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Asymmetric Synthesis of α-Alkyl α-Selenocarbonyl Compounds Catalyzed by Bifunctional Organocatalysts

Vanesa Marcos,[†] Jose Alemán,*[,†] Jose L. Garcia Ruano,[†] Francesca Marini,*[,‡] and Marcello Tiecco[‡]

Departamento de Química Orgánica (C-I), Universidad Autónoma de Madrid, Cantoblanco, 28049 Madrid, Spain, and Dipartimento di Chimica e Tecnologia del Farmaco Sezione di Chimica Organica, Universita di Perugia, 06123 Perugia, Italy

jose.aleman@uam.es; marini@unipg.it

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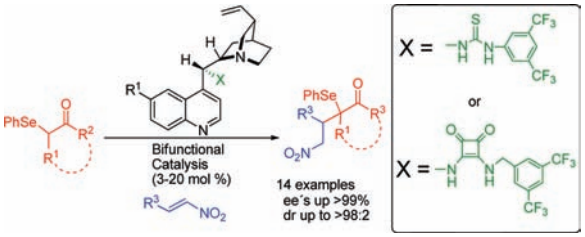
ABSTRACT



A new organocatalytic approach for the synthesis of a variety of α-alkyl, α-phenylselenyl ketones as well as their corresponding esters and amides, by the addition of α-selenocarbonyl derivatives to nitroalkenes catalyzed by thiourea or squaramide cinchona catalysts, is presented. This catalytic system allows the preparation in high yields of enantiomerically enriched selenocarbonyl derivatives bearing two chiral centers with excellent ee's and dr's by using catalytic loadings of 3 mol %.

Organoselenium compounds have become attractive synthetic targets because of their unique chemo-, regio-, and stereoselectivities in organic synthesis and their useful biological and medical properties (antioxidant, antitumoral and antimicrobial).[1] In particular, α-(phenylselenyl) carbonyl compounds are of great importance in synthetic chemistry[2] because of their use as starting materials for preparing α,β-unsaturated ketones[2a] and other synthetically useful compounds,[2b−d,3] as well as intermediates in the synthesis of polycyclic compounds via free-radical cyclization processes.[4] Additionally, Cotgreave et al.[5] reported gluthathione peroxidase-like biological properties for some specific series of α-phenylseleno ketones, which can be employed as antiviral, anticancer, and anti-inflammatory agents. Moreover, it is well-known that α-(phenylselenyl)-carbonyl moieties are present in selenoproteins, which are essential for the human immune system.[6] Despite this

[†] Universidad Autónoma de Madrid.
[‡] Universit di Perugia.

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(5) Cotgreave, I. A.; Moldeus, P.; Brattsand, R.; Hallberg, A.; Anderson, C. M.; Engman, L. *Biochem. Pharmacol.* **1992**, *43*, 793.

(6) In humans, 25 selenoproteins have been identified, many of which have unknown functions and remain to be explored. For leading references, see: (a) Kryukov, G. V.; Castellano, S.; Novoselov, S. V.; Lobanov, A. V.; Zehtab, O.; Guingo, R.; Gladyshev, V. N. *Science* **2003**, *300*, 1439. (b) May, S. W. *Exp. Opin. Invest. Drugs* **1999**, *8*, 1017. (c) Medina, D.; Thompson, H.; Ganther, H.; Ip, C. *Nutr. Cancer*. **2001**, *40*, 12. For recent examples, see: (d) Wang, J.; Li, H.; Mei, Y.; lou, B.; Xu, D.; Xie, D.; Guo, H.; Wang, W. *J. Org. Chem.* **2005**, *70*, 5678 and references cited therein.

