JOC The Journal of Organic Chemistry

pubs.acs.org/joc Article

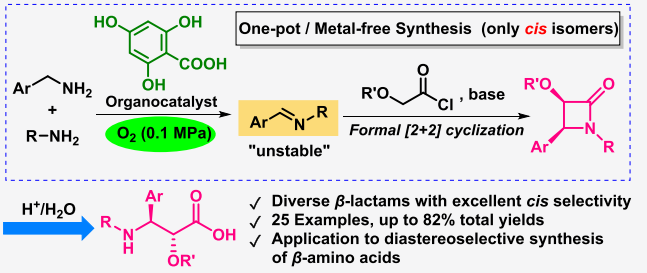
One-Pot Construction of Diverse β-Lactam Scaffolds via the Green Oxidation of Amines and Its Application to the Diastereoselective Synthesis of β-Amino Acids

Yuki Yamamoto, Shintaro Kodama,* Riku Nishimura, Akihiro Nomoto, Michio Ueshima, and Akiya Ogawa*

Cite This: https://doi.org/10.1021/acs.joc.1c01128 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

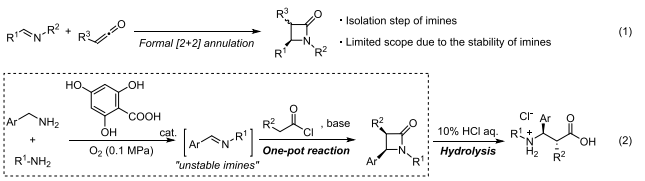
ABSTRACT: In this study, a simple one-pot construction of β-lactam scaffolds was successfully achieved via 4,6-dihydroxysalicylic acid-catalyzed organocatalytic oxidation of amines to imines using molecular oxygen. Although some imines are highly unstable and difficult to isolate by conventional methods, the organocatalytic oxidation of amines described herein, followed by their direct reaction with acyl chlorides in the presence of a base, afforded a series of new β-lactam derivatives with excellent *cis* selectivity, which could not be synthesized and isolated by previously reported methods. Thus, this one-pot protocol will be one of the powerful methods applicable to the synthesis of various potential drug candidates and functional molecules. Furthermore, the subsequent hydrolysis of these β-lactams successfully afforded the corresponding β-amino acids as almost single diastereomers in up to 99% yields.



INTRODUCTION

β-Lactams are important heterocycles used in the synthesis of antibiotics like penicillins and carbacephems, as well as the anticancer drug, paclitaxel (Taxol), and their demand is ever increasing (Figure 1).[1] In addition, β-lactams are important synthetic intermediates because they can be hydrolyzed to the corresponding amino acid derivatives.[2−11] From the viewpoint of diversity, it is highly desirable to develop new synthetic methods for constructing β-lactam derivatives that cannot be synthesized by conventional methods. In particular, new synthetic methods that give β-lactam derivatives intended for drug discovery should allow a wide range of substitution patterns while maintaining excellent stereoselectivity.[12]

Although various methods have been reported for the construction of β-lactam rings (including transition-metal-catalyzed reactions, carbonylations, and enolate-imine condensations),[13−45] Staudinger cycloaddition, which is a formal [2 + 2] cycloaddition of an imine and a ketene, is the most versatile method for fabricating β-lactam rings (eq 1).[46] This method requires highly pure imines, which are generally susceptible to hydrolysis. Thus, there are few reported examples of β-lactams with both aromatic and aliphatic substituents on their rings. To expand the scope of Staudinger cycloaddition and make it more atom-economical in the view of the full transformation from amines to β-lactams, the development of a one-pot method that incorporates the oxidative formation of imines from amines would be beneficial. One-pot reactions that generate unstable imines in situ can be applied to the synthesis of β-lactams with various functional groups. In addition, since the required purity of materials and pharmaceuticals has been increasing in recent years, metal residues in such products have become a serious problem; thus, synthetic methods using metal catalysts and reagents should be avoided. Considering this, metal-free synthetic methods employing mild conditions are in great demand.[47] However, there has only ever been one example of a metal-free, one-pot method involving the oxidative formation of imines from amines.[48] This method required stoichiometric amounts of the reagents for the successful oxidation of amines, and the



Received: May 13, 2021

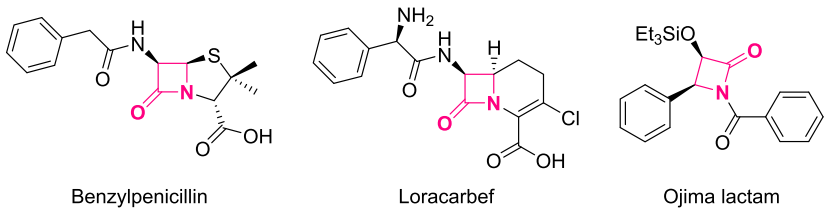
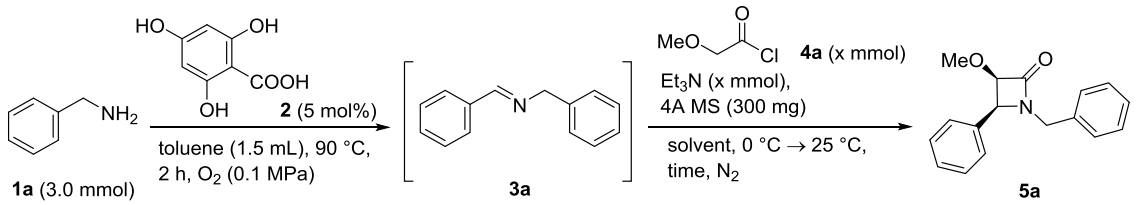


Figure 1. Examples of β-lactam-centered antibiotics and key intermediates in drug discovery.

Table 1. Optimization of Reaction Conditions for β-Lactam Synthesis via the Homocoupling of 1a[a]



entry	x (mmol)	solvent (mL)	time (h)	yield **5a** (%)
1	1.5	CH_3CN (5.0)	24	16
2	4.5	CH_3CN (5.0)	24	52
3	4.5	CH_3CN (3.0)	24	58
4	4.5	CH_3CN (1.5)	24	53
5	4.5	CH_3CN (3.0)	18	82 (72)
6	4.5	CH_3CN (3.0)	6	38
7	4.5	toluene (3.0)	18	50
8	4.5	CH_2Cl_2 (3.0)	18	51
9	4.5	THF (3.0)	18	34
10	4.5	1,4-dioxane (3.0)	18	69

[a]Yields were determined by ^{1}H NMR spectroscopy based on **1a** (isolated yield).

substrates were limited to commercially available secondary amines.

Recently, we have developed a method for oxidizing amines to imines using 4,6-dihydroxysalicyclic acid as an organocatalyst with molecular oxygen as a co-oxidant.[49] This method can be performed under metal-free and mild conditions, which promotes its utilization for metal-free/one-pot formations of functional scaffolds toward pharmaceutical and functional molecules.[50] We have already succeeded in using this catalytic oxidation of amines to synthesize triarylmethane derivatives,[50a] heterocycles,[50b] dipeptides,[50c] and 2,4,6-trisubstituted pyridines.[50d] In this study, we used this organocatalytic formation of imines from primary amines to develop a one-pot method for the synthesis of β-lactam derivatives under metal-free and mild conditions. Surprisingly, most of the β-lactams synthesized in this study were new compounds bearing aromatic and aliphatic groups on their rings. Moreover, the *cis* isomers of all of the products were afforded in moderate-to-good yields and with excellent stereoselectivity. Furthermore, while preserving their stereochemistry, β-lactams can be hydrolyzed to yield β-amino acids derivatives, which are important synthetic intermediates for functional peptides.[51] Therefore, we used this method in the diastereoselective synthesis of β-amino acids (eq 2).

