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N-Heterocyclic Carbene Catalyzed Ring Expansion of 4-Formyl-β-lactams: Synthesis of Succinimide Derivatives

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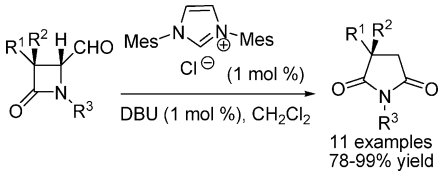
ABSTRACT



***N*-Heterocyclic carbene (NHC) has been employed as an efficient catalyst for ring expansion of 4-formyl-β-lactams, allowing the facile synthesis of succinimide derivatives. This organocatalytic process features readily availability of the catalyst, low catalyst loading, and mild reaction conditions.**

Reversing the reactivity of aldehydes, also known as reactivity Umpolung,[1] by *N*-heterocyclic carbene (NHC) has become an intense research area recently.[2] This approach generally includes the reaction of the Breslow intermediate with various acceptors such as aromatic aldehydes (Benzoin reaction[3]), α,β-unsaturated systems (Stetter reaction[4]), ketones,[5] aziridines,[6] and imines.[7] The extended Umpolung reactions involving the use of α,β-unsaturated aledehydes or α-haloaldehydes have also received great attention and witnessed significant progress in the past several years.[8−10] It was recently reported by Bode and co-workers that formyl-substituted epoxides, aziridines, and cyclopropanes underwent the ring opening during the redox esterifications.[11] Ring opening of 4-formyl-β-lactams triggered by 2-(trimethylsilyl)thiazole and ring expansion of 4-imino-β-lactam catalyzed

(1) (a) Grobel, B. T.; Seebach, D. *Synthesis* **1977**, 357. (b) Seebach, D. *Angew. Chem., Int. Ed.* **1979**, *18*, 239.

(2) For reviews on NHC as organic catalysts: (a) Enders, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, *37*, 534. (b) Johnson, J. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 1326. (c) Zeitler, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 7506. (d) Marion, N.; Díez-González, S.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2988.

(3) (a) Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719. (b) Sheehan, J.; Hunneman, D. H. *J. Am. Chem. Soc.* **1966**, *88*, 3666. (c) Enders, D.; Kallfass, U. *Angew. Chem., Int. Ed.* **2002**, *41*, 1743. (d) Tachibana, Y.; Kihara, N.; Takata, T. *J. Am. Chem. Soc.* **2004**, *126*, 3438.

(4) (a) Stetter, H. *Angew. Chem., Int. Ed.* **1976**, *15*, 639. (b) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 10298. (c) Kerr, M. S.; Rovis, T. *Synlett* **2003**, 1934. (d) Pesch, J.; Harms, K.; Bach, T. *Eur. J. Org. Chem.* **2004**, 2025. (e) Mattson, A. E.; Bharadwaj, A. R.; Scheidt, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 2314. (f) Kerr, M. S.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 8876. (g) Mennen, S. M.; Blank, J. T.; Tran-Dubé, M. B.; Imbriglio, J. E.; Miller, S. J. *Chem. Commun.* **2005**, 195. (h) Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2005**, *127*, 6284. (i) Nakamura, T.; Hara, O.; Tamura, T.; Makino, K.; Hamada, Y. *Synlett* **2005**, 155. (j) Liu, Q.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 2552. (k) Mattson, A. E.; Zuhl, A. M.; Reynolds, T. E.; Scheidt, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 4932.

(5) (a) Hachisu, Y.; Bode, J. W.; Suzuki, K. *J. Am. Chem. Soc.* **2003**, *125*, 8432. (b) Hachisu, Y.; Bode, J. W.; Suzuki, K. *Adv. Synth. Catal.* **2004**, *346*, 1097. (c) Enders, D.; Niemeier, O.; Balensiefer, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 1463. (d) Takikawa, H.; Hachisu, Y.; Bode, J. W.; Suzuki, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 3492. (e) Enders, D.; Niemeier, O.; Raabe, G. *Synlett* **2006**, 2431.

(6) Liu, Y.-K.; Li, R.; Yue, L.; Li, B.-J.; Chen, Y.-C.; Wu, Y.; Ding, L.-S. *Org. Lett.* **2006**, *8*, 1521.

(7) Li, G.-Q.; Dai, L.-X.; You, S.-L. *Chem. Commun.* **2007**, 852 and references cited therein.

