysis or organocatalysis.[9] Despite advances being made, issues concerning substrate dependence, reaction efficiency and selectivity remain elusive; the intrinsic potential of the nitro-Michael reaction has not been fully achieved compared with its parallel nitro-aldol[10] or nitro-Mannich reactions.[11] The development of highly enantioselective nitro-Michael additions of novel unsaturated systems with multifunctional groups and their transformations to synthetically valuable compounds is highly desirable. In this communication, we present an organocatalytic nitro-Michael addition of nitroalkanes to 4-oxo-enoates by means of acid–base catalysis, a nice combination to generate chiral γ-keto esters with complete regioselectivity and high enantioselectivity



Scheme 1 Asymmetric nitro-Michael additions with 4-oxo-enoates.

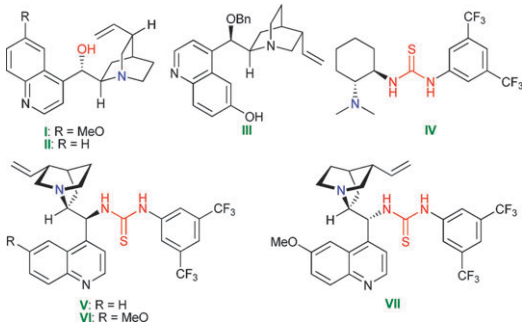


Fig. 1 The bifunctional organocatalysts examined in this study.

(up to 98% ee),[12] further manipulations of which would lead to optically active β²-amino acids (Scheme 1).[13,14]

Our investigations started with the reaction between (*E*)-ethyl-4-phenyl-4-oxo-but-2-enoate (**1a**) and nitromethane (**2a**), and the best result (12 h, 95% yield and 96% ee) was obtained with 5 mol% of bifunctional *Cinchona* alkaloid-based thiourea catalyst **VII** (see Fig. 1) in xylenes at ambient temperature (Table 1, entry 15).[15]

With optimal conditions in hand, we then evaluated the generality of this protocol and the results are summarized in Table 2. As shown in entries 1–4, the reaction appears quite general with respect to the ester group of 4-oxo-enoates. This reaction is general with respect to the benzene architecture of 4-oxo-enoates as well. The steric properties of the aryl 4-oxo-enoates have a minimal impact on the stereoselectivity (entries 5–8). Moreover, further decreasing the catalyst loading, from 5 mol% to 2 mol% of **VII**, is feasible with no influence on the enantio-outcome (entry 5 *vs.* 6). Variation in the electronic nature of the aromatic ring systems is possible. Relatively electron-neutral (entries 1–4), electron-withdrawing (entries 5–8 and 12–16) or electron-donating groups (entries 9–11) on the benzene ring can be tolerated. Other 4-heteroaryl-4-oxo-but-2-enoates can be also employed in this

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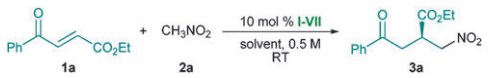
Table 1 Asymmetric Michael additions of nitromethane (**2a**) to (*E*)-ethyl-4-phenyl-4-oxo-but-2-enoate (**1a**) under various conditions[a]



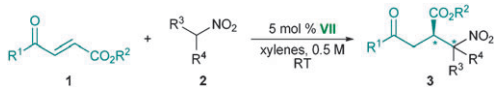
Entry	Catalyst	Solvent	*t*/h	Yield (%)[b]	Ee (%)[c]
1	**I**	Toluene	6	86	−53
2	**II**		90	38	−52
3	**III**		90	23	−70
4	**IV**		6	90	−80
5	**V**		5	91	−80
6	**VI**		5	88	91
7	**VII**		5	87	96
8	**VII**	Xylenes	6	90	96
9		Mesitylene	24	91	96
10		Hexane	5	84	93
11		Et_2O	24	83	95
12		*i*-PrOH	24	78	84
13		Neat	3	86	93
14		H_2O	4	85	88
15[d]		Xylenes	12	95	96

[a] Reactions were carried out with **1a** (0.25 mmol), nitromethane **2a** (1.25 mmol) and catalyst **I–VII** (10 mol%) in solvent (0.5 mL) at RT. [b] Isolated yield. [c] Determined by chiral HPLC. [d] 5 mol% of **VII** was used. RT = room temperature.

reaction with excellent results being obtained (entries 17 and 18). Notably, less active 4-alkyl substituted 4-oxo-enoate **1r** can be used as a Michael acceptor for this transformation, and the corresponding adduct, **3r**, was obtained in 80% ee (entry 19). Perhaps more importantly, nitroalkanes other than nitromethane, can be used as Michael donors in this addition. Preliminary experiments with nitroethane (**2b**) and ethyl 2-nitropropionate (**2c**) revealed that the corresponding products were effectively obtained in high yields and great enantioselectivities, with moderate diastereoselectivities (entries 20 and 21). It is worth noting that adjacent quaternary and tertiary stereocentres were constructed in the latter case. To determine the absolute configuration of the product, **3n** was obtained as a white crystal from a mixture of hexane and ethyl acetate. The absolute configuration of the newly formed stereocentre in compound **3n** was then unambiguously determined to be *R* by X-ray crystallographic analysis (Fig. 2).[16]