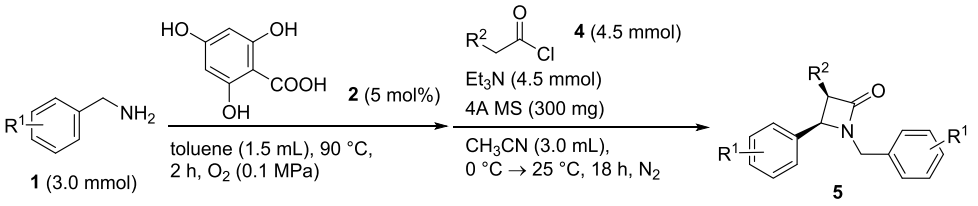
RESULTS AND DISCUSSION

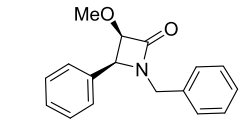
The homocoupling of benzylamine **1a** using trihydroxybenzoic acid (**2**) was conducted according to the method described in our previous paper.[49] After 4A MS (300 mg) was added to the reaction vessel to prevent the hydrolysis of imine **3a**, methoxyacetyl chloride (**4a**) in CH_3CN (5.0 mL) was added dropwise to the reaction mixture alongside Et_3N. The corresponding ketene was thus generated in situ by the dehydrochlorination of **4a**. The reaction mixture was then stirred at 25 °C for 24 h under an inert atmosphere to give the corresponding β-lactam (**5a**), which was obtained in a 16% yield based on the amount of **1a** (Table 1, entry 1). Surprisingly, only the *cis* isomer was produced in this reaction.[52] This result encouraged us to further optimize the reaction conditions (Table 1). When the amounts of **4a** and the base were increased from 1.5 mmol to 4.5 mmol, the yield of **5a** increased to 52% (entry 2). The concentration of **4a** in CH_3CN was also examined (entries 2−4), and the yield of **5a** was found to be optimal when 3.0 mL of CH_3CN was used (entry 3). The second step of the reaction was conducted for 18 h and **5a** was isolated in a 72% yield with excellent *cis* selectivity (entry 5). Reducing the reaction time of the second step to 6 h had no effect on the formation of **5a** (entry 6). The solvent used to dissolve **4a** in the second step was also investigated in detail, where CH_3CN was found to be the optimal solvent for the reaction (entry 5 vs entries 7−10).

Using the optimized reaction conditions (Table 1, entry 5), we then investigated the reaction scope of this β-lactam synthesis (Table 2).[52] A variety of benzylamine derivatives, such as *p*-methyl, *m*-methoxy, and *p*-methoxy benzylamines (**1c**, **1e**, and **1f**), could be oxidized under these conditions. The resultant imine derivatives formed in situ were then successfully reacted with ketenes to produce the corresponding β-lactams (**5c**, **5e**, and **5f**) in good overall yields. Although *p*-*tert*-butyl- and *o*-methoxy-benzylamines (**1b** and **1d**) were also oxidized to imines, the corresponding β-lactams (**5b** and **5d**) were obtained in only moderate yields due to the steric hinderance of the imines formed. Furthermore, the use of 1-

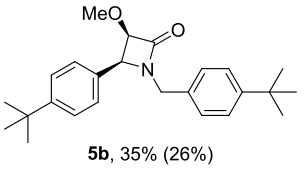
https://doi.org/10.1021/acs.joc.1c01128
J. Org. Chem. XXXX, XXX, XXX−XXX

Table 2. Reaction Scope of β-Lactam Synthesis via the Homocoupling of Benzylamines[a,b]

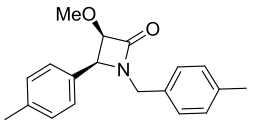




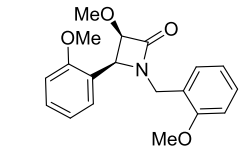
5a, 82% (72%)
67% (58%)[b]



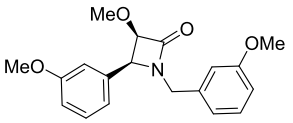
5b, 35% (26%)



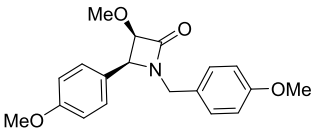
5c, 62% (61%)



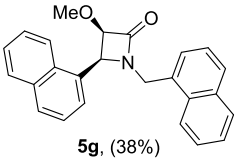
5d, 23% (10%)



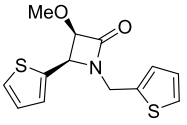
5e, 79% (65%)



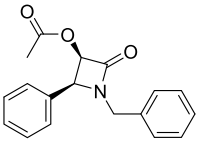
5f, 71% (66%)



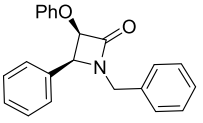
5g, (38%)



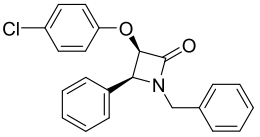
5h, 18% (12%)



5i, 61% (55%)



5j, 68% (42%)



5k, 68% (61%)
78%[b]

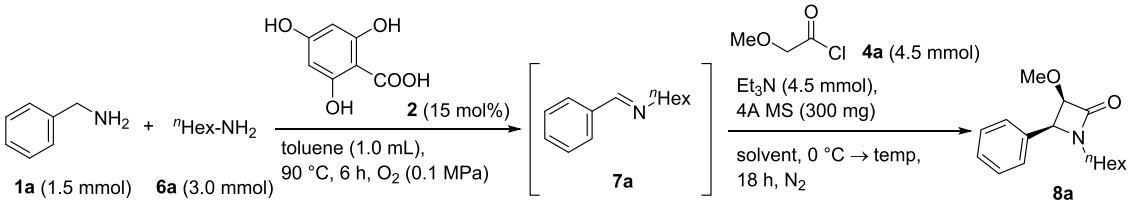
[a]Yields were determined by ^{1}H NMR spectroscopy based on **1** (isolated yields). [b]1st step: Benzylamine **1a** (10 mmol, 1.08 g), **2** (5 mol %), toluene (3.0 mL), 90 °C, 2 h, O_2 (0.1 MPa). 2nd step: **4** (15 mmol), Et_3N (15 mmol), 4A MS (1.0 g), CH_3CN (10 mL), 0 °C → 25 °C, and 18 h.

naphthylmethylamine (**1g**) and 2-thiophenemethylamine (**1h**) was also examined, and *cis*-products **5g** and **5h** were obtained in moderate overall yields. When acetoxyacetyl chloride (**4b**) was used in this reaction, **5i**, which bears an additional carbonyl group on its scaffold, was successfully obtained in a good yield. When phenoxyacetyl chloride (**4c**) and *p*-chlorophenylacetyl chloride (**4d**) were used in this reaction, **5j** and **5k**, respectively, were also obtained in reasonable yields. This method could be used to synthesize *cis*-**5a** and *cis*-**5k** in good yields on a gram scale. Although we have examined some acyl chlorides such as ones bearing a *t*-butyl or a phenyl group as the ketene precursor in this one-pot protocol, the corresponding β-lactams could not be obtained in a good yield, and further optimization is necessary. We consider that the stability of the corresponding ketenes is one of the important factors in the present one-pot protocol. Overall, Table 2 shows that this method led to the synthesis of novel β-lactam derivatives with high stereoselectivity.

To make the method more versatile, we attempted to synthesize β-lactams with three different substituents via the organocatalytic oxidative cross-condensation of two different amines (Table 3). We previously reported the 4,6-dihydroxysalicylic acid-catalyzed oxidative cross-condensation of benzylamines with other amines, which we applied in this work.[50c] In the first step of β-lactam synthesis, benzylamine **1a** and hexylamine (**6a**) were reacted in the presence of a catalytic amount of **2** under an O_2 atmosphere (0.1 MPa) to produce unsymmetrical imine **7a** in situ. This imine (**7a**) was reacted directly with the ketene derived from **4a** and Et_3N, and the resultant reaction mixture was stirred for 18 h to produce only the *cis* isomer of **8a** in a 42% yield (entry 1). Encouraged by this result, we further optimized the reaction conditions for the second step. Specifically, we found that increasing the concentration of **4a** resulted in a slight decrease in the yield of **8a** (entry 2). Moreover, the addition of $BF_3{\cdot}Et_2O$ (10 mol %) as a Lewis acid did not improve the reaction (entry 3). Furthermore, neither changing the amounts of **4a** and Et_3N from 4.5 to 7.5 mmol (entry 4) nor extending the reaction time to 72 h (entry 5) had any effect on the reaction. Surprisingly, the temperature of the second step was found to be important

https://doi.org/10.1021/acs.joc.1c01128
J. Org. Chem. XXXX, XXX, XXX−XXX

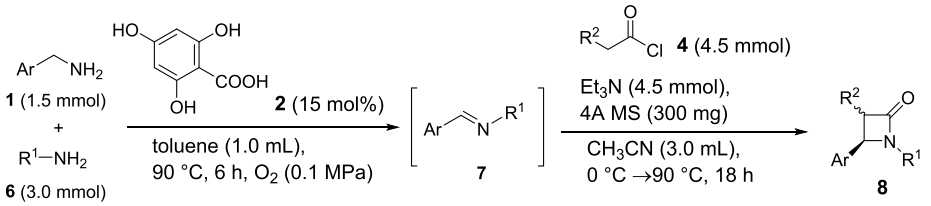
Table 3. Optimization of Reaction Conditions for β-Lactam Synthesis via the Oxidative Cross-Condensation of Two Different Amines[a]

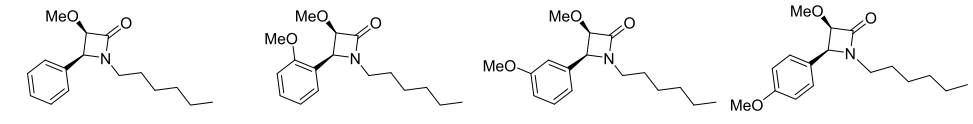


entry	solvent (mL)	temp (°C)	yield **8a** (%)
1	CH_3CN (3.0)	25	42
2	CH_3CN (1.5)	25	33
3[b]	CH_3CN (3.0)	25	39
4[c]	CH_3CN (3.0)	25	44
5[d]	CH_3CN (3.0)	25	43
6	CH_3CN (3.0)	90	53 (42)
7	1,4-dioxane (3.0)	100	40
8	DMF (3.0)	110	41
9	DMSO (3.0)	110	N. D.

