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N-Heterocyclic Carbene and Brønsted Acid Cooperative Catalysis: Asymmetric Synthesis of *trans*-γ-Lactams

Xiaodan Zhao, Daniel A. DiRocco, and Tomislav Rovis*

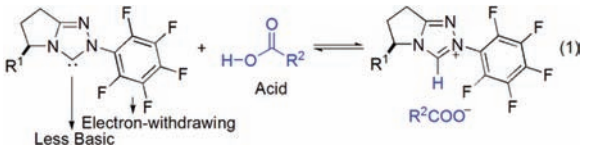
Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523, United States

Supporting Information

ABSTRACT: An efficient enantioselective approach to form *trans*-γ-lactams in up to 99% yield, 93% ee, and >20/1 dr using unactivated imines has been developed. The cyclohexyl-substituted azolium and the weak base sodium *o*-chlorobenzoate are most suitable for this transformation. Notably, the process involves cooperative catalysis by an N-heterocyclic carbene and a Brønsted acid.

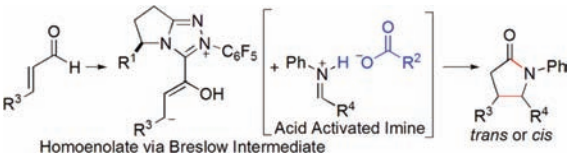
Umpolung reactions catalyzed by N-heterocyclic carbenes (NHCs) have become a quickly growing field in the past decade.[1] Since 2000, our group has focused on the design of carbene precursors and the exploration of new asymmetric reactions by NHC catalysis. We have developed two families of catalysts (morpholine-based and pyrrolidine-based triazolium salts) and successfully applied the azolium salts as precatalysts for Stetter, redox, and cascade reactions that efficiently afford versatile products in good enantioselectivity.[2−4] Of these catalysts, the triazolium precatalysts with an *N*-pentafluorophenyl group installed to tune the electronic and steric nature exhibit excellent catalytic activity. The corresponding carbenes derived from this scaffold are far less basic and thus could be compatible with weak acids. This is in agreement with our previous observation that sodium acetate can deprotonate the pentafluorophenyl triazolium salts to give the free carbenes and acetic acid.[4a] Interestingly, the presence of the Brønsted acid does not interfere with the action of the carbenes.

We hypothesized that if an acid with low pK_a value does not neutralize a carbene (eq 1),[5] the carbene and the acid could play different roles in a reaction system, leading to new types of reactions. On the basis of this hypothesis, we were interested in exploring an NHC/Brønsted acid cooperative strategy in catalysis. Although the concept of cooperative catalysis, such as metal/Brønsted acid,[6] NHC/Ag,[7] and NHC/Mg or Ti,[8] has emerged in organic synthesis, NHC/Brønsted acid cooperative catalysis has not been demonstrated.[9]



Homoenolates generated by the reaction of NHCs with enals are vinylogous acyl anions, and their reactivity was first reported independently by the Glorius and Bode groups in 2004.[10] Since then, investigations have documented their utility to prepare *cis*-γ-lactams,[8a,11] γ-butyrolactones,[12] cyclopentenes,[8b,c,13] and heterocycles,[14] among others.[15] With a few exceptions,[11d,12d,13b,15c] the enantioselective control of homoenolates still remains challenging. Keeping this in mind, we turned our attention to homoenolate chemistry and the design of new types of chiral azolium salts to achieve products with high enantioselectivity.

Scheme 1. Proposed NHC/Brønsted Acid Cooperative Catalysis



We imagined that the conjugate acid of the base used to generate the carbene could be induced to activate a basic functionality such as an imine, with the further prospect that a chiral base would potentially lead to a second means of controlling the stereochemistry in the bond-forming event. This combination may also conceivably give access to an inaccessible diastereomer and prove complementary to existing methods. Thus, combining homoenolates and acid-activated imines[8,16] was expected to generate valuable γ-lactams[17] (Scheme 1). Herein we report an NHC/Brønsted acid-mediated reaction of enals with unactivated imines that affords *trans*-γ-lactams in good yields, high enantioselectivities, and good diastereoselectivities.

