ChemPubSoc Europe

DOI: 10.1002/chem.201500345

CHEMISTRY
A European Journal
Communication

Organocatalysis

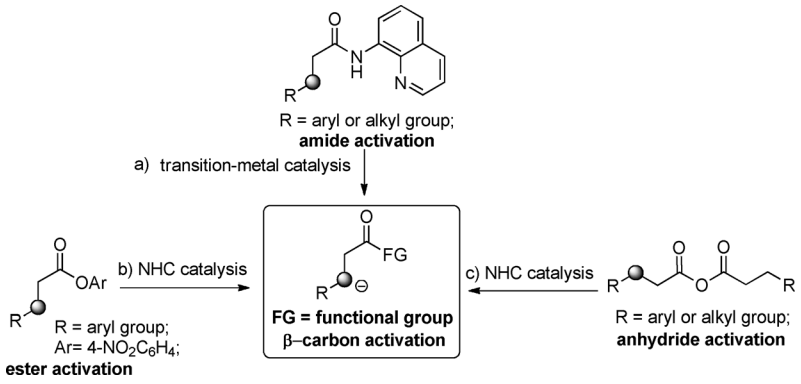
An NHC-Catalyzed In Situ Activation Strategy to β-Functionalize Saturated Carboxylic Acid: An Enantioselective Formal [3+2] Annulation for Spirocyclic Oxindolo-γ-butyrolactones

Yuanwei Xie, Chenxia Yu, Tuanjie Li, Shujiang Tu, and Changsheng Yao*[a]

Abstract: An in situ NHC-catalyzed activation strategy to β-functionalize saturated carboxylic acid was developed. This asymmetric formal [3+2] annulation could deliver spirocyclic oxindolo-γ-butyrolactones from saturated carboxylic acid and isatin in good yields with high to excellent enantioselectivities. The easy availability of the starting materials, direct installation of functional units at unreactive carbon atom and the convergent assembly make this protocol attractive in the field of organic synthesis.

Carbonyl compounds including carboxylic acids, esters, ketones and aldehydes are very useful building blocks employed widely for the synthesis of pharmaceuticals and materials. Thus, much effort has been devoted to the transformation of these important compounds. Traditionally, the conjugate addition of α,β-unsaturated carbonyl compounds with nucleophiles is a powerful strategy for introducing a functional group at the β-position of a carbonyl group.[1] The amino-catalyzed oxidation of saturated aldehydes to the corresponding α,β-unsaturated iminium and subsequent reaction with nucleophilic reagents could also functionalize β carbon atoms circuitously.[2] However, the direct functionalization of unreactive saturated carbon atoms remote from carbonyl group is a great challenge for organic chemists.[3] Recently, several groups disclosed the transition-metal, for example, palladium-catalyzed ββ-functionalization of carbonyl compounds by chelation-assisted C(sp^3)–H activation in the presence of auxiliary groups or directing groups (Scheme 1 a).[4] In addition, MacMillan's group presented an elegant way to set up an aryl or alkyl group at the β-position directly through photoredox one-electron oxidation of enamine to the β-carbon radical.[5] Even so, the direct installation of a functional group at the unreactive β-position of readily available carbonyl compounds, for example, saturated carboxylic acids, deserves further study.

N-heterocyclic carbenes (NHCs) have been confirmed as flexible catalysts for several "umpolung" reactions,[6] such as the benzoin condensation,[7] Stetter reaction,[8] a^3–d^3 umpolung (homoenolate).[9] Moreover, NHC-catalyzed β-carbon functionalizations of derivatives of saturated carboxylic acids including



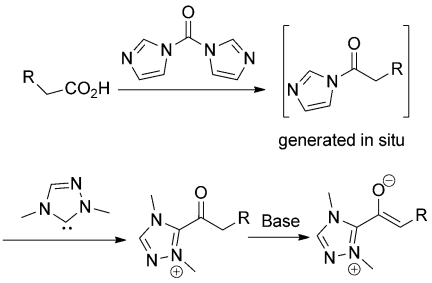
Scheme 1. Some strategies to generate homoenolates or their equivalents.

esters and anhydrides through the generation of homoenolates have been achieved successfully (Scheme 1 b and c).[10] In 2014, Scheidt's group found a facile NHC-promoted generation of enolate from the acyl imidazole formed in situ from the carboxylic acid and carbonyldiimidazole (CDI), which paved a new avenue to the direct activation of α-carbon of carboxylic acid (Scheme 2).[11]

