Organocatalysis

Oxidative N-Heterocyclic Carbene-Catalyzed γ -Carbon Addition of Enals to Imines: Mechanistic Studies and Access to Antimicrobial Compounds

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Abstract: The reaction mechanism of the γ -carbon addition of enal to imine under oxidative *N*-heterocyclic carbene catalysis is studied experimentally. The oxidation, γ -carbon deprotonation, and nucleophilic addition of γ -carbon to imine were found to be facile steps. The results of our study also provide highly enantioselective access to tricyclic sulfonyl amides that exhibit interesting antimicrobial activities against *X. oryzae*, a bacterium that causes bacterial disease in rice growing.

N-Heterocyclic carbene (NHC) organocatalysis has received considerable attention in recent years. Unique activation patterns that are not easily accessible by using other approaches can be realized with the carbene catalysts.^[1] In addition to reaction development, efforts have been directed toward mechanistic understanding. A number of proposed intermediates, including a Breslow intermediate, an aza-Breslow intermediate, homoenolate, and azolium enolates have been detected in the catalytic reactions by ¹H NMR spectrometry, mass spectrometry, or X-ray diffraction analysis, as reported by Bode, Rovis, Studer, Berkessel, and Mayr.^[2] The pathways of several reactions, such as those involving formal addition of nucleophiles to α , β -unsaturated acyl azolium intermediates, have been carefully evaluated by both experimental and DFT calculation methods by Bode, Schoenebeck, and Kozlowski.^[2a, 3] However, in contrast to the rapid discovery and development of new reactions, the mechanistic details of most of the reactions still remain largely unclear. Here, we report an experimental kinetic study of the enal γ -carbon addition to imines under oxidative NHC catalysis

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Scheme 1. Mechanistic study of oxidative NHC catalysis.

(Scheme 1). Our study reveals that the oxidation and γ -carbon addition to imine are facile processes, and the formation of the Breslow intermediate is likely a rate-determine step. In addition, our reaction affords heterocyclic compounds that exhibit antimicrobial activities on *Xanthomonas oryzae pv. oryzae* (*X. oryzae*), a bacterium that cause a most serious bacterial disease in rice growing (bacterial blight of rice).^[4]

Oxidative NHC catalysis provides effective ways for the functionalization of aldehydes that go beyond the conventional acyl anion reactions, as pioneered by Studer, Scheidt, and Rovis.^[5] By using the oxidation system developed by Studer, our laboratory further advanced this chemistry and reported α - and β -functionalization of saturated aldehydes,^[6] and γ -carbon functionalization of α , β -unsaturated aldehydes.^[7] In our previous reactions involving the enal γ -carbon,^[7e] attempts to elucidate the kinetic profile were unsuccessful. One major reason was the lack of a good model reaction that is relatively clean and easy to monitor by conventional analytical methods.

The oxidative carbene catalysis for enal γ -carbon functionalization (Scheme 1) involves at least four components. Thus, our first step was to identify relatively clean and efficient reactions that can be conveniently monitored. We finally found that the reaction between enal **1a** and imine **2a**^[5i,8] under the catalysis of NHC precatalyst **A**^[9] with quinone **B**^[5e] as an external oxidant led to the clean formation of lactam product **3a** (Table 1). The observable side reaction was the oxidation of the enals to carboxylic acids.^[10] The reaction was performed in an NMR tube, and the desired product formation was monitored in situ by ¹H NMR spectrometry, with an internal standard (CH₂Br₂) added. As a technical note, the spin of the NMR spectrometer was set at 20 Hz (equivalent to 1200 rotations per minute) to ensure consistent stirring of the reaction mixture. To reduce the variables in the kinetic studies, we further found that the

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chiral phase HPLC. [d] Conditions used for later syntheses. [e] Conditions used for the mechanistic study. [f] 1.5 equiv oxidant was used.

reaction proceeded effectively without the addition of external bases (Table 1, entry 5).^[11] Notably, Bode^[12a] and Xiao^[12b] have previously found that carbene-catalyzed reactions worked well without adding external bases, as the counter anion of the azolium salt behaves as a weak base.

