Organocatalysis

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A Highly Enantioselective One-Pot Synthesis of Spirolactones by an Organocatalyzed Michael Addition/Cyclization Sequence**

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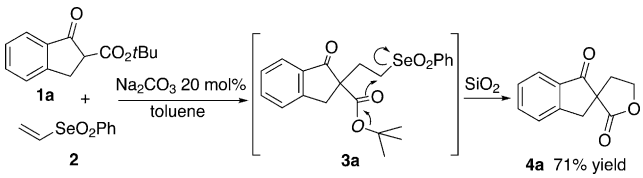
Spirocyclic compounds are attractive targets in organic synthesis because of their broad distribution in biologically active natural products and pharmaceuticals,[1] as well as their increasing use in a range of important chemical and technological processes, such as asymmetric synthesis and organic optoelectronics.[2] On this basis the development of novel methods for the construction of spirocyclic frameworks is of considerable importance, particularly when these methods give rise to the enantioselective formation of an all-carbon quaternary stereocenter, which itself is considered to be a challenging transformation.[3,4] Over the past decade, extensive work on organocatalyzed asymmetric conjugated additions of trisubstituted carbon nucleophiles to electron-deficient alkenes demonstrated that these reactions represent an attractive solution to the problem of selectively generating quaternary stereocenters.[4] Recently several organocatalytic cascade processes involving Michael additions have been successfully applied to the synthesis of spirocyclic compounds.[5] These methods, are based on Michael or Michael/aldol-type sequences and provide access to spiro-oxindoles, spirobenzofuranones, or spiro-3,4-dihydropyrans with high stereocontrol. The use of novel substrate combinations and the development of new cascade or one-pot reactions are significant advances in this field, thus making the asymmetric assembly of structurally diverse spirocyclic compounds possible from simple and readily available precursors. In this field and in continuation of our efforts to expand the scope of privileged organocatalysts in the field of selenium chemistry,[6,7] we herein report the first highly enantioselective synthesis of spirolactones starting from racemic cyclic β-ketoesters and the vinyl selenone catalyzed by bifunctional cinchona-alkaloid-derived catalysts. The operationally simple, one-pot Michael addition/cyclization sequence is based on the peculiar properties of the phenylselenonyl substituent, which plays a dual role as an electron-withdrawing group, during the addition step, and as a leaving group, during the cyclization by intramolecular nucleophilic substitution.

Initial studies were performed with an excess of the *tert*-butyl β-ketoester **1a** and the easily available vinyl selenone **2** in toluene in the presence of a catalytic amount of anhydrous Na_2CO_3 (Scheme 1).



Scheme 1. Reaction of *tert*-butyl β-ketoester **1a** and the vinyl selenone **2**: a one-pot Michael addition/cyclization sequence.

The formation of the Michael intermediate **3a** was clearly demonstrated by ^1H, ^{13}C, and ^{77}Se NMR spectra of the crude reaction mixture. Particularly indicativeare the ^{13}C peak at $\delta = 56$ ppm, characteristic of a methylene linked to a selenonyl group,[6b,8] and the ^{77}Se signal at $\delta = 994$ ppm typical of a phenyl alkyl selenone.[9] This signal is deshielded in comparison with that of the starting conjugated selenone **2**, for which a signal is seen at $\delta = 961$ ppm. We were delighted to observe that the Michael adduct was smoothly converted in 2 hours into the spirolactone **4a** by stirring at room temperature with silica gel. The excellent leaving ability of the selenone group in intramolecular nucleophilic substitutions is well known,[6,10] thus, plausibly this unprecedented ring-closure reaction occurs through nucleophilic displacement of -SeO_2Ph by the ester group. The *tert*-butyl group can be easily cleaved by the free silanol groups of the silica[11] and the released $PhSeO_2H$ is partially trapped by the excess of the β-ketoester.[12] The presence of the *tert*-butyl residue seems to be crucial for the cyclization. In fact the reaction carried out with the corresponding ethyl β-ketoester gave **4a** in very poor yield. To assess the feasibility of an asymmetric organocatalytic strategy, we focused on the use of the easily accessible compounds **5a–g** (Scheme 2), which have recently emerged as potentially general catalysts for a range of 1,4-addition reactions.[4,13]

These organocatalysts, bearing an hydrogen-bond-donor group together witha basic site on a chiral scaffold, are typical bifunctional catalysts. They improve yields and stereoselectivities of 1,4-additions by simultaneous activation of both the Michael acceptor and the pronucleophile. Treatment of the vinyl selenone **2** with the *tert*-butyl β-ketoester **1a** in the presence of 20 mol% of the ureidic or thioureidic catalysts **5a–c**, which have been successfully employed for the activa-

