Heterocycles

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

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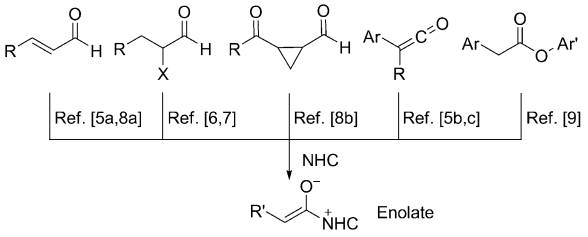
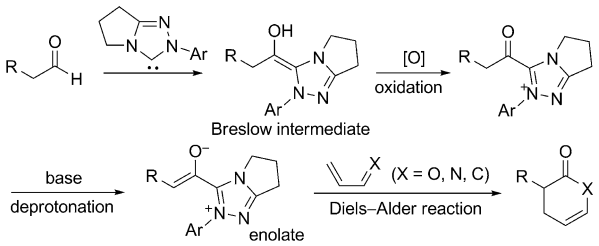
N-heterocyclic carbene (NHC) catalysis has emerged as a powerful tool for synthesis.[1] Among its involvement in several cycloaddition-type reactions for the construction of lactams and lactones, which are abundant in biologically active molecules[2] and broadly used as synthons for complex molecules,[3] NHC catalysis through 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). Treatment of these



Scheme 1. Known enolate precursors.

precursors with dienes presents certain drawbacks. Prime among them is that all precursors are prefunctionalized, thus limiting substrate scope. Therefore, 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 the highly enantioselective synthesis of lactones and lactams under oxidative conditions by NHC catalysis.

Aliphatic aldehydes are bench stable when properly stored and are readily available. Although they provide great advantages compared to known enolate precursors, no approach has been documented using them as enolate precursors without prefunctionalization.[11] We envisioned aliphatic aldehydes serving as enolate precursors with an NHC catalyst and proposed that they could react with dienes to form six-membered ring products as shown in Scheme 2.



Scheme 2. Proposed Diels–Alder reactions through oxidative enolate formation.

Interception of the aliphatic aldehyde by an NHC would give the Breslow intermediate, and subsequent oxidation[12] and deprotonation of the intermediate would yield an enolate.[13] Ultimately, [4+2] cycloaddition would provide a six-membered ring product. In the proposed process, judicious choice of the oxidant and base is the key to a successful transformation.

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

According to our previous finding that acid plays an important role in carbene catalysis,[16] we added 10 mol% of acetic acid to the reaction. Gratifyingly, the conversion increased to greater than 99% to give the *trans* lactam **3a** in greater than 99% *ee* and 8:1 d.r. (Table 1, entry 2). An increase in the amount of the acid used decreases the diastereoselectivity (entry 3). Diisopropyl ethyl amine as the base is not efficient (entry 4) and K_2CO_3 delivers lower d.r. values in THF, presumably because of poor solubility (entry 5). The oxidant **OB**, popularized by Studer and coworkers for use in NHC catalysis,[17] is not effective for this transformation (entry 6), and the use of **OA** as the oxidant makes purification difficult as its polarity is similar to that of the desired product. We investigated a more polar oxidant **OC**. Lower diastereoselectivity was observed when using DBU or K_2CO_3 as the base in THF (entries 7 and 8). To increase the solubility of base in the solvent, a mixed solvent

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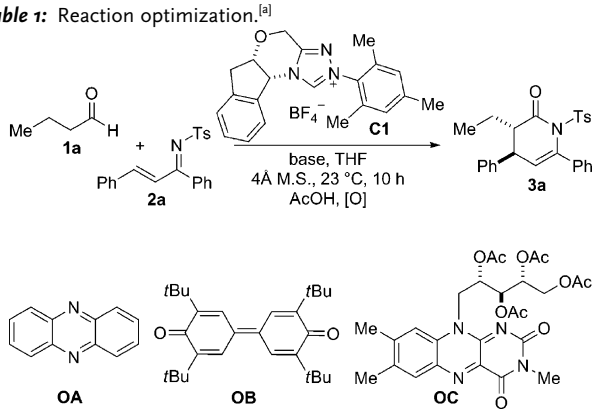
Table 1: Reaction optimization.[a]



