DOI: 10.1002/adsc.200800592

Enantioselective Organocatalytic Michael Addition of α-Substituted Cyanoacetates to α,β-Unsaturated Selenones

Francesca Marini,[a,*] Silvia Sternativo,[a] Francesca Del Verme,[a] Lorenzo Testaferri,[a] and Marcello Tiecco[a]

[a] Dipartimento di Chimica e Tecnologia del Farmaco, Sezione di Chimica Organica, Università degli Studi di Perugia, Via del Liceo 1, 06123 Perugia, Italy
Fax: (+39)-075-585-5116; e-mail: marini@unipg.it

Received: September 23, 2008; Published online: December 19, 2008

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.200800592.

Abstract: A novel enantioselective (up to 90% *ee*) Michael addition of α-substituted cyanoacetates to α,β-unsaturated selenones in the presence of bifunctional urea and thiourea organocatalysts is described. The Michael adducts, containing an all-carbon quaternary stereocenter, are smoothly converted into synthetically useful polyfunctional compounds by taking advantage of the excellent leaving group ability of the selenone group.

Keywords: asymmetric organocatalysis; cyanoacetates; Michael addition; selenones; thiourea catalysts

In recent years asymmetric organocatalysis has emerged as a practical and powerful tool for the stereoselective preparation of chiral molecules with an impressive number of synthetic applications, also in the field of natural or biologically active compounds.[1,2] Fundamental carbon-carbon bond forming processes, such as the Michael reaction, have been widely investigated. Various catalysts, activating the nucleophile or the electrophile by formation of covalent bonds or weaker interactions, such as ion pairing or hydrogen bonding, have found application for this versatile transformation.[1,2] Among them, the so-called bifunctional catalysts,[2] bearing an hydrogen-bond donor group besides a basic site on a chiral scaffold, have received great attention for the enantioselective addition of 1,3-dicarbonyl compounds or their equivalents to electron-deficient alkenes.[1,2] The simultaneous activation of both the nucleophile and the electrophile allows an excellent level of stereocontrol over the addition event. To date nitroalkenes[3] and α,β-unsaturated carbonyl compounds,[4] imides,[5] nitriles[6] or sulfones[7] have been employed as Michael acceptors. The discovery of novel substrate combinations should provide a simple and convenient access to highly functionalized adducts. Our interest in the field of the organoselenium-based asymmetric syntheses[8] prompted us to investigate the addition of carbon-centered nucleophiles to vinyl selenones. Selenones are well recognized intermediates in organic synthesis with peculiar properties in respect to the sulfur analogues. Thus, for instance, the selenonyl group presents an exceptional aptitude to act as a leaving group.[8b–e,9] Herein, we report the first enantioselective addition of α-substituted cyanoacetates to vinyl selenones. The use of these trisubstituted Michael donors in asymmetric conjugate addition represents one of the most attractive solutions to the challenging problem of generating selectively all-carbon quaternary stereocenters.[10]

First experiments were effected on the α-phenyl cyanoacetate **2a** and the vinyl selenone **3** in toluene.[11] The easily accessible bifunctional catalysts **1a–f** reported in Figure 1, containing phenolic (**1a)**, ureidic (**1b, 1d** and **1e)** or thioureidic (**1c** and **1f)** hydrogen donor groups, respectively, have been examined as catalysts. Cinchonine, quinine and the commercially available *Cinchona* alkaloid derivatives $(DHQ)_2Pyr$ and $(DHQ)_2AQN$, that lack an H-bond donor group, have also been tested for comparison. The results of the screening are reported in Table 1.

The urea or thiourea catalysts, particularly **1f**, gave the most promising results demonstrating that the cooperation of urea or thiourea and tertiary amine functionalities is significant to the enantiocontrol. This observation might indicate an activation of the selenone by a double H-bonding interaction, as proposed for the nitro[3b,e,h] and the sulfone groups.[7a]

The effect of catalyst loading and temperature have also been investigated. Comparable results were still

