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NHC-Catalyzed Ring Expansion of Oxacycloalkane-2-carboxaldehydes: A Versatile Synthesis of Lactones

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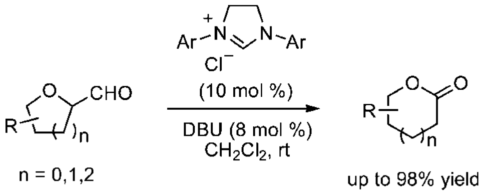
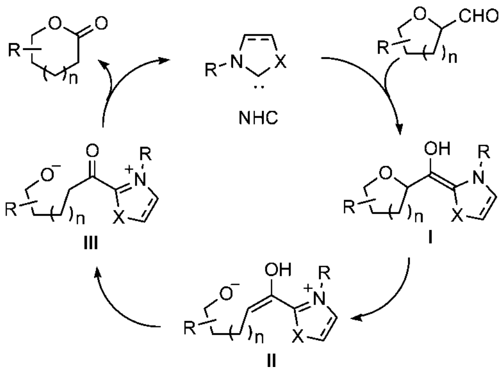
ABSTRACT



Imidazolinium-derived carbenes catalyze the ring-expansion lactonization of oxacycloalkane-2-carboxaldehydes. A variety of functionalized five-, six-, and seven-membered lactones can be formed efficiently under mild reaction conditions. The success of this new method for the construction of lactones is highly influenced by the electronic nature of the carbene catalyst.

In recent years, the use of *N*-heterocyclic carbenes (NHCs) as organocatalysts has attracted a lot of attention.[1] Among the reactions found to be promoted by this family of catalysts, various formal redox transformations of aldehydes bearing reducible functionalities have been described.[2,3] Of those, the conjugate ring opening of strained carbo- and heterocycles represents a particularly useful process.[3] A noteworthy example is the redox esterification of epoxyaldehydes by Chow and Bode, providing rapid access to β-hydroxy esters.[3a] We reasoned that the opening of larger, strain-free oxygen heterocycles would, in principle, provide a tethered alkoxide nucleophile capable of effecting a ring-closure. Successful implementation of this plan would constitute a novel route to synthetically useful and versatile lactones. As illustrated in Scheme 1, we anticipated that an appropriate NHC would combine with an oxacycloalkane-2-carboxaldehyde to form a “Breslow intermediate” **I** poised for ring opening. Following tautomerization of the ring-opened intermediate **II** to the activated carboxylate **III**, intramo-

Scheme 1. Mechanism of Proposed Ring-Expansion Reaction



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(1) (a) Marion, N.; Díez-González, S.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2988–3000. (b) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606–5655.

(2) (a) Reynolds, N. T.; de Alaniz, J. R.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 9518–9519. (b) Chan, A.; Scheidt, K. A. *Org. Lett.* **2005**, *7*, 905–908. (c) Sohn, S. S.; Bode, J. W. *Org. Lett.* **2005**, *7*, 3873–3876. (d) Reynolds, N. T.; Rovis, T. *J. Am. Chem. Soc.* **2005**, *127*, 16406–16407. (e) Zeitler, K. *Org. Lett.* **2006**, *8*, 637–640. (f) Sohn, S. S.; Bode, J. W. *J. Am. Chem. Soc.* **2007**, *129*, 13798–13799. (g) Maki, B. E.; Chan, A.; Scheidt, K. A. *Synthesis* **2008**, 1306–1315. (h) Phillips, E. M.; Wadamoto, M.; Roth, H. S.; Ott, A. W.; Scheidt, K. A. *Org. Lett.* **2009**, *11*, 105–108.

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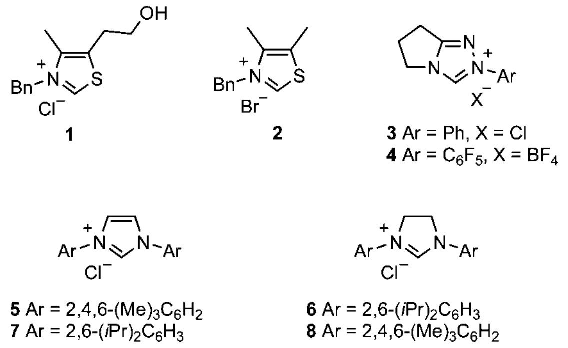
lecular attack of the alkoxide moiety would provide the desired lactone and regenerate the NHC catalyst. Alternatively, intermediate **II** could undergo an alkoxide-induced elimination of the NHC to furnish a hydroxy-ketene which would then cyclize to the lactone. Toward the achievement of this catalytic sequence, the ability of NHCs to promote the unprecedented ring opening of strain-free, unstabilized systems was of particular concern. Indeed, the failure to eliminate simple alkoxides from Breslow intermediates related to **I** was recently underscored by Scheidt and coworkers during their synthesis of coumarins.[2h]

We began our explorations with tetrahydrofurfural as a model substrate and various NHC precatalysts (Figure 1).



