Stereoselective synthesis of cyclopropanes from vinyl selenones via Michael initiated cascade reactions

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Dedicated to Prof. L. Testaferri on the occasion of his retirement

Introduction

Cyclopropane scaffold is an attractive target in organic synthesis because of its broad distribution as key structural element in natural products and in a wide range of synthetic biologically active compounds.[1] Moreover, due to its strong angular strain and good ring-opening ability, the three-membered ring is a well recognized intermediate in the construction of complex molecular architectures.[2] On these grounds, the identification of new synthetic strategies for a stereocontrolled access to variously substituted cyclopropanes is of considerable importance.[3] In the last years great attention has been focused on reactions with chiral catalysts. Currently available methods include asymmetric versions of the Simmons-Smith reaction and cyclopropanations based on metal-catalyzed decomposition of diazo compounds. Very recently, significant advances have been made in the development of new organocatalytic Michael initiated ring closure reactions (MIRC). In these processes the conjugate addition of a carbon nucleophile to an electrophilic alkene produces an enolate, which subsequently undergoes an intramolecular alkylation. Reactions with α-halomalonates or bromonitromethane and electron-deficient alkenes have been widely investigated.[4] Densely functionalized cyclopropanes were achieved in high yields and excellent stereoselectivity in the presence of chiral non racemic amines or acid-base bifunctional catalysts.

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[1] (a) W. A. Donaldson *Tetrahedron* **2001**, *57*, 8589; (b) R. Faust *Angew. Chem. Int. Ed.* **2001**, *40*, 2251; (c) J. Salaun *Curr. Med. Chem.* **1995**, *2*, 511; (d) A. Reichelt, S. F. Martin *Acc. Chem. Res.* **2006**, *39*, 433.

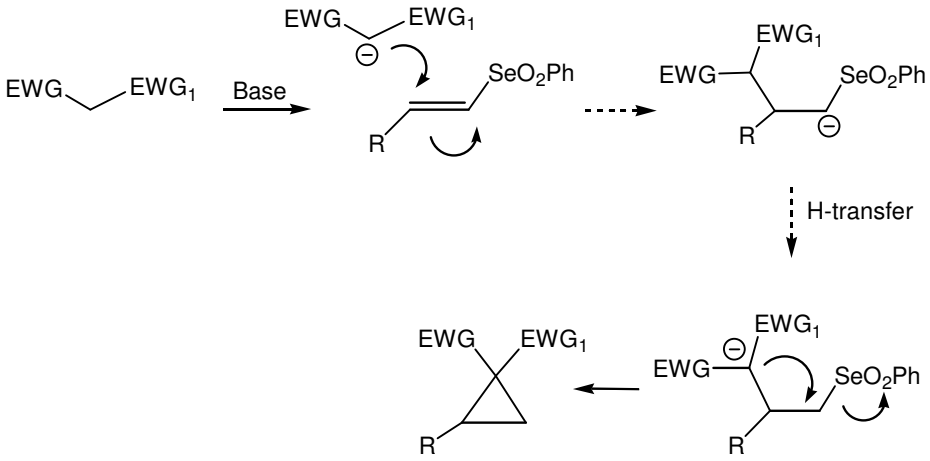
[2] P. Gopinath, S. Chandrasekaran *J. Org. Chem.* **2011**, *76*, 700. For reviews on cyclopropanes as intermediates in organic synthesis see (a) H. N. C. Wong, M. Y. Hon, C. W. Tse, Y. C. Yip, J. Tanko, T. Hudlicky *Chem. Rev.* **1989**, *89*, 165; (b) H.-U. Reissig, R. Zimmer *Chem. Rev.* **2003**, *103*, 1151; (c) M. Rubin, M. Rubina, V. Gevorgyan *Chem. Rev.* **2007**, *107*, 3117.

[3] For recent reviews see: (a) H. Pellissier *Tetrahedron* **2008**, *64*, 7041; (b) H. Lebel, J.-F. Marcoux, C. Molinaro, A. B. Charette *Chem. Rev.* **2003**, *103*, 977.

