NHC Organocatalysis

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Conjugate Umpolung of β,β-Disubstituted Enals by Dual Catalysis with an N-Heterocyclic Carbene and a Brønsted Acid: Facile Construction of Contiguous Quaternary Stereocenters**

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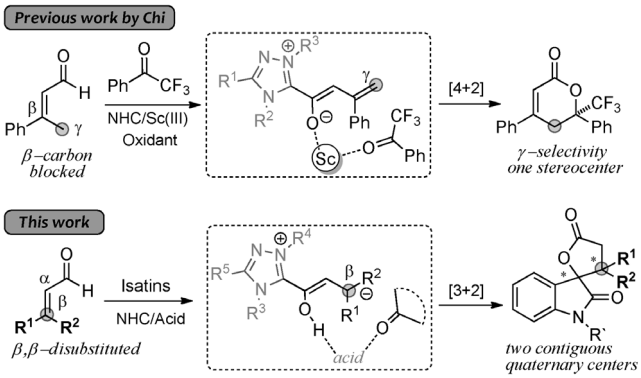
Abstract: *A sterically hindered homoenolate has been generated by the NHC-catalyzed conjugate umpolung of β,β-disubstituted enals and successfully employed in a facile stereoselective annulation with isatins. The strategy provides efficient access to spirocyclic oxindoles bearing two highly congested contiguous quaternary carbon centers. The use of a Brønsted acid cocatalyst was found to be crucial for guaranteeing both excellent reactivity and high stereoselectivity.*

Molecules with structural complexity that present synthetic challenges are not uncommon among biologically active natural products and pharmaceuticals.[1] Therefore, chemists have devoted themselves to the development of new concepts and strategies that employ unprecedented reactivity to address the challenges in organic synthesis.[2] However, the construction of quaternary stereocenters,[3] especially the single-step assembly of compounds with contiguous tetrasubstituted carbon stereocenters, still remains a daunting problem. The impediment to forming such centers is rooted in the inherent tremendous steric congestion imposed by the four non-hydrogen substituents. In order to provide solutions to this challenging issue, rational design and the development of powerful catalytic systems are in high demand.

Over the past decade, N-heterocyclic carbene (NHC) organocatalysis has been extensively studied due to its unique ability to reverse the natural reactivity of a functional group, which offers unconventional access to a set of umpolung reactions.[4] In 2004, we and the group of Bode discovered the unique a^3-d^3 umpolung reactivity of α,β-unsaturated aldehydes in NHC catalysis and independently reported the concept of "conjugate umpolung".[5] From then on, significant advances have been achieved[4] in this field with numerous studies mainly focused on the exploration of various kinds of π-systems such as carbonyl compounds,[6] aldimines,[7] ketimines,[8] *N*-phenyl nitrones,[9] and *N*-acyl hydrazones[10] as electrophiles. Surprisingly, in the vast majority of cases, the range of suitable substrates for conjugate umpolung is limited to simple enals. The investigation of different types of enal substrates is quite limited and still remains in its early stages. Recently, Chi and co-workers developed an elegant NHC-catalyzed [4+2] annulation of β,β-disubstituted enals with trifluoromethyl ketones in the presence of external oxidants.[11a] The substituents at the enal β-carbon were intentionally introduced to suppress homoenolate-type reactivity by means of steric crowding.[11] As a result, the reactivity of the modified enals was smoothly switched from the β-carbon to the γ-position upon oxidation (Scheme 1). In a continuation



Scheme 1. Activation of β,β-disubstituted enals by NHC catalysis.

of our ongoing interest and efforts in NHC umpolung catalysis, we envisaged that the a^3-d^3 umpolung reactivity of the β,β-disubstituted enals might be retained by either increasing the electron density of the corresponding Breslow intermediate or by using a dual activation strategy. Such reactions would represent an efficient and straightforward strategy to synthesize products containing at least one quaternary stereocenter.

