Unsaturated β-ketoesters as versatile electrophiles in organocatalysis†

Susy Piovesana, Daniele M. Scarpino Schietroma, Ludovico G. Tulli, Mattia R. Monaco and Marco Bella*

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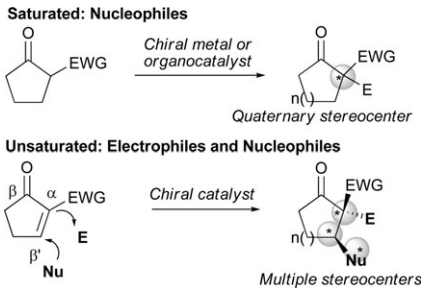
β-Ketoesters, which have widely been employed as nucleophiles, are also useful electrophiles in organocatalytic quinine mediated cascade reactions, leading to the formation of products bearing multiple stereocenters in high stereoselectivity.

Great advance has been achieved in the last few years in the field of asymmetric organocatalyzed cascade reactions, where several stereocenters are formed in one-pot operations and densely functionalized molecules are cast at once with excellent control of the relative and absolute stereochemistry.[1] These fascinating and valuable transformations are mostly mediated by secondary amines; a good number exploits as the catalyst proline or Jørgensen–Hayashi TMS-prolinol,[2] *via* the well known enamine/iminium ion activation.[3] The formation of multiple stereocenters employing tertiary amines, such as the *Cinchona* alkaloid derivatives, is less frequent; some examples are reported by Deng and co-workers, who employed the bifunctional cupreine catalyst derivatives, and by other authors.[4] In these works, the absolute and relative configuration of two stereocenters is controlled within a single reactive event.

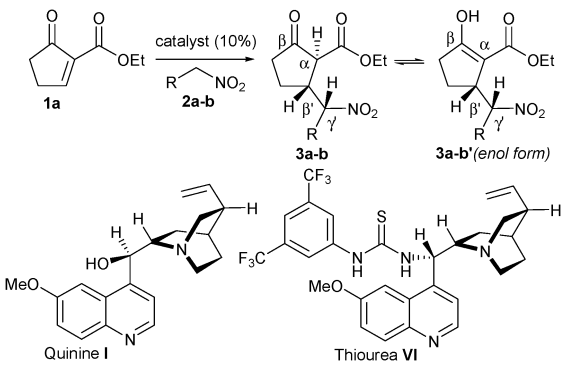
β-Ketoesters, when employed as nucleophiles, can be functionalized by organometal[5] or organic[6] catalysts, leading to highly stereoselective reactions. The first example (proof of concept) of an asymmetric reaction employing a new electrophile is often performed with β-ketoesters as nucleophiles and they are among the mostly exploited substrates for the asymmetric construction of quaternary stereocenters.[7] Here we show that α,β′-unsaturated β-ketoesters[8] are also useful electrophiles in a quinine mediated transformation, where multiple stereocenters are formed in good stereoselectivity (Scheme 1). Cyclic unsaturated β-ketoesters have been recently employed in asymmetric metal catalyzed reactions by Shizuka and Snapper in 2008[9a] and Schotes and Mezzetti in 2010;[9b] Scheidt *et al.* reported in 2007 the intramolecular ring closure of phenols onto unsaturated β-ketoesters.[9c]

Our investigation commenced by reacting nitromethane **2a** with β-ketoester **1a**. In the first attempt, conducted at rt, we isolated in high yield the nitro Michael adduct **3a**, with 79% ee under the non-optimized conditions (Table 1, entry 1). The ^{1}H-NMR spectra showed the presence of both the enol and keto form of **3a**, the keto form as a single diastereoisomer (*trans* relationship between protons in the α and β′ positions, respectively).



Scheme 1 β-Ketoesters as substrates for asymmetric catalysis.