[4] For selected examples see: (a) I. Ibrahem, G.-L. Zhao, R. Rios, J. Vesely, H. Sunden, P. Dziedzic, A. Cordova *Chem. Eur. J.* **2008**, *14*, 7867; (b) H. Xie, L. Zu, H. Li, J. Wang, W. Wang *J. Am. Chem. Soc.* **2007**, *129*, 10886; (c) J. Lv, J. Zhang, Z. Lin, Y. Wang *Chem. Eur. J.* **2009**, *15*, 972; (d) S. H. McCooey, T. McCabe, S. J. Connon *J. Org. Chem.* **2006**, *71*, 7494; (e) Y.-N. Xuan, S.-Z. Nie, L.-T. Dong, J.-M. Zhang, M. Yan *Org. Lett.* **2009**, *11*, 1583.

Sporadic examples of asymmetric cyclopropanations with dinucleophilic C_1 synthons and halogenated electrophilic alkenes are also known in the literature.[5]

In this context and in continuation of our studies concerning the chemistry of bis-electrophilic vinyl selenones,[6] we now report the preliminary results of novel Michael initiated cyclopropanations involving vinyl selenones and various carbon bis-nucleophiles. The success of these cascade reactions is based on the peculiar properties of the selenonyl group, which plays a dual role as an electron-withdrawing group, during the addition step, and as a leaving group, during the following intramolecular nucleophilic substitution. Some examples of cyclopropanations carried out with vinyl selenones and active methylene compounds in DMF or THF in the presence of NaH have been already reported in the literature (scheme 1).[7] We questioned if other bases or nucleophiles might be employed in these processes, also with the aim of developing an asymmetric organocatalytic procedure.



Scheme 1. MIRC approach to cyclopropanes with vinyl selenones and active methylene compounds.

[5] (a) S. Arai, K. Nakayama, T. Ishida, T. Shioiri *Tetrahedron Lett*. **1999**, *40*, 4215; (b) U. Das, Y.-L. Tsai, W. Lin *Org. Biomol. Chem.* **2013**, *11*, 44; (d) X. Dou, Y. Lu C*hem. Eur. J.* **2012**, *18,* 8315.

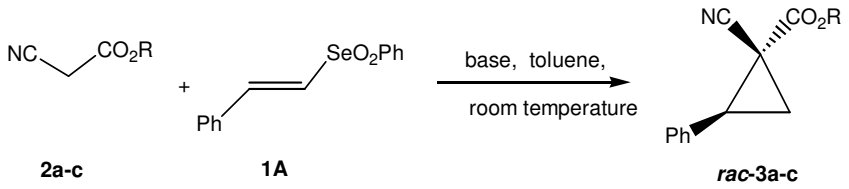
[6] (a) F. Marini, S. Sternativo, F. Del Verme, L. Testaferri, M. Tiecco *Adv. Synth. Catal*. **2009**, *351*, 1801; (b) F. Marini, S. Sternativo, F. Del Verme, L. Testaferri, M. Tiecco *Adv. Synth. Catal*. **2009**, *351*, 103; (c) S. Sternativo, A. Calandriello, F. Costantino, L. Testaferri, M. Tiecco, F. Marini *Angew. Chem. Int. Ed.* **2011**, *50*, 9382; (d) S. Sternativo, O. Walczak, B. Battistelli, L. Testaferri, F. Marini *Tetrahedron* **2012**, *68,* 10536; (e) S. Sternativo, F. Marini *Synlett* **2013**, *24*, 11.

[7] (a) I. Kuwajima, R. Ando, T. Sugawara *Tetrahedron Lett*. **1983**, *24*, 4429; (b) I. Kuwajima, R. Ando, T. Sugawara, M. Shimizu *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2897; (c) M. Tiecco, D. Chianelli, L. Testaferri, M. Tingoli, D. Bartoli *Tetrahedron* **1986**, *42*, 4889; (d) L. Bagnoli, C. Scarponi, L. Testaferri, M. Tiecco *Tetrahedron: Asymmetry* **2009**, *20*, 1506.

Results and discussion

Preliminary experiments were carried out in toluene with cyanoacetates **2a-c** and the (*E*)-vinyl selenone **1A** as the model substrate in the presence of two equivalents of an organic or an inorganic base (Table 1).

Table 1. Base screening.