Spirocyclic oxindoles are a privileged core skeleton in medicinal chemistry owing to their broad application in the discovery of useful biological tools and novel therapeutic agents.[12] A variety of compounds containing such motifs have already been demonstrated to possess promising bioactivity against cancer[13a,b] and HIV,[13c] as well as affecting the activity of K^+ channels.[13d] Keeping this in mind, we decided to employ the NHC conjugate umpolung strategy to inves-

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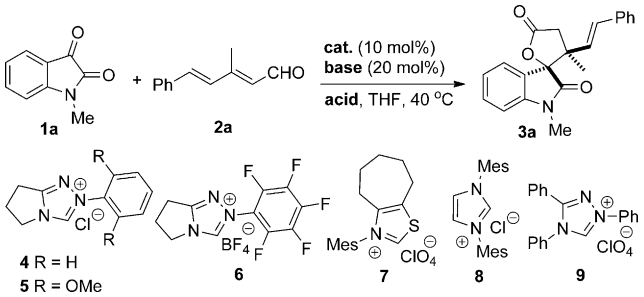
tigate the direct synthesis of spirooxindole frameworks incorporating contiguous quaternary stereocenters (Scheme 1).

Initially, we studied the reaction of *N*-methyl isatin (**1a**) with β,β-disubstituted enal **2a** in the presence of triazolium precatalyst **4** and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in THF. Under these conditions, the desired spirooxindole γ-butyrolactone **3a** was obtained in 66% yield, but the diastereoselectivity was poor. It was pleasing that both the reactivity and the diastereoselectivity could be increased when acetic acid was used as the cocatalyst (Table 1, entry 1). While Brønsted acids have been used previously in NHC organocatalysis, examples in which diastereoselectivity improves are scarce.[7c,14] The electron-richer triazolium salt **5**[15] showed remarkable activity but poorer selectivity, which could be also somewhat increased by adding acetic acid (Table 1, entry 2). Triazolium **6** bearing electron-withdrawing substituents,[15] thiazolium precatalyst **7**, and imidazolium salt **8** were not suitable catalyst for the model reaction without acid; by contrast, the annulated product could be obtained in moderate to excellent yield when the dual catalytic system was applied, although the diastereoselectivity was still unsatisfactory (Table 1, entries 3–5). Pleasingly, it was found that monocyclic triazolium **9** along with acetic acid could provide both outstanding reactivity and selectivity, while no product was observed in the absence of the acid (Table 1, entry 6). Decreasing the acid loading to 0.5 or 0.2 equivalents led to inferior results in terms of both yield and d.r. value (Table 1, entries 7 and 8). However, diastereomeric control could not be further improved when 1.5 equivalents of acetic acid was used (Table 1, entry 9).

Table 1: Screening studies of the NHC-catalyzed diastereoselective annulations of isatin **1a** with β,β-disubstituted enal **2a**.[a]



