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Bifunctional N-Heterocyclic Carbene-Catalyzed Highly Enantioselective Synthesis of Spirocyclic Oxindolo-β-lactams

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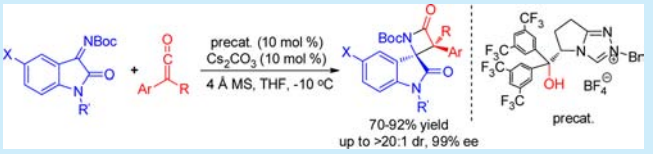
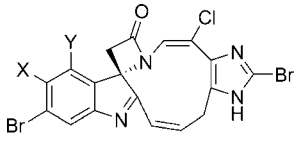
Supporting Information

ABSTRACT: The N-heterocyclic carbene-catalyzed Staudinger reaction of ketenes with isatin-derived ketimines was investigated. The bifunctional NHCs with a free hydroxyl group were demonstrated as efficient catalysts for the reaction, giving the corresponding spirocyclic oxindolo-β-lactams in high yields with excellent diastereo- and enantioselectivities.



Spirocyclic indolo-β-lactams, which combine two unique heterocycles of indole[1] and β-lactam,[2] is a motif found in natural products, such as chartelines isolated from the marine bryozoan *Chartella papyracea* (Scheme 1).[3] Synthetic indolo-β-lactams also showed significant antibacterial,[4] antiviral[5] and antifungal activities.[6] Due to the unique structure and potential bioactivities, the spirocyclic indolo-β-lactams have been interesting targets for organic synthesis. Several approaches, including the cycloaddition of ketenes and imines,[7] cyclization of β-lactam-4-ylidenes with aryl isocyanates,[8] and ring contraction of pyrroloindoline,[9] have been reported. However, the enantioselective construction of spirocyclic indolo-β-lactams remains unrecovered.

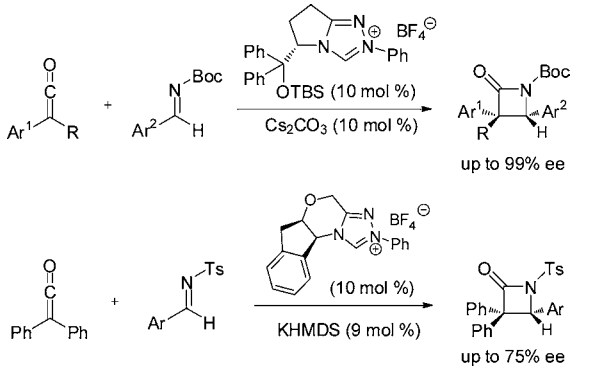
Scheme 1. Chartelines



Charteline **A**, X = Y = Br
Charteline **B**, X = H, Y = Br
Charteline **C**, X = Y = H

First reported by Staudinger, the cycloaddition of ketenes and imines is an efficient way to construct β-lactams.[10] The enantioselective Staudinger reaction was realized by Lectka et al.[11] and Fu et al.,[12] employing the cinchona alkaloids and planar-chiral derivatives of 4-(dimethylamino)pyridine as the catalyst, respectively. In the past decade, N-heterocyclic carbenes (NHCs) were found to be efficient organocatalysts for a wide variety of organic reactions.[13] In 2008, we and Smith et al. independently established the NHC-catalyzed enantioselective Staudinger reaction of ketenes with *aldimines* to give β-lactams (Scheme 2).[14] Later, we developed a series of bifunctional NHCs with a free hydroxyl group, which could form a H-bond with the substrate and thus enhance the reactivity and improve the selectivity.[15] In this paper, we report the bifunctional N-heterocyclic carbene-catalyzed Staudinger reaction of ketenes with isatin-derived *ketimines* for the construction of spirocyclic oxindolo-β-lactams.

