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# Asymmetric Synthesis of Spiro-3,4-dihydropyrans via a Domino Organocatalytic Sequence

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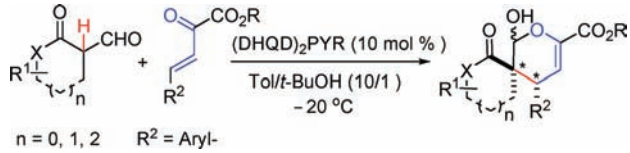
## ABSTRACT




**A cinchona alkaloid-catalyzed domino Michael/hemiacetalization reaction of cyclic $\beta$-oxo aldehydes and aromatic $\beta,\gamma$-unsaturated $\alpha$-keto esters, resulting in the formation of spiro-dihydropyran architectures in good yield with high stereoselectivity (up to 97% ee), is presented.**

Tetrahydropyran and dihydropyran derivatives are structural subunits in many natural products and bioactive molecules;[1] they also serve as versatile and important building blocks in organic synthesis.[2] Consequently, the formation of these compounds especially for their stereocontrolled constructions has enjoyed sustained attention over the past decade. Whereas several elegant organocatalytic approaches to 3,4-dihydropyrans as well as their bicyclic derivatives have been developed,[3] few synthetic methods are available to access the spiro-bicyclic analogues having all-carbon quaternary stereocenters.[4,5]

Recently, we have presented a tertiary amine-mediated cross-cyclization reaction giving rise to functionalized spiro-dihydropyran derivatives.[6] This annulation process presumably proceeds via a zwitterionic enolate (**I**) that undergoes a Michael reaction-triggered domino sequence with enones **2** in a diastereoselective manner (Scheme 1).[7] As the organocatalytic Michael reaction directly taking use of aldehyde enolates has received little attention and still remains a rather unexplored transformation,[8] we sought to expand this methodology to the use of $\beta$-oxo aldehydes **1** upon treatment

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(4) For reviews on stereocontrolled synthesis of spirocyclics, see: (a) Sannigrahi, M. *Tetrahedron* **1999**, *55*, 9007. (b) Pradhan, R.; Patra, M.; Behera, A. K.; Mishra, B. K.; Behera, R. K. *Tetrahedron* **2006**, *62*, 779. (c) Sinibaldi, M.-E.; Canet, I. *Eur. J. Org. Chem.* **2008**, 4391. (d) Kotha, S.; Deb, A. C.; Lahiri, K.; Manivannan, E. *Synthesis* **2009**, 165.

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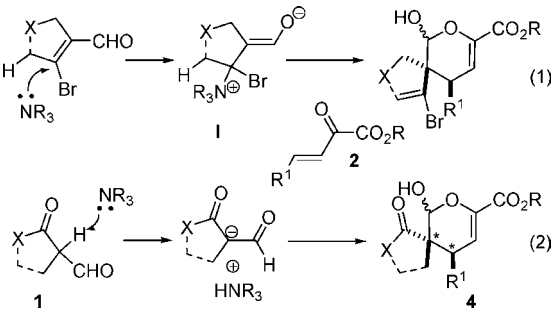
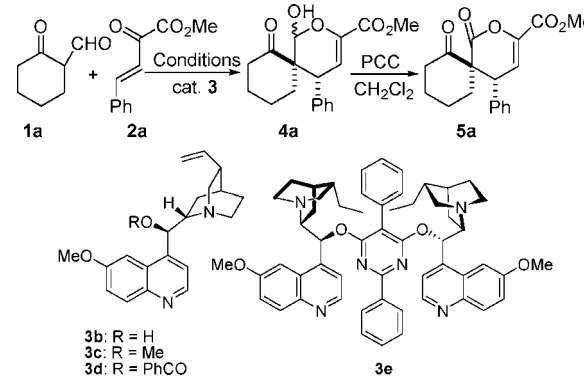
with Brønsted base.[9] Given their synthetic utilities and potential bioactivity, we report herein the first enantioselective construction of spiro-dihydropyran architectures **4** via a cinchona alkaloid-catalyzed domino Michael addition/hemiacetalization reaction of cyclic $\beta$-oxo aldehydes **1** and aromatic $\beta,\gamma$-unsaturated α-keto esters **2** (Scheme 1).[10]