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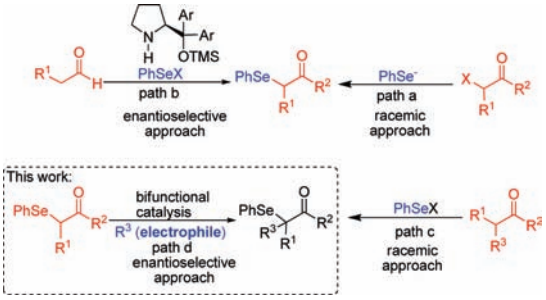
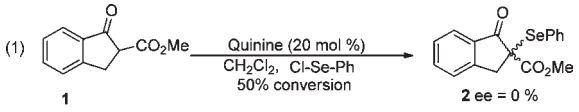
large synthetic and biological importance, presumably more relevant for compounds with the selenium joined to the tertiary carbons (with higher conformational restrictions and precursors of more stable radicals), few methods affording enantiomerically pure α-(phenylselenyl)-carbonyl derivatives have been reported (path b, Scheme 1). The most used procedures for preparing racemic compounds are based on reactions of α-haloketones with phenylselenide (path a, Scheme 1)[7] and those of ketoenols or ketoenolates with a Se electrophilic source (path c, Scheme 1).[8]

Scheme 1. Different Approaches for the Synthesis of Seleno-carbonyl Derivatives



Steric reasons determine that the first method was only successful for secondary halides, thus converting the second one in the only available path for preparing carbonyl compounds with the selenium joined to tertiary carbons. None of them has been applied to the synthesis of enantiomerically enriched compounds. However, organocatalytic methods for preparing secondary centers attached to Se have appeared in recent years.[9] Thus, the first highly enantioselective approach for synthesizing α-selenyl aldehydes was reported in 2007 (path b, Scheme 1).[9b,c] It is based on the reaction of electrophilic Se sources with aldehydes activated with the Jørgensen–Hayashi catalyst which is only valid for aldehydes. However, compounds containing enantioenriched tertiary selenocenters, as far as we know, have never been prepared in highly enantioenriched form. Here, we present the first organocatalytic enantio- and diastereoselective synthesis of α-phenylselenoketone (also ester and amide) derivatives containing selenylated tertiary stereocenters by reaction of the selenocarbonyl derivatives with nitroalkenes (path d, Scheme 1) in the presence of bifunctional thioureas[10]and squaramides.[11]

Our initial trials involved α-selenation of *β*-ketoesters with *N*-(phenylseleno)phthalimide and phenylselenyl chloride (path c, Scheme 1) catalyzed by different cinchona bases. Reactions were chemically successful, yielding the α-seleno-*β*-ketoesters in moderate conversions (eq 1), but racemic compounds were isolated in all the studied cases (see Supporting Information (SI)).



One possible reason for the failure of these reactions could derive from the incompatibility of the electrophilic selenium species with the catalytic systems used in these reactions.[12] For these reasons, we hypothesized that the incorporation of the selenium to the nucleophile (*β*-selenocarbonyl derivatives) and the reaction with an electrophile would make possible the synthesis of the desired α-quaternary-seleno-carbonyl centers (path d, Scheme 1). Thus, the model reaction for optimization was carried out with the α-phenylselenylindanone (**3a**) and nitrostyrene (**4a**) catalyzed by cinchona alkaloids **5a**–**e** and **6b**–**e** (Figure 1). The obtained results are collected in Table 1.

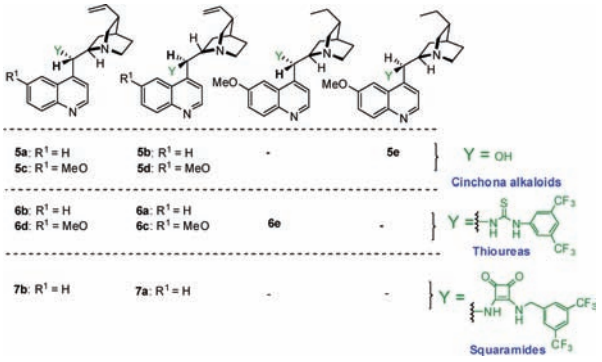


Figure 1. Cinchona alkaloid derivatives (**5**), bifunctional thioureas (**6**), and squaramides (**7**) used in this study.

