ChemPubSoc Europe

DOI: 10.1002/chem.201402002

CHEMISTRY
A European Journal
Communication

Organocatalysis

One-Pot Organocatalytic Enantioselective Michael/Povarov Domino Strategy for the Construction of Spirooctahydroacridine-3,3′-oxindole Scaffolds

Hao Wu and Yong-Mei Wang*[a]

Abstract: An asymmetric organocatalytic one-pot strategy for the construction of spirooctahydroacridine-3,3′-oxindole scaffolds has been successfully developed by means of a domino Michael/Povarov reaction sequence. The one-pot protocol affords the chiral spirocyclohexaneoxindoles bearing an octahydroacridine motif with five stereocenters in good to high yields (up to 89% yield) with excellent to perfect diastereoselectivities (up to >20:1 d.r.) and enantioselectivities (up to >99% *ee*). This highly efficient one-pot domino procedure will allow diversity-oriented syntheses of this intriguing class of compounds with potential biological activities.

Domino, tandem, or cascade reactions that involve the formation of multiple carbon–carbon or carbon–heteroatom bonds and stereocenters in one-pot reactions are a rapidly growing research field within the construction of molecules with great structural complexity by a minimum of manual operations, thereby saving time, effort, and production cost.[1] The design of organocatalytic domino reactions[2] is even more appealing, not only because such processes are more efficient than stepwise reactions, but also because organocatalysts, which allow distinct modes of activation, are environmentally friendly, robust, and nontoxic. Thus, the implementation of asymmetric, organocatalytic, one-pot domino processes remains of great interest to the synthetic community.[3]

The spirocyclicoxindole scaffold defines the characteristic structural core of a large family of alkaloid natural products with strong bioactivity profiles and interesting structural properties.[4] The exceptional promise of a broad therapeutic potential has sparked intense interest in developing concise approaches for generating multifunctionalized chiral spirooxindoles and natural-product-like derivatives.[5] In particular, oxindoles incorporating a cyclohexane moiety are particularly striking structural motifs widely encountered in a number of biologically active natural alkaloids (Figure 1 a).[6] Compared with the spirooxindoles with cyclohexanone[7] and cyclohexene moieties,[8] highly efficient methods for the enantioselective construction of spirocyclohexaneoxindoles have been rarely disclosed.[9] Furthermore, chiral octahydroacridine (OHA) is another core structure with pharmacological interest, acting as gastric acid secretion inhibitors (Figure 1 b).[10] However, access to optically active octahydroacridines has so far exclusively been based on a chiral pool approach and the methodology through asymmetric catalysis is quite limited.[3g] Because of the significant medicinal value and structural complexities of the two class of scaffolds, a sophisticated structure in which the oxindole core is fused with an octahydroacridine moiety at the C3-position might possess remarkable biological activities, thus emerging as an attractive synthetic target (Figure 1 c).[11] Nevertheless, enantiomerically enriched spirooctahydroacridine-3,3′-oxindole scaffolds possessing the potential as an important pharmacophore have not been constructed until now.

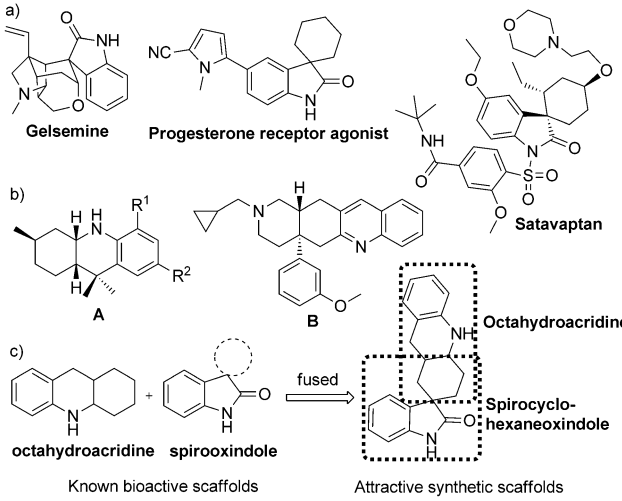


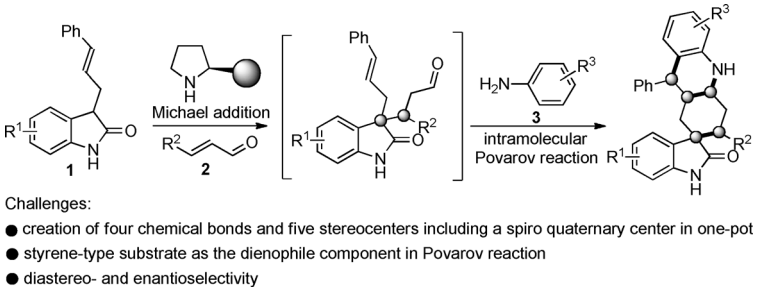
Figure 1. a) Some biologically active compounds with spirocyclohexaneoxindole core. b) Selected examples of biologically important chiral octahydroacridine derivatives. c) Construction of the chiral spirooctahydroacridine-3,3′-oxindole skeleton by two known bioactive scaffolds.

Prompted by the above background and in the context of our ongoing investigations in asymmetric synthesis of chiral spirooxindoles,[5q] we envisioned that the chiral spirooctahydroacridine-3,3′-oxindole skeleton could be constructed in an asymmetric organocatalytic domino Michael/intramolecular

[a] *H. Wu, Prof. Y.-M. Wang*
State Key Laboratory of Elemento-Organic Chemistry
Department of Chemistry, Nankai University
Tianjin 300071 (China)
Fax: (+86) 22-23504439
E-mail: ymw@nankai.edu.cn

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201402002.

