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PAPER

Enantioselective construction of multifunctionalized spirocyclohexaneoxindoles through organocatalytic Michael–Aldol cyclization of isatin derived alkenes with linear dialdehydes†

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Optically active spirocyclohexaneoxindole motifs are very important building blocks for preparations of biologically active complexes, natural products, and pharmaceutical compounds. Herein, we report the syntheses of enantiopure spirocyclohexaneoxindoles through domino Michael–Aldol reactions between isatin derived alkenes and pentane-1,5-dial in the presence of diphenylprolinol silyl ether as an aminocatalyst. As a result, a series of multistereogenic and functionalized spirocyclohexaneoxindoles have been obtained in good yields with moderate diastereoselectivities and excellent enantioselectivities. In addition, electronic circular dichroism (ECD) spectroscopy and time-dependent density functional theory (TD-DFT) were used to investigate the rational structures of spirocyclohexaneoxindoles.

Introduction

Multistereogenic cyclohexanes[1] and oxindoles[2] are two very important types of structural motif, whose derivatives are not only prevalent in natural products, pharmaceutical compounds and biologically active molecules, but also serve as versatile intermediates in organic synthesis. Therefore, chiral multistereogenic spirocyclohexaneoxindole derivatives, which combine the important backbones of cyclohexanes and oxindoles, are particularly intriguing and are featured in a large number of natural products and medicinally relevant compounds (Fig. 1).[3] For instance, compound A, a nonsteroidal PR modulator,[3b,e] is used in female healthcare as a progesterone receptor antagonist, as well as in contraception and the treatment of uterine fibroids, endometriosis and hormone-related cancers. Gelsemine[3c] can excite the central nervous system. SR 121463 A[3a,d] is an effective orally active vasopressin V2 antagonist.

The asymmetric synthesis of spirocyclohexaneoxindoles involves the stereo-controlled installation of a spiroquaternary chiral carbon center, which has been a challenging task.[4] Recently, spirocyclic oxindole skeletons have been constructed by asymmetric organocatalytic domino reactions.[5] In 2009, Melchiorre and co-workers pioneered the synthesis of multistereogenic spiro[cyclohexane-1,3′-indoline]-2′,4-diones *via* [4 + 2] double Michael additions.[6] Gong *et al.*,[7] Wang *et al.*,[8] and our group[9] each reported highly enantioselective syntheses of spiro[cyclohexanone-oxindole] and spiro[cyclohexenone-oxindole] derivatives through organocatalytic cascade transformations. In 2010, Rios' and Chen's groups independently found that six-membered spirocyclic oxindoles, such as spiro[cyclohexenecarbaldehyde-oxindoles] and spiro[cyclohexanol-oxindoles], could be constructed *via* an organocatalytic domino Michael–Michael–Aldol reaction,[10] or Michael–Michael–Michael–Aldol sequences.[11] However, to the best of our knowledge, there is no literature reported for the enantioselective synthesis of six-membered spirocyclohexaneoxindole compounds bearing both formyl and hydroxyl functional groups. Herein, we present our preliminary results on a tandem Michael–Aldol process between isatin derived alkenes and pentane-1,5-dial catalyzed by a diphenylprolinol silyl ether catalyst, which produces a series of multistereogenic and functional spirocyclohexaneoxindoles in good yields with moderate diastereoselectivities and excellent enantioselectivities.

In 2007, Hayashi and co-workers reported the first example of a one-step synthesis of substituted cyclohexane derivatives with

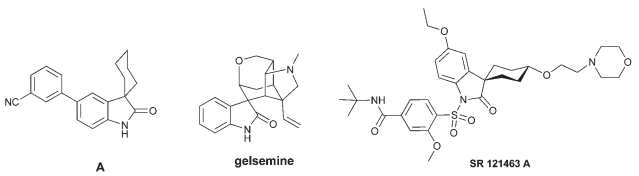

Fig. 1 Naturally occurring and biologically active spirocyclic products.