**Scheme 1.** Domino Reactions Employing Aldehyde Enolates




The cyclization of 2-oxocyclohexanecarbaldehyde (**1a**) with $\beta,\gamma$-unsaturated α-keto ester **2a** was initially carried out using 10 mol % catalyst loading of tertiary amines **3** in toluene at −20 °C (Table 1). Upon treatment with DABCO, a mixture of two anomers of hemiacetal **4a** was obtained in an 8:1 ratio as determined by $^1$HNMR analysis, which afforded α-spiropyranone **5a** as a single diastereomer after PCC oxidation (entry 1).[11] On the basis of these observations, we decided to develop an asymmetric version of this cyclization. As cinchona alkaloids are highly useful organocatalysts for a large number of stereoselective transformations,[12] a brief survey of cinchona alkaloid-derived catalysts was conducted for this process.[13] As shown in Table 1, $(DHQD)_2PYR$ (**3e**) was the most effective among catalysts **3b**−**e**, furnishng **5a** with 85% ee after oxidation (Table 1, entry 5).[14] The disadvantage of the free OH group in the catalyst structure was verified by the poor enantioselectivity of the reaction catalyzed by quindine (entry 2). Thus, cinchona alkaloids did not act as dual-activating organocatalysts herein.[15] The cyclization can be run in a variety of solvents with comparable results (Table 1, entries 5−8). However, we found the reaction to be slightly facilitated by the presence of *t*-BuOH (entry 9) and chose Tol/*t*-BuOH (10:1) for further exploration.

**Table 1.** Catalyst Screening and Optimization of Reaction Conditions[a]




| entry | catalyst **3** | solvent | time (h) | **4a**, yield[b] (%) | **5a**, ee[c] (%) |
|---|---|---|---|---|---|
| 1 | **3a** | toluene | 48 | 78 | |
| 2 | **3b** | toluene | 48 | 87 | 45 |
| 3 | **3c** | toluene | 48 | 59 | 64 |
| 4 | **3d** | toluene | 48 | 70 | 78 |
| 5 | **3e** | toluene | 48 | 76 | 85 |
| 6 | **3e** | THF | 48 | 65 | 84 |
| 7 | **3e** | $CH_2Cl_2$ | 36 | 73 | 82 |
| 8 | **3e** | EtOAc | 144 | 72 | 87 |
| 9 | **3e** | Tol/*t*-BuOH[d] | 48 | 89 | 95 |

[a] Reaction conditions: (i) **1a** (0.4 mmol), **2a** (0.2 mmol), and catalyst **3** (10 mol %) in solvent (2 mL) at −20 °C; (ii) PCC (1.5 equiv), DCM, reflux. [b] Isolated yield of the mixture of two anomers **4a**. [c] The ee value of **5a** was determined by chiral HPLC. [d] Toluene/*t*-BuOH (10:1).

With the optimal reaction conditions, the scope of the domino Michael/hemiacetalization reaction was probed by using various α-keto esters (Table 2). Aromatic $\beta,\gamma$-unsaturated α-keto esters **2** having both electron-donating (Table 2, entries 2 and 3) and electron-withdrawing substituents (Table 2, entries 4−6) can effectively be used in this transformation; the substitution pattern of the arene had little effect on the enantioselectivity of the reaction, although the reactivity may be affected. Accordingly, the electron-poor aryl α-keto esters displayed reactivity higher than that of their electron-rich counterparts, producing the desired hemiacetals **4** in almost quantitatively yields (entries 4, 5 versus

(9) For a recent review on chiral Brønsted base catalyzed reaction, see: Palomo, C.; Oiarbide, M.; López, R. *Chem. Soc. Rev.* **2009**, *38*, 632.

(10) For reviews on organocatalytic domino reactions, see: (a) Grondal, C.; Jeanty, M.; Enders, D. *Nat. Chem.* **2010**, *2*, 167. (b) Alba, A.-N.; Companyó, X.; Viciano, M.; Rios, R. *Curr. Org. Chem.* **2009**, *13*, 1432. (c) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570. (d) Yu, X.; Wang, W. *Org. Biomol. Chem.* **2008**, *6*, 2037.

(11) Attempts to determine the ee value of **4a** directly proved unsuccessful; therefore, product **4a** was further oxidized to the corresponding lactone derivative **5a**. For synthesis of α-spiropyranone, see: (a) Kirillov, N. F.; Gavrilov, A. G. *Russ. J. Org. Chem.* **2008**, *44*, 963. (b) Zou, Y.; Wang, Q.; Goeke, A. *Chem.—Eur. J.* **2008**, *14*, 5335.

(12) For reviews on chiral cinchona alkaloid catalysts, see: (a) Connon, S. J. *Chem. Commun.* **2008**, 2499. (b) Marcelli, T.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 7496. (c) Tian, S.-K.; Chen, Y. G.; Hang, J. F.; Tang, L.; McDaid, P.; Deng, L. *Acc. Chem. Res.* **2004**, *37*, 621. (d) Chen, Y. G.; McDaid, P.; Deng, L. *Chem. Rev.* **2003**, *103*, 2965.