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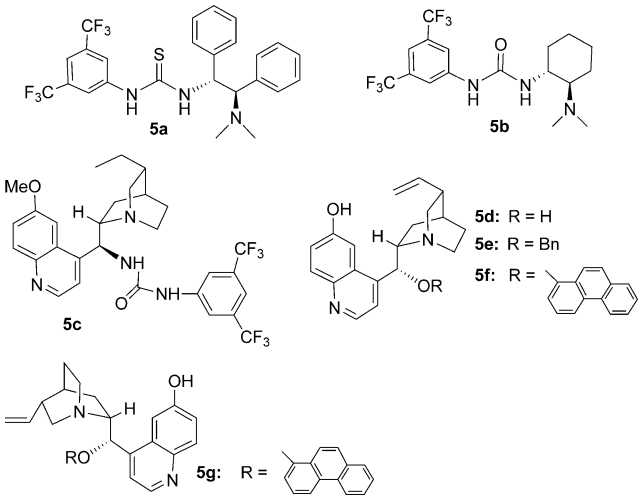
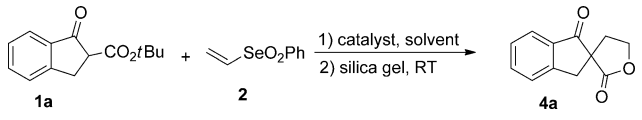


Scheme 2. Catalysts screened for the spirocylic compound formation.

tion of the selenone moiety,[6b–c,7] resulted in clean reactions but low selectivity (Table 1, entries 2–4). Thus, we turned our attention on the use of the 6′-OH cinchona alkaloid derivatives **5d–g**.[14] These catalysts gave **4a** with high yield and excellent enantiocontrol (Table 1, entries 5–14). Experiments carried out with different solvents demonstrated that toluene is the solvent of choice. In fact the desired spirolactone is formed in high yield and excellent selectivity even at room temperature and in a short reaction time. Although, in principle, the presence of water can affect the outcome of the reaction by interactions with the catalyst or by nucleophilic displacement of the selenonyl group of **3a**,[9b] the reactions carried out in the presence and absence of molecular sieves (4 Å) gave comparable results in terms of yield and enantioselectivity (Table 1, entries 6 and 7). The 6′-OH 9-O-(9′-phenanthryl)ether quinine derived catalyst **5f** exhibited the best levels of enantioselectivity and catalytic activity. Comparable results were still achieved when the loading of **5f** was reduced to 5 mol%, albeit an extended reaction time was required to reach complete conversion (Table 1, entries 11–13). Both the enantiomers of the spirolactone are accessible, in fact *ent*-**4a** was prepared in good yield and with a similar *ee* value with the quinidine-derived catalyst **5g** (Table 1, entry 14).

Table 1: Selected examples of catalyst screening and optimization of reaction conditions.

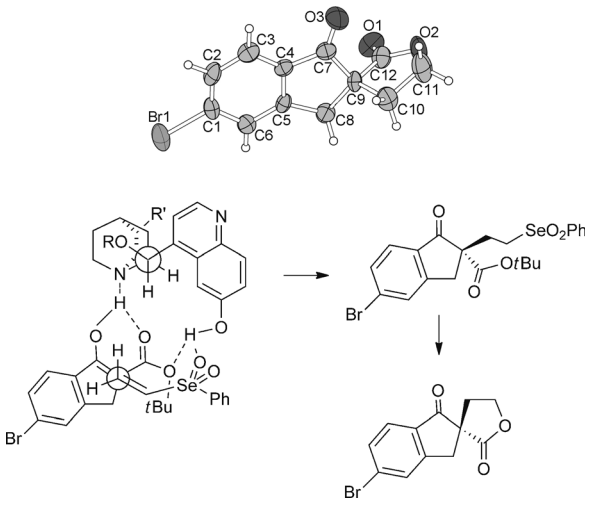


Entry	Cat.	[mol%]	Solvent	*T* [°C]	*t* [h]	Yield [%][a,b]	*ee* [%][c]
1	Na_2CO_3	20	toluene	RT	24	71	–
2	**5a**	20	toluene	RT	10	90[d]	42
3	**5b**	20	toluene	RT	7	99[d]	20
4	**5c**	20	toluene	RT	8	99[d]	28[e]
5	**5d**	20	toluene	RT	6	99	76
6	**5e**	20	toluene	RT	6	99[d]	90
7	**5e**	20	toluene	RT	6	99	91
8	**5e**	20	toluene	0	22	94	92
9	**5e**	20	THF	−45	72	85	88
10	**5e**	20	CH_2Cl_2	−45	53	94	94
11	**5f**	20	toluene	RT	5	96	96
12	**5f**	5	toluene	RT	5	82	96
13	**5f**	5	toluene	RT	24	93	96
14	**5g**	20	toluene	RT	5	80	97[e]