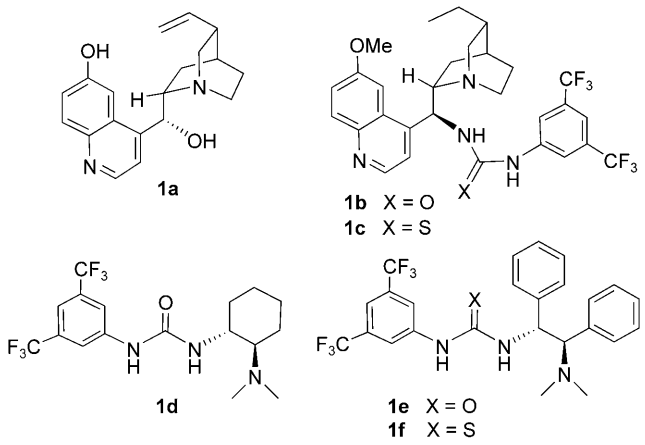
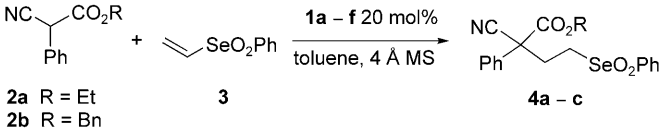


Figure 1. Bifunctional catalysts **1a–f**.

Table 1. Screening results for the Michael addition of **2a–c** to vinyl selenone **3**.



2a R = Et
2b R = Bn
2c R = *i*-Pr

3

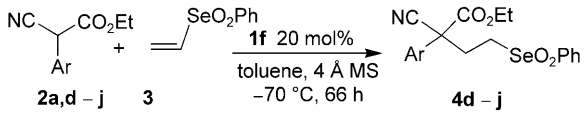
4a – c

Entry	Catalyst		*t* [h]	*T* [°C]		Yield[a] [%]	*ee*[b] [%]
1	cinchonine	**2a**	15	r.t.	**4a**	94	22
2	$(DHQ)_2Pyr$	**2a**	15	r.t.	**4a**	91	16
3	$(DHQ)_2AQN$	**2a**	15	r.t.	**4a**	94	6
4	quinine	**2a**	15	r.t.	**4a**	88	6[c]
5	**1a**	**2a**	15	r.t.	**4a**	85	34
6	**1b**	**2a**	9	r.t.	**4a**	88	44[c]
7	**1b**[d]	**2a**	17	r.t.	**4a**	85	44[c]
8	**1c**	**2a**	15	r.t.	**4a**	80	32[c]
9	**1d**	**2a**	15	r.t.	**4a**	74	40
10	**1e**	**2a**	8	r.t.	**4a**	91	44
11	**1f**	**2a**	8	r.t.	**4a**	96	52
12	**1b**	**2a**	66	−70	**4a**	97	70[c]
13	**1e**	**2a**	48	−70	**4a**	87	74
14	**1f**	**2a**	66	−70	**4a**	90	80
15	**1f**	**2b**	66	−70	**4b**	97	62
16	**1f**	**2c**	66	−70	**4c**	99	70

[a] Yields determined on isolated compounds after flash chromatography.
[b] Determined by chiral HPLC analysis.
[c] The opposite enantiomer was obtained.
[d] 10 mol% of **1b** have been employed.

achieved when the loading of **1b** was reduced to 10 mol%, although with an extended reaction time (Table 1, entry 7). The best enantioselectivity was obtained at −70 °C, with 20 mol% of **1f** (Table 1, entry 14). The α-phenylcyanoacetates **2b** and **2c**, containing benzyl or isopropyl groups at the ester moiety,

Table 2. Enantioselective conjugate addition of α-aryl cyanoacetates to vinyl selenone **3**.



2a,d – j **3** **4d – j**

Entry		Ar		Yield[a,b] [%]	*ee*[c] [%]
1	**2a**	Ph	**4a**	90	80
2	**2d**	*p*-MeO-C_6H_4	**4d**	88	90
3	**2e**	*p*-Me-C_6H_4	**4e**	80	90
4	**2f**	*p*-F-C_6H_4	**4f**	97	82
5	**2g**	*p*-Cl-C_6H_4	**4g**	93	80
6	**2h**	*p*-Br-C_6H_4	**4h**	90	80
7	**2i**	2-naphthyl	**4i**	93	82
8	**2j**	*m*-Me-C_6H_4	**4j**	75	76

[a] The reactions were run with 0.2 mmol of **3** and 0.3 mmol of **2** in 0.8 mL of toluene.
[b] Determined on isolated compounds after flash chromatography.
[c] Determined by chiral HPLC analysis.

