Organocatalytic Asymmetric Synthesis and Use of Organoselenium Compounds

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Dedicated to our mentor Professor Marcello Tiecco

Abstract: In the last ten years organocatalysis has emerged as an efficient and sustainable strategy for the asymmetric synthesis of chiral molecules. Optically active intermediates for novel interesting transformations are generated under mild and operationally simple conditions when selenium-containing compounds are used as reaction partners. The peculiar reactivity of organoselenium compounds has been exploited in practical one-pot sequences for the asymmetric construction of densely functionalized compounds starting from simple precursors.

1   Introduction

In the last few decades organoselenium compounds, because of their high structural diversity, rich chemistry, ready availability, and easy handling, have become very popular in synthetic chemistry.[1] In some respects the structure and reactivity of organoselenium compounds are similar to those of the better-known sulfur analogues, but certain features make selenium derivatives particularly valuable. For example, selenium forms weaker σ-bonds than sulfur, hence, reactions which involve cleavage of C–Se, O–Se, and N–Se bonds occur at a faster rate and under milder conditions. A selenium group is usually introduced in high yield into a target molecule through electrophilic or nucleophilic reagents with a predictable chemo-, regio-, and stereoselectivity. In many cases the insertion is concomitant with the introduction of vicinal functional groups or with the formation of rings and stereocenters. The selenium group can also be used for further elaborations such as ionic or radical substitutions and elimination processes. One of the most attractive aspects of selenium chemistry is the wide applicability in asymmetric synthesis, a topical area of modern organic chemistry.[1,2] Many compounds have been prepared in the

optically active form by asymmetric versions of common selenium-based methodologies. In this field our research group has made several contributions such as asymmetric cyclofunctionalizations of alkenes with optically active diselenides[3] and short synthetic sequences for access to heterocycles with achiral selenium reagents and compounds from the chiral pool.[4] However, with the exception of selenofunctionalization and deselenylation sequences with chiral diselenides and metal-catalyzed reactions in which the organoselenium compound acts as a chiral ligand,[1,2] catalytic asymmetric methods based on selenium chemistry are poorly investigated. This is surprising since the field of asymmetric organocatalysis has recently emerged as a robust and powerful strategy for the enantioselective construction of building blocks, natural products, and molecules of pharmaceutical interest. Pioneering cinchonidine-catalyzed 1,4-additions of benzeneselenol to cyclohexenones[5] and L-prolinamide-catalyzed α-selenenylations of carbonyl compounds[6] gave products with poor enantioselectivity. Very recently, Denmark et al. reported the first catalytic selenoetherification reactions of alkenes by using a BINAM-derived thiophosphoroamide catalyst.[7] In this Account we illustrate our recent efforts to broaden the scope of enantioselective organocatalysis to new processes involving the rich and versatile chemistry of selenium compounds. Privileged organocatalysts, with covalent or non-covalent activation modes, have been employed for the enantioselective synthesis of important classes of organoselenium compounds, such as α-seleno carbonyl compounds, β-hydroxy and β-amino selenides and selenones. Moreover, the ease of handling and the unique reactivity of selenium functionalities have been exploited in the development of new one-pot strategies for a practical asymmetric construction of densely functionalized cyclic compounds from simple precursors.

2   Organocatalytic Asymmetric Synthesis of α-Seleno Carbonyl Compounds and Applications

Our first result was the α-selenenylation of aldehydes[8] via enamine catalysis. Despite the great attention that asymmetric α-functionalization of aldehydes has received and despite the successful insertion of a range of electrophiles by chiral secondary amine catalysis,[9] before our report the only access to highly enantioenriched α-seleno aldehydes

relied on the chiral-pool approach. Our protocol employs commercially available *N*-(phenylseleno)phthalimide (**2**) as a bench-stable electrophilic selenium source and the silyl ether of chiral diarylprolinol **3** in combination with 4-nitrobenzoic acid as the catalyst. As observed for other α-heterofunctionalizations of aldehydes, this catalyst exhibits superior selectivity and much higher catalytic activity than other secondary amines without the bulky silyl group. The operationally simple method has been used successfully for the α-selenenylation of a wide range of aldehyde substituents, including alkyl, alkenyl, and hetero-substituted chains. Scheme 1 shows some representative results.

