ORGANIC LETTERS

2011
Vol. 13, No. 19
5378–5381

Enantioselective Synthesis of Dihydropyridinones via NHC-Catalyzed Aza-Claisen Reaction

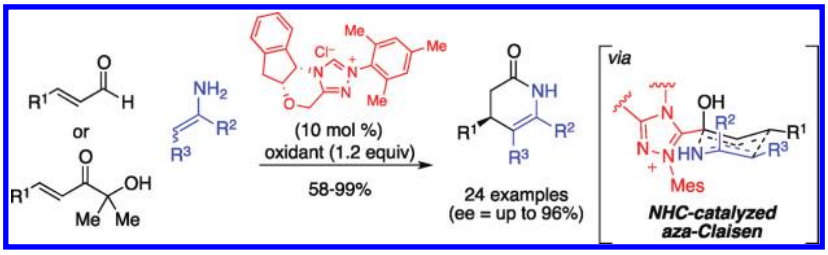
Benedikt Wanner, Jessada Mahatthananchai, and Jeffrey W. Bode*

Laboratorium für Organische Chemie, ETH-Zürich, Zürich 8093, Switzerland

bode@org.chem.ethz.ch

Received August 22, 2011

ABSTRACT



N-Heterocyclic carbene catalyzed aza-Claisen annulations of enals or their α′-hydroxyenone surrogates with vinylogous amides afford dihydropyridinones. The reaction proceeds with a broad range of substrates, and no nitrogen protecting group is required.

NHC-catalyzed annulations of α,β-unsaturated aldehydes and various imine derivatives provide facile entry to a variety of N-heterocycles, often with exceptional enantioselectivity (Scheme 1).[1] The rapid generation of structural and stereochemical diversity from a single class of starting materials and essentially one chiral N-heterocyclic carbene precursor, *N*-mesityl substituted chiral triazolium salt **1**,[2] make these reactions attractive approaches to scaffolds for further elaboration into bioactive compounds. The synthetic utility of the immediate annulation products, however, is diminished by the use of difficult to remove protecting groups. Furthermore, while some of the N-heterocycle forming annulations proceed with aliphatic and heteroaromatic substituents, the majority require aryl derivatives.

In this report we document NHC-catalyzed annulations of enals or their α′-hydroxyenone surrogates and readily prepared primary vinylogous amides. No nitrogen protecting group is employed,[3] and the annulation delivers synthetically and medicinally important dihydropyridinone products[4] suitable for direct biological assay or further elaboration into compounds of contemporary interest. The use of chiral N-heterocyclic carbene precursor **1** delivers the annulation products with good yields and enantioselectivies. The underlying mechanism of this cascade reaction features a novel NHC-catalyzed aza-Claisen rearrangement[5] that evolved from our recent studies of NHC-catalyzed Coates−Claisen rearrangements.

(1) For example: (a) He, M.; Struble, J. R.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 8418–8420. (b) He, M.; Bode, J. W. *J. Am. Chem. Soc.* **2008**, *130*, 418–419. (c) Rommel, M.; Fukuzumi, T.; Bode, J. W. *J. Am. Chem. Soc.* **2008**, *130*, 17266–17267. (d) Raup, D. E. A.; Cardinal-David, B.; Holte, D.; Scheidt, K. A. *Nat. Chem.* **2010**, *2*, 766–771. (e) Zhao, X.; DiRocco, D. A.; Rovis, T. *J. Am. Chem. Soc.* **2011**, *133*, 12466–12469.

(2) For a review of the chemistry of *N*-mesityl catalysts, see: Chiang, P.-C.; Bode, J. W. *TCI MAIL.* **2011**, *149*, 2–17.

(3) Recent examples of cascade reactions of N-protected enamine and α,β-unsaturated aldehydes include: (a) Noole, A.; Borissova, M.; Lopp, M.; Kanger, T. *J. Org. Chem.* **2011**, *76*, 1538–1545. (b) Buchanan, G. S.; Dai, H.; Hsung, R. P.; Gerasyuto, A. I.; Scheinebeck, C. M. *Org. Lett.* **2011**, *13*, 4402–4405.

