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Activation of 1,2-Keto Esters with Takemoto's Catalyst toward Michael Addition to Nitroalkenes

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Abstract: When activated with Takemoto's catalyst, 1,2-keto esters constitute versatile nucleophiles in the Michael addition reaction with nitroalkenes affording synthetically valuable, optically active *anti*-adducts in very good yields and high enantiomeric excesses.

Keywords: asymmetric organocatalysis; 1,2-keto esters; Michael addition; pronucleophiles; Takemoto's catalyst

The Michael addition is one of the most important ways to create C–C bonds in organic synthesis.[1] The last ten years have witnessed the emergence of organocatalysis which is now often employed to develop new stereoselective Michael additions.[2] Nitroalkenes are particularly attractive acceptors because of their high reactivity and thanks to the nitro group, qualified as the "synthetic chameleon",[3] which can be easily transformed into various functionalities.[4] Hence, functionalized Michael adducts represent very useful building blocks[5] or may also be involved in subsequent transformations allowing the development of complex domino processes.[6,7]

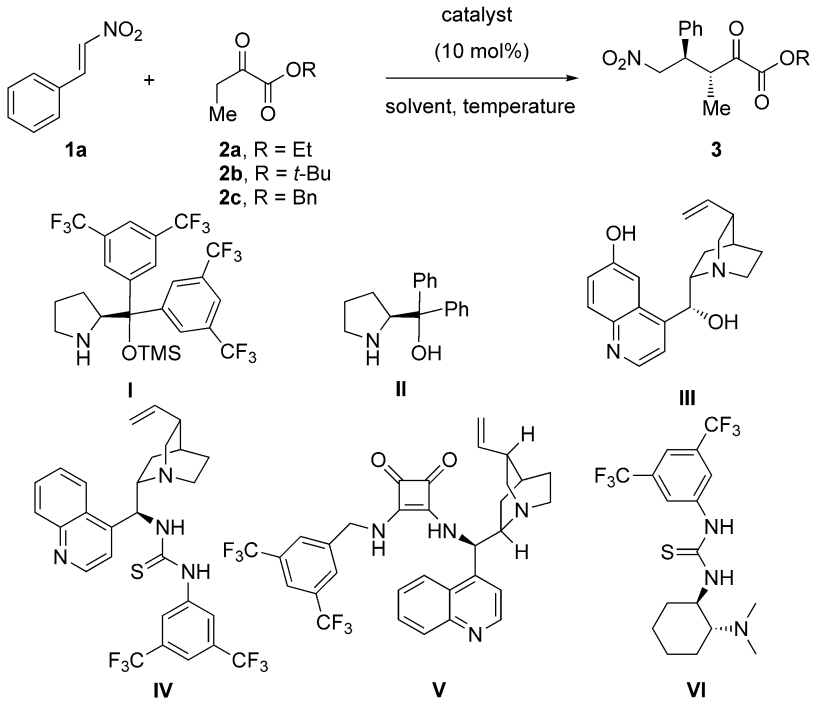
In continuation to our ongoing studies on conjugate additions to nitroolefins,[8] we became interested in the challenging reactivity of α-keto esters as pronucleophiles in organocatalyzed Michael reactions since no example of such a transformation has been reported so far.[9,10] Our own interest in the activation of 1,2-dicarbonyl compounds[11] and the very recent report from Terada and co-workers on an unprecedented enantioselective organocatalyzed amination of α-keto esters using an axially chiral guanidine base,[12] prompted us to disclose our preliminary contributions to this emerging field.

To accomplish this goal, we envisioned a simple methodology involving activation by a bifunctional organocatalyst with nitroalkenes as reactive acceptors. We reasoned that these olefins would act as more powerful electrophiles compared to 1,2-keto esters[13] which should then behave as pronucleophiles. The competitive self-condensation reaction would then be disfavored.[14] Besides, the final Michael adducts would possess very high synthetic potential given their dense and diverse functionalities.

We first selected β-nitrostyrene (**1a**) and ethyl 2-oxobutanoate (**2a**) as model substrates to examine the role of the organocatalyst and the best activation mode (Table 1, entries 1–5).

