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Carbocation catalyzed carboxylic acid activation in Staudinger reaction for stereoselective synthesis of β-lactams

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ABSTRACT

A novel strategy to synthesize stereoselective β-lactams has been disclosed via cyclopropenium-ion-catalyzed reaction of substituted acetic acids with aldimines under mild conditions. Products are formed in high yields (86–95%) and good diastereoselectivity within 3–4 h. The new reaction is focused on the exploration of the scope of cyclopropenium-ion catalysis and introduction of a catalytic version of one-step Staudinger reaction for β-lactam synthesis. The reaction is effective for a range of substituted acetic acids and aldimines.

Long at the forefront of the biological relevance of β-lactams as antibiotics coupled with their usefulness as synthons for further functionalization, they are considered as one of the most important aza-heterocyclic frameworks in organic chemistry.[1a–g] The synthesis and properties of β-lactam derivatives with various functional groups are important and maintain a rarefied place in the history of organic reactions and pharmaceutical fields.[2,3] A plethora of distinctive activities have been shown by β-lactams such as, anticancer,[4a] antifungal,[4b,c] potential antimalarials,[4d] anti-influenza virus,[4e] antihyperglycemic,[4f] central nervous system active agents,[4g] combat of neurological diseases[4h] and as inhibitors.[5] It is therefore no surprise that, in current years, chemical methods leading to the direct and facile synthesis of β-lactams, particularly, catalytic enantioselective methods, remain among the most important reactions for synthetic chemists.

It was Staudinger who developed the first most enduring method for the synthesis of β-lactams by coupling of ketenes and imines.[6] This convergent strategy represents one of the most effective routes for preparing these compounds, and recently, some of its catalytic asymmetric versions have been reported.[7] In addition to acyl halides and tertiary amines, carboxylic acids have also been employed to generate in situ ketenes.[8a] With few exceptions,[8b,c] the majority of these methods involve a combination of two or three reactants that provide the required β-lactam framework in a single step.[8d–f] Numerous one-step protocols for constructing β-lactam ring have been reported in the literature using activated carboxylic acid and imine employing acid activators.[9,10] To note, a variety of acid activators for in situ generation of ketenes have been employed so far, viz., acetic anhydride, cyanuric chloride, (Chloromethylene)dimethylammonium chloride, triphosgene, 1,1-carbonyldi-imidazole, ethyl chloroformate, the Mukaiyama reagent, trifluoroacetic anhydride, *p*-toluenesulfonyl chloride, phosphorus-derived reagents,[10b] and recently cinchona alkaloid and isothioures.[10f] These conceptual approaches to accomplish highly stereoselective azetidinone formation by the annulation of imino compounds with an activated acid are of course high yielding and well established. However, one or more of these methods requires ultra low temperature (−78 °C), expensive reagents in stoichiometric amount, tedious purification of final product, and most importantly concomitant generation of stoichiometric by-products, which impacts severely on the atom efficiency, and adversely on its large-scale applicability in industry. Furthermore, construction of β-lactam ring using oxalyl chloride is also well documented but, except using Vilsmeier reagent, a number of products are obtained in addition to β-lactam ring, which still opens up a challenge for exclusive synthesis of β-lactam using oxalyl chloride.[11]

These literature precedents and our interest in developing new synthetic routes,[12] especially using organocatalyst,[12d] triggered us to search a conceptually new, facile and efficient catalytic activation of carboxylic acid for accessing β-lactams based on

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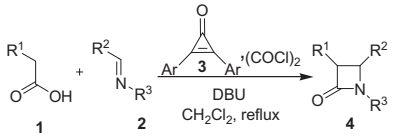
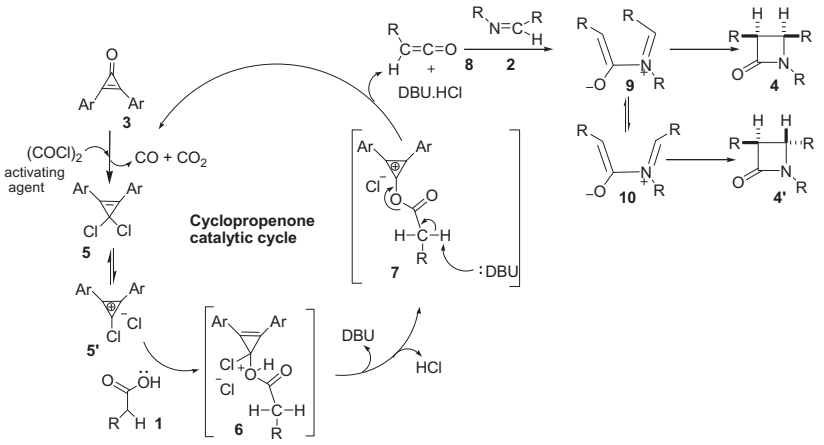


Scheme 1. Cyclopropenone-catalyzed stereoselective synthesis of β-lactams.

