Letter

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Enantioselective Assembly of Spirolactones through NHC-Catalyzed Remote γ-Carbon Addition of Enals with Isatins

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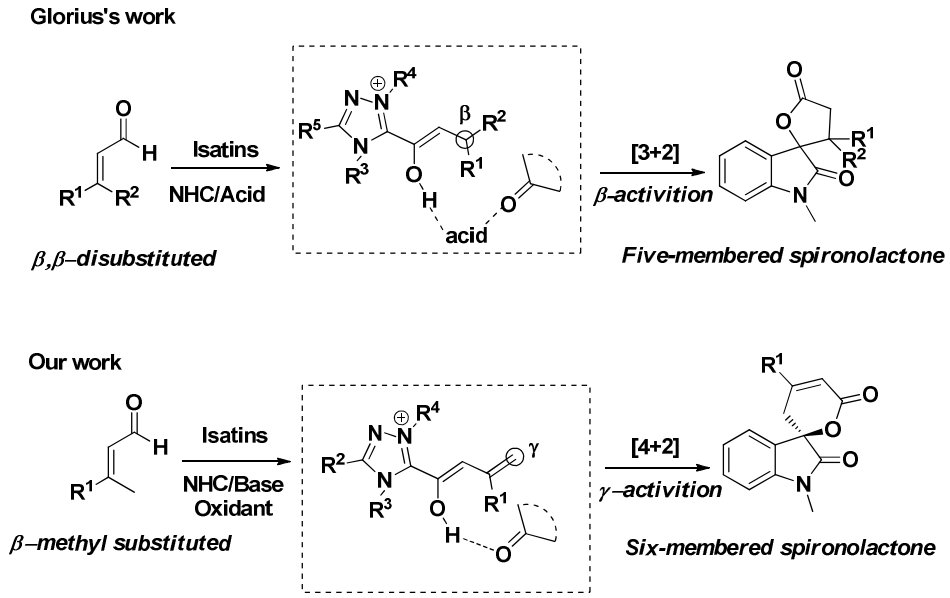
KEYWORDS: isatins; γ-carbon; spirolactones.

ABSTRACT: A chiral *N*-heterocyclic carbene (NHC)-catalyzed formal [4+2] annulation of β-methyl substituted enals with isatins was developed to construct six-membered spirolactones bearing highly congested quaternary carbon stereocentersin good yields and high enantioselectivities. The strategy realized a challenging remote γ-carbon addition of enals and chiral control of β-methyl substituted enals in the presence of the NHC catalyst only.

Introduction

Spiroheterocycles have become attractive targets in organic synthesis because of their widespread distribution in biologically active pharmaceuticals and natural products, and their increasing use in a range of vital chemical and technological processes, such as asymmetric synthesis and organic optoelectronics.[1] Therefore, the development of novel methods to construct spirocyclic frameworks is of great importance, particularly when these methods lead to the enantioselective formation of a quaternary stereocenter, which itself is considered a meaningful transformation.[2,3] Spirolactone is an intriguing spiroheterocyclic compound involving a tetra substituted quaternary stereocenters. Several methods, including alkylation,[4] transition-metal-based approaches,[5] rearrangement-based approaches,[6] ring-expansion method,[7] ring-contraction methods,[8] photochemical approaches,[9] ring closure of geminally disubstituted compounds,[10] the Diels-Alder [4+2] approach,[11] ring-closing-metathesis[12] and other methods, have been employed successfully to construct these pharmacologically intriguing scaffolds. However, the construction of their quaternary stereocenters,[13,14,15] especially the single-step assembly of compounds with congested tetra substituted carbon stereocenters, still remains a serious challenge. The obstacle to forming such centers is rooted in the inherent huge space imposed by the four non-hydrogen substituents. Recently, *N*-heterocyclic carbene (NHC) organocatalysis[16] has been studied widely because of its special ability to deteriorate the natural reactivity of a functional group, which offers unconventional access to a set of umpolung reactions.[17] However, the activation of the γ-carbon of enals[18] still remains a significant challenge: it is very difficult to obtain good chemoselectivity and enantioselectivity because of the occurrence of competitive homoenolate, enolate or acyl anion intermediates and the fact that chiral auxiliaries are more remote from the γ-carbon than α- or β-carbons of carbonyl

compounds.[19] In our previous work, we successfully developed three highly efficient organocatalyzed methods for the asymmetric synthesis of spiro-oxindoles as part of the construction of a natural product-like library for further bioactivity screening,[20,21] and we also successfully achieved γ-carbon activation of carbonyl compounds to enantioselectively assemble δ-lactams with NHC/Brønsted acids cooperative catalysis.[22]



