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NHC-Catalyzed Intramolecular Redox Amidation for the Synthesis of Functionalized Lactams

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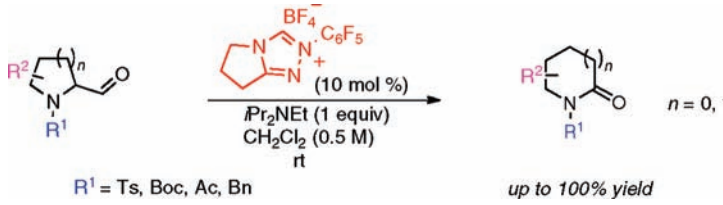
ABSTRACT



A very efficient NHC-catalyzed lactamization reaction is reported. For most cases, the ring expansion reaction proceeds to cleanly furnish five- and six-membered *N*-Ts and *N*-Bn lactams, without the need for further purification. Evidence is presented suggesting a dual role for the stoichiometric base: (1) deprotonation of the triazolium precatalyst and (2) activation of the nitrogen leaving group through hydrogen bonding.

The applications of *N*-heterocyclic carbenes (NHC) as organocatalysts have been intensively investigated in the past decade.[1] An attractive feature of these NHCs is their ability to effect the *umpolung* (inversion of reactivity) of aldehydes. In recent years, various NHC-catalyzed formal redox transformations of aldehydes bearing α-reducible functionalities have been reported.[2]

Following our NHC-catalyzed ring-expansion reaction of oxacycloalkane-2-carboxaldehydes to furnish lactones,[2n] we explored the extension of this methodology to the synthesis of functionalized lactams, which represent a ubiquitous structural feature of many alkaloid natural products and drug candidates. Earlier work by Alcaide et al.[2f,j] and You et al.[2i] demonstrated the ring expansion of strained β-lactams to form succinimide derivatives (Scheme 1a). In subsequent work, Rovis et al. reported the formation of a β-amino amide from the ring opening of an *N*-Ts aziridine in the presence of an amine and a nucleophilic cocatalyst (Scheme 1b).[2k] Other aldehydes bearing good leaving groups at the α position were also shown to lead to amides, again in the

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(1) For selected reviews on NHC-catalyzed reactions, see: (a) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606–5655. (b) Marion, N.; Díez-González, S.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2988–3000. (c) Nair, V.; Vellalath, S.; Babu, B. P. *Chem. Soc. Rev.* **2008**, *37*, 2691–2698. (d) Moore, J. L.; Rovis, T. *Top. Curr. Chem.* **2010**, *291*, 77–144.

(2) Selected examples: (a) Chow, K. Y.-K.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 8126–8127. (b) Reynolds, N. T.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 9518–9519. (c) Chan, A.; Scheidt, K. A. *Org. Lett.* **2005**, *7*, 905–908. (d) Sohn, S. S.; Bode, J. W. *Org. Lett.* **2005**, *7*, 3873–3876. (e) Reynolds, N. T.; Rovis, T. *J. Am. Chem. Soc.* **2005**, *127*, 16406–16407. (f) Alcaide, B.; Almendros, P.; Cabrero, G.; Ruiz, M. P. *Org. Lett.* **2005**, *7*, 3981–3984. (g) Zeitler, K. *Org. Lett.* **2006**, *8*, 637–640. (h) Sohn, S. S.; Bode, J. W. *Angew. Chem., Int. Ed.* **2006**, *45*, 6021–6024. (i) Li, G.-Q.; Li, Y.; Dai, L.-X.; You, S.-L. *Org. Lett.* **2007**, *9*, 3519–3521. (j) Alcaide, B.; Almendros, P.; Cabrero, G.; Ruiz, M. P. *Chem. Commun.* **2007**, 4788–4790. (k) Vora, H. U.; Rovis, T. *J. Am. Chem. Soc.* **2007**, *129*, 13796–13797. (l) Bode, J. W.; Sohn, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 13798–13799. (m) Phillips, E. M.; Wadamoto, M.; Roth, H. S.; Ott, A. W.; Scheidt, K. A. *Org. Lett.* **2009**, *11*, 105–108. (n) Wang, L.; Thai, K.; Gravel, M. *Org. Lett.* **2009**, *11*, 891–893. (o) Li, G.-Q.; Dai, L.-X.; You, S.-L. *Org. Lett.* **2009**, *11*, 1623–1625. (p) Yamaki, Y.; Shigenaga, A.; Li, J.; Shimohigashi, Y.; Otaka, A. *J. Org. Chem.* **2009**, *74*, 3278–3285. (q) Kawanaka, Y.; Phillips, E. M.; Scheidt, K. A. *J. Am. Chem. Soc.* **2009**, *131*, 18028–18029. (r) Ling, K. B., Smith, A. D. *Chem. Commun.* **2011**, DOI: 10.1039/c0cc02456b.

