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A New Stereoselective Synthesis of Cyclopropanes Containing Quaternary Stereocentres *via* Organocatalytic Michael Addition to Vinyl Selenones

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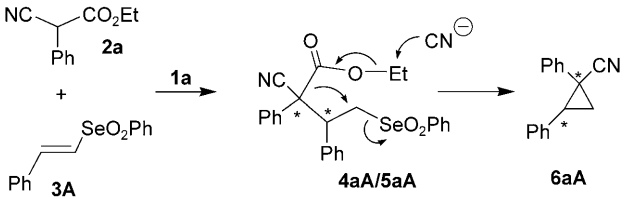
Abstract: A novel organocatalytic method for the stereoselective synthesis of highly substituted cyclopropanes is reported. The Michael adducts, generated through the addition of α-substituted cyanoacetates to easily accessible vinyl selenones catalyzed by a bifunctional ureidic catalyst, smoothly cyclize by intramolecular alkylation induced by a de-ethoxycarbonylation process. The *one-pot* sequence generates cyclopropanes bearing adjacent tertiary and quaternary stereocentres as single *Z*-isomers in moderate to high yields and good enantiomeric excesses.

Keywords: asymmetric organocatalysis; cyclopropanes; Michael addition; quaternary stereocenters; selenones

The cyclopropane ring is the basic structural motif of a wide range of natural products and biologically active compounds, such as conformationally restricted amino acids or peptides, enzyme inhibitors and therapeutic agents with antipsychotic, antifungal, antibacterial, antitumoral or antiviral activities.[1] Furthermore, the three-membered ring, due to its strong angular strain and great ring-opening ability, is a recognized intermediate in the construction of complex molecular skeletons.[2] On these grounds, the development of simple and efficient methods for the stereocontrolled preparation of variously substituted cyclopropanes remains an interesting task for synthetic chemists. In the last years great attention has been focused on the identification of new asymmetric methodologies based on readily available achiral starting materials and chiral catalysts. Thus, asymmetric Simmons–Smith reactions or cyclopropanations of olefins by metal-catalyzed decomposition of diazo compounds have been successfully explored.[3] Very recently significant advances have also been made in the development of organocatalytic cyclopropanations based on *Michael initiated ring closure* reactions (MIRC).[3,4] In these processes, the addition of an ylide or an enolate containing a good leaving group to an electrophilic alkene generates an anionic intermediate, which easily undergoes a ring closure reaction by intramolecular alkylation. During our studies on the asymmetric Michael addition of α-substituted cyanoacetates to vinyl selenones catalyzed by ureidic or thioureidic bifunctional catalysts, we observed that the diastereomeric mixture of Michael adducts **4aA** and **5aA** affords the cyclopropane **6aA** as a single isomer by simple treatment with KCN in DMF (Scheme 1).[5]

We explained this process as a Krapcho-type deethoxycarbonylation, followed by an intramolecular nucleophilic substitution of the selenonyl moiety by the enolate intermediate. The excellent leaving group properties of this species have been already exploited for other synthetically useful inter- or intramolecular substitutions.[5,6] This first result prompted us to study the sequence in detail and develop a novel *one-pot*



Scheme 1. Formation of the cyclopropane **6aA**.

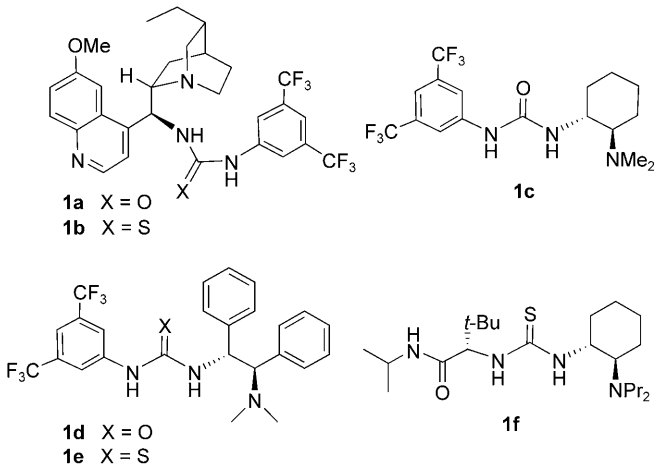


Figure 1. Ureidic or thioureidic catalysts **1a–f**.