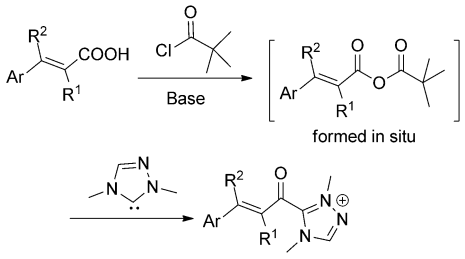
Later, the work of Ye et al. showed that α,β-unsaturated acyl azoliums could be obtained readily from α,β-unsaturated carboxylic acids via mixed anhydrides generated in situ (Scheme 3).[12] The activation of carboxylic acids in situ was proved to be an efficient strategy to give rise to reactive intermediates such as enolates and α,β-unsaturated acyl azoliums under the catalysis of NHC (for the in situ activation of carboxylic acids catalyzed by cinchona alkaloids or isothioureas developed by Smith and Romo, please see ref. [13]). However, as an alternative of classical a^3–d^3 umpolung, a challenging approach

[a] Y. Xie, Prof. C. Yu, T. Li, Prof. Dr. S. Tu, Prof. Dr. C. Yao
School of Chemistry and Chemical Engineering
Jiangsu Key Lab of Green Synthetic Chemistry for Functional Materials
Jiangsu Normal University, Xuzhou, Jiangsu 221116 (P.R. China)
E-mail: csyao@jsnu.edu.cn

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201500345.



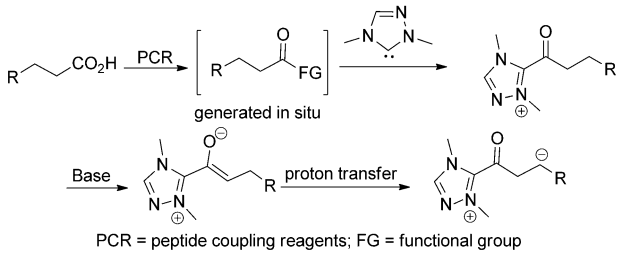
Scheme 2. An in situ strategy for formation of enolate from carboxylic acid.



Scheme 3. An in situ protocol to form α,β-unsaturated acyl azoliums.

with great significance to homoenolate is the direct conversion from carboxylic acids.

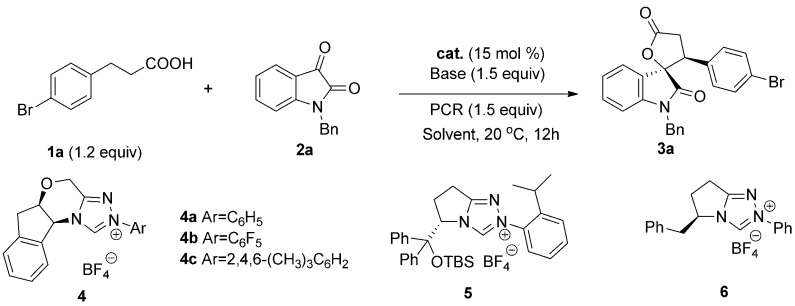
Since the coupling reagents, such as diisopropylcarbodiimide (DIC) and 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU), are employed widely in peptide synthesis to activate the carboxylic acids via intermediates including esters and anhydrides,[14] we envisaged that these intermediates could be produced in situ and their reaction with NHC could also deliver homoenolate in the presence of base effectively (Scheme 4). To continue our interest in the cascade synthesis of heterocycles and NHC catalysis,[15] herein we report our preliminary results of NHC-catalyzed asymmetric annulation for the synthesis of spirocyclic oxindolo-γ-butyrolactones, which are of biological interest, from saturated carboxylic acid through in situ activation strategy in the presence of coupling reagents.[9a,b,16]



Scheme 4. Our proposal for NHC-catalyzed generation of homoenolate.

We commenced our study from the optimization of reaction conditions, which are summarized in Table 1. The NHC-catalyzed formal [3+2] cyclization of 3-(4-bromophenyl)propanoic acid (**1a**) and 1-benzylindoline-2,3-dione (**2a**) was tested as a model reaction. Firstly, we evaluated the reaction conditions by screening the peptide coupling reagents. CDI and BOP-Cl did not work for this reaction (Table 1, entries 1 and 4). Gratifyingly, the desired [3+2] annulation product **3a** could be obtained with 89% *ee* by DCC/HOBt and DIC/HOBt. When HATU was investigated, much better performance was observed (83% yield, 3:1 d.r. and 93% *ee*). Next, we explored the

