PAPER

Check for updates

A C$_1$-symmetric *N*-heterocyclic carbene catalysed oxidative spiroannulation of isatin-derived enals: highly enantioselective synthesis of spirooxindole δ-lactones†

Jun-Bing Lin,‡ Xi-Na Cheng,‡ Xiao-Dong Tian, Guo-Qiang Xu, Yong-Chun Luo [iD] and Peng-Fei Xu [iD] *

A C$_1$-symmetric *N*-heterocyclic carbene (NHC)-catalysed activation of isatin-derived enals under oxidative conditions was achieved. The *in situ* generated α,β-unsaturated acyl azolium species was efficiently trapped by 1,3-dicarbonyl compounds *via* a Michael addition/spiroannualtion cascade, delivering a series of synthetically important spirooxindole δ-lactones with up to 96% enantioselectivity.

Spirooxindoles are present in a wide variety of natural products and biologically active molecules.[1] Polycyclic spirooxindole scaffold with multiple stereocenters are particularly intriguing targets in organic synthesis owing to their structural complexity and potential pharmaceutical value.[2] For example, the spirooxindole δ-lactone constitutes the backbone of many natural products, such as trigolutes A–C (Fig. 1a).[3] However, the catalytic asymmetric synthesis of this privileged scaffold in a highly stereocontrolled fashion is still a challenging task, and very limited protocols were established to this end.[3c,4] In this regard, the development of new, practical and efficient strategy for the highly enantioselective synthesis of spirooxindole δ-lactone scaffold is still in great demand.

Over the past decades, the ability of chiral *N*-heterocyclic carbenes (NHCs)[5] toward activation of aldehyde and activated carboxylic acid derivatives through formation of transient acyl anion,[6] enolate,[7] homoenolate[8] and acyl azolium[9] intermediates was well-investigated for enantioselective C–C, C–O and C–N bond formations. Within the context, the oxidative NHC catalysis strategy enabled generation of acyl azolium from aldehydes *via in situ* oxidation, which provided new opportunities for reaction design and selectivity control, thus remarkably extending the scope of NHC catalysis.[10,11] However, despite fruitful achievements in the oxidative annulation of simple unsaturated aldehydes,[12] oxidative NHC catalysed addition/cyclization of β,β-disubstituted enals, such as isatin-derived enals, was a very attractive yet challenging topic with the

concomitant formation of a congested quaternary center.[13] Recently, we disclosed that C$_1$-symmetric biaryl-saturated imidazolium catalyst was a superior NHC for asymmetric oxidative annulation of α-aryl-substituted α,β-unsaturated aldehydes.[14] With our ongoing interest in the development of practical methods toward asymmetric synthesis of chiral spirooxindole scaffolds,[4b,15] we attempted to explore the catalytic performance of C$_1$-symmetric NHC in oxidative activation of isatin-derived enals.[16] The *in situ* generated isatin-derived α,β-unsaturated acyl azolium could be trapped by readily available 1,3-dicarbonyl compounds *via* a spiro-quaternary carbon-forming Michael addition/cyclization process, eventually delivering synthetically intriguing chiral spirooxindole δ-lactones (Fig. 1b).[17]

Our investigation started with the reaction of isatin-derived α,β-unsaturated aldehyde **1a** (a mixture of *E* and *Z* isomer)

State Key Laboratory of Applied Organic Chemistry, College of Chemistry and Chemical Engineering, Lanzhou University, Lanzhou 730000, P. R. China. E-mail: xupf@lzu.edu.cn

† Electronic supplementary information (ESI) available: CCDC 1010784. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8ra02009d

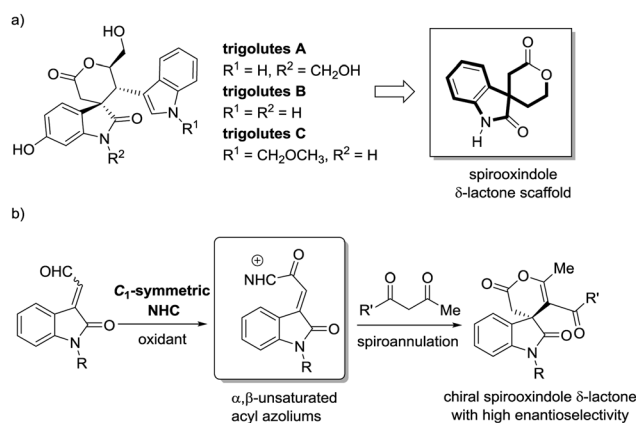‡ The two authors contributed equally to this work.

