CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200903009

Organocatalytic Tandem Reaction to Construct Six-Membered Spirocyclic Oxindoles with Multiple Chiral Centres through a Formal [2+2+2] Annulation

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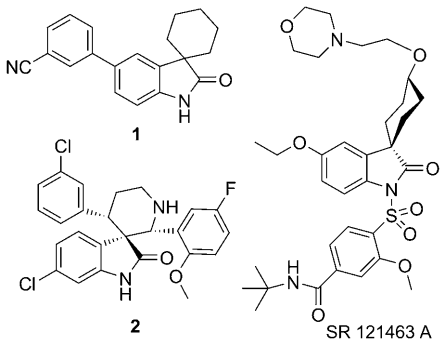
Abstract: An efficient tandem reaction for the asymmetric synthesis of six-membered spirocyclic oxindoles has been successfully developed through a formal [2+2+2] annulation strategy. The amine-catalysed stereoselective Michael addition of aliphatic aldehydes to electron-deficient olefinic oxindole motifs gave chiral C3 components, which were further combined with diverse electrophiles (activated olefins or imines) to afford spirocyclic oxindoles with versatile molecular complexity (up to six contiguous stereogenic centres, high diastereo- and enantioselectivities).

Keywords: annulation · asymmetric catalysis · molecular complexity · spiro compounds · tandem reactions

Introduction

Spirocyclic oxindole structures exist in a large number of natural products and pharmaceutically important molecules.[1] Therefore, considerable efforts have been devoted to developing efficient protocols to access these interesting motifs over the past years.[2] Although great progress has been made for the synthesis of diversely structured spirocyclic oxindoles, new methodologies that can afford ones with more substitution variants are still in high demand. Moreover, the examples that can produce spirocyclic oxindoles in a catalytic asymmetric manner are still limited,[3] especially with the more environmentally friendly organocatalysts.[4]

Recently, we have conducted some research work on the organocatalytic construction of oxindoles with a quaternary C3 chiral centre.[5,6] Later, it was recognised that some oxindoles incorporating a six-membered spirocyclic moiety exhibited broad biological activities. Compound **1** (Scheme 1) is a drug candidate that may be used in female healthcare as a progesterone receptor antagonist, which has effects in contraception, uterine fibroids, endometriosis or hormone-related cancers.[7] SR 121463 A was a potent and selective orally active vasopressin V_2 antagonist. It might be better for use in the clinic than other well-known diuretic agents, such as furosemide or hydrochlorothiazide.[8] In addition, spirocyclic oxindole derivatives with a piperidine structure are of great significance in pharmacochemistry.[9] For example, compound **2** is a potent non-peptide MDM2 inhibitor, which may have utility as an antiproliferative agent, especially as an anticancer agent.[10] Herein, we would like to present an



Scheme 1. Some biologically active six-membered spirocyclic oxindoles.

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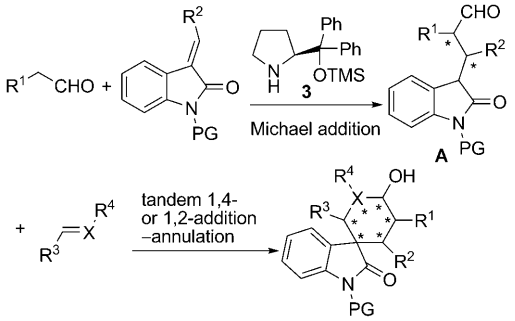
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200903009.

organocatalytic tandem reaction for the synthesis of diverse spirocyclic oxindoles with multiple chiral centres through a formal [2+2+2] annulation strategy.

Results and Discussion

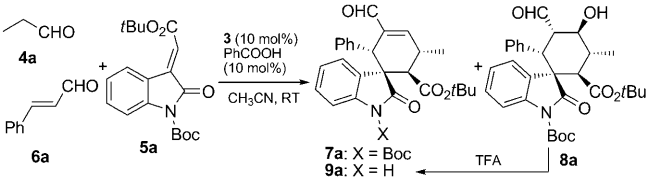
Our synthetic approach is outlined in Scheme 2. The asymmetric Michael addition of aliphatic aldehydes to electron-deficient olefinic oxindoles could be developed by the enamine catalysis of a chiral secondary amine, **3**, to afford the chiral bifunctional intermediate **A**. Subsequently, a tandem reaction could be conducted with various electrophiles at the C3 position of oxindole intermediate **A**, either in a 1,4- or 1,2-addition manner. The following intramolecular cyclisation process would afford the expected six-membered spirocyclic oxindoles with molecular diversity.