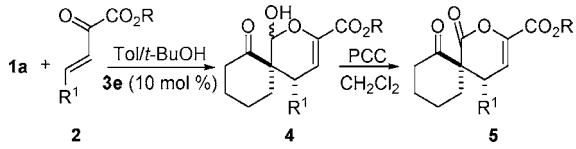
(13) For selected examples of cinchona alkaloid catalyzed domino reactions via other kinds of enolates except aldehyde enolates, see: (a) Kaneko, S.; Yoshino, T.; Katoh, T.; Terashima, S. *Tetrahedron* **1998**, *54*, 5471. (b) Dickmeiss, G; De Sio, V; Udmark, J; Poulsen, T. B; Marcos, V; Jørgensen, K. A *Angew. Chem., Int. Ed.* **2009**, *48*, 6650. (c) Li, L.; Ganesh, M.; Seidel, D. *J. Am. Chem. Soc.* **2009**, *131*, 11648. (d) Tan, B.; Shi, Z.; Chua, P. J.; Zhong, G. *Org. Lett.* **2008**, *10*, 3425. (e) Shi, Z.; Yu, P.; Chua, P. J.; Zhong, G. *Adv. Synth. Catal.* **2009**, *351*, 2797. (f) Zu, L.; Xie, H.; Li, H.; Wang, J.; Jiang, W.; Wang, W. *Adv. Synth. Catal.* **2007**, *349*, 1882. (g) Zu, L.; Wang, J.; Li, H.; Xie, H.; Jiang, W.; Wang, W. *J. Am. Chem. Soc.* **2007**, *129*, 1036. (h) Wang, J.; Xie, H.; Li, H.; Zu, L.; Wang, W. *Angew. Chem., Int. Ed.* **2008**, *47*, 4177. (i) Wang, Y.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 3928. (j) Wang, B.; Wu, F; Wang, Y.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2007**, *129*, 768. (k) Calter, M. A.; Wang, J. *Org. Lett.* **2009**, *11*, 2205.

(14) The absolute configuration of the tandem product was assigned by a single-crystal X-ray analysis of **5a**.

(15) For the first example, see: McDaid, P.; Chen, Y.; Deng, L. *Angew. Chem., Int. Ed.* **2002**, *41*, 338.

3). Additionally, heteroaromatic compounds **2g** and **2h** had also successfully been employed in this process, whereas an extended reaction time was required to get a good yield (Table 2, entries 7 and 8). Unfortunately, (*E*)-methyl 5-methyl-2-oxohex-3-enoate (**2**, R = Me, $R^1$ = *i*-Pr), a $\gamma$-alkyl substituted substrate, cannot undergo the annulation with **1a**. Notably, the optically pure product **5a** (>99% ee) could be obtained through a single recrystallization from $CH_2Cl_2$/hexane (Table 2, entry 1).

**Table 2.** Asymmetric Synthesis of Lactones **5**[a]




2 4 5

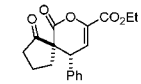
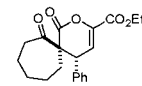
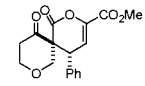
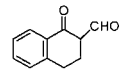
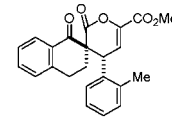
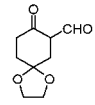
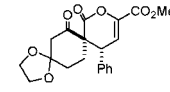
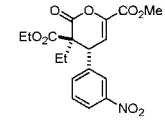
| entry | 2 | R | $R^1$ | time (h) | 4, yield[b] (%) | 5, ee[c] (%) |
|---|---|---|---|---|---|---|
| 1 | **2a** | Me | Ph | 48 | **4a**, 89 | **5a**, 95 (>99)[d] |
| 2 | **2b** | Me | 4-$CH_3$Ph | 48 | **4b**, 97 | **5b**, 88 |
| 3 | **2c** | Me | 4-$CH_3OC_6H_4$ | 72 | **4c**, 71 | **5c**, 90 |
| 4 | **2d** | Et | 3-$NO_2C_6H_4$ | 36 | **4d**, 99 | **5d**, 90 |
| 5 | **2e** | Me | 4-$FC_6H_4$ | 42 | **4e**, 99 | **5e**, 90 |
| 6 | **2f** | Et | 4-$ClC_6H_4$ | 42 | **4f**, 94 | **5f**, 88 |
| 7 | **2g** | Et | 2-thienyl | 72 | **4g**, 76 | **5g**, 92 |
| 8[e] | **2h** | Et | *N*-Tos-indol-3-yl | 108 | **4h**, 67 | **5h**, 97 |

[a] Reaction conditions: (i) **1a** (0.4 mmol), **2** (0.2 mmol), and catalyst **3e** (10 mol %) in Tol/*t*-BuOH (10:1, 2 mL) at −20 °C; (ii) PCC (1.5 equiv), DCM, reflux. [b] Yield of the mixture of two anomers after flash chromatography. [c] The ee value was determined by chiral HPLC. [d] After a single recystallization. [e] Toluene/*t*-BuOH (5:1, 4 mL) was used.