Key findings of our kinetic studies are summarized in Figure 1. The kinetics of the overall reaction were studied by using the conditions without external base added (Table 1, entry 5) by varying the amount of each reaction component. We found that the concentration of enal substrate had significant effect on the rate of product formation (Figure 1 a). The observed reaction rate is of 1.6th-order dependence with respect to aldehyde, partial (0.6) order in the triazolium NHC precatalyst, pseudo-zero order in imine (when using less than 1.0 equiv of imine), and zero order in oxidant (Figure 1). The zero-order dependence on oxidant (Figure 1 c) indicated that the oxidation of the Breslow intermediate I to the α , β -unsaturated azolium ester intermediate II (Scheme 2) was a facile step. Studies of the imine concentration effect (Figure 1 b) showed that at low concentrations the reaction rate is pseudo-zero order in imine. This result suggested that the γ -carbon addition to imine (Scheme 2, addition of III to imine 2a) was a facile step. When the concentration of imine was further increased, the reaction became slower, presumably owing to reaction of the carbene catalyst with the imine substrate. The partial order in regard to catalyst was likely attributed to the reaction between the catalyst and the imine. Similar inhibitory effects from imine substrates were observed by Bode in his reaction between ynal and MeOH.^[2a] Thus, the dependence of observed reaction rate on enal and NHC catalyst concentration suggested that the Breslow intermediate (I) formation was likely the slowest step. The 1.6th order in terms of aldehyde is likely due to the competing reactions of aldehyde and imine substrates with the carbene catalyst. A higher concentration of the aldehyde substrate could





Figure 1. Kinetic study.^[a]



Scheme 2. Mechanistic pathway.

suppress the (undesired) reaction between carbene catalyst and imine substrate leading to faster reaction (and thus greater than first-order dependence on aldehyde concentration). The postulated catalytic cycle is displayed in Scheme 2.

Next, we performed experiments to further understand the γ -carbon deprotonation step (II to III, Scheme 2). One key ques-

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tion we asked was whether this proton transfer step was reversible under our reaction conditions. An enal substrate deuterium labeled at the γ -carbon (D₃-1a) was subjected to our reaction conditions in the absence of additional base (Table 1, entry 5, without external base). No deuterium erosion was observed in the lactam product D₃-3a (Figure 2). The nearly com-



Figure 2. Deuterium labeling and kinetic isotope effect.

plete retention of the deuterium isotope suggested that this proton-transfer process (II to III) was not reversible under our conditions (without external base added). It appears that the addition of III to imines is more favorable than the protonation of III. In the presence of external base, product 3a was obtained with 50% of the deuterium atoms left (~30% D-atom erosion), suggesting that under such conditions this protontransfer process (between II and III) is reversible. The D-labeled enal substrate (D₃-1 a) was stable (no erosion of the D atoms) in the presence or absence of base under the carbene catalysis (see the Supporting Information). The deuterium kinetic isotope effect^[13] on the overall reaction rate was also studied. A secondary kinetic isotope effect ($K_h/K_d = 1.2$, without base) was observed (see the Supporting Information). This small kinetic isotope effect and the retention of deuterium in the lactam product suggest that the γ -carbon deprotonation is a fast process. The γ -carbon deprotonation is not the rate-determine step.

Sulfonyl amide-containing compounds, such as Sinomine^[14a] and Sulfafurazole,^[14b] exhibit interesting biological activities such as antimicrobial activities in both gram-negative and gram-positive organisms. In agriculture chemicals, the sulfonyl amide functional unit is found in a number of commercially available herbicides such as Monosulfuron, Sulfometuron methyl, and Chlorosulfuron.^[15] Our laboratories are interested in developing sulfur amide-containing chiral molecules for the treatment of plant bacterial infections. Our present protocol provides quick access to enantioenriched tricyclic sulfonyl amides. Examples of enals and imines that worked effectively under our conditions are shown in Table 2. In this study on reaction scope, we performed the reactions in the presence of Cs₂CO₃ (Table 1, entry 4) in order to obtain slightly higher yields. With 2a as the model ketimine substrate, enals bearing various substituents all worked well, affording the γ -functionalized products 3a-h with good yields and excellent enantiomeric ratios (88:12-99:1 e.r.). Ketimines derived from sulfamide containing different substituents at the 4-position also worked well (3i-3n). The enal with a methyl substituent on the γ carbon also reacted effectively, leading to 3o as essentially a single diastereomer in 87% yield and 98:2 e.r.