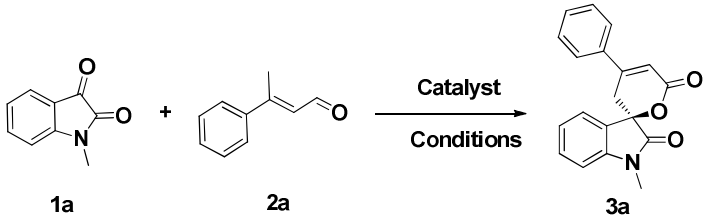
Scheme 1. Activation of γ-disubstituted enals by NHC catalysis.

Recently, Glorius et al. developed an elegant a3-d3 umpolung reactivity of the β, β-disubstituted enals to aid construction of five-membered spirolactones bearing two highly contiguous quaternary stereocenters through a β-carbon activation of enals.[23] To continue our exploration of γ-carbon activation of carbonyl compounds and the intriguing spiroheterocycles, we herein attempted to employ β-methyl substituted enals as substrates to achieve their γ-carbon activation via NHC catalysis, and to construct novel intriguing six-membered spirolactone compounds (Scheme 1).

Results and Discussion

Initially, we explored the reaction of isatin derivative **1a** and *β*-methyl-saturated cinnamaldehyde **2a** in the presence of four different triazolium NHC pre-catalysts in THF solvent using Cs_2CO_3 as the base. The key results of our experiments are summarized in Table 1. Surprisingly, the process could deliver the desired six-membered spirolactone with a moderate yield of 80% and a high enantioselectivity of 81% ee in the presence of the NHC pre-catalyst B (Table 1, entries 1-4). This proof-of-principle result clearly indicated that activation of the *γ*-carbon of enal as a nucleophile using the NHC organocatalyst is feasible. Accordingly, a variety of alternative solvents were investigated. Although desirable products could be observed when MTBE, toluene, Et_2O, CH_2Cl_2, EA, DMF and DMSO were used as the solvent, better results were not obtained (Table 1, entries 5-11). We further explored the influences of different bases, including inorganic and organic bases, and good yields could be obtained; however, only moderate enantioselectivity are detected (Table 1, entries 12-16).

Table 1. Optimization of the reaction conditions.[a]

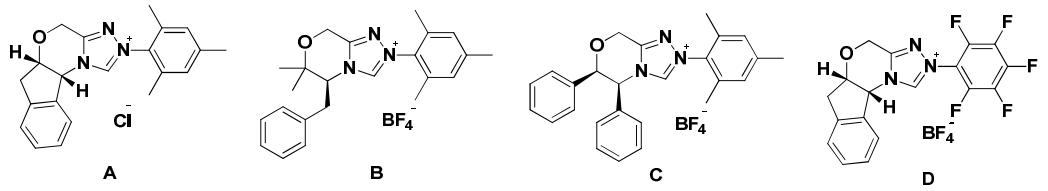


1a 2a 3a

Entry	Cat	Solvent	Base	ee (%)	Yield (%)
1	A	THF	Cs_2CO_3	32	42
2	**B**	**THF**	**Cs_2CO_3**	**81**	**80**
3	C	THF	Cs_2CO_3	60	32
4	D	THF	Cs_2CO_3	/	26
5	B	MTBE	Cs_2CO_3	72	63

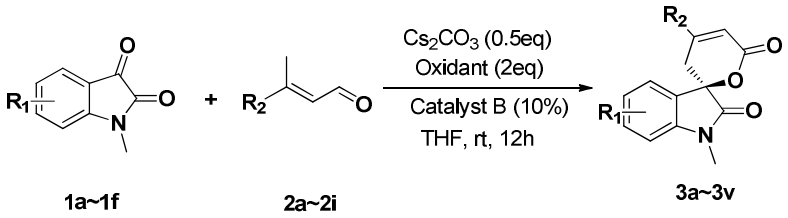
6	B	Toluene	Cs_2CO_3	62	53
7	B	Et_2O	Cs_2CO_3	83	32
8	B	CH_2Cl_2	Cs_2CO_3	40	48
9	B	EA	Cs_2CO_3	75	58
10	B	DMF	Cs_2CO_3	64	48
11	B	DMSO	Cs_2CO_3	47	42
12	B	THF	K_2CO_3	74	69
13	B	THF	KOH	74	42
14	B	THF	tBuOK	73	58
15	B	THF	DBU	70	53
16	B	THF	Et_3N	78	48