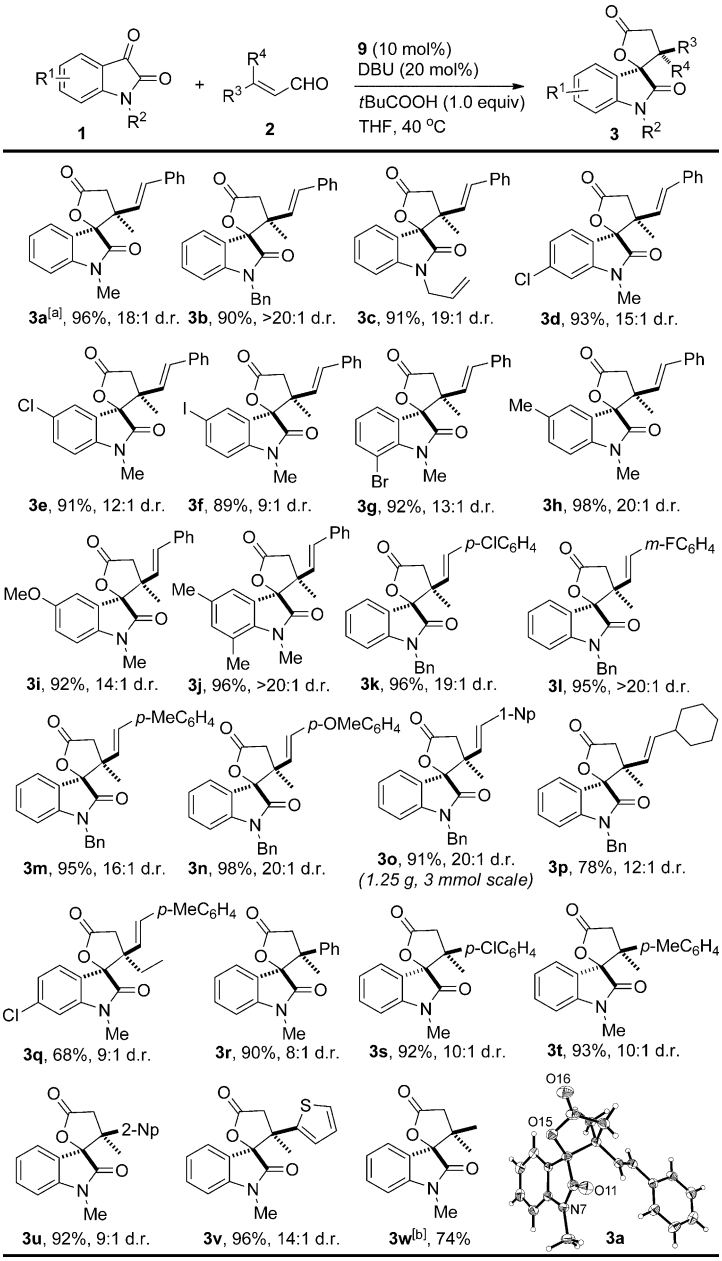
Entry	Cat.	Base	Acid	Yield [%][b]	d.r.[c]
1[d]	**4**	DBU	none	66 (84)	2:1 (6:1)
2[d]	**5**	DBU	none	99 (99)	1.2:1 (4:1)
3[d]	**6**	DBU	none	– (16)	n.d.[i] (4:1)
4[d]	**7**	DBU	none	– (64)	n.d. (1:1)
5[d]	**8**	DBU	none	20 (99)	2:1 (7:1)
6[d]	**9**	DBU	none	– (99)	n.d. (17:1)
7[e]	**9**	DBU	AcOH	99	10:1
8[f]	**9**	DBU	AcOH	42	4:1
9[g]	**9**	DBU	AcOH	99	17:1
10[h]	**9**	K_3PO_4	AcOH	99	17:1
11	**9**	KOAc	AcOH	99	14:1
12	**9**	Et_3N	AcOH	99	17:1
13	**9**	DIPEA	AcOH	70	15:1
14	**9**	DBU	*o*FBA	99	17:1
15	**9**	DBU	*t*BuCO$_2$H	99	18:1
16	**9**	DBU	TsOH	–	n.d.

[a] Unless otherwise noted, reactions were performed with isatin **1a** (0.1 mmol), β,β-disubstituted enal **2a** (0.15 mmol), NHC precatalyst (0.01 mmol), base (0.02 mmol), and acid (0.1 mmol) in THF (1.0 mL) at 40 °C for 6 h. [b] Yield determined by NMR analysis with an internal standard. [c] d.r. determined by ^{1}H NMR spectroscopy. [d] The data in parentheses were obtained when acetic acid was used as cocatalyst. [e] With 0.05 mmol of acetic acid. [f] With 0.02 mmol of acetic acid. [g] With 0.15 mmol of acetic acid. [h] 50 mol% of K_3PO_4 was used due to the low solubility in THF. [i] n.d. = not determined.

Bases such as potassium phosphate, potassium acetate, triethylamine, and Hünig's base (diisopropyl ethyl amine, DIPEA) were also screened, but no better results were gained (Table 1, entries 10–13). A similar result was obtained when the aromatic *o*-fluorobenzoic acid (*o*FBA) was employed, and a slightly higher d.r. value resulted when the sterically bulkier pivalic acid was used (Table 1, entries 14 and 15). Stronger acids such as *p*-toluenesulfonic acid (TsOH) shut down the reaction presumably due to the protonation of the basic NHC catalyst (Table 1, entry 16).