Catalyst **I**[15] proved to be unsuitable for this transformation affording the product in very low yield (10%) although a good diastereomeric ratio was obtained (entry 1). The use of (*S*)-diphenylprolinol **II**[16] with an extra H-bonding site gave the product in low yield with good diastereoselectivity (entry 2). Catalyst **III**, which was efficient in organocatalyzed enantioselective Michael additions with malonate nucleophiles,[8c,17] gave a low yield and a low selectivity (entry 3). More elaborated *Cinchona*-alkaloid derived catalysts **IV** and **V** bearing either the thiourea[18] or the squaramide[19] subunits proved to be efficient providing the product in good yield and acceptable selectivities (entries 4 and 5). Finally, we found that the Takemoto's catalyst **VI**,[20] when used in EtOAc was the most efficient (entry 7), and it was chosen for the following optimization experiments.[21] While the *tert*-butyl ester **2b** afforded the product **3b** in lower diastereoselectivity (entry 8), the use of the benzyl ester **2c** allowed the formation of **3c** in a promising 7:1 *anti*:*syn* ratio and 88% *ee* (entry 9). Finally, decreasing the temperature to 0 °C (entry 10) had a positive impact

Table 1. Optimization of the reaction conditions.[a]



Entry	Catalyst	Temperature	Solvent	2	3	Yield[b] [%]	*dr*[c,d] (*anti*/*syn*)	*ee*[e,f] [%]
1	**I**	r.t.	toluene	**2a**	**3a**	10	7:1	nd
2	**II**	r.t.	toluene	**2a**	**3a**	15	10:1	nd
3	**III**	r.t.	toluene	**2a**	**3a**	18	2:1	nd
4	**IV**	r.t.	toluene	**2a**	**3a**	82	4:1	77
5	**V**	r.t.	toluene	**2a**	**3a**	75	9:1	87
6	**VI**	r.t.	toluene	**2a**	**3a**	77	2:1	89
7	**VI**	r.t.	EtOAc	**2a**	**3a**	91	3.5:1	80 [87]
8	**VI**	r.t.	EtOAc	**2b**	**3b**	95	2:1	93 [96]
9	**VI**	r.t.	EtOAc	**2c**	**3c**	90	7:1	88
10	**VI**	0 °C	EtOAc	**2c**	**3c**	85	9:1	92
11	**VI**	−35 °C	EtOAc	**2c**	**3c**	75	8:1	93

[b] β-Nitrostyrene (**1a**) (0.2 mmol), keto ester **2** (0.4 mmol), solvent (0.4 mL) for 18 h.
[b] Isolated yield after column chromatography.
[c] Determined by ^{1}H NMR analysis of the crude reaction product.
[d] The relative and absolute stereochemistries of the Michael adducts were determined by comparison with reported literature data.[9e,f]
[e] Determined by chiral HPLC analysis.
[f] Values in brackets are for the minor enantiomer.

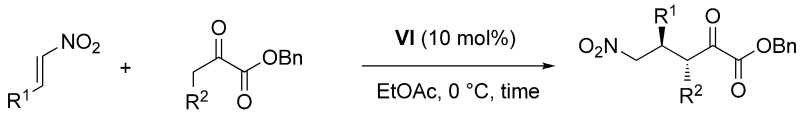
on selectivities albeit in slightly lower yield which was confirmed by reaction at −35 °C (entry 11).

Our methodology was then tested by varying both the nitroalkene **1** and the benzyl keto ester **2** using the optimized reaction conditions (Table 2). With an extra carbon on the keto ester (**2d**, R^2 = Et instead of R^2 = Me in **2c**) the diastereoselectivity was greatly improved (>20:1, entry 1) with equally excellent yield and enantioselectivity.

In the case of aromatic compounds (entries 1–5) including *ortho*-substituted phenylnitroalkenes (entries 4 and 5) and heteroaromatic nitroalkenes (entries 6–8), the reaction proceeded with very good yields and selectivities with no significant effect of the substitution although a longer reaction time was required when 3-indolyl-substituted nitroalkene **1h** was employed.