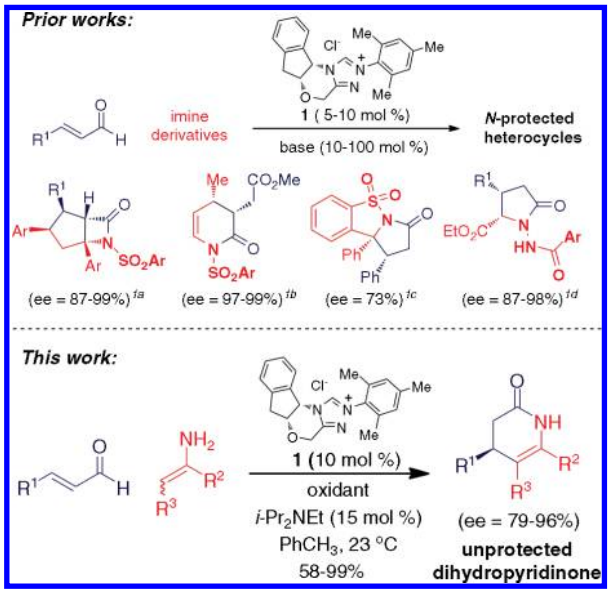
(4) (a) Nantermet, P. G.; Barrow, J. C.; Selnick, H. G.; Homnick, C. F.; Freidinger, R. M.; Chang, R. S. L.; O'Malley, S. S.; Reiss, D. R.; Broten, T. P.; Ransom, R. W.; Pettibone, D. J.; Olah, T.; Forray, C. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1625–1628. (b) Goodman, K. B.; Cui, H.; Dowdell, S. E.; Gaitanopoulos, D. E.; Ivy, R. L.; Sehon, C. A.; Stavenger, R. A.; Wang, G. Z.; Viet, A. Q.; Xu, W.; Ye, G.; Semus, S. F.; Evans, C.; Fries, H. E.; Jolivette, L. J.; Kirkpatrick, R. B.; Dul, E.; Khandekar, S. S.; Yi, T.; Jung, D. K.; Wright, L. L.; Smith, G. K.; Behm, D. J.; Bentley, R.; Doe, C. P.; Hu, E.; Lee, D. *J. Med. Chem.* **2006**, *50*, 6–9.

(5) For reviews of aza-Claisen reactions, see: (a) Nubbemeyer, U. *Top. Curr. Chem.* **2005**, *244*, 149–213. (b) Majumdar, K. C.; Bhattacharyya, T.; Chattopadhyay, B.; Sinha, B. *Synthesis* **2009**, 2117–2142.

(6) Kaeobamrung, J.; Mahatthananchai, J.; Zheng, P.; Bode, J. W. *J. Am. Chem. Soc.* **2010**, *132*, 8810–8812.

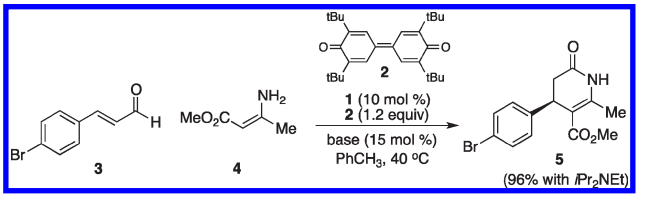
10.1021/ol202272t
Published on Web 09/09/2011

Scheme 1. NHC-Catalyzed Syntheses of N-Heterocycles



In 2010 we reported the enantioselective, NHC catalyzed synthesis of dihydropyranones[6] from ynals and stable enols via catalytically generated α,β-unsaturated acyl azolium intermediates. A conceptually related reaction starting from α,β-unsaturated acyl fluorides and silyl enol ethers to deliver racemic dihydropyranones was reported just prior to our study by Lupton;[7] related annulations were reported by Studer,[8] Xiao,[9] and You[10] shortly after our work. As part of mechanistic studies establishing that the key C−C bond forming event occurs via an NHC-catalyzed variant of the Coates−Claisen rearrangement,[11] we found that the formation of a metastable hemiacetal from the α,β-unsaturated acyl azolium and the enol was key to the success of this reaction. Simultaneously, acyl azoliums have been established to be surprisingly reluctant to effect amidation reactions.[12] Taken together, these observations suggested that stable, unsubstituted enamines would be suitable substrates for an aza-Claisen rearrangement without competing amide-bond formation. The requisite enamines are either commercially available or prepared from 1,3-ketoesters.

