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N-Heterocyclic Carbene-Catalyzed Asymmetric Oxidative Hetero-Diels-Alder Reactions with Simple Aliphatic Aldehydes

Dr Xiaodan Zhao, Kyle E. Ruhl, and Professor Tomislav Rovis*

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

Keywords

N-heterocyclic carbene; oxidation; lactams; lactones aliphatic aldehydes; asymmetric Diels-Alder reaction

N-heterocyclic carbene (NHC) catalysis has emerged as a powerful tool for synthesis.^[1] Among its involvement in several cycloaddition-type reactions for the construction of lactams and lactones, abundant in biologically active molecules^[2] and broadly used as synthons for complex molecules,^[3] NHC catalysis via formal [3+3] or [4+2] strategies is noteworthy.^[4–10] In particular, [4+2] cycloadditions have received more attention than others. In the literature, most NHC-catalyzed [4+2] hetero-Diels-Alder reactions involve an enolate intermediate.^[5–10] To date, NHC-catalyzed enolate formation is achieved from functionalized aldehydes, ketenes or esters (Scheme 1, A1–5). Treatment of these precursors with dienes presents certain drawbacks. Prime among them is that all precursors are prefunctionalized, limiting substrate scope. Thus, a stable, readily available, general enolate precursor is desirable for this kind of [4+2] cycloaddition. Herein, we report that simple aliphatic aldehydes serve as enolate precursors for highly enantioselective synthesis of lactones and lactams under oxidative conditions via NHC catalysis.

Aliphatic aldehydes are bench-stable when properly stored and readily available. Although they provide great advantages compared to known enolate precursors, to the best of our knowledge no approach has been documented using them as enolate precursors without prefunctionalization.^[11] We envisioned that aliphatic aldehydes could serve as enolate precursors with an NHC catalyst and proposed that they could react with dienes to form six-membered products as shown in Scheme 2. Interception of the aliphatic aldehyde by an NHC would give the Breslow intermediate. Consequent oxidation^[12] and deprotonation of the intermediate would yield an enolate.^[13] Ultimately, [4+2] cycloaddition would provide a six-membered product. In the proposed process, judicious choice of oxidant and base would be the key to the successful transformation.

We first treated distilled butyraldehyde (**1a**) with tosyl-protected α,β -unsaturated ketimine **2a** in the presence of 20 mol% mesityl triazolium salt **C1** as the catalyst, DBU as the base, and one equivalent phenazine (**[O]A**) as the oxidant.^[14] The reaction provides *trans*-lactam **3a**^[15] in trace amount (Table 1, entry 1). To shed light on the issue, NMR experiments were performed using **2a**, the catalyst **C1** and DBU, which revealed an interaction between carbene and **2a** causing catalyst inactivation.

* rovis@lamar.colostate.edu.

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According to our previous finding that acid plays an important role in carbene catalysis,^[16] we added 10 mol% acetic acid to the reaction. Gratifyingly, the conversion increased to >99% to give *trans*-lactam in >99% ee and 8:1 dr (Table 1, entry 2). An increase of acid loading decreases diastereoselectivity (entry 3). Diisopropyl ethyl amine as the base is not efficient (entry 4) and K₂CO₃ delivers lower dr in THF presumably due to poor solubility (entry 5). The oxidant **[O]B**, popularized by Stüder for use in NHC catalysis,^[17] is not effective for this transformation (entry 6). Use of **[O]A** as the oxidant makes purification difficult as its polarity is similar to that of the desired product. We investigated a more polar oxidant **[O]C**. Lower diastereoselectivity was observed when using DBU or K₂CO₃ as the base in THF (entries 7–8). To increase the solubility of base in the solvent, a mixed solvent system (THF/CH₃CN, 1:10, v/v) proved beneficial generating *trans*-product in 88% isolated yield, 99% ee and 9:1 dr (entry 9).^[18] Interestingly, when 0.2 eq oxidant is used, the desired product is formed in good yield, 99% ee and 17:1 dr (entry 10), which suggests that the use of catalytic oxidant is possible to give product in high conversion.^[19]

With optimized conditions in hand, the substrate scope of ketimines was evaluated. A variety of six-membered lactams could be obtained in good yields and excellent enantioselectivities (Table 2). Smaller propionaldehyde and larger pentanal deliver the corresponding lactams **3b** and **3c** in 97% ee and 20:1 dr, respectively. When sterically more hindered isovaleraldehyde is utilized, the desired product is generated in trace amount. In contrast, 3-cyclohexylpropanal is an effective substrate for this annulation to give product **3d** in good yield, excellent enantioselectivity and high dr. With electron-withdrawing or electron-donating groups on the aromatic ring at either side of ketimine, the reactions work quite well to give products **3e–h** in good to excellent yields (74–98%) and excellent ee's (>99% for all).