Interestingly, and in sharp contrast with other Michael additions,[22] aliphatic nitroalkenes including iodoalkane **1k**, are suitable substrates affording the Michael adducts with comparable selectivities although a lower yield was generally obtained (entries 9 and 13) and longer reaction times were required.[23] Hindering the nucleophilic carbon of the keto ester by using

Table 2. Scope of the conjugate addition.[a]



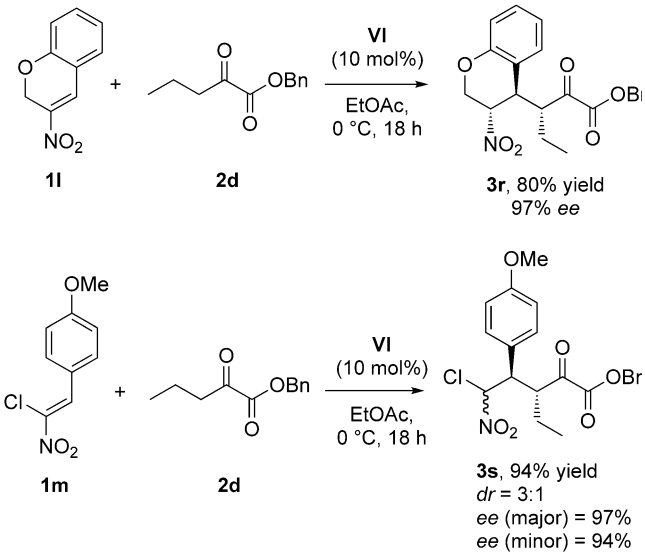
Entry	R^1	1	2	3	Time [h]	Yield[b] [%]	*dr*[c] (*anti*/*syn*)	*ee*[d] [%]
1	Ph	**1a**	**2d**	**3d**	18	89	>20:1	94
2	4-$MeOC_6H_4$	**1b**	**2d**	**3e**	18	84	>20:1	94
3	4-$O_2NC_6H_4$	**1c**	**2d**	**3f**	18	88	>20:1	94
4	2-BrC_6H_4	**1d**	**2d**	**3g**	18	98	>20:1	97
5	2-$O_2NC_6H_4$	**1e**	**2d**	**3h**	18	99	>20:1	98
6	2-thienyl	**1f**	**2d**	**3i**	18	88	>20:1	95
7	3-furanyl	**1g**	**2d**	**3j**	18	72	>20:1	94
8	3-indolyl	**1h**	**2d**	**3k**	72	89	>20:1	94
9	$PhCH_2CH_2$	**1i**	**2d**	**3l**	18	55	>20:1	94
10	Ph	**1a**	**2e**	**3m**	36	36	>20:1	91
11	4-BrC_6H_4	**1j**	**2e**	**3n**	72	41	>20:1	90
12	Ph	**1a**	**2f**	**3o**	18	70	>20:1	80
13	ICH_2CH_2	**1k**	**2f**	**3p**	96	44	>20:1	90
14[e]	Ph	**1a**	**2g**	**3q**	18	87	>20:1	93

[a] *Standard conditions:* nitroalkene **1** (0.2 mmol), keto ester **2** (0.4 mmol) in EtOAc (0.4 mL) at 0 °C.
[b] Isolated yield after column chromatography.
[c] Determined by ^1H NMR analysis of the crude reaction product.
[d] Determined by chiral HPLC analysis.
[e] Reaction performed with 1 mmol of **1a**.

branched keto ester **2e** (entries 10 and 11) or phenyl-substituted keto ester **2f** (entries 12 and 13) slowed down the reaction and had a detrimental effect on the reaction yield. However, in these four cases, both the diastereoselectivity and the enantioselectivity remain excellent.[24] Finally, the use of the benzyl 2-oxo-hex-5-enoate (**2g**) led to the clean formation of the expected allylic functionalized Michael adduct **3q** (entry 14) with very good yield and excellent stereoselectivities.