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



Entry	NHC cat.	Base	PCR[b]	Solvent	Yield [%][c]	d.r.[d]	*ee* [%][e]
1	**4a**	Cs_2CO_3	CDI	dioxane	–	–	–
2	**4a**	Cs_2CO_3	DCC/HOBt	dioxane	67	4:1	89
3	**4a**	Cs_2CO_3	DIC/HOBt	dioxane	55	4:1	89
4	**4a**	Cs_2CO_3[j]	BOP-Cl	dioxane	–	–	–
5	**4a**	Cs_2CO_3	HATU	dioxane	83	3:1	93
6	**4b**	Cs_2CO_3	HATU	dioxane	–	–	–
7	**4c**	Cs_2CO_3	HATU	dioxane	85	7:1	95
8	**5**	Cs_2CO_3	HATU	dioxane	trace	–	–
9	**6**	Cs_2CO_3	HATU	dioxane	80	1.5:1	93
10	**4c**	K_2CO_3	HATU	dioxane	79	5:1	97
11	**4c**	DBU	HATU	dioxane	–	–	–
12	**4c**	DABCO	HATU	dioxane	trace	–	–
13	**4c**	NaOAc	HATU	dioxane	–	–	–
14	**4c**	Cs_2CO_3	HATU	CH_2Cl_2	74	3:1	94
15	**4c**	Cs_2CO_3	HATU	THF	72	4:1	96
16	**4c**	Cs_2CO_3	HATU	toluene	69	2:1	79
17	**4c**	Cs_2CO_3	HATU	DME	85	6:1	98
18	**4c**[f]	Cs_2CO_3	HATU	DME	80	5:1	77
19	**4c**[g]	Cs_2CO_3	HATU	DME	83	5:1	79
20	**4c**[h]	Cs_2CO_3	HATU	DME	80	6:1	93
21	**4c**[i]	Cs_2CO_3	HATU	DME	78	6:1	91

[a] Reaction conditions: **1a** (0.24 mmol), **2a** (0.2 mmol), NHC cat. (0.03 mmol), base (0.3 mmol), PCR (0.3 mmol), solvent (4 mL), 20 °C, 12 h. [b] PCR = peptide coupling reagent. [c] Isolated yields. [d] Diastereomeric ratio determined by ^{1}H NMR spectroscopy. [e] The *ee* values were determined by HPLC. [f] 10 mol% of NHC. [g] 20 mol% of NHC. [h] 0 °C. [i] 40 °C. [j] 2.5 equiv.

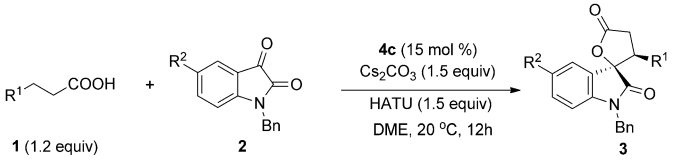
influence of catalysts; in contrast to the NHC precursor **4a** and **6**, precatalyst **4c** gave the product in good yield, diastereo- and enantioselectivity (Table 1, entries 5, 7 and 9), whereas the catalyst **4b** and **5** failed to give the desired annulation product (Table 1, entries 6 and 8). A catalyst loading test indicated that 15 mol% of **4c** would be better. Decreasing or increasing loading of the catalyst showed lower enantioselectivity (Table 1, entries 18 and 19). Then, K_2CO_3, Cs_2CO_3, DABCO (1,4-diazabicyclo [2.2.2]octane), DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) and NaOAc were deployed to assess the scope of the base. The results demonstrated that inorganic bases are more effective than organic bases; screening of inorganic bases revealed that Cs_2CO_3 was the best choice (Table 1, entries 10–13). Subsequently, the influence of different solvents on the reaction of **1a** and **2a** were examined to optimize the conditions (Table 1, entries 14–17); we found that DME is better than 1,4-dioxane, CH_2Cl_2, THF and toluene. Temperature screening showed that 20 °C should be optimal (Table 1, entries 20 and 21). Based on the above results, it was clear that the formation of spirocyclic oxindolo-γ-butyrolactones in high yield with good to excellent enantioselectivity and diastereoselectivity is facilitated by the combination of triazole carbene precursor **4c** and Cs_2CO_3 in DME as the solvent at 20 °C.

