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1,3-Dipolar cycloaddition of isatin *N,N'*-cyclic azomethine imines with α,β -unsaturated aldehydes catalyzed by DBU in water†

 Zhan-Yong Wang,^a Ting Yang,^b Rongxiang Chen,^a Xueji Ma,^a Huan Liu^a and Kai-Kai Wang^{a*}

A simple and green procedure was established by [3 + 3] cycloaddition reaction of isatin derived cyclic imine 1,3-dipoles with α,β -unsaturated aldehydes, giving the desired spiro heterocyclic oxindoles with aza-quaternary centers in good yields and diastereoselectivities. It should be noted that water can be employed as a suitable solvent for the improvement of diastereoselectivity.

Aza-quaternary centers are pivotal structural units, which exist in a variety of bioactive molecules and natural products.¹ In particular, spirooxindoles at the C3 position bearing a quaternarized N-heterocycle have attracted considerable attention because of their privileged structural units with attractive bioactivities,² for example, antimalarial,³ anti-HIV,⁴ antitumor,⁵ anticancer,⁶ inhibitor at the vanilloid receptor,⁷ antituberculosis,⁸ *etc.* (Fig. 1). Due to their remarkable biological importance, great efforts have been made to access spiro heterocyclic oxindoles with aza-quaternary centers. These methods include cycloaddition of imines,⁹ 1,3-dipolar cycloaddition,¹⁰ multicomponent cyclization reaction¹¹ and metal-catalyzed cycloaddition.¹² Among them, 1,3-dipolar cycloaddition is one of the most powerful tools for the construction of diverse spirooxindole fused N-heterocyclic scaffolds. Of these, *N,N'*-cyclic azomethine imines were widely studied for constructing various types of N-heterocyclic skeletons with spirooxindole as a stable and easily accessed 1,3-dipoles. In 2013, Wang's group reported their pioneering studies on Et₃N-catalyzed diastereoselective [3 + 3] annulation of *N,N'*-cyclic azomethine imines with isothiocyanatooxindoles to build 3,3'-triazinylspirooxindoles. In 2017, Wang *et al.* developed a new isatin-derived *N,N'*-cyclic azomethine imine 1,3-dipoles, and successfully applied in the [3 + 2] cycloaddition reaction for the construction of spirooxindoles bearing N-heterocycles (Scheme 1a).^{10c} Very recently, Jin's group reported a Cs₂CO₃-catalyzed [3 + 4] annulation of isatin-derived 1,3-dipole with aza-oQMs (Scheme 1b).^{10d} Furthermore, Moghaddam and coworkers developed an efficient method for the synthesis of pyridazine-fused spirooxindole scaffolds by 1,3-dipolar [3 + 3]

cycloadditions (Scheme 1c).^{10e} On the other hand, α,β -unsaturated aldehydes and their analogs as readily available substrates are also important building blocks in the synthesis of heterocyclic compounds which are widely applied in N-heterocyclic carbenes catalysis and other organocatalysis.¹³ Inspired by these great works and our continuing efforts towards green synthesis of spirooxindole skeletons. We envisioned a quick and efficient way of [3 + 3] cyclization reaction of α,β -unsaturated aldehydes with the new isatin *N,N'*-cyclic azomethine imine 1,3-dipoles *via* oxindole C3 umpolung. We wish to disclose herein that a green and practical access to synthesize pharmacologically interesting spirooxindole derivatives by involving isatin *N,N'*-cyclic azomethine imine 1,3-dipole as nucleophiles and various α,β -unsaturated aldehydes in water using DBU as organocatalyst. Our initial examinations were carried out using isatin derived cyclic imine 1,3-dipole **1a** (0.1 mmol) and α,β -unsaturated aldehyde **2a** (0.12 mmol) as the model substrates, the results of condition optimization are shown in Table 1. At the outset, without catalyst condition and with catalysts were investigated at room temperature in dichloromethane (DCM)

