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Simultaneous Construction of Fused Pyrrolidines and β -Lactones via Carbene-Catalyzed C-N, C-C and C-O Bond Formations

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Abstract: A carbene-catalyzed intermolecular C-N bond formation that initiates a highly selective cascade reaction for the synthesis of pyrrolidine fused β -lactones is disclosed. The nitrogen-containing bicyclic β -lactone products are obtained with good yields and excellent stereo-selectivities. Synthetic transformations of the reaction products to useful functional molecules such as amino catalysts can be efficiently realized under mild conditions. Mechanistically, this study provides insights in modulating the reactivities of heteroatoms such as nitrogen in challenging carbene-catalyzed asymmetric carbon-heteroatom bond forming reactions.

Nitrogen and oxygen atoms are among the most common heteroatoms found in synthetic medicines, biomolecules, and natural products. For example, nitrogen-containing heterocyclic motifs such as pyrrolidines form the key scaffolds of natural amino acid proline and numerous biologically active molecules.^[1] Oxygen-containing heterocycles such as β -lactones^[2] have widely been used in assembling both small molecules^[3a-d] and polymers.^[3e] Examples of fused bicyclic β -lactone-containing natural products with significant biological activities include pancreatic lipase inhibitor vibrallactone **A**^[4a] and proteasome inhibitor salinosporamide **A**^[4b] (Figure 1a). Efficient asymmetric methods to access this class of heterocyclic molecules continues to draw intense attentions from both academic and industrial laboratories.^[5] Most of the reactions reported to date rely on intramolecular process (e.g., intramolecular aldol-lactonization^[6]) and/or start with optically enriched starting materials.^[7] Intermolecular reactions starting with simple achiral substrates are more desired but unfortunately much less developed (Figure 1b). In this regard, Romo^[8a] has reported a chiral isothioureacatalyzed intermolecular Michael-aldol- β -lactonization sequence to form cyclopentane fused β -lactones involving α,β -unsaturated acyl ammonium intermediate.^[8] The carbocycle (cyclopentane) fused β -lactones have also been prepared via *N*-heterocyclic carbene^{[9][10]} (abbreviated as carbene or NHC)-mediated intermolecular reactions. Nair^[11a] and Bode^[11b,c] independently reported the reactions between enals and enones to afford cycl-

Figure 1. Access to bicyclic β -lactones.

opentane fused β -lactones using the β -carbon nucleophilic reactivity of enal via homoenolate intermediates.^[11] In these enal/enone reactions, the formed lactone moiety was typically unstable at room temperature and tended to undergo a decarboxylation process to eventually give cyclopentene as the final product.^[11a,b] Lupton and co-workers reported NHC-catalyzed ring-opening of cyclopropanes to access highly functionalized cyclopentane fused β -lactones.^[12a,b] Studer has disclosed the addition of a malonate α -carbon to α,β -unsaturated acyl azolium intermediate as a key step to synthesize bicyclic β -lactone with two fully substituted stereo-centers.^[12c] Recently, Lupton further reported a (4+2) annulation using donor-acceptor cyclobutane to cyclohexyl β -lactones.^[12d]

Here we demonstrate a new method for asymmetric catalytic synthesis of bicyclic β -lactones (Figure 1c). In addition to the β -lactone moiety, our method simultaneously constructs a new C-N bond to form a fused pyrrolidine ring. Our reaction employs readily available enals (e.g., **1a**) and amino ketones (e.g., **2a**) as the starting materials. The key mechanistic steps include intermolecular addition of a nitrogen nucleophile^[13] to the

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unsaturated acyl azolium intermediate (**I**),^[14] followed by an aldol (**II**) and lactonization process (**III**)^{[9][15]} (see Supporting Information for a complete catalytic cycle). The reactivity of the nitrogen atom in amino ketone substrate **2a** is fine modulated by the Ts group and the alkyl moiety to facilitate the challenging intermolecular aza-Michael addition (from **I** to **II**, Figure 1). The pyrrolidine fused β -lactone products (e.g., **3a**), bearing three contiguous stereogenic centers including one quaternary carbon center, are obtained in good yields and excellent stereo-selectivities.