2a-c **1A** ***rac*-3a-c**

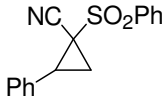
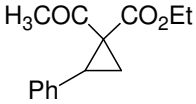
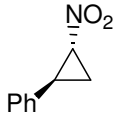
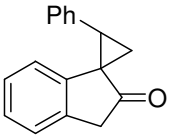
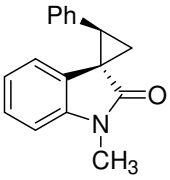
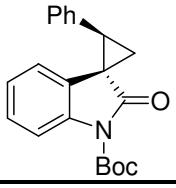
Entry		**R**	**Base**	**Time** (h)	**Yield** (%)[a,b]
1	**2a**	Et	K_2CO_3	46	98
2	**2a**	Et	Na_2CO_3	48	traces
3	**2a**	Et	DABCO	120	39
4	**2a**	Et	Et_3N	120	27
5	**2a**	Et	DBU[c]	0.5	88
6	**2b**	*t*Bu	K_2CO_3	28	46
7	**2b**	*t*Bu	DBU[c]	0.5	77
8	**2c**	Bn	K_2CO_3	24	95
9	**2c**	Bn	DBU[c]	2.5	99

a) The reactions were performed with 0.1 mmol of vinyl selenone **1A**, 2 equivalents of **2a-c** and 2 equivalents of base in toluene (0.4 ml) at room temperature.
b) The relative configuration of compounds **3a** and **3b** was established by comparison of ^{1}H-NMR spectra with those reported in literature.[8] The relative configuration of **3c** was assigned by analogy.
c) The reactions were carried out with 1.1 equivalents of base.

Cyclopropanes **3a-c** were formed in good to excellent yields and high diastereoselectivity with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Weaker organic bases, such as DABCO and Et_3N, gave access to the product but in poorer yields. Among the inorganic bases, K_2CO_3 gave very good results, whereas only traces of **3a** were obtained with Na_2CO_3. Then, we explored other carbon pronucleophiles. As shown in table 2, good results were obtained not only with nitromethane or active methylene compounds, but also with the 2-indanone **2g** and the oxindole derivatives **2h** and **2i**. Compounds of this type have never been employed in cyclopropanations of vinyl selenones.

[8] (a) B. Zhang, X.-Q. Zhu, J.-Y. Lu, J. He, P. G. Wang; J.-P. Cheng *J. Org. Chem*. **2003**, *68*, 3295; (b) S. Zhu, X. Xu, J. A. Perman, X. P. Zhang *J. Am. Chem. Soc*. **2010**, *132*, 12796.

Table 2. Cyclopropanations of vinyl selenones with different dinucleophilic C_1 synthons.

Entry		Base	Solvent	Time (h)	Product		Yield[a,b]
1	**2d**	K_2CO_3	Toluene	120		*rac*-**3d**	81%
2	**2d**	DBU	Toluene	1			90%
3	**2e**	K_2CO_3	Toluene	168		*rac*-**3e**	32%[c]
4	**2e**	DBU	Toluene	24			51%[c]
5	**2f**	K_2CO_3	Toluene	120		*rac*-**3f**	15%
6	**2f**	DBU	Toluene	5.5			58%
7	**2g**	DBU	Toluene	0.5		*rac*-**3g**	45%[d]
8	**2h**	DBU	Toluene	2.5		*rac*-**3h**	99%[e]
9	**2i**	DBU	Toluene	0.5		*rac*-**3i**	80%[e]

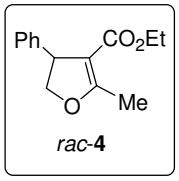
a) The reactions were performed with 0.1 mmol of vinyl selenone **1A**, 2 equivalents of **2** and 1.1 equivalents of base in toluene (0.4 ml) at room temperature. The reactions with K_2CO_3 were carried out with 2 equivalents of base.

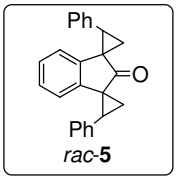
b) The relative configuration of compounds **3f**[9] and **3h**,[10] was established by comparison of ^{1}H-NMR spectra with those reported in literature. The configuration of **3i** was assigned by analogy**.**

c) The O-Alkylation product *rac*-**4** was also formed in 17 and 30% yield, respectively.

d) *Rac*-**5** was also formed in 11% yield.

e) 10% of the diastereoisomeric product is present.