Fig. 1 (a) Examples of spirooxindole-containing natural products. (b) Assembly of spirooxindole δ-lactone scaffolds *via* C$_1$-symmetric NHC-catalysed spiroannulation (this work).

with 1,3-dicarbonyl compound **2a** under the catalysis of C$_1$-symmetric diaryl-saturated imidazolium catalysts **I–III**.[18] To our delight, the desired oxidative annulation product **3a** and its regioisomer **3a'** (6 : 1 rr) were obtained in 23% yield and with high enantioselectivity (89% ee) when catalyst **I**/DBU combination were employed under the oxidation of 3,3′,5,5′-tetra-*tert*-butyldiphenoquinone in THF (Table 1, entry 1), while catalyst **II** and **III** gave a relatively higher stereoselectivity and regioselectivity (Table 1, entries 2 and 3). As a comparison, the catalytic activity of C$_2$-symmetric diaryl-saturated catalyst **IV**, triazolium catalysts **V** and **VI** was further examined, and inferior results with respect to reactivity and selectivity were observed (Table 1, entries 4–6). Then different bases including inorganic and organic bases were varied, and we found that DBU give better stereoselectivity and regioselectivity within a shorter time (Table 1, entries 7–12). Solvent screening revealed that toluene gave rise to a better yield (Table 1, entries 13–17). When the catalyst loading was reduced to 10%, the reaction yield was obviously decreased (Table 1, entry 18). For further investigation, we modulated the ratio of **1** and **2** to 1 : 1, and further improvement in yield was observed (Table 1, entry 19).

With the optimized reaction conditions in hand, the generality of the reaction was explored (Table 2, entries 1–20). A broad range of differently substituted 1,3-dione bearing electron-donating or electron-withdrawing substituents on *meta*- or *para*-position of aromatic rings were well tolerated, whereas the 1,3-dione with substituents on *ortho*-position of aromatic rings gave complex products as a result of steric hindrance. Although no pronounced electronic effect was observed, we discovered that substrates with the nitro group (**2e**, **2n**) gave lower yields and enantioselectivities (Table 2, entries 5 and 14), while substrates with the methyl group (**2g**, **2j**) gave lower regioselectivities but higher yields (Table 2, entries 7, 8 and 10). Heteroaryl-containing substrate (**2o**) also worked well to give the δ-lactone **3o** with excellent regioselectivity in moderate yield (52%) and high ee (83%) (Table 2, entry 15). Aliphatic 1,3-dione **2p** could participate in the oxidative reaction efficiently, giving

Table 1 Optimization of reaction conditions
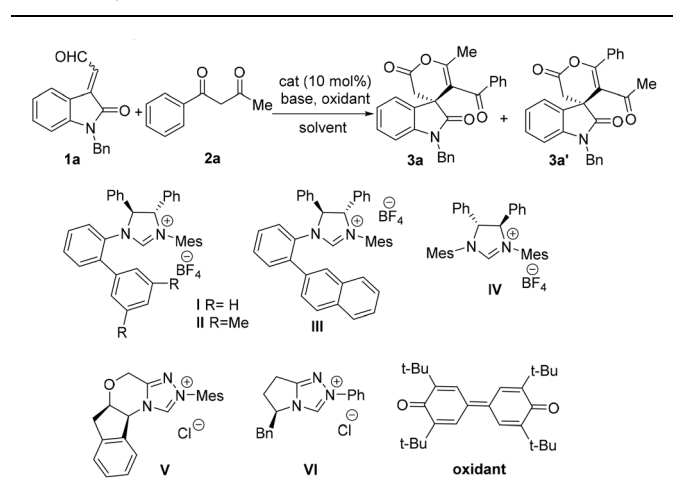
Entry[a]	Cat	Base	Solvent	Time	Yield[b] [%]	Rr[c]	ee[d] [%]
1	**I**	DBU	THF	1 h	23	6 : 1	89
2	**II**	DBU	THF	1 h	67	10 : 1	92
3	**III**	DBU	THF	1 h	65	7 : 1	92
4	**IV**	DBU	THF	4 h	64	8 : 1	39
5	**V**	DBU	THF	10 min	53	2 : 1	59
6	**VI**	DBU	THF	1 h	27	3 : 1	6
7	**II**	*t*-BuOK	THF	1 h	62	6 : 1	72
8	**II**	CsCO$_3$	THF	1 h	62	9 : 1	79
9	**II**	NaOAc	THF	3 h	55	5 : 1	50
10	**II**	DABCO	THF	10 h	52	5 : 1	89
11	**II**	DIPEA	THF	24 h	57	5 : 1	84
12	**II**	NEt$_3$	THF	24 h	40	6 : 1	77
13	**II**	DBU	Toluene	1 h	72	12 : 1	91
14	**II**	DBU	CH$_3$CN	1 h	14	nd	nd
15	**II**	DBU	Et$_2$O	7 h	40	7 : 1	79
16	**II**	DBU	Dioxane	24 h	25	4 : 1	93
17	**II**	DBU	DCM	1 h	49	11 : 1	65
18[e]	**II**	DBU	Toluene	1 h	33	9 : 1	91
19[f]	**II**	DBU	Toluene	1.5 h	77	12 : 1	94