To facilitate workup and avoid racemization during chromatography, the reaction products **4** were isolated as the 1,2-selenoalcohols **5** after in situ reduction of the aldehyde moiety with NaBH₄. Selenoalcohols with different skeleton and stereochemical requirements have been recently synthesized by catalytic asymmetric procedures based on lipase-mediated kinetic resolutions or metal-catalyzed desymmetrizations of *meso*-epoxides.[10]

The highly enantioenriched α-selenoaldehydes and the corresponding alcohols are versatile building blocks with great synthetic utility.[1] Schemes 2 and 3 describe some se-

Selected examples:

5a 99%, 95% ee   **5b** 89%, 99% ee   **5c** 81%, 97% ee

5d 84%, 97% ee   **5e** 94%, 98% ee   **5f** 91%, 98% ee
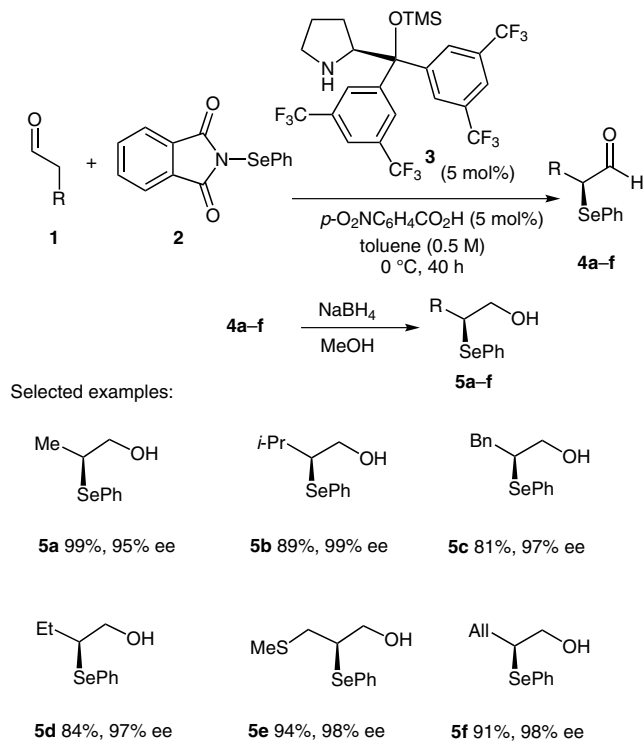
Scheme 1

Biographical Sketches

Francesca Marini obtained her MSc with honors in Chemistry and Pharmaceutical Technology from the University of Perugia in 1990. After an annual fellowship from Mediolanum Farmaceutici S.p.A. working on *Synthesis of Heterocyclic Derivatives of Biological Interest* under the Supervision of Professor A. Fravolini, she received her PhD in Chemical Sciences in 1994 under the Supervision of Professor M. Tiecco with the doctoral thesis *Cyclization Reactions Promoted by Organoselenium Compounds. New Syntheses of Heterocyclic Compounds*. In the same year she became an Assistant Professor at the University of Perugia and since 2006 she is Associate Professor at the same university. Her main scientific interests concern the development of new synthetic methods with organoselenium reagents, particularly in the field of asymmetric synthesis and organocatalysis.

Silvia Sternativo completed her MSc with honors in Chemistry and Pharmaceutical Technology at the University of Perugia in 1999. She obtained her PhD in Chemical Sciences in 2003 under the supervision of Professor M. Tiecco with the dissertation *Asymmetric Syntheses Promoted or Catalyzed by Organoselenium Reagents*. After postdoctoral grants (2003–2007) at the University of Perugia, in 2008 and 2010 she was granted with two C.I.N.M.P.I.S. annual research fellowships on the project *New Organocatalytic Procedures Based on Organoselenium Chemistry for the Stereoselective Synthesis of Polyfunctional Compounds*. Currently, she has a postdoctoral research grant at the University of Perugia under the supervision of Professor Francesca Marini. Her main scientific interest concerns the use of organoselenium reagents in the development of new synthetic methodologies for the diastereo- and enantioselective synthesis of polyfunctional or heterocyclic compounds. Currently, she is working on new organocatalytic asymmetric approaches to synthetically valuable polyfunctional compounds containing all-carbon quaternary stereocenters.

quences that apply this organocatalytic α-selenenylation protocol as a key step for the preparation of synthetically and biologically useful compounds.
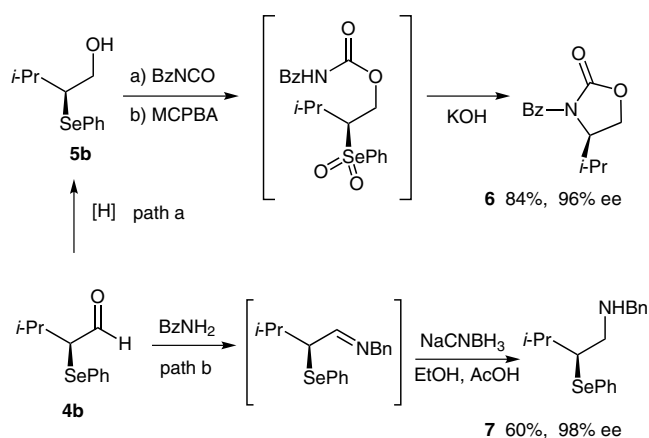
Scheme 2