With the optimized reaction conditions in hand, we turned our attention to the scope of substrates by the variation of saturated carboxylic acids **1** and the isatin derivatives **2**. It was found that both electron-deficient (Cl, Br, NO_2) and electron-rich (CH_3) moieties are tolerated well on the aryl group (**3a**–**3e**). The scope of the isatins **2** was then studied. It was found that isatins with both electron-withdrawing groups (5-F, 5-Cl and 5-Br) and electron-donating group (5-Me) are compatible with the reaction conditions. When isatins with the electron-donating group (Me) at the 5-position were engaged in this reaction, both electron-withdrawing and electron-donating groups on the carboxylic acids worked well to afford the corresponding products in high yields and excellent enantioselectivities (93–98% *ee*). To our pleasure, saturated carboxylic acids with an alkyl group reacted with **2a** to provide the corresponding cascade product (**3m**) with moderate d.r. and high e.r. values, albeit with moderate yield. These results highlighted the wide application scope of this NHC-catalyzed [3+2] reaction.

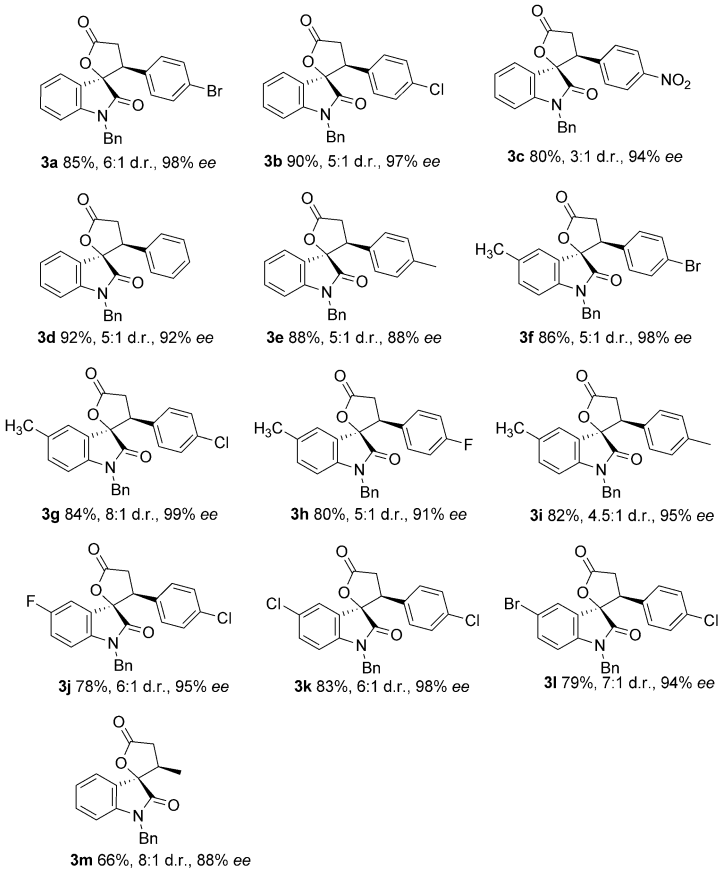
The optical rotation data and HPLC analysis data of spirocyclic oxindolo-γ-butyrolactone **3b** were found to be in good agreement with those reported in the literature; thus, the absolute configuration could be determined by comparison.[17]

A plausible catalytic cycle of this NHC-catalyzed [3+2] annulation of saturated carboxylic acid is illustrated in Scheme 5. The addition of NHC to the ester substrate, which was generated in situ from the saturated carboxylic acid, gave the corresponding NHC-bounded intermediate **A**. It could undergo deprotonation to form the enolate intermediate **B**, which was transformed into intermediate **C** through β-sp^3-H shift similar to the formation of homoenolate in the NHC-catalyzed reactions of derivatives of carboxylic acids.[10] Then intermediate **C**

Table 2. Scope with saturated carboxylic acids **1** and the isatin derivatives **2**.[a]



1 (1.2 equiv) **2** **3**



3a 85%, 6:1 d.r., 98% *ee*; **3b** 90%, 5:1 d.r., 97% *ee*; **3c** 80%, 3:1 d.r., 94% *ee*