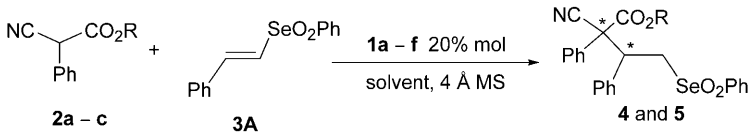
procedure for the enantioselective preparation of substituted cyclopropanes containing adjacent all carbon quaternary and tertiary stereocentres starting from readily available vinyl selenones.[7] Some catalytic approaches for the stereoselective construction of such cyclopropanes are available in the literature[3,4f,k,8] including methods for the preparation of nitrile-substituted cyclopropanes,[9] but only few of them employ organocatalysts.

Preliminary experiments were carried out in order to examine the addition step which is responsible of the enantioselectivity of the sequence. The commercial ethyl α-phenylcyanoacetate **2a** and the (*E*)-vinyl selenone **3A**[6j] were used as the model substrates in the presence of the commercial **1f** or easily accessible **1a–e** chiral urea or thiourea derivatives reported in Figure 1, which have recently emerged as efficient catalysts for a broad range of highly enantioselective Michael additions.[10] These bifunctional catalysts, bearing an hydrogen-bond donor group besides a basic site on a chiral scaffold, accelerate the 1,4-additions and improve yields and stereoselectivities by simultaneous activation of both the Michael acceptor and the carbon nucleophile. The results of the experiments confirmed the efficiency of the ureidic catalyst **1a**, which gave in toluene the best results in terms of yield, diastereo- and enantioselectivity (Table 1).

The stereoinduction is slightly affected by the ester size with a decrement of the enantioselectivity as the size of the ester increases (Table 1, entries 1, 5, 6). When the temperature was raised at 50 °C the reaction time was shortened at 48 h, albeit with a loss of selectivity (Table 1, entry 4). It is interesting to point out that an attempt to effect the addition of **2a** on the phenyl (*E*)-2-phenylethenyl sulfone, structurally related to **3A**, failed indicating a different behaviour between the sulphur[11,12] and the selenium[5] containing compounds.

After the optimization of the addition step, the ring formation was examined. The crude mixture of **4aA**

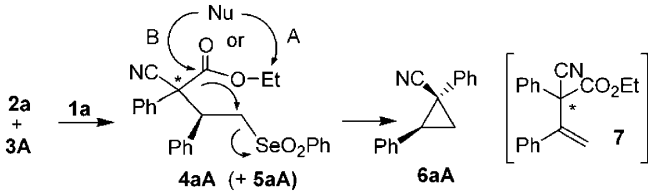
Table 1. Selected results for the Michael addition of **2a–c** to vinyl selenone **3A**.[a]



Entry	Catalyst		R	Solvent	Time [h]	Yield [%][b]	**4:5**[c]	*ee* [%][d]
1	**1a**	**2a**	Et	toluene	90	94	85:15	80
2	**1a**	**2a**	Et	CH_2Cl_2	144	78	78:22	56
3	**1a**	**2a**	Et	THF	144	73	74:26	54
4	**1a**	**2a**	Et	toluene	48[e]	99	82:18	64
5	**1a**	**2b**	Bn	toluene	90	87	79:21	64
6	**1a**	**2c**	*i*-Pr	toluene	90	97	77:23	66
7	**1b**	**2a**	Et	toluene	72	–	–	–
8	**1c**	**2a**	Et	toluene	120	81	78:22	68[f]
9	**1d**	**2a**	Et	toluene	144	21	68:32	58[f]
10	**1e**	**2a**	Et	toluene	144	<20	68:32	56[f]
11	**1f**	**2a**	Et	toluene	144	40	42:58	50[f]

[a] Catalysts **1a–f** (0.02 mmol, 20 mol%) and **3A** (0.1 mmol) were dissolved in the indicated solvent (0.4 mL), then 4 Å MS (20 mg) and **2a–c** (0.15 mmol, 1.5 equiv.) were added at room temperature.
[b] Yields refer to the mixture of diastereoisomers **4** and **5**.
[c] Determined by ^{1}H NMR analysis after passing through a plug of silica gel.
[d] The *ee* values, determined by chiral HPLC analysis, refer to the adducts **4**. The minor diastereomers **5** have *ee* lower than 20%.
[e] The reaction was carried out at 50 °C.
[f] The opposite enantiomer was obtained.