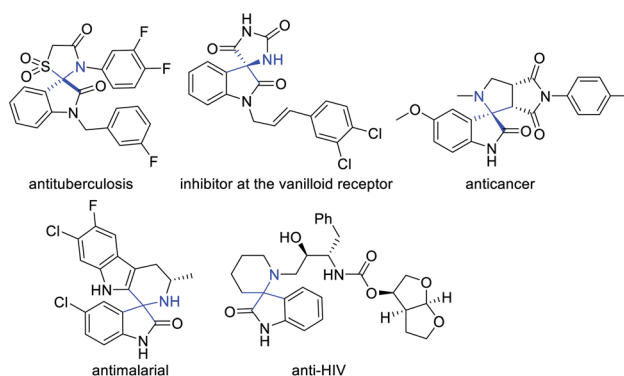


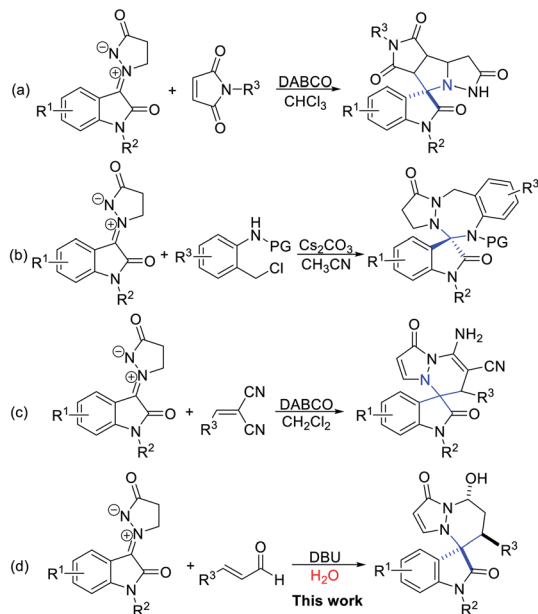
Fig. 1 Selected bioactive products of C3-spirooxindoles with aza-quaternary centers.

^aCollege of Chemistry and Chemical Engineering, Xinxiang University, Xinxiang 453003, P. R. China. E-mail: zhanyongw@126.com

^bMedical College, Xinxiang University, Xinxiang 453003, P. R. China

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Scheme 1 Isatin-derived N,N' -cyclic azomethine imine 1,3-dipoles participated in the construction of N -heterocyclic skeletons with $C3$ -spirooxindole.

Table 1 Optimization of the reaction conditions^a

Entry	Catalyst	Solvent	Time (h)	Yield ^b (%)	3a : 4a ^c
1	—	DCM	24	—	—
2	DABCO	DCM	24	Trace	—
3	DMAP	DCM	24	Trace	—
4	NEt ₃	DCM	3	25	1 : 3.4
5	DIPEA	DCM	24	Trace	—
6	DBU	DCM	0.1	75	1.7 : 1
7	Cs ₂ CO ₃	DCM	1	34	1 : 2.4
8	KOBu ^t	DCM	0.1	25	1 : 2.4
9	PPh ₃	DCM	24	Trace	—
10	Pyrrrolidine	DCM	24	59	1.6 : 1
11 ^d	DBU	DCM	24	61	1.8 : 1
12	DBU	Toluene	0.2	75	1.3 : 1
13	DBU	CH ₃ CN	0.1	20	2.3 : 1
14	DBU	THF	0.1	85	1.2 : 1
15	DBU	CHCl ₃	0.1	86	1.7 : 1
16 ^e	DBU	CHCl ₃	0.1	86	1.5 : 1
17	DBU	EtOH	24	62	1.8 : 1
18	Na ₂ CO ₃	EtOH	24	46	1 : 1.6
19	DBU	H ₂ O	24	61	8 : 1

^a Otherwise specified, all reactions were carried out using **1a** (0.1 mmol), **2a** (0.12 mmol), catalyst (0.1 mmol), solvent (1 ml). ^b Isolated yields of diastereoisomeric mixture. ^c Determined by ¹H NMR. ^d Catalyst (0.01 mmol). ^e Performed at reflux.