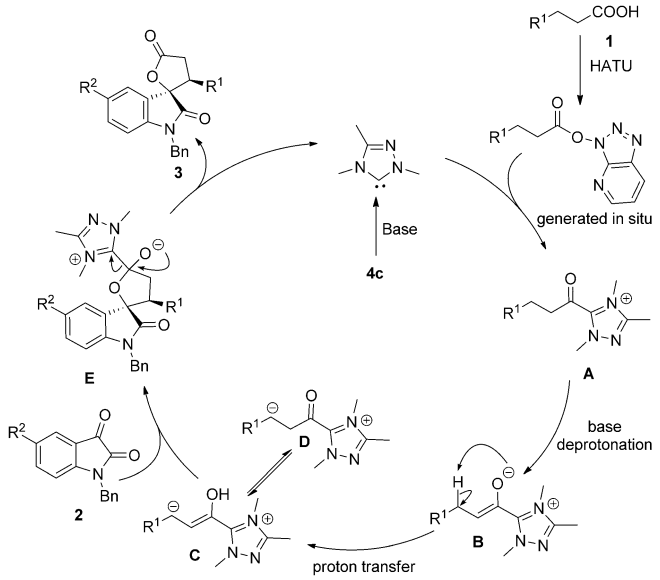
3d 92%, 5:1 d.r., 92% *ee*; **3e** 88%, 5:1 d.r., 88% *ee*; **3f** 86%, 5:1 d.r., 98% *ee*

3g 84%, 8:1 d.r., 99% *ee*; **3h** 80%, 5:1 d.r., 91% *ee*; **3i** 82%, 4.5:1 d.r., 95% *ee*

3j 78%, 6:1 d.r., 95% *ee*; **3k** 83%, 6:1 d.r., 98% *ee*; **3l** 79%, 7:1 d.r., 94% *ee*

3m 66%, 8:1 d.r., 88% *ee*

[a] Reaction conditions: **1** (0.24 mmol), **2** (0.2 mmol), **4c** (0.03 mmol), Cs_2CO_3 (0.3 mmol), HATU (0.3 mmol), DME (4 mL), 20 °C, 12 h; d.r. determined by ^{1}H NMR spectroscopy; the *ee* values were determined by HPLC.



Scheme 5. Plausible catalytic cycle.

reacted with isatin derivatives **2** through nucleophilic addition giving the zwitterionic intermediate **E**. The catalyst could then be regenerated by the release of the final cycloadduct **3**.

In conclusion, we have developed an NHC-catalyzed β-functionalization of saturated carboxylic acid through in situ activation. The present NHC-catalyzed asymmetric process provides an efficient access to spirocyclic oxindolo-γ-butyrolactones in good to high yields with excellent enantioselectivity. Further studies aimed at the expansion of the reaction scope and the further development of analogous cyclization of saturated carboxylic acids are underway in our laboratory.

Experimental Section:

General procedure for the preparation of compounds 3a–3m

An oven-dried 10 mL Schlenk tube equipped with a magnetic stir bar was charged with triazolium salt **4c** (12.6 mg, 0.03 mmol), Cs_2CO_3 (97.5 mg, 0.30 mmol), saturated carboxylic acid **1** (0.24 mmol), isatin **2** (0.2 mmol) and HATU (114.0 mg, 0.3 mmol). This tube was closed with a septum, evacuated, and refilled with nitrogen. To this mixture was added freshly distilled DME (4 mL) with a syringe. Then the mixture was stirred at 0 °C until completion (monitored by TLC). After removal of the solvent under reduced pressure, the resulting crude residue was purified by column chromatography (silicagel, mixtures of petroleum ether/ethyl acetate, 5:1, v/v) to afford the desired product **3**.

Acknowledgements

We are grateful for financial support by National Natural Science Foundation of China (Nos. 21242014, 21372101) and PAPD.

Keywords: annulation · beta-functionalization · N-heterocyclic carbine · organocatalysis · spirocyclic oxindole

[1] a) J. Wang, P. Li, P. Y. Choy, A. S. C. Chan, F. Y. Kwong, *ChemCatChem* **2012**, *4*, 917; b) C. Allais, J.-M. Grassot, J. Rodriguez, T. Constantieux, *Chem. Rev.* **2014**, *114*, 10829; c) M. Fàbregas, A. Gómez-Palomino, M. Pellicena, D. F. Reina, P. Romea, F. Urpí, M. Font-Bardia, *Org. Lett.* **2014**, *16*, 6220; d) C. Schneider, F. Abels, *Org. Biomol. Chem.* **2014**, *12*, 3531; e) M. M. Heravi, P. Hajiabbasi, H. Hamidi, *Curr. Org. Chem.* **2014**, *18*, 489; f) M. Fàbregas, A. Gomez-Palomino, M. Pellicena, D. F. Reina, P. Romea, F. Urpi, M. Font-Bardia, *Org. Lett.* **2014**, *16*, 6220; g) M. Sánchez-Roselló, C. Mulet, M. Guerola, C. del Pozo, S. Fustero, *Chem. Eur. J.* **2014**, *20*, 15697; h) K.-H. Kwon, C. M. Serrano, M. Koch, L. R. Barrows, R. E. Looper, *Org. Lett.* **2014**, *16*, 6048; i) C. He, C. Zhu, B. Wang, H. Ding, *Chem. Eur. J.* **2014**, *20*, 15053.