With the optimal conditions in hand, we then investigated the substrate scope of the annulation process. As shown in Scheme 2, different protecting groups on the nitrogen of the isatin were demonstrated to be well tolerated, affording products with excellent yields and diastereoselectivities (**3a**–**3c**). A spectrum of *N*-methyl-protected isatins **1** with various electron-donating and electron-withdrawing groups performed well in this reaction, and good results were generally obtained (**3d**–**3j**). Different substituents at the phenyl ring of the enals had limited effect on the reaction outcome (**3k**–**3n**). Moreover, enals with naphthalene and cyclohexyl moieties were found to be compatible in the catalytic system (**3o**–**3p**). An enal substrate with a β-ethyl group could also give the desired product with two quaternary centers, although the yield was lower most likely due to steric constraints (**3q**). Importantly, a variety of cinnamaldehydes with β,β-disubstituents exhibited remarkable reactivity, and satisfying results were obtained for the corresponding products (**3r**–**3v**). The less activated 3-methylcrotonaldehyde, a fully aliphatic enal substrate, could also deliver the spirocyclic γ-lactone oxindole when the electron-richer NHC precatalyst **5** was used (**3w**). We have also demonstrated that this methodology could be carried out on a preparative scale, with 1.25 g of the product **3o** being obtained in high yield and excellent diastereoselectivity.

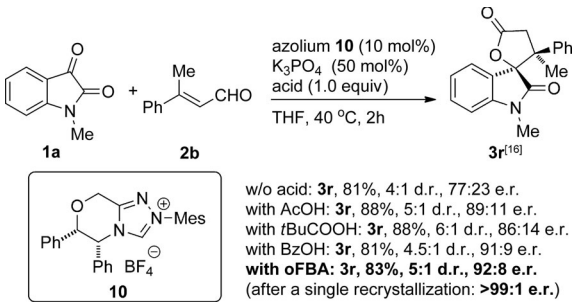
A catalytic enantioselective variant of the annulation process was further explored with a chiral NHC/Brønsted acid catalytic system. It was pleasing that the acid cocatalyst had a beneficial effect on the enantioselectivity of the reaction. As illustrated in Scheme 3, the asymmetric annulation of isatin **1a** and enal **2b** could be catalyzed by the chiral NHC precursor **10** to give the enantioenriched spirooxindole **3r**. However, moderate diastereoselectivity and poor enantioselectivity (77:23 e.r.) was observed in the absence of acid. By contrast, the enantioselectivity improved when acid was employed (an increase in enantiomeric excess of up to 30%). Finally, *o*FBA was found to be the optimal choice, giving **3r** in 83% yield, with a slightly improved d.r. value (5:1 d.r.) and good enantioselectivity (92:8 e.r., which could easily be increased to >99:1 e.r. by a single recrystallization).



Scheme 2. Substrate scope of the diastereoselective [3+2] annulations. Unless otherwise noted, reactions were performed with isatin **1** (0.2 mmol), β,β-disubstituted enal **2** (0.3 mmol), NHC precatalyst (0.02 mmol), DBU (0.04 mmol), and acid cocatalyst (0.2 mmol) in THF (2.0 mL) at 40°C for 4–6 h. Yields are of isolated product after column chromatography. Diastereomeric ratio determined by ^{1}H NMR spectroscopy. [a] Constitution and configuration of **3a** and **3r** were determined by X-ray analysis;[16] other products were assigned by analogy. [b] For the fully aliphatic enal substrate, triazolium **5** (0.02 mmol) and DBU (0.04 mmol) were used in the catalytic system; see the Supporting Information.

Although further optimization of the dual catalytic system was extensively studied, no more improvement could be achieved so far (for details, see the Supporting Information), which highlights the challenges of asymmetric conjugate umpolung of the β,β-disubstituted enals.

