ChemPubSoc Europe

DOI: 10.1002/chem.201402945

CHEMISTRY
A European Journal
Communication

Asymmetric Catalysis

Facile Synthesis of Chiral Spirooxindole-Based Isotetronic Acids and 5-1*H*-Pyrrol-2-ones through Cascade Reactions with Bifunctional Organocatalysts

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Abstract: Unprecedented organocatalyzed asymmetric cascade reactions have been developed for the facile synthesis of chiral spirooxindole-based isotetronic acids and 5-1*H*-pyrrol-2-ones.The asymmetric 1,2-addition reactions of α-ketoesters to isatins and imines by using an acid–base bifunctional 6′-OH cinchona alkaloid catalyst, followed by cyclization and enolization of the resulting adducts, gave chiral spiroisotetronic acids and 5-1*H*-pyrrol-2-ones, respectively, in excellent optical purities (up to 98% *ee*). FT-IR analysis supported the existence of hydrogen-bonding interaction between the 6′-OH group of the cinchona catalyst and an isatin carbonyl group, an interaction that might be crucial for catalyst activity and stereocontrol.

Isotetronic acids are regarded as privileged structural units in a large class of natural products and unnatural compounds.[1]In the past few years, there has been significant progress in developing asymmetric methodology for the synthesis of simple isotetronic acid derivatives.[2] In contrast, spiroisotetronic acids and nitrogen-based analogues of isotetronic acids (5-1*H*-pyrrol-2-ones) have captured much less attention, despite the prominent biological activities of the molecules that contains these motifs.[3,4] Optically pure isotetronic acids with a spiro backbone have primarily been confined to the arena of biosynthesis for a long time.[3a–c] To date, only one non-biosynthetic method has been reported, albeit one that yields the products in racemic form.[5] Meanwhile, the general synthetic approach for chiral pyrrol-2-ones relies on the 1,4-addition of amines containing a chiral auxiliary to β,γ-unsaturated α-oxoesters.[6] So far, there has been only one asymmetric version in which pyrrol-2-one was obtained with disappointing enantioselectivity through a three-component reaction involving chiral phosphoric acid as a catalyst (Scheme 1 a, top reaction).[7] Owing to the importance of discovering new bioactive compounds, the development of efficient methods for the asymmetric synthesis of spiroisotetronic acid derivatives and 5-1*H*-pyrrol-2-ones is in high demand.

Spiroisotetronic acids bearing an oxindole moiety represent a new class of 3,3′-oxindole spiro-fused cyclic compounds,[8] which are promising bioactive candidates for drug screening according to the hybridization concept in medicinal chemistry.[9] As part of our continuing efforts to develop new methods for the synthesis of chiral isotetronic acids and their derivatives,[2d] we envisioned that spiroisotetronic acids and 5-1*H*-pyrrol-2-ones could be accessed through a cascade reaction of α-ketoacids (or esters) **2** with isatins **1** or imines **4** in the presence of an appropriate catalyst (Scheme 1 b). The key step for the synthesis of isotetronic acids or their nitrogen-based analogues in such a cascade sequence would be the cross-aldol reaction or Mannich reaction using α-ketoacids (or esters) **2** as nucleophiles. Traditional organocatalysts for this type of 1,2-addition reaction are the proline-based secondary amine catalysts, which activate α-ketoacids or esters through the formation of an enamine intermediate (Scheme 1 a, lower reaction).[10] However, in our preliminary investigations, enamine catalysis by pyrrolidines was found to be ineffective for promoting the cascade reactions, probably as a result of the severe steric crowding in the coming together of the bulky rigid enamine intermediates and isatins[11] or imines[12] (Scheme 1 b, top reaction; for more details, see the Supporting Information). We thus shifted our attention to base-promoted enolate formation,[13] with the expectation that such an enolate-mediated cascade reaction might be facilitated by a more flexible noncovalent interaction between the protonated base and the enolate (Scheme 1 b, lower reaction). Furthermore, even though there has been no report on the cross-aldol reaction or Mannich reaction with α-ketoesters as donors through enolate activation, the stronger acidity of α-ketoesters compared to unfunctionalized enolizable ketones should also be favorable for the reaction.[14]

Herein, we report an organocatalyzed cascade reaction of α-ketoesters with isatins or imines for the synthesis of spiroisotetronic acids and nitrogen-based analogues of isotetronic acid, respectively. The asymmetric versions of the reactions were accomplished by using a 6′-OH cinchona alkaloid catalyst, thus affording a variety of oxindole-based spiroisotetronic acids and