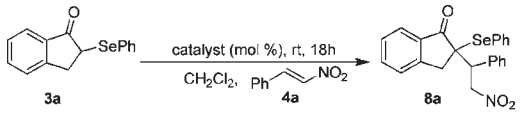
(7) (a) Sharpless, K. B.; Young, M. W.; Lauer, R. F. *Tetrahedron Lett*. **1979**, 1973. (b) Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc*. **1973**, *95*, 2697. (c) Sharpless, K. B.; Lauer, R. F.; Teranishi, A. Y. *J. Am. Chem. Soc*. **1973**, *95*, 6137.

(8) (a) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc*. **1973**, *95*, 6137. (b) Lebarillier, L.; Outurquin, F.; Paulmier, C. *Tetrahedron* **2000**, *56*, 7483 and references cited therein. (c) Brockson, T. G.; Petragnani, N.; Rodriguez, R. *J. Org. Chem*. **1974**, *39*, 2114. (d) Reich, H. J.; Reich, I. L.; Renga, J. M. *J. Am. Chem. Soc*. **1973**, *95*, 5813. (e) Reich, H. J.; Reich, I. L. *J. Am. Chem. Soc*. **1975**, *97*, 5434. (f) Denis, J. M.; Dumont, W.; Krief, A. *Tetrahedron Lett*. **1976**, 453. (g) Houllemarer, D.; Ponthieux, S.; Outurquin, F.; Paulmier, C. *Synthesis* **1996**, 101.

(9) Despite their interest, only a very few methods concerning the organocatalytic synthesis of enantiomerically pure secondary seleno compounds have been reported. For example, see: (a) Winberg, H.; Pluim, H. *Tetrahedron Lett*. **1979**, 1251. (b) Tiecco, M.; Carlone, A.; Sternativo, S.; Marini, F.; Bartoli, G.; Melchiorre, P. *Angew. Chem., Int. Ed*. **2007**, *46*, 6882. (c) Sundén, H.; Rios, R.; Córdova, A. *Tetrahedron Lett*. **2007**, *48*, 7865.

(10) For a recent review about a bifunctional cinchona alkaloid based on thiourea catalysis, see: (a) Connon, S. J. *Chem. Commun*. **2008**, 2499. For an account of multifunctional thioureas, see: (b) Miyabe, H; Takemoto, Y. *Bull. Chem. Soc. Jpn*. **2008**, *81*, 785. For selected recent examples of thiourea bifunctional catalysis, see: (a) Wang, J.; Xie, H.; Wang, W. *Angew. Chem., Int. Ed*. **2008**, *47*, 4177. (b) Alemán, J.; Milelli, A.; Cabrera, S.; Reyes, E.; Jørgensen, K. A. *Chem.—Eur. J*. **2008**, *14*, 10958. (c) García Mancheño, O.; Tangen, P.; Rohlmann, R.; Fröhlich, R.; Alemán, J. *Chem.—Eur. J*. **2011**, *17*, 984. (d) Gao, Y. J.; Ren, Q.; Wu, H.; Li, M. G.; Wang, J. *Chem. Commun*. **2010**, *46*, 9232. (e) Ren, Q.; Gao, Y. J.; Wang, J. *Chem.—Eur. J*. **2010**, *16*, 13594. (f) Gao, Y. J.; Ren, Q.; Siau, W.-Y.; Wang, J. *Chem. Commun*. **2011**, DOI: 10.1039/C1CC11124H.

Table 1. Selected Screening Results for the Michael Addition of **3a** to Nitrostyrene **4a**[a]



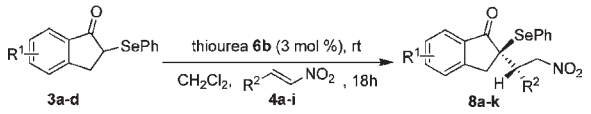
entry	cat. (mol %)	conv[b]	dr[b]	er[c]
1	**5a** (20)	70	86:14	80:20
2	**5b** (20)	70	85:15	81:19
3	**5c** (20)	>98	65:35	60:40
4	**5d** (20)	>98	76:24	66:33
5	**5e** (20)	>98	77:23	60:40
6	**6a** (3)	>98	80:20	87:13
7	**6b (3)**	**>98**	**95:5**	**97:3**
8	**6c** (3)	85	68:32	87:13
9	**6d** (3)	92	80:20	95:5
10	**6e** (3)	96	83:17	70:30