Povarov reaction[12] sequence of rationally designed 3-substituted oxindoles (**1**), α,β-unsaturated aldehydes (**2**), and aniline derivatives (**3**) by means of a one-pot strategy. The two stereocenters of the initial step employing aminocatalysis would direct the subsequent aza-Diels–Alder reaction, hereby controlling the formation of the optically active spirooctahydroacridine-3,3′-oxindole derivatives containing five stereocenters with excellent stereoselectivities (Scheme 1).



Scheme 1. Proposed strategy for the one-pot organocatalytic asymmetric synthesis of spirooctahydroacridine-3,3′-oxindole derivatives and its three challenges.

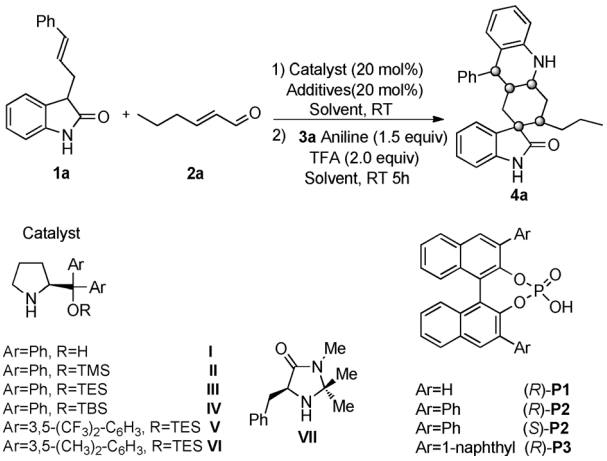
However, three challenges are associated with this one-pot domino process:

1) The simultaneous creation of four new chemical bonds (three carbon–carbon bonds and one carbon–nitrogen bond) and five stereocenters including a spiro quaternary center in one-pot.
2) Less reactive styrene-type substrates as the olefin component in the Povarov reaction (only three examples of an asymmetric catalytic protocol involving styrene derivatives as the dienophiles in Povarov reaction have been reported[11c,12m,j]).
3) The control of diastereo- and enantioselectivity of the products.

Herein, we present the successful implementation of this organocatalytic one-pot domino strategy to access optically active spirooctahydroacridine-3,3′-oxindole derivatives containing five stereocenters including a spiro quaternary center with excellent enantio- and diastereopurities and significant opportunities for structural diversification (up to 89% yield, up to >20:1 d.r., up to >99% *ee*).

In our initial investigation, we examined the reactivity of 3-substituted oxindole (**1a**) towards the proposed one-pot domino reaction with *trans*-hex-2-enal (**2a**) and aniline (**3a**). Gratifyingly, reaction of **1a** and **2a** with 20 mol% of Et_2NH in toluene at room temperature for 24 h, followed by the addition of aniline (**3a**, 1.5 equiv) and trifluoroacetic acid (TFA, 2.0 equiv) with stirring for another 5 h, furnished a 88% yield of the expected product **4a** although in an approximate 1:1 ratio of diastereomers (Table 1, entry 1, 1:1 d.r.). Then some commercially available chiral secondary amines **I**–**VII** were screened, because of their established abilities to activate α,β-unsaturated aldehydes toward asymmetric transformations (Table 1, entries 2–8). To our delight, reactions with the diphenyl prolinol silylether catalysts **I**–**VI** gave promising results with good yields and stereoselectivities. Increasing the diarylprolinol *O*-trimethylsilyl (*O*-TMS) ether to some bulkier ether groups, for example, *O*-triethylsilyl (*O*-TES) and *O*-*tert*-butyl dimethyl (*O*-TBS), led to higher diastereoselectivities and enantioselectivities (Table 1, entries 2 and 3 versus entries 4 and 5). Lower yields and stereoselectivities were obtained when the electronic nature of the aryl group in the catalyst **III** changed (Table 1, entries 6–7). MacMillan's imidazolidinone **VII** gave only traces of the product (entry 8). So the diphenyl prolinol *O*-TES, **III**, was chosen as the optimized catalyst, affording the desired product **4a** in 77% yield with 11:1 d.r. and 92% *ee* (Table 1,

Table 1. Optimization of organocatalytic one-pot domino Michael-Povarov reaction conditions.[a]

