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Organocatalytic Michael addition of indanone carboxylates to vinyl selenone for the asymmetric synthesis of polycyclic pyrrolidines

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Dedicated to the memory of Professor Marcello Tiecco

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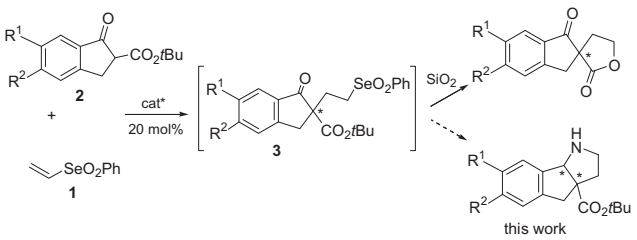
ABSTRACT

A Michael addition of racemic indanone carboxylates to vinyl selenone catalyzed by C6′hydroxyl cinchona derivatives is the key step of a synthetic sequence for a practical access to highly enantioenriched (up to 98% ee) polycyclic pyrrolidines bearing contiguous tertiary and quaternary stereocenters.

1. Introduction

Organoselenium compounds are nowadays considered versatile reagents for many synthetic transformations, which take advantage of the ease with which these compounds effect functional group interconversions. In the last years, they found many interesting applications in the stereoselective preparation of chiral molecules under mild and operationally simple reaction conditions.[1] Despite the explosion of organocatalysis, which has recently emerged as a robust and powerful strategy for the asymmetric construction of valuable building blocks and molecules of pharmaceutical interest, very few organocatalytic processes involving selenium reagents have been explored.[2] In this field, we have recently developed new enantioselective methods for the preparation of important classes of selenium compounds, such as α-selenocarbonyl derivatives.[3] Moreover, the ease of handling and the unique reactivity of vinyl selenones have been exploited in new organocatalytic strategies for the practical asymmetric construction of densely functionalized cyclic compounds from simple precursors.[4] An example is the Michael addition/cyclization sequence with the easily accessible cyclic β-ketoesters **2** and the vinyl selenone **1** catalyzed by C6′hydroxyl cinchona derivatives, which has been successfully employed for the enantioselective synthesis of spirolactones (Scheme 1).[4a] This practical one-pot sequence 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 following cyclization. We now report that the same Michael adducts **3** are useful intermediates in the diastereo- and enantioselective synthesis of polycyclic pyrrolidines bearing a β-aminoester motif. These structures contain synthetically challenging contiguous tertiary and quaternary stereocenters.



Scheme 1.

In the last years novel strategies for the synthesis of compounds that incorporate a pyrrolidine ring have received considerable

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attention.[5–9] Properly substituted indenopyrrolidines **A** have been studied as hypoglycemic agents[6] or as antagonists of NMDA receptor (Fig. 1).[7] Proline derivatives **B** and conformationally restricted rivastigmine analogues **C** have been evaluated as angiotensin converting enzyme inhibitor analogues[8] or acetylcholinesterase inhibitors, respectively.[9] Moreover, in the last decade the asymmetric synthesis of β-aminoacids and derivatives has received great attention[10] and the development of new catalytic methodologies is particularly appreciated. Our method, which employs the easy to handle vinyl selenone for the key addition step, nicely complements procedures based on the catalytic 1,4-addition of cyclic β-ketoesters to nitroethylene followed by reduction and cyclization.[11]

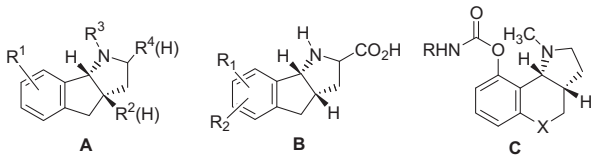


Fig. 1. General structures of biologically active polycyclic pyrrolidines.

