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Enantioselective synthesis of spiro[cyclohexane-1,3′-indolin]-2′-ones containing multiple stereocenters via organocatalytic Michael/aldol cascade reactions

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ABSTRACT

Organocatalytic reactions of 3-olefinic oxindoles and pentane-1,5-dial were investigated to provide access to substituted spirocyclohexane oxindoles via Michael/aldol cascade reactions. Of particular interest, we have examined the stereochemical outcome of electron withdrawing and electron-donating groups on the oxindole ring nitrogen. Interestingly, we have observed that the N-protecting group on the oxindole has critical effect on aldol ring closure leading to ultimate stereochemical outcome of the hydroxyl center. The overall process is quite efficient and afforded products with multiple stereocenters in high yields and excellent enantioselectivities (>99% ee).

Spiro[cyclohexane-1,3′-indolin]-2′-one is an important structural motif for many bioactive natural products as well as for medicinal agents.[1,2] Over the years, various stereoselective synthetic protocols have been developed.[3–5] However, enantioselective and efficient methods for construction of these structural features did not emerge until recently.[6–9] Organocatalytic cascade reactions leading to functionalized cyclohexane rings were earlier developed by Enders et. al.[10] In the context of our design and synthesis of molecular probes, we have incorporated a spiro-indoline structural template as a P2′-ligand in the HIV-1 protease active site.[11] For further access to spiroindoline scaffolds, we have investigated the feasibility of organocatalytic Michael/aldol cascade reactions involving 3-olefinic oxindole and pentane-1,5-dialdehyde.[12–15] Recently, Wang and co-workers have reported a related work and their report prompted us to disclose our investigation in this area.[16] Herein, we report (*R*)-diphenylprolinol silyl ether-catalyzed tandem Michael/aldol reaction leading to the synthesis of a variety of spiro[cyclohexane-1,3′-indolin]-2′-one derivatives with four/five contiguous chiral centers in excellent yield and optical purity. Interestingly, protecting groups on the indolin-2-one nitrogen played important roles in the stereochemical outcome of the final aldol ring closure. The electron-withdrawing N-protecting group in the presence of (*R*)-catalyst provided spiro[cyclohexane-1,3′-indoline] derivatives with 6-(*R*)-hydroxy configuration. On the other hand, the electron-donating N-protecting group furnished spiro[cyclohexane-1,3′-indoline] derivatives with 6-(*S*)-hydroxy configuration as the major product.

We initially investigated a catalytic domino reaction of 3-olefinic oxindole **1a** and pentane-1,5-dial **2**[12,13] using organocalatyst **A** (10 mol %) in THF at ambient temperature, under an aerobic atmosphere as shown in Scheme 1. The desired tandem Michael/aldol product **5a** was isolated in 41% yield. As shown in Table 1, the ratio of diastereomers was moderate (3.5:1:0.5:0.3). However, the major product **5a** showed excellent enantioselectivity (96% ee, Table 1, entry 1) in HPLC analysis.[17] The overall process presumably proceeded through a Michael reaction resulting in intermediate **3** followed by an intramolecular aldol reaction providing intermediate **4**. Addition of an acidic co-catalyst, such as *ortho*-fluorobenzoic acid, trifluoroacetic acid, or acetic acid, failed to improve the yield (Table 1, entries 2–4). We investigated other organic solvents such as CH_2Cl_2, toluene, *N*,*N*-dimethylformamide (DMF), hexane, and CH_3CN (entries 5–9). As it turned out that the choice of solvent was crucial to this Michael-aldol tandem reaction and the best results were obtained using DMF as the solvent, affording **5a** as the major diastereomer (6:1:0.5:0.4) in 80% yield and showed excellent enantioselectivity for the major diastereomer (>99% ee, entry 8). An attempt to perform the reaction at lower temperature resulted in low conversion (entry 10).