β-Amino acids are common units found in natural products and pharmaceuticals.[13] Recent studies have revealed that many peptides containing β-amino acid residues show well-defined secondary structures and display useful biological activities. However, to date, only β^3-amino acids are commercially available with a broad spectrum of substituents. In contrast, β^2-amino acids seem harder to prepare and their synthesis remains a challenge.[14] In principle, the current protocol could be used as the key step for the synthesis of β^2-amino acids. Accordingly, **3a**, **3d** and **3h** were, respectively, prepared in the presence of 3 mol% of **VII** on gram scales (Scheme 2 and eqn 1). Keto protection of **3a** and **3d** were accomplished either with glycol or 1,2-ethanedithiol. Following known procedures, one-pot desulfurization and hydrogenation of **5** by the classical RANEY® nickel method would afford (*S*)-2-(aminomethyl)-4-phenyl-butanoic acid (**6**).[17] Meanwhile, a two-step sequence, $NiCl_2{\cdot}6H_2O$–$NaBH_4$

Table 2 Organocatalytic asymmetric Michael addition reactions of nitroalkanes **2** with 4-oxo-enoates **1** by catalyst **VII**[a]



Entry	R^1	R^2	R^3	R^4	Yield (%)[b]		Ee (%)[c]
1	Ph	Et	H	H	**3a**	95	96
2	Ph	Me	H	H	**3b**	89	96
3	Ph	*i*-Pr	H	H	**3c**	97	96
4	Ph	Bn	H	H	**3d**	98	96
5	*p*-NO_2Ph	Et	H	H	**3e**	94	97
6[d]	*p*-NO_2Ph	Et	H	H	**3e**	78	97
7	*m*-NO_2Ph	Et	H	H	**3f**	95	98
8	*o*-NO_2Ph	Et	H	H	**3g**	65	91
9	*p*-MeOPh	Et	H	H	**3h**	84	98
10	*m*-MeOPh	Et	H	H	**3i**	91	94
11	*p*-MePh	Et	H	H	**3j**	93	96
12	*p*-FPh	Et	H	H	**3k**	93	96
13	*p*-ClPh	Et	H	H	**3l**	96	97
14	*p*-BrPh	Et	H	H	**3m**	91	97
15	*p*-BrPh	Bn	H	H	**3n**	85	97
16	*m*-BrPh	Et	H	H	**3o**	90	97
17	2-Furanyl	Et	H	H	**3p**	92	97
18	2-Thienyl	Et	H	H	**3q**	86	98
19[e]	*t*-Bu	Et	H	H	**3r**	47	80
20[f]	Ph	Et	H	Me	**3s**	89	97, 96
21[g]	Ph	Et	Me	CO_2Et	**3t**	99	68, 92

[a] Reactions were carried out with 4-oxo-enoates **1** (0.25 mmol), nitroalkanes **2** (1.25 mmol, **2a**: R^3 = R^4 = H; **2b**: R^3 = CH_3, R^4 = H; **2c**: R^3 = CH_3, R^4 = CO_2Et) and catalyst **VII** (5 mol%) in xylenes (0.5 mL) at RT. [b] Isolated yield. [c] Determined by chiral HPLC. [d] 2 mol% of **VII** was used. [e] 10 mol% of **VII** was used. [f] d.r. = 65 : 35. [g] d.r. = 81 : 19. d.r. = diastereomeric ratio.

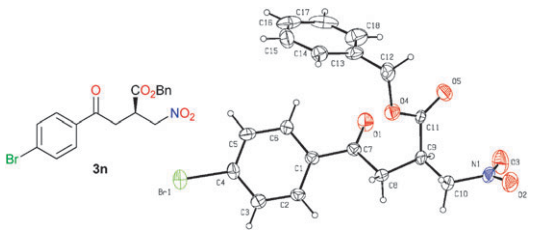
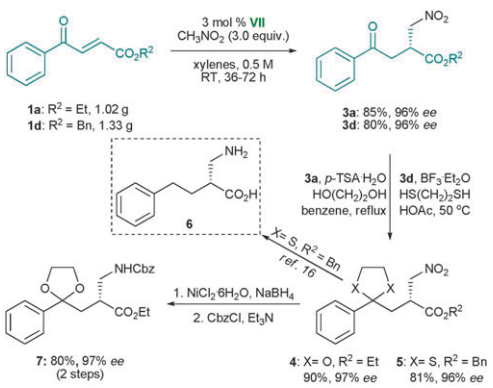


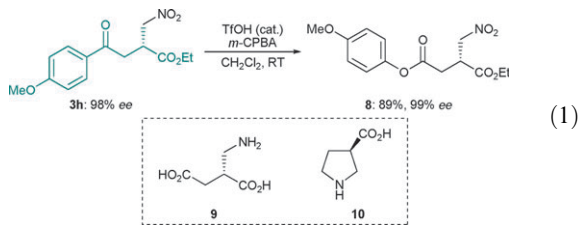
Fig. 2 X-Ray crystal structure of nitro-Michael adduct **3n**.



Scheme 2 Synthesis of β^2-amino acid derivatives.

reduction and subsequent amine protection, provided the desired product **7** in 80% yield. In addition, by subjecting **3h** to Baeyer–Villiger conditions, we successfully obtained

succinate **8**, a valuable precursor for the synthesis of (*R*)-2-(aminomethyl)butanedioic acid (**9**)[18a] and β-proline (**10**).[18] Note that all transformations afforded the corresponding products without loss in optical purity.



(1)

In summary, we have developed a nitro-Michael reaction with 4-oxo-enoates in excellent enantioselectivities and demonstrated its value in the expedient synthesis of β^2-amino acid derivatives. The reaction itself is completely atom-economic and involves simple experimental procedures under benign conditions with low loadings of a bench-stable catalyst.

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