Scheme 2. Tandem reaction to access six-membered spirocyclic oxindoles through a formal [2+2+2] annulation strategy. PG: protecting group; TMS: trimethylsilyl.

Based on these considerations, we initially investigated the three-component domino reaction of propionaldehyde (**4a**), the *N*-Boc-protected olefinic oxindole **5a** and cinnamaldehyde (**6a**) with the cascade enamine–iminium–enamine catalysis of chiral amine **3** (10 mol%) and benzoic acid,[11,12] similar to that reported by Enders and co-workers.[13] To our gratification, the domino reaction proceeded very smoothly in acetonitrile at ambient temperature. The desired spirocyclic cyclohexenecarboxaldehyde **7a** was isolated with excellent diastereo- and enantioselectivity, albeit in moderate yield. [During the preparation of this paper, Melchiorre and co-workers reported a similar three-component domino reaction to access spirocyclic oxindoles with excellent stereocontrol. The free-NH olefinic oxindoles were used as the Michael acceptors; in general, longer reaction times and lower yields were observed.[14]] Interestingly, the aldol intermediate **8a** was also isolated as a single enantiomer. Intermediate **8a** could not be converted into **7a** by simply extending the reaction time under the current catalytic conditions (Table 1, entry 1). Similar results were attained in the other solvents tested (Table 1, entries 2–4). A slower reaction was observed when acetic acid was used as the additive (Table 1, entry 5). The reaction became quite sluggish in the absence of benzoic acid and the aldol adduct **8a** was isolated as the major product (Table 1, entry 6). The domino reaction proceeded very smoothly when the catalyst loading was decreased to 5 mol% (Table 1, entry 7). Finally, we found that the dehydration process could occur upon addition of some trifluoroacetic acid after the domino reaction. The *N*-Boc-deprotected cyclohexenecarboxaldehyde **9a** was then cleanly obtained in high yield (Table 1, entry 8).

Table 1. Screening studies for the three-component domino reaction to access spirocyclic oxindoles.[a]

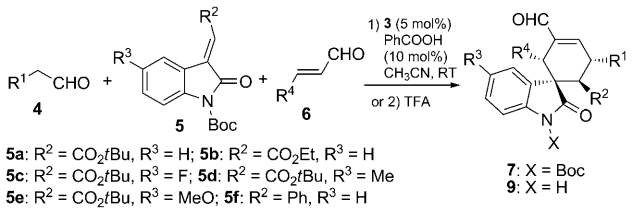


Entry	Solvent	*t* [h]	Yield [%][b] (*ee* [%][c])
1	CH_3CN	1	**7a**: 53 (>99); **8a**: 42 (>99)
2	toluene	4	**7a**: 59 (>99); **8a**: 40 (>99)
3	CH_2Cl_2	4	**7a**: 60 (>99); **8a**: 38 (>99)
4	THF	12	**7a**: 44 (>99); **8a**: 49 (>99)
5[d]	CH_3CN	4	**7a**: 41 (>99); **8a**: 33 (>99)
6[e]	CH_3CN	18	**7a**: 25 (>99); **8a**: 52 (>99)
7[f]	CH_3CN	2	**7a**: 52 (>99); **8a**: 43 (>99)
8[f,g]	CH_3CN	2	**9a**: 88 (99)

[a] Boc: *tert*-butoxycarbonyl; TFA: trifluoroacetic acid. Unless noted otherwise, reactions were performed with **4a** (0.11 mmol), **5a** (0.1 mmol), **6a** (0.12 mmol), **3** (0.01 mmol) and benzoic acid (0.01 mmol) in solvent (0.5 mL) at RT. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis; dr > 99:1. [d] AcOH was used as the acid additive. [e] Without acid additive. [f] With 5 mol% of **3** and 10 mol% of PhCOOH. [g] TFA (0.2 mmol) was added for dehydration.