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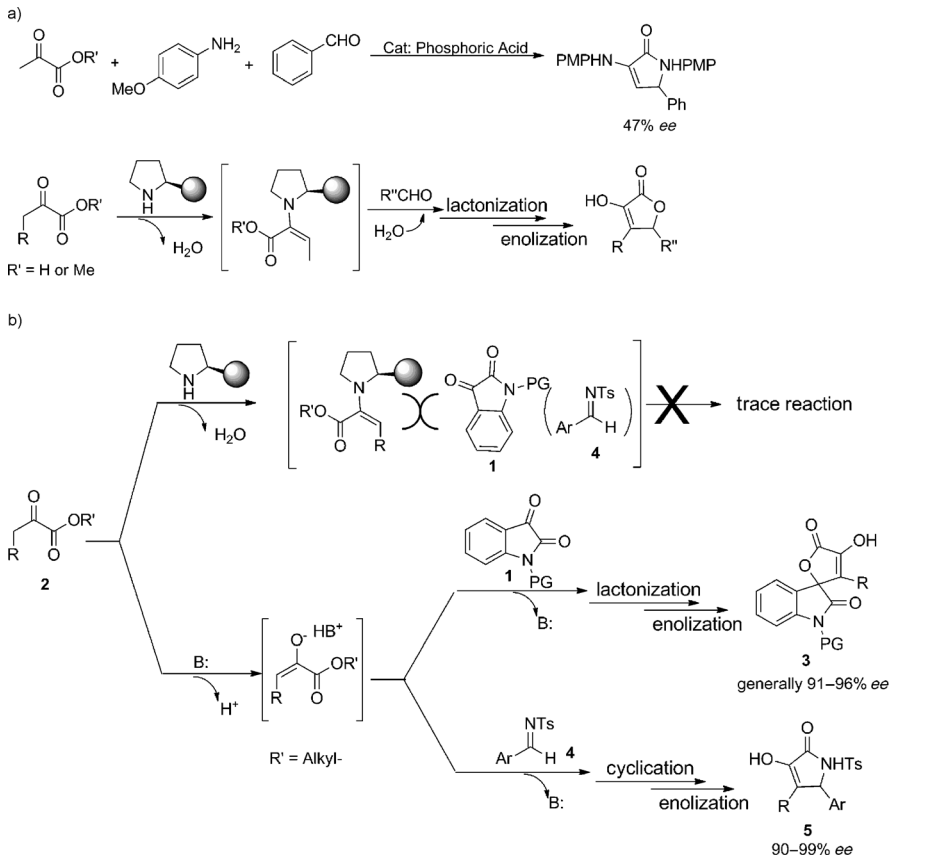
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201402945.



Scheme 1. Catalytic synthesis of chiral isotetronic acids and their nitrogen-based analogues: a) previous methods using acid or enamine catalysis; b) present work using Brønsted base catalysis. PMP = *para*-methoxy phenyl.

5-1*H*-pyrrol-2-ones in high yields (up to 98%) with excellent *ee* values (generally 91–98%). Notably, control experiments and FT-IR analysis support a hydrogen-bonding interaction between the 6′-OH group on catalyst **F** (Figure 1) and a carbonyl group in isatin **1**. This interaction might work in synergy with α-ketoester enolate formation by base catalysis, thus resulting in a highly organized reaction assembly that may account for the excellent catalytic performance.

The study was started by using commercially available ethyl-2-oxobutanoate **2a** and *N*-Me isatin **1a** as the substrates in the presence of catalytic amount of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; 10 mol%). We were pleased to find that the reaction proceeded smoothly within 12 h in dichloromethane at room temperature to give the corresponding racemic spiroisotetronic acid in 70% yield (Table 1, entry 1). Encouraged by this result, we proceeded to examine the catalytic potential of chiral guanidine **A**, which possesses a tertiary amine group that is similar to that in DBU.[15] However, this catalyst fails to promote the cascade reaction (Table 1, entry 2). Bifunctional thiourea–amine catalysts **B** and **C**, which are efficient catalysts for preparing other types of 3,3′-oxindole spiro-fused cyclic frameworks,[16] were also found to be effective in promoting the cascade reaction between **2a** and **1a** (Table 1, entry 3 and 4); however, in both cases, spiroisotetronic acid **3aa** is obtained with poor levels of enantioselectivity. Pleasingly, screening various chiral organic base catalysts led to identification of Deng's 6′-OH cinchona alkaloid catalyst, **F**,[17] the use of which gave **3aa** in 64% *ee* and 89% yield (Table 1, entry 7). The effect of the nature of the ester group (R) of the α-ketoester on the reaction was then investigated. It was found that the size of the ester group had a significant effect on reactivity and enantioselectivity. For example, when ethyl and *n*-propyl 2-oxobutanoate were used as nucleophiles, the levels of reactivity and enantioselectivity were similar (Table 1, entries 7 and 9). In contrast, the more bulky substrates, *tert*-butyl or benzyl 2-oxobutanoate, led to poor levels of reactivity and enantioselectivity (see Table S1 in the Supporting Information). Thus, the ethyl and *n*-propyl esters were adopted for further study. Dichloromethane was identified as the solvent of choice for optimization of the reaction (see Table S1 in the Supporting Information). To improve the enantioselectivity of this cascade reaction, we investigated *N*-substituted isatins. Surprisingly, the products were obtained in higher *ee* values when the size of the *N*-substituent was increased. For example, with catalyst **F**, *N*-methyl and *N*-trityl isatins led to the corresponding products in 64% and 82% *ee*, respectively (Table 1, entries 9 and 10). The enantioselectivity of the product was further increased to 90% *ee* by lowering the reaction temperature (Table 1, entries 11 and 12). The yield could be improved in conjunction with an increase in *ee* value to 93% when an *n*-propyl ester was used as the nucleophile (Table 1, entries 12 and 13). Furthermore, this reaction could be conducted on a gram scale (Table 1, entries 14).