[a] Performed at rt in CH_2Cl_2 (0.2 mL) by using 0.1 mmol of **3a** and 0.13 mmol of **4a**. [b] Determined by ^1H NMR. [c] Determined by chiral-stationary phase HPLC (major isomer).

The use of **5a**−**e** as catalysts gave good conversions but only moderate diastereo- and enantiomeric ratios (entries 1−5). Interestingly, the use of bifunctional thiourea-cinchona catalysts **6a**−**e** (entries 6−10) gave the most promising results, demonstrating that the thiourea and the tertiary amine functionalities cooperate in increasing the diasteo- and enantiocontrol of this reaction providing nearly full conversions, remarkably with only 3 mol % of catalytic loading required. The best results were obtained with **6b** (dr = 95:5 and 94% ee, entry 7).[13]

With these optimized conditions, we studied the scope of the reaction by using different nitroalkenes **4a**−**i** (entries 1−10, Table 2) and selenoindanones **3a**−**d** (entries, 11−13, Table 2). We first checked that the results obtained in the reaction of **4a** with selenoindanone **3a** in the presence of **6b** (entry 7, Table 1 and entry 1, Table 2) are not substantially modified when the reaction was scaled up to 1.0 mmol (Table 2, entry 2). The incorporation of EWG to the aromatic ring of the nitrostyrene (**4b** and **4c**, entries 3−4, Table 2) slightly improved the diastereomeric ratio, but lower yields were obtained. By contrast, a decrease in the dr was observed when EDG at the aromatic group was used (*p*-OMe, **4d**) (entry 5, Table 2). The substitution of the phenyl group by the 2-furyl aromatic ring (**4e**, entry 6, Table 2) had a similar influence. Haloarylnitrostyrenes **4f**−**h** also evolved with a very high enantiomeric ratio and 90:10 dr (entries 7−9, Table 2). Unfortunately, no reaction was observed starting from the alkyl nitroalkene **4i** (Table 2, entry 10) under the same reaction conditions. We also studied the addition of indanones **3b**−**d** to nitrostyrene **4a** (Table 2, entries 11−13). In these cases, the influence of the substituents on the aromatic rings seems to be opposite to that observed in the previous cases; EWG (**3b**, entry 11) decreased the dr whereas EDG (**3c** and **3d**, entries 12 and 13) increased the dr.

Table 2. Results Obtained with Nitroalkenes **4a**−**i** and Indanones **3a**−**d**[a]



entry	R^1	R^2	product (%[b])	dr[c]	er[d]
1	H-**3a**	Ph-**4a**	**8a** (80)	95:5	97:3
2[e]	H-**3a**	Ph-**4a**	**8a** (74)	97:3	97:3
3	H-**3a**	*p*-NO_2-C_6H_4-**4b**	**8b** (53)	96:4	97:3
4	H-**3a**	*p*-CN-C_6H_4-**4c**	**8c** (65)	97:3	97:3
5	H-**3a**	*p*-MeO-C_6H_4-**4d**	**8d** (72)	87:13	97:3
6	H-**3a**	2-Furyl-**4e**	**8e** (56)[g]	85:15	91:9
7	H-**3a**	*p*-F-C_6H_4-**4f**	**8f** (80)	90:10	97:3
8	H-**3a**	*o*-F-C_6H_4-**4g**	**8g** (86)	90:10	95:5
9	H-**3a**	3,4-Dichloro-**4h**	**8h** (70)	90:10	94:6
10	H-**3a**	*n*-Et-**4i**	Nr[f]	–	–
11	6-CF_3-**3b**	Ph-**4a**	**8i** (86)	88:12	95:5
12	5-Me-**3c**	Ph-**4a**	**8j** (70)	97:3	98:2
13	3,4-MeO-**3d**	Ph-**4a**	**8k** (60)	>98:2	>99:1