(Table 1, entries 1–10). The results show that catalyst had a significant effect on the yields. However, it has negligible effect on the diastereoselectivities. Organic bases, such as DABCO, DMAP, Et₃N, DIPEA (N,N -diisopropylethylamine), DBU, were compared and found that DBU could improve the yield obviously with 75% yield (Table 1, entry 6 vs. entries 1–5). While the inorganic bases were used, such as Cs₂CO₃, KOBu^t, failed to improve the reaction yields (Table 1, entries 7, 8). Other catalysts were also tested, but no better results were found (Table 1, entries 9, 10). When the catalyst loading was reduced to 10 mol%, the yield decreased with increasing the reaction time (Table 1, entry 11). Subsequently, a series of solvents were further investigated (Table 1, entries 12–

Table 2 The scope of the [3 + 3] annulation^{a,b,c}

3a	3b	3c
61%, dr = 8:1	80%, dr = 8:1	67%, dr = 5:1
3d	3e	3f
77%, dr = 9:1	40%, dr = 8:1	73%, dr = 15:1
3g	3h	3i
40%, dr > 20:1	58%, dr = 10:1	77%, dr = 8:1
3j	3k	3l
52%, dr = 10:1	52%, dr = 4:1	48%, dr > 20:1
3m	3n	3o
35%, dr > 20:1	61%, dr > 20:1	45%, dr > 20:1

^a All reactions were carried out using **1** (0.1 mmol), **2** (0.12 mmol), DBU (1.0 equiv.) in water (1.0 ml) at room temperature. ^b Isolated yields were diastereoisomeric mixture. ^c dr was determined by ¹H NMR in the crude products.



17). Solvents such as THF and CHCl_3 slightly improved the yields but no positive results were obtained for the diastereoselectivities (Table 1, entries 14, 15). A higher reaction temperature gave no better result (Table 1, entry 16). When DBU or Na_2CO_3 was used in ethanol also gave no satisfactory results (Table 1, entries 17, 18). With the hope of further improving diastereoselectivity, water was chosen as the solvent, the diastereoselectivity was significantly improved but the yield was decreased to 61% (Table 1, entry 19). Finally the optimum process conditions were carried out as follows: **1a/2a/DBU** = 1.0 : 1.2 : 1.0 molar ratio, in water at room temperature (Table 1, entry 19).

Under the optimal reaction conditions, the generality of this reaction was next investigated. As can be seen from Table 2, all reactions proceeded well to give the desired products **3** in moderate to good yields with good to high diastereoselectivities under identical conditions. The scope of isatin derivated cyclic imine 1,3-dipoles **1** were examined under the optimal reaction conditions, both N-Bn **1a** and N-Me **1e** substituted isatin derivated cyclic imine 1,3-dipoles could proceed smoothly and gave the desired products with moderate results (**3a** and **3e**). The 5-substituted electron-withdrawing groups on the aromatic ring of isatin derivated cyclic imine 1,3-dipoles **1** gave better yields compared with the electron-donating counterparts (**3b** vs. **3c**, and **3f** vs. **3g**). Subsequently, the electronic characteristics of α,β -unsaturated aldehydes **2** were studied, while both electron-donating (**3j**, **3k** and **3l**) and mildly electron-withdrawing groups (**3d**, **3m**) on phenyl ring had only a slight impact on yields and diastereoselectivities. Reaction involving heteroaryl aldehyde such as 2-furanacrolein **2i** also gave product **3i** in 77% yield with high diastereoselectivity (8 : 1 dr). Sterically hindered substituent on α,β -unsaturated aldehyde **2o** had little influence on the yield and diastereoselectivity.

Based on our results and previous studies, a plausible catalytic cycle is proposed in Scheme 2. **1a** was promoted by a base

to form more stable intermediate **I**. After this, intermediate **I** underwent 1,4-Michael addition with α,β -unsaturated aldehyde **2a** to form **II**. Next, keto-enol tautomerism occurred to form intermediate **III**. To avoid the steric hindrance, the intermediate **III** attack preferentially to the Re-face of aldehyde, leading to the formation of the major product **3a**.