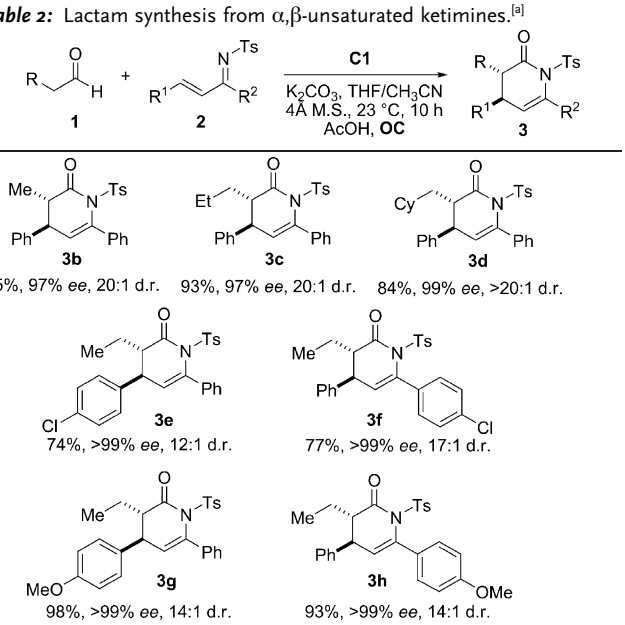
Entry	Base	AcOH (mol%)	Oxidant	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	DBU	0	**OA**	trace	–	–
2	DBU	10	**OA**	99	8:1	>99
3	DBU	50	**OA**	99	3:1	–
4	*i*Pr$_2$NEt	10	**OA**	17	8:1	–
5	K_2CO_3	10	**OA**	99	2:1	>99
6	DBU	10	**OB**	12	11:1	–
7	DBU	10	**OC**	99	3:1	–
8	K_2CO_3	10	**OC**	99	1:1	–
9[e]	K_2CO_3	10	**OC**	96 (88)	9:1	99
10[f]	K_2CO_3	10	**OC**	74	17:1	99

[a] Reaction conditions: **1a** (0.15 mmol), **2a**, (0.1 mmol), **C1** (20 mol%), base (0.5 equiv), oxidant (1 equiv), THF (1.1 mL), at 23 °C in the presence of 4 Å M.S. for 10 h. [b] Determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard (yield of isolated product given within parentheses). [c] Determined by ^{1}H NMR spectroscopy. [d] The *ee* value of *trans*-**3a** was determined by HPLC analysis using a chiral stationary phase. [e] THF/CH_3CN = 1:10 (v/v) instead of THF, 1.1 mL. [f] THF/CH_3CN = 1:10 (v/v) instead of THF, 1.1 mL; **OC**, 0.2 equiv. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, M.S. = molecular sieves, THF = tetrahydrofuran, Ts = 4-toluenesulfonyl.

system (THF/CH_3CN, 1:10, v/v) proved beneficial, thus generating the *trans* product in 88% yield upon isolation with 99% *ee* and 9:1 d.r. (entry 9).[18] Interestingly, when 0.2 equivalents of the oxidant is used, the desired product is formed in good yield with 99% *ee* and 17:1 d.r. (entry 10), which suggests that the use of catalytic oxidant is possible to give product in high conversion.[19]

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

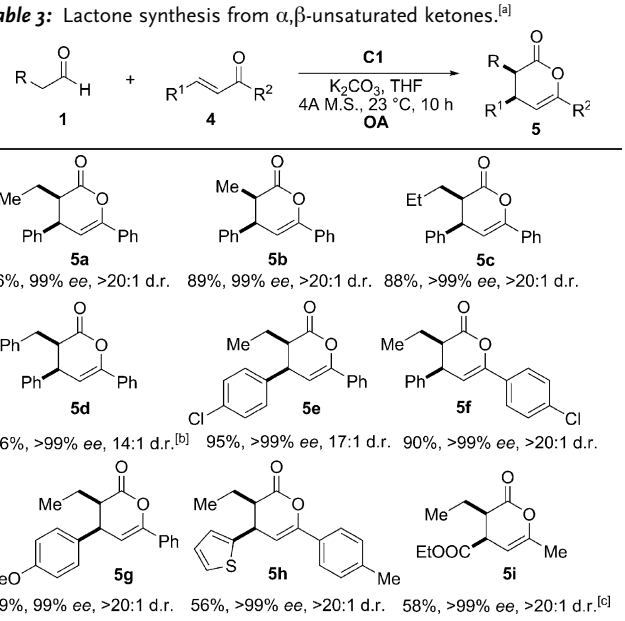
Table 2: Lactam synthesis from α,β-unsaturated ketimines.[a]



[a] Reaction conditions: **1** (0.15 mmol), **2** (0.1 mmol), **C1** (20 mol%), K_2CO_3 (0.5 equiv), AcOH (10 mol%), **OC** (1 equiv), THF/CH_3CN (1:10 (v/v); 1.1 mL), at 23 °C in the presence of 4 Å M.S. for 10 h. The *trans*/*cis* ratio is determined by ^{1}H NMR spectroscopy prior to purification. The *ee* values are determined by HPLC analysis using a chiral stationary phase.

