

γ -Carbon Activation through N-Heterocyclic Carbene/Brønsted Acids Cooperative Catalysis: A Highly Enantioselective Route to δ -Lactams

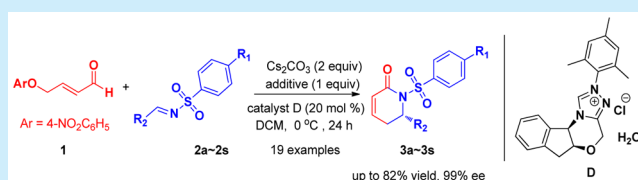
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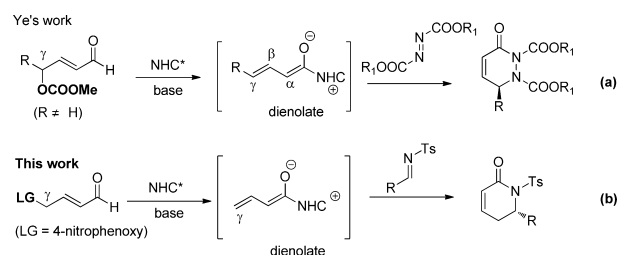
S Supporting Information

ABSTRACT: A γ -carbon activation method that operates through N-heterocyclic carbene/Brønsted acid cooperative catalysis for highly enantioselective synthesis of δ -lactams is reported. The protocol allows the challenging remote γ -carbon control of regioselectivity and enantioselectivity through introduction of an appropriate γ -leaving group in the enals. The reaction offers good yields and excellent enantioselectivities, and the resulting cyclic products can be easily converted into high-value drug-like derivatives.



C–H activation via N-heterocyclic carbene (NHC) catalysis has attracted widespread attention for the rapid synthesis of novel heterocycles.¹ However, the most significant challenge is to control reaction site selectivity.² The activation of enals by NHC generally offers homoenolate,³ enolate,⁴ or acyl anion equivalents⁵ as the nucleophiles. Current studies have mainly involved activation of the α - or β -carbon of carbonyl compounds. Activation of the γ -carbon still remains a significant challenge and has not been thoroughly investigated, with only a few pioneering studies having been reported involving γ -carbon activation that constructs intriguing heterocycles.^{1a,2,6} The heterocyclic lactam motif represents a significant portion of chemical space and is widespread in synthetic biologically active molecules and natural products.^{1b,7} Such molecules are commonly obtained through cyclodehydration reactions of amino acids,⁸ Beckmann rearrangement of cycloketones,⁹ or intramolecular cyclization of amides possessing an alkene,¹⁰ alkyne,¹¹ or allene group.¹² However, it is often difficult for these methods to impart good enantioselectivity. Recently, there have been some reports studying the feasibility for the enantioselective synthesis of lactams via NHC catalysis,^{1b,13} but most of these protocols are limited to the preparation of γ -lactams.¹³ The activation of enal γ -carbons to prepare δ -lactams still faces significant barriers, with frequent difficulty in obtaining good chemoselectivity (reactive position selectivity) due to the presence of some competitive reaction intermediates, such as homoenolate, enolate, or acyl anion intermediates. On the other hand, the fact that chiral auxiliaries may be relatively remote from the γ -carbon of enals makes stereocontrol difficult.² In 2013, Ye et al. reported a pioneering NHC organocatalytic γ -carbon activation of enals, with γ -leaving groups, to generate [4 + 2] annulation products (Scheme 1a).^{6b} However, this protocol requires a substituent in the γ -position of the enal to stabilize the dienolate intermediate

