ORGANIC LETTERS

2012
Vol. 14, No. 11
2894–2897

N-Heterocyclic Carbene (NHC)-Catalyzed Highly Diastereo- and Enantioselective Oxo-Diels–Alder Reactions for Synthesis of Fused Pyrano[2,3-*b*]indoles

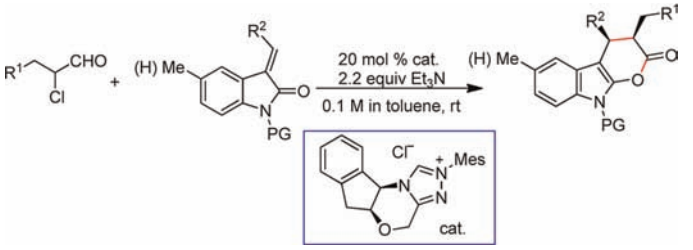
Limin Yang,[†,‡] Fei Wang,[†,‡] Pei Juan Chua,[‡] Yunbo Lv,[‡] Liang-Jun Zhong,[†] and Guofu Zhong*[,†]

College of Materials, Chemistry & Chemical Engineering and School of Medicine, Hangzhou Normal University, Hangzhou 310036, China, and Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, 21 Nanyang Link, Singapore 637371, Singapore

zgf@hznu.edu.cn

Received April 30, 2012

ABSTRACT



A chiral *N*-heterocyclic carbene (NHC)-catalyzed Diels–Alder reaction of 2-oxoindolin-3-ylidenes and α-chloroaldehydes was developed for the synthesis of fused pyrano[2,3-*b*]indoles in good to excellent yields (up to 99%) with high *cis*-diastereoselectivities (>99:1 *dr*) and enantioselectivities (up to >99% *ee*).

The unique electronic characteristics of *N*-heterocyclic carbenes (NHCs) not only promote development of new organometallic processes[1] but also allow them to act as catalysts in organocatalytic reactions.[2] The NHC-catalyzed Diels–Alder reaction,[3] an important milestone in NHC organocatalysis, is different from the traditional a^1-d^1 umpolung (benzoin condensation[4] and Stetter reaction[5]) and a^3-d^3 umpolung (homoenolate cycloaddition) approaches.[6] Very recently, we disclosed a chiral NHC-catalyzed hetero-Diels–Alder reaction of oxodiazene and in situ generated enolate species from α-chloroaldehydes for the synthesis of highly enantioselective α-amino acid derivatives.[7] Our ongoing interest in the NHC-catalyzed hetero-Diels–Alder

[†] Hangzhou Normal University.
[‡] Nanyang Technological University.

(1) For reviews on NHC as ligands, see: (a) Bourissou, D.; Guerret, O.; Gabbai, F. P.; Bertrand, G. *Chem. Rev.* **2000**, *100*, 39–91. (b) Herrmann, W. A.; Weskamp, T.; Bohm, V. P. W. *Adv. Organomet. Chem.* **2001**, *48*, 1–69. (c) Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290–1309. (d) Scott, N. M.; Nolan, S. P. *Eur. J. Inorg. Chem.* **2005**, *44*, 1815–1828.

(2) For reviews on NHC as organocatalysts, see: (a) Seebach, D. *Angew. Chem., Int. Ed.* **1979**, *18*, 239–258. (b) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606–5655. (c) Moore, J. L.; Rovis, T. *Top. Curr. Chem.* **2010**, *291*, 77–144. (d) Marion, N.; Díez-González, S.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2988–3000.

(3) For references of NHC-catalyzed Diels–Alder reactions, see: (a) He, M.; Struble, J. R.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 8418–8420. (b) He, M.; Uc, G. J.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 15088–15089. (c) Struble, J. R.; Kaeobamrung, J.; Bode, J. W. *Org. Lett.* **2008**, *10*, 957–960. (d) He, M.; Beahm, B. J.; Bode, J. W. *Org. Lett.* **2008**, *10*, 3817–3820.