Scheme 2. Reported NHC-Catalyzed Cycloaddition of Ketenes with Aldimines



Initially, the reaction of isatin-derived ketimines **1a** with ethyl(phenyl)ketene **2a** was investigated under NHC catalysis (Table 1). In the presence of 10 mol % of NHCs **A1** and **A2**, which were derived from L-pyroglutamic acid and worked well for the reaction of ketenes with aldimines,[14a] the desired cycloadduct **3a** was obtained in very low yield (entries 1 and 2). The bifunctional NHCs **B1**−**B3** with a free hydroxyl group were then employed for the reaction. We were encouraged to find that the reaction catalyzed by NHC **B1** afforded the desired cycloadduct in 25% yield with 2:1 diasteromerical ratio and 32% ee (entry 3). Better yield and enantioselectivity were observed when NHC **B2** with a more acidic hydroxyl group was utilized (entry 4). The diastereoselectivity and enantioselectivity were dramatically improved when NHC **B3** with a *N*-benzyl group was used (entry 5).[16,17] The reaction catalyzed by tetracyclic NHCs **C1** and **C2** also afforded the cycloadduct **3a** but in relatively low yields and selectivities (entries 6 and 7). Lowering the reaction temperature to −10 °C resulted in better

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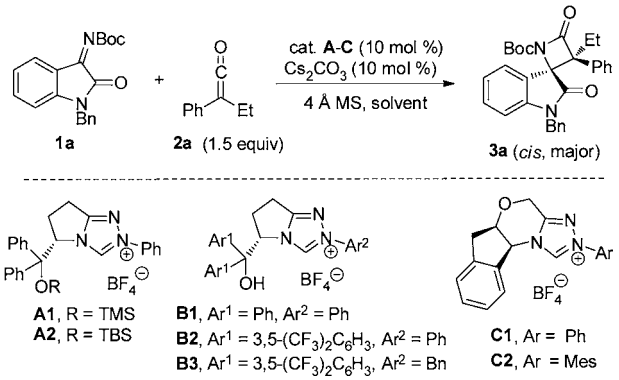
Table 1. Optimization of Reaction Conditions



entry	cat.	solvent	temp (°C)	dr[a]	yield[b] (%)	ee[c] (%)
1	**A1**	THF	rt	2:1	4	
2	**A2**	THF	rt	2:1	5	
3	**B1**	THF	rt	2:1	25 (8)	32 (30)
4	**B2**	THF	rt	2:1	40 (11)	43 (67)
5	**B3**	THF	rt	14:1	53	89
6	**C1**	THF	rt	3:1	42 (10)	−69 (−20)[d]
7	**C2**	THF	rt	1:1	36 (25)	−44 (−17)[d]
8	**B3**	THF	−10	>20:1	68	94
9	**B3**	Et_2O	−10	>20:1	72	95
10	**B3**	toluene	−10	13:1	55	91
11[e]	**B3**	THF	−10	>20:1	89	94

[a]Diastereomeric ratio of *cis*/*trans*, determined by ^{1}H NMR (300 MHz) of the unpurified reaction mixture. [b]Isolated yield of *cis*-**3a**, followed by *trans*-**3a** in parentheses. [c]The ee of *cis*-**3a**, followed by *trans*-**3a** in parentheses. [d]The opposite enantiomer *ent*-**3a** was obtained predominately. [e]Another 1.5 equiv of **2a** was added after 6 h.

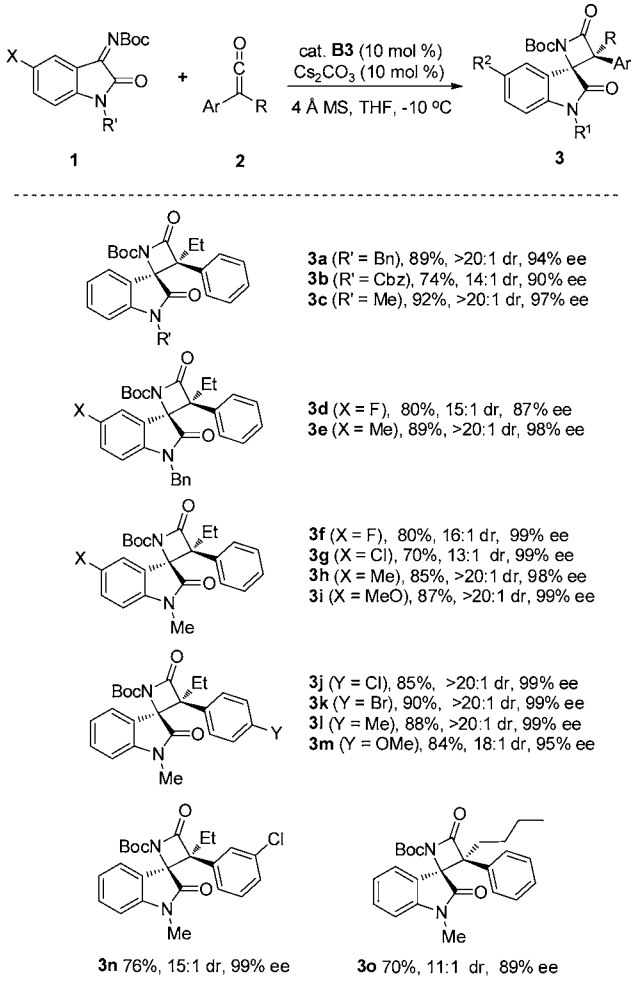
yield, diastereoselectivty (dr >20:1), and enantioselectivity (entry 8). Solvent screening revealed that the reaction performed better in THF and ethyl ether than toluene (entries 8−10). The yield was further improved when another 1.5 equiv of ketene was added (entry 11).