Aldehyde **4b** was converted into the corresponding carbamate and then oxidized in situ in order to generate a selenonyl group (Scheme 2, path a). A ring-closure reaction by stereospecific intramolecular nucleophilic displacement of this good leaving group generated the 4-substituted 1,3-oxazolidinones **6**.[8a] The α-selenenylated aldehyde **4b** was also converted into the amine **7** in good yield without loss of enantiomeric purity (Scheme 2, path b). Enantiomerically pure 1,2-selenoamines are not only appreciated ligands or intermediates for enantioselective reactions and heterocyclic synthesis, but also promising pharmacological agents.[11] Elegant protocols for the asymmetric synthesis of α-hydroxy-β,γ-unsaturated esters **9** by Posner et al.[12] and α-alkyl,α-vinyl amino acids **10** by Armstrong et al.[13] are illustrated in Scheme 3. The crude α-selenoaldehydes prepared by our procedure were subjected to in situ Wittig or Horner–Wadsworth–Emmons olefi-

nations to give the enantiomerically enriched di- and trisubstituted allylic selenides **8**. Selenide to selenoxide oxidations or N-chlorosuccinimide-mediated selenimide formations followed by [2,3]-sigmatropic rearrangements yielded α-hydroxy-β,γ-unsaturated esters **9** and α-alkyl,α-vinyl amino acids **10**, respectively (Scheme 3, path a and b). The products were obtained in high yields and excellent enantiomeric excesses.

Some advantages of the use of these selenium-based protocols over the corresponding sulfur methods are: the synthesis of the starting α-selenoaldehydes from a stable and commercially available selenium reagent, the relative stability of these aldehydes with respect to racemization, and the milder conditions required for scission of selenium bonds. Moreover, the highly enantioenriched γ-substituted-α,β-unsaturated esters **12**[14] were synthesized via 1,3-syn allylic replacement of selenide **8** by chloride to afford **11** followed by 1,3-anti substitutions with methylcuprate or sodium azide (Scheme 3, path c). This process has been carried out on a multigram scale. The chiral γ-methyl-α,β-enoate structural unit is present in many natural products, including pheromones, steroids, macrolides, and squalestatins.

Very recently, the catalytic activity of resin-supported proline derivatives has been evaluated in the asymmetric α-selenenylation of aldehydes, but lower levels of reactivity and selectivity with respect to free catalysts were observed.[15]

Organocatalytic α-selenenylations of ketones are still a challenging task. First experiments carried out by Wang and co-workers with cyclohexanone, N-(phenylseleno)phthalimide and a pyrrolidine trifluoromethanesulfonamide derived from L-proline[6] gave α-selenoketones in good yields but very poor enantioselectivities (ee < 20%).