(8) α,β-Unsaturated aldehydes: (a) Burstein, C.; Glorius, F. *Angew. Chem., Int. Ed.* **2004**, *43*, 6025. (b) Sohn, S. S.; Rosen, E. L.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 14370. (c) Chan, A.; Scheidt, K. A. *Org. Lett.* **2005**, *7*, 905. (d) He, M.; Bode, J. W. *Org. Lett.* **2005**, *7*, 3131. (e) Sohn, S. S.; Bode, J. W. *Org. Lett.* **2005**, *7*, 3873. (f) Zeitler, K. *Org. Lett.* **2006**, *8*, 637. (g) Nair, V.; Vellalath, S.; Poonoth, M.; Mohan, R.; Suresh, E. *Org. Lett.* **2006**, *8*, 507.

(9) α-Haloaldehydes: (a) Reynolds, N. T.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 9518. (b) Reynolds, N. T.; Rovis, T. *J. Am. Chem. Soc.* **2005**, *127*, 16406. (c) He, M.; Uc, G. J.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 15088.

(10) An early report on the transformation of trichloroacetaldehyde to dichloroacetic acid in the presence of cyanide: Wallach, O. *Ann. Chem.* **1873**, *6*, 114.

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by tetrabutylammonium cyanide have also been carried out recently by Alcaide et al.[12] Intrigued by their findings, we envisioned that formyl-substituted-β-lactams in the presence of an NHC catalyst might also undergo the ring opening and possibly the ring expansion to succinimide derivatives[13] by a highly favored five-membered ring formation (Figure 1).

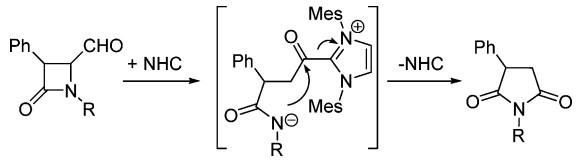


Figure 1. Possible transformation of 4-formyl-β-lactam catalyzed by NHC.

In addition, β-lactam has been extensively studied in the literature,[14] and 4-formyl-β-lactam[15] is also readily accessible, which makes the transformation starting from 4-formyl-β-lactams practical in reality. In this paper, we will report our preliminary results on the NHC-catalyzed ring expansion of 4-formyl-β-lactams to succinimide derivatives in good to excellent yields under mild reaction conditions.

Our studies began with an initial examination of the catalytic reactivity of several NHCs (Figure 2) for the

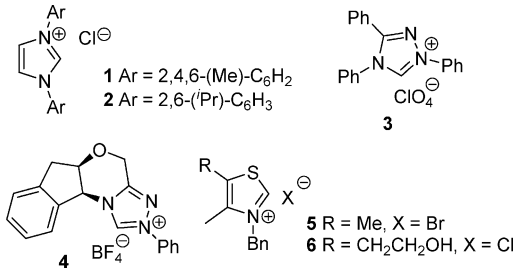
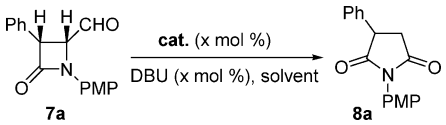


Figure 2. Several readily available NHC precursors.

reaction of 4-formyl-β-lactam **7a**. The results are summarized in Table 1. In the presence of 20 mol % of imidazolium chloride **1** and DBU, 4-formyl-β-lactam **7a** was smoothly converted to succinimide **8a** in 2 h at room temperature in 80% yield. Triazolium salt **3** is also a good catalyst, affording

Table 1. Effects of NHC Catalysts and Reaction Conditions



7a 8a

entry	cat.	x	solvent	time (h)	yield[a] (%)
1	**1**	20	THF	2	80
2	**2**	20	THF	48	<5
3	**3**	20	THF	5	76
4	**4**	20	THF	5	40
5[b]	**5**	20	THF	5	35
6[b]	**6**	20	THF	5	30
7	**1**	20	toluene	5	63
8[b]	**1**	20	Et_2O	5	23
9	**1**	20	DMF	5	54
10	**1**	20	DCE	5	90
11	**1**	20	dioxane	5	87
12	**1**	20	DCM	2	92
13	**1**	5	DCM	4	86
14	**1**	1	DCM	24	21
15[c]	**1**	1	DCM	7	99

[a] Isolated yields. [b] Determined by ^{1}H NMR. [c] The reaction was carried out under reflux.

8a in 76% yield. Several other NHCs derived from **2** and **4**−**6** proved less effective (entries 1−6, Table 1).

Using imidazolium chloride **1** in the presence of DBU, we have tested different solvents and an optimal yield (92%) was obtained when DCM was used (entry 12, Table 1). Lowering the catalyst loading resulted in a decreased yield; however, increasing the temperature accelerated the reaction. A nearly quantitative yield of **8a** was obtained when the reaction was carried out in refluxed DCM in the presence of only 1 mol % of the catalyst (entry 15, Table 1), which was used as the optimized reaction conditions.