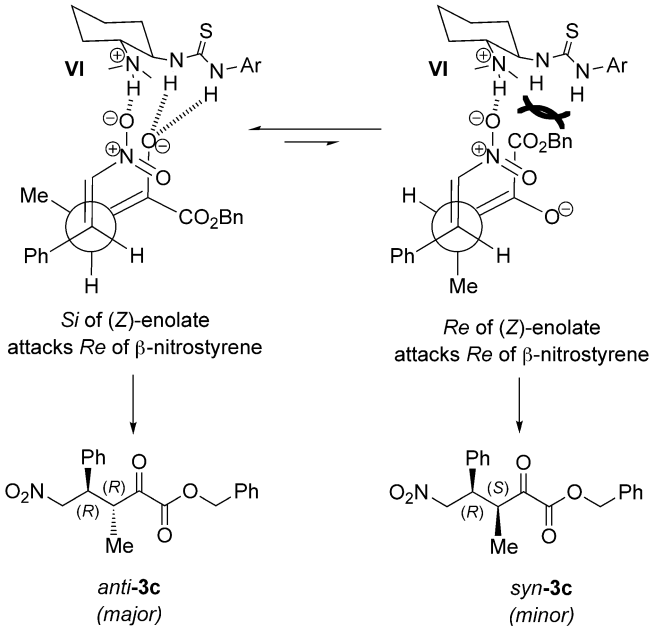
The present methodology was then applied to two challenging α-substituted nitroalkenes **1l** and **1m** as electrophiles (Scheme 1). The use of α-substituted nitroalkenes is relatively limited in organocatalyzed enantioselective Michael addition probably due to the facile retro-Michael reaction.[25] Usually, the Michael adducts are not isolated but "siphoned" in subsequent domino transformations. Gratifyingly, in the first case we were pleased to obtained the desired adduct **3r** bearing an *anti*:*anti* stereo-triad in 80% yield with a total diastereocontrol and 97% *ee*.[26] The α-chloronitroolefin **1m** was also very reactive leading to a 3/1 mixture of only two diastereomers of **3s** in 94% yield and high enantiomeric excess for both diastereomers.

The transition states depicted in Scheme 2 could account for both relative and absolute stereochemistries

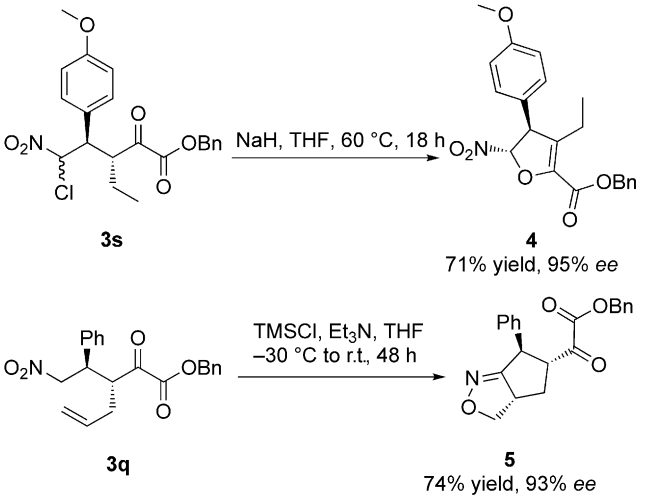


Scheme 1. Michael addition of α-keto esters onto α-substituted nitroalkenes.

observed in the Michael adducts. Following Pápai's model,[27] the protonated tertiary amine of catalyst **VI** binds to the nitro function, hence enhancing the electrophilic character of the nitroalkene, whereas the



Scheme 2. Proposed transition states for the Michael addition.



Scheme 3. Transformations of Michael adducts into hetero- and carbocycles.

thiourea moiety binds to the strongly polarized enolate. In the resulting conformationally restrained environment, the *Si* face of the thermodynamic (*Z*)-enolate[28] preferentially attacks the *Re* face of the nitroalkene accounting for the formation of the *anti*-(*R*,*R*)-Michael adduct. The formation of the *syn* Michael adduct **3c** which would come from the *Re* face attack of the (*Z*)-enolate is minor (*syn:anti* < 1:20). In this transition state, the binding of the thiourea moiety to the enolate is disfavored because of the strong steric interaction between the benzylic ester function and the catalyst.[29]

In order to prove the synthetic usefulness of our methodology, we carried out several transformations of the Michael adducts allowing the formation of various interesting building blocks with increased molecular complexity (Scheme 3). It has already been shown in the literature that these Michael adducts could be easily reduced to the corresponding pyrrolidines.[9e–g] Alternatively, under basic conditions, the Michael adduct **3s** was cleanly converted to the *trans* dihydrofuran **4** with a total chirality transfert.[30,31] Finally, using the conditions we developed previously,[8a,c] **3q** was converted to the highly functionalized five-membered carbocycle **5** bearing three stereogenic centers with good yield and excellent diastereocontrol.