Scheme 1. NHC-Catalyzed Lactams through γ -Carbon Activation of Enals

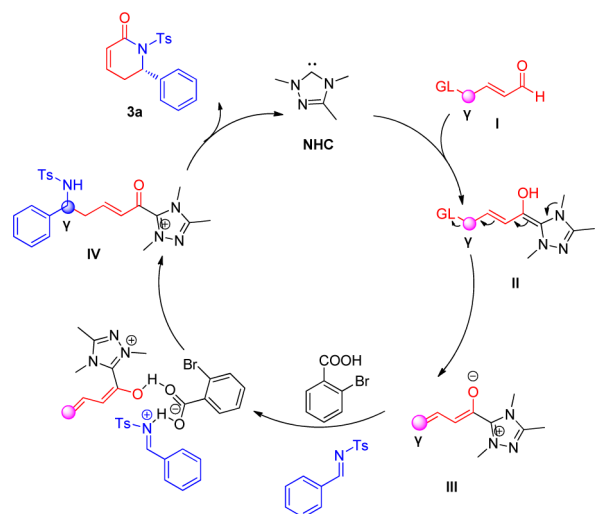


generated during the activation. We envisioned that introducing an appropriate leaving group at the γ -position of an enal might generate a stable γ -unsubstituted homoenolate intermediate, which could then react with an imine to give intriguing δ -lactams (Scheme 1b). The key step would involve addition of the NHC catalyst to the enal substrate **I** to form the γ -unsubstituted homoenolate intermediate **III** following elimination of the γ -leaving group (Scheme 2). The γ -carbon of dienolate intermediate **III** would then undergo nucleophilic addition to the imine to eventually form the δ -lactam via a Mannich reaction and subsequent cyclization. The overall hypothesized pathway may be considered a similar process to that found in the NHC-mediated activation of α,β -unsaturated aldehydes.^{6b,14}

Experimentally, we set out to achieve γ -carbon activation to prepare the target δ -lactam using the enal **1** as a model substrate and imine **2a** as a model electrophile. The key results of extensive studies are summarized in Table 1. Initially, Cs_2CO_3 was selected as a base, and four different triazolium

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Scheme 2. Postulated Catalytic Cycle



NHC precatalysts were screened in CH_2Cl_2 solvent (Table 1, entries 1–4). Surprisingly, the process delivered the desired Mannich adduct (**3a**) in a moderate yield of 36% and a high enantioselectivity of 91% ee when the NHC precatalyst **D** was used (Table 1, entry 4). This proof-of-principle result clearly revealed that activation of the γ -carbon of enal, including a γ -leaving group as a nucleophile using the NHC organocatalyst,

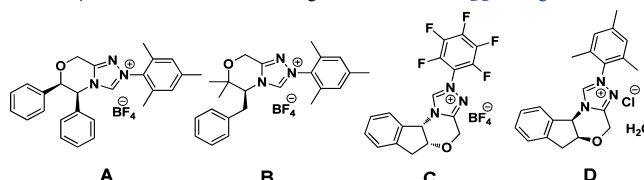
was feasible. Accordingly, a variety of alternative bases were investigated. The results demonstrated that the desired products were observed with NaH , K_2CO_3 , and PhCOONa as the base, whereas no product could be detected in the presence of DBU (Table 1, entries 5–8). We next explored the influence of different solvents, with only a trace of the desired product being found in CH_3OH and no product being observed in THF and dimethyl ether (Table 1, entries 9–11). Some pioneering work from Scheidt and his colleagues has indicated that cooperative catalysis by carbenes and Lewis acids can achieve greater selectivity and more efficient reactivity than either mode individually; in such cooperative catalysis, an optimal Lewis acid catalyst can activate the electrophile by lowering the energy of the lowest unoccupied molecular orbital (LUMO) for the overall productive reaction.^{1c,2,15} Based on these findings, two distinct Lewis acidic magnesium(II) and scandium(III) salts were used, and a higher selectivity and more efficient reactivity were obtained (Table 1, entries 12–13). Further studies showed that the addition of a Brønsted acid (2-Br- PhCOOH) could offer a better result, giving a 72% yield and a 94% ee (Table 1, entries 14–15).^{5c} In addition, some lithium salts, such as LiBr and LiBF_4 , were evaluated. However, good results were not obtained in the model reaction (Table 1, entries 16–17).

With the optimized catalysis conditions identified, a variety of imines were investigated as potential substrates. The results are summarized in Scheme 3. First, we explored a series of