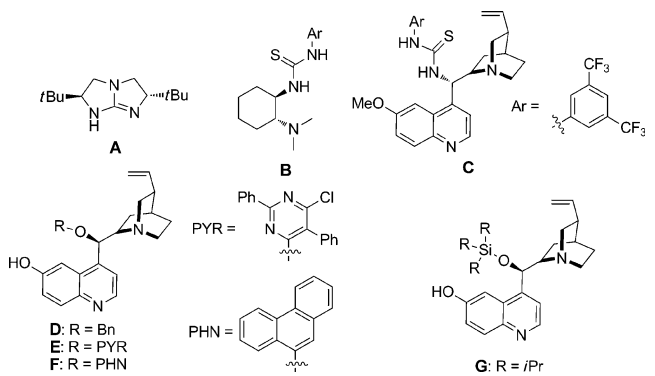
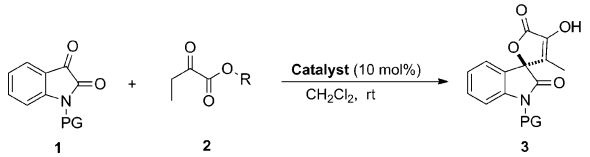


Figure 1. Chiral organic bases screened.

Table 1. Optimization of reaction conditions of cascade reactions of α-keto esters and isatins.[a]

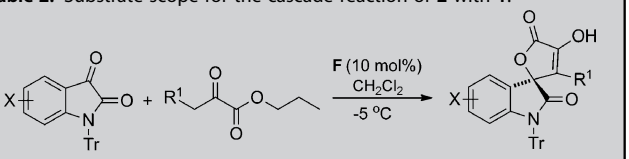


1 2 3

Entry	Cat.	PG	R	*t* [h]	Conv. [%][b]	*ee* [%][c]
1	DBU	Me	Et	12	99 (70)	–
2	**A**	Me	Et	24	N.R.	–
3	**B**	Me	Et	36	99	12
4	**C**	Me	Et	12	99	0
5	**D**	Me	Et	12	99	20
6	**E**	Me	Et	12	99	62
7	**F**	Me	Et	12	99	64
8	**G**	Me	Et	24	99	48
9	**F**	Me	*n*Pr	24	99	63
10	**F**	Tr	Et	10	97	82
11[d]	**F**	Tr	Et	36	99 (90)	88
12[e]	**F**	Tr	Et	36	99 (92)	90
13[e]	**F**	Tr	*n*Pr	48	99 (97)	93
14[e,f]	**F**	Tr	*n*Pr	60	99 (95)	93

[a] Unless otherwise specified, all cascade reactions were conducted with isatin (**1**, 0.30 mmol), α-ketoester (**2**, 2 equiv, 0.6 mmol), and catalyst (0.03 mmol, 10 mol%) in CH_2Cl_2 (1.5 mL, 0.2 M) at rt. [b] Determined by ^1H NMR analysis of the crude mixture; the data in parentheses are the yield of product after column chromatography. [c] Determined by HPLC analysis using a Daicel AD-H column. [d] The tandem reaction was carried out at 0 °C. [e] The cascade reaction was carried out at −5 °C. [f] 3.0 mmol *N*-trityl isatin was used.

Table 2. Substrate scope for the cascade reaction of **2** with **1**.[a]



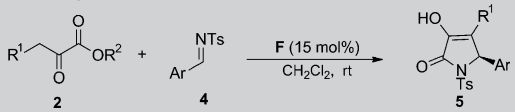
1 2 3

Entry	X	R^1	Yield [%][b]	*ee* [%][c]
1	H	Me	**3a** (97)	93
2	4-Cl	Me	**3b** (85)	95
3	5-Cl	Me	**3c** (88)	91
4	5-Br	Me	**3d** (90)	92
5	5-I	Me	**3e** (99)	93
6	5-Me	Me	**3f** (87)	92
7	5-MeO	Me	**3g** (90)	93
8	5-CF_3O	Me	**3h** (99)	94
9	7-F	Me	**3i** (95)	93
10	5-F	Me	**3j** (91)	93
11	6-Br	Me	**3k** (98)	86
12	5-CF_3O	Et	**3l** (94)	96
13	5-Me	Et	**3m** (84)	94
14	5-MeO	Et	**3n** (92)	95
15[d]	5-MeO	Bn	**3o** (85)	77

[a] Unless otherwise specified, all cascade reactions were conducted with isatin (**1**, 0.30 mmol), α-ketoester (**2**, 2 equiv, 0.60 mmol), and catalyst (**F**, 0.03 mmol, 10 mol%) in CH_2Cl_2 (1.5 mL) at −5 °C, 48–72 h. [b] Yield of product **3** after column chromatography. [c] Determined by HPLC analysis using a Daicel AD-H column. [d] 0.75 mL CH_2Cl_2.