[a] **1a** (0.125 mmol) and catalyst (0.1 eq) in the specified solvent (2 mL) were reacted in a sealed vial under argon atmosphere at rt for 12 h. The Oxidant is 3,3',5,5'-tetra-tert-butyl-[1,1'-bi(cyclohexylidene)]-2,2',5,5'-tetraen-4-one.

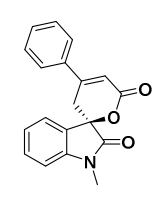


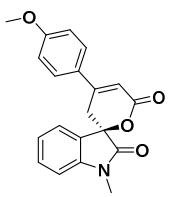
With the optimized catalysis conditions identified (Table 1, entry 2), we further investigated the substrate scope of the annulation process. As shown in Table 2, a variety of *β*-substituted butenals were investigated as potential substrates (Table 2, entries 3a-3i), and the results demonstrated that different substituents, including electron-donating, electron-withdrawing and halogen groups substituted phenyls, heterocyclic aryl, and alkyl groups at *β*-position of butenals were well tolerated, affording the desired annulation products in good yields (56-82%) with good enantioselectivities (66-86%). Simultaneously, we introduced Cl, Br and OCH_3 into the 6-position of isatin to explore the reactivities of the strategy (Table 2, entries 3j-3q), which give good results, especially when treating of 4-Cl, 6-Cl and 6-Br substituted isatins with *β*-(4-

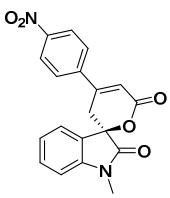
Table 2. Enantioselective synthesis of target compounds.[a]