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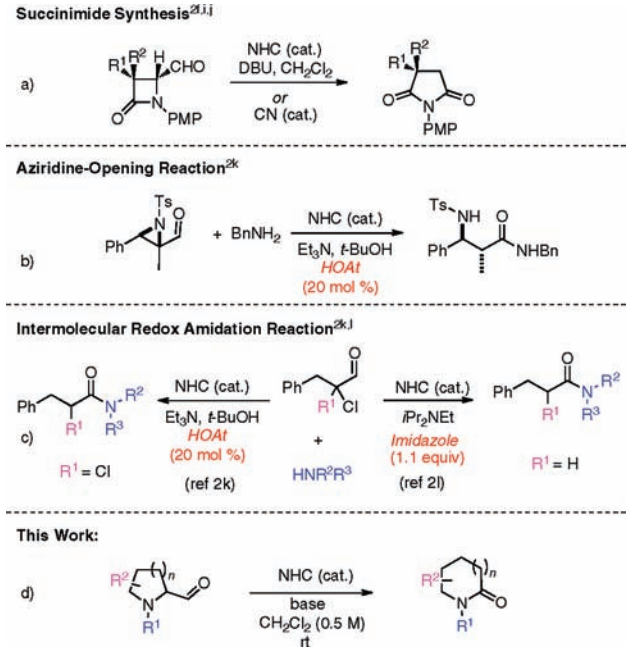
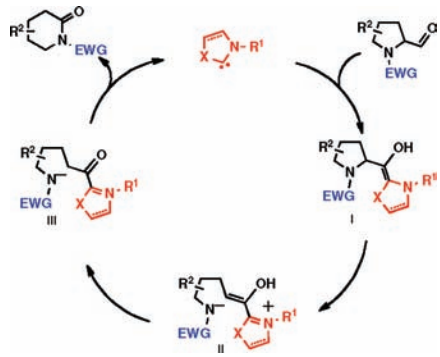
Scheme 1. NHC-Catalyzed Amide Formation



presence of a nucleophilic additive (Scheme 1c).[2k,l] Encouraged by our earlier success with strain-free oxygen-containing substrates,[2n] we set out to find a reaction manifold that would give access to a variety of lactams while obviating the need for strained α-amino aldehydes (Scheme 1d). In the event, we not only succeeded in defining appropriate conditions and nitrogen activating groups for this transformation but also found that simple *unactivated* amines represent ideal substrates. Moreover, our results suggest hydrogen bonding plays an important role in the catalytic cycle.

In line with our proposed mechanism for lactone formation,[2n] we envisioned that the reaction would proceed through the formation of a Breslow intermediate[3] (**I**) poised for ring opening to generate intermediate **II** (Scheme 2). The

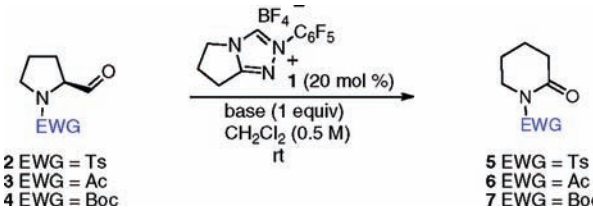
Scheme 2. Proposed Mechanism for Lactam Formation



nature of the electron-withdrawing group would be a defining factor in facilitating the ring-opening step of the reaction. Tautomerization to form the activated carboxylate **III** followed by intramolecular amide bond formation would furnish the desired lactam and regenerate the NHC catalyst.[4]

A brief screen of azolium salts (not shown) rapidly identified triazolium precatalyst **1** as the most promising candidate. Initially, DBU was used to generate the NHC catalyst, but it was also found to slowly cause decomposition of the model *N*-Ts prolinal (**2**). The problem could be avoided by portionwise addition of the base in substoichiometric amounts to afford complete conversion after one day (Table 1, entry 1). A screen of bases was then conducted to increase