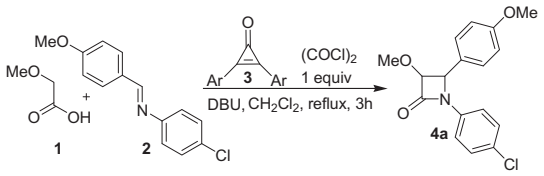
Staudinger reaction. For this purpose, we chose the activated cyclopropenone as organocatalyst, which has propensity of ionization to aromatically stabilized cyclopropenium carbocation, a cornerstone of the present envisaged work. Cyclopropenones were first prepared by Breslow et al.[10a–g] and Volpin et al.[10h,i] separately followed by others.[10j] In recent literature, catalytic behavior of the cyclopropenium-carbocation due to its substantial polarization resulting in an unusual nucleophilicity has been well established.[11] Furthermore, numerous reports by Lambert et al.[12] and others[12] describing the properties and reactions of cyclopropenones led to its recognition recently.

Herein, we report the first example of cyclopropenium-ion mediated catalytic Staudinger [2+2] cycloaddition reaction for the synthesis of β-lactams as depicted in Scheme 1. The importance and potency of this work involves the unique reactivity of the cyclopropenium ion which has proven excellent catalytic behavior compared to sulfur/phosphorus based catalysts or any other catalysts. The method involves a catalytic cycle (shown in Scheme 2) in which cyclopropenone reacts with a stoichiometric amount of oxalyl chloride with concomitant loss of CO_2 and CO, to form 3,3-dichlorocyclopropenium salt. The salt reacts with substrate and regenerates neutral cyclopropenone to the catalytic cycle to reionize cyclopropenium salt. Prior to the present investigation, very few studies concerning the catalytic synthetic method for β-lactam



Scheme 2. A plausible mechanism for the formation of β-lactams **4**.

Table 1
Optimization reaction for stereoselective synthesis of β-lactam **4a**[a]



3a: Ar = 4-$MeOC_6H_4$; **3b**: Ar = C_6H_5; **3c**: Ar = 4-*t*BuC_6H_4
3d: Ar = 2,4-$(MeO)_2C_6H_4$; **3e**: Ar = 3-$NO_2C_6H_4$

Entry	Catalyst	Mol%	Base	Solvent	Yield[b,c] (%)
1	**3a**	5	Pyridine	DCM	77
2	**3b**	5	Pyridine	DCM	51
3	**3c**	5	Pyridine	DCM	57
4	**3d**	5	Pyridine	DCM	69
5	**3e**	5	Pyridine	DCM	58
6	**3a**	5	Et_3N	DCM	72
7	**3d**	5	Et_3N	DCM	61
8	**3a**	5	DBU	DCM	88
9	**3d**	5	DBU	DCM	68
10	**3a**	5	DBU	THF	70
11	**3a**	5	DBU	CH_3CN	65
12	**3a**	5	DBU	Toluene	60
13	**3a**	10	DBU	DCM	88
14	**3a**	2	DBU	DCM	64
15	**3a**	5	Pempidine	DCM	48

[a] For the experimental procedure, see Ref. 15.
[b] Yield of isolated and purified product.
[c] Compound was characterized by spectral (IR, ^1H NMR, ^{13}C NMR, and EIMS) data.

have been reported.[7] We then started to establish whether the cyclopropenium ion, generated in situ from cyclopropenone and oxalyl chloride, was effective for the β-lactam synthesis.