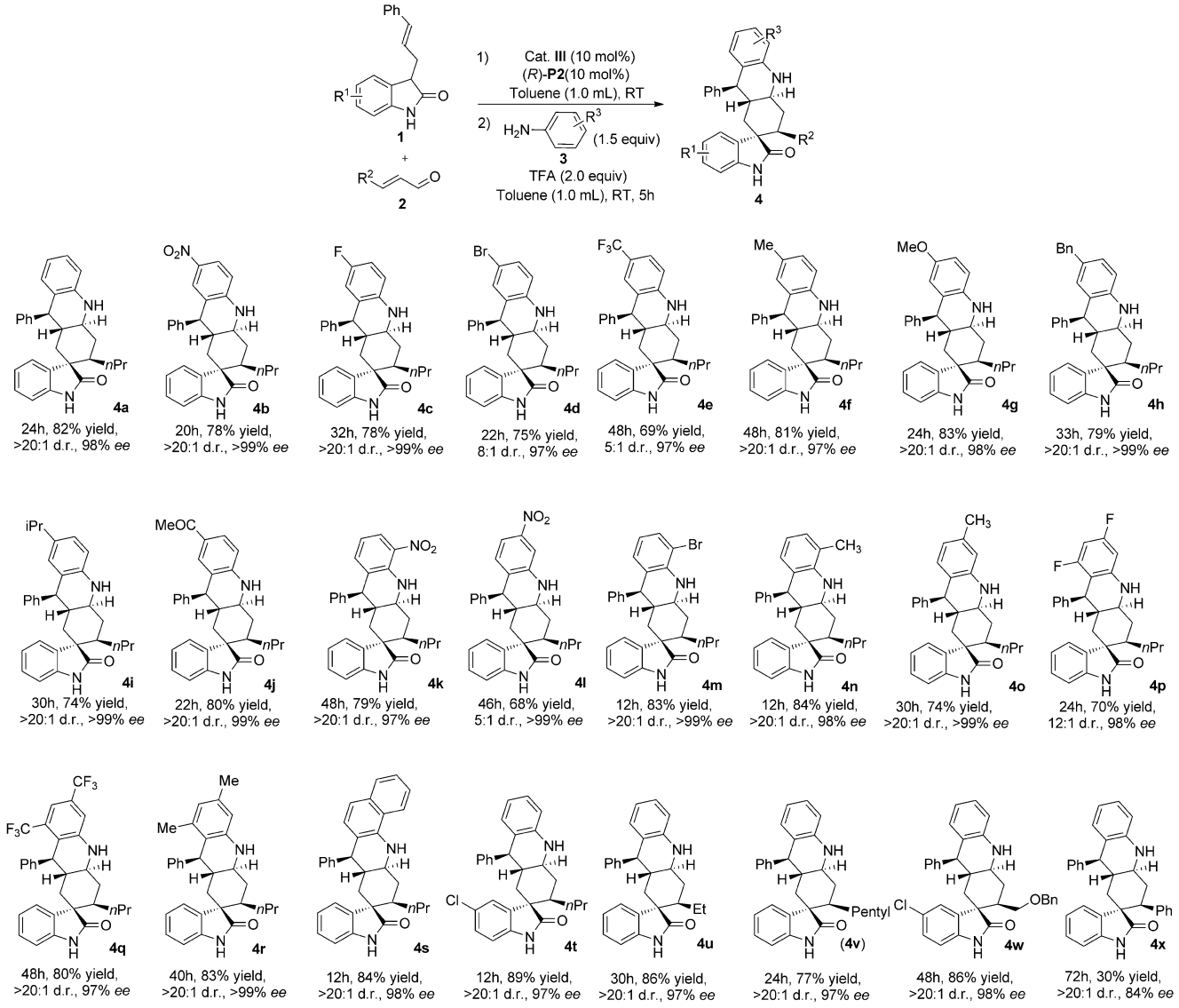


Entry	Cat.	Additive	Solvent	*t* [h]	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	Et_2NH	–	toluene	24	88	1:1	0
2	**I**	$PhCO_2H$	toluene	24	62	2:1	73
3	**II**	$PhCO_2H$	toluene	24	73	5:1	87
4	**III**	$PhCO_2H$	toluene	24	77	11:1	92
5	**IV**	$PhCO_2H$	toluene	24	73	8:1	91
6	**V**	$PhCO_2H$	toluene	24	50	3:1	90
7	**VI**	$PhCO_2H$	toluene	24	70	6:1	84
8	**VII**	$PhCO_2H$	toluene	24	trace	–	–
9	**III**	$PhCO_2H$	ether	24	80	6:1	91
10	**III**	$PhCO_2H$	THF	24	trace	–	–
11	**III**	$PhCO_2H$	MTBE	24	73	8:1	92
12	**III**	$PhCO_2H$	DCM	24	66	7:1	88
13	**III**	$PhCO_2H$	$CHCl_3$	24	72	9:1	86
14[e]	**III**	$PhCO_2H$	toluene	24	76	15:1	94
15[f]	**III**	$PhCO_2H$	toluene	24	78	12:1	94
16[e]	**III**	TFA	toluene	24	56	7:1	72
17[e]	**III**	(*R*)-**P1**	toluene	24	78	16:1	90
18[e]	**III**	(***R***)-**P2**	toluene	24	82	>20:1	98
19[e]	**III**	(*R*)-**P3**	toluene	24	86	15:1	94
20[e]	**III**	(*S*)-**P2**	toluene	24	80	>20:1	97

[a] Unless otherwise specified, all the reactions were performed in 0.1 M **1a** with a 1:2 ratio of **1a**/**2a** at room temperature by employing 20 mol% catalyst and additive. [b] Isolated yields of diastereomeric mixture. [c] Determined by ^1H NMR spectroscopy of a crude reaction mixture. [d] Enantiomeric excess of major diastereoisomer as determined by HPLC analysis. [e] 10 mol% catalyst and 10 mol% additive were used. [f] 15 mol% catalyst and 15 mol% additive were used.

entry 4). No significant improvement was achieved by conducting the one-pot domino reaction in various solvents although comparable enantioselectivities and yields were obtained for diethyl ether and methyl *tert*-butyl ether (MTBE) (entries 9–13). When the catalyst and additive loading were both decreased to 10 mol%, better stereoselectivities were obtained for the product **4a** (Table 1, entry 14, 15:1 d.r., 94% *ee*). Following a screening of various additives revealed that the combination of chiral Brønsted acids with the catalyst **III** afforded the product in higher yield and excellent stereoselectivities (entries 17–20). Eventually, the best outcome was obtained when 10 mol% of (*R*)-**P2** was employed as the additive, thus providing the desired spirooctahydroacridine-3,3′-oxindole **4a** in high yield with excellent diastereoselectivity and enantioselectivity (Table 1, entry 18, 82% yield, >20:1 d.r., 98% *ee*). Replacement of the (*R*)-**P2** to (*S*)-**P2** furnished a comparable result in terms of yield and stereocontrols (entry 20).