With these results in hand, we investigated the substrate scope of the three-component domino reaction. In comparison with the results with oxindole **5a** (Table 2, entry 1), slightly less reaction was observed if **5b**, with an ethyl ester group, was applied (Table 2, entry 2). We then examined a number of α,β-unsaturated aldehydes, **6**, with propionaldehyde (**4a**) and oxindole **5a**. The substrate, **5a**, was generally exhausted within 2 h. Enals bearing various electron-withdrawing or -donating aryl and heteroaryl groups could be well tolerated, and the spirocyclic oxindoles **9c–f** were obtained with excellent enantioselectivities and in good yields after treatment with TFA (Table 2, entries 3–6). It should be noted that *N*-Boc-protected **7g** could be isolated as the single product when the enal with an *o*-bromophenyl group was applied (Table 2, entry 7). Simple acrolein and crotonaldehyde could also be successfully utilised (Table 2, entries 8 and 9). Subsequently, other aliphatic aldehydes were tested. Good results could still be attained, although longer reaction times, higher catalyst loadings and higher temperatures needed to be applied (Table 2, entries 10–12). On the other hand, a few different olefinic oxindoles were explored. The electronic features of the substituents on the aryl ring had little effect on the reactivity, and good results were obtained (Table 2, entries 13–15). Nevertheless, the olefinic oxindole with a β-phenyl group exhibited much lower reactivity, and

Table 2. Substrate scope in the three-component domino reaction.[a]



5a: $R^2 = CO_2tBu$, $R^3 = H$; **5b**: $R^2 = CO_2Et$, $R^3 = H$
5c: $R^2 = CO_2tBu$, $R^3 = F$; **5d**: $R^2 = CO_2tBu$, $R^3 = Me$
5e: $R^2 = CO_2tBu$, $R^3 = MeO$; **5f**: $R^2 = Ph$, $R^3 = H$

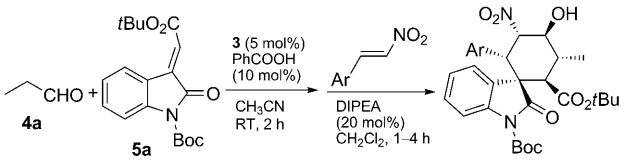
Entry	R^1	5	R^4	t [h]	Yield [%][b] (*ee* [%][c])
1	Me	**5a**	Ph	2	**9a**: 88 (99)
2	Me	**5b**	Ph	4	**9b**: 73 (>99)
3	Me	**5a**	*p*-$CF_3C_6H_4$	1	**9c**: 78 (>99)
4	Me	**5a**	*m*-CNC_6H_4	1	**9d**: 80 (>99)
5	Me	**5a**	*p*-$MeOC_6H_4$	2	**9e**: 83 (>99)
6[d]	Me	**5a**	2-thienyl	1	**9f**: 77 (>99)
7[e]	Me	**5a**	*o*-BrC_6H_4	1	**7g**: 86 (>99)
8	Me	**5a**	H	1	**9h**: 53 (89)
9	Me	**5a**	Me	2	**9i**: 73 (99)
10	Et	**5a**	Ph	5	**9j**: 66 (>99)
11[f]	$PhCH_2$	**5a**	Ph	19	**7k**: 64 (>99)
12[f]	$PhSCH_2$	**5a**	Ph	19	**7l**: 50 (95)
13	Me	**5c**	Ph	2	**9m**: 70 (>99)
14	Me	**5d**	Ph	2.5	**9n**: 80 (99)
15	Me	**5e**	Ph	3.5	**9o**: 83 (>99)
16[g]	Me	**5f**	Ph	32	**7p**: 71 (91)

[a] Unless noted otherwise, reactions were performed with **4** (0.11 mmol), **5** (0.1 mmol), **6** (0.12 mmol), **3** (0.005 mmol) and benzoic acid (0.01 mmol) in CH_3CN (0.5 mL) at RT. After completion, TFA (0.2 mmol) was added and the mixture was stirred at RT for 3 h. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis; dr > 99:1. [d] The absolute configuration of **7f** was determined by X-ray analysis;[15] see the Supporting Information. [e] The aldol product was not observed. [f] With 10 mol% of **3** and 10 mol% of PhCOOH in toluene at 40 °C. [g] With 10 mol% of **3** and 10 mol% of *o*-FPhCOOH in toluene at 40 °C.