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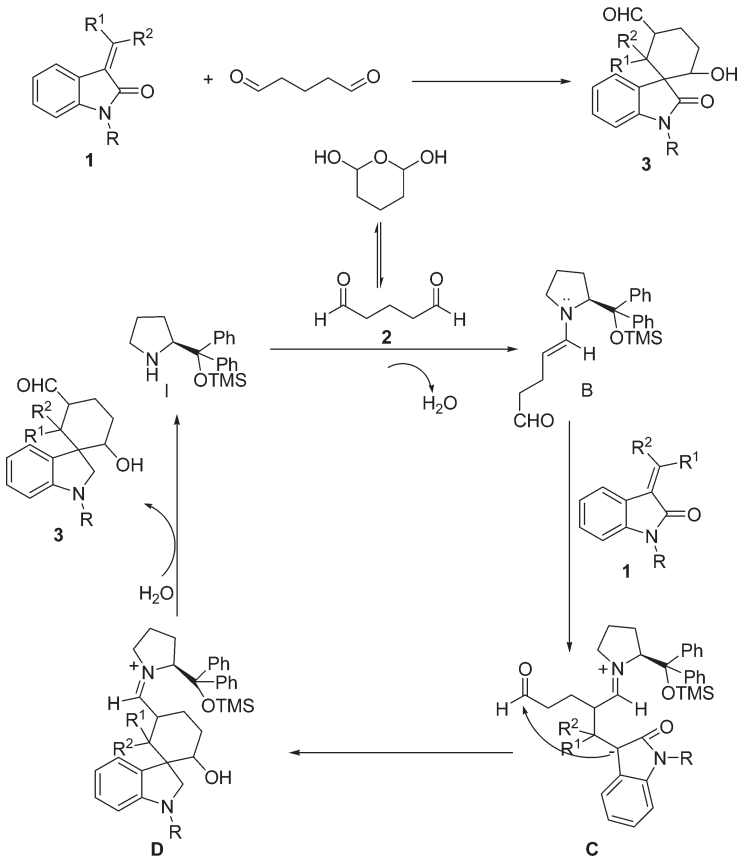
control of four stereogenic centers *via* a Michael–Henry sequence using hexane-1,5-dial and 2-substituted nitroalkenes.[12] Shortly after, Hong *et al.*[13] and Córdova *et al.*[14] found that diphenylprolinol methyl ether[15] could also effectively catalyze the direct domino Michael–Aldol reaction of glutaraldehyde and a Michael acceptor to afford highly functionalized cyclohexane and cyclohexene compounds in high diastereoselectivities and enantioselectivities. Based on these findings, we envisioned that glutaraldehyde would act as a four-carbon unit which would be useful to trigger a [4 + 2] spiroannulation through an asymmetric domino Michael–Aldol reaction with isatin derived alkenes (Scheme 1). It was hypothesized that catalyst **I** would activate glutaraldehyde **2** to generate the intermediate enamine **B**, which would react with the isatin derived electron deficient alkene **1** *via* a Michael addition to form **C**. Subsequently, cyclization would yield **D** through the intramolecular Aldol reaction. The desired six-membered spirocyclic product **3** would then form through hydrolysis of **D** (Scheme 1).