We subsequently explored substrate scope and limitations under the optimized reaction conditions (Fig. 1). As evidenced by the results in Table 2, the reaction proceeded smoothly with aro-

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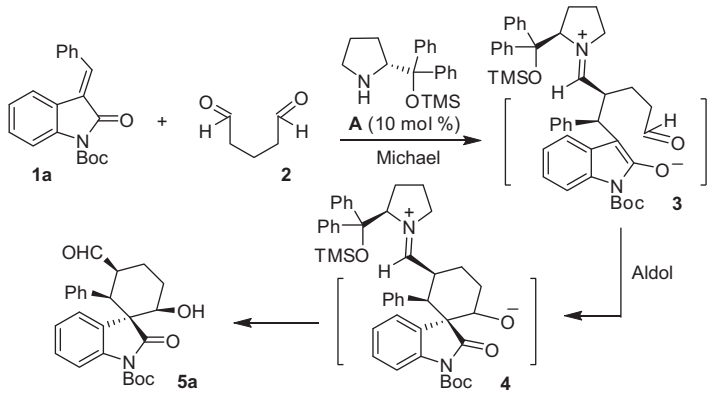
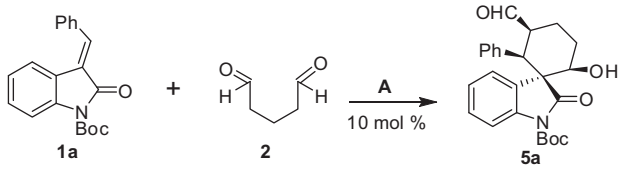


Scheme 1. Michael/aldol cascade with oxindole **1a** and dialdehyde **2**.

Table 1
Michael/aldol reaction optimization[a]



Entry	Solvent	T (h)	Yield[b] (%)	dr[c]	ee[d] (%)
1	THF	48	41	3.5:1:0.5:0.3	96
2[e]	THF	48	<10	n.d.	n.d.
3[f]	THF	48	<5	n.d.	n.d.
4[g]	THF	48	<5	n.d.	n.d.
5	CH_2Cl_2	48	<5	n.d.	n.d.
6	Toluene	48	<5	n.d.	n.d.
7	Hexane	48	<5	n.d.	n.d.
8	DMF	20	80	6:1:0.5:0.4	>99
9	CH_3CN	48	<5	n.d.	n.d.
10[h]	DMF	48	16	7:1:0.5:0.4	99

[a] Unless otherwise noted, the reaction was performed by employing **1a** (0.1 mmol), dialdehyde **2** (50% in water, 0.3 mmol), and organocatalyst **A** (0.01 mmol) in the indicated solvent (0.5 mL) at room temperature. n.d. = not determined.
[b] Isolated yield.
[c] Determined by ^{1}H NMR spectroscopy.
[d] Determined by HPLC of the major diastereomer.
[e] *Ortho*-fluorobenzoic acid (0.01 mmol) was added.
[f] Trifluoroacetic acid (0.01 mmol) was added.
[g] Acetic acid (0.01 mmol) was added.
[h] This reaction was performed at 0 °C.

matic substituents to give desired products in high yields. The substituents on the aryl ring have little effect on the enantioselectivity of the major isomer. Monosubstituted phenyl methyleneindolinones proceeded with excellent enantioselectivity ranging from 98% to 99% ee (entries 1–7). However, electronic properties of aryl substituents showed definite effect on diastereoselectivity. Electron-donating groups resulted in better diastereoselectivity. As shown, a high diastereomeric ratio of 7:1:0.5:0.4 was observed for 3-methoxyphenyl substituted methyleneindolinone, whereas a dr of 3:1:0.7:0.5 was observed for 3-nitro-phenyl substituted methyleneindolinone (entry 3 vs 7). Reactions with both heterocyclic and alkyl methyleneindolinones also proceeded with excellent enantioselectivity (entries 8 and 9). We further examined the cyclization reaction using an *N*-acetyl group in indole in place of an N-Boc protecting group. This resulted in product **5j** in excellent yield with excellent enantioselectivity; however, the diastereomeric ratio (3:1:0.8:0.2; entry 10) was lower compared to the Boc-protected derivative (entry 1).