Optimization experiments were carried out to examine the catalytic activities of cyclopropenones employing substituted acetic acid **1a** and aldimine **2a** that were chosen as model substrates and the reaction was performed at reflux for 3 h. To our delight, the desired reaction proceeded smoothly in the presence of cyclopropenone. To check whether cyclopropenone really catalyzed the reaction, an experiment was performed using oxalyl chloride in the absence of cyclopropenone, but we could not isolate the desired product **4a** rather chlorooxalate was formed. Our experimental observation has also been supported by related literature of cyclopropenone catalysis.[11e] Thus, we relied upon cyclopropenone catalysis in the envisaged reaction and **3a** was found the most efficient catalyst among various cyclopropenones **3a**–**3e** for the present reaction. The effect of substituents of the aryl group in cyclopropenone significantly affects the outcome of the reaction. The EWG (*m*-NO_2) resulted in lower yields while EDG (*p*-^{t}BuC_6H_4, *p*-OMe) afforded better yield with good stereoselectivity. For best results, the amount of molar concentration of cyclopropenone **3a** was found to be 5 mol % (Table 1, entry 8). Investigation of solvent revealed the reaction was found to proceed more efficiently in polar solvents than in non-polar ones, the use of both more polar solvent and less polar solvents gave a significant decrease in conversion. However, DCM was found to be the best choice in terms of conversion and separation of both products (Table 1, entry 1, 6, 8, 13, 14). The scope of the reaction was then explored with several bases, among them DBU, Et_3N, and Pyridine led to the formation of β-lactam in high conversions (Table 1, entries 1–14). However, a decrease in the reaction conversion was observed for the pempidine base (Table 1, entry 15) but the best base used for the reaction is DBU (Table 1, entry 1, 6, 8). We, next explored the scope of substrates, both electron-donating group and electron withdrawing groups responded well in the reaction.

To obtain the mechanistic insights, on the basis of experimental results a plausible reaction pathway is outlined in Scheme 2. The cyclopropenone catalyst **3** undergoes a rapid reaction with oxalyl chloride to generate 3,3-dichloro-1,2-di-(4-methoxy)phenyl-cyclopropenone **5**, which ionizes to form cyclopropenium chloride salt **5′**. The salt then reacts with substituted acetic acid **1** to produce the protonated *O*-cyclo propenyl derivatives **6** and **7,** respectively, which reacts with DBU to afford ketenes **8**. Then ketenes react with

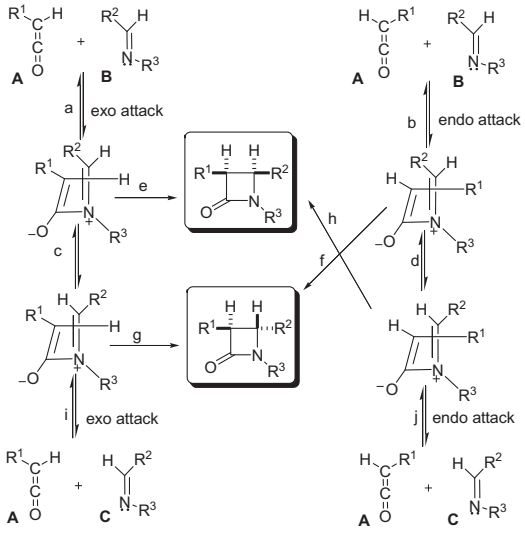
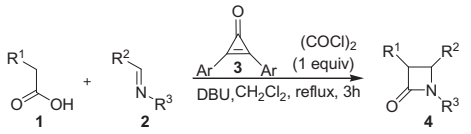


Figure 1. Pathways for formation of *cis*- and *trans*-β-lactam.

Table 2
Stereoselective synthesis of β-lactam **4**[a]