[a] Performed at rt in CH_2Cl_2 (0.2 mL) using 0.1 mmol of **3**, 0.13 mmol of **4**, and catalyst **6b** (3 mol %). [b] Isolated yield of the major diastereoisomer. [c] Determined by ^1H NMR. [d] Determined by chiral-stationary phase HPLC (major isomer). [e] Reaction carried out at 1.0 mmol scale. [f] No reaction. [g] Separation of the diastereisomers was not possible.

Encouraged by these results, we widened the scope, extending the reaction to other α-selenocarbonyl derivatives **9**−**11** (Table 3). α-Selenocyclopentanone **9**[14] did not react with catalyst **6b** (Table 3, entry 1) or other thioureas catalysts **6a**, **6c**, and **6d**. With the α-selenocumarone **10** and the α-selenooxoindol **11** (Table 3, entries 4,7), we observed the formation of **13** and **14** respectively. However both enantiomeric and diastereomeric excesses of these compounds were quite low. These negative results forced us to investigate other bifunctional catalysts. In the past two years, squaramides[11] (such as **7a** and **7b**, Figure 1) have emerged as promising catalysts, strongly increasing in

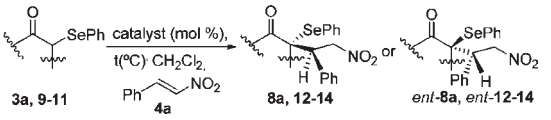
(11) For pioneering work in this field, see: (a) Malerich, J. P.; Hagihara, K.; Rawal, V. H. *J. Am. Chem. Soc.* **2008**, *130*, 14416. (b) For a recent review, see: Storer, R. Ian; Aciro, Caroline; Jones, Lyn H. *Chem. Soc. Rev.* **2011**, *40*, 2330. (c) Alemán, J.; Parra, A.; Jiang, H.; Jørgensen, K. A. *Chem.—Eur. J.* **2011**, DOI: 10.1002/chem.201003694.

(12) We have studied the changes produced in the NMR spectra of the quinine **5c** and thiourea **6b** catalysts by mixing 1 equiv of the corresponding catalyst with 1 equiv of Cl-Se-Ph in CD_2Cl_2 (see SI). The OH group at the quinine is presumably converted into O-Se-Ph (for an example in the reaction of PhSeCl with alcohols, see: Osajda, M.; Młochowski, J. *Tetrahedron* **2002**, *58*, 7531), whereas the thiourea evolves into a very complex mixture of species. It would explain the absence of catalytic activity and the formation of the racemic mixtures. Moreover, we have checked that this reaction occured in the absence of catalyst.

(13) Several and different conditions of varying solvent, temperatures, and equivalence were tried. For more details, see SI.

(14) α-Selenocyclohexanone and the opened derivatives (1,2-diphenyl-2-(phenylselanyl)ethanone and 1-1-phenyl-2-(phenylselanyl)propan-1-one) did not react under any of the catalytic conditions of Tables 2 and 3.

Table 3. Scope of Different Selenocarbonyl Derivatives **3a**, **9**–**11** with Nitrostyrene **4a**[b]



entry	sm[a]	cat. (mol %)	t(°C)/ time (h)	product[c]	dr[d]	er[e]
1		**6b** (20)	35/-	n.r.[f]	-	-
2		**7b** (20)	35/32	**12** (68)	90:10	91:9
3		**7a** (20)	35/32	*ent*-**12** 63	97:3	1:99
4		**6b** (10)	rt/10	**13** 92	37:63	nd[g]
5		**7b** (10)	-78/16	**13** (>98)	88:12	94:6
6		**7a** (10)	-78/16	*ent*-**13** 92	93:7	3:97
7		**6b** (10)	rt/10	**14** 95	46:53	nd[g]
8		**7b** (10)	-78/16	**14** (>98)	80:20	96:4
9		**7a** (10)	-78/16	*ent*-**14** 97	90:10	1:99
10		**6b** (3)	20/18	**8a** 80	95:5	97:3
11		**7a** (20)	35/72	*ent*-**8a** 55	95:5	89:2