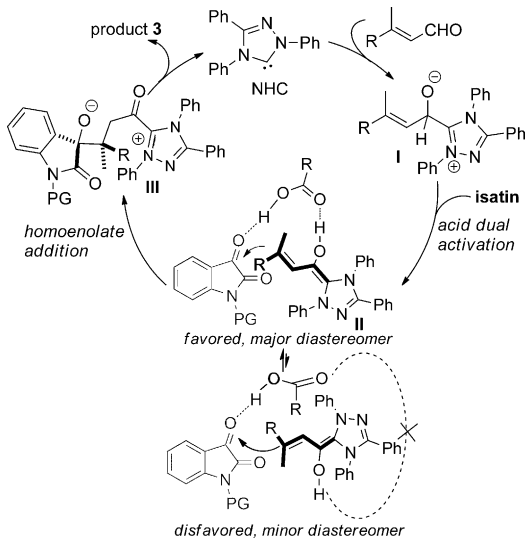
Based on the configuration of the product **3a** determined by X-ray analysis, a plausible mechanism for the reaction is



Scheme 3. Studies on the enantioselectivity of the annulation process. Mes = mesityl.[17]

suggested in Scheme 4. Addition of the NHC catalyst to the enal delivers the tetrahedral intermediate **I**, which leads to the formation of Breslow intermediate **II**.[15b,18] In the presence of acid cocatalyst, this species could feasibly react with the isatin via one of two possible pre-transition-state assemblies. The preference for the favored pathway, which leads to the major observed diastereoisomer, can be rationalized by the presence of two stabilizing hydrogen bonds[19] that might connect the two reaction partners more easily (as opposed to only one such interaction in the disfavored pathway). After diastereoselective formation of the adduct **III**, intramolecular alkoxide attack at the carbonyl group leads to the production of the desired spirooxindoles and regenerates the NHC catalyst.

In conclusion, we have presented an efficient stereoselective annulation of β,β-disubstituted enals with isatins by NHC/Brønsted acid dual catalysis. The reactivity and diastereo- and enantioselectivity of the reaction were found to be highly dependent on the acid cocatalyst. This method provides facile access to a variety of spirocyclic oxindoles bearing two highly



Scheme 4. Proposed mechanism for the NHC/acid dual-catalyzed reaction. PG = protecting group.

congested contiguous quaternary carbon centers. The retained a^3-d^3 umpolung reactivity of such modified enals was disclosed for the first time, which further demonstrates the power of NHC catalysis to overcome challenging issues.[20] We hope that this work will open the door to the use of sterically demanding substrates in NHC organocatalysis and lead to the development of new synthetic methods to access structurally complex products featuring quaternary stereocenters.

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[1] For selected perspectives and reviews, see: a) K. C. Nicolaou, S. A. Snyder, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 11929; b) A. Bauer, M. Brönstrup, *Nat. Prod. Rep.* **2014**, *31*, 35; c) T. Busch, A. Kirschning, *Nat. Prod. Rep.* **2008**, *25*, 318; d) K.-S. Yeung, I. Paterson, *Chem. Rev.* **2005**, *105*, 4237; e) A. Harvey, *Drug Discovery Today* **2000**, *5*, 294.

[2] a) E. J. Corey, X.-M. Cheng, *The Logic of Chemical Synthesis*, Wiley, New York, **1989**; b) K. C. Nicolaou, S. A. Snyder, *Classics in Total Synthesis II: More Targets, Strategies, Methods*, Wiley-VCH, Weinheim, **2003**.