When similar conditions are applied to the cycloaddition with chalcones, lactones are generated but with a *cis* relationship between stereocenters (Table 3). A variety of aliphatic aldehydes give lactones **5a–d** in good yields, excellent ee's and high dr. When an electron-withdrawing group, i.e., 4-Cl- or 4'-Cl- group, is on the aromatic ring of chalcones, the reactions proceed to give the products **5e** and **5f** in the same efficiency. However, the reactions become slower when an electron-donating group 4-MeO- or thiophene is incorporated onto the chalcone, but still give the desired products in excellent ee's (99%) and dr (**5g** and **5h**). Beyond chalcones as substrates, the desired product **5i** can be generated smoothly when a keto ester is employed as the starting material using the oxidant **[O]C** instead of **[O]A** in the mixed solvent THF/CH₃CN. Although lactones such as **5i** have been generated using Bode's system,^[6a] the somewhat less reactive chalcones have not been incorporated into cycloadditions by previously developed methods using NHC catalysis,^[6,20] or by cinchonidine catalysis or enamine catalysis/oxidation approaches.^[21]

The proposed mechanism for *trans*-lactam formation is shown in Scheme 3. Base deprotonates triazolium salt to generate free carbene. Free carbene may react with α,β -unsaturated ketimine to form an adduct by 1,2- or 1,4-addition. In the presence of acid, the adduct releases the carbene. Reaction with aliphatic aldehyde gives Breslow intermediate **A** followed by oxidation to generate acyl azolium **B**. Its deprotonation at the α -position gives enolate **C**. [4+2] Cycloaddition of **C** with α,β -unsaturated ketimine gives zwitterion **D**. The carbene is released from **D**, and the desired lactam is formed.

The mechanism for lactone formation is slightly different from the above pathway. After carbene generation, addition of the carbene to chalcone does not form stable adducts, suggesting that free carbene is present in the reaction. Therefore, addition of acid is not necessary for lactone synthesis. Interestingly, *cis*-lactone is formed in the reaction, the

reasons for which are unclear at this time. The possible intervention of both the enolate (C) and enol (C') intermediates in the two cycloaddition protocols cannot be discounted.

In conclusion, we have developed an NHC-catalyzed^[22] approach to efficiently synthesize *trans*-lactams and *cis*-lactones in high yields, high enantioselectivities and good to excellent dr with simple aliphatic aldehydes. The method involves a new way to generate enolate intermediates via oxidation and deprotonation, and has obvious advantages compared to known enolate precursors. It is quite interesting that *trans*-lactams and *cis*-lactones are formed under similar conditions.^[23] A study aimed at elucidating the factors responsible for the different stereochemistry between *trans*-lactams and *cis*-lactones is in progress.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