Moreover, catalyst **3** is effective only with aldehydes, and our attempts of selenenylation of β-ketoesters with phenylselenyl chloride or N-(phenylseleno)phthalimide in the
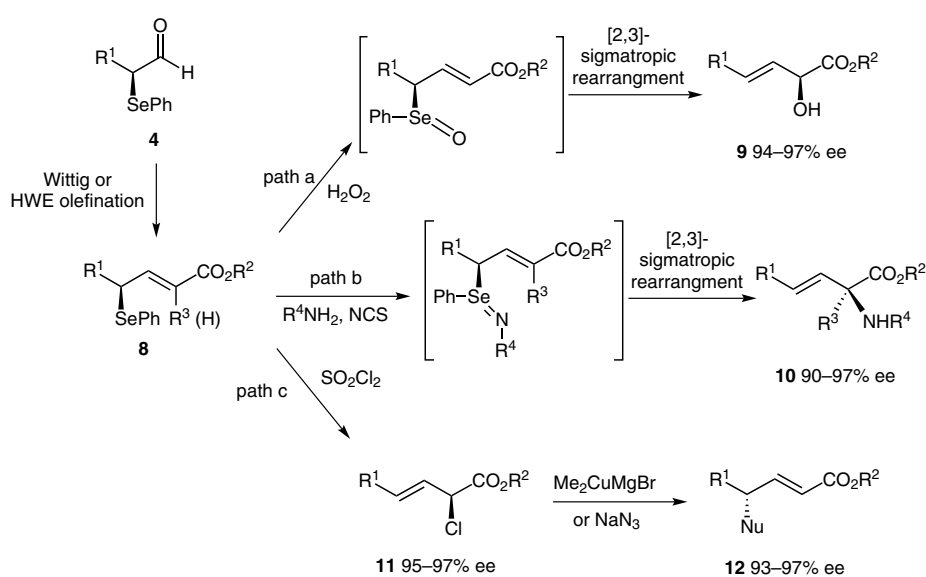
Scheme 3
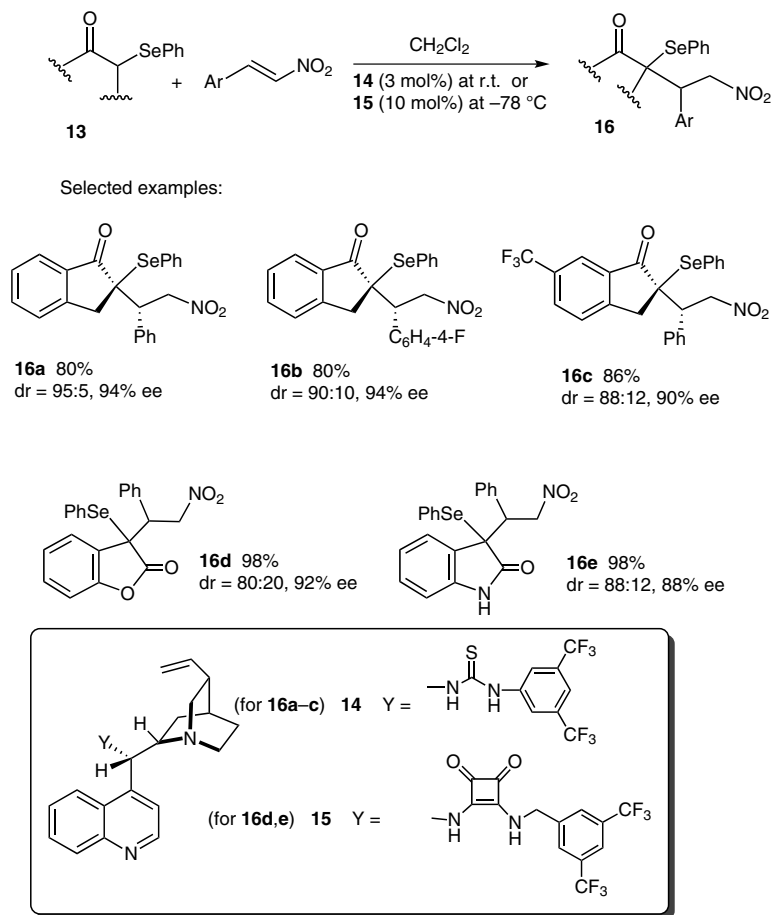
Scheme 4

presence of cinchona derivatives were unsuccessful affording racemic products in moderate conversions.[16] However, as depicted in Scheme 4, we could obtain enantioenriched α-alkyl α-selenocarbonyl derivatives by thiourea-catalyzed addition of cyclic α-selenoketones to nitrostyrenes.[16] Bifunctional thioureidic derivatives are known to catalyze Michael reactions by activation of substrates via noncovalent interactions. Other applications in the field of selenium chemistry will be described in the next paragraph. Addition products with adjacent quaternary and tertiary stereocenters were isolated in good yields, high diastereomeric ratios, and excellent enantiomeric excesses. Interestingly these results were obtained with a low catalyst loading (3 mol%) at room temperature. No reaction occurred using an alkyl-substituted nitroalkene, but the method was extended to cyclic selenoesters and amides using the cinchona-derived squaramide **15**.