[2] a) Y. Hayashi, T. Itoh, H. Ishikawa, *Angew. Chem. Int. Ed.* **2011**, *50*, 3920; *Angew. Chem.* **2011**, *123*, 4006; b) X. Zeng, Q. Ni, G. Raabe, D. Enders, *Angew. Chem. Int. Ed.* **2013**, *52*, 2977; *Angew. Chem.* **2013**, *125*, 3050.

[3] For recent reviews on activation of C–H bonds, see: a) J. Yamaguchi, A. D. Yamaguchi, K. Itami, *Angew. Chem. Int. Ed.* **2012**, *51*, 8960; *Angew. Chem.* **2012**, *124*, 9092; b) B. Li, P. H. Dixneuf, *Chem. Soc. Rev.* **2013**, *42*, 5744; c) J. Wencel-Delord, F. Glorius, *Nat. Chem.* **2013**, *5*, 369; d) B.-J. Li, Z.-J. Shi, *Chem. Soc. Rev.* **2012**, *41*, 5588; e) G. E. Dobereiner, R. H. Crabtree, *Chem. Rev.* **2010**, *110*, 681; f) M. C. Haibach, S. Kundu, M. Brookhart, A. S. Goldman, *Acc. Chem. Res.* **2012**, *45*, 947; g) C. Gunanathan, D. Milstein, *Science* **2013**, *341*, 1229712; h) J. He, M. Wasa, K. S. L. Chan, J.-Q. Yu, *J. Am. Chem. Soc.* **2013**, *135*, 3387.

[4] a) D. Shabashov, O. Daugulis, *J. Am. Chem. Soc.* **2010**, *132*, 3965; b) E. T. Nadres, G. I. F. Santos, D. Shabashov, O. Daugulis, *J. Org. Chem.* **2013**, *78*, 9689; c) L. D. Tran, O. Daugulis, *Angew. Chem. Int. Ed.* **2012**, *51*, 5188; *Angew. Chem.* **2012**, *124*, 5278; d) M. Wasa, K. S. L. Chan, X.-G. Zhang, J. He, M. Miura, J.-Q. Yu, *J. Am. Chem. Soc.* **2012**, *134*, 18570; e) K. S. L. Chan, M. Wasa, L. Chu, B. N. Laforteza, M. Miura, J.-Q. Yu, *Nat. Chem.* **2014**, *6*, 146; f) F. Pan, P.-X. Shen, L.-S. Zhang, X. Wang, Z.-J. Shi, *Org. Lett.* **2013**, *15*, 4758; g) Q. Zhang, K. Chen, W.-H. Rao, Y. Zhang, F.-J. Chen, B.-F. Shi, *Angew. Chem. Int. Ed.* **2013**, *52*, 13588; *Angew. Chem.* **2013**, *125*, 13833; h) G. He, G. Chen, *Angew. Chem. Int. Ed.* **2011**, *50*, 5192; *Angew. Chem.* **2011**, *123*, 5298; i) W. A. Nack, G. He, S.-Y. Zhang, C. Lu, G. Chen, *Org. Lett.* **2013**, *15*, 3440.

[5] a) M. T. Pirnot, D. A. Rankic, D. B. C. Martin, D. W. C. MacMillan, *Science* **2013**, *339*, 1593; b) J. A. Terrett, M. D. Clift, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2014**, *136*, 6858.

[6] For selected recent reviews on NHC catalysis, see: a) D. Enders, O. Niemeier, A. Henseler, *Chem. Soc. Rev.* **2007**, *107*, 5606; b) X. Bugaut, F. Glorius, *Chem. Soc. Rev.* **2012**, *41*, 3511; c) A. Grossmann, D. Enders, *Angew. Chem. Int. Ed.* **2012**, *51*, 314; *Angew. Chem.* **2012**, *124*, 320; d) P. Chauhan, D. Enders, *Angew. Chem. Int. Ed.* **2014**, *53*, 1485; *Angew. Chem.* **2014**, *126*, 1509; e) H. U. Vora, P. Wheeler, T. Rovis, *Adv. Synth. Catal.* **2012**, *354*, 1617; f) X.-Y. Chen, S. Ye, *Synlett* **2013**, 1614; g) J. W. Bode, *Nat. Chem.* **2013**, *5*, 813; h) J. Mahatthananchai, J. W. Bode, *Acc. Chem. Res.* **2014**, *47*, 696; i) D. C. M. Albanesel, N. Gaggero, *Eur. J. Org. Chem.* **2014**, 5631.