- [1]. a) Moore JL, Rovis T. *Top. Curr. Chem.* 2010; 291:77–144. [PubMed: 21494949] b) Vora HU, Rovis T. *Aldrichimica Acta.* 2011; 44:3–11. c) Nair V, Menon RS, Biju AT, Sinu CR, Paul RR, Jose A, Sreekumar V. *Chem. Soc. Rev.* 2011; 40:5336–5346. [PubMed: 21776483] d) Biju AT, Kuhl N, Glorius F. *Acc. Chem. Res.* 2011; 44:1182–1195. [PubMed: 21751790] e) Cohen DT, Scheidt KA. *Chem. Sci.* 2012; 3:53–57. f) Vora HU, Wheeler P, Rovis T. *Adv. Synth. Catal.* 2012; 354:1617–1639. [PubMed: 23538785] g) Bugaut X, Glorius F. *Chem Soc Rev.* 2012; 41:3511–3522. [PubMed: 22377957] h) Grossmann A, Enders D. *Angew. Chem. Int. Ed.* 2012; 51:314–325. For recent reviews, see:
- [2]. a) Nantermet PG, Barrow JC, Selnick HG, Homnick CF, Freidinger RM, Chang RSL, O'Malley SS, Reiss DR, Broten TP, Ransom RW, Pettibone DJ, Olah T, Forray C. *Bioorg. Med. Chem. Lett.* 2000; 10:1625–1628. [PubMed: 10937710] b) Goodman KB, Cui H, Dowdell SE, Gaitanopoulos DE, Ivy RL, Sehon CA, Stavenger RA, Wang GZ, Viet AQ, Xu W, Ye G, Semus SF, Evans C, Fries HE, Jolivet LJ, Kirkpatrick RB, Dul E, Khandekar SS, Yi T, Jung DK, Wright LL, Smith GK, Behm DJ, Bentley R, Doe CP, Hu E, Lee D. *J. Med. Chem.* 2007; 50:6–9. [PubMed: 17201405] c) McMurry JE, Dushin RG. *J. Am. Chem. Soc.* 1990; 112:6942–6949. For representative examples, see:
- [3]. a) Boger, DL.; Weinreb, SM. *Hetero Diels-Alder Methodology in Organic Synthesis.* Academic Press; San Diego: 1987. b) Boucard V, Broustal G, Campagne JM. *Eur. J. Org. Chem.* 2007; 2:225–236.
- [4]. a) Kaeobamrung J, Mahatthananchai J, Zheng P, Bode JW. *J. Am. Chem. Soc.* 2010; 132:8810–8812. [PubMed: 20550127] b) Wanner B, Mahatthananchai J, Bode JW. *Org. Lett.* 2011; 13:5378–5381. [PubMed: 21905682] c) Mahatthananchai J, Kaeobamrung J, Bode JW. *ACS Catal.* 2012; 2:494–503. [PubMed: 22468232] For [3+3] cycloaddition, see:
- [5]. a) He M, Struble JR, Bode JW. *J. Am. Chem. Soc.* 2006; 128:8418–8420. [PubMed: 16802805] b) Jian T-Y, Shao P-L, Ye S. *Chem. Commun.* 2011; 47:2381–2383. c) Lv H, Chen X-Y, Sun L.-h. Ye S. *J. Org. Chem.* 2010; 75:6973–6976. [PubMed: 20843084]
- [6]. a) He M, Uc GJ, Bode JW. *J. Am. Chem. Soc.* 2006; 128:15088–15089. [PubMed: 17117850] b) He M, Beahm BJ, Bode JW. *Org. Lett.* 2008; 10:3817–3820. [PubMed: 18656948] c) Allen SE, Mahatthananchai J, Bode JW, Kozlowski MC. *J. Am. Chem. Soc.* 2012; 134:12098–12103. [PubMed: 22765294] d) Yang L, Wang F, Chua PJ, Lv Y, Zhong L-J, Zhong G. *Org. Lett.* 2012; 14:2894–2897. [PubMed: 22594458]
- [7]. a) Phillips EM, Wadamoto M, Roth HS, Ott AW, Scheidt KA. *Org. Lett.* 2009; 11:105–108. [PubMed: 19049403] b) Ling KB, Smith AD. *Chem. Commun.* 2011; 47:373–375.

