PHENYL VINYL SELENONE AS A USEFUL REAGENT FOR THE STEREOSELECTIVE FORMATION OF CYCLIC β-AMINOESTERS

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Introduction:

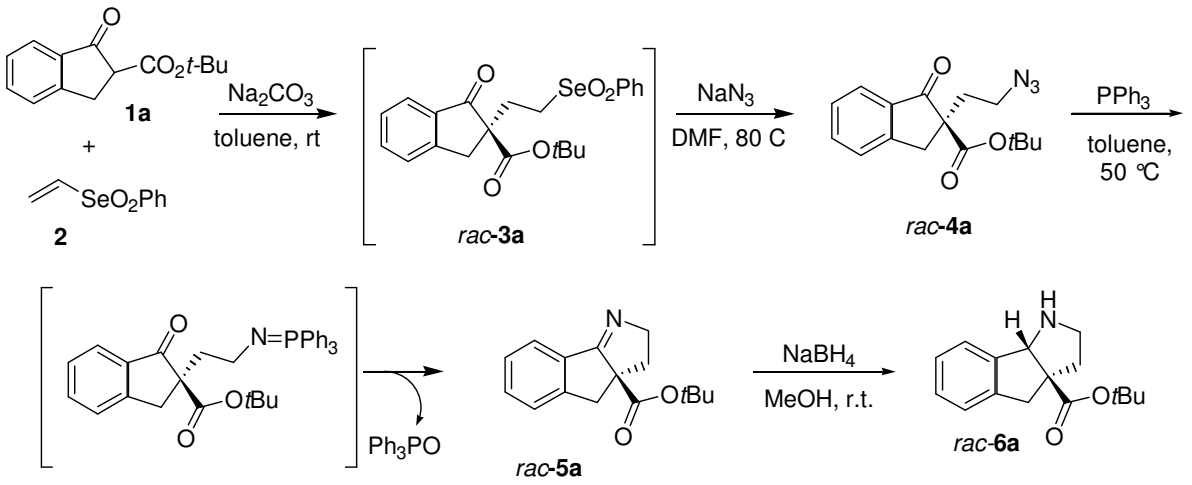
Because of their ready availability, great structural and electronic diversity, easy handling and peculiar chemical behaviour organoselenium compounds are nowadays considered versatile reagents for many synthetic transformations. α,β-Unsaturated selenones represent an interesting example: the electron-withdrawing effect combined with the excellent nucleofugal ability of the phenylselenonyl group makes these compounds useful 1,2-bis(electrophilic) synthons. Recently we have conveniently employed readily available α,β-unsaturated selenones and 1,3-dicarbonyl compounds or cyanoacetates for the organocatalytic asymmetric assembly of structurally complex spiro compounds or cyclopropanes.[1] We now report some preliminary results concerning the use of phenyl vinyl selenone and cyclic β-ketoesters for the diastereo and enantioselective formation of sterically constrained β-aminoesters containing two adjacent stereocenters. In the last decade the stereoselective synthesis of β-aminoesters and acids has received great attention for their presence as key structural motif in natural products and biologically active compounds and their potential application as intermediates and catalysts.[2] The development of new catalytic methodologies is particularly apreciated.[2a] In our approach the highly enantioselective conjugate addition of a cyclic β-ketoester to the phenyl vinyl selenone catalyzed by the easily accessible C6'hydroxyl quinidine-derivative **C6'OH-QD** is the key step of a synthetic sequence providing a practical access to enantiomerically enriched polycyclic β-aminoesters bearing contiguous tertiary and quaternary stereocenters.

Results and discussion

First experiments were carried out in the racemic version in order to assess the feasibility of the strategy (Scheme 1). Thus, the *tert*-butyl 1-indanone carboxylate **1a** and the easily available vinyl selenone **2** were treated in toluene with a catalytic amount of anhydrous Na_2CO_3. As previously demonstrated in our recent paper[1a] under these reaction conditions the racemic Michael adduct **3a** is formed quantitatively. The crude product, after removal

of the toluene by vacuum distillation, was directly submitted to treatment with NaN_3 in DMF at 80 °C. Since the selenonyl group is an excellent leaving group, the nucleophilic substitution was complete after 1 h and the *rac*-**4a** was isolated in 80% yield. A cyclization via a Staudinger/aza-Wittig[3] sequence was then attempted and the azide was treated with triphenylphosphine in toluene. The formation of the iminophosphorane intermediate was not observed because it rapidly reacts intramolecularly with the carbonyl group. The polycyclic ketoimine **5a** was obtained in pure form after column chromatography on silica gel in 78% of yield.