(4) (a) Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719–3726. (b) Sheehan, J.; Hunneman, D. H. *J. Am. Chem. Soc.* **1966**, *88*, 3666–3667. (c) Enders, D.; Breuer, K. *Comprehensive Asymmetric Catalysis*; Springer-Verlag: Heidelberg, Germany, 1999; Vol. 3, pp 1093–1102.

(5) (a) Stetter, H. *Angew. Chem., Int. Ed.* **1976**, *15*, 639–647. (b) Enders, D. *Stereoselective Synthesis*; Springer-Verlag: Heidelberg, Germany, 1993; pp 63–90. (c) Enders, D.; Breuer, K.; Runsink, J.; Teles, J. H. *Helv. Chim. Acta* **1996**, *79*, 1899–1902.

(6) (a) Yang, L.; Tan, B.; Wang, F.; Zhong, G. *J. Org. Chem.* **2009**, *74*, 1744–1746. (b) Sohn, S. S.; Rosen, E. L.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 14370–14371. (c) Burstein, C.; Glorius, F. *Angew. Chem., Int. Ed.* **2004**, *43*, 6205–6208. (d) He, M.; Bode, J. W. *Org. Lett.* **2005**, *7*, 3131–3134. (e) Chan, A.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 5334–5335. (f) Phillips, E. M.; Reynolds, T. E.; Scheidt, K. A. *J. Am. Chem. Soc.* **2008**, *130*, 2416–2417.

10.1021/ol301175z
Published on Web 05/18/2012

reaction[8] of in situ generated enolate species prompted us to investigate the cycloaddition with α,β-unsaturated amide to afford dihydropyranone moieties, which are important building blocks in the synthesis of natural products, and biologically active compounds.[9]

The synthesis of an α,β-unsaturated amide could be classically carried out from commercially available isatins. Presumably, activation of the isatin C3−O double bond via a simple one-step Wittig−Horner reaction results in the formation of 2-oxoindolin-3-ylidenes in excellent yields. Moreover, this strategy being based on the annulation of indoles opens up a new avenue for the synthesis of fused pyran[2,3-*b*]indole skeletons, one of the most important heterocycles and key structural units of biologically active alkaloids.[10] Although significant advances have been achieved in the development of these derivatives for the synthesis of biologically important compounds,[11] enantioselective variants are still very limited.

A study that was carried out by Ye and co-workers presented a formal [4 + 2] cycloaddition of ketenes with oxindoles yielding indole-fused dihydropyranones.[12] However, the diastereo- and enantioselectivities obtained were quite unsatisfactory.

To address the challenge of achieving high optical purity, *N*-mesityl-substituted triazolium salt[13] (refer to cat.) was chosen as the catalyst for this reaction and racemic α-chloroaldehyde **1** was used as the dienophile precursor to generate in situ the enolate species from elimination of HCl from the NHC-α-chloroaldehyde adduct. We envisioned that excellent diastereoselectivities and absolute stereochemistries can be rationalized due to the highly preferred *endo*-*cis*-transition state. The hypothesis was based on DFT calculations that determined that *cis*-enolates are thermodynamically more stable than the *trans* forms by approximately 3.9−6.5 kcal/mol.[7] In the active *cis*-enolate, the *N*-substituted group is prone to be "*trans*" to the oxo group and this mode is reinforced by the presence of the bulky triazolium moiety. The stereochemistry of 2-oxoindolin-3-ylidenes in this [4 + 2] cycloaddition reaction proved to exhibit an (*E*)-configuration.[14] The *cis*-diastereoselectivity would arise from a *cis*-enolate reacting as the dienophile with (*E*)-2-oxoindolin-3-ylidenes via an endo-transition state. In this transition state mode, the *re*-face is completely blocked by the indane moiety of the carbene catalyst, leaving the *si*-face more accessible for the [4 + 2] cycloaddition with the 2-oxoindolin-3-ylidene substrate (Figure 1).

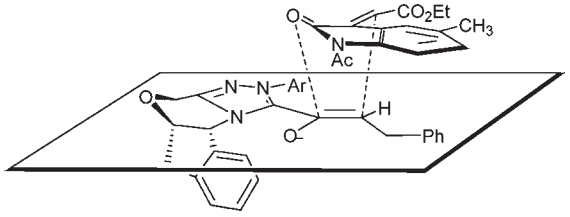


Figure 1. Proposed transtion state.