In conclusion, we have disclosed a novel metal-free DBU-catalyzed [3 + 3] cycloaddition reaction *via* C3 umpolung strategy of oxindole. Varieties of isatin derivated cyclic imine 1,3-dipoles and α,β -unsaturated aldehydes were compatible with this protocol under mild conditions, and afforded spiro heterocyclic oxindoles with aza-quaternary center in good yields with good to high diastereoselectivities. Notably, water as a green solvent had positive effect on the diastereoselectivities.

Conflicts of interest

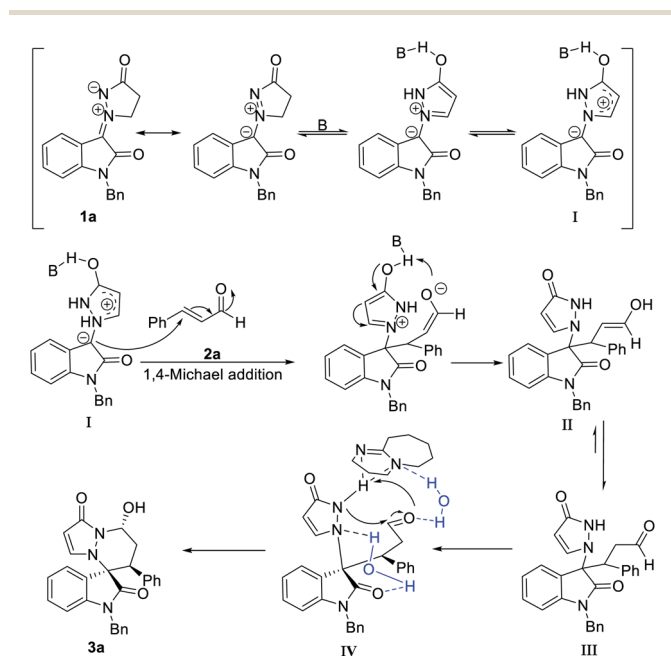
There are no conflicts to declare.

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Notes and references

- (a) J. Clayden, M. Donnard, J. Lefranc and D. J. Tetlow, Quaternary centres bearing nitrogen (α -tertiary amines) as products of molecular rearrangements, *Chem. Commun.*, 2011, **47**, 4624; (b) A. K. Mailyan, J. A. Eickhoff, A. S. Minakova, Z. Gu, P. Lu and A. Zakarian, Cutting-Edge and Time-Honored Strategies for Stereoselective Construction of C-N Bonds in Total Synthesis, *Chem. Rev.*, 2016, **116**, 4441; (c) A. Hager, N. Vrieling, D. Hager, J. Lefranc and D. Trauner, Synthetic approaches towards alkaloids bearing α -tertiary amines, *Nat. Prod. Rep.*, 2016, **33**, 491; (d) G. Dake, Recent Approaches to the Construction of 1-Azaspiro[4.5]decenes and Related 1-Azaspirocycles, *Tetrahedron*, 2006, **62**, 3467; (e) M. C. Jennings, K. P. C. Minbiole and W. M. Wuest, Quaternary Ammonium Compounds: An Antimicrobial Mainstay and Platform for Innovation to Address Bacterial Resistance, *ACS Infect. Dis.*, 2015, **1**, 288; (f) B. Trost, J. Tracy and T. Saget, Direct catalytic enantioselective amination of ketones for the formation of tri- and tetrasubstituted stereocenters, *Chem. Sci.*, 2018, **9**, 2975; (g) C. J. Pierce, M. Nguyen and C. H. Larsen, Copper/titanium catalysis forms fully substituted carbon centers from the direct coupling of acyclic ketones, amines, and alkynes, *Angew. Chem., Int. Ed.*, 2012, **51**, 12289.
- (a) R. Dalpozzo, G. Bartoli and G. Bencivenni, Recent advances in organocatalytic methods for the synthesis of disubstituted 2- and 3-indolinones, *Chem. Soc. Rev.*, 2012, **41**, 7247; (b) J. Bariwal, L. G. Voskressensky and E. V. Van der Eycken, Recent advances in spirocyclization of indole derivatives, *Chem. Soc. Rev.*, 2018, **47**, 3831; (c) Q. Zhao,



Scheme 2 A plausible catalytic cycle.