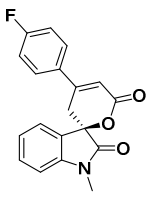


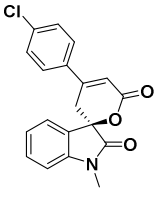
1a~1f 2a~2i 3a~3v

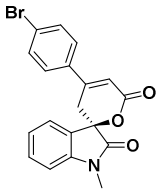

3a, 80% Yield, 81% ee

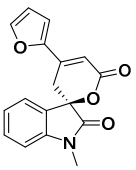

3b, 56% Yield, 86% ee

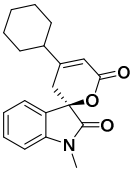

3c, 76% Yield, 74% ee

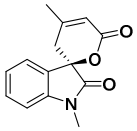

3d, 78% Yield, 75% ee

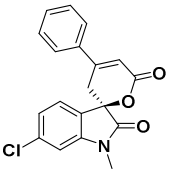

3e, 77% Yield, 82% ee

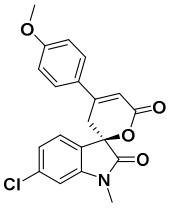

3f, 82% Yield, 81% ee

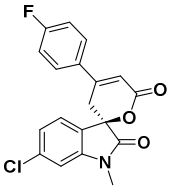

3g, 71% Yield, 82% ee

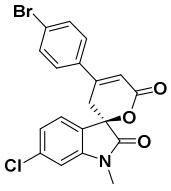

3h 76% Yield, 66% ee

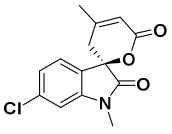

3i, 72% Yield, 70% ee

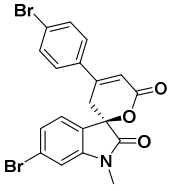

3j, 58% Yield, 36% ee

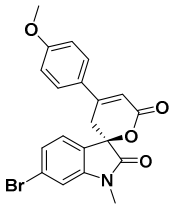

3k, 61% Yield, 97% ee

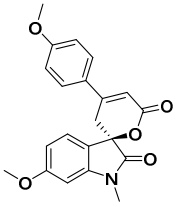

3l, 68% Yield, 74% ee

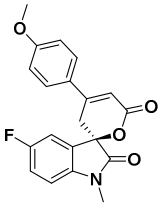

3m, 35% Yield, 72% ee

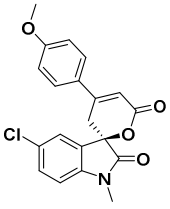

3n, 77% Yield, 36% ee

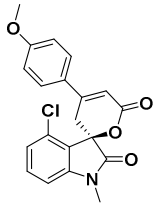

3o, 65% Yield, 64% ee

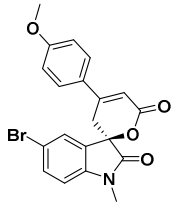

3p, 55% Yield, 98% ee

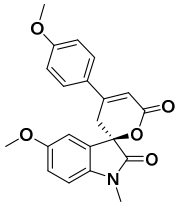

3q, 47% Yield, 84% ee

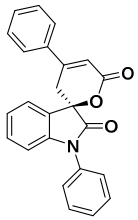

3r, 59% Yield, 77% ee


3s, 62% Yield, 84%


3t, 59% Yield, >99% ee

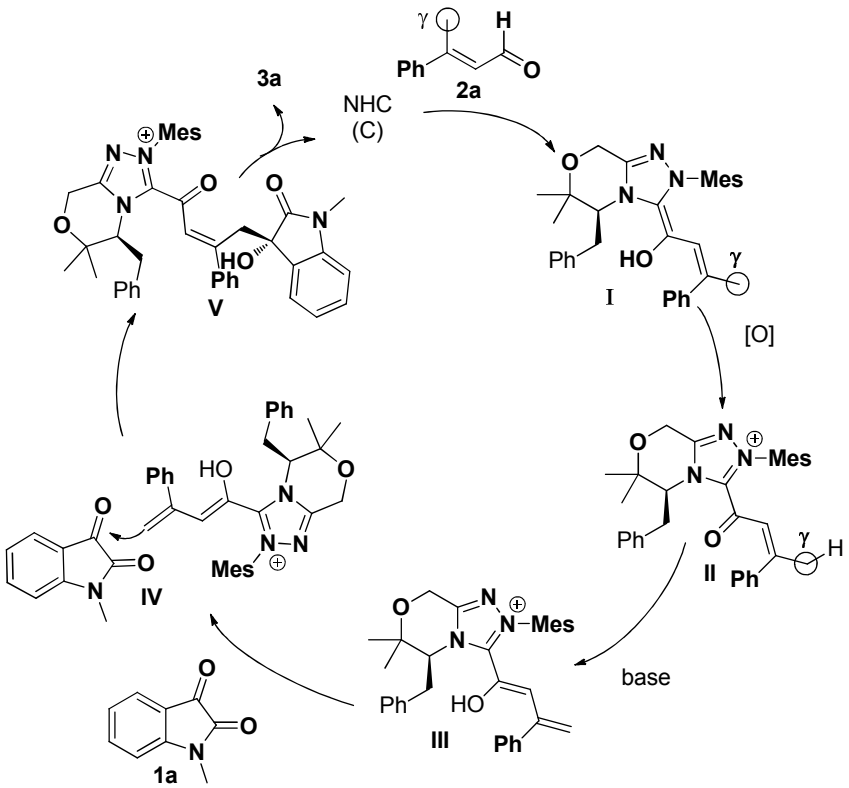

3u, 54% Yield, 58% ee


3v, 46% Yield, 71% ee


3w 56% Yield, 74% ee

[a] **1** (0.125 mmol) and catalyst (0.1 eq) in the specified solvent (2 mL) were reacted in a sealed vial under argon atmosphere at rt for 12 h. The Oxidant is 3,3',5,5'-tetra-tert-butyl-[1,1'-bi(cyclohexylidene)]-2,2',5,5'-tetraen-4-one.

methoxylphenyl)-butenal, producing excellent enantioselectivities at 97%, 98%, >99% ee, (Table 2, entries 3k, 3p and 3t). We further investigated the tolerance of the process by varying the R_1 group at other positions (Table 2, entries 3q-3v). The diversified substrates also produced annulation products with good yields (46%-62%) and high enantioselectivities (58%-86%). We further explored the reactivity of the N-phenyl isatin and obtained both a good yield and enantioselectivity (compound 3w). The absolute configuration of compound **3f** (Tables 2, entry 3f) was determined by X-ray analysis (see Figure S1 in the Supporting Information).