[a]Yields were determined by ^{1}H NMR spectroscopy based on **1a** (isolated yield). [b]$BF_3{\cdot}Et_2O$ (10 mol %) was added. [c]**4a** (7.5 mmol) and Et_3N (7.5 mmol) were used. [d]Reaction time: 72 h.

Table 4. Scope of β-Lactam Synthesis via the Oxidative Cross-Condensation of Two Different Amines[a]

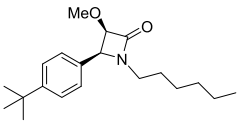


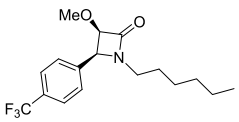

8a, 53% (42%)

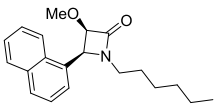
8b, (43%)

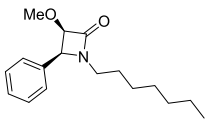
8c, (38%)

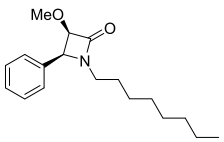
8d, 38% (36%)

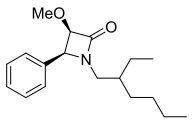

8e, 50% (45%)

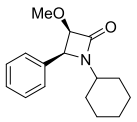

8f, 30% (27%)

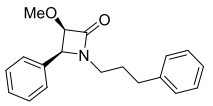

8g, (30%)

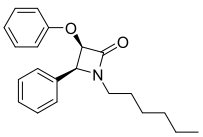

8h, 53% (43%)

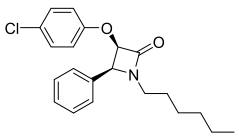

8i, 58% (58%)


8j, 32% (26%)


8k, 32% (31%)


8l, 34% (27%)


8m, 40% (18%)


8n, 40% (21%)

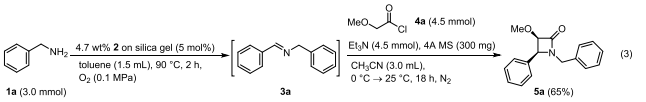
[a]Yields were determined by ^{1}H NMR based on **1** (isolated yields).

https://doi.org/10.1021/acs.joc.1c01128
J. Org. Chem. XXXX, XXX, XXX−XXX

for the formation of **8a**. When the second step was conducted at 90 °C, **8a** was formed in a 53% yield (entry 6). Although other solvents were examined to increase the reaction temperature in the second step (entries 6−9), CH_3CN was found to be the optimal solvent for the reaction (entry 6).

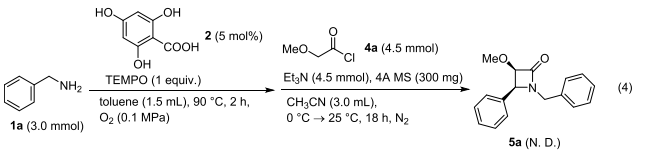
Using the optimized conditions (Table 3, entry 6), we next investigated the scope of the reaction for β-lactam synthesis by the organocatalytic oxidative cross-condensation of two different amines (Table 4). *o*-Methoxy-, *m*-methoxy-, *p*-methoxy-, *p*-*tert*-butyl-, and *p*-trifluoromethyl-benzylamines (**1b**−**1f**), as well as 1-naphthylmethanamine (**1g**), could be used to synthesize unsymmetrical imines (**7**) by oxidative cross-condensation with **6a**. The following reaction of the unsymmetrical imines (**7**; formed in situ) with ketenes yielded the corresponding β-lactams (**8a**−**8g**) in moderate-to-good yields. Compared to the reactions employing aliphatic amines (**6**) with shorter chains, the reactions conducted with aliphatic amines bearing longer chains (**6h** and **6i**) gave more stable imines that subsequently gave the corresponding β-lactams (**8h** and **8i**) in greater yields. 2-Ethylhexylamine (**6j**) and cyclohexylamine (**6k**) afforded β-lactams **8j** and **8k**, respectively. 3-Phenylpropylamine (**6l**), whose nitrogen atom bears a large substituent, could be converted to β-lactam **8l** in a moderate total yield. Several acyl chlorides, such as phenylacetyl chloride (**4m**) and *p*-chlorophenylacetyl chloride (**4n**), were also examined, and the corresponding desired β-lactams (**8m** and **8n**) were successfully obtained.

It is not surprising that the above multistep reaction (Tables 3 and 4) would produce many byproducts, but, in fact, few byproducts were obtained other than those listed below. The main byproduct was the amide compounds produced by the reaction of unreacted amines with ketenes generated from acyl chlorides and Et_3N. In addition, the unsymmetrical imines produced in situ were susceptible to hydrolysis under the reaction conditions, and therefore, some of them were converted into the corresponding aldehydes. However, the present one-pot protocol does not need the isolation of such unstable imines and could afford a variety of new β-lactams with aromatic and aliphatic groups on the rings with excellent *cis* selectivity in moderate-to-good total yields. In the 1st step of the present one-pot protocol, oxidation of benzylamines to



the corresponding imines could be conducted under mild reaction conditions with excellent reaction selectivity, whereas aliphatic amines were hardly converted to imines under the same mild conditions. Therefore, the present reaction enables the selective formation of symmetrical and unsymmetrical imines having the aryl groups derived from benzylamines. From the viewpoints of the utilization in pharmaceutical fields, β-lactam that contains an aryl group on the ring is among the potentially important compounds. Thus, this method can easily provide a variety of β-lactams for practical utilization in drug discovery.

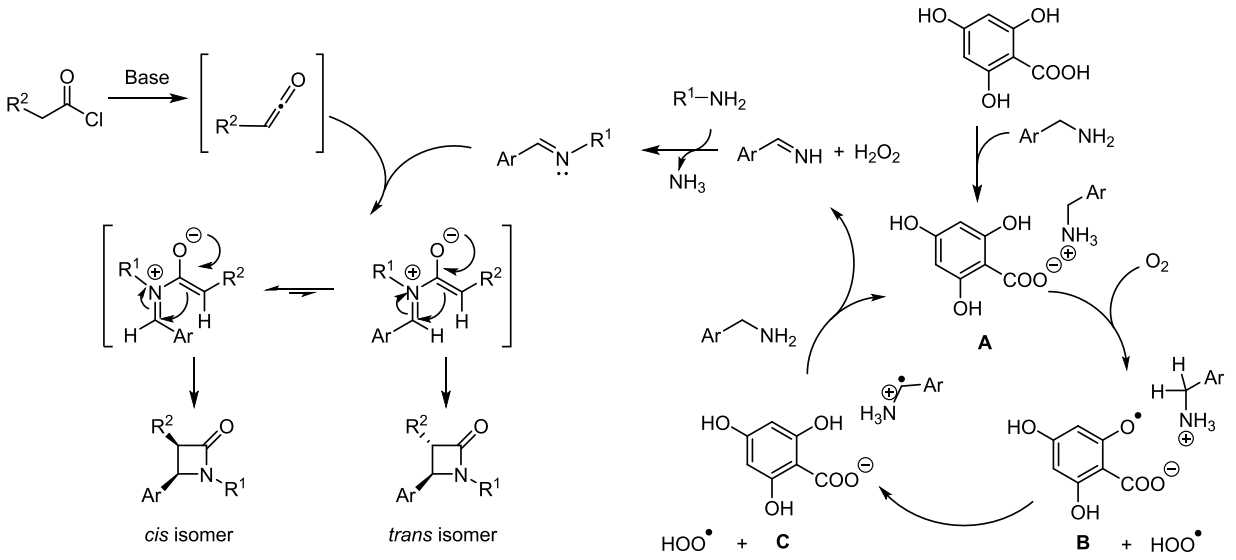
It should be noted that all of the products (Tables 2 and 4) were obtained with excellent *cis* selectivity (*cis* isomers only),



and most of them were synthesized and isolated for the first time in this work by our developed method.