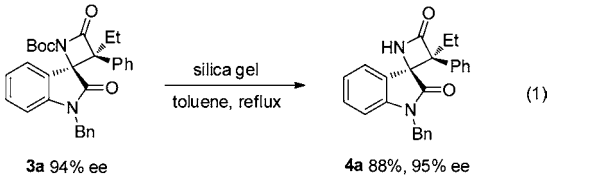
With the optimized reaction conditions in hand, the scope of substrates was then briefly investigated (Scheme 3). It was found that the *N*-protecting group of isatin could be benzyl, benzylcarbonyl, and methyl, while the one with *N*-methyl led to the best diastereo- and/or enantioselectivity (**3a**,**b** vs **3c**). All the isatin-derived ketimines with 5-substitutent (5-fluoro, 5-chloro, 5-methyl, 5-methoxy) worked well for the reaction and somewhat better diastereoselectivties were observed for those with electron-donating substituent (cycloadduct **3d** vs **3e**, and **3f**−**3g** vs **3h**−**3i**). Both electron-withdrawing substituent (4-ClC_6H_4, 4-BrC_6H_4) and electron-donating substituent (4-MeC_6H_4, 4-$MeOC_6H_4$) were tolerable for the alkyl(aryl)ketene, giving the cycloadducts **3j**−**m** in good yields with high enantioselectivities. The reaction of 3-chlorophenyl(ethyl) ketene also furnished the cycloadduct **3n** in 76% yield with 15:1 dr and 99% ee. The ketene with butyl afforded the corresponding cycloadduct **3o** in 70% yield with somewhat decreased but still high diastereo- and enantioselectivity.

The resulting *N*-Boc-protected *β*-lactam **3a** could be easily deprotected to afford the free *β*-lactam **4a** in high yield without erosion of enantiopurity (eq 1).

The absolute configuration of the spirocyclic oxindolo-*β*-lactam **3g** was assigned by the X-ray analysis of its single crystal (Figure 1).

Scheme 3. Enantioselective Staudinger Reaction of Ketenes with Isatin-Derived Ketimines





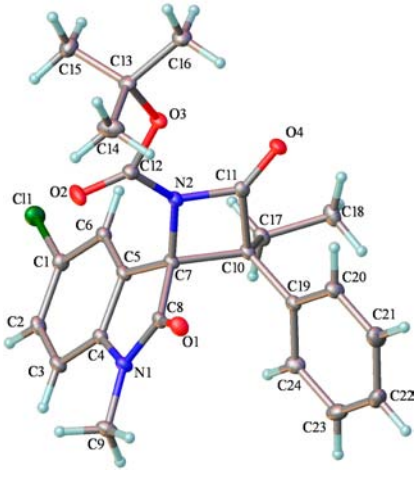


Figure 1. X-ray crystal structure of **3g**.

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In conclusion, the bifunctional NHCs with a free hydroxyl group were demonstrated as efficient catalysts for the reaction of ketenes with isatin-derived ketimines, giving the corresponding spirocyclic oxindolo-β-lactams in high yields with excellent diastereo- and enantioselectivities.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and NMR and HPLC spectra for obtained compounds; X-ray data for **3g** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Prof. Li-Xin Dai on the occasion of his 90th birthday.