rac-**4**


rac-**5**

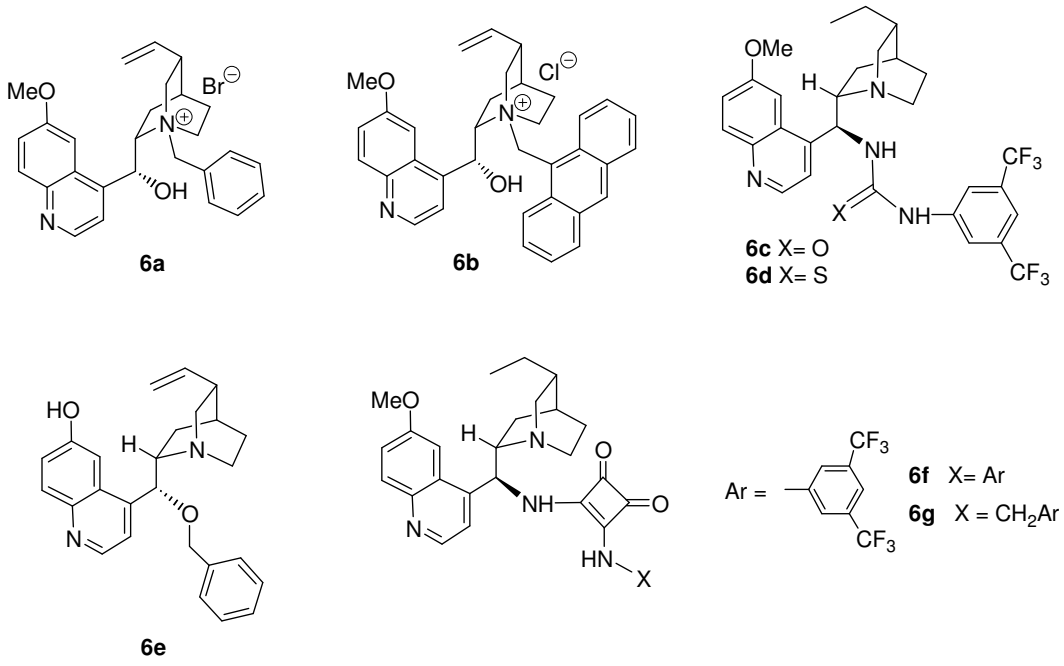
[9] B. Moreau, A. B. Charette *J. Am. Chem. Soc.* **2005**, *127*, 18014.

[10] Z.-Y. Cao, F. Zhou, Y.-H. Yu, J. Zhou *Org. Lett.* **2013**, *15*, 42.

Asymmetric variants of these reactions have been also investigated. The easily accessible cinchona alkaloid-derivatives **6a-g** reported in figure 1 were used for the screening. First experiments were carried out with the vinyl selenone **1A** and the cyanoacetate **2a** in the presence of an inorganic base and 10 mol% of the quaternary ammonium salt **6a** or **6b** as the phase-transfer catalyst (Table 3, entry 1-6). Recently, phase transfer catalysts have found interesting applications in enantioselective Michael reactions under biphasic conditions.[11] However in our case both catalysts proved to be ineffective, leading to the formation of an almost racemic product.

Thus, we turned our attention to easily accessible **6c-g** quinine derivatives, which have recently emerged as efficient catalysts for enantioselective Michael additions of a range of electrophilic alkenes,[12] included vinyl selenones.[6] 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 pronucleophile. The use of the ureidic compound **6c** afforded encouraging results giving **3a** in 85% yield and 46% *ee* (Table 3, entry 7). To reduce the loading of **6c**, initially employed in stoichiometric amount, the cyclopropanation was carried out by adding a basic additive to remove the benzeneseleninic acid formed during the cyclization and regenerate the catalyst. In fact, in the absence of any additive, only traces of **3a** were formed (Table 3, entry 8). The use of 20 mol% of **6c** and a stoichiometric amount of Na_2CO_3 enabled the formation of the cyclopropane **3a** in a high yield and with an enantioselectivity comparable with that observed with the stoichiometric loading of the catalyst. Similar results were achieved with $(NH_4)_2CO_3$ in a shorter reaction time (Table 3, compare entries 14 and 19).

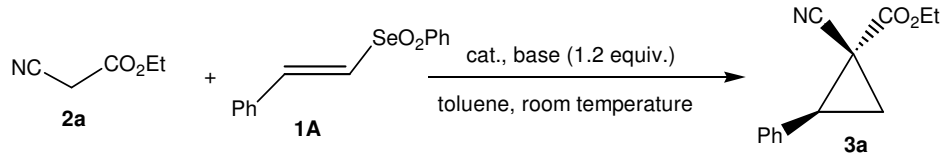
Figure 1. Catalysts for the screening.