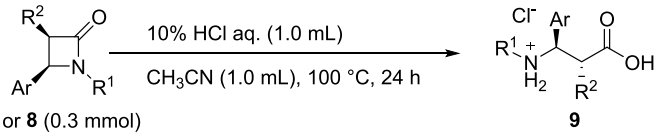
The present one-pot synthesis of β-lactams could also be conducted using 4,6-dihydroxysalicylic acid supported on a silica gel as a catalyst. As shown in eq 3, 5 mol % silica gel-supported catalyst (4.7 wt % **2** on silica gel) was used for the oxidation of benzylamine **1a** (3.0 mmol) under atmospheric oxygen in the first step.[49] Then, in the second step, methoxyacetyl chloride **4a** (4.5 mmol), Et_3N (4.5 mmol), and 4A MS (300 mg) were added, and the reaction mixture was stirred at 25 °C for 18 h. To our delight, this protocol successfully afforded the corresponding β-lactam **5a** in 65% yields with excellent *cis* selectivity. To gain insight into the reaction pathway, an additional experiment was conducted. In our previous report, this salicylic acid-catalyzed oxidation system might involve a radical reaction because the oxidation

Scheme 1. Proposed Reaction Pathways for the Organocatalytic Oxidative Formation of β-Lactams

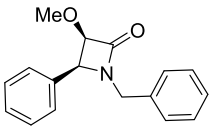
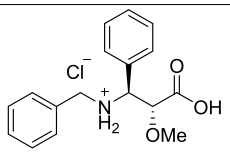
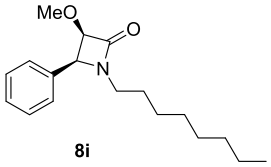
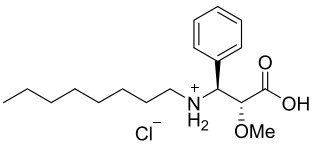


https://doi.org/10.1021/acs.joc.1c01128
J. Org. Chem. XXXX, XXX, XXX−XXX

Table 5. Application of the Developed Method to the Diastereoselective Synthesis of β-Amino Acids[a]



5 or **8** (0.3 mmol) **9**

Entry	Substrate	Product	Yield (%)
1	 **5a**	 **9a**	99
2	 **8i**	 **9b**	92

[a]Isolated yields.

of benzylamine did not proceed smoothly in the presence of TEMPO as a radical scavenger.[49] Similarly, the formation of β-lactam was completely inhibited by adding 1 equiv of TEMPO. These results clearly indicate that the present β-lactam synthesis, especially the organocatalytic oxidative imination of benzylamines, involves the radical pathway. Based on the results of previous studies[49,50] and the reported mechanisms of Staudinger cycloadditions using imines and ketenes,[53] a reaction pathway was proposed herein (Scheme 1). The key catalytic species is the corresponding salt generated from a salicylic acid catalyst and benzylamine. As to the synthesis of imines, the salt-forming salicylic acid reacts with oxygen to generate the corresponding phenoxy radicals, which might abstract hydrogen from the salt-forming benzylamine to form phenylmethanimine, which could react with another amine to give the corresponding symmetrical or unsymmetrical imines:[49,50c] Namely, benzylamine (**1**) reacts with 4,6-dihydroxysalicylic acid to produce salt **A** at first, which is then activated under an O_2 atmosphere to form phenoxy radical **B**. The radical species (**B**) abstracts $H^{\bullet}$ from **1** to generate **C**, and the concomitantly formed $HOO^{\bullet}$ abstracts $H^{\bullet}$ from another molecule of **1** to produce the corresponding imine, together with the regeneration of the salicylic acid catalyst. The subsequent amino group exchange reaction with another amine yields the corresponding symmetrical (**3**) or unsymmetrical (**7**) imines. In the second step, the imine formed in situ reacts with the ketene generated by the dehydrochlorination of the acyl chloride (**4**) by the base, producing zwitterionic intermediates. Subsequent intramolecular cyclization forms the desired β-lactam scaffold (**8**). The stereoselectivity of the β-lactams is affected by the structure and stability of a zwitterion.[53−57] When an electron-donating alkoxy group is substituted on a ketene, the zwitterion becomes unstable and the cyclization is promoted, resulting in the selective formation of *cis* β-lactams based on kinetic control.

Furthermore, we calculated the E-factor for the present one-pot method for the synthesis of β-lactam from amine and compared it with several other known methods. The results indicated that the one-pot protocol presented in this study has a much lower E-factor than those of the known methods. The E-factor was sufficiently low not only in the case of β-lactam synthesis via homocoupling of two amines (E-factor = 14.0) but also in the case of β-lactam synthesis via cross-coupling (E-factor = 21.5, see Scheme S1 in the Supporting Information). Furthermore, if the silica gel-supported organocatalyst described above is used, the E-factor of this system is expected to further reduce because the organocatalyst can be recycled. From these insights, the present one-pot method is environmentally friendly and less wasteful for the conversion of amine to β-lactam.

In this study, various novel β-lactam derivatives could be synthesized with excellent *cis* selectivity. Therefore, as a powerful synthetic application of this method, we next investigated the diastereoselective synthesis of β-amino acids by the hydrolysis of these β-lactam derivatives (Table 5). β-Lactams could be hydrolyzed to the corresponding β-amino acids while maintaining the stereochemistry of the C_2 and C_3 positions of the fused rings. Therefore, β-lactams **5a** or **8i**, synthesized and isolated in this study, were directly reacted with 10% HCl aq. (1.0 mL) in CH_3CN (1.0 mL) at 100 °C for 24 h. As expected, the corresponding β-amino acids (**9a** and **9b**) were obtained in excellent yields as single diastereomers.

CONCLUSIONS

We have developed a simple, metal-free, one-pot method for the synthesis of β-lactam derivatives that comprises the 4,6-dihydroxysalicylic acid-catalyzed oxidative condensation of primary amines to generate imines. This method does not include an imine isolation step, making the system environmentally friendly and versatile in its reaction scope. Using this method, a variety of new β-lactam derivatives were synthesized with excellent *cis* selectivity, which could not be synthesized and isolated by previously reported methods. Thus, this one-pot protocol will be one of the powerful methods applicable to

https://doi.org/10.1021/acs.joc.1c01128
J. Org. Chem. XXXX, XXX, XXX−XXX

the synthesis of various potential drug candidates and functional molecules. Furthermore, our protocol was extended to the gram scale and diastereoselective synthesis of β-amino acids was successfully achieved via hydrolysis of the β-lactam derivatives constructed by our protocol. The reactions demonstrated, herein, highlight the importance and convenience of β-lactam derivatives as synthetic intermediates in chemical and pharmaceutical fields.

EXPERIMENTAL SECTION

General Remarks. Unless otherwise stated, all starting materials and catalysts were purchased from commercial sources and used without further purification. All solvents were distilled and degassed with nitrogen before use. The 4.7 wt % 4,6-dihydroxysalicylic acid **2** on a silica gel was synthesized by a previously reported method.[49] ^{1}H NMR spectra were recorded on a JEOL JNM-ECS400 (400 MHz) FT NMR system or a JEOL JNM-ECX400 (400 MHz) FT NMR system in $CDCl_3$ with Me_4Si as an internal standard. ^{13}C NMR spectra were recorded on a JEOL JNM-ECX400 (100 MHz) FT NMR or a JEOL JNM-ECS400 (100 MHz) FT NMR in $CDCl_3$. High-resolution mass spectroscopy (HRMS) was conducted on a Bruker micrOTOF II ESI/TOF analyzer or Waters Synapt G2 HDMS.