slightly harsher reaction conditions were required (Table 2, entry 16).[14]

As α,β-unsaturated aldehydes could proceed in the Michael addition/aldol reaction sequences with intermediate **A** depicted in Scheme 2, we proposed that other electrophiles could also be used in similar formal [4+2] annulation reactions with intermediate **A**; thus, spirocyclic oxindoles with different substitution patterns could be generated. We found that nitroolefins could act as good candidates.[6g,h] After the Michael reaction of propionaldehyde (**4a**) to oxindole **5a** was complete, nitroolefins were added. Better results could be obtained by using dichloromethane as the solvent and *N*,*N*-diisopropylethylamine (DIPEA) was used as the base catalyst. The tandem Michael addition/Henry reaction sequences were generally accomplished within 4 h, and the desired cyclic products, **10a–d**, with six contiguous stereogenic centres were isolated in high yields with excellent enantioselectivities and good diastereoselectivities (Scheme 3). However, nitroolefins bearing β-alkyl groups exhibited much lower reactivity and failed to afford the corresponding spirocyclic oxindoles.

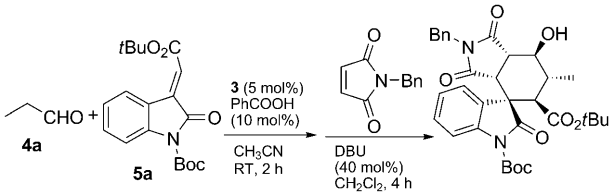
Moreover, the one-pot, three-component tandem reaction of aldehyde **4a**, oxindole **5a** and *N*-benzylmaleimide could be efficiently conducted. In this case, 1,8-diazabicyclo-



10a: Ar = Ph (85%, 95% *ee*, dr = 8:1)
10b: Ar = *m*-ClPh (82%, 94% *ee*, dr = 10:1)
10c: Ar = *p*-MePh (90%, 90% *ee*, dr = 10:1)
10d: Ar = 2-thienyl (85%, 95% *ee*, dr = 6:1)

Scheme 3. One-pot, three-component tandem reaction to access spirocyclic oxindoles.

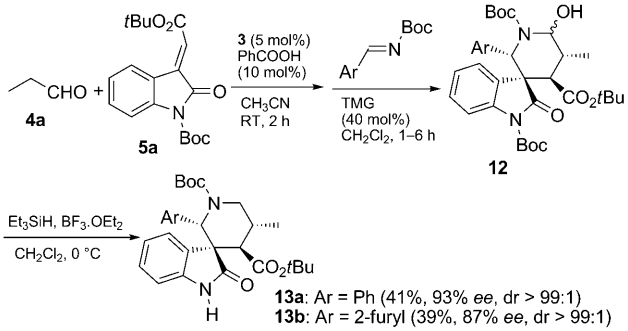
[5.4.0]undec-7-ene (DBU) was the preferable base promoter in the later Michael addition/aldol reaction sequences. The spirocyclic oxindole **11** with multiple functionalities was also obtained with excellent stereocontrol (Scheme 4).



11 (50%, 90% *ee*, dr > 99:1)

Scheme 4. One-pot, three-component tandem reaction to access spirocyclic oxindoles with a tetracyclic skeleton. Bn: benzyl.

Furthermore, we developed a tandem process to construct spirocyclic oxindoles incorporating a piperidine motif, which might be quite valuable for the design of biologically important materials.[10] As depicted in Scheme 5, *N*-Boc-imines



13a: Ar = Ph (41%, 93% *ee*, dr > 99:1)
13b: Ar = 2-furyl (39%, 87% *ee*, dr > 99:1)

Scheme 5. One-pot, three-component tandem reaction to access spirocyclic oxindoles incorporating a piperidine motif. TMG: 1,1,3,3-tetramethylguanidine.

could be used as the electrophiles in the reaction with intermediate **A**.[5a] A highly diastereoselective Mannich reaction could be catalysed by TMG. The resultant hemiaminals **12** were directly dehydroxylated to give the piperidine derivatives **13a** and **13b** with high enantioselectivities and in fair yields after isolation.[16]

Conclusion

We have developed an efficient and convenient one-pot, three-component tandem reaction for the asymmetric synthesis of a diverse spirocyclic oxindoles with excellent diastereo- and enantioselectivities. This protocol proceeded through a formal [2+2+2] annulation strategy by sequential amine-based organocatalytic reactions. A series of spiro oxindolic carbocyclic and heterocyclic derivatives with versatile molecular complexity have been constructed, which might find applications in the further synthesis of compounds with potential biological activities. We also believe that the strategy demonstrated here may be utilised in other asymmetric reactions to efficiently produce chiral materials with complex structures. More results will be reported in due course.