Scheme 2. The plausible mechanism.

A plausible mechanism for the reaction is illustrated in Scheme 2. Addition of the NHC catalyst to the enal delivers the intermediate **I**, which is further oxidized and deprotonated to form the vinyl enolate intermediate **III**.[24] Vinyl enolate **III** then undergoes nucleophilic addition

to isatins **1a** to give the adduct **V**, after which intra molecular alkoxide attacks at the carbonyl group, leading to the production of the desired spirolactone **3a**.

Conclusion

In summary, we developed a chiral NHC-catalyzed formal [4+2] annulation of *β*-methyl substituted enals with isatins to prepare six-membered spirolactones with good yields and high enantioselectivities. The biggest challenge was to realize remote activation and chiral control of *γ*-carbon of enals using only an NHC catalyst. The mild reaction conditions, good enantioselectivities and wide reaction scope make this *γ*-carbon activation strategy potentially useful for the synthesis of biologically active molecules or natural product analogs. The mechanistic details, the further activation and chiral control of remote carbons of enals for the asymmetric synthesis of diversified spirohetercylcles are under study in our laboratory.

Supporting Information. General experimental methods, ^{1}H- and ^{13}C-NMR spectrum of all products, optical data, X-ray, as well as chiral HPLC spectrum. The supporting information is available free of charge via the Internet at http://pubs.acs.org.

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REFERENCES

(1) (a) Saragi, T. P. I.; Spehr, T.; Siebert, A.; Fuhrmann, L. T.; Salbeck, J. Spiro compounds for organic optoelectronics. *Chem. Rev*. **2007**, *107*, 1011-1065. (b) Chou, C. H.; Gong, C. L.; Chao, C. C.; Lin, C. H.; Kwan, C. Y.; Hsieh, C. L.; Leung, Y. M. Rhynchophylline from Uncaria rhynchophylla Functionally Turns Delayed Rectifiers into A-Type K+ Channels. *J. Nat. Prod* **2009**, *72*, 830-834. (c) Lo, M. M. C.; Neumann, C. S.; Nagayama, S.; Perlstein, E. O.; Schreiber, S. L. A library of spirooxindoles based on a stereoselective three-component coupling reaction. *J. Am. Chem. Soc*. **2004**, *126*, 16077-16086.

(2) Pradhan, R.; Patra, M.; Behera, A. K.; Mishra, B. K.; Behera, R. K. A synthon approach to spiro compounds. *Tetrahedron* **2006**, *62*, 779-828.

(3) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. Enantioselective catalytic formation of quaternary stereogenic centers. *Eur. J. Org. Chem*. **2007**, *36*, 5969-5994.

(4) Gary, H. P； Terence, G. H. An Asymmetric Total Synthesis of Fragrant Spiro[4.5]decane Sesquiterpene (-)-p-Vetivone via an Enantiomerically Pure Vinylic Sulfoxide. *J. Org. Chem*. **1988**, *53*, 6031-6035.

(5) Villar，J. M.; Delgado,A.; Llebaria, J. M.; Moreto, E.; and Miravitlles, C. Asymmetric Approaches to Cyclopentenones in the Ni(0)-promoted Cyclocarbonylation Reaction of Allyl Halides and Acetylenes. *Tetrahedron* **1996**, *31*, 10525-10546.

(6) Koshio, C.; Koshio, H. New Cyclization Reaction of 2-(Trimethylsilylmethyl)pentadienal. Synthesis of Spiro [4, 5] decane Ring System. *Chem. Lett*. **2000**, *8*, 962-963.

(7) Gregory, R. D.; Michaël, D. B. F.; Mélissa, F.; and Brian, O. P. Investigations of r-Siloxy-Epoxide Ring Expansions Forming 1-Azaspirocyclic Ketones. *J. Org. Chem*. **2004**, *69*, 5676-5683.

(8) Jih, R. H.; John, M. W. Silicon-Promoted Ring Contractions in the Formation of Carbocyclic Spiro Compounds. *J. Org. Chem*. **1991**, *57*, 922-928.