With the optimized conditions in hand, we subsequently performed a study to probe the generality of our one-pot domino strategy in synthesizing substituted spirooctahydroacridine-3,3′-oxindole derivatives by focusing upon variation of 3-substituted oxindoles (**1**), α,β-unsaturated aldehydes (**2**), and aniline derivatives (**3**). The results are summarized in Scheme 2. All of the reactions catalysed by the catalyst **III** proceeded smoothly, affording the desired spirooctahydroacridine-3,3′-oxindole derivatives in good to high yields (30–89% yield) with excellent diastereoselectivities (5:1–>20:1 d.r.) and excellent enantioselectivities (84–>99% *ee*). Notably, minimal impact on reactive efficiencies, enantioselectivities and diastereoselectivities was observed, regardless of the electronic nature or bulki-



Scheme 2. Synthesis of spirooctahydroacridine-3,3′-oxindole derivatives with five stereocenters. Unless otherwise specified, all the reactions were performed in 0.1 M **1a** with a 1:2 ratio of **1a**/**2a** at room temperature by employing 10 mol% catalyst and additive at room temperature. The reported yields are of the sum of the diastereoisomers. The d.r. values were determined by ^{1}H NMR spectroscopy of the crude mixture. The *ee* values were determined by chiral HPLC on a Chiralcel column.

ness of 4-substituted aniline derivatives (Scheme 2, **4a**–**j**). In addition, other different substitution patterns of the anilines were also explored. There appears to be significant tolerance towards electronic variations and positions of the substituents of the anilines to access a variety of products (Scheme 2, **4k**–**o**). Three disubstituted anilines with electron-withdrawing groups and electron-donating groups as well as 1-aminonaphthalene were utilized in the strategy, accessing the optically active products **4p**–**s** with tetrasubstituted aromatic moieties in high yields with excellent stereocontrol (Scheme 2). Further exploration of the substrate scope was focused upon various 3-substituted oxindoles (**1**) and α,β-unsaturated aldehydes (**2**). Minimal impact of the chain length of aliphatic enals upon the efficiencies and stereoselectivities was observed, though lower yield and stereocontrol was obtained when cinnamaldehyde was used (Scheme 2, **4u**–**x**). Another 3-substituted bifunctional oxindole **1b** was also compatible under the optimized reaction conditions, thus offering excellent stereoselectivities of the products (Scheme 2, **4t** and **4w**). However, when conducting the reaction with nucleophiles without the aromatic substituent on the double bond, no cyclization was observed (see the Supporting Information, **4y**). This may indicate the necessity of the aryl substituent on the double bond to finish the intramolecular Povarov reaction.[12a] The absolute configuration of the stereogenic centers of the spirooctahydroacridine-3,3′-oxindole derivative (**4d**) was unambiguously determined by X-ray crystallographic analysis (Figure 2).[13]

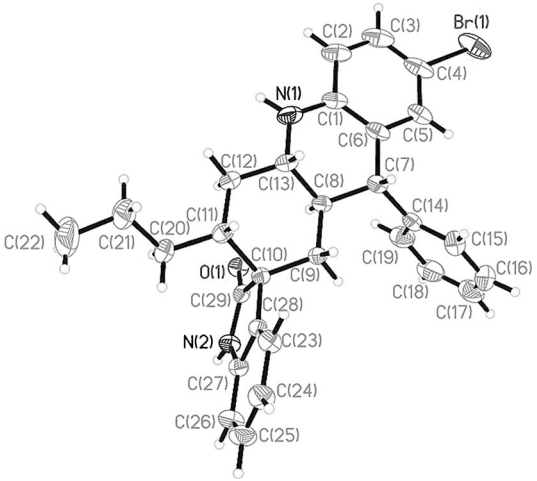
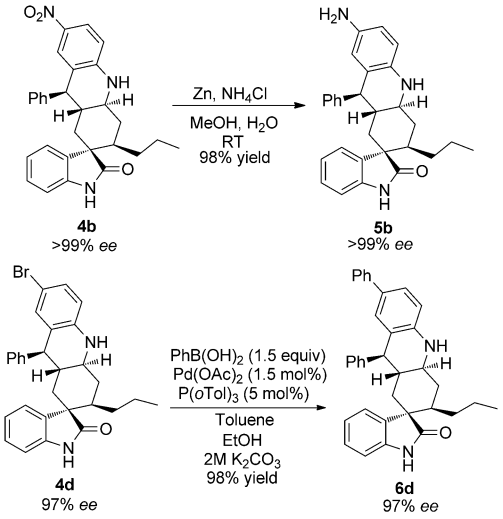


Figure 2. X-ray crystal structure of compound **4d**.

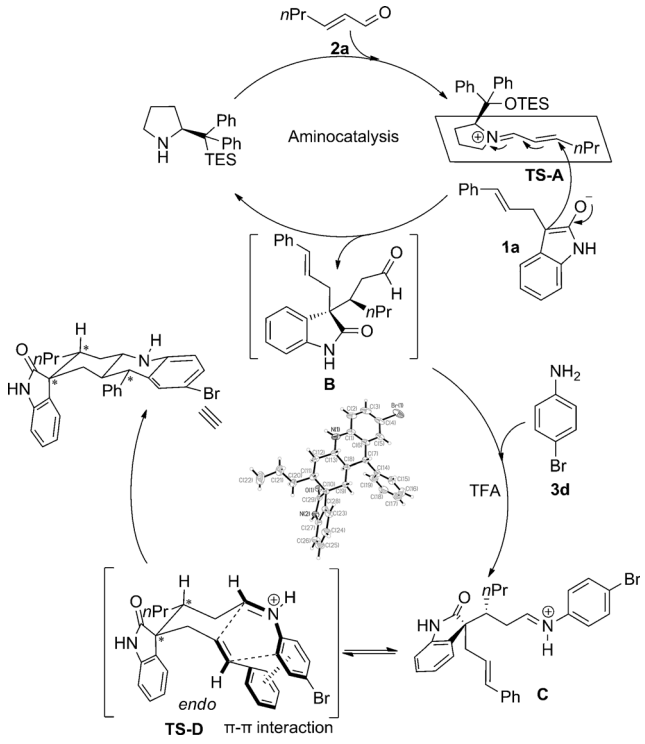
To further expand the potential of this reaction, the versatile transformations of the products into other structurally diverse spirooctahydroacridine-3,3′-oxindole derivatives were performed. As illustrated in Scheme 3, the 4-nitro moiety of the spirooxindole **4b** was smoothly reduced to 4-amino moiety **5b**, which was incompatible to our one-pot domino strategy, in 98% yield by a simple treatment with zinc powder and NH_4Cl in $MeOH/H_2O$ within 20 min. In addition, aryl bromide moiety of **4d** could be introduced a phenyl group in the position of Br atom by means of a Suzuki coupling to give **6d** in



Scheme 3. Transformation of the products into other spirooctahydroacridine-3,3′-oxindole derivatives.

almost quantitative yield. It is worth noting that no great changes took place in the enantioselectivity during the above transformations.