[a] Unless otherwise mentioned, all reactions were performed using **1a** (0.1 mmol) and **2a** (0.2 mmol) in solvent (1.0 mL) in the presence of catalyst (20 mol%), base (20 mol%), and oxidant (0.2 mmol) at room temperature. [b] Combined yields of **3a** and **3a'**. [c] Rr refers to ratio of **3a** and **3a'**, which is determined by ^{1}H NMR analysis. [d] Determined by HPLC analysis on a chiral column. [e] 10 mol% catalyst was used. [f] 0.1 mmol **1a** and 0.1 mmol **2a** were used.

Table 2 Scope of the reaction

1a, R=Bn; **1b**, R=Me; **1c**, R=allyl; **1d**, R=*n*-Bu

Entry[a]	R^1/R^2 (**2**)	**3**	Yield[b] [%]	Rr[c]	Ee[d] [%]
1	Ph/Me (**2a**)	**3a**	77	12 : 1	94
2	4-BrC$_6$H$_4$/Me (**2b**)	**3b**	75	14 : 1	92
3	4-FC$_6$H$_4$/Me (**2c**)	**3c**	78	14 : 1	92
4	4-ClC$_6$H$_4$/Me (**2d**)	**3d**	69	17 : 1	93
5	4-NO$_2$C$_6$H$_4$/Me (**2e**)	**3e**	50	18 : 1	84
6	4-CF$_3$C$_6$H$_4$/Me (**2f**)	**3f**	65	14 : 1	90
7	4-MeC$_6$H$_4$/Me (**2g**)	**3g**	82	7 : 1	95
8	4-*t*-BuC$_6$H$_4$/Me (**2h**)	**3h**	74	5 : 1	94
9	3-MeOC$_6$H$_4$/Me (**2i**)	**3i**	79	12 : 1	94
10	3- MeC$_6$H$_4$/Me (**2j**)	**3j**	84	6 : 1	94
11	3-BrC$_6$H$_4$/Me (**2k**)	**3k**	69	16 : 1	92
12	3-ClC$_6$H$_4$/Me (**2l**)	**3l**	72	16 : 1	92
13	3-FC$_6$H$_4$/Me (**2m**)	**3m**	76	17 : 1	93
14	3-NO$_2$C$_6$H$_4$/Me (**2n**)	**3n**	45	19 : 1	83
15	2-Thienyl/Me (**2o**)	**3o**	52	>25 : 1	83
16	Me/Me (**2p**)	**3p**	58	—	90
17[e]	Ph/Me (**2a**)	**3q**	62	>20 : 1	94
18[f]	Ph/Me (**2a**)	**3r**	74	12 : 1	94
19[g]	Ph/Me (**2a**)	**3s**	52	8 : 1	94
20	Ph/Ph (**2q**)	**3t**	60	—	96