Table 1. Optimization of Enantioselective Annulation of Enal[a]



base or additive	ee %	base or additive	ee %
no base (3 days)	66	i-Pr_2NEt	80
K_2CO_3	68	i-Pr_2NEt + $NaBF_4$	80
t-BuOK	73	i-Pr_2NEt + 4 Å MS	80
NMM	79	i-Pr_2NEt at 23 °C	86

[a] Reaction conditions: 0.1 M $PhCH_3$, 12 h at 40 °C unless noted.

Although the key α,β-unsaturated acyl azolium can be generated via an internal redox reaction of ynals and an NHC,[13] we choose to catalytically generate this species via an oxidation of the Breslow intermediate formed from the combination of enals and an NHC. Our studies began by examining the NHC-catalyzed annulation of enal **3** and enamine **4** in the presence of *N*-mesityl catalyst **1** (Table 1). Oxidant **2**, reported by Kharasch[14] and utilized by Studer,[8,12g] was found to be the most effective for this reaction. The choice of base had a subtle effect. Amine bases such as DBU, NMM, and i-Pr_2NEt were found to give higher enantioselectivity than inorganic bases (K_2CO_3, t-BuOK, or Cl^-). Additives such as molecular sieves[9b] or $NaBF_4$[10] did not improve the selectivity. Simply lowering the reaction temperature to 23 °C (room temperature) led to an agreeable increase in enantioselectivity. However, further decreasing the temperature to 0 °C prolonged the reaction time without significant enhancement of the selectivity.

With the optimized conditions, we explored the scope of this variant of the aza-Claisen reaction. A number of stable, unprotected enamines containing cyano, ester, or nitro groups cleanly afforded the corresponding dihydropyridinones in good yields and enantioselectivities (Scheme 2). Similarly, a broad range of α,β-unsaturated aldehydes (aliphatic, alkenyl, or aromatic) proved to be suitable reaction partners. The best result (96% ee, entry **12**) was obtained from coupling (*E*)-4-methylpent-2-enal and (*Z*)-3-aminobut-2-enenitrile. Less sterically hindered enals led to slightly diminished selectivity (entries **9** to **11**). Aromatic groups either on the enals (entries **6** to **8**) or the enamines (entries **16** to **17**) afforded the expected dihydropyridinones in greater yield than the aliphatic counterparts. It is worth noting that the geometry of the

(7) (a) Ryan, S. J.; Candish, L.; Lupton, D. W. *J. Am. Chem. Soc.* **2009**, *131*, 14176–14177. (b) Candish, L.; Lupton, D. W. *Org. Lett.* **2010**, *12*, 4836–4839.

(8) De Sarkar, S.; Studer, A. *Angew. Chem., Int. Ed.* **2010**, *49*, 9266–9269.

(9) (a) Zhu, Z. Q.; Xiao, J. C. *Adv. Synth. Catal.* **2010**, *352*, 2455–2458. (b) Zhu, Z.-Q.; Zheng, X.-L.; Jiang, N.-F.; Wan, X.; Xiao, J.-C. *Chem. Commun.* **2011**, *47*, 8670–8672.

(10) Rong, Z.-Q.; Jia, M.-Q.; You, S.-L. *Org. Lett.* **2011**, *13*, 4080–4083.

(11) Mahatthananchai, J.; Zheng, P.; Bode, J. W. *Angew. Chem., Int. Ed.* **2011**, *50*, 1673–1677.