(9) Emil, R. K. and Amos, B. S. Intramolecular [2+2] Photochemical Cycloadditions Perhydrohistrionicotoxin Synthetic Studies: Synthesis of Spiro [4, 5] decanones via Intramolecular [2+2] Photocycloaddition. *J. Org. Chem*. **1984**, *49*, 832-836.

(10) Srikrishna, A.; Kumar, P. P. Claisen Rearrangement Based Methodology for the Spiroannulation of a Cyclopentane Ring. Formal Total Synthesis of (+)-Acorone and Isoacorones. *Tetrahedron* **2000**, *41*, 8189-8195.

(11) Back, T. G.; Payne, J. E. A concise total synthesis of (+/-)-bakkenolide a by means of an intramolecular Diels-Alder reaction. *Org. Lett*. **1999**, *1*, 663-665.

(12) Rene´ M.; Lemieux, P. N. D.; Mark, F. M.; and Meyers, A. I. An Asymmetric Route to Novel Chiral Cyclohexenones with Spiro-Connected Cyclopentenes. Further Utility of Chiral Bicyclic Thiolactams and the [3, 3] Thio-Claisen Products. *J. Org. Chem* **1999**, *10*, 3585-3591.

(13) Chen, Z.; Sun, J. Enantio- and diastereoselective assembly of tetrahydrofuran and tetrahydropyran skeletons with all-carbon-substituted quaternary stereocenters. *Angew. Chem. Int. Ed.* **2013**, *52*, 13593-13596.

(14) Li, C.; Breit, B. Rhodium-catalyzed chemo- and regioselective decarboxylative addition of beta-ketoacids to allenes: efficient construction of tertiary and quaternary carbon centers. *J. Am. Chem. Soc.* **2014**, *136*, 862-865.

(15) Chen, Z. S.; Duan, X. H.; Zhou, P. X.; Ali, S.; Luo, J. Y.; Liang, Y. M. Palladium-catalyzed divergent reactions of alpha-diazocarbonyl compounds with allylic esters: construction of quaternary carbon centers. *Angew. Chem. Int. Ed.* **2012**, *51*, 1370-1374.

(16) (a) Zeitler, K. Extending mechanistic routes in heterazolium catalysis--promising concepts for versatile synthetic methods. *Angew. Chem. In.t Ed.* **2005**, *44,* 7506-7510. (b) Marion, N.; Diez-Gonzalez, S.; Nolan, S. P. N-heterocyclic carbenes as organocatalysts. *Angew. Chem. Int. Ed.* **2007**, *46*, 2988-3000. (c) Rovis, T. Development of Chiral Bicyclic Triazolium Salt Organic Catalysts: The Importance of the N-Aryl Substituent. *Chem. Lett*. **2008**, *37*, 2-7. (d) Akkattu, T.; Biju, N. K.; and Frank, G. Extending NHC-Catalysis: Coupling Aldehydes with Unconventional Reaction Partners. *Chem. Res.* **2011**, *44*, 1182-1195. (e) Hirano, K.; Piel, I.; Glorius, F. Dual Activation in N-Heterocyclic Carbene-organocatalysis. *Chem. Lett*. **2011**, *40*, 786-791. (f) Rong, Z. Q.; Zhang, W.; Yang, G. Q.; and You, S. L. N-Heterocyclic Carbene-Catalyzed Redox Reactions of *Curr. Org. Chem*. **2011**, *15*, 3077-3090; (g) Xiao, Z.; Yu, C.; Li, T.; Wang, X. S.; Yao, C. *N*-heterocyclic carbene/Lewis acid strategy for the stereoselective synthesis of spirocyclic oxindole-dihydropyranones. *Org. Lett.* **2014,** *16*, 3632-5; (h) Wang, M.; Huang, Z.; Xu, J.; Chi, Y. R. *N*-heterocyclic carbene-catalyzed [3+4]

cycloaddition and kinetic resolution of azomethine imines. *J. Am. Chem. Soc.* **2014,** *136* , 1214-7; (i) Xu, J. F.; Chi, Y. G. Organocatalytic Enantioselective *γ*-Aminoalkylation of Unsaturated Ester: Access to Pipecolic Acid Derivatives. *Org. Lett.* **2013,** *15*, 5028-5031.