- C. Peng, H. Huang, S.-J. Liu, Y.-J. Zhong, W. Huang, G. He and B. Han, Asymmetric synthesis of tetrahydroisoquinoline-fused spirooxindoles as Ras-GTP inhibitors that inhibit colon adenocarcinoma cell proliferation and invasion, *Chem. Commun.*, 2018, **54**, 8359; (d) J. P. MacDonald, J. J. Badillo, G. E. Arevalo, A. Silva-Garcia and A. K. Franz, Catalytic stereoselective synthesis of diverse oxindoles and spirooxindoles from isatins, *ACS Comb. Sci.*, 2012, **14**, 285; (e) N. Ye, H. Chen, E. A. Wold, P.-Y. Shi and J. Zhou, Therapeutic potential of spirooxindoles as antiviral agents, *ACS Infect. Dis.*, 2016, **2**, 382; (f) N. R. Ball-Jones, J. J. Badillo and A. K. Franz, Strategies for the enantioselective synthesis of spirooxindoles, *Org. Biomol. Chem.*, 2012, **10**, 5165.
- 3 (a) M. Rottmann, C. McNamara, B. K. Yeung, M. C. Lee, B. Zou, B. Russell, P. Seitz, D. M. Plouffe, N. V. Dharia and J. Tan, Spiroindolones, a potent compound class for the treatment of malaria, *Science*, 2010, **329**, 1175; (b) B. K. Yeung, B. Zou, M. Rottmann, S. B. Lakshminarayana, S. H. Ang, S. Y. Leong, J. Tan, J. Wong, S. Keller-Maerki and C. Fischli, Spirotetrahydro β -Carbolines (Spiroindolones): A New Class of Potent and Orally Efficacious Compounds for the Treatment of Malaria, *J. Med. Chem.*, 2010, **53**, 5155.
- 4 (a) A. K. Ghosh, G. Schiltz, R. S. Perali, S. Leshchenko, S. Kay, D. E. Walters, Y. Koh, K. Maeda and H. Mitsuya, Design and synthesis of novel HIV-1 protease inhibitors incorporating oxyindoles as the P2'-ligands, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 1869; (b) G. Kumari, M. Modi, S. K. Gupta and R. K. Singh, ChemInform Abstract: Rhodium(II) Acetate-Catalyzed Stereoselective Synthesis, SAR and anti-HIV Activity of Novel Oxindoles Bearing Cyclopropane Ring, *Eur. J. Med. Chem.*, 2011, **46**, 1181.
- 5 R. F. George, N. S. M. Ismail, J. Stawinski and A. S. Girgis, Design, synthesis and QSAR studies of dispiroindole derivatives as new antiproliferative agents, *Eur. J. Med. Chem.*, 2013, **68**, 339.
- 6 (a) Y. Arun, G. Bhaskar, C. Balachandran, S. Ignacimuthu and P. T. Perumal, Facile one-pot synthesis of novel dispirooxindole-pyrrolidine derivatives and their antimicrobial and anticancer activity against A549 human lung adenocarcinoma cancer cell line, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 1839; (b) A. Czarna, B. Beck, S. Srivastava, G. M. Popowicz, S. Wolf, Y. Huang, M. Bista, T. A. Holak and A. Dömling, Robust Generation of Lead Compounds for Protein-Protein Interactions by Computational and MCR Chemistry: p53/Hdm2 Antagonists, *Angew. Chem., Int. Ed.*, 2010, **49**, 5352.
- 7 K. Ding, Y. Lu, Z. Nikolovska-Coleska, G. Wang, S. Qiu, S. Shangary, W. Gao, D. Qin, J. Stuckey and K. Krajewski, Structure-based design of spiro-oxindoles as potent, specific small-molecule inhibitors of the MDM2-p53 interaction, *J. Med. Chem.*, 2006, **49**, 3432.
- 8 V. V. Vintonyak, K. Warburg, H. Kruse, S. Grimme, K. Hübel, D. Rauh and H. Waldmann, Identification of Thiazolidinones Spiro-Fused to Indolin-2-ones as Potent and Selective Inhibitors of the Mycobacterium tuberculosis Protein Tyrosine Phosphatase B, *Angew. Chem., Int. Ed.*, 2010, **49**, 5902.