3   Organocatalytic Additions to Vinyl Selenones for the Enantioselective Construction of Quaternary Stereocenters

Currently, the asymmetric assembly of molecules with all-carbon quaternary stereocenters is one of the most dynamic areas in organic synthesis. Due to the high steric hindrance, this formation has long been considered an important, yet challenging task. The growing number of biologically active natural products and pharmaceutical agents that possess quaternary stereogenic carbons adds interest to enantioselective synthesis. In the past two decades, intensive investigations have reached a high level of productivity for various reaction types. Among different approaches, the combination of trisubstituted carbon nucleophiles with a variety of electrophiles in conjugated additions catalyzed by bifunctional organocatalysts has emerged as a very popular strategy.[17] Bifunctional organocatalysts bearing an hydrogen-bond donor group besides a basic site on a chiral scaffold simultaneously orient and activate both the Michael donor and the acceptor and allow an excellent level of stereocontrol over the addition event. Usually, a tertiary amine site serves to deprotonate the carbon nucleophile and a weak Brønsted acid functionality activates the electron-poor alkene by establishing hydrogen-bonding interactions. Inspired by the excellent results obtained with nitroalkenes, α,β-unsaturated carbonyl compounds, acrylonitriles, and vinyl sulfones, we questioned whether these powerful organocatalysts might successfully catalyze Michael additions to selenium-containing electron-deficient alkenes such as vinyl selenones. These compounds are easily accessible from the corresponding selenides by oxidation with 3-chloroperbenzoic acid. We focused our attention

on the conjugate addition of α-substituted cyanoacetates[18,19] or cyclic β-ketoesters[20] to vinyl selenones and discovered that easily accessible diamine-derived ureas or thioureas or C6′-hydroxyl cinchona derivatives (Figure 1) can accelerate these 1,4-addition reactions, improve yields, and control the stereoselectivity. Chen et al. demonstrated that also 2-oxindoles are suitable nucleophiles for enantioselective thiourea-catalyzed additions to vinyl selenones in an ionic liquid.[21]
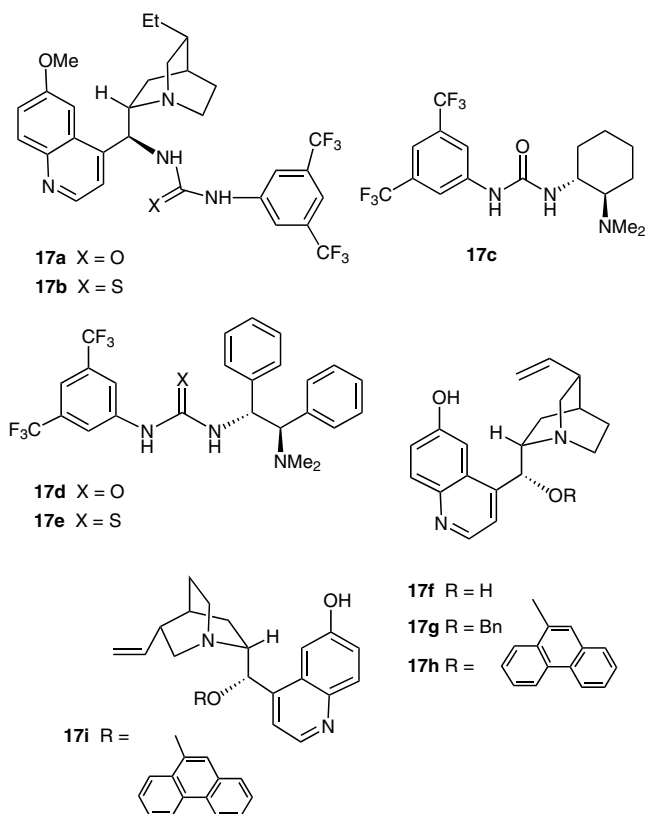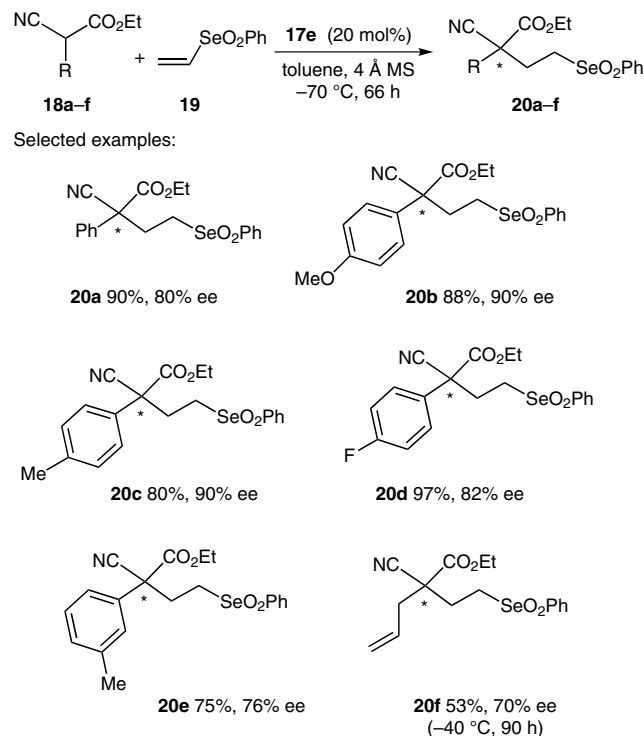
tions proved to be effective for the addition of a range of α-aryl substituted cyanoacetates with different electronic and steric properties. Selected examples are reported in Scheme 5. The highly functionalized addition products **20a–e** were isolated in good to excellent yields and high enantiomeric excesses. α-Alkyl cyanoacetates proved to be significantly less reactive, and **20f** was obtained in 53% yield albeit the reaction was carried out at a higher temperature and for a longer reaction time.