Entry	R^1	R^2	R^3	**4**/*cis*/*trans*	Time (h)	Yield[b,c] (%)
1	MeO	4-$MeOC_6H_4$	4-ClC_6H_4	**4a**/*cis*	3	88
2	MeO	4-$EtOC_6H_4$	4-$NO_2C_6H_4$	**4b**/*cis*	4	86
3	2,4-$Cl_2C_6H_3O$	4-$EtOC_6H_4$	4-ClC_6H_4	**4c**/*cis*	4	95
4	2,4-$Cl_2C_6H_3O$	4-$EtOC_6H_4$	4-$NO_2C_6H_4$	**4d**/*cis*	4	91
5	CH_2=CH	4-$MeOC_6H_4$	4-$MeOC_6H_4$	**4e**/*trans*	4	90
6	CH_2=CH	4-$EtOC_6H_4$	4-$NO_2C_6H_4$	**4f**/*trans*	3	92
7	2-Naphthyloxy	4-$EtOC_6H_4$	4-MeC_6H_4	**4g**/*cis*	3	87
8	2-Naphthyloxy	4-$EtOC_6H_4$	4-$NO_2C_6H_4$	**4h**/*cis*	4	89
9	Cl	4-$EtOC_6H_4$	4-ClC_6H_4	**4i**/*cis*	3	94
10	Cl	4-$MeOC_6H_4$	Ph	**4j**/*cis*	4	93
11	Cl	4-$MeOC_6H_4$	4-$MeOC_6H_4$	**4k**/*cis*	4	94
12	N_3	4-$EtOC_6H_4$	4-$NO_2C_6H_4$	**4l**/*cis*	3	92
13	N_3	Ph	Ph	**4m**/*cis*	4	91
14	N_3	4-$MeOC_6H_4$	4-ClC_6H_4	**4n**/*cis*	3	95
15	Ph	Ph	Ph	**4o**/*cis*	4	89
16	Ph	Ph	4-MePh	**4p**/*cis*	4	91
17	Ph	Ph	4-MeOPh	**4q**/*cis*	4	88
18	Ph	4-MePh	Ph	**4r**/*trans*	3	90
19	Ph	4-MeOPh	Ph	**4s**/*trans*	4	90
20	Ph	4-CF_3Ph	Ph	**4t**/*cis*	3	93
21	Ph	4-CF_3Ph	4-MeOPh	**4u**/*cis*	3	91
22	Ph	Furyl	Ph	**4v**/*cis*	3	92

[a] For the experimental procedure, see Ref. 15.
[b] Yield of isolated and purified product.
[c] Compound was characterized by spectral (IR, ^{1}H NMR, ^{13}C NMR and EIMS) data.

imines to form zwitterionic intermediate **9** and **10**, which undergoes conrotatory ring closure to produce β- lactam and regenerate the catalyst **3** to complete the catalytic cycle. Motivated by this result, it is unequivocal that the electronic nature of the substituents of ketenes (formed in situ from substituted acetic acids) and imines (R1, R2, and R3, Scheme 1) is the crucial factor that determines the yield and stereochemistry of the Staudinger reaction.

This is in conformity with the stereochemistry of the β-lactam products and has been already explained by the torquoelectronic model in Figure 1. According to this, the *cis*-β-lactam formation takes place when the zwitterionic intermediate of the transition state, undergoes conrotatory ring closure, with the electron-donating group (EDGs) on ketene moiety favoring occupying the inward position, which led to the outward position occupied at C3 of the β-lactam ring, leading to the formation of *cis*-β-lactam (e.g., R_1) *p*-MeOPh, Table 2, entry 1); whereas the formation of *trans*-β-lactam (e.g., R_3) *p*-NO_2Ph, Table 2, entry 6) takes place when the substituent on the ketene moiety is the electron-withdrawing group (EWGs).[13] Again it was found that the electronic effect of substituents on imines plays an important role, they even reverse the stereo selectivity with a strong electron donating group (4-Me, 4-MeO), the product is predominantly *trans* (Table 2, entry 18, 19), while for imines with the electron withdrawing group (CF_3), the product is exclusively found to be *cis* (Table 2, entry 20, 21). The *cis* and *trans* stereochemistry is well studied and supported by NOEs. Strong NOEs were observed between 2-H and 3-H of the β-lactam ring in the compounds **4a**–**4d**, **4g**–**4q,** and **4t**–**4v** in the range of 11.4–12.9%. However no NOE signal between 2-H and 3-H is observed in **4e**, **4f**, **4r**, **4s** but NOEs are obtained in these compounds between 3-H and the *ortho* proton of the aromatic ring at position 2 of the β-lactam ring in the range of 16.2–18.9%.

Furthermore, this shows that the presence of measurable NOEs between 2-H and 3-H indicates that **4a**–**4d**, **4g**–**4q,** and **4t**–**4v** have *cis*-stereochemistry for 2-H and 3-H whereas the absence of NOEs between 2-H and 3-H and the presence of NOEs between 3-H and *ortho* proton of the aromatic ring at position 2 of the β-lactam ring **4e**, **4f**, **4r**, **4s** have *trans* stereochemistry for 2-H and 3-H. This result matches well with those reported in the literature.[14] Xu et al. have also mentioned that results correlate well with the Hammette equation.[14]

In conclusion, we have outlined a new general straightforward strategy for catalytic cyclopropenone-based activation and synthesis of β-lactams in high yields following the Staudinger reaction between substituted acetic acid and imines.