1

2

3 Ar = Ph, X = Cl
4 Ar = C_6F_5, X = BF_4

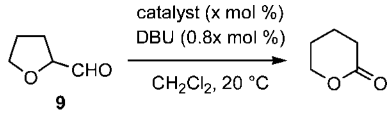
5 Ar = 2,4,6-$(Me)_3C_6H_2$
7 Ar = 2,6-$(i\text{Pr})_2C_6H_3$

6 Ar = 2,6-$(i\text{Pr})_2C_6H_3$
8 Ar = 2,4,6-$(Me)_3C_6H_2$

Figure 1. Precatalysts screened for the synthesis of lactones.

In contrast to the redox esterification of epoxy aldehydes,[3a] we found that the use of thiazolium-derived catalysts led to complex reaction mixtures (Table 1, entries 1 and 2).

Table 1. Reaction Optimization[a]



entry	catalyst	catalytic loading(×)	concentration (M)	time (h)	yield[b] (%)
1	**1**	50	0.02	5	5
2	**2**	50	0.02	5	38
3	**3**	50	0.02	5	<5
4	**4**	50	0.02	5	42
5	**5**	50	0.02	5	<5
6	**6**	50	0.02	5	82
7	**6**	10	0.5	13	78
8	**8**	10	0.5	17	35
9	**7**	50	0.02	4	<5

[a] All reactions were performed on a 0.4−0.6 mmol scale; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene. [b] Yield of pure, isolated product.

Similarly, triazolium catalyst **3** afforded trace amounts of the lactone, along with many unidentified side products (entry 3). Remarkably, triazolium catalyst **4** bearing an electron-withdrawing aryl group provided the desired product in moderate yield (entry 4). The use of imidazolium catalyst **5** did not provide any of the expected lactone but instead slowly gave rise to small amounts of the presumed benzoin product (entry 5). In sharp contrast, imidazolinium catalyst **6** led to a clean and quantitative conversion to the somewhat volatile lactone (entry 6). A reduction in the catalytic loading was accomplished through simultaneous increase of the concentration, with no detrimental effect on the yield (entry 7). Intrigued by the dramatically different outcomes obtained with catalysts **5** and **6**, we decided to test imidazolium **7** and imidazolinium **8** to determine whether this discrepancy was due to steric or electronic factors. The results shown in entries 5−9 clearly rule out the difference as arising from steric factors. Along with the results from entries 3 and 4, it further demonstrates that electronic factors play a major role in this reaction. The conditions from entry 7, using imidazolinium catalyst **6**, were chosen to study the scope of the reaction. Interestingly, imidazolinium-catalyzed transformations of aldehydes have received very little attention thus far. To the best of our knowledge, there is only one other example of a reaction proceeding through an imidazolinium-derived Breslow intermediate.[4]

We then examined the synthesis of a variety of functionalized lactones, as shown in Table 2. Tetrahydrofuran derivatives with substituents at the 3, 4, and 5 position all provided the corresponding monosubstituted lactones very efficiently (entries 2−6).[5] Of note, the use of benzyl or trialkylsilyl protecting groups was well tolerated (entries 2 and 3). Specifically, no side-products originating from a possible 1,2-silyl transfer were detected in entry 3. Both *trans*- and *cis*-fused bicyclic tetrahydrofuran derivatives smoothly afforded bicyclic lactones (entries 7 and 8), making this process particularly interesting in a synthetic context.

This new lactonization reaction is not limited to the synthesis of six-membered lactones. Oxetane 2-carboxaldehydes, readily accessed from ketones and allylic alcohols in two steps,[6] undergo a ring expansion to form γ-butyrolactone derivatives in high yield (entry 9). It is also possible to form seven-membered lactones through the use of tetrahydropyran-2-carboxaldehydes, albeit in reduced yield (entry 10). In this case, only trace amounts of impurities were observed in the crude reaction mixture following workup, suggesting the formation of water-soluble or polymeric side products. This last example is quite striking in that the closure of the