We initiated our study by examining the reaction of sterically unhindered and unactivated *N*-(4-methoxycinnamylidene)aniline (**1a**) with strongly electrophilic and commercially available ethyl *trans*-4-oxo-2-butenoate (**2a**) (Table 1). This reaction was carried out in CH_2Cl_2 at room temperature in the presence of base[18] and 4 Å molecular sieves (MS) for 15 h using benzyl-substituted triazolium salt **C1** as the catalyst. When strong bases such as KHMDS or Et_3N were used, the product lactam was generated in poor yield and selectivity. Under these conditions, enal **2a** competitively hydrates or oxidizes with adventitious water or oxygen to form a carboxylic acid, which may serve as the activator of the imine. Indeed, when Et_3N was used as a stoichiometric base, this pathway was eliminated (entry 2). The use of carboxylate bases, on the other hand, was expected to generate stronger conjugate acids capable of activating aldimine **1a**. With NaOAc, the reaction afforded the annulation product, lactam **3a**, in 62% yield.[19] Surprisingly, the *trans*-lactam (42% ee) was formed in preference to the cis isomer (entry 4). This is the first NHC-catalyzed synthesis of a *trans*-γ-lactam as the major

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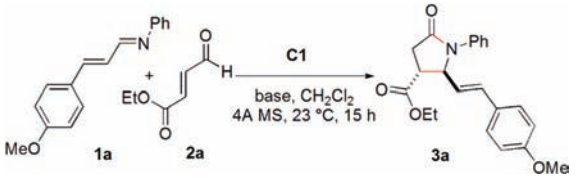
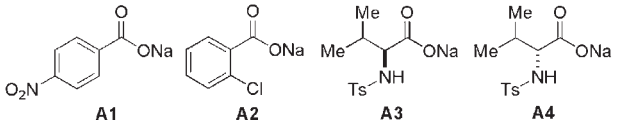
Table 1. Base Screen[a]



entry	base	yield (%)[b]	dr[c]	ee (%)[d]
1	Et_3N	39	9:1	14
2[e]	Et_3N	trace	---	---
3	KHMDS	25	5/1	23
4	NaOAc	62	5/1	42
5	PhCOONa	72	6/1	50
6	**A1**	94	5/1	57
7	**A2**	94	5/1	59
8	**A3**	76	6/1	33
9	**A4**	80	6/1	41

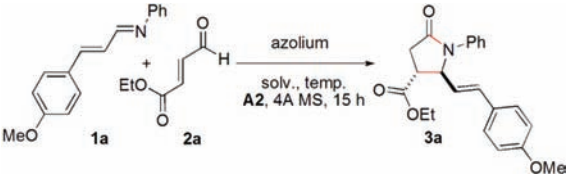


[a] Conditions: **2a**, 0.2 mmol; **1a**, 0.1 mmol; base, 20 mol %; **C1** (structure shown in Table 2), 20 mol %; CH_2Cl_2, 1 mL; 4 Å MS under Ar. [b] NMR yields of the trans and cis diastereomers (internal standard). [c] The trans/cis ratio, as determined by ^{1}H NMR analysis. [d] ee of *trans*-**3a** as determined by chiral HPLC. [e] 1.2 equiv of Et_3N was used.

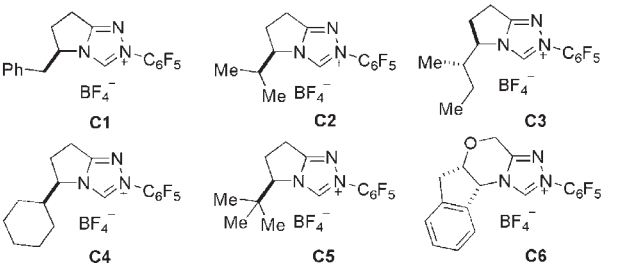
product.[8a] When the slightly weaker base PhCOONa was employed, **3a** was formed in 72% yield and 50% ee (entry 5). Following this trend, the use of the much weaker bases **A1** and **A2** (conjugate acids: *p*-$NO_2C_6H_4COOH$, pK_a[H_2O] = 3.1; *o*-ClC_6H_4COOH, pK_a[H_2O] = 2.9) afforded **3a** in higher yields and higher ee's (entries 6 and 7). When the bases **A3** and **A4** derived from chiral amino acids were used, **3a** was formed in lower enantioselectivity, with the difference between the two entries indicating a match and mismatch (entries 8 and 9). Notably, the weak bases **A3** and **A4** were still capable of deprotonating the azolium to generate the active catalyst.