Subsequently, the substrate scope for isatins and α-ketoesters was investigated under the optimized reaction conditions. A broad range of *N*-trityl isatins with diverse electronic and steric properties are readily converted into the corresponding products **3a**–**o** in high yields with excellent levels of enantioselectivity (Table 2). For example, *N*-trityl isatins with electron-donating methyl and methoxy groups and electron-withdrawing fluoro, chloro, bromo, trifluoromethoxy, and iodo groups at the 4, 5, or 7 position are converted into the corresponding products in up to 99% yield with 91–95% *ee* (Table 2, entries 1–10). Nevertheless, the *ee* values were slightly lower with substituents at the 6-position (Table 2, entry 11, 86% *ee*). With an extra carbon atom on the ketoester (R^1 = Et), the enantioselectivity was slightly improved (Table 2, entries 12–14, 94–96% *ee*) with equally excellent yield. Hindering the nucleophilic carbon center of the α-ketoester by using a benzyl-substituted α-ketoester slowed down the reaction and had a detrimental effect on the enantioselectivity (Table 2, entry 15). Encouraged by the successful development of the above cascade reactions, we then attempted to extend the 1,2-addition reaction to a Mannich reaction[18] for the synthesis of chiral 5-1*H*-pyrrol-2-ones. After the investigation of a model reaction between **2a** and *N*-Ts protected imine **4a**, we found that the same catalytic systems were suitable for the new reaction with higher catalyst loading under mild reaction conditions. Imines with both electron-donating and electron-withdrawing substituents at different positions on the phenyl ring give the corresponding products, **5**, with excellent levels of enantioselectivity (Table 3, entries 1–13, 87–98% *ee*). A substrate bearing a 2-thienyl ring was also tolerated (Table 3, entry 14). The absolute configuration of **3k** was unambiguously established to be *S* on the

Table 3. The asymmetric cascade reaction of **2** with **4**.[a]



2 4 5

Entry	R^1	R^2	Ar	Yield [%][b]	*ee* [%][c]
1	Me	Et	C_6H_5	**5a** (90)	96
2[d]	Me	Me	C_6H_5	**5a** (87)	96
3	Me	Et	4-ClC_6H_4	**5b** (89)	92
4	Me	Et	3-$CF_3C_6H_4$	**5c** (78)	98
5	Me	Et	3-ClC_6H_4	**5d** (73)	97
6	Me	Et	2-ClC_6H_4	**5e** (72)	94
7	Me	Et	2-FC_6H_4	**5f** (77)	95
8	Me	Et	3-MeC_6H_4	**5g** (80)	95
9	Me	Et	4-$MeOC_6H_4$	**5h** (79)	90
10	Me	Et	4-BrC_6H_4	**5i** (83)	93
11	Et	*n*Pr	C_6H_5	**5j** (90)	90
12	Et	*n*Pr	4-ClC_6H_4	**5k** (78)	87
13	Et	*n*Pr	4-BrC_6H_4	**5l** (74)	89
14	Me	Et	2-thienyl	**5m** (76)	91

[a] Unless otherwise specified, all cascade reactions were conducted with imine (**4**, 0.30 mmol), α-ketoester (**2**, 2 equiv, 0.60 mmol), and catalyst (**F**, 0.045 mmol, 15 mol%) in CH_2Cl_2 (1.0 mL) at rt, 48..72 h. [b] Yield of product **5** based on column chromatography. [c] Determined by HPLC analysis using a chiral column. [d] See ref. [19].

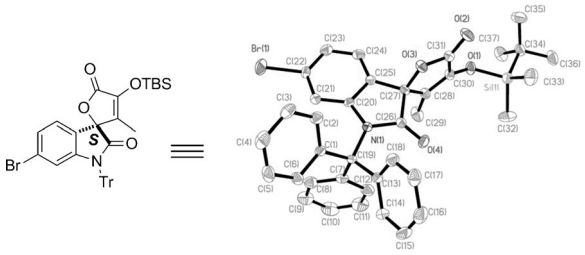
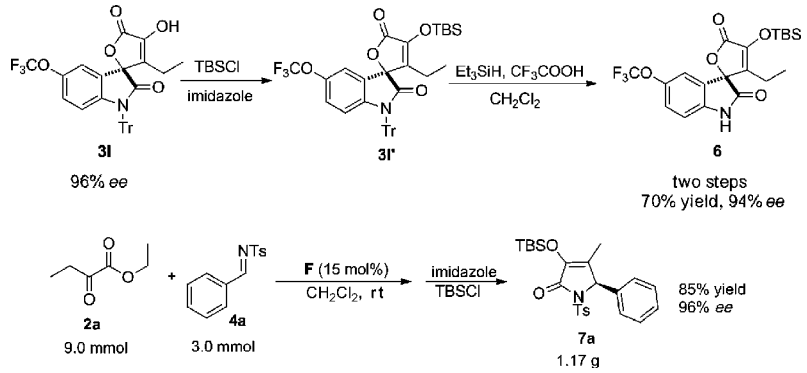


Figure 2. X-ray crystal structure of TBS-protected **3k′**.

basis of X-ray crystallographic analysis of its TBS ether, **3k′** (Figure 2), and those of others were assigned by analogy.