Table 1. Reaction Optimization[a]



entry	substrate	base	pK_a[b]	time (h)	conv (%)[c]
1[d]	**2**	DBU	16.6 (−)	24	>95
2[e]	**2**	KHMDS	25.8 (−)	24	<5
3	**2**	*i*Pr$_2$NEt	12.5 (10.8)	2	>95
4	**2**	Cs_2CO_3	−(10.3)	5	>95
5	**2**	DMAP	11.2 (9.7)	4	80
6	**2**	imidazole	−(7.0)	24	<5
7	**2**	pyridine	5.5 (5.2)	24	<5
8[f]	**2**	*i*Pr$_2$NEt		5	>95
9[f]	**3**	*i*Pr$_2$NEt		24	>95
10[f]	**4**	*i*Pr$_2$NEt		7 d	80

[a] The base (1 equiv) was added to the aldehyde (1 equiv) and precatalyst **1** (20 mol %) in CH_2Cl_2 (0.5 M of aldehyde). [b] pK_a of the conjugate acid in THF;[5] values in H_2O[6] are given in parentheses. The values for Et_3N are given in entry 7. [c] Conversion determined by ^{1}H NMR analysis of the crude reaction mixture. [d] DBU was added in two portions (0.32 equiv). [e] Catalyst was preformed by adding KHMDS (16 mol %) to the precatalyst **1** (20 mol %) in CH_2Cl_2 (0.5 M), and then aldehyde **2** (1 equiv) was added. [f] 10 mol % **1** was used. KHMDS = potassium bis(trimethylsilyl)amide, DBU = 1,8-diazabicycloundec-7-ene, DMAP = 4-dimethylaminopyridine.

the reaction rate and to make the procedure more convenient. Thus, bases of varying strength were screened using *N*-Ts prolinal (**2**) as the model substrate (Table 1). No reaction was observed when the strong base KHMDS was used to preform the carbene catalyst (entry 2). Whereas the use of *i*Pr$_2$NEt, Cs_2CO_3, or 4-dimethylaminopyridine provided the desired transformation, *i*Pr$_2$NEt proved to be superior (entries 3−5). However, weak bases such as imidazole and pyridine returned the starting material (entries 6 and 7). Lowering the catalyst loading to 10 mol % still resulted in a clean and rapid reaction (entry 8). The influence of the electron-withdrawing group on the efficiency of the reaction was

(3) Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719–3726.

(4) An intermediate related to **III** was proposed in homoenolate additions to sulfonimines: (a) He, M.; Bode, J. W. *Org. Lett.* **2005**, *7*, 3131–3134. (b) Nair, V.; Varghese, V.; Babu, B. P.; Sinu, C. R.; Suresh, E. *Org. Biomol. Chem.* **2010**, *8*, 761–764.

investigated next. Amide **3** and carbamate **4** were both found to require much longer reaction times (entries 9 and 10) than sulfonamide **2**.

The observation that strong or weak bases do not provide an effective conversion while intermediate ones are remarkably efficient is noteworthy.[2d] Presumably, the role of the base in this reaction is 2-fold: (1) to generate the carbene catalyst and (2) to activate the sulfonamide leaving group through hydrogen bonding via its conjugate acid (Figure 1).[7]

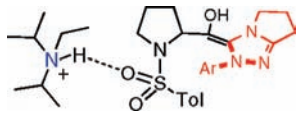


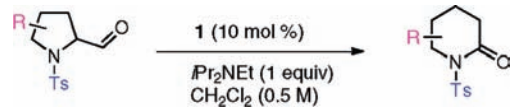
Figure 1. Proposed mode of hydrogen bonding activation.

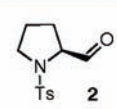
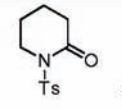
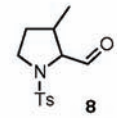
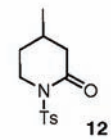
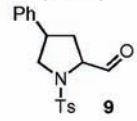
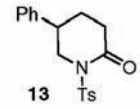
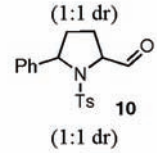
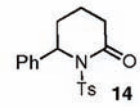
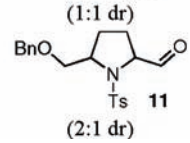
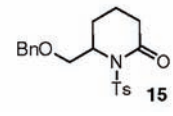
Thus, the base needs to be strong enough to deprotonate the triazolium precatalyst but weak enough for its conjugate acid to participate in hydrogen bonding catalysis.[8]