We envisioned that moderately increased steric hindrance on the azolium would provide a better chiral environment since the nucleophilic carbanion on the intermediate homoenolate is distant from the chiral center. When isopropyl-substituted triazolium salt **C2** was employed as a catalyst with **A2**, **3a** was generated in 66% ee (Table 2, entry 1). The azoliums **C3** and **C4**, which have slightly bulkier groups than in **C2** and were prepared from the corresponding amino acids, delivered higher enantioselectivities (71 and 76% ee, respectively; entries 2 and 3). The much bulkier azolium **C5** was ineffective (entry 4). Triazolium salt **C6** exhibited moderate catalytic activity, affording **3a** with low ee (46%) (entry 5). Next, the reaction temperature and solvent were investigated using the best catalyst (**C4**) and base (**A2**). When the temperature was lowered to 0 °C, the yield, dr, and ee were improved (entry 6). A further decrease in the temperature to −10 °C affected the enantioselectivity slightly (entry 7). Common solvents such as toluene, $CHCl_3$, and $ClCH_2CH_2Cl$ were less effective than CH_2Cl_2. The use of other solvents (e.g., THF, ether, alcohols) delivered **3a** in only trace amounts. However, the use of acetonitrile as a solvent provided **3a** with 91% ee, albeit in moderate yield (entry 8). Satisfyingly, when inexpensive acrylonitrile was used as the solvent instead of

Table 2. Optimization of Azolium, Temperature, and Solvent[a]



entry	cat.	solvent	temp (°C)	yield[b] (%)	dr[c]	ee[d] (%)
1	**C2**	CH_2Cl_2	23	97	6/1	66
2	**C3**	CH_2Cl_2	23	96	6/1	71
3	**C4**	CH_2Cl_2	23	93	6/1	76
4	**C5**	CH_2Cl_2	23	trace	---	---
5	**C6**	CH_2Cl_2	23	72	5/1	46
6	**C4**	CH_2Cl_2	0	98(99)	9/1	87
7	**C4**	CH_2Cl_2	-10	97	9/1	88
8	**C4**	CH_3CN	0	76	10/1	91
9	**C4**	CH_3CH_2CN	0	66	12/1	87
10	**C4**	H_2C=CHCN	0	96(93)	11/1	91



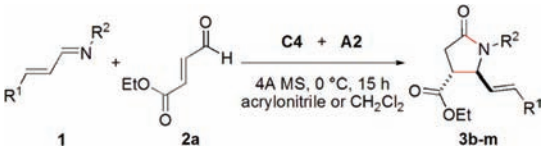
[a] Conditions: **2a**, 0.2 mmol; **1a**, 0.1 mmol; **A2**, 20 mol %; azolium cat., 20 mol %; solvent, 1 mL; 4 Å MS under Ar. [b] NMR yields of the trans and cis diastereomers (internal standard). Entries in parentheses are isolated yields. [c] The trans/cis ratio, as determined by ^{1}H NMR analysis. [d] ee of *trans*-**3a** as determined by chiral HPLC.

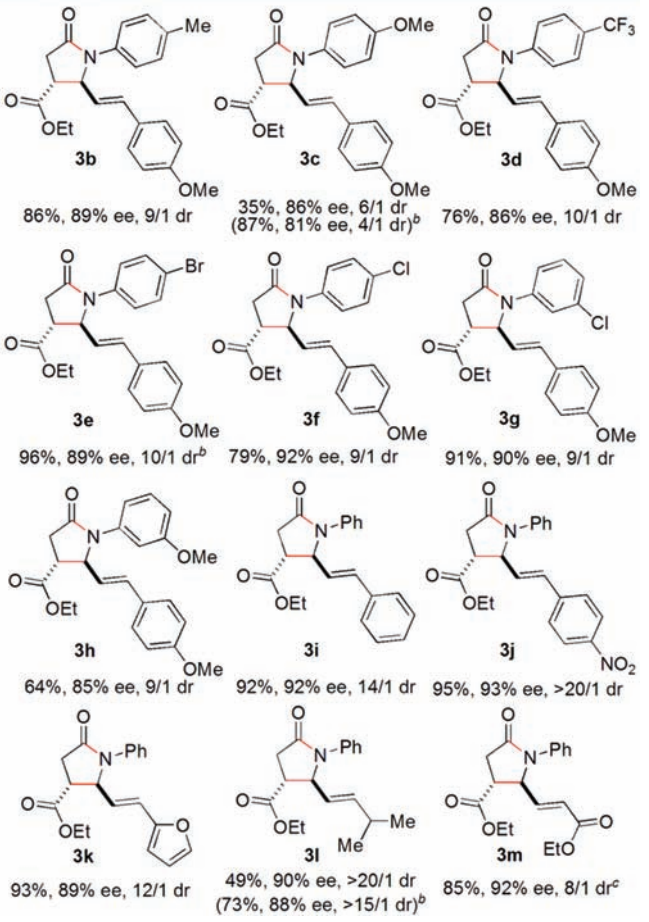
CH_3CN, **3a** was generated in excellent yield (93%), good ee (90%), and good diastereoselectivity (11/1) (entry 10).