To further expand the synthetic utility of the reaction, structural variation in the aldehyde partner has also been examined (Table 3). Pleasingly, good to high enantioselectivities were observed for a variety of five-, six-, and seven-membered cyclic systems. Notably, 2-oxocyclopentanecarbaldehyde (**1b**) accomplished the reaction with **2i** quite quickly, furnishing the target compound **4i** in excellent yield after 12 h with diminished enantioselectivity under the standard conditions. On the other hand, while reducing the catalyst loading of **3e** from 10 mol % to 0.5 mol %, the reaction enantioselectivity should significantly improve to 90% ee, albeit with a little decrease in yield (Table 3, entries 1 and 2). Moreover, substituents and heteroatoms were introduced onto the six-membered scaffold without considerably affecting stereoinduction (Table 2, entries 4−6). To our delight, acyclic aldehyde **1g** with an ester substituent at the $\beta$-position also provided the desired product in excellent yield with a similar enantioselectivity (Table 3, entry 7).

In addition, lactone **1h** reacted smoothly with ester **2f** in the presence of catalyst **3e** (1 mol %), rendering the desired product **4o** in excellent yield. After acylation with acetyl chloride in the presence of triethyl amine, as expected, only two diastereomers of ester **6** bearing three continuous stereogenic centers were obtained from **4o** with high level of diastereoselectivity (dr 94:6) and moderate ee value of

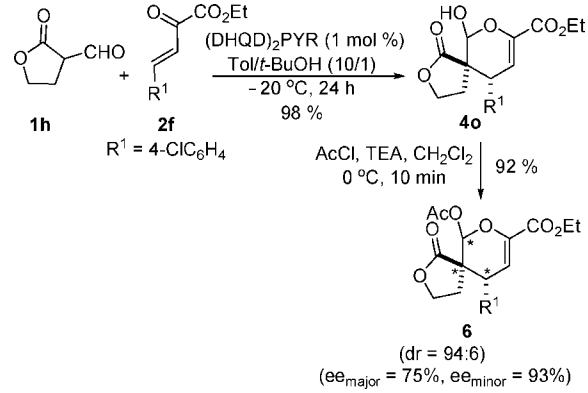
**Table 3.** Substrate Scope for the Cyclization of Aldehydes **1** and Enone **2**[a]

| entry | 1 | 2 | time(h) | 4,yield[b] | 5, ee[c](%) |
|---|---|---|---|---|---|
| 1 |  **1b** | **2i** | 12 | **4i**, 96% |  **5i**, 66 |
| 2[d] | **1b** | **2i** | 72 | **4i**, 79% | **5i**, 90 |
| 3 |  **1c** | **2i** | 48 | **4j**, 62% |  **5j**, 84 |
| 4 |  **1d** | **2a** | 48 | **4k**, 94% |  **5k**, 92 |
| 5 |  **1e** | **2j** | 48 | **4l**, 81% |  **5l**, 95 |
| 6 |  **1f** | **2a** | 48 | **4m**, 80% |  **5m**, 91 |
| 7 |  **1g** | **2d** | 24 | **4n**, 97% |  **5n**, 89 |

[a] Reaction conditions: (i) **1** (0.4 mmol), **2** (0.2 mmol), and catalyst **3e** (10 mol %) in Tol/*t*-BuOH (10:1, 2 mL) at −20 °C; (ii) PCC (1.5 equiv), DCM, reflux. [b] Yield of the mixture of two anomers after flash chromatography. [c] The ee value was determined by chiral HPLC. [d] **3e** (0.5 mol %).

75% for the major diastereomer and 93% ee for the minor (Scheme 2).[16]

**Scheme 2.** Stereoselective Construction of Product **4o** and **6** ((DHQD)$_2$PYR = hydroquinidine-2,5-diphenyl-4,6-pyrimidinediyl diether)



In conclusion, we have demonstrated a highly stereoselective domino Michael/hemiacetalization reaction of cyclic $\beta$-oxo aldehydes and aromatic $\beta,\gamma$-unsaturated $\gamma$-keto esters upon treatment with a cinchona alkaloid catalyst. High levels of diastereoselectivities and enantioselectivities (up to 97% ee) were observed for a broad spectrum of substrates under mild conditions. The reaction thus offers a new and promising method for the synthesis of complicated spiro-3,4-dihydropyran structures with potential synthetic and biological uses.

(16) The dr and ee values were determined by chiral HPLC analyses; the absolute configuration of **6** was not examined.

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**Supporting Information Available:** Experimental details, spectral data, and CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

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