- [8]. a) Fang X, Chen X, Chi YR. *Org. Lett.* 2011; 13:4708–4711. [PubMed: 21809839] b) Lv H, Mo J, Fang X, Chi YR. *Org. Lett.* 2011; 13:5366–5369. [PubMed: 21877756]
- [9]. Hao L, Du Y, Lv H, Chen X, Jiang H, Shao Y, Chi YR. *Org. Lett.* 2012; 14:2154–2157. [PubMed: 22486921]
- [10]. a) De Sarkar S, Studer A. *Angew. Chem. Int. Ed.* 2010; 49:9266–9269. b) Zhu Z-Q, Zheng X-L, Jiang N-F, Wan X, Xiao J-C. *Chem. Commun.* 2011; 47:8670–8672. c) Rong Z-Q, Jia M-Q, You S-L. *Org. Lett.* 2011; 13:4080–4083. [PubMed: 21732659]
- [11]. Mo J, Chen X, Chi YR. *J. Am. Chem. Soc.* 2012; 134:8810–8813. [PubMed: 22571795] Chi has recently demonstrated an oxidative approach to converting β -methyl enals into dienolate/azolium intermediates and their subsequent conversion into δ -lactones; see:
- [12]. Knappke CEI, Imami A, Jacobi von Wangelin A. *ChemCatChem.* 2012; 4:937–941. For a review on NHC-catalyzed oxidative transformations, see:
- [13]. Belmessieri D, Morrill LC, Simal C, Slawin AMZ, Smith AD. *J. Am. Chem. Soc.* 2011; 133:2714–2720. [PubMed: 21302961] b) Morrill L, Lebel T, Slawin AMZ, Smith AD. *Chem. Sci.* 2012; 3:2088–2093. Smith has reported formation of ammonium enolate by deprotonation of the corresponding acyl ammonium; see:
- [14]. Uno T, Inokuma T, Takemoto Y. *Chem. Commun.* 2012; 48:1901–1903. Phenazine and riboflavin are known to oxidize alkyl Breslow intermediate to acyl azolium; see:
- [15]. Han B, Li J-L, Ma C, Zhang S-J, Chen Y-C. *Angew. Chem. Int. Ed.* 2008; 47:9971–9974. Han B, He Z-Q, Li J-L, Li R, Jiang K, Liu T-Y, Chen Y-C. *Angew. Chem. Int. Ed.* 2009; 48:5474–5477. b) Simal C, Lebl T, Slawin AMZ, Smith AD. *Angew. Chem. Int. Ed.* 2012; 51:3653–3657. The lactam **3a** is known and can be produced in two steps by enamine catalysis and subsequent oxidation; see: For alternative organocatalytic [4+2] reactions, see:
- [16]. a) Zhao X, DiRocco DA, Rovis T. *J. Am. Chem. Soc.* 2011; 133:12466–12469. [PubMed: 21780842] b) DiRocco DA, Oberg KM, Rovis T. *J. Am. Chem. Soc.* 2012; 134:6143–6145. [PubMed: 22455368] c) DiRocco DA, Rovis T. *J. Am. Chem. Soc.* 2012; 134:8094–8097. [PubMed: 22548244] d) DiRocco DA, Rovis T. *Angew. Chem. Int. Ed.* 2012; 51:5904–5906. e) Chan A, Scheidt KA. *Org. Lett.* 2005; 7:905–908. [PubMed: 15727471] f) Sohn SS, Bode JW. *Org. Lett.* 2005; 7:3873–3876. [PubMed: 16119920] g) Thai K, Wang L, Dudding T, Bilodeau F, Gravel M. *Org. Lett.* 2010; 12:5708–5711. [PubMed: 21080709] h) Liu G, Wilkerson PD, Toth CA, Xu H. *Org. Lett.* 2012; 14:858–861. [PubMed: 22263957] For related work, see:
- [17]. a) De Sarkar S, Grimme S, Studer A. *J. Am. Chem. Soc.* 2010; 132:1190–1191. [PubMed: 20055393] b) De Sarkar S, Studer A. *Org. Lett.* 2010; 12:1992–1995. [PubMed: 20359171] c) Biswas A, De Sarkar S, Fröhlich R, Studer A. *Org. Lett.* 2011; 13:4966–4969. [PubMed: 21863845] d) Biswas A, De Sarkar S, Tebben L, Studer A. *Chem. Commun.* 2012; 48:5190–5192.
- [18]. Methanesulfonyl in place of tosyl as the protecting group on the ketimine is tolerated, delivering the desired lactam in 92% isolated yield and 4:1 dr under the same conditions.
- [19]. The stoichiometric oxidant may be one of several. Rigorous exclusion of oxygen (freeze/pump/thaw of solvent mixture prior to reaction) resulted in identical yield. Conducting the reaction under oxygen resulted in only low yield (<20%). We note the formation of 1,3-diphenyl-1-propanone (18% yield) upon aqueous workup of the reaction involving catalytic oxidant suggesting that the imine **2a** may function as a reoxidant for the reduced riboflavin.
- [20]. When reaction of chalcone with α -chloroaldehyde was carried out using mesityl carbene as the catalyst in THF in the presence of Et₃N, no reaction took place.
- [21]. a) Mukaiyama T, Nagao H, Yamane Y. *Chem. Lett.* 2006; 35:916–917. b) Wang J, Yu F, Zhang X, Ma D. *Org. Lett.* 2008; 10:2561–2564. [PubMed: 18476713] Cinchonidine catalysis or enamine catalysis/oxidation delivers *trans*-lactones as the products; see:
- [22]. The use of 10 mol% catalyst in reaction of **1a** and **2a** leads to **3a** in 67% yield, 10:1 dr and 99% ee. The use of 5 mol% catalyst in reaction of **1a** and **4a** leads to **5a** in 68% yield, >20:1 dr and 99% ee.
- [23]. When the reaction of chalcone with aliphatic aldehyde is carried out under the same conditions as that used in lactam synthesis, the desired product *cis*-lactone is still generated as the major adduct.