(17) Hopkinson, M. N.; Richter, C.; Schedler, M.; Glorius, F. An overview of N-heterocyclic carbenes. *Nature* **2014**, *510*, 485-496.

(18) Shen, L. T.; Shao, P. L.; and Ye, S. N-Heterocyclic Carbene-Catalyzed Cyclization of UnsaturatedAcyl Chlorides and Ketones. *Adv. Synth. Catal* **2011,** 353, 1943-1948. (b) Liu, R.; Yu, C.; Xiao, Z.; Li, T.; Wang, X.; Xie, Y.; Yao, C. NHC-catalyzed oxidative gamma-addition of alpha,beta-unsaturated aldehydes to isatins: a high-efficiency synthesis of spirocyclic oxindole-dihydropyranones. *Org. Biomol. Chem.* **2014,** *12* (12), 1885-91

(19) (a) Que, Y.; Li, T.; Yu, C.; Wang, X. S.; Yao, C. Enantioselective assembly of spirocyclic oxindole-dihydropyranones through NHC-catalyzed cascade reaction of isatins with N-hydroxybenzotriazole esters of alpha,beta-unsaturated carboxylic acid. *J. Org. Chem*. **2015**, *80*, 3289-94. (b) Fu, Z.; Xu, J.; Zhu, T.; Leong, W. W.; Chi, Y. R. *β*-Carbon activation of saturated carboxylic esters through *N*-heterocyclic carbene organocatalysis. *Nat. Chem*. **2013**, *5*, 835-9. (c) Zhang, J.; Xing, C.; Tiwari, B.; Chi, Y. R. Catalytic activation of carbohydrates as formaldehyde equivalents for Stetter reaction with enones. *J. Am. Chem. Soc*. **2013**, *135*, 8113-8116. (d) Raup, D. E.; Cardinal-David, B.; Holte, D.; Scheidt, K. A. Cooperative catalysis by carbenes and Lewis acids in a highly stereoselective route to gamma-lactams. *Nat. Chem*. **2010**, *2*, 766-771. (e) Lv, H.; Jia, W. Q.; Sun, L. H.; Ye, S. *N*-heterocyclic carbene catalyzed [4+3] annulation of enals and o-quinone methides: highly enantioselective synthesis of benzo-epsilon-lactones. *Angew. Chem. Int. Ed.* **2013**, *52*, 8607-8610. (f) Xu, J.; Mou, C.; Zhu,

T.; Song, B. A.; Chi, Y. R. N-Heterocyclic carbene-catalyzed chemoselective cross-aza-benzoin reaction of enals with isatin-derived ketimines: access to chiral quaternary aminooxindoles. *Org. Lett*. **2014**, *16*, 3272-3275. (g) Burstein, C.; Glorius, F. Organocatalyzed conjugate umpolung of *α*, *β*-unsaturated aldehydes for the synthesis of gamma-butyrolactones. *Angew. Chem. Int. Ed.* **2004**, *43*, 6205-6208. (h) Mo, J.; Chen, X.; Chi, Y. R. Oxidative gamma-addition of enals to trifluoromethyl ketones: enantioselectivity control via Lewis acid/*N*-heterocyclic carbene cooperative catalysis. *J. Am. Chem. Soc*. **2012**, *134* , 8810-8813. (i) Wang, M.; Huang, Z.; Xu, J.; Chi, Y. R. *N*-heterocyclic carbene-catalyzed [3+4] cycloaddition and kinetic resolution of azomethine imines. *J. Am. Chem. Soc*. **2014**, *136*, 1214-1217. (j) Xiao, Z.; Yu, C.; Li, T.; Wang, X. S.; Yao, C. *N*-heterocyclic carbene/Lewis acid strategy for the stereoselective synthesis of spirocyclic oxindole-dihydropyranones. *Org. Lett*. **2014**, *16*, 3632-3635. (k) Xu, J. F.; Jin, Z. C.; and Chi,Y. R. Organocatalytic Enantioselective *γ*-Aminoalkylation of Unsaturated Ester: Access to Pipecolic Acid Derivatives. *Org. Lett*. **2013**, *15*, 5028-5031.