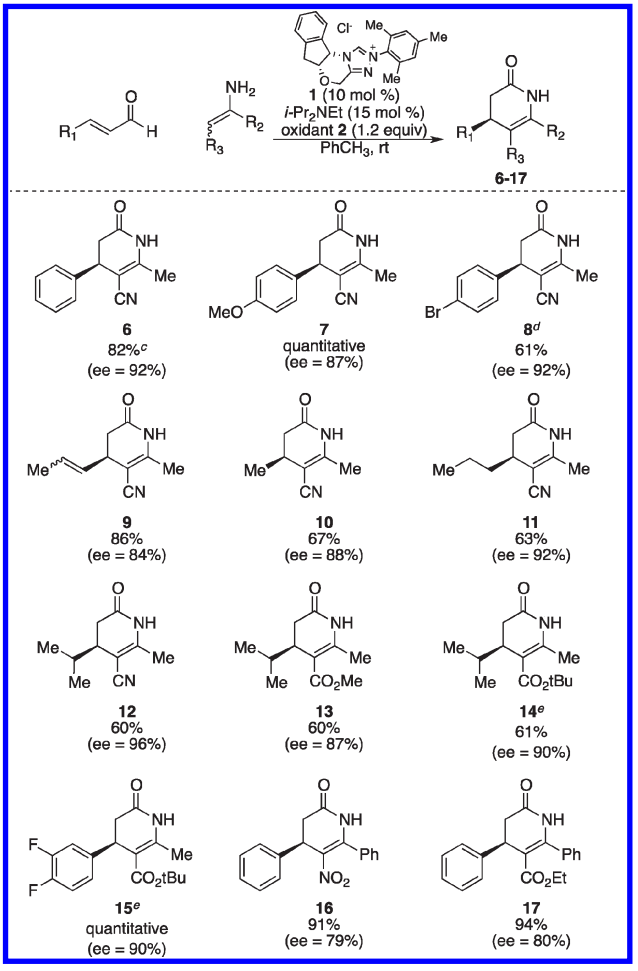
(12) (a) Daigo, K.; Reed, L. J. *J. Am. Chem. Soc.* **1962**, *84*, 659–662. (b) Owen, T. C.; Richards, A. *J. Am. Chem. Soc.* **1987**, *109*, 2520–2521. (c) Owen, T. C.; Harris, J. N. *J. Am. Chem. Soc.* **1990**, *112*, 6136–6137. (d) Movassaghi, M.; Schmidt, M. A. *Org. Lett.* **2005**, *7*, 2453–2456. (e) Bode, J. W.; Sohn, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 13798–13799. (f) Vora, H. U.; Rovis, T. *J. Am. Chem. Soc.* **2007**, *129*, 13796–13797. (g) De Sarkar, S.; Grimme, S.; Studer, A. *J. Am. Chem. Soc.* **2010**, *132*, 1190–1191.

(13) Zeitler, K. *Org. Lett.* **2006**, *8*, 637–640.

(14) Kharasch, M. S.; Joshi, B. S. *J. Org. Chem.* **1957**, *22*, 1439–1443.

enamine (either *E* or *Z* such as for entries **13** and **14**) did not play a role in either reactivity or selectivity. In a preliminary attempt, α-methyl cinnamaldehyde did not participate in this reaction.

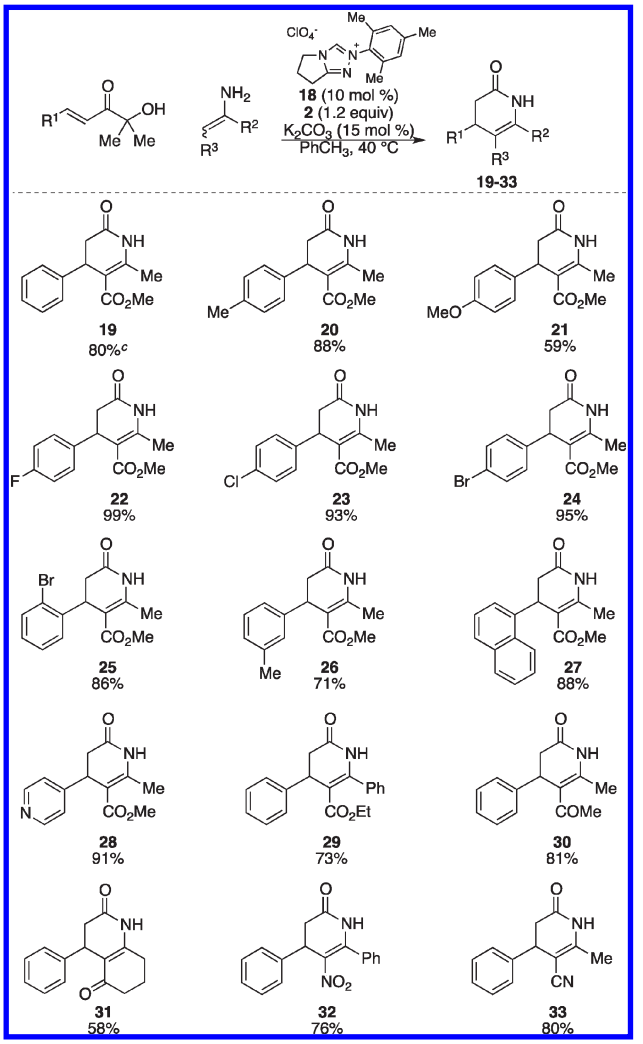
Scheme 2. Enantioselective Annulation of Enals and Enamines[a,b]



[a] Reaction conditions: 0.1 M $PhCH_3$, 12 h, rt. [b] (*Z*)-Enamines were used, unless noted. [c] Yield refers to isolated yield after chromatography. [d] The absolute configuration of (*R*)-**8** was established by X-ray analysis; others were assigned by analogy. [e] An (*E*)-enamine was used.