We then examined the effect of electron-donating N-protecting groups on the oxindole. Interestingly, this resulted in aldol ring closure with opposite hydroxyl stereochemistry as the major diastereomer. The results in Table 3 show various *N*-alkyl protecting groups, such as methyl, allyl, and benzyl groups, provided products **5k**–**5m** as the major diastereomers in excellent yields (70–84%) and excellent enantioselectivity for the major diastereomer (>99%, entries 1–3). Furthermore, both electron-donating (Me) and electron-withdrawing (Cl) substituents at the C4-position of the phenyl group afforded the corresponding products in high yields with excellent enantioselectivity for the major diastereomer

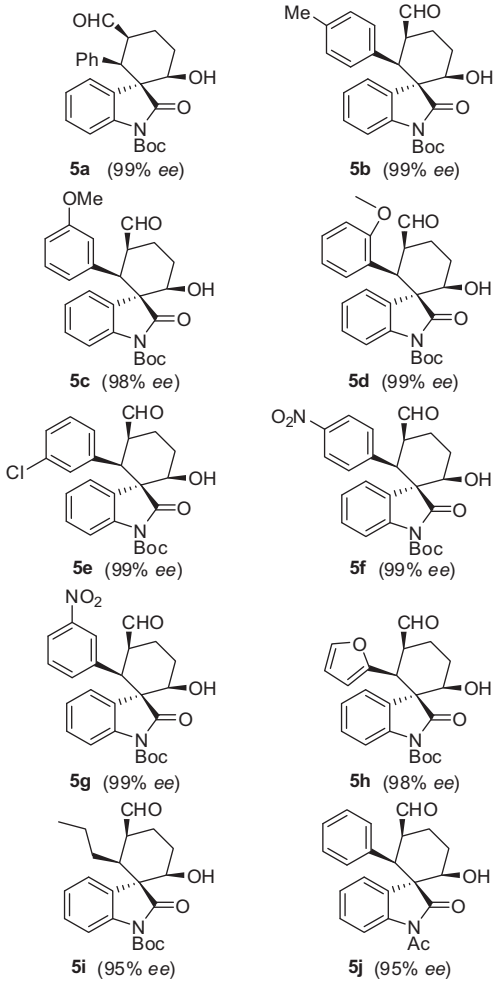
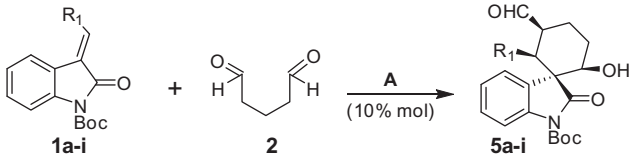


Figure 1. Structure and enantioselectivity of major isomer.

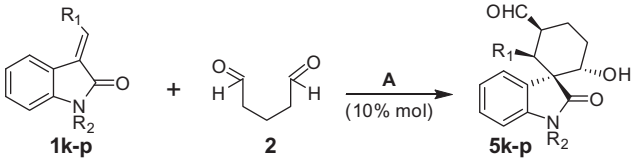
Table 2
Enantioselective syntheses of spirooxindoles[a]



Entry	R_1	Pdt[b] (Y %)	dr[c] (ee %)[d]
1	Ph	**5a** (80)	6:1:0.5:0.4 (99)
2	4-Me-Ph	**5b** (82)	6:1:0.5:0.3 (99)
3	3-OMePh	**5c** (82)	7:1:0.5:0.4 (98)
4	2-OMe-Ph	**5d** (84)	5.5:1:0.5 (99)
5	3-Cl-Ph	**5e** (74)	5.2:1:0.5:0.5 (99)
6	4-NO_2-Ph	**5f** (80)	3:1:0.5 (99)
7	3-NO_2-Ph	**5g** (74)	3:1:0.7:0.5 (99)
8[e]	2-furyl	**5h** (80)	6:1:0.5:0.3 (98)
9[e]	Pr	**5i** (54)	6:1:0.7 (95)
10[f]	Ph	**5j** (90)	3:1:0.8:0.2 (95)