The *N*-trityl protecting group that is necessary for achieving high enantioselectivity in this title cascade reaction could be easily removed by using a reported procedure[20] to give TBS-protected product **6** in good yield with almost no loss of enantioselectivity (Scheme 2, top reaction). To demonstrate the synthetic practicality of this methodology, the cascade reaction of **2a** and **4a** was carried out on a gram scale under optimized reaction conditions with catalyst **F**. The corresponding product, TBS protected 5-1*H*-pyrrol-2-ones **7a**, could be obtained with 85% yield and 96% *ee* (Scheme 2, lower equation).



Scheme 2. Deprotection of the trityl group and gram-scale experiment. TBS = *tert*-butyldimethylsilyl, Tr = trityl, Ts = *para*-toluenesulfonyl.

To gain further insight into the structural elements of the catalyst that affect the key step, control experiments were performed on the reaction of **1a** with **2a** by using catalyst **H** wherein the 6′-OH is blocked with a methyl group. In sharp contrast with the high activity of 6′-OH catalyst **F**, no product was detected in the presence of 6′-OMe protected catalyst **H**, even after a prolonged reaction time (72 h). These results suggested that there may exist a hydrogen-bonding between the hydroxyl group of catalyst **F** and a carbonyl group of **1a**, which plays an important role in the reactivity and enantioselectivity of the reaction between **1** and **2**. This presence of this weak hydrogen-bonding interaction was also supported by FT-IR spectral analysis of isatin in the presence or absence of the catalyst. The IR spectrum of isatin **1a** in CH_2Cl_2 (0.02 M) is shown in Figure 3 (left, black line). When the same amount of catalyst was added to the above solution, most of peaks do not shift, except the peaks in the range from 1700 to 1760 cm^{-1} (Figure 3; left, red line) which are assigned to stretching vibrations of carbonyl groups located on the isatin **1a**. Enlarging this area (Figure 3, right), it is clear that the peaks at 1726 cm^{-1} and 1746 cm^{-1} for the isatin **1a** converge into one nonsymmetric peak upon addition of the catalyst (Figure 3; right, red line) which can be considered as the combination of two peaks: 1726 cm^{-1} (Figure 3; right, blue line) and 1741 cm^{-1} (Figure 2; right, green line) after calculation. The red shift from 1746 cm^{-1} to 1741 cm^{-1} of the keto carbonyl group of **1a** indicates the existence of hydrogen bonding between the carbonyl group and catalyst **F**. To our best knowledge, this study represents the first spectral evidence for a hydrogen-bonding interaction between a substrate and a hydroxyl group within a bifunctional catalyst.[21]

On the basis of the observed stereochemistry, the control experiments, and the FT-IR study, a possible transition state for the aldol addition of α-ketoesters to isatins is depicted in Scheme 3. For this aldol reaction, bifunctional catalysis involves electrophilic activation of the isatin through a hydrogen-bonding interaction and concomitant deprotonation of the α-ketoester

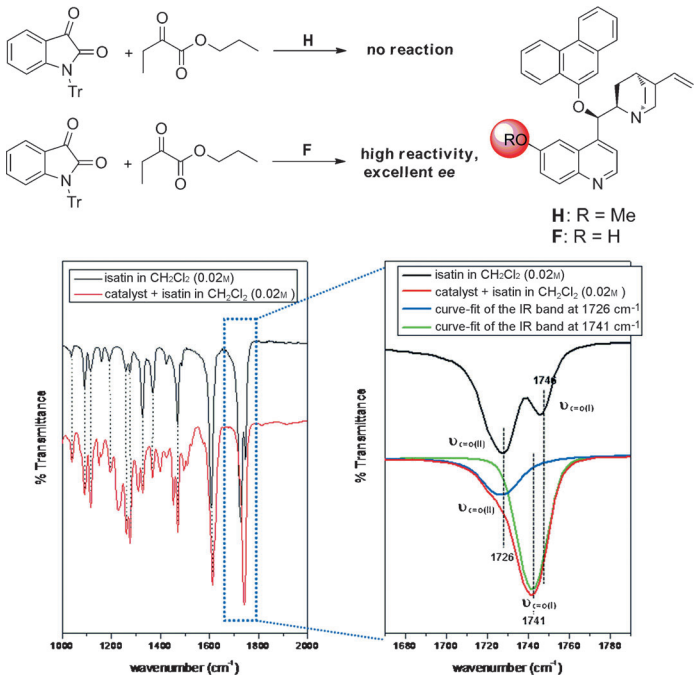
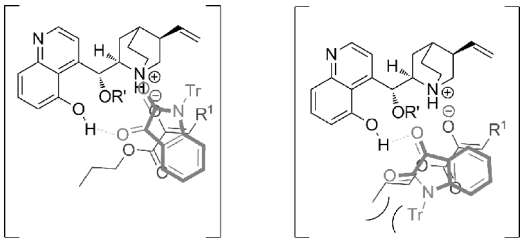


Figure 3. Control experiments and FT-IR analysis.



Scheme 3. Proposed transition states for the tandem reaction.

by the tertiary amine basic center (quinuclidine). The *Re* face of the thermodynamically stable (*Z*)-enolate preferentially attacks the *Si* face of the isatin (**TS-1**) compared to the sterically more congested *Re* face (**TS-2**). Consequently, the reaction of **1** and **2** catalyzed by **F** provides the *S* isomers predominantly. **TS-1** is also in accordance with the substituent effects observed for the isatin N position, as well as that for the R^1 and ester group of the α-ketoester.