To test the concept, we carried out the reaction using 2.0 equiv of α-chloroaldehyde **2a** and 3-alkylenyloxindole **1a** with *N*-mesityl-substituted triazolium salt in the presence of base. The results were summarized in Table 1. As expected, 20 mol % of *N*-mesityl substituted triazolium salt effectively promoted the reaction in the presence of Et_3N in dichloromethane at room temperature and delivered the desired product with excellent diastereo- and enantioselectivity (Table 1, entry 1). Next, the use of different bases and solvents was evaluated for this reaction. DIPEA was found to slightly decrease the enantioselectivity (entry 2). When DBU was employed, the yield decreased dramatically even though there was no loss in diastereo- and enantioselectivity (entry 3). We observed that the inorganic bases were deemed to be unsuitable for the reaction, as they led to lowered yields and enantioselectivities (entries 4 and 5).

The screening of solvents revealed that toluene was the most ideal (entry 12), while ethyl acetate gave the worst result with a 65% yield, 85% *ee*, and uncompromised diastereoselectivity (entry 6). *n*-Hexane afforded comparable results to that of toluene with a prolonged reaction time (18 h, entry 10). When the catalyst loading was lowered to 10 mol %, similar results were obtained, albeit with a longer reaction time (entry 13). However, when the catalyst loading was further decreased to 5 mol %, a prolonged reaction time (18 h) was required and it resulted

(7) For a computational study regarding NHC-catalyzed oxo-Diels−Alder reaction, see: (a) Kaeobamrung, J.; Kozlowski, M. C.; Bode, J. W. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 20661–20665. (b) Yang, L.; Wang, F.; Lee, R.; Lv, Y.; Huang, K.-W.; Zhong, G. Submitted.

(8) Other approaches to NHC-catalyzed oxo-Diels−Alder reactions: (a) Zhang, Y.-R.; Lv, H.; Zhou, D.; Ye, S. *Chem.—Eur. J.* **2008**, *14*, 8473–8476. (b) Kobayashi, S.; Kinoshita, T.; Uehara, H.; Sudo, T.; Ryu, I. *Org. Lett.* **2009**, *11*, 3934–3937. (c) Fang, X.; Chen, X.; Chi, Y. R. *Org. Lett.* **2011**, *13*, 4708–4711. (d) Ling, K. B.; Smith, A. D. *Chem. Commun.* **2011**, *47*, 373–375.

(9) (a) Das, B.; Laxminarayana, K.; Krishnaiah, M.; Kumar, D. N. *Bioorg. Med. Chem. Lett.* **2009**, *22*, 6396–6398. (b) Kasaplar, P.; Yilmazer, O.; Cagir, A. *Bioorg. Med. Chem.* **2009**, *1*, 311–314. (c) Hamilton, H. W.; Tait, B. D.; Gajda, C.; Hagen, S. E.; Ferguson, D.; Lunney, E. A.; Pavlovsky, A.; Tummino, P. J. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 719–724.

(10) (a) Dewick, P. M. *Medicinal Natural Products: A Biosynthetic Approach*, 2nd ed.; Wiley: New York, 2002; pp 189200. (b) Gataullin, R. R. *J. Org. Chem.* **2008**, *45*, 321–354.

(11) (a) Ohnuma, T.; Kasuya, H.; Kimura, Y.; Ban, Y. *Heterocycles* **1982**, *17*, 377–380. (b) Nakagawa, M.; Sodeoka, M.; Yamaguchi, K.; Hino, T. *Chem. Pharm. Bull.* **1984**, *32*, 1373–1384. (c) Fritz, H.; Losacker, P. *Justus Liebigs Ann. Chem.* **1967**, *709*, 135–150. (d) Feldman, K. S.; Karatjas, A. G. *Org. Lett.* **2004**, *6*, 2849–2852. (e) Kam, T. S.; Tan, S. J.; Ng, S. W.; Komiyama, K. *Org. Lett.* **2008**, *10*, 3749–3752. (f) Reh, S.; Bergman, J. *Tetrahedron* **2005**, *61*, 3115–3123.