Table 1 Screening of catalysts and solvents for the addition of nitroalkanes **2a–b** to α,β′-unsaturated β-ketoester **1a**



Entry[a]	R	Catalyst	Solvent	T/°C	Y[b] (%)	dr[c]	ee[c] (%)
1	H, **2a**	Quinine **I**	DCM	Rt	92	—	79
2	H, **2a**	Cinchonine **II**	DCM	Rt	91	—	67
3	H, **2a**	$[DHQ]_2PHAL$ **III**	DCM	Rt	86	—	32
4	H, **2a**	$[DHQ]_2PYR$ **IV**	DCM	Rt	90	—	32
5	H, **2a**	DHQ **V**	DCM	Rt	92	—	78
6	H, **2a**	Quinine **I**	MeOH	Rt	82	—	30
7	H, **2a**	Quinine **I**	Et_2O	Rt	92	—	80
8	H, **2a**	Quinine **I**	EtOAc	Rt	94	—	80
9	H, **2a**	Quinine **I**	EtOAc	−20	87	—	85
10	H, **2a**	Quinine **I**	PhI	Rt	85	—	81
11	H, **2a**	Quinine **I**	$PhCH_3$	Rt	92	—	80
12	H, **2a**	Quinine **I**	$PhCH_3$	4	90	—	85
13	H, **2a**	Quinine **I**	$PhCH_3$	−20	92	—	89
14	H, **2a**	Thiourea **VI**	$PhCH_3$	−20	91	—	−89[d]
15	Et, **2b**	Quinine **I**	$PhCH_3$	Rt	93	2 : 1	69/50
16	Et, **2b**	Quinine **I**	$PhCH_3$	4	90	10 : 1	91/nd
17	Et, **2b**	Quinine **I**	EtOAc	−20	91	20 : 1	92/nd
18	Et, **2b**	Quinine **I**	$PhCH_3$	−20	93	70 : 1	94/nd

[a] Reaction condition: 0.07 mmol **1a**, 3 eq. **2a–b**, 0.7 mL solvent; 10 mol% **I–VI** (structures: see ESI†); time: 12 h for reactions at rt and up to 72 h for reactions at −20 °C. [b] Isolated yield. [c] ee and dr determined by CSP-GC; see ESI† for stereochemistry determination. [d] Negative ee indicates the formation of the opposite enantiomer.

Dipartimento di Chimica, "Sapienza" University of Roma and Istituto di Chimica Biomolecolare del CNR, P.le Aldo Moro 5, 00185 Roma, Italy. E-mail: Marco.Bella@uniroma1.it; Fax: +39 06 490631

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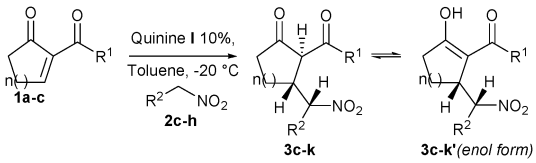
The ratio between the two tautomers is influenced by the sample concentration (low concentrations favor the enol form); however, when these mixtures were analyzed by CSP-GC or CSP HPLC, only the keto form of compound **3a** could be detected. A quick screening of other *Cinchona* alkaloid derivatives did not lead to the identification of a better performing catalyst (entries 2–5); compound **3a** was obtained with similar enantioselectivity in most of the solvents tested (entries 7–13), with the exception of methanol (entry 6).[10] The lowering of the reaction temperature (entries 9, 12 and 13) resulted in the increase of the enantiomeric excess of compound **3a** to 89%. Finally, we tested quinine-based thiourea **VI**, because it has been recently reported by several authors as privileged catalyst in several stereoselective asymmetric reactions.[11] Under the optimized conditions, catalyst **VI** performed well, affording the nitro adduct **3a** with similar enantioselectivity (89% ee, entry 14), producing, however, the *opposite* enantiomer with respect to the reaction mediated by quinine **I**. Since this compound is obtained through a multistep synthetic sequence from quinine **I**,[11e] we did not investigate further this catalyst.

Significant results were also achieved by employing in the reaction other nitroalkanes as the nucleophile, such as 1-nitropropane **2b**, where essentially only one of the eight potential stereoisomers of **3b** was isolated. Initially, when the reaction was conducted at rt, the additional stereogenic center formed in the γ′-position (α-position with respect to the nitro group) is obtained essentially in both configurations, while the *trans* relationship between the protons in the α and β′-position is kept (entry 15). Also in this case, the lowering of the temperature to −20 °C resulted in the formation of adduct **3b** with excellent control of diastereoselectivity (70 : 1, mixture of epimers at the γ′-position) and enantioselectivity (92–94% ee, entries 17 and 18).