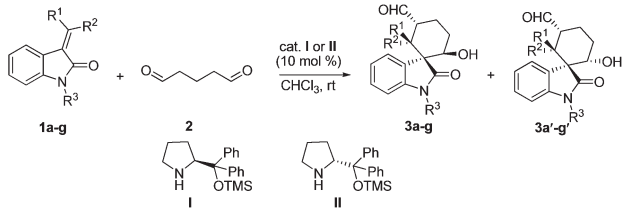
Results and discussion

Initially, the above mentioned organocascade strategy was evaluated by conducting a reaction between diethyl 2-(2-oxoindolin-3-ylidene)malonate **1a** and pentane-1,5-dial **2** (50% aqueous solution of tetrahydro-2*H*-pyran-2,6-diol) with 10 mol% of L-diphenylprolinol silyl ether **I** in chloroform at room temperature for 14 hours (Table 1, entry 1). The desired product **3a** was obtained in 30% yield (total 54% yield with 1.2 : 1 dr), albeit with 98% ee for the major diastereomer. Then, the reactions with substrates **1b** and **1c** bearing electron-donating groups (–CH_3 and –Bn) were tested, which afforded the desired products **3b** and **3c** with lower yields of 17% and 11%, respectively (Table 1, entries 2 and 3). Subsequently, diethyl 2-(1-(benzyloxycarbonyl)-2-oxoindolin-3-ylidene)malonate **1d** was used for this reaction, which produced **3d** in 72% yield (total 87% yield with 4.8 : 1 dr) and 95% ee (Table 1, entry 4). Encouraged by this outcome, the reaction of diethyl 2-(1-(*tert*-butoxycarbonyl)-2-oxoindolin-3-ylidene)malonate **1e** was investigated, and *ent*-**3e** was obtained in 79% yield (total 90% yield with 7.3 : 1 dr) with 96% ee (Table 1, entry 5). By comparison, D-diphenylprolinol silyl ether **II**, as an enantiomer of catalyst **I**, was also examined for this transformation, and the corresponding desired product **3e** was obtained in 81% yield (total 92% yield with 7.3 : 1 dr) with 98% ee (Table 1, entry 6). Then –Boc protected **1f** and **1g** were investigated for this transformation with catalysts **I** and **II**. The corresponding products were obtained in 48–54% yields, with 95–≥99% ee values (Table 1, entries 7–10). Therefore, **1e** was selected as a model substrate and D-diphenylprolinol silyl ether **II** as the optimal catalyst to further investigate the Michael–Aldol sequence. To our delight, the spirocyclohexaneoxindole structure in the crystalline solid state of *ent*-**3e** was finally



Scheme 1 Envisaged mechanism for the organocatalytic asymmetric Michael–Aldol spiroannulation of isatin derived alkenes with linear dialdehydes.

Table 1 Evaluation of model substrates and catalysts[a]



Entry	Catalyst	Product	Yield[b] (%)	dr[c]	ee[d] (%)
1	I	R^1, R^2 = COOEt, R^3 = H (**1a**)	30 (54)/**3a**	1.2 : 1	98
2	I	R^1, R^2 = COOEt, R^3 = CH_3 (**1b**)	— (17)/**3b**	n. d.[e]	n. d.
3	I	R^1, R^2 = COOEt, R^3 = Bn (**1c**)	— (11)/**3c**	n. d.	n. d.
4	I	R^1, R^2 = COOEt, R^3 = Cbz (**1d**)	72 (87)/**3d**	4.8 : 1	95
5	I	R^1, R^2 = COOEt, R^3 = Boc (**1e**)	79 (90)/*ent*-**3e**	7.3 : 1	−96
6[f]	II	R^1, R^2 = COOEt, R^3 = Boc (**1e**)	81 (92)/**3e**	7.3 : 1	98
7[g]	I	R^1 = Ph, R^2 = H, R^3 = Boc (**1f**)	48 (88)/*ent*-**3f**	1.2 : 1	−99
8[g]	II	R^1 = Ph, R^2 = H, R^3 = Boc (**1f**)	52 (92)/**3f**	1.3 : 1	95
9[h]	I	R^1 = COOEt, R^2 = H, R^3 = Boc (**1g**)	51 (85)/*ent*-**3g**	1.5 : 1	−96
10[h]	II	R^1 = COOEt, R^2 = H, R^3 = Boc (**1g**)	54 (90)/**3g**	1.5 : 1	>99

[a] Reactions were performed with **1** (0.2 mmol), **2** (50% in water, 91 μL, 0.5 mmol) and 10 mol% catalyst in 1.0 mL CH_2Cl_2 at room temperature for 14 h. [b] Isolated yield for the major diastereomer. Total yields for both diastereomers in parentheses. [c] Determined by chiral HPLC analysis or by ^{1}H NMR. [d] Determined by chiral HPLC analysis for the major enantiomer. [e] n. d. = not detected. [f] For 10 h. [g] For 35 h. [h] For 0.5 h.