General Procedure for the Synthesis of β-Lactams via Homocoupling of Amines (Table 2). Benzylamines **1** (3.0 mmol), 2,4,6-trihydroxybenzoic acid monohydrate (28.2 mg, 0.15 mmol, 5 mol %), and toluene (1.5 mL) were added to a 20 mL two-neck flask equipped with an O_2 balloon at room temperature and stirred at 90 °C in an oil bath under an O_2 atmosphere for 2 h. Then, the O_2 balloon was removed and the reaction mixture was cooled to room temperature. To the reaction mixture, 4A MS (300 mg) and Et_3N (627 μL, 4.5 mmol, 1.5 equiv) were added, and acyl chloride **4** (4.5 mmol, 1.5 equiv) in CH_3CN (3.0 mL) was added dropwise at 0 °C. The resulting solution was stirred at 25 °C for 18 h under a N_2 atmosphere. After the reaction was finished, the resulting mixture was filtered and the filtrate was extracted with AcOMe (10 mL). The organic layer was washed with H_2O (10 mL × 2) and brine (10 mL) and dried with anhydrous Na_2SO_4. The solvent was concentrated under reduced pressure. Finally, the residue was purified by silica-gel chromatography (AcOMe/*iso*-hexane) and gel permeation chromatography (eluent: CH_2Cl_2) to give product **5**.

*(±)-cis-1-Benzyl-3-methoxy-4-phenylazetidin-2-one (**5a**).*[48] Colorless oil, 286.5 mg, 72%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.34 (m, 3H), 7.30−7.26 (m, 5H), 7.12 (m, 2H), 4.82 (d, *J* = 14.7 Hz, 1H), 4.66 (d, *J* = 4.6 Hz, 1H), 4.56 (d, *J* = 4.6 Hz, 1H), 3.81 (d, *J* = 15.1 Hz, 1H), 3.09 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 166.9, 135.0, 133.5, 128.9, 128.70, 128.69, 128.6, 128.5, 127.9, 85.9, 61.1, 58.2, 44.0.

*(±)-cis-1-(4-(tert-Butyl)benzyl)-4-(4-(tert-butyl)phenyl)-3-methoxyazetidin-2-one (**5b**).* Yellow oil, 149.1 mg, 26%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40−7.36 (m, 2H), 7.32−7.29 (m, 2H), 7.23−7.20 (m, 2H), 7.08−7.06 (m, 2H), 4.79 (d, *J* = 14.5 Hz, 1H), 4.64 (d, *J* = 4.5 Hz, 1H), 4.58 (d, *J* = 4.5 Hz, 1H), 3.78 (d, *J* = 15.0 Hz, 1H), 3.12 (s, 3H), 1.33 (s, 9H), 1.30 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 167.0, 151.6, 150.8, 132.2, 130.4, 128.4, 128.3, 125.7, 125.4, 85.8, 60.8, 58.3, 43.5, 34.7, 34.6, 31.42, 31.41; HRMS (ESI) *m*/*z* calcd for $C_{25}H_{33}NNaO_2$ [M + Na]$^+$: 402.2409, found: 402.2408.

*(±)-cis-3-Methoxy-1-(4-methylbenzyl)-4-(p-tolyl)azetidin-2-one (**5c**).* White solid, 271.4 mg, 61%, mp 63.2−64.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18 (s, 4H), 7.10 (d, *J* = 7.8 Hz, 2H), 7.01 (d, *J* = 8.2 Hz, 2H), 4.80 (d, *J* = 14.7 Hz, 1H), 4.61 (d, *J* = 4.1 Hz, 1H), 4.51 (d, *J* = 4.6 Hz, 1H), 3.73 (d, *J* = 14.7 Hz, 1H), 3.11 (s, 3H), 2.37 (s, 3H), 2.32 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 166.9, 138.5, 137.6, 132.0, 130.4, 129.5, 129.3, 128.6, 128.5, 85.8, 60.7, 58.2, 43.5, 21.3, 21.2; HRMS (ESI) *m*/*z* calcd for $C_{19}H_{21}NNaO_2$ [M + Na]$^+$: 318.1470, found: 318.1473.

*(±)-cis-3-Methoxy-1-(2-methoxybenzyl)-4-(2-methoxyphenyl)-azetidin-2-one (**5d**).* Yellow solid, 51.3 mg, 10%, mp 98.0−99.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30−7.22 (m, 3H), 7.14 (dd, *J* = 7.5, 1.6 Hz, 1H), 6.98 (t, *J* = 7.5 Hz, 1H), 6.87 (t, *J* = 7.2 Hz, 2H), 6.78 (d, *J* = 8.2 Hz, 1H), 5.05 (d, *J* = 4.5 Hz, 1H), 4.76 (d, *J* = 14.5 Hz, 1H), 4.65 (d, *J* = 4.5 Hz, 1H), 4.09 (d, *J* = 14.5 Hz, 1H), 3.78 (s, 3H), 3.62 (s, 3H), 3.12 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 167.5, 157.6, 157.5, 130.4, 129.3, 128.9, 128.3, 123.5, 122.8, 120.6, 120.5, 110.23, 110.17, 85.8, 58.3, 56.2, 55.4, 55.0, 39.5; HRMS (ESI) *m*/*z* calcd for $C_{19}H_{21}NNaO_4$ [M + Na]$^+$: 350.1368, found: 350.1366.

*(±)-cis-3-Methoxy-1-(3-methoxybenzyl)-4-(3-methoxyphenyl)-azetidin-2-one (**5e**).* Yellow oil, 321.0 mg, 65%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (t, *J* = 8.0 Hz, 1H), 7.20 (t, *J* = 7.7 Hz, 1H), 6.90−6.87 (m, 2H), 6.82−6.79 (m, 2H), 6.71 (d, *J* = 7.7 Hz, 1H), 6.66 (t, *J* = 1.8 Hz, 1H), 4.78 (d, *J* = 14.5 Hz, 1H), 4.66 (d, *J* = 4.1 Hz, 1H), 4.56 (d, *J* = 4.1 Hz, 1H), 3.83 (d, *J* = 15.0 Hz, 1H), 3.78 (s, 3H), 3.75 (s, 3H), 3.13 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 166.8, 160.0, 159.8, 136.5, 135.2, 129.9, 129.5, 120.9 (overlapped), 114.2, 114.1, 113.9, 113.6, 85.9, 61.2, 58.3, 55.33, 55.29, 44.1; HRMS (ESI) *m*/*z* calcd for $C_{19}H_{21}NNaO_4$ [M + Na]$^+$: 350.1368, found: 350.1366.

*(±)-cis-3-Methoxy-1-(4-methoxybenzyl)-4-(4-methoxyphenyl)-azetidin-2-one (**5f**).* Colorless oil, 326.2 mg, 66%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23−7.19 (m, 2H), 7.05-7.02 (m, 2H), 6.92−6.88 (m, 2H), 6.83-6.80 (m, 2H), 4.73 (d, *J* = 15.0 Hz, 1H), 4.60 (d, *J* = 4.5 Hz, 1H), 4.49 (d, *J* = 4.5 Hz, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 3.74 (d, *J* = 14.5 Hz, 1H), 3.11 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 166.8, 159.9, 159.3, 130.0, 129.8, 127.1, 125.3, 114.2, 113.9, 85.7, 60.4, 58.2, 55.3 (overlapped), 43.2; HRMS (ESI) *m*/*z* calcd for $C_{19}H_{21}NNaO_4$ [M + Na]$^+$: 350.1368, found: 350.1375.

*(±)-cis-3-Methoxy-4-(naphthalen-1-yl)-1-(naphthalen-1-ylmethyl)azetidin-2-one (**5g**).* Light yellow solid, 206.6 mg, 38%, mp 125.2−126.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13-8.09 (m, 1H), 7.89-7.84 (m, 3H), 7.76 (d, *J* = 8.2 Hz, 1H), 7.63 (dd, *J* = 11.4, 7.8 Hz, 2H), 7.55 (d, *J* = 7.8 Hz, 1H), 7.52−7.48 (m, 2H), 7.46 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.41−7.37 (m, 1H), 7.20 (dd, *J* = 8.1, 7.0 Hz, 1H), 7.07 (d, *J* = 6.4 Hz, 1H), 5.51 (d, *J* = 14.7 Hz, 1H), 5.13 (d, *J* = 4.6 Hz, 1H), 4.72 (d, *J* = 4.6 Hz, 1H), 4.40 (d, *J* = 14.7 Hz, 1H), 2.95 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 167.0, 134.0, 133.8, 131.5, 131.4, 130.4, 129.5, 129.2, 129.1, 128.9, 128.8, 128.4, 127.1, 126.4, 126.3, 125.8, 125.44, 125.35, 125.2, 123.6, 122.2, 86.3, 58.9, 57.6, 42.4; HRMS (ESI) *m*/*z* calcd for $C_{25}H_{21}NNaO_2$ [M + Na]$^+$: 390.1470, found: 390.1475.