We then evaluated the in vitro antibacterial activity of our products bearing tricyclic sulfur amides against *X. oryzae* by the turbidimeter test.^[16a] The commercially available and com-



monly applied bacteriocide bismerthiazol was used as the positive control, and DMSO was used as the negative control (Table 3). A number of our compounds showed promising antibacterial activities. For example, at a concentration of 200 μ g mL⁻¹, compound **3 n** showed a similar inhibitory rate to the commercial bacteriocide bismerthiazol against *X. oryzae* (73.7 versus 72.0%, respectively).

In summary, we have investigated the γ -carbon addition of enal to ketimine under oxidative NHC catalysis. Our mechanistic study revealed that the oxidation of the Breslow intermediate, γ -carbon deprotonation of the α , β -unsaturated azolium ester intermediate, and nucleophilic addition of the γ -carbon of the

| Table 3. Antibacterial activity of the products. | | | | | | |
|--|--|---|--|--|--|--|
| Product | X. oryzae pv. ory 100 μg mL ⁻¹ | <i>ae</i> inhibition rate [%] ^[a] 200 μg mL ⁻¹ | | | | |
| 3a | 27.6 | 22.3 | | | | |
| 3c | 32.9 | 46.8 | | | | |
| 3ј | 28.5 | 61.8 | | | | |
| 3 m | 23.8 | 50.9 | | | | |
| 3 n | 34.2 | 73.7 | | | | |
| Bismerthiazol ^(b) | 54.0 | 72.0 | | | | |
| negative control ^[c] | 0.0 | 0.0 | | | | |
| [a] Average of three replicates. [b] Commercial bacteriocide, used as the positive control. [c] DMSO was used as the negative control. | | | | | | |



vinyl enolate intermediate to the imine substrate were all facile steps. The slowest step in this oxidative catalysis process is likely the formation of the Breslow intermediate between the enal substrate and the NHC catalyst. Synthetically, our method allows efficient access to enantiomerically enriched tricyclic sulfur amides that exhibit interesting antimicrobial activities.

Experimental Section

Ketimine 1 (0.14 mmol), enal 2 (0.16 mmol), triazolium salt **B** (0.027 mmol), Cs_2CO_3 (0.034 mmol), and oxidant 4 (0.16 mmol) were added to a dry Schlenk tube equipped with a magnetic stir bar. The tube was closed with a septum, evacuated, and refilled with nitrogen. Freshly distilled THF (2 mL) was added and the reaction mixture was then stirred at room temperature until the enal was completely consumed (monitored by TLC). The mixture was concentrated under reduced pressure. The resulting crude residue was purified by column chromatography on silica gel (1:3 hexanes/ EtOAc) to afford the desired product **3**.

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Keywords: antimicrobial activity \cdot $\gamma\text{-carbon addition}$ \cdot enals \cdot N-heterocyclic carbenes \cdot organocatalysis \cdot reaction mechanisms