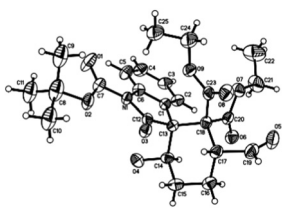
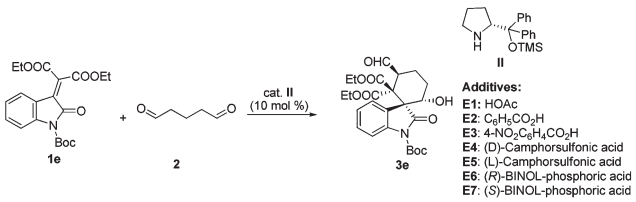


Fig. 2 X-ray crystal structure of *ent*-**3e**.

determined by single crystal X-ray diffraction analysis (Fig. 2), which showed that the formyl and hydroxy groups are in the *trans* configuration.[18]

Using the optimal model substrate and catalyst, other parameters were further optimized, including the reaction solvent, additive, reactant ratio and temperature, and the results are summarized in Table 2. In protic solvents such as methanol and water, no conversion was detected (Table 2, entries 2 and 3). When aprotic solvents such as dichloromethane, tetrahydrofuran, toluene, acetonitrile, methyl *tert*-butyl ether, and dimethyl formamide were employed, moderate to good yields (48–86%), low to moderate diastereoselectivities, and excellent enantioselectivities were obtained (>94% ee, 1.8 : 1 to 8.5 : 1 dr, Table 2, entries 4–9). Based on the screening results, dichloromethane was found to be the best reaction medium for this reaction, which gave **3e** in 86% yield with >99% ee, 8.5 : 1 dr within 8 hours (Table 2, entry 4). The effects of acid counteranions[16] on the reaction were investigated, including acetic acid, benzoic acid and its derivative, D- and L-camphorsulfonic acids, as well as *R*- or *S*-binolphosphoric acids. However, the results revealed that acid additives had a detrimental effect on the reactivity, as evidenced by lower yields (Table 2, entries 10–16). When the amount of

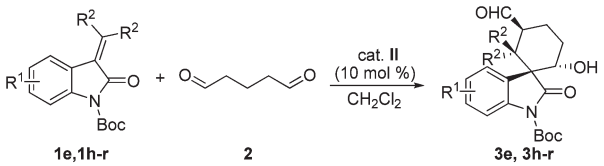
Table 2 Optimization of reaction conditions[a]



Entry	Solvent	Additive	Time (h)	Yield[b] (%)	dr[c]	ee[d] (%)
1	$CHCl_3$	—	10	81	7.3 : 1	98
2	H_2O	—	12	<5	—	n. d.[h]
3	MeOH	—	12	<5	—	n. d.
4	CH_2Cl_2	—	8	86	8.5 : 1	>99
5	THF	—	23	64	6.9 : 1	96
6	Toluene	—	33	58	7.6 : 1	96
7	CH_3CN	—	9	55	1.8 : 1	99
8	MTBE	—	23	77	7.5 : 1	97
9	DMF	—	23	48	3.2 : 1	94
10	CH_2Cl_2	E1	27	77	7.6 : 1	99
11	CH_2Cl_2	E2	27	38	—	97
12	CH_2Cl_2	E3	27	12	—	n. d.
13	CH_2Cl_2	E4	27	56	6.2 : 1	>99
14	CH_2Cl_2	E5	27	60	6.6 : 1	99
15	CH_2Cl_2	E6	15	<5	—	n. d.
16	CH_2Cl_2	E7	15	84	8.3 : 1	99
17[e]	CH_2Cl_2	—	8	79	8.1 : 1	>99
18[f]	CH_2Cl_2	—	8	85	8.4 : 1	>99
19[g]	CH_2Cl_2	—	3.5	81	7.7 : 1	>99