We have previously acknowledged the relative difficulty of preparing cinnamaldehyde derivatives and introduced α′-hydroxyenones[15] as easily prepared (one step from commercial materials) and stored surrogates. The increased sterics of these substrates preclude the use of chiral NHCs but smaller, achiral variants effect most of the known NHC-catalyzed annulations to give racemic products. In many cases, the synthesis of the racemic heterocycles is desirable for testing or reaction screening, and the enantioselective variant can be accomplished by preparing, when necessary, the corresponding enals. In order to test this new NHC-catalyzed annulation with a greater variety of aromatic and heteroaromatic substituents we developed conditions for annulations of vinylogous amides and α′-hydroxyenones with achiral *N*-mesityl triazolium salt **18**. Consistent with our previous study,[16] triazolium catalysts lacking an ortho-substitution were found to be ineffective for this reaction (see Supporting Information for screening). The reaction proceeded cleanly and efficiently with these substrates and gave uniformly high yields from α′-hydroxyenones bearing electron-rich, electron-deficient, and hetero aromatic groups (Scheme 3). Again, a range of stable, unprotected enamines containing cyano,

Scheme 3. Annulation of α′-Hydroxyenone and Enamines[a,b]



[a] Reaction conditions: 0.1 M $PhCH_3$, 12 h at 40 °C, [b] (*Z*)-Enamines were used. [b] Yield refers to isolated yield after chromatography.

(15) (a) Chiang, P.-C.; Rommel, M.; Bode, J. W. *J. Am. Chem. Soc.* **2009**, *131*, 8714–8718. (b) Chiang, P.-C.; Kim, Y.; Bode, J. W. *Chem. Commun.* **2009**, 4566–4568.

(16) Mahatthananchai, J.; Bode, J. W. *Chem. Sci.* **2011**, DOI: 10.1039/c1sc00397f.

(17) (a) Hargreaves, J. R.; Hickmott, P. W.; Hopkins, B. J. *J. Chem. Soc. C* **1968**, 2599–2603. (b) Hickmott, P. W.; Sheppard, G. *J. Chem. Soc. C* **1971**, 2112–2115.

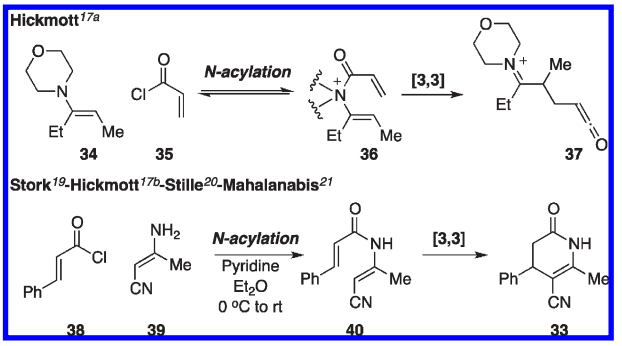
(18) The issue of selective N-acylation vs C-alkylation of enamines is a subject of Mayr's recent review on ambident reactivity: Maji, B.; Breugst, M.; Mayr, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 6915–6919.

(19) Stork, G.; Kretchmer, R. A.; Schlessinger, R. H. *J. Am. Chem. Soc.* **1968**, *90*, 1647–1648.

ester, ketone (acyclic and cyclic), or nitro groups all participated in this reaction.

Two examples from Schemes 2 and 3 are worth noting. Compound **15** (Scheme 2), prepared in quantitative yield and high enantiomeric excess from the corresponding enal and a vinylogous amide, constitutes an asymmetric synthesis of a precursor for an α_{1a} adrenergic receptor antagonist with low nano- to picomolar potency, in which no other method for catalytic enantioselective synthesis is available.[4a] Similarly, compound **22** (Scheme 3) represents a facile catalytic synthesis of a precursor for selective Rho-kinase inhibitors[4b] from a readily prepared α′-hydroxyenone.[15]