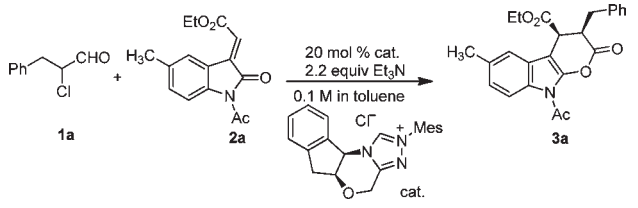
(12) Lv, H.; Chen, X.-Y.; Sun, L.-H.; Ye, S. *J. Org. Chem.* **2010**, *75*, 6973–6976.

(13) (a) For review of the chemistry of *N*-mesityl catalysts, see: Chiang, P.-C.; Bode, J. W. *TCI MAIL* **2011**, *149*, 2–17. (b) For their syntheses, see: Struble, J. R.; Bode, J. W. *Org. Synth.* **2010**, *87*, 362–376. (c) For mechanistic studies, see: Mahatthananchai, J.; Bode, J. W. *Chem. Sci.* **2012**, *3*, 192–197.

(14) (a) Long, D. R.; Richards, C. G.; Ross, M. S. F. *J. Hetereocycl. Chem.* **1978**, *15*, 633–636. (b) Autrey, R. L.; Tahk, F. C. *Tetrahedron* **1967**, *23*, 901–917. (c) Jones, G.; Rae, W. J. *Tetrahedron* **1966**, *22*, 3021–3026.

in a slight decrease in both yield and *ee* (entry 14). So a 10 mol % catalyst loading was chosen for this reaction. Lowering of the reaction temperature led to a longer reaction time (10 h) and unsatisfactory results (entry 15). When the reaction was performed at 30 °C, the reaction was completed within 10 min, but with a lower yield, possibly due to the decomposition of α-chloroaldehyde (Table 1, entry 16). It is particularly noteworthy that, in all cases, the diastereoselectivity of the reaction was excellent (> 99:1 *dr*).

Table 1. Optimization of Reaction Conditions[a]

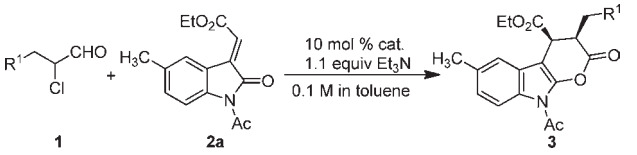


entry	solvent	base	*t* (h)	yield (%)[b]	*ee* (%)[c]	*dr*[d]
1	CH_2Cl_2	Et_3N	6.5	64	90	>99:1
2	CH_2Cl_2	DIPEA	7	60	86	>99:1
3	CH_2Cl_2	DBU	5	20	90	>99:1
4	CH_2Cl_2	Cs_2CO_3	3	43	83	>99:1
5	CH_2Cl_2	*t*-BuOK	1.5	50	88	>99:1
6	EA	Et_3N	0.3	65	85	>99:1
7	Et_2O	Et_3N	4	80	87	>99:1
8	THF	Et_3N	1	67	85	>99:1
9	$CHCl_3$	Et_3N	0.5	73	94	>99:1
10	*n*-hexane	Et_3N	18	80	96	>99:1
11	PhCl	Et_3N	3	60	87	>99:1
12	toluene	Et_3N	0.5	82	97	>99:1
13[e]	toluene	Et_3N	0.6	82	97	>99:1
14[f]	toluene	Et_3N	18	75	92	>99:1
15[g]	toluene	Et_3N	10	70	95	>99:1
16[h]	toluene	Et_3N	0.2	60	95	>99:1

[a] Unless otherwise specified, the reaction was performed on a 0.2 mmol scale in solvent (2 mL) at rt. [b] Yields of isolated products. [c] *ee* values determined by HPLC analysis on Chiralcel IA, IB, or IC column (see the Supporting Information). [d] *dr* values determined by ^1H NMR. [e] Used 10 mol % of catalyst and 1.1 equiv of Et_3N. [f] 5 mol % of catalyst used. [g] Performed at 0 °C. [h] Performed at 30 °C.