To explain the stereochemical outcome of this one-pot domino transformation, we have proposed a plausible mechanism (Scheme 4). Initial nucleophilic attack of 3-substituted oxindole (**1a**) on the iminium-activated α,β-unsaturated aldehyde (**2a**) via **TS-A** from the *Re*-face under the catalyst control by efficient shielding of the *Si*-face afforded the Michael addition



Scheme 4. Proposed mechanism for the one-pot domino transformation.

adduct **B**, which was then reacted with 4-bromoaniline (**3d**) and TFA through condensation to provide iminium intermediate **C**. Subsequently, the intermediate **C** underwent the intramolecular Povarov reaction via an *endo* transition state (**TS-D**), preferring the stabilized π–π stacking and chairlike conformation, to furnish the desired product **4d** with the observed diastereoselectivity. This π–π interaction could also be proved when conducting the experiment with the substrate **1** bearing no aromatic substituent on the double bond and thereby lacking the ability to be involved in π–π interaction, no cyclization was observed (see the Supporting Information, **4y**). Notably, the reaction demonstrated a proof-of-principle of the control of stereoselectivity in Povarov reaction by the remote stereogenic center generated in situ by the one-pot domino organocatalytic reaction.

In conclusion, we have developed an efficient organocatalytic one-pot domino Michael/intramolecular Povarov reaction to provide the enantiomerically enriched spirooctahydroacridine-3,3′-oxindole derivatives containing five stereogenic centers in good to high yields with excellent diastereo and enantioselectivities. Under optimal conditions, this protocol displays a great tolerance towards a variety of different substrates. This strategy not only adds to the limited repertory of examples of asymmetric synthesis of chiral spirocyclohexaneoxindoles and octahydroacridines, but also demonstrates a one-pot consecutive synthesis with an ecological and economical protocol. These one-pot tactics and the benign reaction media at ambient temperature further manifest the merit of this strategy. We believe that these novel compounds based on spirooctahydroacridine-3,3′-oxindole skeletons prepared here might possess some biological activities. The application of this strategy to synthesize more promising candidates for the biological evaluation is currently underway.

Experimental Section

Typical experimental procedure for one-pot construction of chiral spirooctahydroacridine-3,3′-oxindole derivatives

3-Substituted oxindole **1** (0.10 mmol, 1.0 equiv) was added to a solution of cat. **III** (0.01 mmol, 0.1 equiv), (*R*)-**P2** (0.01 mmol, 0.1 equiv), and **2** (0.20 mmol, 2.0 equiv) in toluene (1.0 mL) at room temperature. The reaction was stirred for 24–48 h. Then the reaction mixture was diluted with toluene (1.0 mL). Aniline derivative **3** (0.15 mmol, 1.5 equiv) was then added in the same pot followed by TFA (0.2 mmol, 2 equiv) and the mixture was stirred for 5 h at room temperature. When the reaction was completed, the mixture was washed with 1 M aq. HCl (2×3 mL) and sat. aq. Na_2CO_3 (2×2 mL), dried, and concentrated. The crude product was purified by silica-gel chromatography to give the corresponding products **4**.

Data for compound 4a

$[\alpha]_D^{25} = +86.8$ ($c = 0.3$, CH_2Cl_2); HPLC: Chiralpak AD-H (hexane/*i*PrOH = 90/10, flow rate 1.0 mL min^{-1}, $\lambda = 254$ nm), t_R (major) = 7.119 min, t_R (minor) = 10.910 min; 98% *ee*; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.07$ (s, 1H), 7.44 (d, $J = 7.4$ Hz, 1H), 7.22–7.08 (m, 4H), 7.05 (d, $J = 7.1$ Hz, 2H), 7.02–6.91 (m, 2H), 6.86 (d, $J = 7.7$ Hz, 1H), 6.59 (d, $J = 7.9$ Hz, 1H), 6.52 (t, $J = 7.3$ Hz, 1H), 6.45 (d, $J = 7.5$ Hz, 1H), 4.05 (s, 1H), 3.73 (d, $J = 10.8$ Hz, 1H), 3.43 (t, $J = 8.9$ Hz, 1H), 2.47–2.31 (m, 1H), 2.16 (m, 2H), 1.70 (m, 2H), 1.39 (d, $J = 13.4$ Hz, 1H), 1.29 (m, 1H), 1.14 (m, 1H), 0.90 (m, 1H), 0.77–0.57 ppm (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 182.84$, 144.37, 143.36, 140.61, 132.12, 130.20, 129.31, 128.51, 127.63, 127.17, 126.52, 125.88, 125.25, 122.09, 117.91, 114.10, 110.21, 55.33, 53.83, 51.04, 40.28, 40.04, 37.40, 33.97, 32.94, 20.25, 14.08 ppm; HRMS (ESI): *m/z* calcd for $C_{29}H_{30}N_2O+H$ [*M*+H]: 423.2431; found: 423.2436.

Acknowledgements

We thank for the grants from the National Basic Research Program of China (973 Program: 2010CB833300) and the State Key Laboratory of Elemento-Organic Chemistry.