■ REFERENCES

(1) (a) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875. (b) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873. (c) Bandini, M.; Eichholzer, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9608. (d) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209. (e) Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748. (f) Trost, B. M.; Brennan, M. K. *Synthesis* **2009**, 3003. (g) Zhou, F.; Liu, Y.-L.; Zhou, J. *Adv. Synth. Catal.* **2010**, *352*, 1381. (h) Ball-Jones, N. R.; Badillo, J. J.; Franz, A. K. *Org. Biomol. Chem.* **2012**, *10*, 5156. (i) Dalpozzo, R.; Dalpozzo, R.; Bartoli, G.; Bencivenni, G. *Chem. Soc. Rev.* **2012**, *41*, 7247. (j) Jiang, K.; Tiwari, B.; Chi, Y. R. *Org. Lett.* **2012**, *14*, 2382. (k) Cai, S.; Du, L.; Gerea, A. L.; King, J. B.; You, J.; Cichewicz, R. H. *Org. Lett.* **2013**, *15*, 4186. (l) Yin, Q.; You, S.-L. *Org. Lett.* **2013**, *15*, 4266. (m) Hao, X.; Liu, X.; Li, W.; Tan, F.; Chu, Y.; Zhao, X.; Lin, L.; Feng, X. *Org. Lett.* **2014**, *16*, 134.

(2) (a) Jiao, L.; Liang, Y.; Xu, J. *J. Am. Chem. Soc.* **2006**, *128*, 6060. (b) Dhawan, R.; Dghaym, R. D.; Syr, D. J.; Arndtsen, B. A. *Org. Lett.* **2006**, *8*, 3927. (c) Zhao, L.; Li, C.-J. *Chem. Asian. J.* **2006**, *1*, 203. (d) Ye, M.-C.; Zhou, J.; Tang, Y. *J. Org. Chem.* **2006**, *71*, 3576. (e) Shintani, R.; Fu, G. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 4082. (f) Lo, M. M.-C.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 4572. (g) Zhang, Z.; Liu, Y.; Ling, L.; Li, Y.; Dong, Y.; Gong, M.; Zhao, X.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2011**, *133*, 4330. (h) Xie, P.; Qian, B.; Huang, H.; Xia, C. *Tetrahedron Lett.* **2012**, *53*, 1613. (i) Chen, J.-H.; Liao, S.-H.; Sun, X.-L.; Shen, Q.; Tang, Y. *Tetrahedron Lett.* **2012**, *53*, 5042. (j) Chen, Z.; Lin, L.; Wang, M.; Liu, X.; Feng, X. *Chem.—Eur. J.* **2013**, *19*, 7561. (k) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Rev.* **2007**, *107*, 4437. (l) Pitts, C. R.; Lectka, T. *Chem. Rev.* **2014**, DOI: 10.1021/cr4005549.

(3) (a) Chevolot, L.; Chevolot, A.-M.; Gajhede, M.; Larsen, C.; Anthoni, U. *J. Am. Chem. Soc.* **1985**, *107*, 4542. (b) Anthoni, U.; Bock, K.; Chevolot, L.; Larsen, C.; Nielsen, P. H.; Christophersen, C. *J. Org. Chem.* **1987**, *52*, 5638. (c) Nielsen, P. H.; Anthoni, U.; Christophersen, C. *Acta Chem. Scand.* **1988**, *B42*, 489.

(4) Luntha, P.; Singh, G. S. *Eur. J. Med. Chem.* **2009**, *44*, 2265.

(5) Skiles, J. W.; McNeil, D. *Tetrahetron Lett.* **1990**, *31*, 7277.

(6) Kumar, R.; Giri, S.; Nizamuddin, J. *Agric. Food Chem.* **1989**, *37*, 1094.

(7) (a) Lin, X.; Weinreb, S. M. *Tetrahedron Lett.* **2001**, *42*, 2631. (b) Sun, C.; Lin, X.; Weinreb, S. M. *J. Org. Chem.* **2006**, *71*, 3159. (c) Jarrahpour, A.; Khalili, D. *Tetrahedron Lett.* **2007**, *48*, 7140.