[a] Reactions were performed with **1e** (0.2 mmol), **2** (50% in water, 91 μL, 0.5 mmol) and 10 mol% catalyst **II** in 1.0 mL solvent at room temperature. [b] Isolated major diastereomer. [c] Determined by ^{1}H NMR of crude products. [d] Determined by chiral HPLC analysis. [e] 1.5 equiv. of **2** was used. [f] 5 equiv. of **2** were used. [g] At 40 °C. [h] n. d. = not detected.

Table 3 Substrate scope in the reaction[a]



Entry	Products	Time (h)	Yield[b] (%)	dr[c]	ee[d] (%)
1	R^1 = H, R^2 = CO_2Et (**3e**)	8	86	8.5 : 1	>99
2	R^1 = 5-CH_3, R^2 = CO_2Et (**3h**)	10	84	8.9 : 1	>99
3	R^1 = 5-OCH_3, R^2 = CO_2Et (**3i**)	7	88	11.2 : 1	99
4	R^1 = 5,7-$(CH_3)_2$, R^2 = CO_2Et (**3j**)	15	71	11.7 : 1	98
5	R^1 = 5-F, R^2 = CO_2Et (**3k**)	1.5	82	8.7 : 1	98
6	R^1 = 5-Cl, R^2 = CO_2Et (**3l**)	1	79	7.9 : 1	97
7	R^1 = 5-Br, R^2 = CO_2Et (**3m**)	1	83	7.6 : 1	98
8	R^1 = 6-Br, R^2 = CO_2Et (**3n**)	2	74	5.2 : 1	98
9	R^1 = H, R^2 = CO_2Me (**3o**)	4	67	4.9 : 1	98
10	R^1 = H, R^2 = $CO_2{}^iPr$ (**3p**)	4	87	11.5 : 1	>99
11	R^1 = H, R^2 = CO_2Bn (**3q**)	5	83	11.2 : 1	>99
12	R^1 = H, R^2 = CO_2Cy (**3r**)	10	88	11.8 : 1	>99

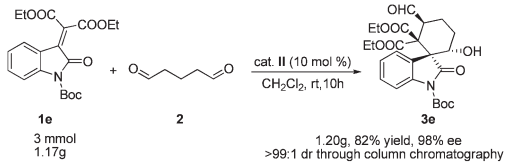
[a] Reactions were performed with **1** (0.2 mmol), **2** (50% in water, 91 μL, 0.5 mmol) and 10 mol% catalyst **II** in 1.0 mL CH_2Cl_2. [b] Isolated major diastereomer. [c] Determined by ^1H NMR of crude products. [d] Determined by chiral HPLC analysis.

glutaraldehyde **2** was decreased from 2.5 to 1.5 equiv., the yield dropped slightly to 79%, albeit with maintained enantioselectivity (Table 2, entry 17 *vs.* 4). When 5.0 equiv. of **2** was used, neither the yield nor the enantioselectivity were found to be obviously affected in comparison with those using 2.5 equiv. (Table 2, entry 18 *vs.* 4). In addition, the reaction in dichloromethane proceeded faster at 40 °C, which resulted in the optically pure product **3e** in a lower yield of 81% (Table 2, entry 19 *vs.* 4). Thus, the established optimal reaction conditions were a molar ratio of 1 : 2.5 between **1** and **2**, a 10 mol% catalyst loading of **II** and dichloromethane as the reaction solvent at room temperature.