Experimental Section

General procedure for the three-component domino reaction: Propionaldehyde (**4a**; 7.9 μL, 0.11 mmol), activated olefinic oxindole **5a** (35.0 mg, 0.1 mmol), cinnamaldehyde (**6a**; 15.0 μL, 0.12 mmol), catalyst **3** (1.6 mg, 5 mol %) and benzoic acid (1.3 mg, 10 mol %) were stirred in acetonitrile (0.5 mL) at room temperature for 2 h. After the consumption of oxindole **5a**, the solvent was removed. The residue was purified by flash chromatography to give the cyclohexenecarboxaldehyde **7a** and aldol product **8a**. For the dehydration process, TFA (16.0 μL, 0.2 mmol) was added to the reaction mixture and stirred at room temperature for 3 h. The *N*-Boc-deprotected product **9a** was isolated after flash chromatography.

Compound 7a: 52 % yield; $[\alpha]_D^{20}=-95.3$ ($c=1.35$ in EtOH); >99 % *ee*, as determined by chiral HPLC analysis (Daicel chiralcel OD-H, *n*-hexane/*i*PrOH 90:10, 1.0 mL min^{-1}, $\lambda=254$ nm, $t_{major}=5.45$ min, $t_{minor}=6.99$ min); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=9.49$ (s, 1H), 7.84 (d, $J=8.0$ Hz, 1H), 7.35–6.99 (m, 6H), 6.68 (td, $J=7.6$, 0.8 Hz, 1H), 6.53 (d, $J=6.8$ Hz, 1H), 5.49 (dd, $J=7.6$, 0.8 Hz, 1H), 3.92 (s, 1H), 3.55–3.49 (m, 1H), 2.84 (d, $J=10.4$ Hz, 1H), 1.64 (s, 9H), 1.42 (d, $J=7.6$ Hz, 3H), 0.99 ppm (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=192.4$, 174.4, 169.9, 155.3, 149.5, 139.6, 138.1, 137.3, 133.3, 128.5, 128.0, 127.7, 127.3, 127.1, 125.8, 122.9, 114.2, 84.1, 81.6, 51.7, 50.9, 45.3, 32.1, 28.1, 27.1, 18.4 ppm; ESI-HRMS: *m/z* calcd for $C_{30}H_{29}NO_5$+Na: 540.2362; found: 540.2391.

Compound 8a: 43 % yield; $[\alpha]_D^{20}=-33.3$ ($c=0.6$ in EtOH); >99 % *ee*, as determined by chiral HPLC analysis (Daicel chiralcel OD-H, *n*-hexane/*i*PrOH 90:10, 1.0 mL min^{-1}, $\lambda=254$ nm, $t_{major}=7.05$ min, $t_{minor}=9.83$ min); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=9.41$ (s, 1H), 7.81 (d, $J=8.0$ Hz, 1H), 7.38 (br s, 2H), 7.30–7.27 (m, 1H), 7.16 (t, $J=8.0$ Hz, 1H), 7.06 (br s, 1H), 6.65 (t, $J=7.2$ Hz, 1H), 6.44 (br s, 1H), 5.60 (d, $J=7.6$ Hz, 1H), 4.44 (td, $J=10.0$, 3.2 Hz, 1H), 4.04–4.00 (m, 1H), 3.65 (d, $J=6.4$ Hz, 1H), 3.11 (d, $J=3.2$ Hz, 1H), 3.02–2.95 (m, 1H), 2.85 (d, $J=12.4$ Hz, 1H), 1.68 (s, 9H), 1.23 (d, $J=6.4$ Hz, 3H), 1.02 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=204.1$, 175.4, 169.4, 149.5, 139.3, 136.7, 133.5, 128.6, 128.3, 126.9, 125.8, 123.1, 114.3, 84.4, 81.5, 71.6, 54.3, 53.6, 51.3, 48.2, 33.4, 28.1, 27.2, 16.1 ppm; ESI-HRMS: *m/z* calcd for $C_{32}H_{27}NO_3$+Na: 558.2500; found: 558.2473.