Figure 1

Moreover, we disclosed that Michael addition–cyclization sequences can be employed for the asymmetric formation of cyclopropanes[19] and spirolactones[20] bearing all-carbon quaternary stereocenters. These processes are based on the peculiar properties of the phenylselenonyl group. It combines a strong electron-withdrawing effect with a good leaving-group ability and makes vinyl selenones potential biselectrophiles. This chemical behavior has no parallel in sulfone chemistry.[22] The next Schemes illustrate our results in detail. First experiments were carried out on the α-phenyl cyanoacetate **18a** and the vinyl selenone **19** with the common ureidic and thiouredic catalysts **17a–e** as well as with cinchonine, quinine, and other commercially available cinchona derivatives that lack a H-bond donor group.[18] We found that the cooperation of the urea or thiourea and tertiary amine functionalities is essential for an efficient enantiocontrol. The best results were obtained in toluene at −70 °C with the thioureidic catalyst **17e** (20 mol%). The optimized reaction condi-

Scheme 5

Scheme 6 shows some conversions of the enantioenriched Michael adduct **20a** that take advantage of the leaving-group ability of the phenylselenonyl group. The formation of alkene **24** is particularly interesting. In fact, in the literature few enantioselective organocatalytic protocols for the formal α-vinylation of activated methylenic compounds have been described,[23] and the development of alternative approaches is still in great demand. Attempts to generalize this process are currently under investigation in our laboratory.
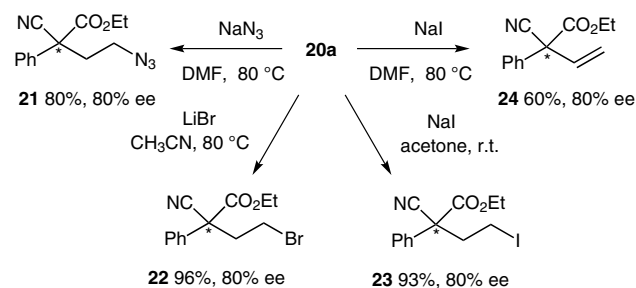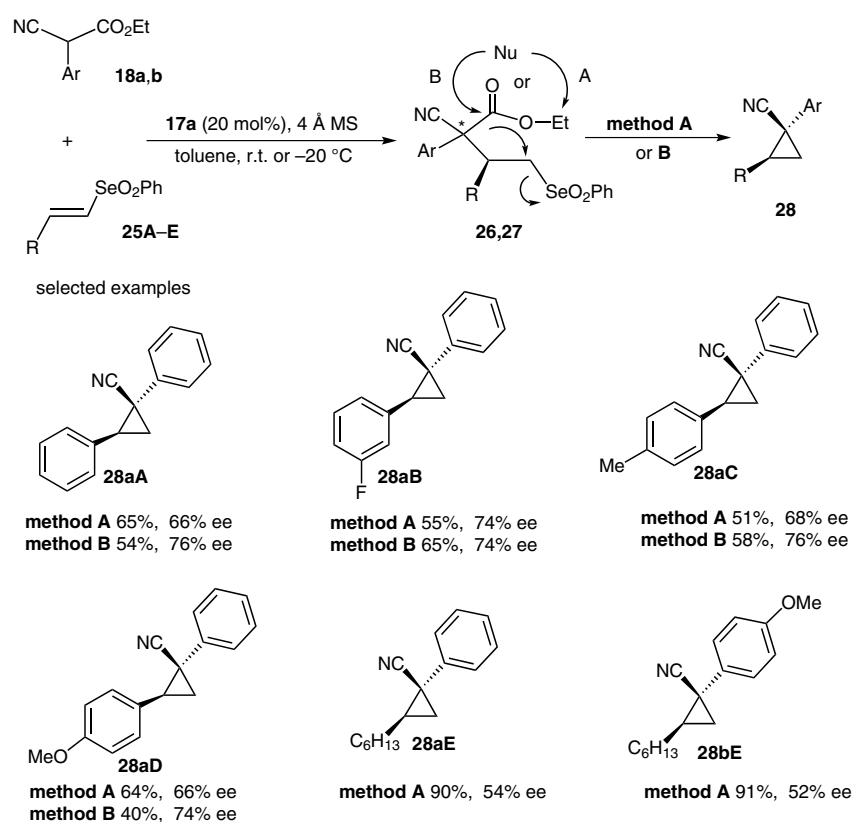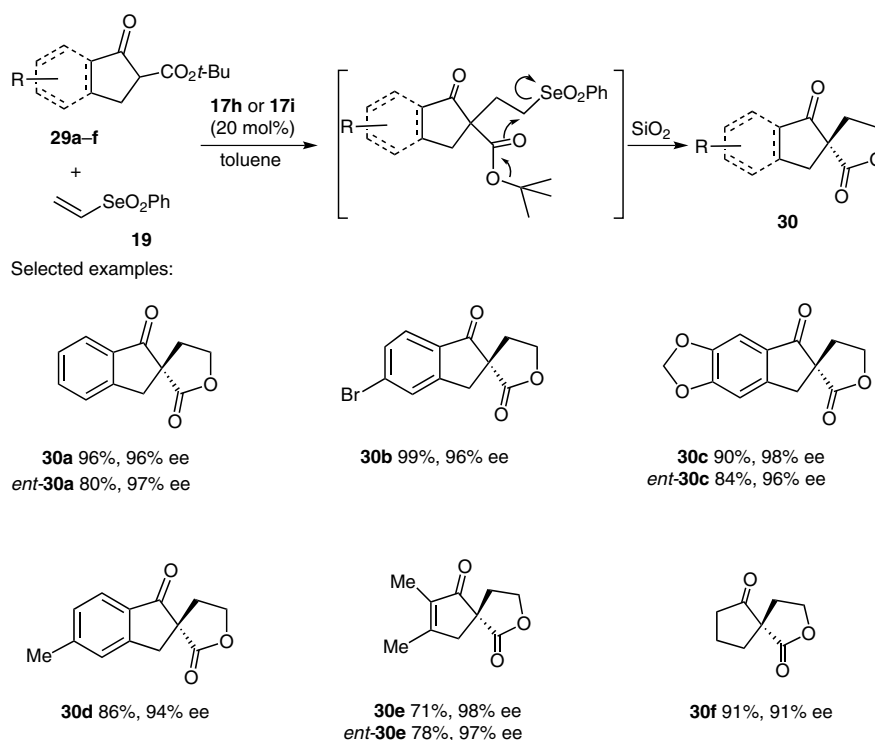