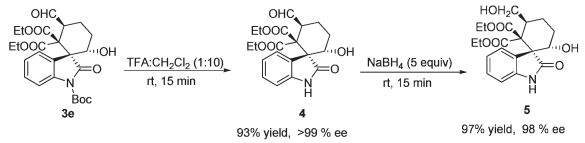
Having established the optimal reaction conditions, we further explored the scope of the **II** catalyzed cascade Michael–Aldol sequence between isatylidene malonic esters **1e**, **1h–r** and glutaraldehyde **2**, and the results are summarized in Table 3. For diethyl 2-(1-(*tert*-butoxycarbonyl)-2-oxoindolin-3-ylidene)malonates **1e** and **1h–n**, moderate to high yields (71–88%), moderate diastereoselectivities (5.2 : 1 to 11.7 : 1), and excellent enantioselectivities (97% to >99%) were obtained through this cascade approach, irrespective of the variation in the electronic and steric properties of the substituents attached to the phenyl rings of the oxindole backbones (Table 3, entries 1–8). However, the reactivities of these reactions were found to be obviously effected by the electronic properties of the substituents on the phenyl rings of the oxindole backbones. Notably, the Michael–Aldol reactions with substrates **1h–j** bearing electron-donating groups (–Me, –OMe) generally required longer reaction times (7–15 hours), providing the desired products **3h–j** in 71–88% yields with moderate diastereoselectivities and excellent enantioselectivities (Table 3, entries 2–4). In contrast, the substrates **1k–n** bearing halogen substituents (–F, –Cl, –Br) on the oxindole backbones performed very well in the corresponding cascade reactions in less than two hours, resulting in the desired products **3k–n** in 74–83% yields with 5.2 : 1 to 8.7 : 1 dr and over 97% ee (Table 3, entries 5–8). In addition, the other dialkyl 2-(1-(*tert*-butoxycarbonyl)-2-oxoindolin-3-ylidene)malonates **1o–r**, containing dimethyl, diisopropyl, dibenzyl and dicyclohexyl groups, were also investigated for this transformation, and all reactions proceeded smoothly to produce the expected products in 67–88% yields with 98% to over 99% ee, and 4.9 : 1 to 11.8 : 1 dr (Table 3, entries 9–12). The catalytic results showed that the substrate **1o**, with the less bulky dimethyl substituent, gave the product in a lower yield of 67% with 98% ee, whereas substrate **1r** bearing the more bulky dicyclohexyl group was less reactive, although it generated the desired product **3r** in 88% yield with over 99% ee (Table 3, entry 12).

A gram-scale synthesis of **3e** was performed in the presence of 10 mol% of catalyst **II**. As a result, 1.20 g of the desired product **3e** was readily isolated through column chromatography in 82% yield with over 99 : 1 dr and 98% ee (Scheme 2). Furthermore, the –Boc protecting group was easily removed in TFA–CH_2Cl_2 (1 : 10), and the desired product **4** was obtained in 93% yield with over 99% ee. Finally, the spiro[cyclohexandiol-oxindole] compound **5** could be converted from **4** through $NaBH_4$ reduction in 97% yield with 98% ee (Scheme 3).

Finally, the absolute configuration (AC) of the spirocyclohexaneoxindoles were determined by means of chiroptical methods.[17] In this study, ECD spectra were calculated by the TD-DFT method, which has been proven to be useful in predicting ECD spectra and assigning the AC of organic molecules.[19] Based on the relative configuration obtained by X-ray diffraction of **3e**, the TD-DFT method was performed to calculate the electronic circular dichroism (ECD) spectra at the B3LYP/6-31G* level. All conformations were calculated at the same level to confirm their stability (no imaginary frequencies).[20] As shown in



Scheme 2 Operation of the reaction at gram-scale.



Scheme 3 Synthesis of the spiro[cyclohexandiol-oxindole] compound **5**.