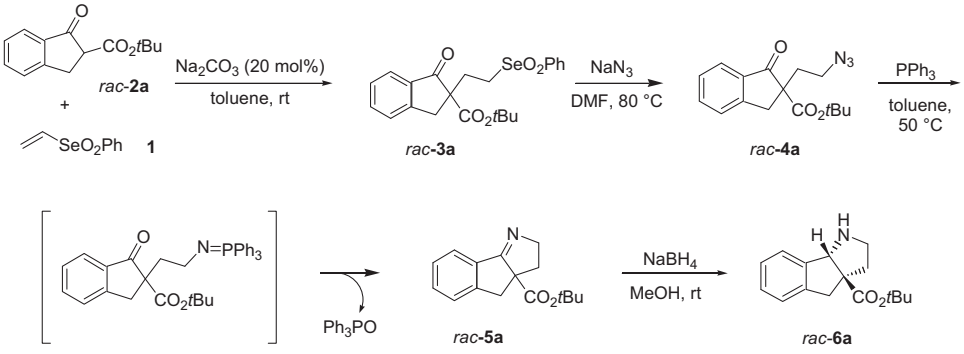
2. Results and discussion

For preliminary studies we chose the reaction of *tert*-butyl indanone carboxylate *rac*-**2a** (2 equiv) and the vinyl selenone **1**. When these compounds were treated in toluene with a catalytic amount of anhydrous Na_2CO_3 (Scheme 2) the Michael adduct *rac*-**3a** was formed quantitatively. We hypothesized that the conversion of **3a** into the corresponding alkyl azide could give access to indenopyrrolidines via a Staudinger/aza-Wittig sequence.[12] Due to the good leaving group properties of the phenylselenonyl unit, the nucleophilic substitution was complete after 1 h and *rac*-**4a** was isolated after column chromatography in 80% yield. The cyclization by treatment with triphenylphosphine in toluene gave *rac*-**5a** in 78% yield in 1 h. The formation of the iminophosphorane intermediate was not observed because it rapidly reacts chemoselectively with the carbonyl group. In order to save time and resources, minimize the generation of chemical waste and reduce manual operations, the multi-reaction sequence was carried out excluding unnecessary purification processes. Thus, the crude *rac*-**3a** was used for the nucleophilic substitution after toluene evaporation and only an aqueous work-up was employed for the next DMF removal. Under these conditions *rac*-**5a** was isolated in 80% overall yield. Finally, the reduction was carried out with an excess of sodium borohydride in MeOH. Reductions of imines by hydride transfer are well documented, but most examples are restricted to nonhindered derivatives.[13] Although ^{1}H NMR analysis of the crude reaction mixture showed the complete conversion of the starting imine and the presence of *rac*-**6a** as the sole reaction product, it was recovered after column chromatography in acceptable 50% yield. The cis stereochemistry at the ring junction was assigned by a NOESY experiment. A diagnostic dipolar interaction between the ring junction hydrogen and the *tert*-butyl group was observed. Encouraged by these results, we focused on the asymmetric variant of the process (Table 1). In the previous report concerning the synthesis of spirolactones,[4a] we demonstrated that quinidine C6′-OH 9-*O*-(9′-phenanthryl) ether **C6′OH-QD** exhibits a high catalytic activity and an excellent enantiocontrol over the formation of addition product **3a**, which is also the key intermediate in the construction of the indeno pyrrolidine **6a**. Thus, the same bifunctional catalyst was used for the new cyclization sequence affording **5a** with an excellent enantiomeric excess (98% ee by chiral HPLC). Interestingly, decreasing of the catalyst loading from 20 mol % to 5 mol % do not affect the chemical and optical yields.[14] As expected, the reduction gave **6a** as a single diastereoisomer without loss of enantiomeric purity. The cyclization sequence and the following reduction were applied to some indanone derivatives bearing electron-withdrawing or electron-donating groups on the aromatic ring. Reaction conditions, chemical yields and enantiomeric excesses of the final products are reported in Table 1. The indenopyrrolidines were prepared with complete diastereoselectivity and high enantiomeric excesses. Both enantiomers are readily accessible. In fact replacement of catalyst **C6′OH-QD** with its pseudoenantiomer **C6′OH-Q** led to the formation of *ent*-**6a** and *ent*-**6b** in comparable yields and enantiomeric excesses (Table 1, entries 1 and 2). The method was extended to the trans Michael donor *rac*-**2e** containing an additional stereocenter and the compound **6e** was obtained as a single diastereoisomer in 95% ee. Under the usual conditions, the chiral catalyst not only controls the absolute configuration at the quaternary stereocenter formed during the addition but also reacts almost exclusively with one of the enantiomers of *rac*-**2e**.

Finally we try to adapt the strategy to the synthesis of benzoindoles (Table 1, entry 6), but compounds **5f** an **6f** were obtained in very poor stereoselectivities. A slow rate of reduction and a poor diastereoselectivity have been already observed in these ring systems.[13b]

3. Conclusions

In conclusion a practical synthetic sequence for the asymmetric construction of indeno[1,2-*b*]pyrrolidines starting from easily available starting materials has been described. The reactions proceed with good chemical yields and generate compounds with



Scheme 2.