Scheme 4. N-Acylation of Enamines and Their Rearrangements



Mechanistically, we propose that the N-heterocyclic carbene, generated by deprotonation of the corresponding triazolium salt, adds irreversibly[16] to the enal to generate the Breslow intermediate **I**. This species is oxidized by **2** to form the key α,β-unsaturated acyl azolium **II**. Hickmott[17] has demonstrated that the reaction of enamines such as **34** with α,β-unsaturated acid chlorides **35** proceeded first via N-acylation over C-alkylation,[18] which gave an intermediate that underwent a sigmatropic rearrangement, possibly via the intermediacy of a ketene (Scheme 4). Building on these results and those of Stork[19] and Stille,[20] Mahalanabis[21] has invoked this mechanistic rationale in the synthesis of **33** from acyl chloride **38** and enamine **39** (Scheme 4). In a slight departure from these precedents, we favor a reversible 1,2 addition of the enamine to **II** to form hemiaminal **III**, an argument that parallels our previous studies[6,11] and the well-documented properties of acyl azoliums.[12a–c]

The metastable hemiaminal **III** is poised for an aza-Claisen rearrangement, the enantiodetermining step, in which the sense of asymmetric induction is identical to that observed in our dihydropyranone synthesis.[6] This rearrangement is followed by lactam formation and catalyst turnover to afford dihydropyridinone products (Figure 1).

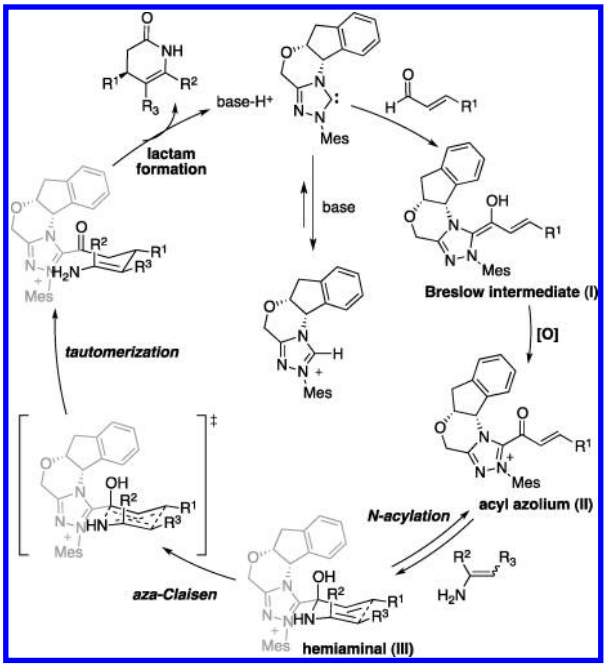


Figure 1. Proposed mechanism of an NHC-catalyzed aza-Claisen annulation cascade.

In summary, we have reported the annulation of enals or their α′-hydroxyenones surrogates with readily prepared vinylogous amides via an NHC-catalyzed aza-Claisen rearrangement. The reaction proceeds with a broad range of substrates to afford synthetically useful dihydropyridinones in good yields and enantioselectivities. This reaction also constitutes an NHC-catalyzed N-heterocycle formation, in which neither imines nor nitrogen protecting groups are required.

Acknowledgment. This work was supported by ETH-Zürich and a predoctoral fellowship from Novartis to J.M. The authors thank Pei-Chen Chiang (UPenn) for the preparation of α′-hydroxyenones.

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

(20) (a) Paulvannan, K.; Stille, J. R. *J. Org. Chem.* **1992**, *57*, 5319–5328. (b) Benovsky, P.; Stephenson, G. A.; Stille, J. R. *J. Am. Chem. Soc.* **1998**, *120*, 2493–2500. The authors thank a referee for pointing out these reports.

(21) Chowdhury, S. K. D.; Sarkar, M.; Chowdhury, S. R.; Mahalanabis, K. K. *Synth. Commun.* **1996**, *26*, 4233–4251.

(22) Other examples of NHC-catalyzed lactam formation include ref 1 and (a) Zhang, Y.-R.; He, L.; Wu, X.; Shao, P.-L.; Ye, S. *Org. Lett.* **2008**, *10*, 277–280. (b) Duguet, N.; Campbell, C. D.; Slawin, A. M. Z.; Smith, A. D. *Org. Biomol. Chem.* **2008**, *6*, 1108–1113. (c) Thai, K.; Wang, L.; Dudding, T.; Bilodeau, F.; Gravel, M. *Org. Lett.* **2010**, *12*, 5708–5711.