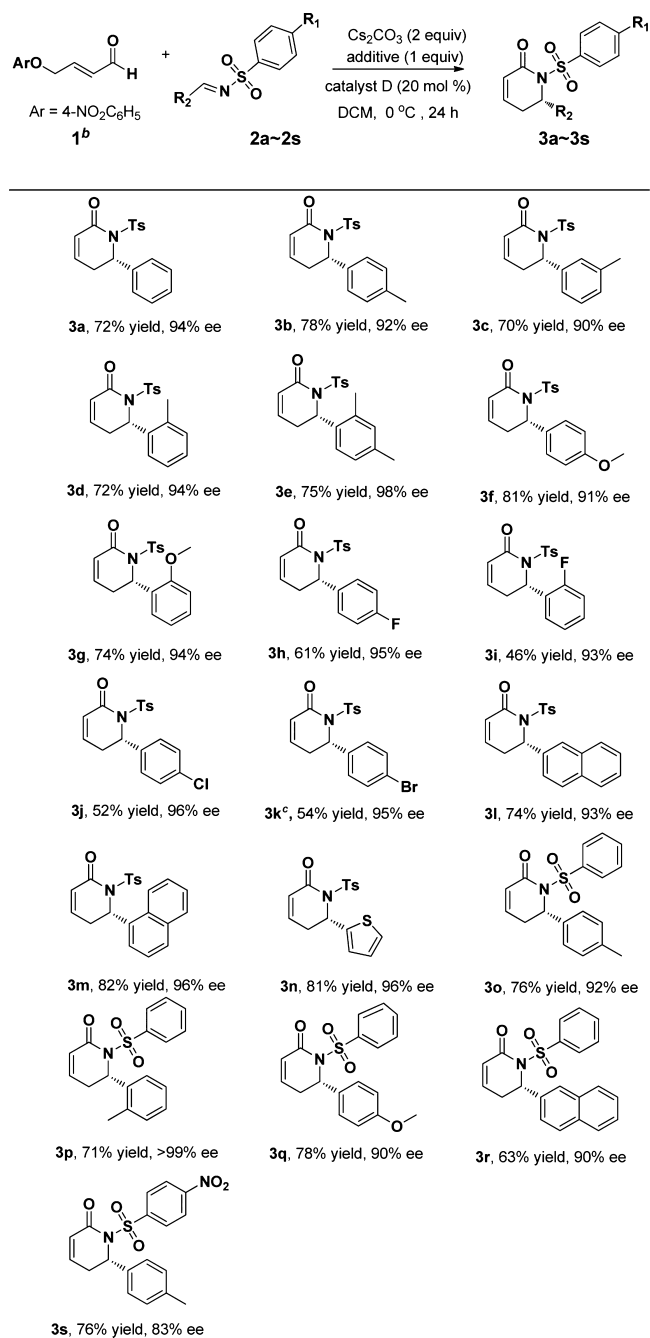
Table 1. Optimization of the Reaction Conditions of Synthesis of **3a**^a

entry	catalyst	base	solvents	additive ^b	yield (%)	ee ^c (%)
1	A	Cs_2CO_3	CH_2Cl_2	— ^d	—	—
2	B	Cs_2CO_3	CH_2Cl_2	—	—	—
3	C	Cs_2CO_3	CH_2Cl_2	—	trace	—
4	D	Cs_2CO_3	CH_2Cl_2	—	36	91
5	D	NaH	CH_2Cl_2	—	45	71
6	D	DBU	CH_2Cl_2	—	—	—
7	D	K_2CO_3	CH_2Cl_2	—	24	72
8	D	PhCOONa	CH_2Cl_2	—	27	78
9	D	Cs_2CO_3	THF	—	—	—
10	D	Cs_2CO_3	CH_3OCH_3	—	—	—
11	D	Cs_2CO_3	CH_3OH	—	trace	92
12	D	Cs_2CO_3	CH_2Cl_2	$\text{Sc}(\text{OTf})_3$	43	87
13	D	Cs_2CO_3	CH_2Cl_2	$\text{Mg}(\text{OTf})_2$	41	92
14	D	Cs_2CO_3	CH_2Cl_2	4-Br- PhCOOH	64	94
15	D	Cs_2CO_3	CH_2Cl_2	2-Br- PhCOOH	72	94
16	D	Cs_2CO_3	CH_2Cl_2	LiBr	29	94
17	D	Cs_2CO_3	CH_2Cl_2	LiBF_4	46	92

^aReaction conditions: **1** (0.1 mmol), **2a** (0.2 mmol), catalyst A–D (0.02 mmol), base (0.2 mmol), solvent (2–3 mL), at 0 °C for 24 h under Ar protection. ^bAdditive (0.1 mmol). ^cEnantiomeric excess of **3a** determined via chiral phase HPLC analysis; absolute configuration of the major enantiomer was assigned on the basis of X-ray structure of **3k** (see Figure S1 in the Supporting Information). ^dNo desired product found.