(20) (a) Chen, X. J.; Chen, H.; Ji, X.; Jiang, H. L.; Yao, Z. J.; and Liu, H. Asymmetric One-Pot Sequential Mannich/Hydroamination Reaction by Organoand Gold Catalysts: Synthesis of Spiro[pyrrolidin-3,20-oxindole] Derivatives. *Org. Lett*. **2013**, *15*, 1846-1849. (b) Chen, X.; Zhu, W.; Qian, W.; Feng, E. G.; Zhou, Y.; Wang, J.; Jiang, H. L.; Yao, Z. J.; Liu, H. Highly Enantioselective Michael Addition of 2-Oxindole-3-carboxylate Esters to Nitroolefins Promoted by Cinchona Alkaloid-Thiourea-Bronsted Acid Cocatalysts. *Adv. Syn. Catal.* **2012**, *354*, 2151-2156.

(21) Cai, H.; Zhou, Y.; Zhang, D.; Xu, J.; Liu, H. A Mannich/cyclization cascade process for the asymmetric synthesis of spirocyclic thioimidazolidineoxindoles. *Chem. Comm*. **2014**, *50*, 14771-14774.

(22) Xiao, Y. L.; Wang, J. X.; Xia, W. J.; Shu, S. J.; Jiao, S. C.; Zhou, Y.; Liu, H. *γ*-Carbon Activation through *N*-Heterocyclic Carbene/Bronsted Acids Cooperative Catalysis: A Highly Enantioselective Route to delta-Lactams. *Org. Lett*. **2015**, 17, 3850-3853.

(23) Li, J. L.; Sahoo, B.; Daniliuc, C. G.; Glorius, F. Conjugate umpolung of *β*, *β*-disubstituted enals by dual catalysis with an *N*-heterocyclic carbene and a Bronsted acid: facile construction of contiguous quaternary stereocenters. *Angew. Chem. Int. Ed.* **2014**, *53*, 10515-10519.

(24) (a) Collett, C. J.; Massey, R. S.; Maguire, O. R.; Batsanov, A. S.; O'Donoghue, A. C.; Smith, A. D. Mechanistic insights into the triazolylidene-catalysed Stetter and benzoin reactions: role of the N-aryl substituent. *Chem. Sci.* **2013**, *4*, 1514-1522. (b) Schrader, W.; Handayani, P. P.; Burstein, C.; Glorius, F. Investigating organocatalytic reactions: mass spectrometric studies of a conjugate umpolung reaction. *Chem. Comm*. **2007**, *7*, 716-718. (c) Miyashita, A.; Kurachi, A.; Matsuoka, Y.; Tanabe, N.; Suzuki, Y.; Iwamoto, K.; Higashino, T. Synthesis and reactivities of 1,3-dimethyl-2-(alpha-hydroxybenzyl)imidazolium and 1,3-dimethyl-2-(alpha-hydroxybenzyl)-benzimidazolium iodides. *Heterocycles.* **1997**, *44*, 417-426.

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Enantioselective Assembly of Spirolactones through NHC-Catalyzed Remote *γ*-Carbon Addition of Enals with Isatins

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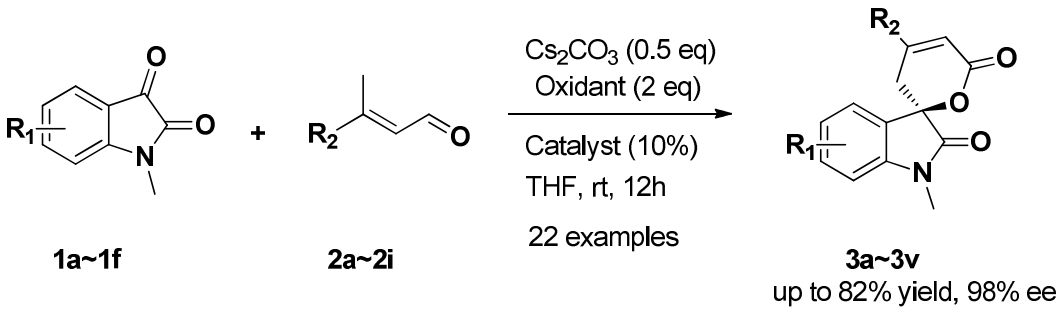

1a~1f **2a~2i** **3a~3v**

up to 82% yield, 98% ee