In conclusion, we have realized a highly enantioselective cascade reaction of α-ketoesters with isatins and imines by using a 6′-OH cinchona alkaloids catalyst, to give spiroisotetronic acids bearing quaternary stereocenters and 5-1*H*-pyrrol-2-ones. This method also represents the first example of an asymmetric cross-aldol reaction and Mannich reaction involving enolate intermediates from α-ketoester donors. Furthermore, a hydrogen-bonding interaction between the 6′-OH cinchona alkaloid catalyst and the acceptor was observed through an FT-IR study.

Acknowledgements

This work was financially supported by the Natural Science Foundation of China (21322202, 2100210) and National Basic Research Program of China (2010CB833300).

Keywords: pyrrol-2-ones · cascade reactions · isatins · isotetronic acids · organocatalysis

[1] a) I. Blank, J. M. Lin, R. Fumeaux, D. H. Welti, L. B. Fay, *J. Agric. Food Chem.* **1996**, *44*, 1851 – 1856; b) A. J. Pallenberg, J. D. White, *Tetrahedron Lett.* **1986**, *27*, 5591 – 5594; c) Y. S. Rao, *Chem. Rev.* **1964**, *64*, 353 – 388; d) H. Sulser, J. Depizzol, W. Buchi, *J. Food Sci.* **1967**, *32*, 611 – 615.

[2] For an organocatalytic asymmetric synthesis of simple isotetronic acids, see: a) P. Dambruoso, A. Massi, A. Dondoni, *Org. Lett.* **2005**, *7*, 4657 – 4660; b) D. Lee, S. G. Newman, M. S. Taylor, *Org. Lett.* **2009**, *11*, 5486 – 5489; c) J. M. Vincent, C. Margottin, M. Berlande, D. Cavagnat, T. Buffeteau, Y. Landais, *Chem. Commun.* **2007**, 4782 – 4784; d) B. Zhang, Z. Jiang, X. Zhou, S. Lu, J. Li, Y. Liu, C. Li, *Angew. Chem.* **2012**, *124*, 13336 – 13339; *Angew. Chem. Int. Ed.* **2012**, *51*, 13159 – 13162; for simple isotetronic acids prepared by metal catalysis, see: e) N. Gathergood, K. Juhl, T. B. Poulsen, K. Thordrup, K. A. Jørgensen, *Org. Biomol. Chem.* **2004**, *2*, 1077 – 1085; f) K. Juhl, N. Gathergood, K. A. Jørgensen, *Chem. Commun.* **2000**, 2211 – 2212; g) V. Liautard, D. Jardel, C. Davies, M. Berlande, T. Buffeteau, D. Cavagnat, F. Robert, J. M. Vincent, Y. Landais, *Chem. Eur. J.* **2013**, *19*, 14532 – 14539.

[3] For selected examples, see: a) B. Irlinger, H. J. Kramer, P. Mayser, W. Steglich, *Angew. Chem.* **2004**, *116*, 1119 – 1121; *Angew. Chem. Int. Ed.* **2004**, *43*, 1098 – 1100; b) K. Justus, R. Herrmann, J. D. Klamann, G. Gruber, V. Hellwig, A. Ingerl, K. Polborn, B. Steffan, W. Steglich, *Eur. J. Org. Chem.* **2007**, 5560 – 5572; c) H. J. Krämer, D. Kessler, U. C. Hipler, B. Irlinger, W. Hort, R. H. Bodeker, W. Steglich, P. Mayser, *ChemBioChem* **2005**, *6*, 2290 – 2297; d) K. Zuther, P. Mayser, U. Hettwer, W. Y. Wu, P. Spiteller, B. L. J. Kindler, P. Karlovsky, C. W. Basse, J. Schirawski, *Mol. Microbiol.* **2008**, *68*, 152 – 172; e) O. A. Mascaretti, C. J. Chang, D. Hook, H. Otsuka, E. F. Kreutzer, H. G. Floss, *Biochemistry* **1981**, *20*, 919 – 924; for selected bioactive spiroisotetronic acids, see the Scheme S1 in the Supporting.

[4] For selected examples of bioactive pyrrol-2-one compounds, see: a) Z. Q. Feng, X. Z. Li, G. J. Zheng, L. Huang, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2112 – 2115; b) T. R. K. Reddy, C. Li, X. X. Guo, H. K. Myrvang, P. M. Fischer, L. V. Dekker, *J. Med. Chem.* **2011**, *54*, 2080 – 2094; c) A. Richter, R. Rose, C. Hedberg, H. Waldmann, C. Ottmann, *Chem. Eur. J.* **2012**, *18*, 6520 – 6527; d) Y. X. Zhao, Q. Wang, Q. Q. Meng, D. Z. Ding, H. Y. Yang, G. W. Gao, D. W. Li, W. L. Zhu, H. C. Zhou, *Bioorg. Med. Chem.* **2012**, *20*, 1240 – 1250; e) C. L. Zhuang, Z. Y. Miao, L. J. Zhu, G. Q. Dong, Z. Z. Guo, S. Z. Wang, Y. Q. Zhang, Y. L. Wu, J. Z. Yao, C. Q. Sheng, W. N. Zhang, *J. Med. Chem.* **2012**, *55*, 9630 – 9642; f) V. L. Gein, A. V. Popov, W. E. Kolla, N. A. Popova, *Pharmazie* **1993**, *48*, 107 – 109; for selected examples of bioactive 1,5-dihydro-2*H*-pyrrol-2-ones, see Scheme S1 in the Supporting Information.