In conclusion, we have developed the first efficient Takemoto's catalyst-promoted activation of 1,2-keto esters in an enantioselective Michael addition with nitroalkenes. The method is simple and can be applied to many substrates with excellent yields and selectivities. Moreover the versatility of the condensation has been demonstrated with the easy transformation of the Michael adducts to five-membered carbo- and heterocyles with the creation and control of additional stereocenters.

Experimental Section

General Procedure for the Enantioselective Michael Addition

Catalyst **VI** (10 mol%) was added to a solution of nitroalkene (0.2 mmol, 1.0 equiv.) and α-keto ester (0.4 mmol, 2.0 equiv.) in EtOAc (0.4 mL) at 0 °C. The reaction mixture was stirred until complete conversion of the starting materials (monitored by TLC). Purification by flash column chromatography (silica gel, petroleum ether/AcOEt) afforded the pure Michael adduct. The *anti*/*syn* diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude mixture and the enantiomeric excess (*ee*) was determined by HPLC analysis on a chiral phase.

(3*R*,4*R*)-Benzyl 3-Ethyl-5-nitro-2-oxo-4-phenylpentanoate (3d)

This compound was isolated as a white solid; yield: 63 mg (89%); mp 75–77 °C; R_f = 0.47 (ethyl acetate/petroleum ether = 1:4); *dr anti*/*syn* > 20:1; HPLC (Chiralpak IC, hexane/*i*-PrOH = 80/20, flow rate = 1.0 mL min^{-1}, λ = 254 nm): t_{major} = 12.47 min, t_{minor} = 7.83 min, *ee* = 94%; $[\alpha]_D^{22}$: +13.2 (*c* = 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.34 (3H, m, ArH), 7.29–7.27 (2H, m, ArH), 7.23–7.20 (3H, m, ArH), 5.14 (1H, d, *J* = 12.1 Hz, C*H*$_2$Ph), 5.10 (1H, d, *J* = 12.1 Hz, C*H*$_2$Ph), 4.71 (1H, dd, *J* = 12.8, 5.4 Hz, C*H*$_2$NO$_2$), 4.66 (1H, dd, *J* = 12.8, 9.4 Hz, C*H*$_2$NO$_2$), 3.85 (1H, ddd, *J* = 9.4, 9.4, 5.4 Hz, PhC*H*), 3.74 (1H, ddd, *J* = 9.4, 9.4, 3.7 Hz, C*H*C=O), 1.84 (1H, ddq, *J* = 13.5, 9.4, 7.4 Hz, C*H*$_2$CH$_3$), 1.73 (1H, dqd, *J* = 13.5, 7.4, 3.7 Hz, C*H*$_2$CH$_3$), 0.88 (3H, t, *J* = 7.4 Hz, CH$_2$C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.1, 160.6, 136.8, 134.1, 129.0 (2C), 128.8, 128.7 (2C),

128.6 (2C), 128.1, 128.0 (2C), 77.7, 68.1, 51.5, 44.7, 22.2, 11.3; MS (ES+): $m/z = 373.1759$, calcd. for $C_{20}H_{25}N_2O_5$ $[M+NH_4]^+$: 373.1758].

Acknowledgements

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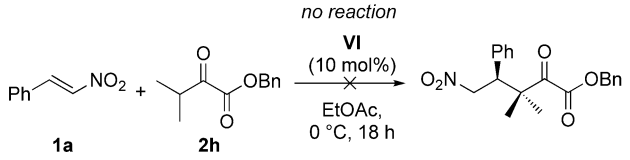
[24] Further increasing the steric hindrance of the nucleophilic center by using α,α-disubstituted keto ester **2h** resulted in complete inhibition of the reaction.



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