*(±)-cis-3-Methoxy-4-(thiophen-2-yl)-1-(thiophen-2-ylmethyl)-azetidin-2-one (**5h**).* Yellow oil, 51.6 mg, 12%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (dd, *J* = 5.0, 0.9 Hz, 1H), 7.24 (dd, *J* = 5.0, 1.4 Hz, 1H), 7.09−7.07 (m, 1H), 7.05 (dd, *J* = 5.0, 3.6 Hz, 1H), 6.94 (dd, *J* = 5.2, 3.4 Hz, 1H), 6.85 (d, *J* = 3.2 Hz, 1H), 4.96 (d, *J* = 4.5 Hz, 1H), 4.92 (d, *J* = 15.4 Hz, 1H), 4.68 (d, *J* = 4.1 Hz, 1H), 4.10 (d, *J* = 15.4 Hz, 1H), 3.25 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 165.8, 137.0, 136.4, 128.1, 127.4, 127.23, 127.18, 126.9, 126.0, 85.8, 58.6, 56.7, 38.0; HRMS (ESI) *m*/*z* calcd for $C_{13}H_{13}NNaO_2S_2$ [M + Na]$^+$: 302.0285, found: 302.0300.

*(±)-cis-1-Benzyl-2-oxo-4-phenylazetidin-3-yl acetate (**5i**).*[58] Colorless oil, 242.1 mg, 55%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36−7.34 (m, 3H), 7.31−7.28 (m, 3H), 7.21 (dd, *J* = 7.1, 3.0 Hz, 2H), 7.14 (dd, *J* = 7.1, 2.1 Hz, 2H), 5.77 (d, *J* = 4.6 Hz, 1H), 4.88 (d, *J* = 14.7 Hz, 1H), 4.75 (d, *J* = 4.6 Hz, 1H), 3.91 (d, *J* = 14.7 Hz, 1H), 1.65 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 169.2, 164.8, 134.5, 132.5, 129.0, 128.9, 128.6, 128.5, 128.4, 128.2, 77.5, 61.0, 44.6, 19.9.

*(±)-cis-1-Benzyl-3-phenoxy-4-phenylazetidin-2-one (**5j**).*[48] White solid, 209.0 mg, 42%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33−7.26 (m, 8H), 7.17−7.15 (m, 2H), 7.11−7.06 (m, 2H), 6.86−6.82 (m, 1H), 6.71−6.69 (m, 2H), 5.39 (d, *J* = 4.6 Hz, 1H), 4.89 (d, *J* = 14.7 Hz, 1H), 4.75 (d, *J* = 4.6 Hz, 1H), 3.86 (d, *J* = 14.7 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 165.7, 157.0, 134.8, 132.8, 129.3, 129.0, 128.80, 128.77, 128.4, 128.1, 122.1, 115.6, 114.8, 82.2, 61.5, 44.3.

*(±)-cis-1-Benzyl-3-(4-chlorophenoxy)-4-phenylazetidin-2-one (**5k**).* White solid, 333.4 mg, 61%, mp 125.8−126.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33−7.23 (m, 8H), 7.16−7.14 (m, 2H), 7.06−7.02 (m, 2H), 6.66−6.62 (m, 2H), 5.34 (d, *J* = 4.5 Hz, 1H), 4.89 (d, *J* = 15.0 Hz, 1H), 4.74 (d, *J* = 4.5 Hz, 1H), 3.87 (d, *J* = 15.0 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 165.3, 155.5, 134.7, 132.5, 129.2, 129.01, 128.95, 128.75, 128.70, 128.5, 128.2, 127.0, 116.9, 82.2,

https://doi.org/10.1021/acs.joc.1c01128
J. Org. Chem. XXXX, XXX, XXX−XXX

61.3, 44.3; HRMS (ESI) m/z calcd for $C_{22}H_{18}ClNNaO_2$ $[M + Na]^+$: 386.0924, found: 386.0929.

Gram-Scale Synthesis of β-Lactams via Oxidative Coupling of Benzylamine (Tables 2, 5a). Benzylamine **1a** (10.0 mmol, 1.08 g), 2,4,6-trihydroxybenzoic acid monohydrate (5 mol %), and toluene (3 mL) were added to a 50 mL two-neck flask equipped with an O_2 balloon at room temperature and stirred at 90 °C in an oil bath under an O_2 atmosphere for 2 h. Then, the O_2 balloon was removed and the reaction mixture was cooled to room temperature. To the reaction mixture, 4A MS (1.0 g) and Et_3N (15 mmol, 1.5 equiv) were added, and methoxyacethyl chloride **4a** (15 mmol, 1.5 equiv) in CH_3CN (10 mL) was added dropwise at 0 °C. The resulting solution was stirred at 25 °C for 18 h under a N_2 atmosphere. After the reaction was finished, the resulting mixture was filtered and the filtrate was extracted with AcOMe (30 mL). The organic layer was washed with H_2O (30 mL × 2) and brine (30 mL) and dried with anhydrous Na_2SO_4. The solvent was concentrated under reduced pressure. Finally, the residue was purified by silica-gel chromatography (AcOMe/*iso*-hexane) to give product **5a** (colorless oil, 0.7789 g, 58%).

General Procedure for the Synthesis of β-Lactams via Cross-Coupling of Amines (8). Benzylamines **1** (1.5 mmol), amines **2** (3.0 mmol), 2,4,6-trihydroxybenzoic acid monohydrate (42.3 mg, 0.225 mmol, 15 mol %), and toluene (1.0 mL) were added to a 20 mL two-neck flask equipped with an O_2 balloon at room temperature and stirred at 90 °C in an oil bath under an O_2 atmosphere for 6 h. Then, the O_2 balloon was removed and the reaction mixture was cooled to room temperature. To the reaction mixture, 4A MS (300 mg) and Et_3N (627 μL, 4.5 mmol, 3 equiv) were added, and acyl chloride **4** (4.5 mmol, 3 equiv) in CH_3CN (3.0 mL) was added dropwise at 0 °C. The resulting solution was stirred at 90 °C in an oil bath under a N_2 atmosphere for 18 h. After the reaction was finished, the resulting mixture was filtered and the filtrate was extracted with AcOMe (10 mL). The organic layer was washed with H_2O (10 mL×2) and brine (10 mL) and dried with anhydrous Na_2SO_4. The solvent was concentrated under reduced pressure. Finally, the residue was purified by silica-gel chromatography (AcOMe/*iso*-hexane) and gel permeation chromatography (eluent: CH_2Cl_2) to give product **8**.

*(±)-cis-1-Hexyl-3-methoxy-4-phenylazetidin-2-one (**8a**).* Yellow oil, 164.4 mg. 42%; ^1H NMR (400 MHz, $CDCl_3$): δ 7.41−7.33 (m, 5H), 4.73 (d, J = 4.6 Hz, 1H), 4.68 (d, J = 4.1 Hz, 1H), 3.48-3.41 (m, 1H), 3.10 (s, 3H), 2.92−2.85 (m, 1H), 1.49−1.41 (m, 2H), 1.28−1.23 (m, 6H), 0.87−0.83 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 167.2, 134.0, 128.7, 128.5 (overlapped), 85.6, 61.9, 58.2, 40.3, 31.4, 27.4, 26.8, 22.5, 14.0; HRMS (ESI) m/z calcd for $C_{16}H_{23}NNaO_2$ $[M + Na]^+$: 284.1626, found: 284.1624.

*(±)-cis-1-Hexyl-3-methoxy-4-(2-methoxyphenyl)azetidin-2-one (**8b**).* Yellow oil, 188.5 mg, 43%; ^1H NMR (400 MHz, $CDCl_3$): δ 7.34−7.26 (m, 2H), 7.01 (t, J = 7.5 Hz, 1H), 6.91 (d, J = 8.2 Hz, 1H), 5.22 (d, J = 4.5 Hz, 1H), 4.69 (d, J = 4.5 Hz, 1H), 3.86 (s, 3H), 3.57−3.49 (m, 1H), 3.13 (s, 3H), 2.93−2.86 (m, 1H), 1.54−1.43 (m, 2H), 1.31−1.22 (m, 6H), 0.89−0.82 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 167.6, 157.6, 129.2, 128.4, 122.5, 120.6, 110.3, 85.6, 58.3, 55.7, 55.5, 40.3, 31.4, 27.3, 26.7, 22.6, 14.1; HRMS (ESI) m/z calcd for $C_{17}H_{25}NNaO_3$ $[M + Na]^+$: 314.1732, found: 314.1733.