[a] all reactions were performed using **1a** (0.1 mmol) and **2** (0.1 mmol) in toluene (1.0 mL) in the presence of catalyst **B** (20 mol%), DBU (20 mol%), and oxidant (0.2 mmol) at room temperature. [b] Combined yields of **3** and **3'**. [c] Determined by ^{1}H NMR analysis. [d] Determined of the major isomer by HPLC analysis on a chiral column. [e] **1b** was used. [f] **1c** was used. [g] **1d** was used.
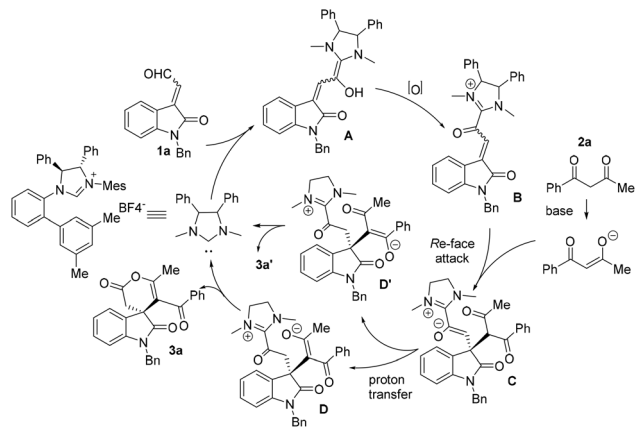
Scheme 1 Proposed catalytic cycle.

rise to the product in 58% yield and 90% ee within 10 minutes (Table 2, entry 16), while biaryl-substituted substrate **2q** give the corresponding product **3t** in 60% yield and 96% ee over 24 h (Table 2, entry 20). Further investigation revealed that this method was compatible with different *N*-substituted enals, affording the desired δ-lactone **3q-3s** in moderate yield with good regioselectivities and excellent enantioselectivities (Table 2, entries 17–19).

The absolute configuration of the product **3a** was assigned to be *S* by X-ray crystallographic analysis (Cu target, see ESI†).[19] Based on our experimental results and previous literature reports, a proposed catalytic cycle is shown in Scheme 1. The free NHC catalyst, derived from precatalyst by *in situ* deprotonation, could react with isatin-derived unsaturated aldehyde **1a**, giving rise to Breslow intermediate **A**, which could be converted to acyl azolium intermediate **B** through two-electron oxidation and deprotonation. Subsequent Re-face Michael attack of **2a**-derived enolate to species **B** along with the proton transfer sequentially produced intermediates **C** and **D**. Intramolecular cyclization of **D** gave the product **3a** and released the NHC catalyst to next catalytic cycle. Mechanistically, the formation of byproduct **3a′** arose from intramolecular annulation of intermediate **D′**, which was generated from Michael adduct **C** *via* undesired competing proton transfer step.[20]

Conclusions

In conclusion, we have developed a C_1-symmetric NHC catalyzed oxidative spiroannulation of isatin-derived enals. The *in situ* generated isatin-derived α,β-unsaturated acyl azolium species was efficiently trapped by 1,3-dicarbonyl compounds *via* a Michael addition/cyclization process. A series of synthetically intriguing spirooxindole δ-lactones was readily obtained in moderate to high yields with excellent enantioselectivities under mild conditions. Further application of the C_1-symmetric NHCs to novel and challenging transformations toward synthesis of synthetically or pharmaceutically valuable molecules are currently underway.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Notes and references

1 For selected reviews, see:(*a*) C. Marti and E. M. Carreira, *Eur. J. Org. Chem.*, 2003, 2209; (*b*) C. V. Galliford and K. A. Scheidt, *Angew. Chem., Int. Ed.*, 2007, **46**, 8748; (*c*) R. Dalpozzo, G. Bartoli and G. Bencivenni, *Chem. Soc. Rev.*, 2012, **41**, 7247; (*d*) N. R. Ball-Jones, J. J. Badillo and A. K. Franz, *Org. Biomol. Chem.*, 2012, **10**, 5165.

2 For selected examples, see:(*a*) X. H. Chen, Q. Wei, S. W. Luo, H. Xiao and L. Z. Gong, *J. Am. Chem. Soc.*, 2009, **131**, 13819; (*b*) A. P. Antonchick, C. Gerding-Reimers, M. Catarinella, M. Schürmann, H. Preut, S. Ziegler, D. Rauh and H. Waldmann, *Nat. Chem.*, 2010, **2**, 735; (*c*) B. Tan, N. R. Candeias and C. F. Barbas III, *Nat. Chem.*, 2011, **3**, 473; (*d*) Y. Liu, M. Nappi, E. Arceo, S. Vera and P. Melchiorre, *J. Am. Chem. Soc.*, 2011, **133**, 15212; (*e*) G. Zhan, M. L. Shi, Q. He, W. J. Lin, Q. Ouyang, W. Du and Y. C. Chen, *Angew. Chem., Int. Ed.*, 2016, **55**, 2147; (*f*) X. Han, W. L. Chan, W. Yao, Y. Wang and Y. Lu, *Angew. Chem., Int. Ed.*, 2016, **55**, 6492.