Scheme 1.
Known enolate precursors.

Scheme 2.

Proposed Diels-Alder reactions through oxidative enolate formation.

Scheme 3.
Proposed pathway for *trans*-Lactam formation.

Table 1

Reaction optimization.^[a]

Entry	Base	AcOH (mol%)	[O]	Yield (%) ^[b]	dr ^[c]	ee (%) ^[d]
1	DBU	0	[O]A	trace	---	---
2	DBU	10	[O]A	99	8/1	>99
3	DBU	50	[O]A	99	3/1	---
4	<i>t</i> -Pr ₂ NEt	10	[O]A	17	8/1	---
5	K ₂ CO ₃	10	[O]A	99	2/1	>99
6	DBU	10	[O]B	12	11/1	---
7	DBU	10	[O]C	99	3/1	---
8	K ₂ CO ₃	10	[O]C	99	1/1	---
9 ^[e]	K ₂ CO ₃	10	[O]C	96(88)	9/1	99
10 ^[f]	K ₂ CO ₃	10	[O]C	74	17/1	99

^[a] Conditions: **1a**, 0.15 mmol; **2a**, 0.1 mmol; **C1**, 20 mol%; base, 0.5 eq.; oxidant, 1 eq.; THF, 1.1 mL; all the reactions were carried out at 23 °C in the presence of 4A MS under argon atmosphere for 10 h.

^[b] Total NMR yields of *trans* and *cis*-diastereomers with 1,3,5-trimethoxybenzene as an internal standard (isolated yield in parentheses).

^[c] The ratio of *trans/cis* determined by ¹H NMR.

^[d] Ee of *trans*-**3a** determined by HPLC on a chiral stationary phase.

^[e] THF/CH₃CN = 1:10 (v/v) instead of THF, 1.1 mL.

^[f] THF/CH₃CN = 1:10 (v/v) instead of THF, 1.1 mL; **[O]C**, 0.2 eq.

Table 2

Lactam synthesis from α,β -unsaturated ketimines.^[a]

^[a] Conditions: **1**, 0.15 mmol; **2**, 0.1 mmol; **C1**, 20 mol%; K₂CO₃, 0.5 eq.; AcOH, 10 mol%; [**O**]C, 1 eq.; THF/CH₃CN = 1:10 (v/v), 1.1 ml; all the reactions were carried out at 23 °C in the presence of 4A MS under argon atmosphere for 10 h. The *trans/cis* ratio is determined by ¹H NMR prior to purification. The ee's are determined by HPLC on a chiral stationary phase.

Table 3

Lactone synthesis from α,β -unsaturated ketones.^[a]

^[a] Conditions: **1**, 0.15 mmol; **4**, 0.1 mmol; **C1**, 20 mol%; K₂CO₃, 0.5 eq.; **[O]A**, 1 eq.; THF, 1.0 ml; all the reactions were carried out at 23 °C in the presence of 4A MS under argon atmosphere for 10 h. The *trans/cis* ratio is determined by ¹H NMR prior to purification. The ee's are determined by HPLC on a chiral stationary phase.

^[b] Phenyl propionaldehyde, 0.12 mmol.

^[c] **[O]C** instead of **[O]A**, 1 eq.; THF/CH₃CN = 1:10 (v/v) instead of THF, 1.1 ml.