With the optimal reaction conditions established, the scope of this [4 + 2] cycloaddition was investigated (Tables 2 and 3). The reaction proceeded smoothly for a broad spectrum of α-chloroaldehydes to afford the desired products in good yields and excellent optical purity (Table 2), with the exception of 3-(benzyloxy)-2-chloropropanal (entry 7). The lower enantioselectivity of **3g** was presumably due to the easier formation of *trans*-enolate species by using 3-(benzyloxy)-2-chloropropanal than other α-chloroaldehydes. In general, α-chloroaldehydes derived from linear aliphatic aldehydes favor the [4 + 2] cycloaddition reaction with 3-alkylenyloxindole **2a** to deliver good results (Table 2, entries 4, 5, and 8). The reaction was also

Table 2. Substrate Scope of NHC-Catalyzed [4 + 2] Cycloaddition[a]



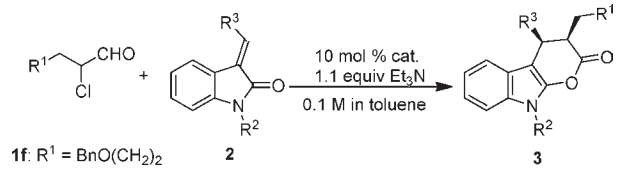
entry	R^1 (**1**)	*t* (h)	yield (%)[b]	*ee* (%)[c]	*dr*[d]
1	C_6H_5 (**1a**)	0.6	82 (**3a**)	97	>99:1
2	4-BrBnOC_2H_4 (**1b**)	0.5	87 (**3b**)	98	>99:1
3	TBSOC_2H_4 (**1c**)	14	70 (**3c**)	95	>99:1
4	C_3H_7 (**1d**)	6	82 (**3d**)	98	>99:1
5	CH_3 (**1e**)	0.5	90 (**3e**)	>99	>99:1
6	BnOC_2H_4 (**1f**)	0.3	92 (**3f**)	>99	>99:1
7	BnO (**1g**)	1	72 (**3g**)	82	>99:1
8	C_6H_{13} (**1h**)	0.3	93 (**3h**)	99	>99:1

[a] Reaction was performed in 0.2 mmol scale in anhydrous toluene (2 mL) at rt. [b] Yields of isolated products. [c] *ee* values determined by HPLC analysis on Chiralcel IA, IB, or IC column (see the Supporting Information). [d] *dr* values determined by ^1H NMR.

very well tolerated with 5-(benzyloxy)-2-chloropentanal in which optically pure products were obtained quantitatively within 30 min (Table 2, entry 6).

A wide range of 2-oxoindolin-3-ylidenes was also tested using 5-(benzyloxy)-2-chloropentanal under the optimized conditions (Table 3). In most cases, the reactions were completed within 30 min except in the case of the nonprotected 2-oxoindolin-3-ylidene. Different *N*-protecting groups were also investigated in the reaction. The nonprotected counterpart was well tolerated in the reaction, affording excellent enantio- and diastereoselectivity despite

Table 3. Substrate Scope of NHC-Catalyzed [4 + 2] Cycloaddition[a]



entry	R^2, R^3	*t* (h)	yield (%)[a]	*ee* (%)[a]	*dr*[a]
1	Ac, CO_2Et (**2b**)	0.3	95 (**3i**)	96	>99:1
2	Ac, CO_2Me (**2c**)	0.5	86 (**3j**)	98	>99:1
3	Ac, COMe (**2d**)	0.3	75 (3k)	97	>99:1
4	H, CO_2Et (**2e**)	5	61 (**3l**)	>99	>99:1
5	Ac, CO_2Bn (**2f**)	0.5	78 (**3m**)	97	>99:1
6	Bz, CO_2Et (**2g**)	0.2	84 (**3n**)	98	>99:1
7	Boc, CO_2Et (**2h**)	0.2	99 (**3o**)	>99	>99:1
8	Ts, CO_2Et (**2i**)	0.2	71 (**3p**)	99	>99:1

[a] See corresponding column footnote in Table 2.

the lower yield and longer reaction time needed (Table 3, entry 4). The *N*-Boc-protected 2-oxoindolin-3-ylidene gave the best result, affording the corresponding optically pure product with quantitative yield.