[a] General reaction conditions: oxindole (0.1 mmol), dialdehyde **2** (50% in water, 0.3 mmol), and organocatalyst **A** (0.01 mmol) in DMF (0.5 mL) at 23 °C.
[b] Isolated combined yield.
[c] Determined by ^{1}H NMR of crude product.
[d] The ee was determined by chiral-phase HPLC analysis of major diastereomer.
[e] The reaction was performed for 3 days.
[f] Oxindole is protected as *N*Ac.

Table 3
Syntheses of spirooxindoles with *N*-alkyl groups[a]



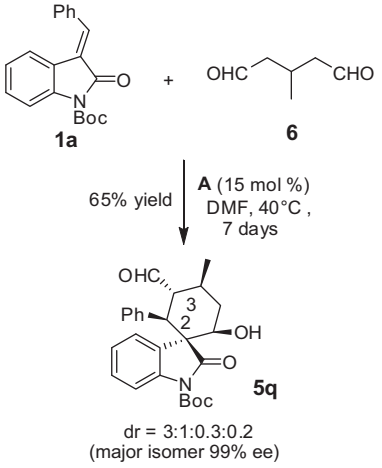
Entry	R_1	R_2	Pdt[b] (Y%)	dr[c] (ee %)[d]
1	Ph	Me	**5k** (70)	6.5:1:0.5 (99)
2	Ph	Bn	**5l** (82)	6:1:0.5:0.3 (99)
3	Ph	Allyl	**5m** (84)	7:1:0.4 (99)
4	*p*-ClPh	Allyl	**5n** (74)	6.5:1:0.3:0.2 (99)
5	p-MePh	Allyl	**5o** (74)	7:1:0.5:0.5 (99)
6	pNO2Ph	Allyl	**5p** (70)	2:1:0.5 (99)

[a] General reaction conditions: the reaction was performed by employing 3-olefinic oxindole (0.1 mmol), dialdehyde **2** (50% in water, 0.3 mmol), and organocatalyst A (0.01 mmol) in DMF (0.5 mL) at room temperature for 2 days.
[b] Isolated yield.
[c] Determined by ^{1}H NMR of crude product.
[d] The ee was determined by chiral-phase HPLC analysis of major diastereomer.

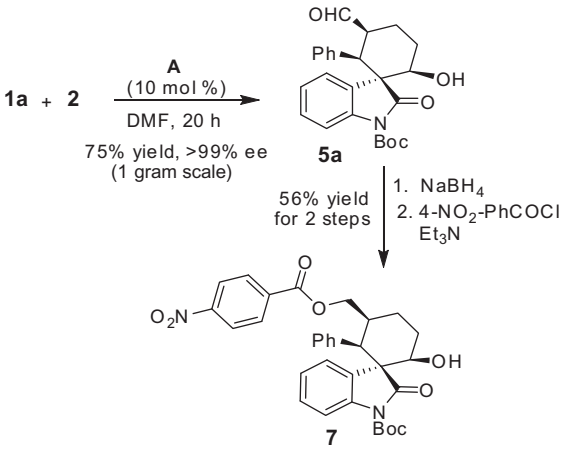
(>99% ee, entries 4 and 5). Interestingly, the electron-withdrawing 4-NO_2 derivative furnished moderate diastereoselectivity (entry 6) compared to 4-Cl substituent (entry 4). However, the major isomer showed excellent enantioselectivity.

We have also explored this Michael/aldol reaction with 3-methylpentane-1,5-dial **6**[18] as shown in Scheme 2. This reaction proceeded smoothly and afforded spirocyclic oxindole **5q** with five consecutive stereogenic centers in 65% yield and excellent enantioselectivity (99% ee). Interestingly, the aldehyde functionality at the C3-position was isomerized from the axial to equatorial position leading to the formation of the more stable C2–C3 *anti*-product.