Under these optimized conditions, the substrate scope of α,β-unsaturated imines was evaluated, and the results are shown in Table 3.[20] The electronic nature of the imine was investigated first. When an electron-neutral group (−Me) or an electron-deficient group (*p*−CF_3, *p*−Br, *p*−Cl, *m*−Cl, *m*−MeO) was resident on the phenyl group of the aldimine, the cyclization was slightly affected but afforded the products **3b** and **3d**−**h**, respectively, in good yield, good dr, and high enantioselectivity (86−92% ee). In contrast, the reaction was more efficient in CH_2Cl_2 when a methoxy group was placed at the para or meta position (i.e., **3c**, 35% yield, 86% ee, 6/1 dr in acrylonitrile and 87% yield, 81% ee, 4/1 dr in CH_2Cl_2). When the aldimines derived from cinnamaldehyde, *p*-nitrocinnamaldehyde, and 3-(2-furyl)acrylaldehyde were used, the corresponding products **3i**−**k** were obtained in excellent yields and good enantioselectivities (92, 93, and 89% ee, respectively). The imine from (*E*)-4-methylpent-2-enal underwent cyclization to give **3l** in low yield in acrylonitrile as a result of decomposition of the imine.[21] The reaction proceeded well in CH_2Cl_2 to yield **3l** in 73% yield and 88% ee. However, the imine generated in situ from enal and aniline gave **3m** in 85% yield, 92% ee, and 8/1 dr.

A variety of enals as suitable substrates were explored (Table 4). Using a ketone as a substituent on the enal gave the desired lactam **3n** in 62% yield and >15/1 dr but only 66% ee (entry 1). Less nucleophilic *p*-nitrocinnamaldehyde was fully

Table 3. Evaluation of the Imine Substrate Scope[a]





[a] Conditions: **2a**, 0.2 mmol; imine **1**, 0.1 mmol; **A2**, 20 mol %; **C4**, 20 mol %; solvent, 0.8 mL. All reactions were carried out under Ar in the presence of 4 Å MS at 0 °C for 15 h. The trans/cis ratios were determined by ^{1}H NMR analysis prior to purification. The ee's were determined by chiral HPLC. [b] CH_2Cl_2 was used as the solvent instead of acrylonitrile. [c] The starting imine was formed in situ.

converted to **3o** in 93% ee and 14/1 dr. In contrast, much less nucleophilic *p*-bromocinnamaldehyde and cinnamaldehyde underwent cyclization less efficiently to give **3p** and **3q** in 56 and 48% yield, respectively, with good ee's and dr's.

In order to probe the role of the acid in our system, the reaction of α,β-unsaturated imine **1a** with enal **2a** was examined using an achiral carbene and chiral, enantioenriched amino acids. We found that amino acids bearing more strongly electron-withdrawing groups on nitrogen gave higher enantioselectivities. Product *ent*-**3a** was obtained in 96% isolated yield, 17% ee, and 3/1 dr using **A3** as the base (eq 2).[22] Although the enantioselectivity was low, this result suggests that hydrogen bonding exists in the transformation and indicates that it is possible to develop an approach with achiral carbenes and chiral acids[16] to deliver products with high enantioselectivity.