*(±)-cis-1-Hexyl-3-methoxy-4-(3-methoxyphenyl)azetidin-2-one (**8c**).* Yellow oil, 165.6 mg, 38%; ^1H NMR (400 MHz, $CDCl_3$):δ 7.28−7.32 (m, 1H), 6.87−6.94 (m, 3H), 4.70 (d, J = 4.5 Hz, 1H), 4.67 (d, J = 4.5 Hz, 1H), 3.82 (s, 3H), 3.41−3.49 (m, 1H), 3.13 (s, 3H), 2.91 (m, 1H), 1.42−1.50 (m, 2H), 1.20−1.29 (m, 6H), 0.85 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 167.1, 159.7, 135.7, 129.5, 120.8, 114.1, 113.9, 85.6, 61.8, 58.3, 55.4, 40.3, 31.4, 27.4, 26.8, 22.6, 14.0; HRMS (ESI) m/z calcd for $C_{17}H_{25}NNaO_3$ $[M + Na]^+$: 314.1732, found: 314.1731.

*(±)-cis-1-Hexyl-3-methoxy-4-(4-methoxyphenyl)azetidin-2-one (**8d**).* Yellow oil, 158.7 mg, 36%; ^1H NMR (400 MHz, $CDCl_3$):δ 7.27 (td, J = 5.8, 3.4 Hz, 2H), 6.92 (dt, J = 9.2, 2.4 Hz, 2H), 4.68 (d, J = 4.1 Hz, 1H), 4.64 (d, J = 4.1 Hz, 1H), 3.82 (s, 3H), 3.37−3.47 (m, 1H), 3.11 (s, 3H), 2.83−2.93 (m, 1H), 1.38−1.48 (m, 2H), 1.18−1.28 (m, 6H), 0.85 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 167.2, 159.9, 129.7, 125.8, 113.9, 85.5, 61.4, 58.1, 55.3, 40.1, 31.4, 27.4, 26.8, 22.6, 14.0; HRMS (ESI) m/z calcd for $C_{17}H_{25}NNaO_3$ $[M + Na]^+$: 314.1732, found: 314.1734.

*(±)-cis-4-(4-(tert-Butyl)phenyl)-1-hexyl-3-methoxyazetidin-2-one (**8e**).* Yellow oil, 209.9 mg, 45%; ^1H NMR (400 MHz, $CDCl_3$): δ 7.39 (dt, J = 8.5, 1.9 Hz, 2H), 7.25−7.27 (m, 2H), 4.71 (d, J = 4.1 Hz, 1H), 4.66 (d, J = 4.6 Hz, 1H), 3.44 (m, 1H), 3.12 (s, 3H), 2.84−2.91 (m, 1H), 1.41−1.48 (m, 2H), 1.33 (s, 9H), 1.19−1.28 (m, 6H), 0.85 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 167.3, 151.6, 130.8, 128.1, 125.4, 85.5, 61.6, 58.2, 40.2, 34.7, 31.4, 27.4, 26.7, 22.5, 14.1; HRMS (ESI) m/z calcd for $C_{20}H_{31}NNaO_2$ $[M + Na]^+$: 340.2252, found: 340.2255.

*(±)-cis-1-Hexyl-3-methoxy-4-(4-(trifluoromethyl)phenyl)-azetidin-2-one (**8f**).* Colorless oil, 134.0 mg, 27%; ^1H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, J = 8.2 Hz, 2H), 7.48 (d, J = 8.2 Hz, 2H), 4.80 (d, J = 4.1 Hz, 1H), 4.72 (d, J = 4.1 Hz, 1H), 3.42−3.49 (m, 1H), 3.14 (s, 3H), 2.85−2.92 (m, 1H), 1.39−1.50 (m, 2H), 1.18−1.30 (m, 6H), 0.85 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 167.0, 138.4, 131.0, 128.8, 125.5, 125.4, 85.7, 61.4, 58.4, 40.5, 31.3, 27.4, 26.7, 22.5, 14.0; HRMS (ESI) m/z calcd for $C_{17}H_{22}F_3NNaO_2$ $[M + Na]^+$: 352.1500, found: 352.1492.

*(±)-cis-1-Hexyl-3-methoxy-4-(naphthalen-1-yl)azetidin-2-one (**8g**).* Yellow oil, 140.8 mg, 30%; ^1H NMR (400 MHz, $CDCl_3$): δ 8.02 (d, J = 8.2 Hz, 1H), 7.92 (d, J = 8.2 Hz, 1H), 7.85 (d, J = 7.7 Hz, 1H), 7.50−7.59 (m, 4H), 5.60 (d, J = 4.5 Hz, 1H), 4.91 (d, J = 4.5 Hz, 1H), 3.67 (dt, J = 15.0, 7.0 Hz, 1H), 2.96−3.06 (overlapped: 1H (m) and 3H (s)), 1.50−1.58 (m, 2H), 1.22−1.32 (m, 7H), 0.85 (t, J = 6.8 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 167.1, 133.5, 131.2, 129.5, 128.9, 128.3, 126.2, 125.5, 125.1, 124.7, 121.8, 85.9, 58.5, 58.0, 40.3, 31.0, 27.0, 26.5, 22.2, 13.7; HRMS (ESI) m/z calcd for $C_{20}H_{25}NNaO_2$ $[M + Na]^+$: 334.1783, found: 334.1781.

*(±)-cis-1-Heptyl-3-methoxy-4-phenylazetidin-2-one (**8h**).* Brown oil, 177.9 mg, 43%; ^1H NMR (400 MHz, $CDCl_3$): δ 7.41−7.33 (m, 5H), 4.74 (d, J = 4.5 Hz, 1H), 4.68 (d, J = 4.5 Hz, 1H), 3.48−3.41 (m, 1H), 3.10 (s, 3H), 2.93−2.86 (m, 1H), 1.46−1.43 (m, 2H), 1.27−1.22 (m, 8H), 0.87-0.84 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 167.3, 134.0, 128.7, 128.5, 127.0, 85.5, 61.9, 58.2, 40.3, 31.7, 28.8, 27.4, 27.0, 22.6, 14.1; HRMS (ESI) m/z calcd for $C_{17}H_{25}NNaO_2$ $[M + Na]^+$: 298.1783, found: 298.1784.

*(±)-cis-1-Octyl-3-methoxy-4-phenylazetidin-2-one (**8i**).* Brown solid, 252.3 mg, 58%, mp 31.0−32.0 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.38−7.36 (m, 5H), 4.74 (d, J = 3.6 Hz, 1H), 4.69 (d, J = 3.6 Hz, 1H), 4.06-4.06 (m, 1H), 3.47-3.43 (m, 2H), 3.10 (s, 3H), 2.93−2.86 (m, 1H), 1.44−1.44 (m, 1H), 1.22−1.22 (m, 9H), 0.88−0.85 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 167.4, 133.9, 128.7, 128.5, 128.3, 85.4, 61.9, 58.2, 40.3, 31.8, 29.2, 29.1, 27.4, 27.1, 22.7, 14.1; HRMS (ESI) m/z calcd for $C_{18}H_{27}NNaO_2$ $[M + Na]^+$: 312.1939, found: 312.1935.

*(±)-cis-1-(2-Ethylhexyl)-3-methoxy-4-phenylazetidin-2-one (**8j**).* Yellow oil, 111.0 mg, 26%; ^1H NMR (400 MHz, $CDCl_3$): δ 7.32−7.42 (m, 5H), 4.73−4.70 (2H, overlapped: δ 4.72 (d, J = 4.4 Hz, 1H), 4.71 (d, J = 5.2 Hz, 1H)), 3.47−3.37 (1H), 3.11 (s, 3H), 2.77−2.68 (1H), 1.41−1.50 (m, 1H), 1.11−1.33 (m, 7H), 0.77−0.92 (m, 7H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 167.7, 133.8, 128.7, 128.5, 128.5, 85.5, 62.9, 62.8 (d, J = 22.9 Hz), 43.3 (d, J = 4.8 Hz), 38.0 (d, J = 24.8 Hz), 31.0 (d, J = 22.9 Hz), 28.6, 24.4 (d, J = 9.5 Hz), 23.0 (d, J = 7.6 Hz), 14.1, 10.6 (d, J = 20.0 Hz); HRMS (ESI) m/z calcd for $C_{18}H_{27}NNaO_2$ $[M + Na]^+$: 312.1939, found: 312.1932.