We chose readily available enal (**1a**) and α -amino ketone (**2a**) as the starting materials (Table 1). Ye^[16] has previously used similar α -amino ketones as substrates in NHC catalysis, in which the α -carbon of ketone behaves as a nucleophilic center to form a C-C bond. Key results in searching for suitable conditions, by using quinone (**DQ**) as an oxidant pioneered by Studer,^[14a-c] are summarized in Table 1. The use of triazolium NHC catalyst **A**^[17a] led to the formation of desired product **3a** with 40% yield. Among the amino indanol-derived NHCs,^[17b,c] nitro substituted catalyst (**D**) afforded the desired lactone **3a** in moderate yield and 87:13 er (entry 4). The use of catalyst **E**^[17d] gave **3a** with excellent yield, albeit in a much lower er value (entry 5). Switch of base to Cs₂CO₃ led to improved yield and er (entry 6). The use of CHCl₃ as the solvent provided a slight while consistent improvement of er value (from 90:10 to 93:7 er, entries 6 and 7). We then found that the employment of sulfonyl amide **4** (10 mol%) as an additive could

Table 1. Screening of conditions for the reaction of **1a** with **2a**.^[a]

Entry	NHC	Base	Solvent	3a Yield [%] ^[b]	e.r.
1	A	K ₂ CO ₃	CH ₂ Cl ₂	40	-
2	B	K ₂ CO ₃	CH ₂ Cl ₂	43	71:29
3	C	K ₂ CO ₃	CH ₂ Cl ₂	50	83:17
4	D	K ₂ CO ₃	CH ₂ Cl ₂	48	87:13
5	E	K ₂ CO ₃	CH ₂ Cl ₂	85	34:66
6	D	Cs ₂ CO ₃ ^[c]	CH ₂ Cl ₂	61	90:10
7	D	Cs ₂ CO ₃ ^[c]	CHCl ₃	64	93:7
8 ^[d]	D	Cs ₂ CO ₃ ^[c]	CHCl ₃	65	96:4
9 ^[e]	D	Cs ₂ CO ₃ ^[c]	CHCl ₃	76 (74)	96:4

[a] Reaction conditions: **1a** (0.065 mmol, 1.3 equiv.), **2a** (0.05 mmol, 1.0 equiv.), NHC (15 mol%), K₂CO₃ (1.5 equiv.) and **DQ** (1.2 equiv.), 4 Å MS (50 mg) in solvent (0.05 M) at RT for 20 h. [b] Yields determined by NMR analysis with an internal standard. Isolated yield in parentheses based on **2a**. [c] 1.0 equiv. of Cs₂CO₃ was used instead. [d] 10 mol% of **4** was added. [e] 10 mol% of **4**, 1.5 equiv. of **1a** and 1.4 equiv. of **DQ** were used. Ts = 4-methylbenzenesulfonyl.

further consistently improve the reaction er (96:4 er, entry 8). However, the exact role of this additive remains unclear at this point. Finally, by increasing the loadings of enal **1a** (from 1.3 to 1.5 equiv.) and oxidant (from 1.2 to 1.4 equiv.), the product **3a** was obtained in an acceptable yield (74%) with excellent diastereoselectivity (d.r.>20:1) and 96:4 er (entry 9).

Table 2. Substrate scope.^[a]

Variation of aldehyde **1** (with **2a** as the model amino ketone)

3a , 74%, 96:4 e.r. R = F, 3b , 75%, 95:5 e.r. R = Br, 3d , 74%, 95:5 e.r. R = Cl, 3c , 80%, 96:4 e.r. R = NO ₂ , 3e , 74%, 90:10 e.r.		
R = CH ₃ , 3f , 70%, 96:4 e.r. R = OCH ₃ , 3g , 67%, 98:2 e.r.		
3i , 66%, 95:5 e.r.		
3j , 70%, 96:4 e.r. (CCDC 1518922) R = OAllyl, 3k , 55%, 99:1 e.r. 3m , 45%, 98:2 e.r. R = CO ₂ CH ₃ , 3l , 71%, 98:2 e.r.		
3n , 76%, 92:8 e.r. R = Ts, 3o ^[b] , 65%, 87:13 e.r. 3p ^[b] , 62%, 91:9 e.r.		

Variation of ketone **2** (with **1a** as the model enal)

3r , 78%, 95:5 e.r. 3s ^[c] , 81%, 93:7 e.r. (NHC = E) 3t , 87%, 96:4 e.r.		
3u , 44%, 91:9 e.r. 3v , 64%, 98:2 e.r. 3w , 73%, 97:3 e.r.		

[a] Reaction conditions: **1** (1.5 equiv.), **2** (0.10 mmol, 1.0 equiv.), **D** (15 mol%), Cs₂CO₃ (1.0 equiv.), **4** (10 mol%) and **DQ** (1.4 equiv.), 4 Å MS (100 mg) in CHCl₃ (0.05 M) at RT for 20 h. Yields (after SiO₂ chromatography purification) based on **2**. [b] 2.0 equiv. of enal **1** was used, and reaction was carried out at 40 °C. [c] Catalyst **E** was used instead of **D**. Mts = 2,4,6-trimethylbenzenesulfonyl.