- 9 (a) M.-X. Zhao, L. Jing, H. Zhou and M. Shi, Cinchona alkaloid thiourea mediated asymmetric Mannich reaction of isocyanacetates with isatin-derived ketimines and subsequent cyclization: enantioselective synthesis of spirooxindole imidazolines, *RSC Adv.*, 2015, **5**, 75648; (b) Y. Zhu, Y. Li, Q. Meng and X. Li, An organocatalytic enantioselective vinylogous Mannich reaction of α,α -dicyanoolefins with isatin N-Boc ketimines, *Org. Chem. Front.*, 2016, **3**, 709; (c) Y.-M. Wang, H.-H. Zhang, C. Li, T. Fan and F. Shi, Catalytic asymmetric chemoselective 1,3-dipolar cycloadditions of an azomethine ylide with isatin-derived imines: diastereo- and enantioselective construction of a spiro[imidazolidine-2,3'-oxindole] framework, *Chem. Commun.*, 2016, **52**, 1804; (d) B. Li, F. Gao, X. Feng, M. Sun, Y. Guo, D. Wen, Y. Deng, J. Huang, K. Wang and W. Yan, Highly efficient enantioselective synthesis of bispiro [benzofuran-oxindole-pyrrolidine]s through organocatalytic cycloaddition, *Org. Chem. Front.*, 2019, **6**, 1567; (e) M.-C. Yang, C. Peng, H. Huang, L. Yang, X.-H. He, W. Huang, H.-L. Cui, G. He and B. Han, Organocatalytic Asymmetric Synthesis of Spiro-oxindole Piperidine Derivatives That Reduce Cancer Cell Proliferation by Inhibiting MDM2-p53 Interaction, *Org. Lett.*, 2017, **19**, 6752.
- 10 (a) P. Saraswat, G. Jeyabalan, M. Z. Hassan, M. U. Rahman and N. K. Nyola, A Review of Synthesis and Various Biological Activities of Spiro Heterocyclic Compounds Comprising Oxindole and Pyrrolidine Moieties, *Synth. Commun.*, 2016, **46**, 1643; (b) G. Zhu, W. Sun, C. Wu, G. Li, L. Hong and R. Wang, Base-catalyzed diastereoselective [3+3] annulation of 3-isothiocyanatooxindoles and azomethine imines, *Org. Lett.*, 2013, **15**, 4988; (c) X. Wang, P. Yang, Y. Zhang, C.-Z. Tang, F. Tian, L. Peng and L.-X. Wang, Isatin N,N'-Cyclic Azomethine Imine 1,3-Dipole and Abnormal [3+2]-Cycloaddition with Maleimide in the Presence of 1,4-Diazabicyclo [2.2.2] octane, *Org. Lett.*, 2017, **19**, 646; (d) Q. Jin, J. Zhang, C. Jiang, D. Zhang, M. Gao and S. Hu, Self [3+4] cycloadditions of isatin N,N'-cyclic azomethine imine 1,3-dipole with N-(o-chloromethyl) aryl amides, *J. Org. Chem.*, 2018, **83**, 8410; (e) F. M. Moghaddam, M. Eslami, A. Siahpoosh and G. Hoda, Diastereoselective construction of a functionalized dihydro-pyridazine-based spirooxindole scaffold via C-3 umpolung of isatin N,N'-cyclic azomethine imine, *New J. Chem.*, 2019, **43**, 10318; (f) S. Hu, J. Zhang and Q. Jin, DMAP-catalyzed alkylation of isatin N,N'-cyclic azomethine imine 1,3-dipoles with Morita-Baylis-Hillman carbonates, *New J. Chem.*, 2018, **42**, 7025; (g) C. Yin, L. Lin, D. Zhang, J. Feng, X. Liu and X. Feng, Asymmetric [3+2] Cycloaddition of Methyleneindolinones with N,N'-Cyclic Azomethine Imines Catalyzed by a N,N'-Dioxide-Mg(OTf)₂ Complex, *J. Org. Chem.*, 2015, **80**, 9691.
- 11 (a) J. Yue, S. Chen, X. Zuo, X.-L. Liu, S.-W. Xu and Y. Zhou, Diversity-oriented one-pot multicomponent synthesis of chromanone-based 3,3'-pyrrolidinyl-spirooxindoles via a 1,3-dipolar cycloaddition reaction, *Tetrahedron Lett.*,