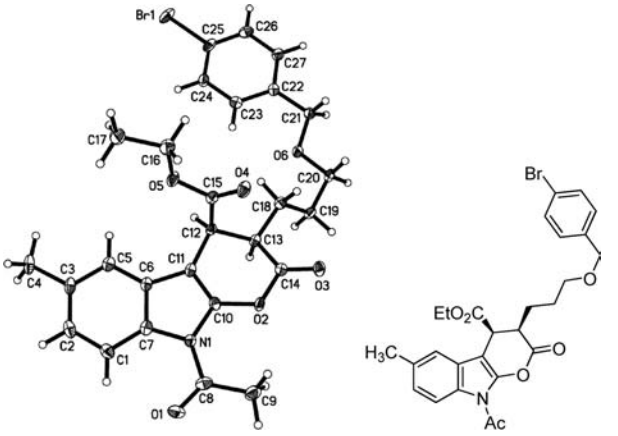
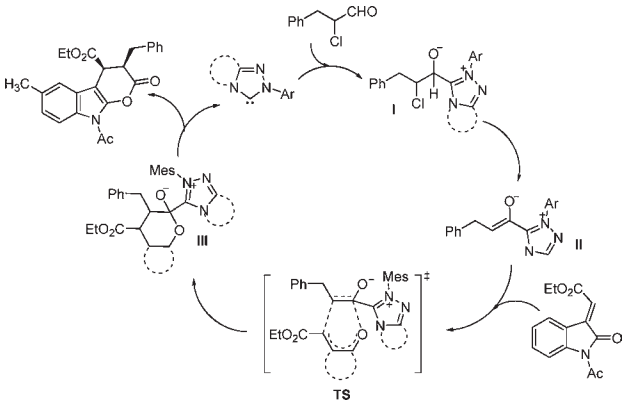


Figure 2. X-ray crystal structure of **3b**. Thermal ellipsoids were shown at 50% probability.

To determine the stereochemistry of the 3,4-dihydropyrano[2,3-*b*]indol-2(9*H*)-one obtained from the chiral NHC-catalyzed [4 + 2] cycloaddition of α-chloroaldehydes with 2-oxoindolin-3-ylidenes, the X-ray crystallographic analysis of the product **3b** was performed to provide the absolute configuration (Figure 2). The chiral *cis*-*N*-mesityl substituted triazolium salt prepared from (1*S*,2*R*)-(+)-*cis*-1-aminoindan-2-ol afforded exclusively the *cis*-(3*R*,4*S*)-3,4-dihydropyrano[2,3-*b*]indol-2(9*H*)-one **3b**.

Our proposed pathway of this [4 + 2] cycloaddition reaction (Scheme 1) first involves the nucleophilic addition of an NHC organocatalyst to an α-chloroaldehyde affording adduct **I**. It is followed by elimination of hydrogen chloride to provide enolate species **II**. The enolate species then participates in the [4 + 2] cycloaddition with 2-oxoindolin-3-ylidene to give adduct **III**. Subsequent

Scheme 1. Proposed Mechanism



acylation completes the catalytic cycle and releases the enantioenriched pyran[2,3-*b*]indole and regenerates the NHC catalyst.

In conclusion, a chiral NHC-catalyzed Diels–Alder reaction of 2-oxoindolin-3-ylidenes and α-chloroaldehydes was developed for the synthesis of fused 3,4-dihydropyrano[2,3-*b*]indol-2(9*H*)-ones in good to excellent yields (up to 99%) with high *cis*-diastereoselectivities (> 99:1 *dr*) and enantioselectivities (up to 99% ee). This protocol holds great potential in the synthesis of biologically active fused pyrano[2,3-*b*]indole derivatives in high enantiomeric purity.

Acknowledgment. We are thankful for financial support for this work provided by the Hangzhou Normal University and the MOE in Singapore (ARC 12/07 #T206B3225).

Supporting Information Available. Experimental details and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.