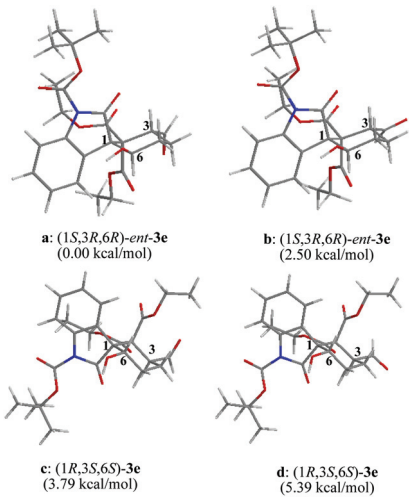


Fig. 3 Optimization conformations of compound **3e** (energies in kcal mol^{-1}).

Fig. 3, two most stable conformations of *ent*-**3e** (**a** and **b**), which differ in the disposition of the CHO group, were located by DFT (B3LYP/6-31G*) calculations. The structure of **a** is more stable than **b**, with an energy difference of 2.50 kcal mol^{-1}.

Calculation of the ECD spectra of **a** (*ent*-**3e**) and **c** (**3e**) was carried out using the TD-DFT-B3LYP/6-31G(d) level, as shown in Fig. 4. Electronic excitation energies (nm) and rotational strengths ($\Delta\varepsilon$) were calculated for **a** and **c**. In order to cover the 220–300 nm range, 30 transitions were calculated. As shown in Fig. 4, the simulated spectra are in good agreement with the spectral data, and the 1*S*,3*R*,6*R* configuration could be reliably assigned to compound *ent*-**3e**, catalyzed by **I**. The 1*R*,3*S*,6*S* configuration of **3e** was in agreement with that catalyzed by **II**.

Conclusions

In summary, we have developed an efficient asymmetric methodology for the construction of formyl, hydroxy, and ester functionalized spirocyclohexaneoxindoles *via* a cascade Michael–Aldol cyclization of isatin derived alkenes with linear

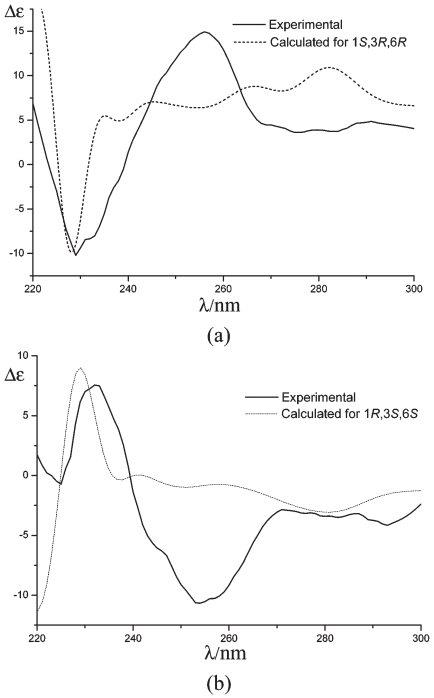


Fig. 4 Experimental ECD spectra (full trace) and simulated spectra (dashed trace) proving (a) the 1*S*,3*R*,6*R*-*ent*-**3e** absolute configuration catalyzed by **I** (L-diphenylprolinol silyl ether) and (b) the 1*R*,3*S*,6*S*-**3e** absolute configuration catalyzed by **II** (D-diphenylprolinol silyl ether).

dialdehydes catalyzed by readily available chiral diphenylprolinol silyl ether. The final products could be achieved in moderate to good yields with excellent enantioselectivities and moderate diastereoselectivities. The rational configurations of *ent*-**3e** and **3e** were assigned by means of TD-DFT calculations of the ECD. The theoretical data are in good agreement with the experimental ECD spectra. There are several salient features of the present protocol, including the use of aqueous starting materials, operational simplicity, excellent stereoselective control in the multistereogenic formation, and the highly efficient one-pot synthesis of the spirocyclohexaneoxindole structures. Further expansion of the substrate scope of this catalytic system, as well as biological evaluations of the resulting spiro compounds, are ongoing in our laboratory.

Acknowledgements

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