The nucleophilic addition of nitrocompounds is one of the oldest organocatalyzed asymmetric reactions;[12] a variety of electrophiles have been employed as Michael acceptors.[13] The new chiral centers formed are generally present on the electrophile partner of the reaction; the control of the stereocenter formed in the α-position with respect to the nitro group is quite challenging, because of the acidity of this proton; the corresponding stereocenter is therefore prone to epimerization. Nevertheless, control of diastereoselectivity has been achieved in the addition of nitroalkanes to aldehydes[14a] or imines;[14b] furthermore, a few months ago Zhu and Lu described the Michael addition of nitroalkanes to vinyl sulfones in 72–84% ee, obtaining products that bear a stable tertiary stereocenter without observing racemization.[11a] We believe that the success of controlling the diastereoselection in our transformation is possible thanks to the use of quinine **I**, which is not a strong base, thus preventing the stereocenter epimerization in the γ′-position (α-position to the nitro group) of compounds **3**, which in these experimental condition is configurationally stable.

Table 2 illustrates further examples where several nitroalkanes are added to β-dicarbonyl compounds **1** under the optimized reaction conditions. All the transformations proceed in high stereoselectivity. Examples include other nitroalkanes such as nitroethane **2c** or 1-nitrobutane **2d** (Table 2, entries 1 and 2). As expected, employing quinidine **VII**

Table 2 Quinine-mediated addition of nitrocompounds **2c–h** to α,β′-unsaturated β-dicarbonyl compounds **1a–c**



Entry[a]	*n*, R^1	R^2	Y[b] (%)	dr[c]	ee[c] (%)
1	1, OEt, **1a**	Me, **2c**	**3c**, 92	40 : 1	94
2	1, OEt, **1a**	*n*Pr, **2d**	**3d**, 93	30 : 1	94
3[d]	1, OEt, **1a**	*n*Pr, **2d**	**3d**, 96	9 : 1	−93[e]
4	1, OEt, **1a**	Bn, **2e**	**3e**, 94	6 : 1	88
5	1, OEt, **1a**	CH_2OTIPS, **2f**	**3f**, 90	20 : 1	98
6	1, OEt, **1a**	$(CH_2)_2CO_2Me$, **2g**	**3g**, 94	5 : 1	91
7[f]	1, OEt, **1a**	Br, **2h**	**3h**, 45	25 : 1	92
8	2, OEt, **1b**	H, **2a**	**3i**, 87	—	87
9	2, OEt, **1b**	Me, **2c**	**3j**, 84	2 : 1	79/76
10	1, Me, **1c**	H, **2a**	**3k**, 90	—	52

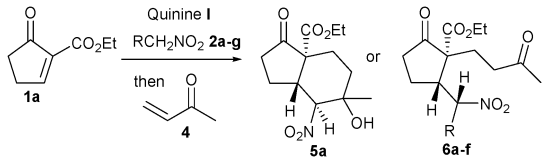
[a] Reaction condition: 0.35 mmol **1**, 3 eq. nitrocompund **2**, 3.5 mL toluene, 10 mol% quinine **I**, −20 °C, 3 days. [b] Yield referred to pure isolated compounds after FC. [c] dr and ee determined by CSP-GC, or by CSP-HPLC equipped with an IB chiralpack column, ee of the major diastereoisomer. [d] Quinidine **VII** employed as the catalyst. [e] Negative ee indicates the formation of the opposite enantiomer. [f] The isolated product is the cyclopropyl derivative **3h**, see ref. 15 and ESI† for details about the stereochemical determination.