[11] T. Ooi, K. Maruoka *Angew. Chem. Int. Ed.* **2007**, *46*, 4222.

[12] E. M. O. Yeboah, S. O. Yeboah, G.S. Singh *Tetrahedron* **2011**, *67*, 1725.

Table 3. Catalyst screening.



Entry	Cat.	Base	Time (h)	Yield[a] (%)	*ee*[b](%)
1	**6a**	K_2CO_3 6 equiv.	48	76	4
2	**6a**	K_2CO_3 6 equiv. in DCM	96	35	2
3	**6a**	K_2CO_3 6 equiv. in DMSO	7	69	0
4	**6b**	K_2CO_3	24	83	5
5	**6b**	KF	24	30	15
6	**6b**	Na_2CO_3 6 equiv.	24	44	15
7[c]	**6c** 1 equiv.	-	17(72)	85 (26)	46 (53)
8	**6c**	-	120	traces	-
9	**6c**	DABCO	24	35	44
10	**6c**	DBU	0.5	83	0
11	**6c**	K_2CO_3	17	87	15
12	**6c**	Li_2CO_3 6 equiv.	24	traces	48
13	**6c**	Na_2CO_3 6 equiv.	24	30	48
14	**6c**	Na_2CO_3	93	87	48
15	**6d**	Na_2CO_3	70	24	19
16	**6e**	Na_2CO_3	99	24	-21
17	**6f**	Na_2CO_3	120	29	20
18	**6g**	Na_2CO_3	96	49	26
19	**6c**	$(NH_4)_2CO_3$	24	64	44

a) Unless otherwise specified, reactions were run with 0.1 mmol of vinyl selenone **1A**, 2 equivalents of **2a,** 10 mol% (**6a**, **6b, 6f, 6g**) or 20 mol% (**6c-e**) of the catalyst and 1.2 equivalents of base in toluene (0.4 ml) at room temperature.

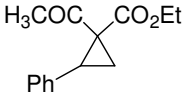
b) The *ee* values were determined by chiral HPLC analysis. The absolute configurations were determined by comparison of optical rotations with those reported in literature.[8b]

c) The values in brackets refer to a reaction carried out at -10 °C.

As expected, the addition of stronger bases such as K_2CO_3 or DBU gave cyclopropanes with excellent yields, but with a significant loss of enantiocontrol (Table 3, entries 10-11) due to undesired background reactions. Finally, catalysts **6d-g** showed poor catalytic activity and enantioselectivity (Table 3, entries 15-18).

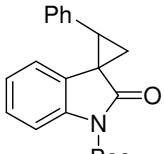
Table 4 shows the results of other experiments performed with **2a**, **2e** or **2i** as nucleophiles and **1A** or the β-alkyl substituted vinyl selenone **1B** ($CH_3(CH_2)_5CH{=}CHSeO_2Ph$). In all the cases product were formed with a moderate enantiocontrol.

Table 4. Other asymmetric cyclopropanations of vinyl selenones.



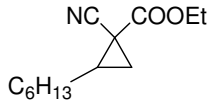
3e

40%[a] (94h), *ee* 9%



3i

47%[a,b] (120h), *ee* 30%



3j

75%[a] (43h), *ee* 36%

a) The reactions were run with 0.1 mmol of vinyl selenone **1A** or **1B**, 2 equivalents of **2,** 20 mol% of the catalyst and 1.2 equivalents of $(NH_4)_2CO_3$ (or Na_2CO_3 for **3e**) in toluene (0.4 ml) at room temperature.

b) The reaction was carried out with 10 mol% of catalyst.

Conclusions

In conclusion, a new MIRC approach to densely functionalized cyclopropanes by using vinyl selenones and carbon pronucleophiles with bases such as DBU or K_2CO_3 has been described. Variously substituted cyclopropanes were obtained in good yields and high diastereoselectivity. The feasibility of asymmetric reactions under phase-transfer catalysis or acid-base bifunctional catalysis has been also investigated. The quinine-derived ureidic bifunctional catalyst **6c** in the presence of Na_2CO_3 or $(NH_4)_2CO_3$ as the stoichiometric base afforded the desired cyclopropanes with moderate enantioselectivity (up to 48%). Further studies for catalyst's optimization will be necessary in order to improve the efficiency of the process.