Compound 9a: 88 % yield; $[\alpha]_D^{20}=-76.92$ ($c=0.66$ in EtOH); 99 % *ee*, as determined by chiral HPLC analysis (Daicel chiralpak AD-H, *n*-hexane/*i*PrOH 70:30, 1.0 mL min^{-1}, $\lambda=254$ nm, $t_{major}=13.84$ min, $t_{minor}=7.63$ min); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=9.45$ (s, 1H), 8.09 (d, $J=18.0$ Hz, 1H), 7.34–7.23 (m, 2H), 7.10–7.01 (m, 4H), 6.79 (d, $J=7.2$ Hz, 1H), 6.58–6.54 (m, 2H), 5.47 (d, $J=7.6$ Hz, 1H), 3.91 (s, 1H), 3.61–3.56 (m, 1H), 2.86 (d, $J=10.8$ Hz, 1H), 1.39 (d, $J=7.6$ Hz, 3H), 1.00 ppm (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=192.5$, 178.8, 170.9, 155.3, 140.8, 138.3, 138.0, 133.2, 128.3, 127.9, 127.5, 126.7, 120.8, 109.0, 81.3, 51.5, 50.9, 44.6, 31.9, 28.8, 27.3, 18.4 ppm; ESI-HRMS: *m/z* calcd for $C_{26}H_{27}NO_4$+Na: 440.1838; found: 440.1813.

General procedure for the one-pot, three-component tandem reaction to access spirocyclic oxindoles: Propionaldehyde (**4a**; 7.9 μL, 0.11 mmol), olefinic oxindole **5a** (35.0 mg, 0.1 mmol), catalyst **3** (1.6 mg, 5 mol %) and benzoic acid (1.3 mg, 10 mol %) were stirred in acetonitrile (0.5 mL) at room temperature for 2 h. The solvent was then removed and CH_2Cl_2 (0.5 mL), nitrostyrene (18.0 mg, 0.12 mmol) and DIPEA (3.6 μL, 0.02 mmol) were added. The reaction was stirred at room temperature for 1–4 h. The mixture was concentrated and the residue was purified by chromatography to afford spirocyclic oxindole **10a**. For the synthesis of compound **11**, *N*-benzylmaleimide (22.5 mg, 0.12 mmol) and DBU (6.0 μL, 40 mol %) were added instead of the nitroolefin and DIPEA.

Compound 10a: 85 % yield; $[\alpha]_D^{20}=+79.67$ ($c=0.60$ in EtOH); dr = 8:1, as determined by ^{1}H NMR analysis; 95 % *ee*, as determined by chiral HPLC analysis (Daicel chiralpak IC, *n*-hexane/*i*PrOH 95:5, 1.0 mL min^{-1}, $\lambda=254$ nm, $t_{major}=15.68$ min, $t_{minor}=33.78$ min); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.46$–7.35 (m, 2H), 7.20–6.99 (m, 7H), 6.21 (dd, $J=12.0$, 2.4 Hz, 1H), 4.58 (s, 1H), 4.06 (d, $J=12.4$ Hz, 1H), 3.37–3.25 (m, 2H), 2.73 (s, 1H), 1.56 (s, 9H), 1.14 (d, $J=6.4$ Hz, 3H), 1.05 ppm (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=174.9$, 169.8, 148.4, 139.3, 132.8, 128.8, 127.9, 127.8, 127.7, 124.2, 122.8, 121.6, 114.6, 114.4, 86.7, 83.9, 81.5, 71.9, 54.4, 52.1, 46.6, 32.4, 31.5, 28.0, 27.9, 27.4, 27.2, 15.6, 14.2, 14.0 ppm; ESI-HRMS: *m/z* calcd for $C_{30}H_{36}N_2O_8$+Na: 575.2369; found: 575.2366.