- 2019, **60**, 137; (b) N. Zohreh and A. Alizadeh, Uncatalyzed one-pot synthesis of highly substituted pyridazines and pyrazoline-spirooxindoles via domino SN/condensation/aza-ene addition cyclization reaction sequence, *ACS Comb. Sci.*, 2013, **15**, 278; (c) Z. Tang, Z. Liu, Y. An, R. Jiang, X. Zhang, C. Li, X. Jia and J. Li, Isocyanide-based multicomponent bicyclization with substituted allenoate and isatin: synthesis of unusual spirooxindole containing [5.5]-fused heterocycle, *J. Org. Chem.*, 2016, **81**, 9158.
- 12 (a) H.-W. Zhao, L.-R. Wang, J.-M. Guo, W.-Q. Ding, X.-Q. Song, H.-H. Wu, Z. Tang, X.-Z. Fan and X.-F. Bi, Formal [5+3] Cycloaddition of Vinyl ethylene Carbonates with Isatin-Based α -(Trifluoromethyl) imines for Diastereoselective Synthesis of Medium-Heterocycle-Fused Spirooxindoles, *Adv. Synth. Catal.*, 2019, **361**, 4761; (b) H.-W. Zhao, B. Li, H.-L. Pang, T. Tian, X.-Q. Chen, X.-Q. Song, W. Meng, Z. Yang, Y.-D. Zhao and Y.-Y. Liu, Diastereoselective 1,3-Dipolar Cycloadditions of N,N'-Cyclic Azomethine Imines with Iminooxindoles for Access to Oxindole Spiro-N,N-bicyclic Heterocycles, *Org. Lett.*, 2016, **18**, 848.
- 13 (a) X. Chen, Q. Liu, P. Chauhan and D. Enders, N-Heterocyclic Carbene Catalysis via Azolium Dienolates: An Efficient Strategy for Remote Enantioselective Functionalizations, *Angew. Chem., Int. Ed.*, 2018, **57**, 3862; (b) L.-L. Zhao, X.-S. Li, L.-L. Cao, R. Zhang, X.-Q. Shi and J. Qi, Access to dihydropyridinones and spirooxindoles: application of N-heterocyclic carbene-catalyzed [3+3] annulation of enals and oxindole-derived enals with 2-aminoacrylates, *Chem. Commun.*, 2017, **53**, 5985; (c) Y. Reddi and R. B. Sunoj, Origin of Stereoselectivity in Cooperative Asymmetric Catalysis Involving N-Heterocyclic Carbenes and Lewis Acids toward the Synthesis of Spirooxindole Lactone, *ACS Catal.*, 2017, **7**, 530; (d) Z.-Y. Wang, T. Yang, K.-K. Wang, R. Chen, M. Liu and H. Liu, Oxidative N-heterocyclic carbene-catalyzed [3+3] annulation reaction of enals with benzofuran-3-ones: efficient access to benzofuran-fused δ -lactones, *Org. Chem. Front.*, 2020, **7**, 1011; (e) Y. Liu, X. Zhang, R. Zeng, Y. Zhang, Q.-S. Dai, H.-J. Leng, X.-J. Gou and J.-L. Li, Recent Advances in the Synthesis of Spiroheterocycles via N-Heterocyclic Carbene Organocatalysis, *Molecules*, 2017, **22**, 1882; (f) Y. Li, C. Barløse, J. Jørgensen, B. D. Carlsen and K. A. Jørgensen, Asymmetric Catalytic Aza-Diels-Alder/Ring-Closing Cascade Reaction Forming Bicyclic Azaheterocycles by Trienamine Catalysis, *Chem.-Eur. J.*, 2017, **23**, 38.