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15. *General procedure for the synthesis of β-lactams* **4***:* To a stirred mixture of substituted acetic acid **1** (1 equiv) and 3,3-dichloro-1,2-di-(4-methoxy) phenylcyclopropenone (5 mol %) in DCM (10 mL) in a flame-dried round bottom flask was added oxalyl chloride (1 equiv) through a syringe and DBU (3 equiv) in DCM slowly and then a solution of desired imine in 5 mL of DCM was then added through a dropping funnel during 15 min. The resulting solution was stirred for another 3 h at reflux (Table 2). After completion of the reaction as indicated by TLC, the reaction mixture was diluted with dichloromethane and washed with water (3 × 5 mL). The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to give the crude product, which was purified by silica gel flash chromatography, eluting with a 4:1 hexane chromatography, eluting with a 4:1 hexane–ethyl acetate mixture to afford analytically pure **4**. The structure of products **4** were confirmed by their IR, ^{1}H NMR, ^{13}C NMR and EIMS data and comparison of those known β-lactams prepared by the literature methods.[14] Characterization data of the representative compounds **4**. **4a**: Yellowish oil, yield 88%. IR (KBr) ν_{max} 1751 (C═O, β-lactam) cm^{-1}. ^{1}H NMR (400 MHz; $CDCl_3$) δ = 3.28 (s, 3H, OMe), 3.69 (s, 3H, OMe), 4.89 (d, 1H, J = 4.6 Hz, 3-H), 5.37 (d, 1H, J = 4.6 Hz, 4-H), 6.72–7.64 (m, 8H, ArH). ^{13}C NMR (100 MHz; $CDCl_3$) δ = 54.9, 56.4, 60.1, 86.9, 114.1, 123.1, 127.9, 129.2, 130.1, 134.7, 138.9, 158.2, 165.3. EIMS (*m*/*e*): 317, 319 (M^+, M^+ +2). Anal. Calcd for $C_{17}H_{16}ClNO_3$: C, 64.26; H, 5.08; N, 4.41; Found: C, 63.85; H, 5.40; N, 4.62. **4f**: Yellowish oil, yield 92%. IR (KBr) ν_{max} 1752 (C═O, β-lactam) cm^{-1}. ^{1}H NMR (400 MHz; $CDCl_3$) δ = 1.37 (t, 3H, J = 7.2 Hz, Me), 3.67 (dd, 1H, J = 6.9 Hz, 3-H), 3.95 (q, 2H, J = 7.2 Hz, OCH_2), 4.61 (d, 1H, J = 6.9 Hz, 4-H), 5.22-5.35 (m, 2H, vinilic), 5.70–5.77 (m, 1H, vinilic), 6.71-7.60 (m, 8H, ArH). ^{13}C NMR (100 MHz; $CDCl_3$) δ = 14.2, 47.8, 59.6, 64.9, 114.9, 116.4, 121.3, 123.5, 127.4, 134.8, 136.5, 144.5, 147.9, 156.2, 165.9. EIMS (*m*/*e*): 338 (M^+). Anal. Calcd for $C_{19}H_{18}N_2O_4$: C, 67.44; H, 5.36; N, 8.28; Found: C, 67.12; H, 5.57; N, 8.01. **4m**: Yellowish oil, yield 91%. IR (KBr) 1745 (C═O, β-lactam), 2130 (N_3) cm^{-1}. ^{1}H NMR (400 MHz; $CDCl_3$) δ = 5.11 (d, 1H, J = 5.3 Hz, 3-H), 5.39 (d, 1H, J = 5.3 Hz, 4-H), 6.71–7.89 (m, 10H, ArH). ^{13}C NMR (100 MHz; $CDCl_3$) δ = 61.0, 64.7, 120.9, 124.7, 127.0, 127.9, 128.7, 129.6, 141.5, 143.8, 160.6. EIMS (*m*/*e*): 264 (M^+). Anal. Calcd for $C_{15}H_{12}N_4O$: C, 68.17; H, 4.58; N, 21.20; Found: C, 68.40; H, 4.31; N, 21.49.