Compound 11: 50 % yield; $[\alpha]_D^{20}=-98.16$ ($c=0.38$ in EtOH); 90 % *ee*, dr > 99:1, as determined by HPLC analysis (Daicel chiralpak AD-H, *n*-hexane/*i*PrOH 90:10, 1.0 mL min^{-1}, $\lambda=254$ nm, $t_{major}=5.41$ min, $t_{minor}=8.64$ min); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.69$ (d, $J=8.0$ Hz, 1H), 7.31–7.24 (m, 3H), 7.23–7.17 (m, 3H), 6.89 (d, $J=7.6$ Hz, 1H), 6.67 (t, $J=7.6$ Hz, 1H), 4.61 (d, $J=14.0$ Hz, 1H), 4.47 (d, $J=14.0$ Hz, 1H), 3.88–3.79 (m, 2H), 3.75 (d, $J=10.4$ Hz, 1H), 3.30 (d, $J=18.8$ Hz, 1H), 2.96–2.90 (m, 1H), 2.10 (d, $J=19.2$ Hz, 1H), 1.64 (s, 9H), 1.52 (d, $J=7.2$ Hz, 3H), 1.41 ppm (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=178.7$, 178.4, 174.5, 169.5, 148.2, 140.2, 135.1, 129.2, 128.8, 128.6, 128.0, 125.0, 124.5, 123.6, 114.9, 85.4, 83.2, 81.7, 62.5, 60.0, 58.3, 47.1, 42.5, 32.4, 29.7, 28.0, 27.8, 27.5, 18.6 ppm; ESI-HRMS: *m/z* calcd for $C_{33}H_{38}N_2O_8$+Na: 613.2526; found: 613.2517.

General procedure for the one-pot, three-component tandem reaction to access spirocyclic oxindoles incorporating a piperidine motif: Propionaldehyde (**4a**; 7.9 μL, 0.11 mmol), olefinic oxindole **5a** (35.0 mg, 0.1 mmol), catalyst **3** (1.6 mg, 5 mol %) and benzoic acid (1.3 mg, 10 mol %) were stirred in acetonitrile (0.5 mL) at room temperature for 2 h. The solvent was then removed and CH_2Cl_2 (0.5 mL), *N*-Boc-phenylimine (25.0 mg, 0.12 mmol) and TMG (2.5 μL, 0.02 mmol) were added. The mixture was stirred at room temperature. After completion, the mixture was concentrated and the residue was purified by flash chromatography to afford hemiaminal **12**. $BF_3{\cdot}Et_2O$ (25.0 μL, 0.2 mmol) was added to a solution of **12** and triethylsilane (46.5 mg, 0.4 mmol) in anhydrous CH_2Cl_2 (1.0 mL) with ice cooling. After 2 min, the reaction was quenched with aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography on silica gel to give piperidine derivative **13a**.

Compound 13a: 41 % yield; $[\alpha]_D^{20}=+49.7$ ($c=0.31$ in EtOH); 93 % *ee*, dr > 99:1, as determined by chiral HPLC analysis (Daicel chiralpak IC, *n*-hexane/*i*PrOH 90:10, 1.0 mL min^{-1}, $\lambda=254$ nm, $t_{major}=6.34$ min, $t_{minor}=7.51$ min); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.45$ (d, $J=7.2$ Hz, 1H), 7.23–7.19 (m, 2H), 7.14–7.02 (m, 3H), 6.72 (d, $J=6.8$ Hz, 2H), 6.60 (d, $J=7.2$ Hz, 1H), 5.25 (s, 1H), 4.60 (q, $J=6.8$ Hz, 1H), 4.03 (d, $J=13.6$ Hz, 1H), 2.69–2.60 (m, 1H), 1.29 (s, 9H), 1.21 (d, $J=6.8$ Hz, 3H), 1.06 ppm (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=176.0$, 171.2, 155.5, 141.0, 138.6, 131.4, 128.8, 127.8, 127.2, 125.9, 123.9, 122.2, 109.0, 81.1, 80.0, 64.3, 55.5, 54.4, 46.7, 29.9, 28.2, 27.4, 20.5 ppm; ESI-HRMS: *m/z* calcd for $C_{29}H_{36}N_2O_5$+H: 493.2702; found: 493.2702.

Acknowledgements

We are grateful for financial support from the National Natural Science Foundation of China (grant nos. 20772084 and 20972101), PCSIRTC (grant no. IRT0846) and the National Basic Research Program of China (973 Program) (grant no. 2010CB833303).

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Received: October 31, 2009
Published online: January 28, 2010