3 (*a*) Y. G. Chen, J. C. Wu, G. Y. Chen, C. R. Han and X. P. Song, *Chem. Biodiversity*, 2011, **8**, 1958; (*b*) S. S. Ma, W. L. Mei, Z. K. Guo, S. B. Liu, Y. X. Zhao, D. L. Yang, Y. B. Zeng, B. Jiang and H. F. Dai, *Org. Lett.*, 2013, **15**, 1492; (*c*) J. Z. Huang, C. L. Zhang, Y. F. Zhu, L. L. Li, D. F. Chen, Z. Y. Han and L. Z. Gong, *Chem.–Eur. J.*, 2015, **21**, 8389.

4 (*a*) D. Du, Z. Y. Hu, J. L. Jin, Y. Y. Lu, W. F. Tang, B. Wang and T. Lu, *Org. Lett.*, 2012, **14**, 1274; (*b*) S. Zhao, J. B. Lin, Y. Y. Zhao, Y. M. Liang and P. F. Xu, *Org. Lett.*, 2014, **16**, 1802.

5 For selected reviews, see:(*a*) D. Enders, O. Niemeier and A. Henseler, *Chem. Rev.*, 2007, **107**, 5606; (*b*) V. Nair, S. Vellalath and B. P. Babu, *Chem. Soc. Rev.*, 2008, **37**, 2691; (*c*) A. Grossmann and D. Enders, *Angew. Chem., Int. Ed.*, 2012, **51**, 314; (*d*) J. Izquierdo, G. E. Hutson, D. T. Cohen and K. A. Scheidt, *Angew. Chem., Int. Ed.*, 2012, **51**, 11686; (*e*) X. Bugaut and F. Glorius, *Chem. Soc. Rev.*, 2012, **41**, 3511; (*f*) S. J. Ryan, L. Candish and D. W. Lupton, *Chem. Soc. Rev.*, 2013, **42**, 4906; (*g*) M. N. Hopkinson, C. Richter, M. Schedler and F. Glorius, *Nature*, 2014, **510**, 485; (*h*) J. Mahatthananchai and J. W. Bode, *Acc. Chem. Res.*, 2014, **47**, 696; (*i*) D. M. Flanigan, F. Romanov-Michailidis, N. A. White and T. Rovis, *Chem. Rev.*, 2015, **115**, 9307; (*j*) Y. Wang, D. Wei and W. Zhang, *ChemCatChem*, 2018, **10**, 338; (*k*) X. Y. Chen, Q. Liu, P. Chauhan and D. Enders, *Angew. Chem., Int. Ed.*, 2018, **57**, 3862.

6 (*a*) T. Ukai, S. Tanaka and S. Dokawa, *J. Pharm. Soc. Jpn.*, 1943, **63**, 296; (*b*) D. Enders, K. Breuer, J. Runsink and

J. H. Teles, *Helv. Chim. Acta*, 1996, **79**, 1899; (*c*) D. Enders and U. Kallfass, *Angew. Chem., Int. Ed.*, 2002, **41**, 1743; (*d*) M. S. Kerr, J. R. Alaniz and T. Rovis, *J. Am. Chem. Soc.*, 2002, **124**, 10298; (*e*) Y. Hachisu, J. W. Bode and K. Suzuki, *J. Am. Chem. Soc.*, 2003, **125**, 8432; (*f*) H. Y. Zhao, F. W. Foss and R. Breslow, *J. Am. Chem. Soc.*, 2008, **130**, 12590; (*g*) Q. Liu, S. Perreault and T. Rovis, *J. Am. Chem. Soc.*, 2008, **130**, 14066; (*h*) S. P. Lathrop and T. Rovis, *J. Am. Chem. Soc.*, 2009, **131**, 13628; (*i*) A. T. Biju, N. E. Wurz and F. Glorius, *J. Am. Chem. Soc.*, 2010, **132**, 5970; (*j*) T. Jousseaume, N. E. Wurz and F. Glorius, *Angew. Chem., Int. Ed.*, 2011, **50**, 1410; (*k*) X. Fang, X. Chen, H. Lv and Y. R. Chi, *Angew. Chem., Int. Ed.*, 2011, **50**, 11782; (*l*) C. A. Rose, S. Gundala, C. L. Fagan, J. F. Franz, S. J. Connon and K. Zeitler, *Chem. Sci.*, 2012, **3**, 735; (*m*) M. Schedler, D. S. Wang and F. Glorius, *Angew. Chem., Int. Ed.*, 2013, **52**, 2585.