With an acceptable condition in hand, we next investigated the generality of the reaction. Initially, we examined the scope of β -aryl and β -alkyl enals in the cascade process by using α -amino ketone **2a** as a model substrate (Table 2). Various substituents and substitution patterns on the β -phenyl ring of enals were well tolerated to give the products with acceptable yields and good er values (**3a–3l**). Enals bearing readily transferrable functional units, such as Br (**3d**), and carboxylic ester (**3l**) units were also used to give corresponding β -lactones. The β -phenyl unit of **1a** could be replaced with heteroaryl substituents, such as furyl (**3m**) and pyridinyl units (**3n**). Additionally, β -alkyl enals were also screened in our approach (**3o–q**). In these reactions using β -alkyl enals, the use of amino ketone protected with a slightly bulkier Mts (2,4,6-trimethylbenzenesulfonyl) group provided the lactone adduct (**3p**) with a slightly higher er than that using Ts group-protected amino ketone substrate (**3o**).

We next studied the scope of the amino ketones by using **1a** as the model enal substrate (Table 2). The ethyl unit of **2a** could be replaced with a methyl (**3r**), isopropyl (**3s**), *n*-butyl (**3t**), benzyl (**3u**), or cyclohexyl unit (**3v**). As a technical note, when amino ketone substrate bearing a relatively bulky isopropyl unit was used under the standard condition with **D** as the NHC catalyst, the product (**3s**) was obtained in a low yield (29%). In this case, the use of **E** as the NHC catalyst promoted the formation of **3s** with 81% yield and 93:7 er. Acetal group in the amino ketone substrate was tolerated in our reaction as well (**3w**).

Scheme 1. Examples of α -amino aryl ketone substrates.

When α -amino ketones with aryl substituents were employed, the use of catalyst **ent-B** (enantiomer of **B**) gave better yields compared to that of catalyst **D** (see Table S4, SI) (Scheme 1). In these cases, the initially formed bicyclic β -lactones underwent a spontaneous decarboxylation^[11a,b] to form the corresponding 3-pyrroline products (**5a–d**) with good yields and excellent er values. When these reactions were carried out at room temperature, a side adduct resulted from the ketone α -carbon reaction previously reported by Ye^[16] was observed (approximately 10% yield). This side reaction was neglectable when the reaction temperature was decreased to 0 °C (see SI).

Our cascade approach for bicyclic lactones is amenable for gram scale synthesis (**3a**, Scheme 2a). The optically enriched pyrrolidine fused β -lactone products obtained in our catalytic reaction can readily undergo further transformations. For example, the lactone unit of **3a** was subjected to DIBAL-H reduction to furnish the corresponding diol **6** in 83% yield without erosion of the er value. The tosyl (Ts) group on the nitrogen of **3a** was

Scheme 2. Synthetic transformations and catalytic application of the products.

deprotected with Mg/MeOH after mild alcoholysis to afford β -proline methyl ester **7** in 74% yield and 96:4 er. A preliminary application of the β -proline derivative **7** as an organocatalyst revealed that **7** could catalyze the Michael addition^[18] of aldehyde (**9**) to nitroalkene (**10**) to afford the adduct **11** with 70% yield and a promising enantioselectivity (90:10 er) without any optimizations (Scheme 2b). Decarboxylation of **3a** followed by an epoxidation reaction using *m*-CPBA gave bicyclic epoxide **8** with 81% overall yield and 96:4 er. The oxabicyclic structure of **8** is commonly found as a core moiety in numerous antibiotic molecules and natural products, such as (+)-epogymnolactam.^[19]

In summary, we have developed a highly efficient organic catalytic method for rapid access to pyrrolidine fused β -lactones. The reaction starts with a challenging intermolecular addition of a nitrogen nucleophile to the catalytically generated unsaturated acyl azolium intermediate as a key step to form a new C–N bond. Direct asymmetric construction of C–N bond on the β -carbon of the carbonyl compound is a most effective method to prepare non-natural amino acid derivatives and N-heterocycles. Our carbene catalyst-enabled asymmetric C–N, C–C, and C–O bond forming cascade readily afford bicyclic pyrrolidine fused β -lactones with good yields and excellent stereo-selectivities. Mechanistically, this study provides insights in modulating the reactivities of nitrogen and other hetero-atoms in asymmetric reactions mediated by carbene catalysts. Further reaction development and evaluation of the bio-activity of pyrrolidine fused β -lactones are under progress in our laboratory.

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Layout 2:

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**Simultaneous Construction of Fused
Pyrrolidines and β -Lactones via
Carbene-Catalyzed C-N, C-C and C-O
Bond Formations**

Pyrrolidine fused β -lactones: A challenging intermolecular addition of a nitrogen nucleophile to the catalytically generated unsaturated acyl azolium intermediate provides a highly efficient method for asymmetric access to pyrrolidine fused β -lactones. The unique bicyclic β -lactone structure, bearing three contiguous stereogenic centers, are readily transformed to useful functional molecules such as amino catalysts.