[a] Starting material. [b] Performed in CH_2Cl_2 (0.2 mL) at 0.1 mmol scale. [c] Isolated yields after flash chromatography except cases in parentheses which are conversions determined by ^{1}H NMR. [d] Diastereomeric ratio determined by ^{1}H NMR. [e] Enantiomeric ratio determined by chiral-stationary phase HPLC. [f] No reaction. [g] Not determined.

many cases the reactivity of many substrates. Thus we studied reactions of **9** with nitroalkene **4a** catalyzed by **7b** (entry 2, Table 3). To our delight, **12** was obtained in 68% conversion, in very good diastereomeric and enantiomeric ratios. Better conversions and good results were obtained in reactions of the amide **10** and the lactone **11** with **4a** and catalyst **7b**, affording **13** and **14**, respectively (entries 5 and 8). The major enantiomer obtained in these reactions was the same as that obtained by using **6b** as the catalyst, which is not unexpected taking into account that **6b** and **7b** have the same relative configuration (see Figure 1). At this point we also studied the reactions of **9**–**11** with **4a** under **7a** catalysis (it is the *pseudo*-enantiomer of **7b**). As it was expected, the major compounds obtained in these reactions are the enantiomers of those resulting under **7b** catalysis. It is remarkable that enantiomeric and diastereomeric excesses obtained under **7a** catalysis are slightly better than those resulting with **7b**. Finally reaction of **3a** with **4a** catalyzed by **7a** affords *ent*-**8a** (entry 11), the enantiomer of **8a** which had been obtained under **6b** catalysis (entry 10, Table 3).

The absolute configuration of products **8** was unequivocally determined by X-ray analysis of appropriated crystals of **8a** (right, Figure 2; see SI for more details).[15] The configuration of *ent*-**8a** was established by comparison of its specific rotation and HPLC data. The same criteria were used to assign the absolute configuration of **12**–**14** and their enantiomers.

Based on previous mechanistic proposals,[10,11] the direct approach of the deprotonated β-selenoketone from the *Re*-face to the nitroalkene would justify the observed stereochemistry (left, Figure 2) for the formation of products **8**. The H-bond association of the Se could aid this approach.[16]

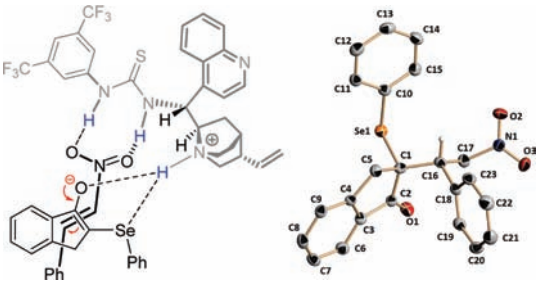


Figure 2. X-ray ORTEP structure of **8a** and stereochemical proporsal.

In conclusion, we have found a new approach for the synthesis of a variety of α-seleno ketones, esters, and amides with quaternary carbons joined to selenium. It consists of the addition of β-selenocarbonyl derivatives to nitroalkenes catalyzed by thiourea or squaramide cinchona catalysts. This catalytic system allows the synthesis of optically enriched selenocarbonyl derivatives with two chiral centers with excellent ee's, dr's and good yields. Very low catalytic loadings (3 mol %) are required with bifunctional thiourea catalysts.

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Supporting Information Available. Experimental procedures and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(15) CCDC 809359 (**8a**) contains the supplementary crystallographic data. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [E-mail: deposit@ccdc.cam.ac.uk].

(16) For a computational study of the H-bond with Se compounds, see: Madzhidov, T. I.; Chmutova, G. A. *J. Mol. Struct.* **2010**, *959*, 1.