(the pseudoenantiomer of quinine **I**) the major product is the opposite enantiomer of compound **3d** (entry 3). Nitrocompounds bearing additional functional groups, such as an aromatic moiety (nucleophile **2e**, entry 4), protected alcohol or ester (**2f** and **2g** respectively, entries 5 and 6), perform well in all cases, showing good control of diastereoselectivity (5 : 1 to 40 : 1) and enantioselectivity (up to 98% ee). Bromonitromethane **2h** (entry 7) presents a similar reactivity; however, in this case the isolated adduct is the cyclopropyl derivative **3h**, resulting from an internal S_N2 process.[15] The low yield observed in this case depends upon the formation of byproducts derived from the opening of the strained bicyclo-[3.1.0]hexane system.

Finally, other α,β′-unsaturated β-dicarbonyl compounds as the electrophile have been tested, such as 6-membered ring α,β′-unsaturated β-ketoester **1b**, which reacted with nitromethane **2a**, affording the corresponding nitro Michael adduct with an erosion of enantioselectivity (87% ee, Table 2, entry 8, to be compared with 89% ee of the 5-membered ring **1a**, Table 1, entry 13). The reaction between **1b** and nitroethane **2c** is less stereoselective (dr = 2 : 1 and ee = 79/76, entry 9). The reaction gave the desired adduct in good yields also when α,β′-unsaturated β-diketone **1c** is employed as the electrophile, however, in this case the enantioselectivity is only moderate (52% ee, entry 10). Secondary (α,α′-disubstituted) nitrocompounds employed as nucleophiles, or acyclic unsaturated β-ketoesters as electrophiles, such as the ethyl ester of 2-acetyl-3 phenyl acrylic acid, react significantly slower; only *E*/*Z* isomerization is observed after 2 days in the reaction with quinine **I** and nitromethane **2a**.

We also achieved a tandem three component reaction with an additional electrophile such as methyl vinyl ketone **4**, added directly once the Michael adducts **3** are formed. In this case,

Table 3 Quinine-mediated tandem addition of nitrocompounds **2a–g** and methyl vinyl ketone **4** to **1a**



Entry[a]	R	Y^b (%)	**6** : **5**	dr[c]	ee[c] (%)
1	H, **2a**	**5–6a**, 85	1 : 4	>10 : 1	>97
2	Et, **2b**	**6b**, 67	>10 : 1	>10 : 1	96
3	Me, **2c**	**6c**, 78	>10 : 1	>10 : 1	95
4	Bn, **2e**	**6d**, 78	>10 : 1	>10 : 1	95
5	CH_2OTIPS, **2f**	**6e**, 83	>10 : 1	>10 : 1	93
6	$(CH_2)_2CO_2Me$, **2g**	**6f**, 78	>10 : 1	>10 : 1	96

[a] Reaction condition: 0.35 mmol **1a**, 3 eq. nitrocompund **2**, 1 mL toluene, 10 mol% quinine **I**, −20 °C, 24 h, then 3 eq. methyl vinyl ketone **4**, 3 days. [b] Yield referred to pure isolated compounds after FC. [c] dr and ee determined by CSP-HPLC equipped with an IB chiralpack column. [d] For **5a**: ee of the more polar epimer; stereochemistry determined *via* NOESY spectra, see ESI† for details; **5a** as 1(more polar) : 1.5 (less polar) mixture of epimers. For the stereochemical determination see ESI.†

adduct **6a**, derived from the addition of nitromethane to **1a**, cyclizes spontaneously to afford **5a** (Table 3, entry 1) differently from the other products derived from primary nitroalkanes **2b**, **c** and **e–g** (entries 2–6). The synthetic versatility and usefulness of the functional nitro group is witnessed by its several reported transformations.[16]

In conclusion, herein is presented the addition of nitroalkanes to α,β′-unsaturated β-ketoesters. The reactions proceed with excellent stereoselectivity, affording Michael adducts **3**. A tandem reaction affords in good yields and stereoselectivity densely functionalized compounds **5a** or **6**. This control of multiple stereocenters is especially significant in the field of *Cinchona* alkaloids catalysis or when nitroalkanes are employed as nucleophiles; we believe that compounds **1** are attractive electrophiles whose synthetic potential can be harvested in several other asymmetric transformations.

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