We have carried out the reaction of oxindole **1a** and dialdehyde **2** up to a gram scale providing **5a** in 75% yield (Scheme 3). This product showed excellent enantioselectivity as well. The relative configurations of compounds were assigned by extensive NOE analyses of compounds **5a**, **5d**, **5o**, and **5q**. The absolute configurations of the tandem Michael/aldol products were determined



Scheme 2. Reaction of oxindole **1a** and 3-methylpentane-1,5-dial **6**.



Scheme 3. Synthesis of benzoate **7**.

unambiguously through X-ray crystallographic analysis. As shown in Scheme 3, benzoate derivative **7** was prepared by reduction of **5a** with $NaBH_4$ followed by reaction of the resulting alcohol with 4-nitrobenzoyl chloride in the presence of Et_3N in 56% yield over two-steps. This was later recrystallized from methanol (23 °C). Subsequent single crystal X-ray crystallographic analysis supported the assignment of the relative and absolute stereochemistry shown in Figure 2 (see Supplementary data for the details of X-ray analysis).[19]

In conclusion, we have developed a diastereoselective organocatalytic Michael/aldol cascade reaction that provided convenient access to functionalized spirooxindoles with up to five consecutive stereogenic centers, including a spiro quaternary center. The products were obtained in excellent yield and the major diastereomer showed excellent enantioselectivity. In addition, depending upon our selection of N-protecting group on the oxindole, we were able to effectively control the stereochemical outcome of the hydroxyl center upon aldol ring closure. Further studies and applications of this methodology are the subject of current investigation in our laboratory.

Acknowledgments

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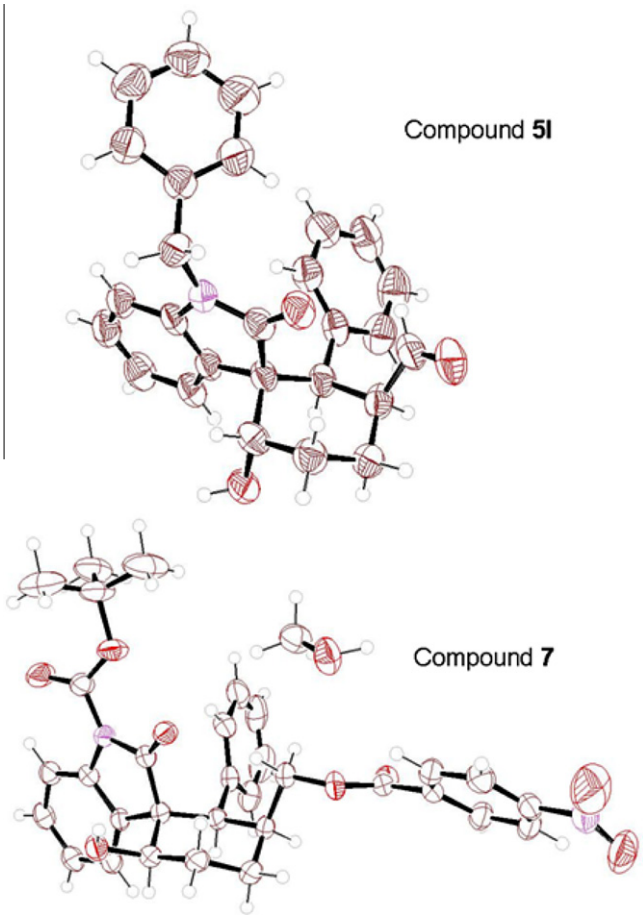

Figure 2. ORTEP drawing of **5l** and **7**.

Supplementary data

Supplementary data (experimental procedures and ^{1}H, ^{13}C NMR data) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.02.030.

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19. CCDC 897144 (**5l**) and CCDC 897143 (**7**) contain the Supplementary crystallographic data for this Letter. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.