Keywords: domino reactions · Michael reaction · organocatalysis · Povarov reaction · spirooctahydroacridine-3,3′-oxindoles

[1] For reviews see: a) L. F. Tietze, G. Brasche, K. Gericke, *Domino Reactions in Organic Synthesis*, Wiley-VCH, Weinheim, **2006**, p. 672–682; b) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115–136; c) K. C. Nicolaou, D. J. Edmonds, P. G. Bulger, *Angew. Chem.* **2006**, *118*, 7292–7344; *Angew. Chem. Int. Ed.* **2006**, *45*, 7134–7186; d) H. Guo, J. Ma, *Angew. Chem.* **2006**, *118*, 362–375; *Angew. Chem. Int. Ed.* **2006**, *45*, 354–366; e) K. C. Nicolaou, J. S. Chen, *Chem. Soc. Rev.* **2009**, *38*, 2993–3009; f) H. Clavier, H. Pellissier, *Adv. Synth. Catal.* **2012**, *354*, 3347–3403; g) L. Q. Lu, J. R. Chen, W. J. Xiao, *Acc. Chem. Res.* **2012**, *45*, 1278–1293.

[2] For reviews on organocatalytic domino reactions see: a) D. Enders, C. Grondal, M. R. M. Hüttl, *Angew. Chem.* **2007**, *119*, 1590–1601; *Angew. Chem. Int. Ed.* **2007**, *46*, 1570–1581; b) A. Dondoni, A. Massi, *Angew. Chem.* **2008**, *120*, 4716–4739; *Angew. Chem. Int. Ed.* **2008**, *47*, 4638–4660; c) X. H. Yu, W. Wang, *Org. Biomol. Chem.* **2008**, *6*, 2037–2046; d) C. Grondal, M. Jeanty, D. Enders, *Nat. Chem.* **2010**, *2*, 167–178; e) C. M. Marson, *Chem. Soc. Rev.* **2012**, *41*, 7712–7722; f) K. L. Jensen, G. Dickmeiss, H. Jiang, L. Albrecht, K. A. Jørgensen, *Acc. Chem. Res.* **2012**, *45*, 248–264.

[3] For selected examples of organocatalytic asymmetric domino reactions see: a) N. Halland, P. S. Aburell, K. A. Jørgensen, *Angew. Chem.* **2004**, *116*, 1292–1297; *Angew. Chem. Int. Ed.* **2004**, *43*, 1272–1277; b) Y. Huang, A. M. Walji, C. H. Larsen, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 15051–15053; c) D. Enders, M. R. M. Hüttl, C. Grondal, G. Raabe, *Nature* **2006**, *441*, 861–863; d) A. Carlone, S. Cabrera, M. Marigo, K. A. Jørgensen, *Angew. Chem.* **2007**, *119*, 1119–1122; *Angew. Chem. Int. Ed.* **2007**, *46*, 1101–1104; e) G.-L. Zhao, R. Rios, J. Vesely, L. Eriksson, A. Cordova, *Angew. Chem.* **2008**, *120*, 8596–8600; *Angew. Chem. Int. Ed.* **2008**, *47*, 8468–8472; f) C. Chandler, P. Galzerano, A. Michrowska, B. List, *Angew. Chem.* **2009**, *121*, 2012–2014; *Angew. Chem. Int. Ed.* **2009**, *48*, 1978–1980; g) G. Dickmeiss, K. L. Jensen, D. Worgull, P. T. Franke, K. A. Jørgensen, *Angew. Chem.* **2011**, *123*, 1618–1621; *Angew. Chem. Int. Ed.* **2011**, *50*, 1580–1583; h) Z. Mao, Y. Jia, Z. Xu, R. Wang, *Adv. Synth. Catal.* **2012**, *354*, 1401–1406; i) E. R. T. Robinson, C. Fallan, C. Simal, A. M. Z. Slawin, A. D. Smith, *Chem. Sci.* **2013**, *4*, 2193–2200.

[4] a) C. V. Galliford, K. A. Scheidt, *Angew. Chem.* **2007**, *119*, 8902–8912; *Angew. Chem. Int. Ed.* **2007**, *46*, 8748–8758; b) M. Rottmann, *Science* **2010**, *329*, 1175–1180; c) G. Periyasami, R. Raghunathan, G. Surendiran, N. Mathivanan, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2342–2345; d) R. Murugan, S. Anbazhagan, S. S. Narayanan, *Eur. J. Med. Chem.* **2009**, *44*, 3272–3279; e) R. R. Kumar, S. Perumal, P. Senthilkumar, P. Yogeeswari, D. Sriram, *Eur. J. Med. Chem.* **2009**, *44*, 3821–3829.

[5] For selected examples of the catalytic enantioselective construction of spirooxindoles, see: a) C. Martin, E. M. Carreira, *Eur. J. Org. Chem.* **2003**, 2209–2219; b) B. M. Trost, M. K. Brennan, *Synthesis* **2009**, 3003–3025; c) R. Rios, *Chem. Soc. Rev.* **2012**, *41*, 1060–1074; d) L. Hong, R. Wang, *Adv. Synth. Catal.* **2013**, *355*, 1023–1052; e) B. M. Trost, N. Cramer, S. M. Silverman, *J. Am. Chem. Soc.* **2007**, *129*, 12396–12397; f) X. H. Chen, Q.