[3] For reviews, see: a) J. Christoffers, A. Baro, *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis*, Wiley-VCH, Weinheim, **2005**; b) C. J. Douglas, L. E. Overman, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5363; c) E. A. Peterson, L. E. Overman, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 11943; d) B. M. Trost, C. Jiang, *Synthesis* **2006**, 369; e) A. Steven, L. E. Overman, *Angew. Chem.* **2007**, *119*, 5584; *Angew. Chem. Int. Ed.* **2007**, *46*, 5488; f) B. Wang, Y. Q. Tu, *Acc. Chem. Res.* **2011**, *44*, 1207; for selected recent examples, see: g) C. Li, B. Breit, *J. Am. Chem. Soc.* **2014**, *136*, 862; h) Z. Chen, J. Sun, *Angew. Chem.* **2013**, *125*, 13838; *Angew. Chem. Int. Ed.* **2013**, *52*, 13593; i) Z.-S. Chen, X.-H. Duan, P.-X. Zhou, S. Ali, J.-Y. Luo, Y.-M. Liang, *Angew. Chem.* **2012**, *124*, 1399; *Angew. Chem. Int. Ed.* **2012**, *51*, 1370; j) B. Tan, N. R. Candeias, C. F. Barbas III, *Nat. Chem.* **2011**, *3*, 473; k) L. Gao, G.-S. Hwang, D. H. Ryu, *J. Am. Chem. Soc.* **2011**, *133*, 20708; l) S. Simaan, I. Marek, *J. Am. Chem. Soc.* **2010**, *132*, 4066; m) J. P. Das, H. Chechik, I. Marek, *Nat. Chem.* **2009**, *1*, 128.

[4] For reviews on NHC catalysis, see: a) M. N. Hopkinson, C. Richter, M. Schedler, F. Glorius, *Nature* **2014**, *510*, 485; b) J. Mahatthananchai, J. W. Bode, *Acc. Chem. Res.* **2014**, *47*, 696; c) S. J. Ryan, L. Candish, D. W. Lupton, *Chem. Soc. Rev.* **2013**, *42*, 4906; d) M. Fèvre, J. Pinaud, Y. Gnanou, J. Vignolle, D. Taton, *Chem. Soc. Rev.* **2013**, *42*, 2142; e) X. Bugaut, F. Glorius, *Chem. Soc. Rev.* **2012**, *41*, 3511; f) D. T. Cohen, K. A. Scheidt, *Chem. Sci.* **2012**, *3*, 53; g) A. Grossmann, D. Enders, *Angew. Chem.* **2012**, *124*, 320; *Angew. Chem. Int. Ed.* **2012**, *51*, 314; h) J. Mahatthananchai, J. W. Bode, *Chem. Sci.* **2012**, *3*, 192; i) J. Izquierdo, G. E. Hutson, D. T. Cohen, K. A. Scheidt, *Angew. Chem.* **2012**, *124*, 11854; *Angew. Chem. Int. Ed.* **2012**, *51*, 11686; j) H. U. Vora, P. Wheeler, T. Rovis, *Adv. Synth. Catal.* **2012**, *354*, 1617; k) A. T. Biju, N. Kuhl, F. Glorius, *Acc. Chem. Res.* **2011**, *44*, 1182; l) H. U. Vora, T. Rovis, *Aldrichimica Acta* **2011**, *44*, 3; m) V. Nair, R. S. Menon, A. T. Biju, C. R. Sinu, R. R. Paul, A. Jose, V. Sreekumar, *Chem. Soc. Rev.* **2011**, *40*, 5336; n) H. U. Vora, T. Rovis, *Aldrichimica Acta* **2011**, *44*, 3; o) P.-C. Chiang, J. W. Bode, *TCI Mail* **2011**, *149*, 2; p) K. Hirano, I. Piel, F. Glorius, *Chem. Lett.* **2011**, *40*, 786; q) J. L. Moore, T. Rovis, *Top. Curr. Chem.* **2010**, *291*, 77; r) E. M. Phillips, A. Chan, K. A. Scheidt, *Aldrichimica Acta* **2009**, *42*, 55; s) V. Nair, S. Vellalath, B. P. Babu, *Chem. Soc. Rev.* **2008**, *37*, 2691; t) N. Marion, S. Díez-González, S. P. Nolan, *Angew. Chem.* **2007**, *119*, 3046; *Angew. Chem. Int. Ed.* **2007**, *46*, 2988; u) D. Enders, O. Niemeier, A. Henseler, *Chem. Rev.* **2007**, *107*, 5606; v) D. Enders, T. Balensiefer, *Acc. Chem. Res.* **2004**, *37*, 534.