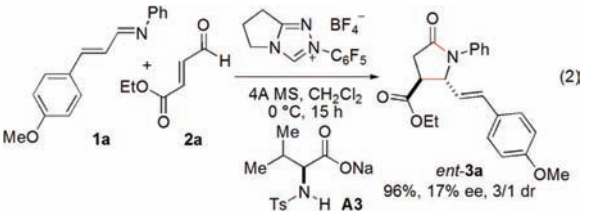
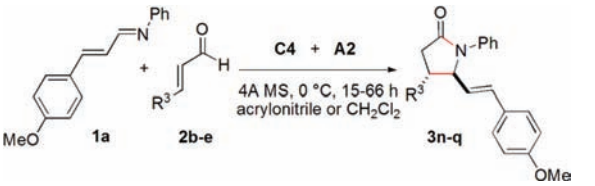


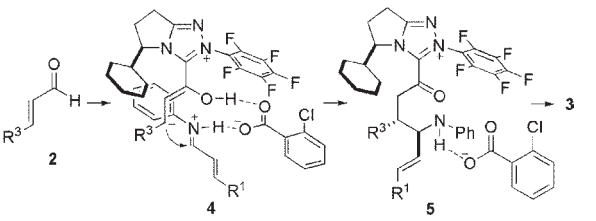
Table 4. Exploration of Various Enals[a]



entry	R^3		product	yield (%)	dr	ee (%)
1[b]	Me	**2b**	**3n**	62	11/1	66
2[c]	4-NO_2-C_6H_4	**2c**	**3o**	99	14/1	93
3[d]	4-Br-C_6H_4	**2d**	**3p**	58	17/1	91
4[d]	Ph	**2e**	**3q**	48	20/1	90

[a] Conditions: aldehyde **2**, 0.2 mmol; **1a**, 0.1 mmol; **A2**, 20 mol %; **C4**; 20 mol %; solvent, 0.8 mL. All reactions were carried out under Ar in the presence of 4 Å MS at 0 °C. The trans/cis ratios were determined by ^{1}H NMR analysis prior to purification. The ee's were determined by chiral HPLC. [b] 15 h in acrylonitrile. [c] 36 h in CH_2Cl_2. [d] 66 h in CH_2Cl_2.

Scheme 2. Proposed Pathway for *trans*-γ-Lactam Formation



A few possible reaction pathways involving homoenolate equivalents have been proposed in the literature.[11,14] A plausible mechanism for our reaction is shown in Scheme 2. The enal **2** first reacts with the carbene to generate a Breslow intermediate, which attacks the acid-activated imine, perhaps via hydrogen-bonding intermediate **4**. Steric hindrance leads to an anti orientation of R^3 and the alkenyl. Proton transfer then results in the formation of acyl carboxylate **5**. The nitrogen species replaces the carbene to afford the product **3** and the free carbene.

In conclusion, we have developed an efficient NHC-catalyzed asymmetric approach for synthesizing *trans*-γ-lactams in high yields, high enantioselectivities, and >20/1 dr with unactivated imines. It is noteworthy that electron-rich carbenes have historically been used to catalyze homoenolate chemistry.[1b] Our findings are promising in the application of homoenolates using electron-deficient carbene catalysis. This method involves cooperative NHC/Brønsted acid catalysis. In the transformation, cyclohexyl-substituted carbene and *o*-chlorobenzoic acid are

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most efficient. The application of cooperative catalysis in other reactions and the utility of chiral carbenes for asymmetric homoenolate transformations are in progress.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, characterization data, determination of the absolute configurations of products, NMR and HPLC spectra, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
rovis@lamar.colostate.edu

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■ REFERENCES

(1) For selected reviews, see: (a) Enders, D.; Niemeier, O.; Hensler, A. *Chem. Rev.* **2007**, *107*, 5606. (b) Nair, V.; Vellalath, S.; Babu, B. P. *Chem. Soc. Rev.* **2008**, *37*, 2691. (c) Read de Alaniz, J.; Rovis, T. *Synlett* **2009**, 1189. (d) Phillips, E. M.; Chan, A.; Scheidt, K. A. *Aldrichimica Acta* **2009**, *42*, 55. (e) Moore, J. L.; Rovis, T. *Top. Curr. Chem.* **2010**, *291*, 77. (f) Vora, H. U.; Rovis, T. *Aldrichimica Acta* **2011**, *44*, 3.

(2) For asymmetric Stetter reactions, see: (a) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 10298. (b) Kerr, M. S.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 8876. (c) Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2005**, *127*, 6284. (d) Liu, Q.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 2552. (e) Cullen, S. C.; Rovis, T. *Org. Lett.* **2008**, *10*, 3141. (f) Liu, Q.; Perreault, S.; Rovis, T. *J. Am. Chem. Soc.* **2008**, *130*, 14066. (g) Liu, Q.; Rovis, T. *Org. Lett.* **2009**, *11*, 2856. (h) DiRocco, D. A.; Oberg, K. M.; Dalton, D. M.; Rovis, T. *J. Am. Chem. Soc.* **2009**, *131*, 10872. (i) DiRocco, D. A.; Rovis, T. *J. Am. Chem. Soc.* **2011**, *133*, 10402.