The synthesis of functionalized *N*-Ts lactams was then investigated with the optimized conditions (Table 2). The model substrate **2** furnished the desired lactam in high yield (entry 1). Prolinal derivatives with substituents at the 3, 4, or 5 position were efficiently converted to the corresponding lactams (entries 2−4). Surprisingly, substrate **11** resulted in a lower yield and the presence of numerous side products (entry 5). The sluggish reaction rates of aldehydes **8**, **10**, and **11** were initially thought to be a result of the relative configuration of the substituents; however, aliquots taken from the reaction mixture indicated that the reactivity of each diastereomer is similar (entries 2, 4, and 5). The reason behind the inefficient transformation of **11** could be that of functional group incompatibility (vide infra).

Intrigued by the postulated hydrogen bonding effect of the conjugate acid, we then examined the importance of the electron-withdrawing group. If the nitrogen-containing functional group is indeed activated through hydrogen bonding, the electron-withdrawing group may not be necessary at all. If this hypothesis holds true, simple amines should form stronger hydrogen bonds than sulfonamides, making them

Table 2. Scope of the Reaction



entry	substrate[a]	product	time (h)	yield (%)[b]
1[c]	 **2**	 **5**	5	90
2	 **8** (2:1 dr)	 **12**	72	81
3	 **9** (1:1 dr)	 **13**	2	83
4	 **10** (1:1 dr)	 **14**	24	82
5	 **11** (2:1 dr)	 **15**	24	49

[a] Unless otherwise noted, all reactions were performed using racemic susbtrate (see Supporting Information for details). [b] Yield of isolated, pure product. [c] Enantiomerically enriched substrate (>99% ee) was used.

viable leaving groups. To our delight, the reaction with *N*-benzyl prolinal **16** quickly furnished the desired lactam in quantitative yield following a simple filtration of the crude reaction mixture through a short pad of silica (Table 3, entry 1). In contrast to previously reported NHC-catalyzed redox amidation reactions using aliphatic amines, no nucleophilic cocatalyst or additive is required for this methodology.[2k,l] Presumably, the tethered secondary amine released during the catalytic cycle rapidly undergoes lactamization before any side reaction or inhibition can take place.

Intrigued with the result obtained with the *N*-alkyl substrate, we investigated the scope and limitations of the reaction (Table 3). The use of substituents bearing silyl protecting groups is well tolerated, furnishing the desired lactam in high yield (entry 2). As was also observed for *N*-Ts substrate **11**, the 5-benzyloxymethyl substituent in **18** resulted in a sluggish reaction and the formation of unidentified side products (entry 3). In contrast, the allyl substituent at the same position is well tolerated (entry 4). Thus, benzyl ethers do not appear to be compatible with these reaction conditions, although the reason for this incompatibility is not clear at the moment. Interestingly, both *cis* and *trans* diastereomers of substrates with a substituent at position 5 were consumed at similar rates (entries 3 and 4). Whereas the attempted formation of seven-membered lactam **27** only provided a

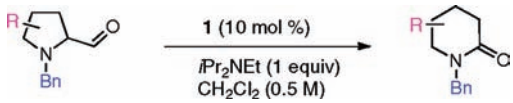
(5) (a) Fraser, R. R.; Mansour, T. S.; Savard, S. *J. Org. Chem.* **1985**, *50*, 3232–3234. (b) Rodima, T.; Kaljurand, I.; Pihl, A.; Mäemets, V.; Leito, I.; Koppel, I. A. *J. Org. Chem.* **2002**, *67*, 1873–1881.

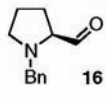
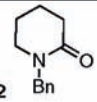
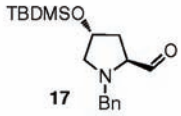
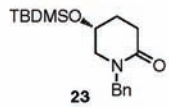
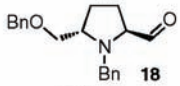
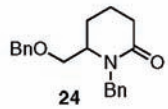
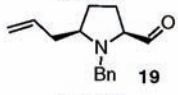
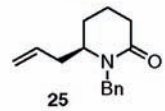
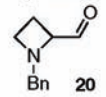
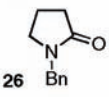
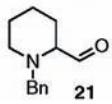
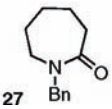
(6) (a) Perrin, D. D. *Dissociation Constants of Organic Bases in Aqueous Solution*; Butterworths: London, 1965. (b) Smith, M. B.; March, J. *March's Advanced Organic Chemistry*; Wiley: NY, 2007.