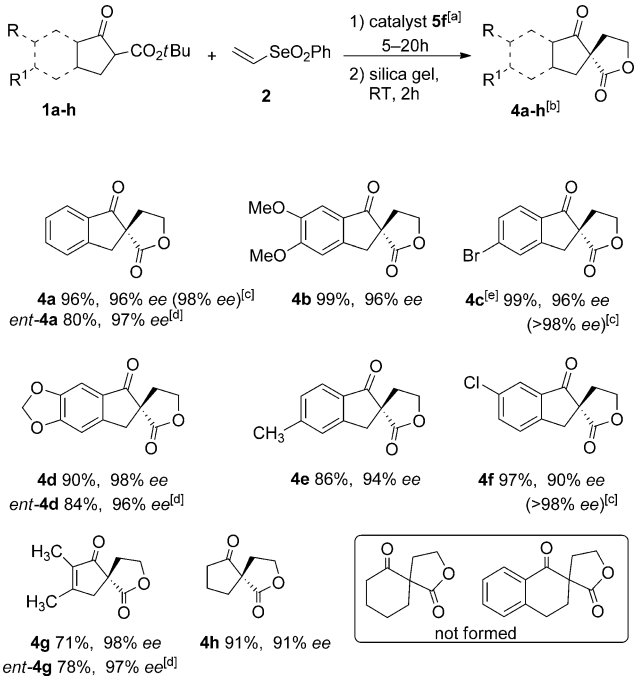
[a] The reactions were performed on a 0.1 mmol scale in the indicated solvent (0.4 mL) with 2 equivalents of the β-ketoester **1a**. The indicated temperatures and times refer to the addition step. Then silica gel (0.5 g) was added and the reaction mixtures were stirred at room temperature for additional 2 h. [b] Yield of the isolated product after flash chromatography on silica gel. [c] The *ee* values were determined by HPLC analysis using a chiral column. [d] The reaction was carried out in the presence of molecular sieves (4 Å). [e] The opposite enantiomer was formed. THF = tetrahydrofuran.

With the optimized reaction conditions established, we explored the scope and limitations of the asymmetric Michael/cyclization sequence. As summarized in Scheme 4, indanone-derived *tert*-butyl β-ketoesters **1b–f**, having various substituents, were found to be suitable for this catalytic transformation and provided products in high yields and excellent enantioselectivities in short reaction times. The presence of either electron-withdrawing or electron-donating groups on the aromatic ring gave comparable results. Cyclopentanone-derived *tert*-butyl β-ketoesters **1g** and **1h** were also successfully employed in the one-pot sequence, thus generating, under the same reaction conditions, the spirolactones **4g** and **4h**. On the contrary, reactions carried out starting from β-ketoesters with a cyclohexanone core were unsuccessful. The Michael additions to the selenone **2** proceeded very slowly and the adducts formed could not be transformed into the corresponding spirolactones by treatment with silica gel.

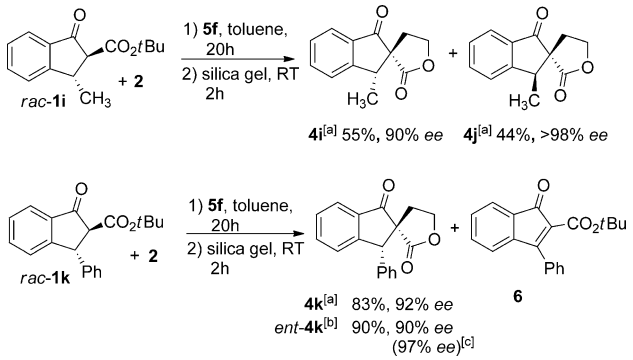
Recrystallization of the spirolactone **4c** followed by single-crystal X-ray analysis allowed the *S* configuration to be assigned (Scheme 3).[15] The absolute stereochemical configurations of the other products were assigned by analogy. The step responsible for the enantioselectivity of



Scheme 3. Absolute configuration of **4c** (thermal ellipsoids are shown at 50% probability) and the proposed stereochemical model for the reaction of **1c** and **2** with the catalyst **5f**.



Scheme 4. Scope of the one-pot Michael addition/cyclization reaction. [a] Unless otherwise specified, the reactions were performed at RT on a 0.2 mmol scale in toluene (0.8 mL) with 2 equivalents of the β-ketoesters **1a–h** and 20 mol% of the catalyst **5f**. [b] The *ee* values of **4a–h** were determined by HPLC analysis using a chiral stationary phase. [c] The *ee* value obtained after a single crystallization (EtOAc) is reported in brackets. [d] Reaction performed with the catalyst **5g**. [e] By single-crystal X-ray analysis (+)-**4c** was determined to be *S*-configured and the absolute configurations of all the other products were assigned by analogy.