[5] V. L. Gein, E. B. Levandovskaya, V. N. Vichegjanina, *Chem. Heterocycl. Compd.* **2010**, *46*, 931 – 933.

[6] F. Palacios, J. Vicario, D. Aparicio, *Eur. J. Org. Chem.* **2006**, 2843 – 2850.

[7] For pioneering work on the synthesis of 1,5-dihydro-2*H*-pyrrol-2-ones by using a chiral phosphoric acid as catalyst, see: X. Li, H. Deng, S. Luo, J. P. Cheng, *Eur. J. Org. Chem.* **2008**, 4350 – 4356; for an achiral example by using ytterbium as a catalyst, see: A. S. Nagarajan, B. S. R. Reddy, *Synth. Commun.* **2013**, *43*, 1229 – 1236.

[8] For recent reviews about the asymmetric organocatalytic construction of 3,3′-spirocyclic oxindoles, see: a) R. Dalpozzo, G. Bartoli, G. Bencivenni, *Chem. Soc. Rev.* **2012**, *41*, 7247 – 7290; b) L. Hong, R. Wang, *Adv. Synth. Catal.* **2013**, *355*, 1023 – 1052; c) G. S. Singh, Z. Y. Desta, *Chem. Rev.* **2012**, *112*, 6104 – 6155; d) D. Cheng, Y. Ishihara, B. Tan, C. F. Barbas, *ACS Catal.* **2014**, *4*, 743 – 762.

[9] For an example of the hybridization concept in drug molecule design, see: S. Gemma, G. Campiani, S. Butini, B. P. Joshi, G. Kukreja, S. S. Coccone, M. Bernetti, M. Persico, V. Nacci, I. Fiorini, E. Novellino, D. Taramelli, N. Basilico, S. Parapini, V. Yardley, S. Croft, S. Keller-Maerki, M. Rottmann, R. Brun, M. Coletta, S. Marini, G. Guiso, S. Caccia, C. Fattorusso, *J. Med. Chem.* **2009**, *52*, 502 – 513.

[10] a) B. List, *Acc. Chem. Res.* **2004**, *37*, 548 – 557; b) B. List, R. A. Lerner, C. F. Barbas, *J. Am. Chem. Soc.* **2000**, *122*, 2395 – 2396.

[11] For selected examples of the use of isatins as activated ketones in organocatalytic aldol reactions, see: a) C. Cassani, P. Melchiorre, *Org. Lett.* **2012**, *14*, 5590 – 5593; b) J. R. Chen, X. P. Liu, X. Y. Zhu, L. Li, Y. F. Qiao, J. M. Zhang, W. J. Xiao, *Tetrahedron* **2007**, *63*, 10437 – 10444; c) N. Hara, S. Nakamura, N. Shibata, T. Toru, *Chem-Eur. J.* **2009**, *15*, 6790 – 6793; d) T. Itoh, H. Ishikawa, Y. Hayashi, *Org. Lett.* **2009**, *11*, 3854 – 3857; e) X. X. Jiang, Y. M. Cao, Y. Q. Wang, L. P. Liu, F. F. Shen, R. Wang, *J. Am. Chem. Soc.* **2010**, *132*, 15328 – 15333; f) A. V. Malkov, M. A. Kabeshov, M. Bella, O. Kysilka, D. A. Malyshev, K. Pluhackova, P. Kocovsky, *Org. Lett.* **2007**, *9*, 5473 – 5476; g) T. Min, J. C. Fettinger, A. K. Franz, *ACS Catal.* **2012**, *2*, 1661 – 1666; h) S. Nakamura, N. Hara, H. Nakashima, K. Kubo, N. Shibata, T. Toru, *Chem. Eur. J.* **2008**, *14*, 8079 – 8081; i) A. J. Pearson, S. Panda, *Org. Lett.* **2011**, *13*, 5548 – 5551; j) I. Saidalimu, X. Fang, X. P. He, J. Liang, X. Y. Yang, F. H. Wu, *Angew. Chem.* **2013**, *125*, 5676 – 5680; *Angew. Chem. Int. Ed.* **2013**, *52*, 5566 – 5570.

[12] For selected reviews on the organocatalytic asymmetric Mannich reaction, see: a) J. M. M. Verkade, L. J. C. van Hemert, P. J. L. M. Quaedflieg, F. P. J. T. Rutjes, *Chem. Soc. Rev.* **2008**, *37*, 29 – 41; b) X. H. Cai, B. Xie, *Arkivoc* **2013**, 264 – 293.