[5] a) C. Burstein, F. Glorius, *Angew. Chem.* **2004**, *116*, 6331; *Angew. Chem. Int. Ed.* **2004**, *43*, 6205; b) S. S. Sohn, E. L. Rosen, J. W. Bode, *J. Am. Chem. Soc.* **2004**, *126*, 14370; c) C. Burstein, S. Tschan, X. Xie, F. Glorius, *Synthesis* **2006**, 2418.

[6] For selected recent examples, see: a) K. P. Jang, G. E. Hutson, R. C. Johnston, E. O. McCusker, P. H.-Y. Cheong, K. A. Scheidt, *J. Am. Chem. Soc.* **2014**, *136*, 76; b) J. Dugal-Tessier, E. A. O'Bryan, T. B. H. Schroeder, D. T. Cohen, K. A. Scheidt, *Angew. Chem.* **2012**, *124*, 5047; *Angew. Chem. Int. Ed.* **2012**, *51*, 4963; c) L.-H. Sun, L.-T. Shen, S. Ye, *Chem. Commun.* **2011**, *47*, 10136; d) Y. Li, Z.-A. Zhao, H. He, S.-L. You, *Adv. Synth. Catal.* **2008**, *350*, 1885; e) V. Nair, S. Vellalath, M. Poonoth, R. Mohan, E. Suresh, *Org. Lett.* **2006**, *8*, 507; f) V. Nair, S. Vellalath, M. Poonoth, E. Suresh, *J. Am. Chem. Soc.* **2006**, *128*, 8736; g) P.-C. Chiang, J. Kaeobamrung, J. W. Bode, *J. Am. Chem. Soc.* **2007**, *129*, 3520; h) B. Cardinal-David, D. E. A. Raup, K. A. Scheidt, *J. Am. Chem. Soc.* **2010**, *132*, 5345; i) X. Fang, K. Jiang, C. Xing, L. Hao, Y. R. Chi, *Angew. Chem.* **2011**, *123*, 1950; *Angew. Chem. Int. Ed.* **2011**, *50*, 1910; j) W. W. Y. Leong, X. Chen, Y. R. Chi, *Green Chem.* **2013**, *15*, 1505.

[7] a) M. He, J. W. Bode, *Org. Lett.* **2005**, *7*, 3131; b) V. Nair, V. Varghese, B. P. Babu, C. R. Sinu, E. Suresh, *Org. Biomol. Chem.* **2010**, *8*, 761; c) X. Zhao, D. A. DiRocco, T. Rovis, *J. Am. Chem. Soc.* **2011**, *133*, 12466.

[8] a) M. Rommel, T. Fukuzumi, J. W. Bode, *J. Am. Chem. Soc.* **2008**, *130*, 17266; b) P. Zheng, C. A. Gondo, J. W. Bode, *Chem. Asian J.* **2011**, *6*, 614; c) B. Zhang, P. Feng, L. H. Sun, Y. X. Cui, S. Ye, N. Jiao, *Chem. Eur. J.* **2012**, *18*, 9198; d) H. Lv, B. Tiwari, J. Mo, C. Xing, Y. R. Chi, *Org. Lett.* **2012**, *14*, 5412.

[9] E. M. Phillips, T. E. Reynolds, K. A. Scheidt, *J. Am. Chem. Soc.* **2008**, *130*, 2416.

[10] D. E. A. Raup, B. Cardinal-David, D. Holte, K. A. Scheidt, *Nat. Chem.* **2010**, *2*, 766.

[11] a) J. Mo, X. Chen, Y. R. Chi, *J. Am. Chem. Soc.* **2012**, *134*, 8810; b) X. Chen, S. Yang, B.-A. Song, Y. R. Chi, *Angew. Chem.* **2013**, *125*, 11340; *Angew. Chem. Int. Ed.* **2013**, *52*, 11134; c) M. Wang, Z. Huang, J. Xu, Y. R. Chi, *J. Am. Chem. Soc.* **2014**, *136*, 1214.