Scheme 6

Also, less reactive β-substituted vinyl selenones **25** are suitable substrates for Michael additions with α-aryl cyanoacetates (Scheme 7). During preliminary experiments we observed that the treatment of the diastereomeric mixture of Michael adducts **26aA** and **27aA** with KCN or LiCl in polar aprotic solvents generated the cyclopropane **28aA** as the single *Z*-isomer, instead of the expected substitution products. The process can be explained as a Krapcho-type de-ethoxy carbonylation, followed by a ring-closure reaction via intramolecular nucleophilic displacement of the phenylselenonyl group by the enolate intermediate. This unexpected result prompted us to study the sequence in detail in order to prepare densely functionalized enantioenriched cyclopropanes by a practical multistep one-pot procedure.[19] To date only a limited number of diastereo- and enantioselective protocols for the organocatalyzed formation of cyclopropanes are available in the literature, typically Michael-initiated ring-closure reactions (MIRC) in which the cyclization of the adduct occurs by nucleophilic substitution of an halide initially positioned on the Michael donor.[24] The optimization of the addition step, which governs the enantioselectivity of the sequence, revealed the efficiency of the ureidic catalyst **17a**, which gave the best results in terms of yield, diastereoselectivity, and enantioselectivity. The addition of **18a** to the β-phenyl-substituted vinyl selenone **25A** with 20 mol% of **17a** in toluene at room temperature gave a diastereomeric mixture of **26aA** and **27aA** in a 85:15 diastereomeric ratio and 80% enantiomeric excess

for the major isomer. We examined a variety of salts and solvents for the ring formation by Krapcho-type protocols, and the best results were obtained with LiCl in HMPA (method A). The one-pot process, in which the addition, the de-ethoxycarbonylation, and the cyclization steps were carried out sequentially without isolation of the intermediates, was applied to several α-aryl cyanoacetates and β-aryl and alkyl vinyl selenones. A selection of the results is reported in Scheme 7. The cyclopropanes **28** were generated in moderate to good yields, complete diastereoselectivity, and good enantioselectivity. Further experiments demonstrated that the use of carcinogenic HMPA can be avoided. In fact the ring-closure reactions can be carried out by treatment with EtONa in EtOH (method B).