Table 2. Optimization of the cyclization step.



Entry	Reaction Conditions[a]	Yield [%][b]	*ee* [%][c]
1	LiCl, HMPA, 80 °C, 2 h	65	66
2	LiCl, toluene/HMPA 1:1, 100 °C, 24 h	31[d]	66
3	LiCl, DMSO, 160 °C, 2 h	[37][e]	–
4	LiCl, toluene, 12-crown-4, 80 °C, 24 h	[48][e]	–
5	NaBr, DMSO, 100 °C, 5 h	[51][e]	–
6	aq. NaOH, MeOH, r.t., 24 h	[f]	–
7	EtONa/EtOH, 0 °C→r.t., 2 h	54	76
8	EtONa/EtOH, 0 °C→r.t., 2 h	41	64 [g]

[a] **1a** (0.02 mmol, 20 mol%) and **3A** (0.1 mmol) were dissolved in toluene (0.4 mL), then 4 Å MS (20 mg) and **2a** (0.15 mmol, 1.5 equiv.) were added at room temperature. After 90 h the toluene (if necessary) was removed under reduced pressure and the indicated reagents and solvent were added.

[b] Determined on isolated **6aA**.

[c] The *ee* values were determined by chiral HPLC analysis.

[d] Products of nucleophilic substitution of the selenonyl group by chloride ion were also formed.

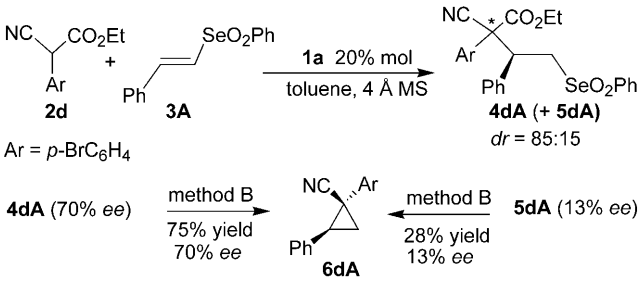
[e] The alkene **7** was recovered as the main product with the yield reported in parentheses.

[f] A complex mixture of products was formed.

[g] The opposite enantiomer was obtained by using catalyst **1c**.

and **5aA**, obtained by simple removal of the toluene under vacuum, was submitted to treatment with LiCl or NaBr in a polar aprotic solvent (Krapcho-type protocols)[13] or with an aqueous solution of NaOH in MeOH[14] (Table 2). An alternative treatment with NaOEt in EtOH was also attempted. Only in the presence of LiCl in HMPA (method A) and NaOEt in EtOH (method B) was the cyclopropane **6aA** formed in good yields.

The stereochemical assignment of **6aA**[15] allows us to assign the 3*S* absolute configuration at the tertiary stereocenter of the major adduct **4aA**. Reasonably, the LiCl or the NaOEt, respectively, attack the ethyl or the carbonyl group of the ester moiety forming a nitrile enolate which promotes the 3-*exo-tet* ring closure reaction. The process is completely diastereoselective, giving the sole *Z*-isomer with good enantiomeric excesses (Table 2, entries 1 and 7). In the other conditions more complex reaction mixtures, containing products generated by intermolecular nucleophilic substitution of the selenonyl group or considerable amounts of the elimination product **7**, were obtained. The cyclization with method B generates the cyclopropane **6aA** with an enantiomeric excess which is almost identical to that of the major adduct **4aA** and seems not affected by the presence of the poorly enantioenriched minor adduct **5aA**. This observation suggests that under these conditions only **4aA** is quantitatively converted into the cyclic compound **6aA**.



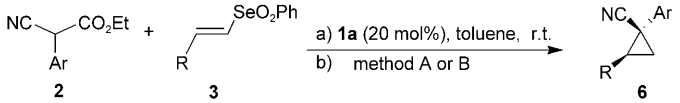
Scheme 2. Cyclization of adducts **4dA** and **5dA**.