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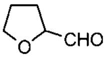
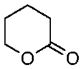
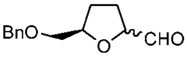
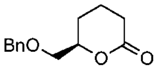
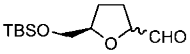
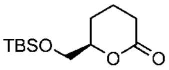
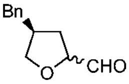
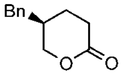
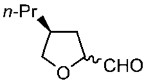
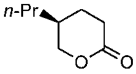
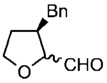
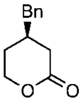
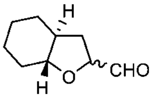
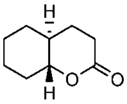
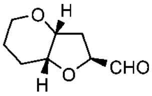
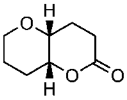
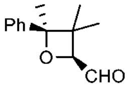
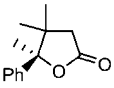
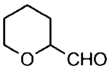
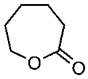
(3) (a) Chow, K. Y.-K.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 8126–8127. (b) Sohn, S. S.; Bode, J. W. *Angew. Chem., Int. Ed.* **2006**, *45*, 6021–6024. (c) Vesely, J.; Ibrahem, I.; Zhao, G.-L.; Rios, R.; Córdova, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 778–781. (d) Li, G.-Q.; Li, Y.; Dai, L.-X.; You, S.-L. *Org. Lett.* **2007**, *9*, 3519–3521. (e) Zhao, G.-L.; Córdova, A. *Tetrahedron Lett.* **2007**, *48*, 5976–5980. (f) Vora, H. U.; Rovis, T. *J. Am. Chem. Soc.* **2007**, *129*, 13796–13797. (g) Bode, J. W.; Sohn, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 13798–13799. (h) Alcaide, B.; Almendros, P.; Cabrero, G.; Ruiz, M. P. *Chem. Commun.* **2007**, 4788–4790. (i) Li, G.-Q.; Li, Y.; Dai, L.-X.; You, S.-L. *Adv. Synth. Catal.* **2008**, *350*, 1258–1262. (j) Ibrahem, I.; Zhao, G.-L.; Rios, R.; Vesely, J.; Sundén, H.; Dziedzic, P.; Córdova, A. *Chem.—Eur. J.* **2008**, *14*, 7867–7879. (k) Du, D.; Wang, Z. *Eur. J. Org. Chem.* **2008**, 4949–4954. (l) Vora, H. U.; Moncecchi, J. R.; Epstein, O.; Rovis, T. *J. Org. Chem.* **2008**, *73*, 9727–9731.

(4) Matsumoto, Y.; Tomioka, K. *Tetrahedron Lett.* **2006**, 5843–5846.

(5) No reaction was observed when 2-alkyloxacycloalkane-2-carboxaldehydes were used.

(6) Adam, W.; Stegmann, V. R. *Synthesis* **2001**, 1203–1214.

Table 2. Reaction Scope[a]

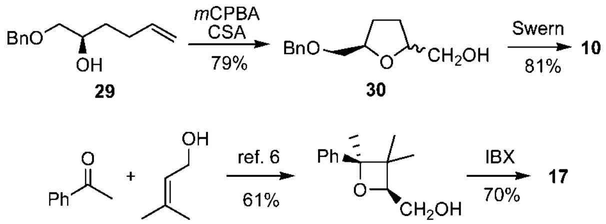
entry	substrate	product	yield[b] (%)
1	 **9**	 **19**	78
2[c]	 **10**	 **20**	98[d]
3[e,f]	 **11**	 **21**	30 (>95)[g]
4	 **12**	 **22**	90
5	 **13**	 **23**	94
6[f,h]	 **14**	 **24**	98
7	 **15**	 **25**	88
8[e,f]	 **16**	 **26**	62 (>95)[i]
9	 **17**	 **27**	86
10[j]	 **18**	 **28**	48

[a] Unless otherwise noted, all reactions were performed using racemic substrates at 0.5 M in CH_2Cl_2 at 20 °C for 12−24 h using 10 mol % of **6** and 8 mol % of DBU. Substrates **10**−**15** and **18** were used as a ~1:1 mixture of epimers (see the Supporting Information for details). [b] Yield of pure, isolated product; conversion based on ^1H NMR analysis of the crude reaction mixture is shown in parentheses. [c] Enantiomerically enriched substrate (>99% ee) was used. [d] >99% ee. [e] 30 mol % of catalyst was used. [f] The presence of small amounts of Dess−Martin-derived impurities in the substrate mandated the use of a higher catalytic loading. [g] The product was found to be unstable to chromatography. [h] 20 mol % catalyst was used. [i] Isolation of the product proved problematic due to difficulty in detection by thin-layer chromatography. [j] Reaction performed at 40 °C for 10 days.

medium-sized ring was effected at an unusually high concentration (0.5 M).

Remarkably, although the reactions shown in Table 2 are routinely performed under an inert atmosphere, we found that they can also be conducted under air without any detrimental effect on the yield. In addition, we did not detect the formation of benzoin-type dimers in any of these reactions.

Scheme 2. Preparation of Substrates **10** and **17**



The substrates required for this transformation are readily obtained, and two representative examples are shown in Scheme 2. Enantiomerically pure alcohol **29**, derived in two steps from (*S*)-glycidol,[7] undergoes a tandem epoxidation−cyclization when submitted to *m*-CPBA to furnish tetrahydrofuranyl alcohol **30** as an inconsequential mixture of epimers. This alcohol is then converted to the corresponding aldehyde **10** through a Swern oxidation. Oxetane **17** is obtained in very high regio- and diastereoselectivity from the [2 + 2] photocycloaddition of acetophenone and prenol,[6] followed by oxidation with IBX.[8]

In summary, we have developed a new lactonization reaction based on the NHC-catalyzed ring expansion of oxacycloalkane-2-carboxaldehydes. Five-, six-, and seven-membered lactones are readily accessed using this process. We have also demonstrated that imidazolinium-derived catalysts are uniquely suited for this transformation, due to electronic factors. A rationale for this behavior as well as synthetic applications of this new reaction are currently under investigation.

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Supporting Information Available: Experimental procedures, characterization data, and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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