[13] For examples of organocatalyzed enantioselective direct aldol reactions of ketones through the enolate mechanism, see: a) J. Guang, Q. S. Guo, J. C. G. Zhao, *Org. Lett.* **2012**, *14*, 3174 – 3177; b) Q. S. Guo, M. Bhanushali, C. G. Zhao, *Angew. Chem.* **2010**, *122*, 9650 – 9654; *Angew. Chem. Int. Ed.* **2010**, *49*, 9460 – 9464; c) M. Markert, M. Mulzer, B. Schetter, R. Mahrwald, *J. Am. Chem. Soc.* **2007**, *129*, 7258 – 7259; d) T. K. M. Shing, H. M. Cheng, *Org. Lett.* **2008**, *10*, 4137 – 4139.

[14] Notably, isatins and Ts-protected imines have been established as a class of excellent electrophiles, the use of which avoids the potentially competing homoaldol reaction of α-ketoesters. For examples of base-promoted homoaldol reactions of α-ketoesters, see: a) H. S. Chen, X. P. Ma, Z. M. Li, Q. R. Wang, F. G. Tao, *Arkivoc* **2009**, 87 – 105; b) D. Tejedor, A. Santos-Exposito, F. Garcia-Tellado, *Chem. Commun.* **2006**, 2667 – 2669; c) D. Tejedor, A. Santos-Exposito, F. Garcia-Tellado, *Chem-Eur. J.* **2007**, *13*, 1201 – 1209.

[15] For selected reviews on chiral guanidine catalyzed enantioselective reactions, see: D. Leow, C. H. Tan, *Chem. Asian. J.* **2009**, *4*, 488 – 507, and references therein; for seminal work on chiral guanidine catalysis, see: E. J. Corey, M. J. Grogan, *Org. Lett.* **1999**, *1*, 157 – 160.

[16] For selected examples, see: a) F. Pesciaioli, P. Righi, A. Mazzanti, G. Bartoli, G. Bencivenni, *Chem. Eur. J.* **2011**, *17*, 2842 – 2845; b) W. S. Sun, G. M. Zhu, C. Y. Wu, G. F. Li, L. Hong, R. Wang, *Angew. Chem.* **2013**, *125*, 8795 – 8799; *Angew. Chem. Int. Ed.* **2013**, *52*, 8633 – 8637; c) B. Tan, X. F. Zeng, W. W. Y. Leong, Z. G. Shi, C. F. Barbas, G. F. Zhong, *Chem. Eur. J.* **2012**, *18*, 63 – 67.

[17] a) H. M. Li, J. Song, X. F. Liu, L. Deng, *J. Am. Chem. Soc.* **2005**, *127*, 8948 – 8949; b) H. M. Li, Y. Wang, L. Tang, L. Deng, *J. Am. Chem. Soc.* **2004**, *126*, 9906 – 9907; c) H. M. Li, Y. Wang, L. Tang, F. H. Wu, X. F. Liu, C. Y. Guo, B. M. Foxman, L. Deng, *Angew. Chem.* **2005**, *117*, 107 – 110; *Angew. Chem. Int. Ed.* **2005**, *44*, 105 – 108; d) X. F. Liu, H. M. Li, L. Deng, *Org. Lett.* **2005**, *7*, 167 – 169. e) Y. Wang, L. Deng, *Asymmetric Acid – Base Bifunctional Catalysis with Organic Molecules in Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), Wiley, Hoboken, New Jersey, **2010**, Chap. 2.2B. 59.

[18] For examples of Mannich reactions involving pyruvates or α-ketoamides as nucleophiles, as catalyzed by Lewis acids and that cannot be used to prepare 5-1*H*-pyrrol-2-ones, see: a) K. Juhl, N. Gathergood, K. A. Jørgensen, *Angew. Chem.* **2001**, *113*, 3083 – 3085; *Angew. Chem. Int. Ed.* **2001**, *40*, 2995 – 2997; b) G. Lu, H. Morimoto, S. Matsunaga, M. Shibasaki, *Angew. Chem.* **2008**, *120*, 6953 – 6956; *Angew. Chem. Int. Ed.* **2008**, *47*, 6847 – 6850; c) Y. J. Xu, G. Lu, S. Matsunaga, M. Shibasaki, *Angew. Chem.* **2009**, *121*, 3403 – 3406; *Angew. Chem. Int. Ed.* **2009**, *48*, 3353 – 3356.

[19] The fact that all products **5** obtained in this study are liquids or amorphous solids hampers the direct determination of the absolute configuration of the stereogenic centers by X-ray crystal structure analysis. Thus, a comparison of the experimental ECD spectra of compound **5a**′ (in $CHCl_3$, blue line) with the calculated spectra for (*R*)-**5a**′ (red line 1) and (*S*)-**5a**′ (black line 2) allows us to speculate that the absolute configuration of compound **5** is *R*. For details, see Scheme S2 in the Supporting Information.

[20] E. Vedejs, A. Klapars, D. L. Warner, A. H. Weiss, *J. Org. Chem.* **2001**, *66*, 7542 – 7546.

[21] For an example of spectral evidence for a hydrogen-bonding interaction between a substrate and a thiourea-containing bifunctional catalyst, see: T. Inokuma, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2006**, *128*, 9413 – 9419.

Received: February 28, 2014
Published online on June 4, 2014