Except in the case of alkyl-substituted cyclopropanes, comparable results or even higher enantiomeric excesses were obtained. An organocatalytic cascade process in which the vinyl selenone **19** behaves as a bis-electrophile is described in Scheme 8. The addition of the cyclic β-ketoesters **29** to **19** has been employed as the key step for the enantioselective synthesis of spirolactones.[20] This sterically constrained structure is present in many biologically active natural products and compounds of pharmaceutical interest. In first experiments, we noted that the initially formed Michael adducts could be smoothly converted into the corresponding spirolactones by treatment with silica gel. Reasonably, this unprecedented ring-closure reaction occurs through nucleophilic displacement of SeO₂Ph by the ester group. The presence of the *tert*-butyl residue,

Scheme 7 *Reagents and conditions*: LiCl in HMPA at 80 °C (method A); EtONa in EtOH at r.t. (method B)
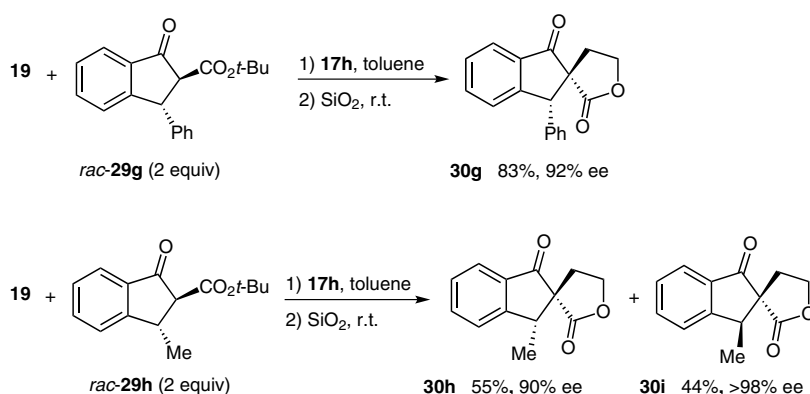
Scheme 8

which can be removed by the free silanol groups of the silica, seems to be essential for the cyclization. In fact, the reaction carried out with the corresponding ethyl β-ketoester gave the spirolactone in very poor yield. We screened the catalysts reported in Figure 1 to assess the feasibility of the asymmetric, organocatalytic cascade strategy. Exposure of the Michael substrates to ureidic or thioureidic catalysts gave clean but low-selective reactions. Thus, we turned our attention to C6′-OH-cinchona-derived catalysts and observed that the bulkier 9-phenantryl derivatives **17h** and **17i** exhibited an excellent level of enantiocontrol and catalytic activity, even at room temperature.

A reversal in the sense of asymmetric induction was observed with the two catalysts, so that the final products are accessible in both enantiomeric forms with high enantiomeric enrichment. Interestingly, comparable levels of se-

lectivity were still achieved when the loading of the catalyst was reduced from 20 mol% to 5 mol%, albeit with extended reaction times. Experiments carried out in order to explore the scope of the protocol indicated that aryl or alkyl β-substituted vinyl selenones are unreactive under the reaction conditions employed, even after prolonged reaction times. Indanone- and cyclopentanone-derived ketoesters were found to be suitable nucleophiles, but not acyclic and cyclohexanone-derived ketoesters. Further experiments with Michael donors containing an additional stereocenter gave interesting results (Scheme 9). The ketoester **29h** gave the two highly enantioenriched diastereomeric spirolactones *cis*-**30h** and *trans*-**30i**. This is an example of a stereodivergent reaction of a racemic mixture, an under-utilized strategy to access optically active compounds, where each enantiomer of the starting material reacts with the chiral catalyst to generate two separa-

Scheme 9

ble, enantioenriched diastereomeric products.[25] In our case, the quaternary stereocenter was formed with an excellent catalyst control regardless of the configuration of the other stereocenter, and both products were accessible in high yields and enantiomeric excesses. In the case of *rac*-**29g**, one of the enantiomers was preferentially converted into the spirolactone *cis*-**30g** again with an excellent enantiomeric enrichment.

4   Concluding Remarks

In conclusion, our studies expand the use of privileged organocatalysts in the field of selenium chemistry. The ease of handling and the peculiar reactivity of organoselenium compounds provided us with opportunities to devise new synthetic strategies for the construction of versatile building blocks and densely functionalized cyclic compounds. We hope that the chemistry described in this Account will trigger further advances in this up to now scarcely explored area.

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