- For recent reviews on NHC catalysis, see:a) D. Enders, T. Balensiefer, Acc. Chem. Res. 2004, 37, 534; b) K. Zeitler, Angew. Chem. Int. Ed. 2005, 44, 7506; Angew. Chem. 2005, 117, 7674; c) V. Nair, S. Vellalath, B. P. Babu, Chem. Soc. Rev. 2008, 37, 2691; d) T. Rovis, Chem. Lett. 2008, 37, 2; e) A. T. Biju, N. Kuhl, F. Glorius, Acc. Chem. Res. 2011, 44, 1182; f) J. Izquierdo, G. E. Hutson, D. T. Cohen, K. A. Scheidt, Angew. Chem. Int. Ed. 2012, 51, 11686; Angew. Chem. 2012, 124, 11854; g) S. De Sarkar, A. Biswas, R. C. Samanta, A. Studer, Chem. Eur. J. 2013, 19, 4664; h) S. J. Ryan, L. Candish, D. W. Lupton, Chem. Soc. Rev. 2013, 42, 4906; i) L. C. Morrill, A. D. Smith, Chem. Soc. Rev. 2014, 43, 6214; j) J. W. Bode, Nat. Chem. 2013, 5, 813; k) M. N. Hopkinson, C. Richter, M. Schedler, F. Glorius, Nature 2014, 510, 485.
- [2] a) J. Mahatthananchai, P. Zheng, J. W. Bode, Angew. Chem. Int. Ed. 2011, 50, 1673; Angew. Chem. 2011, 123, 1711; b) D. A. DiRocco, K. M. Oberg, T. Rovis, J. Am. Chem. Soc. 2012, 134, 6143; c) R. C. Samanta, B. Maji, S. DeSarkar, K. Bergander, R. Fröhlich, C. Mück-Lichtenfeld, H. Mayr, A. Studer, Angew. Chem. Int. Ed. 2012, 51, 5234; Angew. Chem. 2012, 124, 5325; d) B. Maji, H. Mayr, Angew. Chem. Int. Ed. 2012, 51, 10408; Angew. Chem. 2012, 124, 10554; e) A. Berkessel, S. Elfert, V. Reddy Yatham, J.-M. Neudörfl, N. E. Schlörer, J. Teles Henrique, Angew. Chem. Int. Ed. 2013, 51, 12370; Angew. Chem. 2012, 124, 12537; f) A. Berkessel, V. R. Yatham, S. Elfert, J.-M. Neudçrfl, Angew. Chem. Int. Ed. 2013, 52, 11158; Angew. Chem. 2013, 125, 11364; g) B. Maji, H. Mayr, Angew. Chem. Int. Ed. 2013, 52, 11163; Angew. Chem. 2013, 125, 11370; h) A. Berkessel, S. Elfert, Adv. Synth. Catal. 2014, 356, 571.