(7) For computational evidence of hydrogen bonding activation of substrates in an NHC-catalyzed reaction, see: (a) Dudding, T.; Houk, K. N. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5770–5775. For other examples of catalytic hydrogen bonding or Lewis acid activation of substrates in NHC-promoted *umpolung* reactions, see: (b) Mennen, S. M.; Blank, J. T.; Tran-Dubé, M. B.; Imbriglio, J. E.; Miller, S. J. *Chem. Commun.* **2005**, 195–197. (c) Mattson, A. E.; Zuhl, A. M.; Reynolds, T. E.; Scheidt, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 4932–4933. (d) O'Toole, S. E.; Connon, S. J. *Org. Biomol. Chem.* **2009**, *7*, 3584–3593. (e) Cardinal-David, B.; Raup, D. E. A.; Scheidt, K. A. *J. Am. Chem. Soc.* **2010**, *132*, 5345–5347. (f) Raup, D. E. A.; Cardinal-David, B.; Holte, D.; Scheidt, K. A. *Nature Chem.* **2010**, *2*, 766–771.

(8) For a discussion of hydrogen bonding in sulfonamides, see: Adsmond, D. A.; Grant, D. J. W. *J. Pharm. Sci.* **2001**, *90*, 2058–2077.

Table 3. Scope of the Reaction



entry	substrate[a]	product	time (h)	yield (%)[b]
1[c]	 16	 22	30 min.	100
2[c]	 17	 23	20 min.	100
3	 18 (6:1 dr)	 24	24	49
4[c]	 19 (5:1 dr)	 25	24	93
5	 20	 26	30 min.	100
6	 21	 27	24	<5%

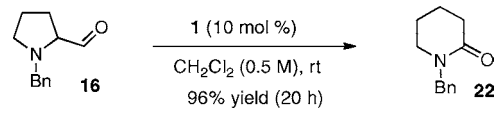
[a] Unless otherwise noted, all reactions were performed using racemic substrates (see Supporting Information for details). [b] Yield of isolated, pure product. [c] Enantiomerically enriched substrate (>99% ee) was used.

trace of the desired product, five-membered lactam **26** was obtained with great efficiency. Of note, the rate of the reactivity of azetidine substrate **20** was found to be similar to that of prolinal model substrate **16** despite the increased strain in the former.

To further investigate the dual role of the base, substrate **16** was subjected to the conditions of Table 3 using DBU instead of *i*Pr_2NEt.[9] The observed reaction was appreciably slower compared to the one using *i*Pr_2NEt (<20% vs >98% conversion after 30 min).[10] These results are consistent with the proposal that hydrogen bonding is involved in the ring-opening step of the reaction.

When considering the reaction with the *N*-benzyl substrates, we reasoned that the tertiary amine substrate could itself act as the base instead of *i*Pr_2NEt. To test this hypothesis, the model substrate **16** was subjected to the lactamization conditions in the absence of *i*Pr_2NEt (Scheme 3). Interestingly, the reaction proceeded to completion, although the rate of the reaction suffered significantly compared to the reaction performed in the presence of *i*Pr_2NEt (20 h vs 30 min, respectively). It is not clear at this point whether the basicity of the substrate (and thus the acidity of its conjugate acid) relative to that of *i*Pr_2NEt can alone explain the dramatic difference in reaction rates.

Scheme 3. NHC-Catalyzed Lactamization in the Absence of an External Base



In summary, we developed an efficient intramolecular redox lactamization reaction catalyzed by a triazolium-derived carbene. Both *N*-Ts and *N*-Bn substrates efficiently furnish the desired lactams in high yield. In addition to its role in the in situ generation of the carbene catalyst, the tertiary amine base is postulated to act as a hydrogen bonding cocatalyst to facilitate the ring-opening step. Nonetheless, a different mode of acceleration by the base can not be excluded at this point. Further investigations into the mechanism of this reaction are underway, including the exact role of *i*Pr_2NEt and the nature of the hydrogen bonding interaction.

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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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(9) We thank a reviewer for this suggestion.

(10) Slow decomposition of the aldehyde was observed in the presence of DBU; therefore, the stated conversion (formation of lactam product with respect to remaining aldehyde substrate) is an approximate value determined by ^{1}H NMR.