Additional experiments performed on the chromatographically separated adducts, generated from cyanoacetate **2d** and the vinyl selenone **3A**, confirmed this hypothesis. In fact, the cyclization of the major adduct **4dA** proceeds smoothly, while the conversion of the minor isomer **5dA** generates **6dA** in a very poor yield (28% yield) together with unidentified by-products (Scheme 2). As demonstrated by the ^{1}H NMR analyses of the crude reaction mixtures in both cases the *E*-cyclopropane was not present.

The *one-pot* process, in which the addition, de-ethoxycarbonylation and cyclization steps are carried out sequentially and without isolation of the intermediates, was applied to a range of β-aryl-substituted vinyl selenones containing electron-withdrawing or electron-donating groups at different positions of the phenyl ring. Different α-aryl cyanoacetates were also used as the Michael donor. Methods A and B were both used for the cyclization. The cyclopropanes **6** were generated in moderate to good yields, complete diastereoselectivity and good enantioselectivity (Table 3 entries 1–8). The results obtained with EtONa in EtOH are particularly interesting. In fact, this strategy provide higher enantiomeric excesses and comparable yields than those with the Krapcho protocol which involves the hazardous HMPA. The β-alkyl-substituted vinyl selenone **3G** was also examined as the Michael acceptor in the presence of the α-arylcyanoacetates **2a** and **2f**. The addition step proceeded smoothly and at a faster rate than in the presence of the corresponding aryl compounds. Only the treatment with LiCl in HMPA gave the *Z*-2-alkyl-substituted cyclopropanes **6aG** and **6fG**[16] in high yields and moderate selectivity (Table 3, entries 9–11).

Further experiments demonstrated that the presence of an α-aryl group on the starting cyanoacetate **2** is essential for the de-ethoxycarbonylation of the adducts **4**. In fact, the reactions between the α-allylcya-

Table 3. Formation of the cyclopropanes **6**.



Entry		Ar		R		Method A[a] Yield [%][c]	Method A[a] *ee* [%][d]	Method B[b] Yield [%][c]	Method B[b] *ee* [%][d]
1	**2a**	Ph	**3A**	Ph	(−)-**6aA**	65	66	54	76
2	**2a**	Ph	**3B**	*p*-MeO-C_6H_4	(−)-**6aB**	64	66	40	74
3	**2a**	Ph	**3C**	*p*-Me-C_6H_4	(−)-**6aC**	51	68	58	76
4	**2a**	Ph	**3D**	*p*-Cl-C_6H_4	(−)-**6aD**	40	72	40	72
5	**2a**	Ph	**3E**	*m*-F-C_6H_4	(−)-**6aE**	55	74	65	74
6	**2a**	Ph	**3F**	*o*-Me-C_6H_4	(−)-**6aF**	56	48	45	68
7	**2d**	*p*-Br-C_6H_4	**3A**	Ph	(−)-**6dA**	52	61	50	70
8	**2e**	*p*-F-C_6H_4	**3D**	*p*-Cl-C_6H_4	(−)-**6eD**	42	74	66	66
9	**2a**	Ph	**3G**	C_6H_{13}	(−)-**6aG**	81	48	18	54
10	**2a**	Ph	**3G**	C_6H_{13}	(−)-**6aG**	90[e]	54	–	–
11	**2f**	*p*-MeO-C_6H_4	**3G**	C_6H_{13}	(−)-**6fG**	91	52	–	–

[a] Method A: LiCl (2.5 equiv.) in HMPA.
[b] Method B: EtONa (2.5 equiv.) in EtOH.
[c] Determined on isolated compounds.
[d] Determined by chiral HPLC analysis.
[e] Reaction carried out at −20 °C for 144 h.

noacetate and **3A** under the experimental conditions described in Table 3 did not afford any cyclopropanation product.

The stereochemical assignment of the cyclopropanes **6aA** and **6fG**[15,16] suggests that in the presence of **1a** the Michael addition occurs preferentially on the *Re* face of the β-substituted unsaturated selenones. Thus, the facial selectivity is opposite to that observed in similar reactions with Michael acceptors containing nitro or carbonyl groups and urea and thiourea-substituted 9-*epi*-dihydroquinine derivatives.[17]