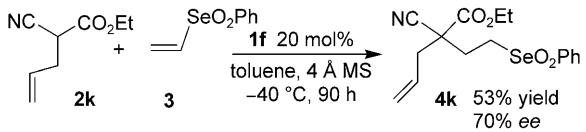
gave products **4b** and **4c** with excellent yields, but lower enantioselectivities (Table 1, entries 15 and 16).

The optimized reaction conditions proved to be effective for the addition of a wide range of α-arylcyanoacetates with different electronic and steric properties. Highly functionalized addition products, bearing an all-carbon quaternary stereocenter, have been isolated in excellent yields and high enantiomeric excesses (Table 2).

α-Alkylcyanoacetates proved to be significantly less reactive as Michael donors than the aryl-substituted compounds.

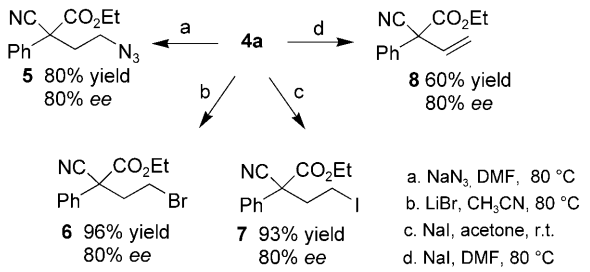
In fact, the addition of the ethyl α-allylcyanoacetate **2k** to selenone **3** gave the product **4k** with 53% yield and 70% *ee*, although the reaction was carried out at higher temperature and for a longer reaction time (Scheme 1).

The addition of α-substituted cyanoacetates to vinyl selenones is a valuable tool for the preparation of a range of synthetically useful compounds under mild reaction conditions. In fact not only the phenylselenonyl group activates the alkene toward the nucleophilic addition, but it also offers an electrophilic site for further synthetic transformations. The excellent leaving group properties of the phenylselenonyl group[8b–e,9] have been exploited for the reactions de-

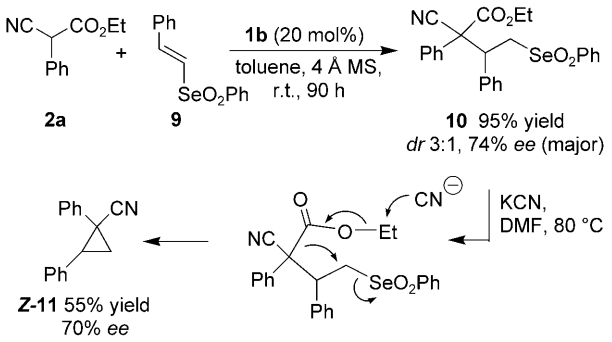


2k **3**

Scheme 1. Conjugate addition of ethyl α-allylcyanoacetate **2k** to vinyl selenone **3**.



Scheme 2. Facile conversions of **4a** into synthetically valuable enantioenriched compounds.



Scheme 3. Conjugate addition of **2a** to β-substituted selenone **9**.

scribed in Scheme 2. The enantiomerically enriched compounds **5–8** have been isolated in good to excellent yields without loss of enantiomeric purity. Compound **8**, as suggested by the TLC analysis, is formed by elimination of the intermediate iodide **7**.

Finally, **1b**[12] revealed to be an effective catalyst for the stereocontrolled creation of adjacent quaternary and tertiary stereocenters by conjugate addition of **2a** to the β-substituted selenone **9** (Scheme 3) at room temperature. Compound **10** was formed with moderate diastereo- and good enantioselectivity. Treatment of the mixture of the diastereoisomers with KCN in DMF gave the cyclopropane **11** as the single ***Z*** isomer[13] in 70% *ee*. This transformation can be rationalized as a Krapcho-type deethoxycarbonylation,[14] followed by a ring closure reaction mediated by nucleophilic substitution of the selenone.

In summary, the enantioselective addition of α-substituted cyanoacetates to vinyl selenones represents a new process catalyzed by bifunctional ureidic or thioureidic catalysts. The simple protocol constitutes the first access to highly functionalized, enantioenriched selenones bearing an all-carbon quaternary stereocenter with good to excellent *ee*s.

Moreover, the great nucleofugal ability of the selenone group has been used for the preparation of some synthetically valuable polyfunctional compounds under mild experimental conditions and without loss of the enatiomeric purity.

Attempts to expand the scope of these reactions to other nucleophiles and to develop sequential or domino reactions employing vinyl selenones as Michael acceptors are currently underway.