(3) For redox reactions, see: (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) Vora, H. U.; Rovis, T. *J. Am. Chem. Soc.* **2007**, *129*, 13796. (d) Vora, H. U.; Moncecchi, J. R.; Epstein, O.; Rovis, T. *J. Org. Chem.* **2008**, *73*, 9727. (e) Vora, H. U.; Rovis, T. *J. Am. Chem. Soc.* **2010**, *132*, 2860.

(4) For cascade reactions, see: (a) Lathrop, S. P.; Rovis, T. *J. Am. Chem. Soc.* **2009**, *131*, 13628. (b) Filloux, C. M.; Lathrop, S. P.; Rovis, T. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 20666. (c) Ozboya, K. E.; Rovis, T. *Chem. Sci.* [Online early access]. DOI: 10.1039/C1SC00175B. Published Online: June 16, 2011.

(5) An equilibrium certainly exists between azolium + base and carbene + conjugate acid. However, through the use of an acidic azolium with a weak base, we hoped to generate the NHC and conjugate acid in significant enough quantities to engage in productive cooperative catalysis. For a report involving the use of another very weak base in NHC catalysis, see: Kaeobamrung, J.; Mahatthananchai, J.; Zheng, P.; Bode, J. W. *J. Am. Chem. Soc.* **2010**, *132*, 8810.

(6) For selected examples, see: (a) Hu, W.; Xu, X.; Zhou, J.; Liu, W.-J.; Huang, H.; Hu, J.; Yiang, L.; Gong, L.-Z. *J. Am. Chem. Soc.* **2008**, *130*, 7782. (b) Li, C.; Villa-Marcos, B.; Xiao, J. *J. Am. Chem. Soc.* **2009**, *131*, 6967. (c) Lu, Y.; Johnstone, T. C.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2009**, *131*, 11284. (d) Zhou, S.; Fleischer, S.; Junge, K.; Beller, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 5120.

(7) Chen, Z.; Yu, X.; Wu, J. *Chem. Commun.* **2010**, *46*, 6356. For compatible catalysis of NHC/Pd, see: (a) Nemoto, T.; Fukuda, T.; Hamada, Y. *Tetrahedron Lett.* **2006**, *47*, 4365. (b) Lebeuf, R.; Hirano, K.; Glorius, F. *Org. Lett.* **2008**, *10*, 4243. (c) He, J.; Tang, S.; Liu, J.; Sun, Y.; Pan, X.; She, X. *Tetrahedron Lett.* **2009**, *50*, 430.

(8) (a) Raup, D. E. A.; Cardinal-David, B.; Holte, D.; Scheidt, K. A. *Nat. Chem.* **2010**, *2*, 766. (b) Cardinal-David, B.; Raup, D. E. A.; Scheidt, K. A. *J. Am. Chem. Soc.* **2010**, *132*, 5345. (c) Cohen, D.; Cardinal-David, B.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 1678. (d) Cohen, D.; Cardinal-David, B.; Roberts, J. M.; Sarjeant, A. A.; Scheidt, K. A. *Org. Lett.* **2011**, *13*, 1068.

(9) Hydrogen bonding to improve the enantioselectivity in NHC catalysis has been reported. See: (a) Mennen, S. M.; Blank, J. T.; Tran-Dube, M. B.; Imbriglio, J. E.; Miller, S. J. *Chem. Commun.* **2005**, 195. (b) He, L.; Zhang, Y.-R.; Huang, X.-L.; Ye, S. *Synthesis* **2008**, 2825. (c) O'Toole, S. E.; Connon, S. J. *Org. Biomol. Chem.* **2009**, *7*, 3584.

(10) (a) Burstein, C.; Glorius, F. *Angew. Chem., Int. Ed.* **2004**, *43*, 6205. (b) Sohn, S. S.; Rosen, E. L.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 14370.