[7] Y. Cheng, J. H. Peng, Y. J. Li, X. Y. Shi, M. S. Tang, T. Y. Tan, *J. Org. Chem.* **2011**, *76*, 1844.

[8] a) Q. Liu, T. Rovis, *J. Am. Chem. Soc.* **2006**, *128*, 2552; b) D. A. DiRocco, E. L. Noey, K. N. Houk, T. Rovis, *Angew. Chem. Int. Ed.* **2012**, *51*, 2391; *Angew. Chem.* **2012**, *124*, 2441; c) M. Q. Jia, S. L. You, *Chem. Commun.* **2012**, *48*, 6363; d) N. E. Wurz, C. G. Daniliuc, F. Glorius, *Chem. Eur. J.* **2012**, *18*, 16297; e) M. Schedler, D. S. Wang, F. Glorius, *Angew. Chem. Int. Ed.* **2013**, *52*, 2585; *Angew. Chem.* **2013**, *125*, 2645; f) A. Patra, A. Bhunia, A. T. Biju, *Org. Lett.* **2014**, *16*, 4798.

[9] a) V. Nair, S. Vellalth, M. Poonoth, R. Mohan, E. Suresh, *Org. Lett.* **2006**, *8*, 507; b) J. Dugal-Tessier, E. A. O'Bryan, T. B. H. Schroeder, D. T. Cohen, K. A. Scheidt, *Angew. Chem. Int. Ed.* **2012**, *51*, 4963; *Angew. Chem.* **2012**, *124*, 5047; c) H. Lv, W. Q. Jia, L. H. Sun, S. Ye, *Angew. Chem. Int. Ed.* **2013**, *52*, 8607; *Angew. Chem.* **2013**, *125*, 8769; d) X. Chen, X. Fang, Y. R. Chi, *Chem. Sci.* **2013**, *4*, 2613; e) C. Guo, M. Schedler, C. G. Daniliuc, F. Glorius, *Angew. Chem. Int. Ed.* **2014**, *53*, 10232; *Angew. Chem.* **2014**, *126*, 10397; f) S. Bera, R. C. Samanta, C. G. Daniliuc, A. Studer, *Angew. Chem. Int. Ed.*

2014, *53*, 9622; *Angew. Chem.* **2014**, *126*, 9776; g) M. Wang, Z.-Q. Rong, Y. Zhao, *Chem. Commun.* **2014**, *50*, 15309.

[10] a) Z. Fu, J. Xu, T. Zhu, W. W. Y. Leong, Y. R. Chi, *Nat. Chem.* **2013**, *5*, 835; b) Z. Fu, K. Jiang, T. Zhu, J. Torres, Y. R. Chi, *Angew. Chem. Int. Ed.* **2014**, *53*, 6506; *Angew. Chem.* **2014**, *126*, 6624; c) Z. Jin, S. Chen, Y. Wang, P. Zheng, S. Yang, Y. R. Chi, *Angew. Chem. Int. Ed.* **2014**, *53*, 13506; *Angew. Chem.* **2014**, *126*, 13724.

[11] A. Lee, A. Younai, C. K. Price, J. Izquierdo, R. K. Mishra, K. A. Scheidt, *J. Am. Chem. Soc.* **2014**, *136*, 10589.

[12] X.-Y. Chen, Z.-H. Gao, C.-Y. Song, C.-L. Zhang, Z.-X. Wang, S. Ye, *Angew. Chem. Int. Ed.* **2014**, *53*, 11611; *Angew. Chem.* **2014**, *126*, 11795.