When similar reaction conditions are applied to the cycloaddition with chalcones, lactones are generated but with a *cis* relationship between the stereocenters (Table 3). A

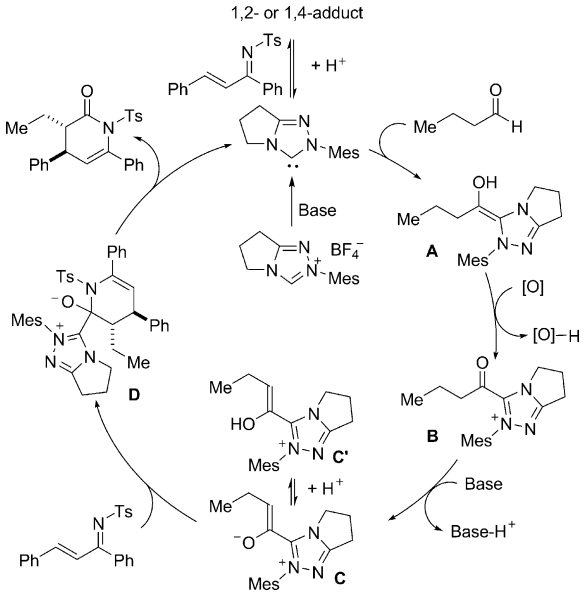
Table 3: Lactone synthesis from α,β-unsaturated ketones.[a]



[a] Reaction conditions: **1** (0.15 mmol), **4** (0.1 mmol), **C1** (20 mol%), K_2CO_3 (0.5 equiv), **OA** (1 equiv), THF (1.0 mL) at 23 °C in the presence of 4 Å M.S. for 10 h. The d.r. values were determined by ^{1}H NMR spectroscopy prior to purification. The *ee* values were determined by HPLC analysis using a chiral stationary phase. [b] Phenyl propionaldehyde, 0.12 mmol. [c] **OC** instead of **OA**, 1 equiv; THF/CH_3CN = 1:10 (v/v) instead of THF, 1.1 mL.

variety of aliphatic aldehydes give the lactones **5a**–**d** in good yields with excellent *ee* values and high d.r values. When an electron-withdrawing group, such as a 4-chloro or 4′-chloro group is on the aromatic ring of the chalcone, the reaction proceeds to give the corresponding products **5e** and **5f** in the same efficiency. The reactions become slower when an electron-donating group such as a 4-methoxy or a thiophene is incorporated into the chalcone, but the desired products are still obtained with excellent *ee* (99%) and d.r. values (**5g** and **5h**). Beyond chalcones as substrates, the desired product **5i** can be generated smoothly when a ketoester is employed as the starting material and **OC** is used as the oxidant instead of **OA** in the mixed solvent system of THF/CH_3CN (1:10). Although lactones such as **5i** have been generated using the system reported by Bode and co-workers,[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. The base deprotonates the triazolium salt to generate a free carbene, which may react with the α,β-unsaturated ketimine to form an adduct by either 1,2- or 1,4-addition. In the presence of acid, the adduct releases the carbene. Reaction with aliphatic aldehyde gives the Breslow intermediate **A** with subsequent oxidation to generate the acyl azolium **B**. Deprotonation of **B** at the α position gives the enolate **C**, which undergoes [4+2] cycloaddition with the α,β-unsaturated ketimine to give zwitterion **D**. The carbene is released from **D**, and the desired lactam is formed.



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

The mechanism for lactone formation is slightly different from the above pathway. After carbene generation, addition of the carbene to the chalcone does not form stable adducts, thus suggesting that the free carbene is present in the reaction. Therefore, addition of acid is not necessary for lactone synthesis. Interestingly, the *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 with high enantioselectivities and good to excellent d.r. values from simple aliphatic aldehydes. The method involves a new way to generate enolate intermediates by 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 reaction conditions.[23] A study aimed at elucidating the factors responsible for the different stereochemistry between *trans* lactams and *cis* lactones is in progress.

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[18] Methanesulfonyl in place of 4-toluenesulfonyl as the protecting group on the ketimine is tolerated, thus delivering the desired lactam in 92% yield and 4:1 d.r. under the same reaction 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 an 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, thus 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 the mesityl carbene as the catalyst in THF, no reaction took place.

[21] Cinchonidine catalysis or enamine catalysis/oxidation delivers *trans* lactones as the products. See: a) T. Mukaiyama, H. Nagao, Y. Yamane, *Chem. Lett.* **2006**, *35*, 916 – 917; b) J. Wang, F. Yu, X. Zhang, D. Ma, *Org. Lett.* **2008**, *10*, 2561 – 2564.

[22] The use of 10 mol% catalyst in the reaction of **1a** and **2a** leads to **3a** in 67% yield, 10:1 d.r., and 99% *ee*. The use of 5 mol% catalyst in the reaction of **1a** and chalcone leads to **5a** in 68% yield, > 20:1 d.r., and 99% *ee*.

[23] When the reaction of chalcone with aliphatic aldehyde is carried out under the same reaction conditions as those used in the lactam synthesis, the desired *cis* lactone is still generated as the major adduct.