Under the above-optimized reaction conditions, various 4-formyl-β-lactams have been tested to investigate the generality of the reaction. The results are summarized in Table 2. For the R^1 group, substrate **7b** with a *p*-methoxyphenyl is well tolerated; whereas *p*-chlorophenyl-substituted substrate **7c** requires a higher reaction temperature, in refluxed dioxane, to give a satisfactory yield (entries 2 and 3, Table 2). Besides the substituted phenyl as the R^1 group, the ring-expansion chemistry is also suitable for substrates having 2-thienyl group and alkyl groups such as methyl, *n*-pentyl, and isopropyl (entries 4−7, Table 2). In addition, 4-formyl-β-lactams **7h-i** containing quaternary carbon centers underwent the ring expansion to afford their corresponding products in excellent yields (entries 8 and 9, Table 2). When the PMP group on the nitrogen was changed to a Mes group, 78% yield was obtained in the presence of 5 mol % of the catalyst (entry 10, Table 2).

(11) (a) Chow, K. Y.-K.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 8126. (b) Sohn, S. S.; Bode, J. W. *Angew. Chem., Int. Ed.* **2006**, *45*, 6021.

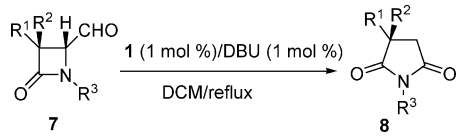
(12) Selected examples for the synthesis and application of succinimide derivatives: (a) Abell, A. D.; Oldham, M. D. *J. Org. Chem.* **1997**, *62*, 1509. (b) Obrecht, D.; Abrecht, C.; Altorfer, M.; Bohdal, U.; Grieder, A.; Kleber, M.; Pfyffer, P.; Müller, K. *Helv. Chim. Acta* **1996**, *79*, 1315. (c) Brière, J. F.; Charpentier, P.; Dupas, G.; Quèguiner, G.; Bourguignon, J. *Tetrahedron* **1997**, *53*, 2075. (d) Reddy, P. Y.; Kondo, S.; Toru, T.; Ueno, Y. *J. Org. Chem.* **1997**, *62*, 2652. (e) Vo-Hoang, Y.; Gasse, C.; Vidal, M.; Garbay, C.; Galons, H. *Tetrahedron Lett.* **2004**, *45*, 3603. (f) Barker, D.; Lin, D. H.-S.; Carland, J. E.; Chu, C. P.-Y.; Chebib, M.; Brimble, M. A.; Savage, G. P.; McLeoda, M. D. *Bioorg. Med. Chem.* **2005**, *13*, 4565.

(13) (a) Alcaide, B.; Almendros, P.; Redondo, M. C. *Org. Lett.* **2004**, *6*, 1765. (b) Alcaide, B.; Almendros, P.; Cabrero, G.; Ruiz, M. P. *Org. Lett.* **2005**, *7*, 3981.

(14) For reviews: (a) Manhas, M. S.; Wagle, D. R.; Chiang, J.; Bose, A. K. *Heterocycles* **1988**, *27*, 1755. (b) Ojima, I.; Delaloge, F. *Chem. Soc. Rev.* **1997**, *26*, 377. (c) France, S.; Weatherwex, A.; Taggi, A. E.; Lectka, T. *Acc. Chem. Res.* **2004**, *37*, 592.

(15) For reviews: (a) Alcaide, B.; Almendros, P. *Chem. Soc. Rev.* **2001**, *30*, 226. (b) Alcaide, B. Almendros, P. *Synlett* **2002**, 381. (c) Liddell, J. R. *Nat. Prod. Rep.* **2002**, *19*, 773.

Table 2. NHC-Catalyzed Ring Expansion of 4-Formyl-β-lactams



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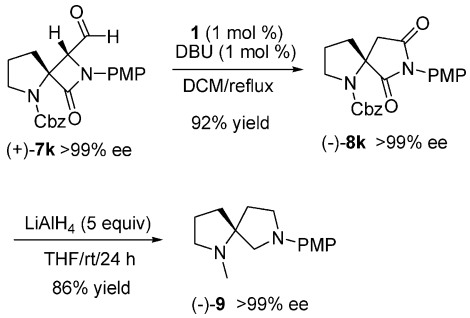
entry	substrate, R^1, R^2, R^3	product	time (h)	yield[a] (%)
1	**7a**, Ph, H, PMP	**8a**	8	99
2	**7b**, PMP, H, PMP	**8b**	12	98
3[b]	**7c**, *p*-Cl-Ph, H, PMP	**8c**	36	93
4	**7d**, 2-thienyl, H, PMP	**8d**	24	85
5	**7e**, Me, H, PMP	**8e**	32	91
6	**7f**, n-C_5H_{11}, H, PMP	**8f**	24	99
7	**7g**, *i*-Pr, H, PMP	**8g**	24	93
8[c]	**7h**, Me, Me, PMP	**8h**	24	97
9[b–d]	**7i**, Ph, Et, PMP	**8i**	24	97
10[c,e]	**7j**, Ph, H, Mes	**8j**	16	78

[a] Isolated yields. [b] The reaction was carried out in refluxed dioxane. [c] 5 mol % of the catalyst was used. [d] Single isomer with unknown stereochemistry. [e] Mes = 2,4,6-trimethylphenyl.