Scheme 5. Organocatalytic one-pot Michael addition/cyclization sequence of **1i** and **1k**. [a] The relative configuration was assigned by a NOESY experiment and the absolute configuration was assigned by analogy. [b] Reaction performed with the catalyst **5g**. [c] The *ee* value after a single crystallization (EtOAc).

the sequence is the addition step, and the stereochemical models previously reported for other conjugate additions catalyzed by C6′-OH cinchona alkaloid derivatives correctly predict the observed stereochemistry.[14] As shown in Scheme 3 the active *gauche* open conformer of the quinine-derived catalyst **5f** in the transition state orients and activates simultaneously both the enolic tautomer of the pronucleophile and the electrophilic vinyl selenone by a network of hydrogen-bonding interactions.

To extend the method, Michael donors containing an additional stereocenter, such as racemic *trans*-**1i** and *trans*-**1k** were also investigated (Scheme 5). The reactions were carried out under the optimized reaction conditions with two equivalents of the pronucleophile. Compound *rac*-**1i** gave the two highly enantioenriched diastereomeric spirolactones *cis*-**4i** and *trans*-**4j**, which were easily separated by flash column chromatography on silica gel.[16] This is an example of a stereodivergent parallel kinetic resolution (PKR)[17] or, as it is nowadays more properly defined, of a stereodivergent reaction of a racemic mixture (stereodivergent RRM),[18] and in this transformation both the enantiomers of a racemic substrate are transformed at similar rates into enantioenriched diastereomeric products by effect of a chiral reagent or catalyst.

In the present case the chiral catalyst strictly controls the configuration of the stereogenic center formed during the addition step regardless of the stereochemistry of the other stereogenic center, thus each of the diastereomeric compounds is generated with high enantioselectivity.

Although several examples of stereodivergent reactions catalyzed by enzymes are known, those with organocatalysts are less common.[17,18]

From the reaction of *rac*-**1k** the compound **4k** was obtained as the single *cis* isomer in 83% yield and 92% *ee*, thus demonstrating that, in this case, one of the enantiomers is preferentially converted into the spirocyclic compound (Scheme 5).[19] Attempts to recover unreacted **1k** failed and only a mixture containing **6** as the main product was isolated by column chromatography.[12] Compound *ent*-**4k** was prepared with a high enantiomeric excess using the pseudo-enantiomeric catalyst **5g** under the optimized reaction conditions.

In conclusion, an organocatalytic protocol for the synthesis of spirolactones from cyclic β-ketoesters and an easily accessible vinyl selenone by a one-pot Michael addition/cyclization reaction has been described.[20] The novelty of the transformation, the simplicity of the procedure, and the high levels of efficiency and stereoselectivity (*ee* values range from 90 to 98%) are the most attractive aspects of this transformation. The enantioselective formation of spirolactones is a challenging task[1c] requiring control in the construction of a sterically constrained quaternary carbon center. Moreover, the spirolactone skeleton is present in natural products and biologically important compounds such as bakkenolides[1] and structural analogues of the antitumoral podophyllotoxin.[21] The present method also confirms the synthetic value of the vinyl selenone as a 1,2-bis(electrophilic) synthon and expands its applicability in the field of asymmetric organocatalysis, introducing a novel Michael-initiated ring-closure process that has no parallel in the related sulfur chemistry.[22]

Experimental Section

General procedure for the enantioselective formation of spirocyclic compounds **4**: In a vial equipped with a Teflon-coated stir bar, catalyst **5f** or **5g** (0.04 mmol, 20 mol%) and vinyl selenone **2** (0.2 mmol) were dissolved in undistilled toluene (0.8 mL) under air. The β-ketoesters

1a–i, **k** (0.4 mmol, 2 equiv) were added at room temperature and the resulting solution was stirred for 5–20 h. When **2** was completely consumed, as indicated by TLC analysis, silica gel (1 g) and toluene (0.8 mL) were added and the reactions were stirred for 2 h. The crude mixtures were directly submitted to flash column chromatography on silica gel using *n*-hexane/ethyl acetate mixtures as the eluent. The fractions were collected and concentrated in vacuo to give the products **4a–k**.

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[16] Racemic samples of **4i** and **4j** were obtained in overall 87% yield and 55:45 diastereomeric ratio from the reaction with Na_2CO_3 (20 mol%). The products were easily separated by flash column chromatography on silica gel.

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[19] A racemic sample of **4k** was obtained as a single *cis* isomer in 76% yield from the reaction with Na_2CO_3 (20 mol%).

[20] Michael reactions between **1a** and an alkyl- or aryl-substituted β-vinyl selenone, were unsuccessful and the addition products were not formed even after prolonged reaction times.

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