- [3] a) S. E. Allen, J. Mahatthananchai, J. W. Bode, M. C. Kozlowsk, J. Am. Chem. Soc. 2012, 134, 12098; b) E. Lyngvi, J. W. Bode, F. Schoenebeck, Chem. Sci. 2012, 3, 2346; c) S. E. Allen, S.-Y. Hsieh, O. Gutierrez, J. W. Bode, M. C. Kozlowsk, J. Am. Chem. Soc. 2014, 136, 11783.
- [4] a) Y. Xu, X. F. Zhu, M. G. Zhou, J. Kuang, Y. Zhang, Y. Shang, J. X. Wang, J. Phytopathol. 2010, 158, 601; b) A. Evidente, V. Venturi, M. Masi, G. Degrassi, A. Cimmino, L. Maddau, A. Andolf, J. Nat. Prod. 2011, 74, 2520.
- [5] For related works on oxidative NHC catalysis, see: a) B. E. Maki, A. Chan, E. M. Phillips, K. A. Scheidt, Org. Lett. 2007, 9, 371; b) J. Guin, S. De Sarkar, S. Grimme, A. Studer, Angew. Chem. Int. Ed. 2008, 47, 8727; Angew. Chem. 2008, 120, 8855; c) B. E. Maki, K. A. Scheidt, Org. Lett. 2008, 10, 4331; d) B. E. Maki, A. Chan, E. M. Phillips, K. A. Scheidt, Tetrahedron 2009, 65, 3102; e) S. De Sarkar, S. Grimme, A. Studer, J. Am. Chem. Soc. 2010, 132, 1190; f) S. De Sarkar, A. Studer, Angew. Chem. Int. Ed. 2010, 49, 9266; Angew. Chem. 2010, 122, 9452; g) S. De Sarkar, A. Studer, Org. Lett. 2010, 12, 1992; h) X. Zhao, K. E. Ruhl, T. Rovis, Angew. Chem. Int. Ed. 2012, 51, 12330; Angew. Chem. 2012, 124, 12496; i) A. G. Kravina, J. Mahatthananchai, J. W. Bode, Angew. Chem. Int. Ed. 2012, 51, 9433; Angew. Chem. Int. Ed. 2012, 124, 9568; j) S. Bera, R. C. Samanta, C. G. Daniliuc, A. Studer, Angew. Chem. Int. Ed. 2014, 53, 9622; Angew. Chem. 2014, 126, 9776.
- [6] a) J. Mo, R. Yang, X. Chen, B. Tiwari, Y. R. Chi, Org. Lett. 2013, 15, 50; b) J.
 Mo, L. Shen, Y. R. Chi, Angew. Chem. Int. Ed. 2013, 52, 8588; Angew.
 Chem. 2013, 125, 8750.
- [7] For γ-activation of enals by oxidative NHC catalysis from this group and others, see: a) J. Mo, X. Chen, Y. R. Chi, J. Am. Chem. Soc. 2012, 134, 8810; b) X. Chen, S. Yang, B.-A. Song, Y. R. Chi, Angew. Chem. Int. Ed. 2013, 52, 11134; Angew. Chem. 2013, 125, 11340; c) X.-Y. Chen, F. Xia, J.-T. Cheng, S. Ye, Angew. Chem. Int. Ed. 2013, 52, 10644; Angew. Chem. 2013, 125, 10838; d) J. Xu, Z. Jin, Y. R. Chi, Org. Lett. 2013, 15, 5028; e) M. Wang, Z. Huang, J. Xu, Y. R. Chi, J. Am. Chem. Soc. 2014, 136, 1214.
- [8] a) M. Rommel, T. Fukuzumi, J. W. Bode, J. Am. Chem. Soc. 2008, 130, 17266; b) P. Zheng, C. A. Gondo, J. W. Bode, Chem. Asian J. 2011, 6, 614.
- [9] a) R. L. Knight, F. J. Leeper, J. Chem. Soc. Perkin Trans. 1 1998, 1891; b) D. Enders, U. Kallfass, Angew. Chem. Int. Ed. 2002, 41, 1743; Angew. Chem. 2002, 114, 1822; c) M. S. Kerr, J. R. deAlaniz, T. Rovis, J. Am. Chem. Soc. 2002, 124, 10298; d) H. Takikawa, Y. Hachisu, J. W. Bode, K. Suzuki, Angew. Chem. Int. Ed. 2006, 45, 3492; Angew. Chem. 2006, 118, 3572; e) J. R. Struble, J. W. Bode, Org. Synth. 2010, 87, 362.
- [10] B. Maji, S. Vedachalam, X. Ge, S. Cai, ; X.-W. Liu, J. Org. Chem. 2011, 76, 3016; X.-W. Liu, J. Org. Chem. 2011, 76, 3016.
- [11] For more details about the experiment, please see the Supporting Information.
- [12] a) J. Kaeobamrung, J. Mahatthananchai, P. Zheng, J. W. Bode, J. Am. Chem. Soc. 2010, 132, 8810; b) Z. Q. Zhu, X. L. Zheng, N. F. Jiang, X. Wan, J. C. Xiao, Chem. Commun. 2011, 47, 8670.
- [13] For studies about the KIE, please see: a) E. M. Simmons, J. F. Hartwig, Angew. Chem. Int. Ed. 2012, 51, 3066; Angew. Chem. 2012, 124, 3120;
 b) X. Ye, G. Liu, B. V. Popp, S. S. Stahl, J. Org. Chem. 2011, 76, 1031; c) M. Gómez-Gallego, M. A. Sierra, Chem. Rev. 2011, 111, 4857.
- [14] a) M. Ma, Y. Cheng, Z. Xu, P. Xu, H. Qu, Y. Fang, T. Xu, L. Wen, *Eur. J. Med. Chem.* **2007**, *42*, 93; b) R. O'Shea, H. E. Moser, *J. Med. Chem.* **2008**, *51*, 2871.
- [15] a) I. Braschi, L. Calamai, M. A. Cremonini, P. Fusi, C. Gessa, O. Pantani, Alba. Pusino, J. Agric. Food Chem. **1997**, 45, 4495; b) J. Wang, H. Tan, Y. Li, Y. Ma, Z. Li, L. W. Guddat, J. Agric. Food Chem. **2011**, 59, 9892; c) M. F. Winchell, N. J. Snyder, J. Agric. Food Chem. **2014**, 62, 348.
- [16] a) X. Wang, P. Li, Z. Li, J. Yin, M. He, W. Xue, Z. Chen, B. Song, J. Agric. Food Chem. 2013, 61, 9575 ; b) W. M. Xu, F. F. Han, M. He, D. Y. Hu, J. He, S. Yang, B.-A. Song, J. Agric. Food Chem. 2012, 60, 1036.
- [17] For ORTEPs of products 3c and 3o see Supporting Information. CCDC 1019457 (3c) and CCDC 1019458 (3o) contain supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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