[12] For selected reviews on spirocyclic oxindoles, see: a) L. Mander, H.-W. Liu, *Natural Products Structural Diversity II*, Elsevier, New York, **2010**; b) D. Cheng, Y. Ishihara, B. Tan, C. F. Barbas III, *ACS Catal.* **2014**, *4*, 743; c) G. S. Singh, Z. Y. Desta, *Chem. Rev.* **2012**, *112*, 6104; d) R. Rios, *Chem. Soc. Rev.* **2012**, *41*, 1060; e) C. V. Galliford, K. A. Scheidt, *Angew. Chem.* **2007**, *119*, 8902; *Angew. Chem. Int. Ed.* **2007**, *46*, 8748; f) B. M. Trost, M. K. Brennan, *Synthesis* **2009**, 3003.

[13] a) K. Ding, Y. Lu, Z. Nikolovska-Coleska, S. Qiu, Y. Ding, W. Gao, J. Stuckey, K. Krajewski, P. P. Roller, Y. Tomita, D. A. Parrish, J. R. Deschamps, S. Wang, *J. Am. Chem. Soc.* **2005**, *127*, 10130; b) M. M.-C. Lo, C. S. Neumann, S. Nagayama, E. O. Perlstein, S. L. Schreiber, *J. Am. Chem. Soc.* **2004**, *126*, 16077; c) G. Kumari, M. M. Nutan, S. K. Gupta, R. K. Singh, *Eur. J. Med. Chem.* **2011**, *46*, 1181; d) C.-H. Chou, C.-L. Gong, C.-C. Chao, C.-H. Lin, C.-Y. Kwan, C.-L. Hsieh, Y.-M. Leung, *J. Nat. Prod.* **2009**, *72*, 830.

[14] For selected examples, see: a) D. A. DiRocco, T. Rovis, *J. Am. Chem. Soc.* **2011**, *133*, 10402; b) Z. Fu, H. Sun, S. Chen, B. Tiwari, G. Li, Y. R. Chi, *Chem. Commun.* **2013**, *49*, 261; c) S. Kuwano, S. Harada, B. Kang, R. Oriez, Y. Yamaoka, K. Takasu, K. Yamada, *J. Am. Chem. Soc.* **2013**, *135*, 11485.

[15] For the effect of the *N*-aryl substituent in the NHC, see: a) T. Rovis, *Chem. Lett.* **2008**, *37*, 2; b) C. J. Collett, R. S. Massey,

O. R. Maguire, A. S. Batsnaov, A. C. O'Donoghue, A. D. Smith, *Chem. Sci.* **2013**, *4*, 1514; c) M. Schedler, R. Fröhlich, C.-G. Daniliuc, F. Glorius, *Eur. J. Org. Chem.* **2012**, 4164.

[16] The absolute configuration of **3r** was determined by X-ray analysis. CCDC 1001625 (**3a**) and 1001626 (**3r**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[17] For more details of the asymmetric screening studies of the annulation process, see the Supporting Information.

[18] a) A. Miyashita, A. Kurachi, Y. Matsuoka, N. Tanabe, Y. Suzuki, K. Iwamoto, T. Higashino, *Heterocycles* **1997**, *44*, 417; b) R. Breslow, R. Kim, *Tetrahedron Lett.* **1994**, *35*, 699; c) W. Schrader, P. P. Handayani, C. Burstein, F. Glorius, *Chem. Commun.* **2007**, 716.

[19] For reviews on hydrogen-bonding catalysis, see: a) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713; b) T. Akiyama, *Chem. Rev.* **2007**, *107*, 5744; c) S.-L. You, Q. Cai, M. Zeng, *Chem. Soc. Rev.* **2009**, *38*, 2190.

[20] Other less activated carbonyl coupling partners (for example, ethyl benzoylformate or 2,2,2-trifluoroacetophenone) could not give the [3+2] γ-lactone with the current catalytic system.