(8) Cheng, Y.; Wang, B.; Cheng, L.-Q. *J. Org. Chem.* **2006**, *71*, 4418.

(9) (a) Baran, P. S.; Shenvi, R. A.; Mitsos, C. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3714. (b) Black, P. J.; Hecker, E. A.; Magnus, P. *Tetrahedron Lett.* **2007**, *48*, 6364.

(10) (a) Staudinger, H. *Justus Liebigs Ann. Chem.* **1907**, *356*, 51. (b) Goloobov, Y. G. *Tetrahedron* **1992**, *48*, 1353. (c) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Cur. Med. Chem.* **2004**, *11*, 1837.

(11) (a) Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Drury, W. J., III; Lectka, T. *J. Am. Chem. Soc.* **2000**, *122*, 7831. (b) Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Ferraris, D. F.; Lectka, T. *J. Am. Chem. Soc.* **2002**, *124*, 6626. (c) France, S.; Shah, M. H.; Weatherwax, A.; Wack, H.; Roth, J. P.; Lectka, T. *J. Am. Chem. Soc.* **2005**, *127*, 1206. (d) France, S.; Weatherwax, A.; Taggi, A. E.; Lectka, T. *Acc. Chem. Res.* **2004**, *37*, 592.

(12) (a) Lee, E. C.; Hodous, B. L.; Bergin, E.; Shih, C.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 11586. (b) Hodous, B. L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 1578. (c) Fu, G. C. *Acc. Chem. Res.* **2004**, *37*, 542.

(13) For the reviews of NHC-catalyzed reactions, see: (a) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606. (b) Enders, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, *37*, 534. (c) Moore, J. L.; Rovis, T. *Top. Curr. Chem.* **2010**, *291*, 77. (d) Bugaut, X.; Glorius, F. *Chem. Soc. Rev.* **2012**, *41*, 3511. (e) Izquierdo, J.; Hutson, G. E.; Cohen, D. T.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 11686. (f) Vora, H. U.; Wheeler, P.; Rovis, T. *Adv. Synth. Catal.* **2012**, *354*, 1617. (g) Chen, X.-Y.; Ye, S. *Synlett* **2013**, *24*, 1614. (h) Ryan, S. J.; Candish, L.; Lupton, D. W. *Chem. Soc. Rev.* **2013**, *42*, 4906. (i) Bode, J. W. *Nat. Chem.* **2013**, *5*, 813. (j) Mahatthananchai, J.; Bode, J. W. *Acc. Chem. Res.* **2014**, *47*, 696.

(14) (a) Zhang, Y.-R.; He, L.; Wu, X.; Shao, P.-L.; Ye, S. *Org. Lett.* **2008**, *10*, 277. (b) Duguet, N.; Campbell, C. D.; Slawin, M. Z.; Smith, A. D. *Org. Biomol. Chem.* **2008**, *6*, 1108.

(15) (a) He, L.; Zhang, Y.-R.; Huang, X.-L.; Ye, S. *Synthesis* **2008**, 2825. (b) Huang, X.-L.; He, L.; Shao, P.-L.; Ye, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 192. (c) Huang, X.-L.; Ye, S. *Chin. Sci. Bull.* **2010**, *55*, 1753. (d) Baragwanath, L.; Rose, C. A.; Zeitler, K.; Connon, S. J. *J. Org. Chem.* **2009**, *74*, 9214. (e) Lv, H.; Jia, W.-Q.; Sun, L. H.; Ye, S. *Angew. Chem., Int. Ed.* **2013**, *52*, 8607. (f) Sun, L.-H.; Liang, Z.-Q.; Jia, W.-Q.; Ye, S. *Angew. Chem., Int. Ed.* **2013**, *52*, 5803.

(16) The H-bonding of the free-hydroxy at NHC catalyst and the imines may enhance the reactivity and selectivity. The $\pi-\pi$ interactions between the aryl substituents at the NHC and the substrate may also contribute to outcome of the enantioselectivity.

(17) Enders, D.; Han, J.; Henseler, A. *Chem. Commun.* **2008**, 3989.