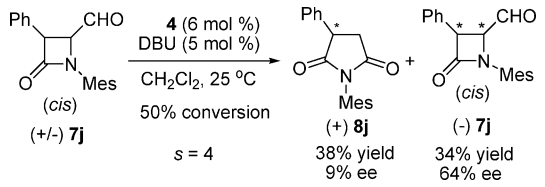
Interestingly, when 4-formyl spiro β-lactam (+)-**7k** (>99% ee)[16] was subjected to the optimized reaction conditions, bicyclic compound (−)-**8k** was afforded (Scheme 1). Treatment of (−)-**8k** with 5 equiv of $LiAlH_4$ in THF led to a spiro bicyclic diamine (−)-**9**. It should be noted the spiro bicyclic diamine structures exist extensively in pharmaceutical compounds,[17] and the current methodology provides a facile excess to their optically pure form.

Scheme 1. Enantioselective Synthesis of Bicyclic Diamine **9** with a Spiro Chiral Center



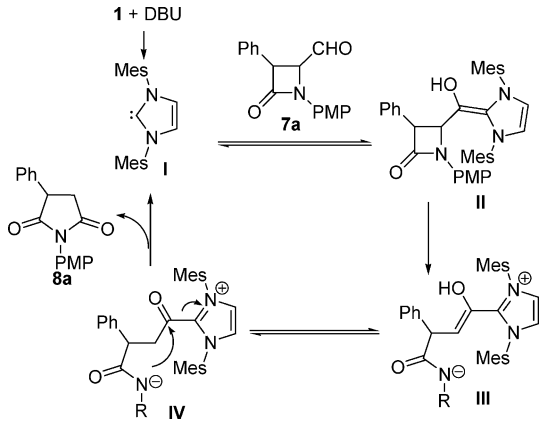
A study on the kinetic resolution of racemic 4-formyl-β-lactams by chiral NHC such as **4** was also carried out (Scheme 2). With 5 mol % of the catalyst derived from **4**, kinetic resolution of (±)-**7j** gave (+)-**8j** in 38% yield with 9% ee and recovered (−)-**7j** in 34% yield with 64% ee. It should be noted that the ee of the recovered aldehyde **7j** is determined after reduction of the aldehyde to its corresponding alcohol by $NaBH_4$.[18] The reaction of enantiopure **7j** in the presence of an achiral NHC, derived from **1**, gave a racemic product **8j**.

Scheme 2. Chiral NHC-Catalyzed Kinetic Resolution of Racemic **7j**



A plausible catalytic cycle was proposed as illustrated in Scheme 3. Carbene **I** is generated by deprotonation of imidazolium chloride **1** in the presence of DBU. **I** reacts with 4-formyl-β-lactam **7a** to give the Breslow intermediate **II**, which could induce the ring opening of 4-formyl-β-lactam releasing the amide nucleophile in **III**. The amide nucleophile in **IV**, an equilibrium form of **III**, occurs an intramolecular cyclization to give succinimide **8a**, during which the carbene catalyst **I** was released to finish the catalytic cycle.

Scheme 3. Proposed Catalytic Cycle for NHC-Catalyzed Ring Expansion of 4-Formyl-β-lactam



In summary, we have found the readily available NHC efficiently catalyzes the ring expansion of 4-formyl-β-lactams. This organocatalytic process affords succinimide derivatives smoothly, featuring readily availability of the catalyst, low catalyst loading and mild reaction conditions. Further exploration of the reaction scope and improvement of the kinetic resolution process are currently underway.

Acknowledgment. We gratefully acknowledge the Chinese Academy of Sciences and the National Natural Science Fondation of China for financial support.

Supporting Information Available: Experimental procedures and analysis data for **7**−**9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Macías, A.; Alonso, E.; Pozo, C. D.; Venturini, A.; González, J. *J. Org. Chem.* **2004**, *69*, 7004.

(17) Selected examples: (a) Janssens, F. E.; Coupa, S.; Poncelet, A. P.; Simonnet, Y. R. F.; Schoentjes, B. (Janssen Pharmaceutica), PCT Int. Appl. WO06094948A1, 2006. (b) Bhatti, B. S.; Gatto, G. J.; Klucik, J. (Targacept, Inc.), PCT Int. Appl. WO06023630A2, 2006.

(18) For details, see the Supporting Information.