Scheme 1



In order to avoid unnecessary separation processes, save time and resources and increase the yield, the three steps were carried out in one-pot without chromatographic purification of the azide. Only an aqueous work-up was employed for the solvent exchange. Under these conditions *rac*-**5a** was isolated in 80% overall yield. In the final step the reduction of the imine with $NaBH_4$ in MeOH gave the *rac*-**5a**. Although reductions of imines with hydrides are widely studied, reported examples are restricted to non hindered derivatives. In fact, to the best of our knowledge, only two recent papers describe the reduction by hydride transfer of β-imino esters bearing a pre-existing quaternary stereocenter. Monitoring of the reaction by ^1H NMR demonstrated that an excess of the reducing agent and long reaction times (24h) are necessary to reach full conversion. The formation of only one of the two possible diastereoisomers was also observed. The single amino ester *rac*-**6a**, purified by column chromatography on $NaHCO_3$ deactivated silica gel,[4] was recovered in 50% yield. The relative configuration initially assigned considering that the *cis*-fused 5,5-azabicycle is thermodynamically more stable than the corresponding

trans, was confirmed by a NOESY experiment. A cross-peak indicates a strong dipolar interaction between the ring-junction hydrogen and the *tert*-butyl group.

Encouraged by these results, we focused on the asymmetric synthesis of compounds **6a-d** (Table 1) and examined the Michael addition step which is responsible of the stereoselectivity of the whole process. The choice of the catalyst is based on the results presented in our recent paper.[1a] in which it has been demonstrated that 6'-hydroxyl quinine and quinidine derivatives are excellent catalysts for the formation of adducts **3a-d**. In particular, the phenantrenyl derivative **6'OH-QD** exhibits an high catalytic activity and an excellent enantiocontrol even at room temperature. On these grounds, the Michael addition of the *tert*-butyl indanone derived carboxylates **1a-d** to the vinyl selenone **2** have been carried out with only 5 mol% of the organocatalyst in 24-48 hours without compromising the chemical and the optical yields. The next conversions for the transformation of the Michael adducts **3a-d** into the cyclic imines **5a-d** and the β-amino esters **6a-d** were carried out according to the previously described racemic sequence. Reaction products, chemical yields and enantiomeric excesses of chiral sequences performed are reported in Table 1. The enantiomeric excesses of the final β-amino esters were determined by HPLC analyses with chiral columns after Boc-protection of the amine group with di-*tert*-butyl dicarbonate. Carbon pro-nucleophiles bearing electron-withdrawing or electron-donating groups on the aromatic ring gave comparable results in terms of chemical yields and enantiomeric excesses. The absolute configurations at the newly created quaternary stereocenter have been assigned according to our previous work concerning the formation of spiro compounds[1a]. In fact, the adducts **3a-d** are common intermediates for the two synthetic sequences. The models previously proposed to rationalise the stereochemical outcome of conjugate additions to nitroalkenes, α,β-unsaturated carbonyl compounds, nitriles or sulfones catalyzed by 6'-OH cinchona alkaloid derivatives correctly predict the observed stereochemistry.[5]