The presence of the non-planar selenonyl group should modify the spatial arrangement of the ternary complex formed by the catalyst, the Michael acceptor and the nucleophile. In conclusion, we have described the first organocatalytic synthesis of enantioenriched cyclopropanes starting from β-substituted vinyl selenones. The key step of this procedure is the Michael addition of α-aryl-substituted cyanoacetates to β-substituted vinyl selenones,[18] followed by a de-ethoxycarbonylation and a ring closure reaction. In most cases, the reactions can be carried out with comparable or even better results using EtONa in EtOH which avoids the use of HMPA with advantages for health and environment. The practical one-pot sequence, which occurs with complete diastereoselectivity and good enantioselectivity, is based on the peculiar properties of the selenonyl moiety which acts both as an electron-withdrawing group during the addition step and as a leaving group during the cyclization. Our procedure nicely complements the recent rhodium-catalyzed cyclopropanation of electron-rich olefins by 2-diazo-2-phenylacetonitrile, which selectively affords enantioenriched *E*-nitrile-substituted cyclopropanes.[9a] Moreover, it expands the use of privileged organocatalysts in the field of selenium chemistry and opens attractive prospects for up to now scarcely explored organocatalytic selenium-based transformations.

Experimental Section

General Procedure for the *One-Pot* Synthesis of Enantioenriched *Z*-Cyclopropanes 6

In an ordinary vial equipped with a Teflon-coated stir bar, catalyst **1a** (0.04 mmol, 20 mol%) and the selenones **3A–F**[19] or **3G**[20] (0.2 mmol) were dissolved in undistilled toluene (0.8 mL) with 20 mg of 4 Å MS. The α-substituted cyanoacetate **2a, d–f** (0.3 mmol, 1.5 equiv.) were added at room temperature (15–18 °C) and the resulting mixtures were stirred in air for 48–144 h. The solvent was removed under reduced pressure and the crude reaction mixtures were submitted to cyclization following method A or B.

Method A: the crude reaction mixtures were dissolved in HMPA (1.5 mL). Then LiCl (0.5 mmol) was added and the mixtures were stirred at 80 °C for 2–4 h. The reactions were quenched with water (20 mL) and extracted with diethyl ether (3×10 mL). The organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under vacuum. The residues were purified by flash chromatography to yield the cyclopropanes **6**.

Method B: the crude residues were dissolved in EtOH (1 mL) and a solution of EtONa (0.5 mmol) in EtOH

(1 mL) was added at 0 °C. The resulting solutions were allowed to warm to room temperature and stirred for 1–4 h. The reaction mixtures were quenched with water (20 mL) and extracted with diethyl ether (3 × 10 mL). The organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under vacuum. The residues were purified by flash chromatography to yield the cyclopropanes **6**.

Acknowledgements

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[15] The relative configuration of **6aA** was assigned by comparison of the ^{1}H NMR spectrum with that reported in the literature (ref.[15a]). The absolute configuration was assigned as 1*S*,2*S* by its (−) optical rotation typical for the (2*S*)-isomers of 2-phenyl substituted cyclopropanecarboxylic derivatives. See: a) W. von E. Doering, L. R. Robertson, E. E. Ewing, *J. Org. Chem.* **1983**, *48*, 4280; b) A. B. Chmurny, D. J. Cram, *J. Am. Chem. Soc.* **1973**, *95*, 4237.

[16] The relative and absolute configuration (1*S*,2*R*) of compound **6fG** was assigned by comparison of its ^{1}H NMR spectrum and specific optical rotation, respectively, with those reported in the literature. See: T. Kusumoto, A. Nakayama, K. Sato, T. Hiyama, S. Takehara, T. Shoji, M. Osawa, T. Kuriyama, K. Nakamura, T. Fujisawa, *Tetrahedron Lett.* **1991**, *32*, 939.

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[18] Simple cyanoacetates or other unsubstituted activated methylenic compounds add to β-substituted vinyl selenones generating directly 2-substituted cyclopropanecarboxylic esters through an alternative cascade process which involves a Michael addition, a proton exchange and a cyclization by displacement of the $PhSeO_2$ group.[6j,l,m] The organocatalytic version of this process merits investigations. These are currently under way in our laboratory.

[19] According to Tiecco's procedure (ref.[6j]), the (*E*)-vinyl selenones **3A–F** were prepared from the corresponding commercial or easily available vinyl bromides. See: a) H.-W. You, . K.-J. Lee *Synlett* **2001** 105; b) C. Kuang, H. Senboku, M. Tokuda, *Tetrahedron* **2005**, *61*, 637.

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