[13] a) L. C. Morrill, A. D. Smith, *Chem. Soc. Rev.* **2014**, *43*, 6214; b) D. Belmessieri, L. C. Morrill, C. Simal, A. M. Z. Slawin, A. D. Smith, *J. Am. Chem. Soc.* **2011**, *133*, 2714; c) L. C. Morrill, J. Douglas, T. Lebl, A. M. Z. Slawin, D. J. Fox, A. D. Smith, *Chem. Sci.* **2013**, *4*, 4146; d) D. G. Stark, L. C. Morrill, P.-P. Yeh, A. M. Z. Slawin, T. J. C. O'Riordan, A. D. Smith, *Angew. Chem. Int. Ed.* **2013**, *52*, 11642; *Angew. Chem.* **2013**, *125*, 11856; e) D. G. Stark, T. J. C. O' Riordan, A. D. Smith, *Org. Lett.* **2014**, *16*, 6496; f) S. R. Smith, J. Douglas, H. Prevet, P. Shapland, A. M. Z. Slawin, A. D. Smith, *J. Org. Chem.* **2014**, *79*, 1626; g) G. S. Cortez, R. L. Tennyson, D. Romo, *J. Am. Chem. Soc.* **2001**, *123*, 7945; h) C. A. Leverett, V. C. Purohit, A. G. Johnson, R. L. Davis, D. J. Tantillo, D. Romo, *J. Am. Chem. Soc.* **2012**, *134*, 13348; i) K. A. Morris, K. M. Arendt, S. H. Oh, D. Romo, *Org. Lett.* **2010**, *12*, 3764; j) G. Liu, M. E. Shirley, D. Romo, *J. Org. Chem.* **2012**, *77*, 2496; k) C. A. Leverett, V. C. Purohit, D. Romo, *Angew. Chem. Int. Ed.* **2010**, *49*, 9479; *Angew. Chem.* **2010**, *122*, 9669; l) M. E. Abbasov, D. Romo, *Nat. Prod. Rep.* **2014**, *31*, 1318.

[14] A. El-Faham, F. Albericio, *Chem. Soc. Rev.* **2011**, *111*, 6557.

[15] a) C. Yao, D. Wang, J. Lu, T. Li, W. Jiao, C. Yu, *Chem. Eur. J.* **2012**, *18*, 1914; b) C. Yao, Z. Xiao, R. Liu, T. Li, W. Jiao, C. Yu, *Chem. Eur. J.* **2013**, *19*, 456; c) C. Yao, W. Jiao, Z. Xiao, R. Liu, T. Li, C. Yu, *Tetrahedron* **2013**, *69*, 1133; d) Z. Xiao, C. Yu, T. Li, X. Wang, C. Yao, *Org. Lett.* **2014**, *16*, 3632.

[16] a) A. K. Franz, P. D. Dreyfuss, S. L. Schreiber, *J. Am. Chem. Soc.* **2007**, *129*, 1020; b) G. S. Singh, Z. Y. Desta, *Chem. Rev.* **2012**, *112*, 6104; c) S. Buttachon, A. Chandrapatya, L. Manoch, A. Silva, L. Gales, C. Bruyere, R. Kiss, A. Kijjoa, *Tetrahedron* **2012**, *68*, 3253; d) M. S. Poslusney, B. J. Melancon, P. R. Gentry, D. J. Sheffler, T. M. Bridges, T. J. Utley, J. S. Daniels, C. M. Niswender, P. J. Conn, C. W. Lindsley, *Bioorg. Med. Chem. Lett.* **2013**, *23*, 1860.

[17] L.-H. Sun, L.-T. Shen, S. Ye, *Chem. Commun.* **2011**, *47*, 10136.

Received: January 27, 2015
Published online on ■■ ▮▮, 0000

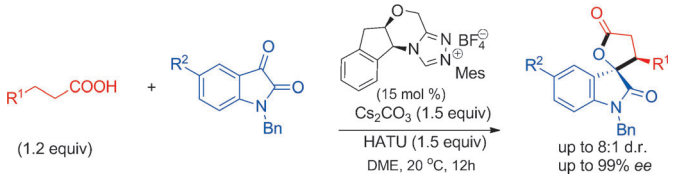
COMMUNICATION

Organocatalysis

*Y. Xie, C. Yu, T. Li, S. Tu, C. Yao**

■■ – ■■

An NHC-Catalyzed In Situ Activation Strategy to β-Functionalize Saturated Carboxylic Acid: An Enantioselective Formal [3+2] Annulation for Spirocyclic Oxindolo-γ-butyrolactones



Top cat: An in situ NHC-catalyzed activation strategy to β-functionalize saturated carboxylic acid was developed (see scheme). This asymmetric formal [3+2] annulation delivered spirocyclic oxindolo-γ-butyrolactones from saturated carboxylic acid and isatin in good yields with high to excellent enantioselectivities. The availability of the starting materials, direct installation of functional units at unreactive carbon atom and the convergent assembly make this protocol attractive for organic synthesis.