(11) (a) He, M.; Bode, J. W. *Org. Lett.* **2005**, *7*, 3131. (b) Rommel, M.; Fukuzumi, T.; Bode, J. W. *J. Am. Chem. Soc.* **2008**, *130*, 17266. (c) Nair, V.; Varghese, V.; Babu, B. P.; Sinu, C. R.; Suresh, E. *Org. Biomol. Chem.* **2010**, *8*, 761. (d) Zheng, P.; Gondo, C. A.; Bode, J. W. *Chem.—Asian J.* **2011**, *6*, 614.

(12) (a) Sohn, S. S.; Rosen, E. L.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 14370. (b) Burstein, C.; Tschan, S.; Xie, X.; Glorius, F. *Synthesis* **2006**, 2418. (c) Nair, V.; Vellalath, S.; Poonoth, M.; Mohan, R.; Suresh, E. *Org. Lett.* **2006**, *8*, 507. (d) Li, Y.; Zhao, Z.-A.; He, H.; You, S.-L. *Adv. Synth. Catal.* **2008**, *350*, 1885.

(13) (a) Nair, V.; Vellalath, S.; Poonoth, M.; Suresh, E. *J. Am. Chem. Soc.* **2006**, *128*, 8736. (b) Chiang, P.-C.; Kaeobamrung, J.; Bode, J. W. *J. Am. Chem. Soc.* **2007**, *129*, 3520. (c) Chiang, P.-C.; Rommel, M.; Bode, J. W. *J. Am. Chem. Soc.* **2009**, *131*, 8714.

(14) (a) He, M.; Struble, J. R.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 8418. (b) Chan, A.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 5334. (c) He, M.; Bode, J. W. *J. Am. Chem. Soc.* **2008**, *130*, 418. (d) Phillips, E. M.; Reynolds, T. E.; Scheidt, K. A. *J. Am. Chem. Soc.* **2008**, *130*, 2416. (e) Chan, A.; Scheidt, K. A. *J. Am. Chem. Soc.* **2008**, *130*, 2740. (f) Seayad, J.; Patra, P. K.; Zhang, Y.; Ying, J. Y. *Org. Lett.* **2008**, *10*, 953.

(15) (a) Nair, V.; Babu, B. P.; Vellalath, S.; Varghese, V.; Raveendran, A. E.; Suresh, E. *Org. Lett.* **2009**, *11*, 2507. (b) Nair, V.; Sinu, C. R.; Babu, B. P.; Varghese, V.; Jose, A.; Suresh, E. *Org. Lett.* **2009**, *11*, 5570. (c) Fang, X.; Jiang, K.; Xing, C.; Hao, L.; Chi, Y. R. *Angew. Chem., Int. Ed.* **2011**, *50*, 1910.

(16) For selected examples and reviews, see: (a) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (b) You, S.-L.; Cai, Q.; Zeng, M. *Chem. Soc. Rev.* **2009**, *38*, 2190. (c) Hashimoto, T.; Kimura, H.; Maruoka, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 6844.

(17) (a) Sun, P.-P.; Chang, M.-Y.; Chiang, M. Y.; Chang, N.-C. *Org. Lett.* **2003**, *5*, 1761. (b) Roberson, C. W.; Woerpel, K. A. *J. Org. Chem.* **1999**, *64*, 1434. (c) Pohmakotr, M.; Yotapan, N.; Tuchinda, P.; Kuhakarn, C.; Reutrakul, V. *J. Org. Chem.* **2007**, *72*, 5016. For examples of *trans*-γ-lactams as cores of natural products, see: (d) Barrett, A. G. M.; Head, J.; Smith, M. L.; Stock, N. S.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **1999**, *64*, 600. (e) Feeling, R. H.; Buchanan, G. O.; Mincer, T. J.; Kauffman, C. A.; Jensen, P. R.; Fenical, W. *Angew. Chem., Int. Ed.* **2003**, *42*, 355.

(18) When the reaction was carried out in the absence of a base, trace desired product was generated.

(19) Under these conditions, the residual product derived from in situ imine exchange, **3m**, was also formed (7%).

(20) Other imines: *N*-Bn and *N*-acyl α,β-unsaturated imines afforded trace amounts of the desired lactams. *N*-Ts imine did not produce the lactam. The *N*-phenylaldimine derived from *p*-bromobenzaldehyde delivered the lactam in modest yield and selectivity under these conditions (~50% yield, 2:1 trans/cis, 62/58% ee).

(21) No lactam product resulting from (*E*)-4-methylpent-2-enal as a homoenolate was observed.

(22) When Boc-protected L-valine was utilized, **3a** was formed with lower enantioselectivity.