Experimental Section

General Procedure for the Enantioselective Michael Addition of α-Substituted Cyanoacetates 2a–k to Vinyl Selenones 3 or 9

In an ordinary vial equipped with a Teflon-coated stir bar, catalyst **1f** or **1b** (0.04 mmol, 20 mol%) and selenone **3** or **9** (0.2 mmol) were dissolved in undistilled toluene (0.8 mL) with 20 mg of 4 Å MS without any precaution to remove air. The α-substituted cyanoacetate **2a–k** (0.3 mmol, 1.5 equiv.) was added at −70 °C or at room temperature and the resulting solution was stirred for 66 or 90 h. The reaction mixture was directly poured into a flash chromatographic column and the crude products **4a–k** and **10** were purified using mixtures of hexane/ethyl acetate as eluent.

Acknowledgements

Financial support from MIUR, National Projects PRIN 2005, University of Perugia and Consorzio CINMPIS, Bari is gratefully acknowledged.

References

[1] For recent reviews on organocatalysis, see: a) P. Melchiorre, M. Marigo, A. Carlone, G. Bartoli, *Angew. Chem.* **2008**, *120*, 6232; *Angew. Chem. Int. Ed.* **2008**, *47*, 6138; b) A. Mielgo, C. Palomo, *Chem. Asian J.* **2008**, *3*, 922; c) A. Dondoni, A. Massi, *Angew. Chem.* **2008**, *120*, 4716; *Angew. Chem. Int. Ed.* **2008**, *47*, 4638; d) H. Pellissier, *Tetrahedron* **2007**, *63*, 9267; e) M. J. Gaunt, C. C. C. Johansson, A. McNally, N. C. Vo, *Drug Discovery Today* **2007**, *12*, 8; f) S. B. Tsogoeva, *Eur. J. Org. Chem.* **2007**, 1701; g) D. Almasi, D. A. Alonso, C. Najera, *Tetrahedron: Asymmetry* **2007**, *18*, 299; h) J. L. Vicario, D. Badia, L. Carrillo, *Synthesis* **2007**, 2065.

[2] For recent reviews on hydrogen bond-facilitated organocatalysis, see: a) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713; b) M. S. Taylor, E. N. Jacobsen, *Angew. Chem.* **2006**, *118*, 1550; *Angew. Chem. Int. Ed.* **2006**, *45*, 1520; c) S. J. Connon, *Chem. Eur. J.* **2006**, *12*, 5418; d) S. J. Connon, *Chem. Commun.* **2008**, 2499.

[3] a) T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672; b) T. Okino, Y. Hoashi, T. Furukawa, X. Xu, Y. Takemoto, *J. Am. Chem. Soc.* **2005**, *127*, 119; c) H. Li, Y. Wang, L. Tang, L. Deng, *J. Am. Chem. Soc.* **2004**, *126*, 9906; d) H. Li, Y. Wang, L. Tang, F. Wu, X. Liu, C. Guo, B. M. Foxman, L. Deng, *Angew. Chem.* **2005**, *117*, 107; *Angew. Chem. Int. Ed.* **2005**, *44*, 105; e) J. Wang, H. Li, W. Duan, L. Zu, W. Wang, *Org. Lett.* **2005**, *7*, 4713; f) J. Ye, D. J. Dixon, P. S. Hynes, *Chem. Commun.* **2005**, 4481; g) C. J. Wang, Z.-H.

Zhang, X.-Q. Dong, X.-J. Wu, *Chem. Commun.* **2008**, 1431; h) F.-Z. Peng, Z.-H. Shao, B.-M. Fan, H. Song, G.-P. Li, H.-B. Zhang, *J. Org. Chem.* **2008**, *73*, 5202; i) J. M. Andres, R. Manzano, R. Pedrosa, *Chem. Eur. J.* **2008**, *14*, 5116; j) Y. Xiong, Y. Wen, F. Wang, B. Gao, X. Liu, X. Huang, X. Feng, *Adv. Synth. Catal.* **2007**, *349*, 2156; k) Z. Yang, J. Liu, X. Liu, Z. Wang, X. Feng, Z. Su, C. Hu, *Adv. Synth. Catal.* **2008**, *350*, 2001.