7 (*a*) M. He, J. R. Struble and J. W. Bode, *J. Am. Chem. Soc.*, 2006, **128**, 8418; (*b*) M. He, G. J. Uc and J. W. Bode, *J. Am. Chem. Soc.*, 2006, **128**, 15088; (*c*) J. Kaeobamrung, M. C. Kozlowski and J. W. Bode, *Proc. Natl. Acad. Sci. U. S. A.*, 2010, **107**, 20661; (*d*) L. Hao, Y. Du, H. Lv, X. Chen, H. Jiang, Y. Shao and Y. R. Chi, *Org. Lett.*, 2012, **14**, 2154; (*e*) L. Wang, Q. Ni, M. Blgmel, T. Shu, G. Raabe and D. Enders, *Chem.–Eur. J.*, 2015, **21**, 8033.

8 (*a*) C. Burstein and F. Glorius, *Angew. Chem., Int. Ed.*, 2004, **43**, 6205; (*b*) S. S. Sohn, E. L. Rosen and J. W. Bode, *J. Am. Chem. Soc.*, 2004, **126**, 14370; (*c*) C. Guo, M. Schedler, C. G. Daniliuc and F. Glorius, *Angew. Chem., Int. Ed.*, 2014, **53**, 10232; (*d*) C. Guo, B. Sahoo, C. G. Daniliuc and F. Glorius, *J. Am. Chem. Soc.*, 2014, **136**, 17402; (*e*) C. Guo, M. Fleige, D. Janssen-Müller, C. G. Daniliuc and F. Glorius, *Nat. Chem.*, 2015, **7**, 842; (*f*) L. Wang, S. Li, M. Blümel, R. Puttreddy, A. Peuronen, K. Rissanen and D. Ender, *Angew. Chem., Int. Ed.*, 2017, **56**, 8516.

9 (*a*) S. J. Ryan, L. Candish and D. W. Lupton, *J. Am. Chem. Soc.*, 2009, **131**, 14176; (*b*) F. G. Sun, L. H. Sun and S. Ye, *Adv. Synth. Catal.*, 2011, **353**, 3134; (*c*) J. Cheng, Z. Huang and Y. R. Chi, *Angew. Chem., Int. Ed.*, 2013, **52**, 8592.

10 For reviews on oxidative NHC catalysis, see:(*a*) C. E. I. Knappke, A. Imami and A. J. Wangelin, *ChemCatChem*, 2012, **4**, 937; (*b*) S. D. Sarkar, A. Biswas, R. C. Samanta and A. Studer, *Chem.–Eur. J.*, 2013, **19**, 4664.

11 (*a*) J. Guin, S. De Sarkar, S. Grimme and A. Studer, *Angew. Chem., Int. Ed.*, 2008, **47**, 8727; (*b*) B. E. Maki, A. Chan, E. M. Phillips and K. A. Scheidt, *Org. Lett.*, 2007, **9**, 371; (*c*) S. D. Sarkar, S. Grimme and A. Studer, *J. Am. Chem. Soc.*, 2010, **132**, 1190; (*d*) S. D. Sarkar and A. Studer, *Org. Lett.*, 2010, **12**, 1992; (*e*) X. Zhao, K. E. Ruhl and T. Rovis, *Angew. Chem., Int. Ed.*, 2012, **51**, 12330; (*f*) J. Mo, X. Chen and Y. R. Chi, *J. Am. Chem. Soc.*, 2012, **134**, 8810; (*g*) E. G. Delany, C. L. Fagan, S. Gundala, A. Mari, T. Broja, K. Zeitler and S. J. Connon, *Chem. Commun.*, 2013, **49**,

6510; (*h*) J. Mo, L. Shen and Y. R. Chi, *Angew. Chem., Int. Ed.*, 2013, **52**, 8588; (*i*) H. Inoue and K. Higashiura, *J. Chem. Soc., Chem. Commun.*, 1980, 549.