***Figure* 1**

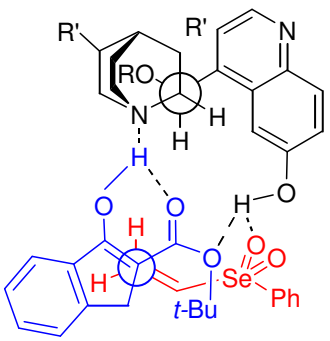
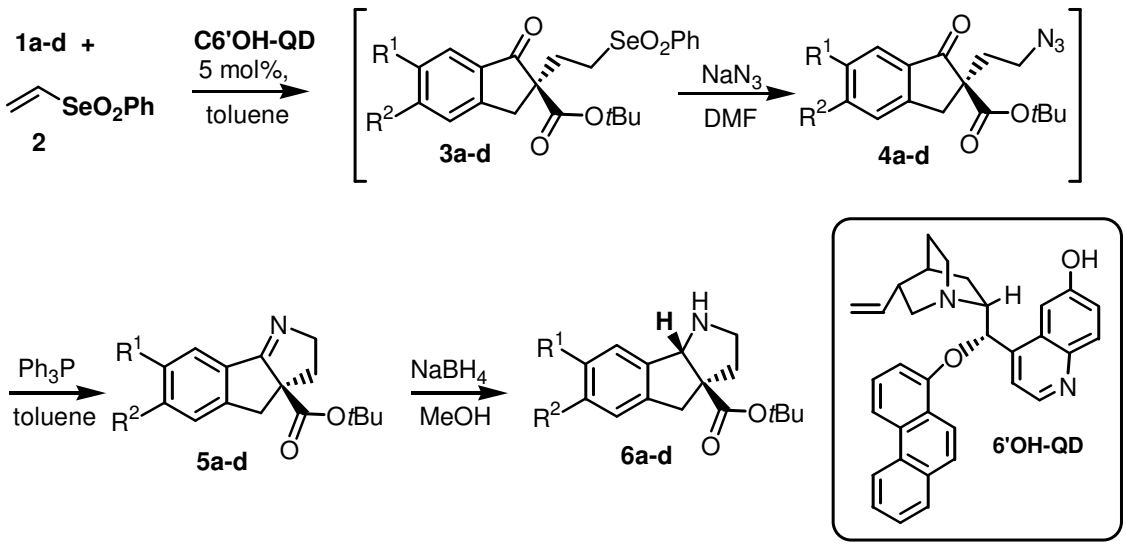
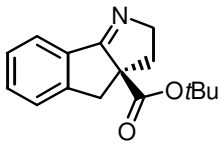
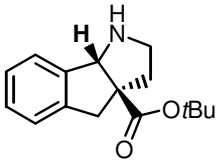
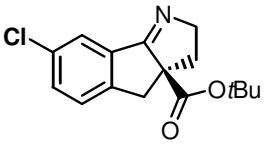
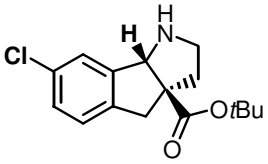
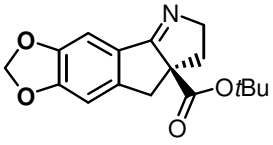
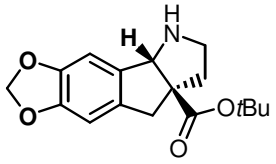
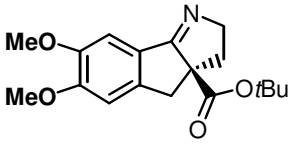
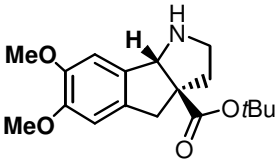


Table 1



	Cyclic iminoester		% yield[a,b]	Cyclic aminoester[c]		% yield[b]	% *ee*[d]
1		**5a**	65		**6a**	53	97
2		**5b**	85		**6b**	57	96
3		**5c**	74		**6c**	43	96
4		**5d**	[e]		**6d**	44[f]	96

[a] The reactions were performed on a 0.4 mmol scale starting from phenyl vinyl selenone **2** and 2 equivalents of the β-ketoesters **1a-d** with 5 mol% of the catalyst **6'OH-QD**. The next steps were carried out without isolation of the intermediates. [b] Yield of the isolated product after column chromatography. [c] The relative configurations were assigned on the basis of a NOESY experiment carried out on **6a**. For the absolute configurations at the quaternary stereocenter see reference 1a. [d] The *ee* values of **6a-d** were determined by HPLC analysis with chiral columns after Boc-protection of the amine group. [e] The yield was not determined because the product isolated by column chromatography was impure of Ph_3PO. [f] Overall yield calculated on the starting vinyl selenone **2**.

The bifunctional quinidine derived catalyst simultaneously activates and orients the electrophilic selenone and the Michael donor via a network of hydrogen bonding interactions, which involves the phenolic free hydroxyl group and the quinuclidine nitrogen atom (Figure 1).

Conclusions

In conclusion a practical synthetic sequence for the stereoselective construction of conformationally constrained β-amino esters containing adjacent tertiary and quaternary stereocenters starting from easily available starting materials has been described. The reactions proceed with good chemical yields and with an excellent diastereo and enantiocontrol. Further studies to expand the substrate scope and the synthetic applications of the present sequence are currently underway.

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References:

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