[4] a) T.-Y. Liu, R. Li, Q. Chai, J. Long, B.-J. Li, Y. Wu, L.-S. Ding, Y.-C. Chen, *Chem. Eur. J.* **2007**, *13*, 319; b) F. Wu, R. Hong, J. Khan, X. Liu, L. Deng, *Angew. Chem.* **2006**, *118*, 4407; *Angew. Chem. Int. Ed.* **2006**, *45*, 4301; c) C. Gu, L. Liu, Y. Sui, J-L. Zhao, D. Wang, Y-J Chen, *Tetrahedron: Asymmetry* **2007**, *18*, 455.

[5] a) Y. Hoashi, T. Okino, Y. Takemoto, *Angew. Chem.* **2005**, *117*, 4100; *Angew. Chem. Int. Ed.* **2005**, *44*, 4032; b) T. Inokuma, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2006**, *128*, 9413.

[6] a) Y. Wang, X. Liu, L. Deng, *J. Am. Chem. Soc.* **2006**, *128*, 3928; b) Y. Wang, X. Liu, L. Deng, *J. Am. Chem. Soc.* **2007**, *129*, 768.

[7] a) T.-Y. Liu, J. Long, B.-J. Li, L. Jiang, R. Li, Y. Wu, L.-S. Ding, Y.-C. Chen, *Org. Biomol. Chem.* **2006**, *4*, 2097; b) H. Li, J. Song, X. Liu, L. Deng, *J. Am. Chem. Soc.* **2005**, *127*, 8948.

[8] For some recent examples, see: a) M. Tiecco, L. Testaferri, F. Marini, S. Sternativo, F. Del Verme, C. Santi, L. Bagnoli, A Temperini, *Tetrahedron* **2008**, *64*, 3337; b) M. Tiecco, A. Carlone, S. Sternativo, F. Marini, G. Bartoli, P. Melchiorre, *Angew. Chem.* **2007**, *119*, 7006; *Angew. Chem. Int. Ed.* **2007**, *46*, 6882; c) M. Tiecco, L. Testaferri, A. Temperini, R. Terlizzi, L. Bagnoli, F. Marini, C. Santi, *Org. Biomol. Chem.* **2007**, *5*, 3510; d) M. Tiecco, L. Testaferri, L. Bagnoli, G. Scarponi, A. Temperini, F. Marini, C. Santi, *Tetrahedron: Asymmetry* **2007**, *18*, 2758; e) M. Tiecco, L. Testaferri, A. Temperini, L. Bagnoli, F. Marini, C. Santi, *Chem. Eur. J.* **2004**, *10*, 1752.

[9] a) A. Krief, W. Dumont, J.-N. Denis, *J. Chem. Soc., Chem. Commun.* **1985**, 571; b) A. Krief, W. Dumont, A. F. De Mahieu, *Tetrahedron Lett.* **1988**, *29*, 3269; c) A. Toshimitsu, C. Hirosawa, S. Tanimoto, S. Uemura, *Tetrahedron Lett.* **1992**, *33*, 4017; d) M. A. Cooper, A. D. Ward, *Aust. J. Chem.* **1997**, *50*, 181; e) V. R. Ward, M. A. Cooper, A. D. Ward, *J. Chem. Soc., Perkin Trans. 1* **2001**, 944; f) M. Tiecco, D. Chianelli, L. Testaferri, M. Tingoli, D. Bartoli, *Tetrahedron* **1986**, *42*, 4889; g) R. Ando, T. Sugawara, M. Shimizu, I. Kuwajima, *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2897; for an application of the organoselenones to drug design as biological alkylating agents, see: h) S.-I. Kang, C. P. Spears, *J. Med. Chem.* **1990**, *33*, 1547.

[10] For a recent review on the enantioselective formation of quaternary stereogenic centers, see: P. G. Cozzi, R. Hilgraf, N. Zimmermann, *Eur. J. Org. Chem.* **2007**, 5969.

[11] The addition of **2a** to **3** was also performed in other solvents with 20 mol% of the catalyst **1b** at room temperature in 15 h obtaining lower enantioselectivities: $CHCl_3$ (94% yield, 34% *ee*); TBME (93% yield, 38% *ee*).

[12] The reaction carried out with **1f** gave **10** in low yield ($<25\%$) and 58% *ee*.

[13] W. von E. Doering, L. R. Robertson, E. E. Ewing, *J. Org. Chem.* **1983**, *48*, 4280.

[14] P. Krapcho, *Synthesis* **1982**, 893.