12 For selected examples, see:(*a*) S. D. Sarkar and A. Studer, *Angew. Chem., Int. Ed.*, 2010, **49**, 9266; (*b*) A. Biswas, S. D. Sarkar, R. Fröhlich and A. Studer, *Org. Lett.*, 2011, **13**, 4966; (*c*) Z. Q. Rong, M. Q. Jia and S. L. You, *Org. Lett.*, 2011, **13**, 4080; (*d*) Z. Q. Zhu, X. L. Zheng, N. F. Jiang, X. L. Wan and J. C. Xiao, *Chem. Commun.*, 2011, **47**, 8670; (*e*) A. G. Kravina, J. Mahatthananchai and J. W. Bode, *Angew. Chem., Int. Ed.*, 2012, **51**, 9433; (*f*) S. Bera, R. C. Samanta, C. G. Daniliuc and A. Studer, *Angew. Chem., Int. Ed.*, 2014, **53**, 9622; (*g*) X. X. Wu, B. Liu, Y. X. Zhang, M. Jeret, H. L. Wang, P. C. Zheng, S. Yang, B. A. Song and Y. R. Chi, *Angew. Chem., Int. Ed.*, 2016, **55**, 12280.

13 For one report concerning trapping isatin-derived unsaturated acyl azolium by performed enamine, see:(*a*) D. Xie, L. Yang, Y. Lin, Z. Zhang, D. Chen, X. Zeng and G. Zhong, *Org. Lett.*, 2015, **17**, 2318, For a racemic example, see: (*b*) L. L. Zhao, X. S. Li, L. L. Cao, R. Zhang, X. Q. Shi and J. Qi, *Chem. Commun.*, 2017, **53**, 5985.

14 H. Lu, J. Y. Liu, C. G. Li, J. B. Lin, Y. M. Liang and P. F. Xu, *Chem. Commun.*, 2015, **51**, 4473.

15 (*a*) Y. Wang, H. Lu and P. F. Xu, *Acc. Chem. Res.*, 2015, **48**, 1832; (*b*) T. P. Gao, J. B. Lin, X. Q. Hu and P. F. Xu, *Chem. Commun.*, 2014, **50**, 8934; (*c*) L. Tian, X. Q. Hu, Y. H. Li and P. F. Xu, *Chem. Commun.*, 2013, **49**, 7213; (*d*) Y. Y. Zhao, S. Zhao, J. K. Xie, X. Q. Hu and P. F. Xu, *J. Org. Chem.*, 2016, **81**, 10532.

16 (*a*) R. Liu and J. Zhang, *Org. Lett.*, 2013, **15**, 2266; (*b*) R. Liu and J. Zhang, *Chem.–Eur. J.*, 2013, **19**, 7319; (*c*) T. Mukaiyama, K. Ogata, I. Sato and Y. Hayashi, *Chem.– Eur. J.*, 2014, **20**, 13583.

17 For a racemic synthesis of this scaffold using isatin-derived 2-bromoenals, see:(*a*) J. Xu, W. Zhang, Y. Liu, S. Zhu, M. Liu, X. Hua, S. Chen, T. Lu and D. Du, *RSC Adv.*, 2016, **6**, 18601, For a catalytic asymmetric synthesis using isatin-derived unsaturated acids with moderate ees, see: (*b*) W. Zhang, J. Xu, J. Cao, C. Fang, J. Zhu, T. Lu and D. Du, *Tetrahedron*, 2017, **73**, 3249.

18 (*a*) K. P. Jang, G. E. Hutson, R. C. Johnston, E. O. McCusker, P. H. Y. Cheong and K. A. Scheidt, *J. Am. Chem. Soc.*, 2014, **136**, 76; (*b*) A. Lee and K. A. Scheidt, *Angew. Chem., Int. Ed.*, 2014, **53**, 7594.

19 CCDC 1010784 (**3a**).

20 With regard to the mechanism, the hemiacetal formation-Coates-Claisen rearrangement pathway proposed by Bode *et al.* cannot be ruled out at current stage, see: (*a*) J. Mahatthananchai, P. Zheng and Jeffrey W. Bode, *Angew. Chem., Int. Ed.*, 2011, **50**, 1673; (*b*) J. Mahatthananchai, J. Kaeobamrung and J. W. Bode, *ACS Catal.*, 2012, **2**, 494; (*c*) E. Lyngvi, J. W. Bode and F. Schoenebeck, *Chem. Sci.*, 2012, **3**, 2346.