Scheme 3. Enantioselective Mannich Reactions with 4-(4-Nitrophenoxy)but-2-enal^a



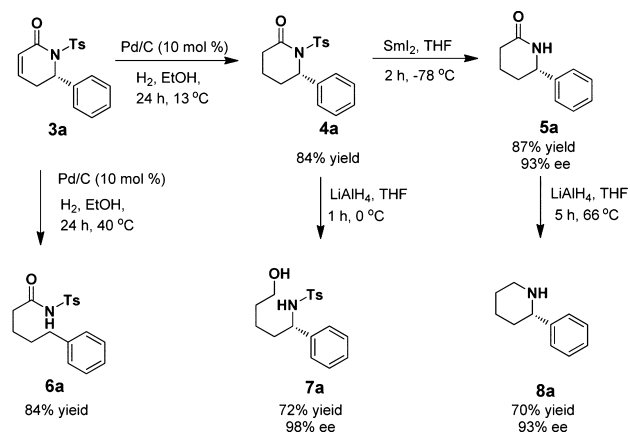
^aReaction conditions: **1** (0.1 mmol), **2a** ~ **2s** (0.2 mmol), catalyst **D** (0.02 mmol), Cs₂CO₃ (0.2 mmol), additive (2-bromobenzoic acid, 0.1 mmol), DCM (2–3 mL), at 0 °C for 24 h under Ar protection. ^b4-(*p*-Methylphenoxy)but-2-enal is also tested, but no desired product is observed. ^cThe CCDC number of **3k** is CCDC1024375.

imine substrates in which R₁ was a methyl group (**3a–3n**). Electron-donating, electron-withdrawing, and halogen groups on the phenyl ring of R₂ were tolerated and offered the desired annulation products in good yields (**3a–3k**, 46–81%) with excellent enantioselectivities (90–98%). Fused aromatic groups (1-naphthyl and 2-naphthyl) and a heterocyclic group (2-thienyl) also gave excellent results, with 74–82% yields and 93–96% ee values (**3l–3n**). We further investigated the tolerance of the process by varying the R₁ group; the diversified

substrates also gave the annulation products in good yields (**3o–3s**, 63%–78%) and high enantioselectivities (83%–99%). The *S* configuration of **3k** was determined by X-ray analysis (Figure S1 in the Supporting Information).

The cyclic products from this novel strategy can be easily converted into high-value derivatives,¹⁶ thereby leveraging the utility of the overall process (Scheme 4).¹⁷ For example, under

Scheme 4. Synthetic Transformations of **3a**



different reaction temperatures, we found that cyclic product **3a** can be reduced to the long-chain amide **6a** and the saturated δ -lactams **4a** and **5a**. The saturated δ -lactam **5a** is not only an intriguing pharmacophore¹⁸ but also a known intermediate for the synthesis of piperidine **8a**, which is widely observed in synthetic biologically active molecules and natural products, such as the local anesthetic ropivacaine,¹⁹ the thrombin inhibitor argatroban,²⁰ the HIV-protease inhibitor palinavir,²¹ and the antitumor antibiotic tetrazomine,²² along with top-selling pharmaceuticals that include paroxetine (a disubstituted piperidine).²³ The alkyl amide **6a** has been widely used in the material dye industry²⁴ and pharmaceutical industry.²⁵ In addition, the δ -lactam **4a** can be converted into the chiral amino alcohol **7a** in 72% yield with 93% ee;^{1b} this compound is generally used as a basic building block.

In summary, we have developed a highly effective catalytic system for the enantioselective construction of a diverse array of δ -lactams in good yields and with excellent enantioselectivities. The challenge of attaining high enantioselectivity at the remote γ -carbon of an enal was achieved by introducing an appropriate γ -leaving group. The reaction tolerates different kinds of imines. The resulting cyclic products can be easily converted into high-value derivatives, such as δ -lactams, piperidines, amino alcohols, and alkyl amides, thereby broadening the utility of the overall process. The widely available substrates, excellent enantioselectivity, mild reaction conditions, and wide reaction scope make this γ -carbon activation strategy potentially useful for the synthesis of biologically active molecules or natural products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01827.

Crystallographic data (CIF)

Detailed experimental procedures; spectral data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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