Wei, S. W. Luo, H. Xiao, L. Z. Gong, *J. Am. Chem. Soc.* **2009**, *131*, 13819 – 13825; g) A. P. Antonchick, C. G. Reimers, M. Catarinella, M. Schürmann, H. Preut, S. Ziegler, D. Rauh, H. Waldmann, *Nat. Chem.* **2010**, *2*, 735 – 740; h) X. X. Jiang, Y. M. Cao, Y. Wang, L. Liu, F. Shen, R. Wang, *J. Am. Chem. Soc.* **2010**, *132*, 15328 – 15333; i) B. Tan, N. R. Candeias, C. F. Barbas III, *Nat. Chem.* **2011**, *3*, 473 – 477; j) F. R. Zhong, X. Y. Han, Y. Q. Wang, Y. X. Lu, *Angew. Chem.* **2011**, *123*, 7983 – 7987; *Angew. Chem. Int. Ed.* **2011**, *50*, 7837 – 7841; k) G. Bergonzini, P. Melchiorre, *Angew. Chem.* **2012**, *124*, 995 – 998; *Angew. Chem. Int. Ed.* **2012**, *51*, 971 – 974; l) N. V. Hanhan, N. R. Ball-Jones, N. T. Tran, A. K. Franz, *Angew. Chem.* **2012**, *124*, 1013 – 1016; *Angew. Chem. Int. Ed.* **2012**, *51*, 989 – 992; m) B. Tan, X. F. Zeng, W. W. Y. Leong, Z. G. Shi, C. F. Barbas, III, G. F. Zhong, *Chem. Eur. J.* **2012**, *18*, 63 – 67; n) X. Tian, P. Melchiorre, *Angew. Chem.* **2013**, *125*, 5468 – 5471; *Angew. Chem. Int. Ed.* **2013**, *52*, 5360 – 5363; o) W. Sun, G. Zhu, C. Wu, G. Li, L. Hong, R. Wang, *Angew. Chem.* **2013**, *125*, 8795 – 8799; *Angew. Chem. Int. Ed.* **2013**, *52*, 8633 – 8637; p) M. Silvi, I. Chatterjee, Y. Liu, P. Melchiorre, *Angew. Chem.* **2013**, *125*, 10980 – 10983; *Angew. Chem. Int. Ed.* **2013**, *52*, 10780 – 10783; q) H. Wu, L. L. Zhang, Z. Q. Tian, Y. D. Huang, Y. M. Wang, *Chem. Eur. J.* **2013**, *19*, 1747 – 1753; r) D. Du, Y. Jiang, Q. Xu, M. Shi, *Adv. Synth. Catal.* **2013**, *355*, 2249 – 2256.

[6] a) F. Wong, H. Watson, A. Gerbes, H. Vilstrup, S. Badalamenti, M. Bernardi, P. Ginès, *Gut* **2012**, *61*, 108 – 116; b) P. Ginès, F. Wong, H. Watson, S. Milutinovic, L. R. del Arbol, D. Olteanu, *Hepatology* **2008**, *48*, 204 – 213; c) G. C. Bignan, K. Battista, P. J. Connolly, M. J. Orsini, J. Liu, S. A. Middleton, A. B. Reitz, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5022 – 5026.

[7] For recent examples of the catalytic enantioselective construction of spirooxindoles fused with cyclohexanone moiety, see: a) G. Bencivenni, L. Y. Wu, A. Mazzanti, B. Giannichi, F. Pesciaioli, M. P. Song, G. Bartoli, P. Melchiorre, *Angew. Chem.* **2009**, *121*, 7336 – 7339; *Angew. Chem. Int. Ed.* **2009**, *48*, 7200 – 7203; b) K. Jiang, Z. J. Jia, S. Chen, L. Wu, Y. C. Chen, *Chem. Eur. J.* **2010**, *16*, 2852 – 2856; c) L. L. Wang, L. Peng, J. F. Bai, Q. C. Huang, X. Y. Xu, L. X. Wang, *Chem. Commun.* **2010**, *46*, 8064 – 8066; d) F. Zhong, X. Han, Y. Wang, Y. Lu, *Chem. Sci.* **2012**, *3*, 1231 – 1234; e) Y. B. Lan, H. Zhao, Z. M. Liu, G. G. Liu, J. C. Tao, X. W. Wang, *Org. Lett.* **2011**, *13*, 4866 – 4869.

[8] For recent examples of the catalytic enantioselective construction of spirooxindoles fused with cyclohexene moiety, see: a) X. Companyó, A. Zea, A. R. Alba, A. Mazzanti, A. Moyano, R. Rios, *Chem. Commun.* **2010**, *46*, 6953 – 6955; b) Q. Wei, L. Z. Gong, *Org. Lett.* **2010**, *12*, 1008 – 1011; c) K. Jiang, Z. J. Jia, X. Yin, L. Wu, Y. C. Chen, *Org. Lett.* **2010**, *12*, 2766 – 2769; d) Z. J. Jia, H. Jiang, J. -Long, B. Gschwend, Q. Z. Li, X. Yin, J. Grouleff, Y. C. Chen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2011**, *133*, 5053 – 5061; e) B. Tan, G. H. Torres, C. F. Barbas, III, *J. Am. Chem. Soc.* **2011**, *133*, 12354 – 12357; f) L. T. Shen, W. Q. Jia, S. Ye, *Angew. Chem.* **2013**, *125*, 613 – 616; *Angew. Chem. Int. Ed.* **2013**, *52*, 585 – 588; g) X. Zeng, Q. Ni, G. Raabe, D. Enders, *Angew. Chem.* **2013**, *125*, 3050 – 3054; *Angew. Chem. Int. Ed.* **2013**, *52*, 2977 – 2980; h) G. Li, T. Liang, L. Wojtas, J. C. Antilla, *Angew. Chem.* **2013**, *125*, 4726 – 4730; *Angew. Chem. Int. Ed.* **2013**, *52*, 4628 – 4632; i) X. M. Shi, W. P. Dong, L. P. Zhu, X. X. Jiang, R. Wang, *Adv. Synth. Catal.* **2013**, *355*, 3119 – 3123.

[9] For recent examples of the catalytic enantioselective construction of spiroox-indoles fused with cyclohexane moiety, see: a) Y. K. Liu, M. Nappi, E. Arceo, S. Vera, P. Melchiorre, *J. Am. Chem. Soc.* **2011**, *133*, 15212 – 15218; b) I. Chatterjee, D. Bastida, P. Melchiorre, *Adv. Synth. Catal.* **2013**, *355*, 3124 – 3130; c) B. Zhou, Y. Yang, J. Shi, Z. Luo, Y. Li, *J. Org. Chem.* **2013**, *78*, 2897 – 2907.

[10] R. G. Jacob, G. Perin, G. V. Botteselle, E. J. Lenardão, *Tetrahedron Lett.* **2003**, *44*, 6809 – 6812.

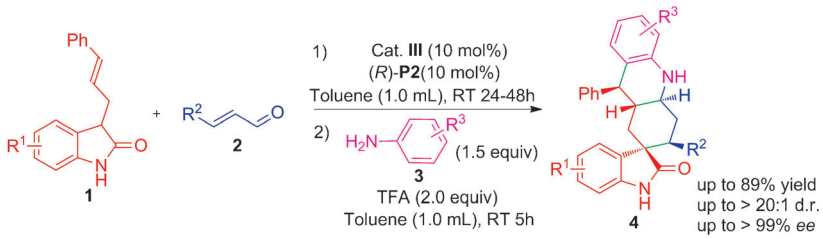
[11] a) Y. Y. Han, W. Y. Han, X. Hou, X. M. Zhang, W. C. Yuan, *Org. Lett.* **2012**, *14*, 4054 – 4057; b) W. Yang, D. M. Du, *Chem. Commun.* **2013**, *49*, 8842 – 8844; c) F. Shi, G. J. Xing, R. Y. Zhu, W. Tan, S. Tu, *Org. Lett.* **2013**, *15*, 128 – 131; d) H. Mao, A. Lin, Y. Tang, Y. Shi, H. Hu, Y. Cheng, C. Zhu, *Org. Lett.* **2013**, *15*, 4062 – 4065.

[12] For recent examples of enantioselective catalytic Povarov reaction, see: a) V. V. Kouznetsov, *Tetrahedron* **2009**, *65*, 2721 – 2750; b) G. Masson, C. Lalli, M. Benohoud, G. Dagousset, *Chem. Soc. Rev.* **2013**, *42*, 902 – 923; c) X. Jiang, R. Wang, *Chem. Rev.* **2013**, *113*, 5515 – 5546; d) H. Sundén, I. Ibrahem, L. Eriksson, A. Córdova, *Angew. Chem.* **2005**, *117*, 4955 – 4958; *Angew. Chem. Int. Ed.* **2005**, *44*, 4877 – 4880; e) H. Mandai, K. Mandai, M. L. Snapper, A. H. Hoveyda, *J. Am. Chem. Soc.* **2008**, *130*, 17961 – 17969; f) H. Liu, G. Dagousset, G. Masson, P. Retailleau, J. Zhu, *J. Am. Chem. Soc.* **2009**, *131*, 4598 – 4599; g) H. Xu, S. J. Zuend, M. G. Woll, Y. Tao, E. N. Jacobsen, *Science* **2010**, *327*, 986 – 990; h) M. Xie, X. Chen, Y. Zhu, B. Gao, L. Lin, X. Liu, X. Feng, *Angew. Chem.* **2010**, *122*, 3887 – 3890; *Angew. Chem. Int. Ed.* **2010**, *49*, 3799 – 3802; i) G. Bergonzini, L. Gramigna, A. Mazzanti, M. Fochi, L. Bernardi, A. Ricci, *Chem. Commun.* **2010**, *46*, 327 – 329; j) M. Xie, X. Liu, Y. Zhu, X. Zhao, Y. Xia, L. Lin, X. Feng, *Chem. Eur. J.* **2011**, *17*, 13800 – 13805; k) G. Dagousset, J. Zhu, G. Masson, *J. Am. Chem. Soc.* **2011**, *133*, 14804 – 14813; l) K. L. Jensen, G. Dickmeiss, B. S. Donslund, P. H. Poulsen, K. A. Jørgensen, *Org. Lett.* **2011**, *13*, 3678 – 3681; m) G. Dagousset, P. Retailleau, G. Masson, J. Zhu, *Chem. Eur. J.* **2012**, *18*, 5869 – 5873; n) F. Shi, G. J. Xing, Z. L. Tao, S. W. Luo, S. J. Tu, L. Z. Gong, *J. Org. Chem.* **2012**, *77*, 6970 – 6979; o) Z. Chen, B. Wang, Z. Wang, G. Zhu, J. Sun, *Angew. Chem.* **2013**, *125*, 2081 – 2085; *Angew. Chem. Int. Ed.* **2013**, *52*, 2027 – 2031; p) L. Caruana, M. Fochi, S. Ranieri, A. Mazzanti, L. Bernardi, *Chem. Commun.* **2013**, *49*, 880 – 882; q) D. Huang, F. Xu, T. Chen, Y. Wang, X. Lin, *RSC Adv.* **2013**, *3*, 573 – 578.

[13] CCDC 978219 (**4 d**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data request/cif.

Received: February 1, 2014
Published online on ■■ ▮▮, 0000

COMMUNICATION



Domino construction: An efficient organocatalytic one-pot domino Michael/intramolecular Povarov reaction has been developed to provide enantiomerically enriched spirooctahydroacridine-3,3′-oxindole derivatives containing five stereogenic centers in good to high yields with excellent diastereo- and enantioselectivities (see scheme). This strategy not only adds to the limited repertory of examples of asymmetric synthesis of chiral spirocyclohexane-oxindoles and octahydroacridines, but also demonstrates a one-pot consecutive synthesis with an ecological and economical protocol.

Organocatalysis

*H. Wu, Y.-M. Wang**

■■ – ■■

One-Pot Organocatalytic Enantioselective Michael/Povarov Domino Strategy for the Construction of Spirooctahydroacridine-3,3′-oxindole Scaffolds