*(±)-cis-1-Cyclohexyl-3-methoxy-4-phenylazetidin-2-one (**8k**).* White solid, 118.9 mg, 31%, mp 95.0−95.6 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.35−7.41 (m, 5H), 4.75 (d, J = 4.5 Hz, 1H), 4.59 (d, J = 4.5 Hz, 1H), 3.46 (m, 1H), 3.05 (s, 3H), 1.94 (m, 1H), 1.69−1.78 (m, 2H), 1.48−1.64 (m, 3H), 0.97−1.28 (m, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 166.8, 135.3, 128.6, 128.6, 128.3, 84.7, 60.9, 58.1, 52.5, 31.6, 30.5, 25.1; HRMS (ESI) m/z calcd for $C_{16}H_{21}NNaO_2$ $[M + Na]^+$: 282.1470, found: 282.1480.

*(±)-cis-3-Methoxy-4-phenyl-1-(3-phenylpropyl)azetidin-2-one (**8l**).* White solid, 120.3 mg, 27%, mp 52.0−53.0 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.32−7.41 (m, 5H), 7.24−7.27 (m, 2H), 7.15−7.19

https://doi.org/10.1021/acs.joc.1c01128
J. Org. Chem. XXXX, XXX, XXX−XXX

(m, 1H), 7.10−7.12 (m, 2H), 4.66 (d, J = 4.5 Hz, 1H), 4.61 (d, J = 4.1 Hz, 1H), 3.44−3.52 (m, 1H), 3.09 (s, 3H), 2.93−3.00 (m, 1H), 2.53−2.64 (m, 2H), 1.71−1.86 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 167.3, 141.0, 133.9, 128.8, 128.5, 128.5, 128.4, 126.2, 85.5, 62.0, 58.2, 40.1, 33.5, 29.0; HRMS (ESI) m/z calcd for $C_{19}H_{21}NNaO_2$ $[M + Na]^+$: 318.1470, found: 318.1471.

*(±)-cis-1-Hexyl-3-phenoxy-4-phenylazetidin-2-one (**8m**).* Light brown solid, 88.7 mg, 18%, mp 88.0−89.0 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.27−7.34 (m, 5H), 7.09−7.14 (m, 2H), 6.86 (t, J = 7.2 Hz, 1H), 6.72 (d, J = 7.7 Hz, 2H), 5.43 (d, J = 4.1 Hz, 1H), 4.93 (d, J = 4.5 Hz, 1H), 3.48−3.55 (m, 1H), 2.92−2.99 (m, 1H), 1.46−1.53 (m, 2H), 1.23−1.31 (m, 6H), 0.86 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 166.1, 157.0, 133.3, 129.2, 128.7, 128.3, 122.0, 115.7, 114.8, 81.9, 62.3, 40.6, 31.4, 27.4, 26.8, 22.6, 14.1; HRMS (ESI) m/z calcd for $C_{21}H_{25}NNaO_2$ $[M + Na]^+$: 346.1783, found: 346.1791.

*(±)-cis-3-(4-Chlorophenoxy)-1-hexyl-4-phenylazetidin-2-one (**8n**).* White solid, 111.1 mg, 21%, mp 108.5−109.5 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.30 (s, 5H), 7.06 (d, J = 9.1 Hz, 2H), 6.66 (d, J = 8.6 Hz, 2H), 5.37 (d, J = 4.1 Hz, 1H), 4.92 (d, J = 4.5 Hz, 1H), 3.47−3.55 (m, 1H), 2.92−2.99 (m, 1H), 1.49 (m, 2H), 1.25−1.29 (m, 6H), 0.86 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 165.6, 155.6, 133.0, 129.2, 128.9, 128.6, 128.40, 127.0, 117.0, 81.9, 62.1, 40.6, 31.4, 27.9, 26.8, 22.6, 14.1; HRMS (ESI) m/z calcd for $C_{21}H_{24}ClNNaO_2$ $[M + Na]^+$: 380.1393, found: 380.1398.

One-Pot Synthesis of β-Lactam 5a Using Silica-Supported 4,6-Dihydroxysalicylic Acid as the Catalyst for Oxidation of Benzylamine 1a (eq 3). Benzylamine **1a** (321.5 mg, 3.0 mmol), 4.7 wt % **2** on a silica gel (0.15 mmol, 5 mol %), and toluene (1.5 mL) were added to a 20 mL two-neck flask equipped with an O_2 balloon at room temperature and stirred at 90 °C in an oil bath under an O_2 atmosphere for 2 h. Then, the O_2 balloon was removed and the reaction mixture was cooled to room temperature. To the reaction mixture, 4A MS (300 mg) and Et_3N (627 μL, 4.5 mmol, 1.5 equiv) were added, and methoxyacetyl chloride **4a** (488.3 mg, 4.5 mmol, 1.5 equiv) in CH_3CN (3.0 mL) was added dropwise at 0 °C. The resulting solution was stirred at 25 °C for 18 h under a N_2 atmosphere. After the reaction was finished, the resulting mixture was filtered and the filtrate was extracted with AcOMe (10 mL). The organic layer was washed with H_2O (10 mL × 2) and brine (10 mL) and dried with anhydrous Na_2SO_4. The solvent was concentrated under reduced pressure. The yield of β-lactam **5a** was confirmed by ^1H NMR spectroscopy using 1,3,5-trioxane as an internal standard.

Hydrolysis of the β-Lactams to Diastereoselective Synthesis of β-Amino Acids (Table 5). β-Lactam (**5** or **8**, synthesized by this reported method, 0.3 mmol) was dissolved in CH_3CN (1.0 mL) in a 10 mL test tube, and 10% HCl aq. (1.0 mL) was added to the reaction vessel. The mixture was heated at 100 °C in an oil bath for 24 h. After the reaction was completed, the solvent was removed under the reduced pressure, and then recrystallization using CH_2Cl_2 and *iso*-hexane was conducted. The resulting solid was washed with *iso*-hexane (10 mL × 2) and then dissolved in EtOH (10 mL). The solution was filtered over cotton and concentrated under reduced pressure to give corresponding pure β-amino acids **9**.

*N-Benzyl-2-carboxy-2-methoxy-1-phenylethan-1-aminium chloride (**9a**).* White solid, 95.6 mg, 99%, mp 205.0−206.0 °C; ^1H NMR (400 MHz, CD_3OD): δ 7.55−7.49 (m, 5H), 7.43−7.40 (m, 3H), 7.39−7.36 (m, 2H), 4.43 (dd, J = 22.4, 8.7 Hz, 2H), 4.07 (dd, J = 33.0, 13.3 Hz, 2H), 3.56 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, CD_3OD): δ 170.1, 130.5, 130.4, 130.2, 129.9, 129.4, 129.3, 129.2, 128.9, 81.2, 62.6, 57.9, 49.1; HRMS (ESI) m/z calcd for $C_{17}H_{20}NO_3^+$ $[M]^+$:286.1438, found: 286.1454.

*N-(2-Carboxy-2-methoxy-1-phenylethyl)octan-1-aminium chloride (**9b**).* Light brown solid, 94.6 mg, 92%, mp. 190.5−191.0 °C; ^1H NMR (400 MHz, CD_3OD): δ 7.57−7.53 (m, 2H), 7.51−7.48 (m, 3H), 4.52 (d, J = 8.2 Hz, 1H), 4.31 (d, J = 7.7 Hz, 1H), 3.56 (s, 3H), 2.90-2.82 (m, 1H), 2.75−2.68 (m, 1H), 1.75−1.56 (m, 2H), 1.29−1.25 (m, 9H), 0.90−0.86 (m, 4H); ^{13}C {^1H} NMR (100 MHz, CD_3OD): δ 170.3, 130.7, 130.1, 129.2, 129.1, 81.2, 63.1, 57.8, 45.7, 31.5, 28.7, 28.7, 26.2, 25.3, 22.3, 13.1; HRMS (ESI) m/z calcd for $C_{18}H_{30}NO_3^+$ $[M]^+$: 308.2220, found: 308.2225.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c01128.

^1H NMR and ^{13}C NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Shintaro Kodama − *Department of Applied Chemistry, Graduate School of Engineering, Osaka Prefecture University, Osaka 599-8531, Japan;* orcid.org/0000-0003-4190-9539; Email: skodama@chem.osakafu-u.ac.jp

Akiya Ogawa − *Department of Applied Chemistry, Graduate School of Engineering, Osaka Prefecture University, Osaka 599-8531, Japan;* orcid.org/0000-0002-8543-2560; Email: ogawa@chem.osakafu-u.ac.jp

Authors

Yuki Yamamoto − *Department of Applied Chemistry, Graduate School of Engineering, Osaka Prefecture University, Osaka 599-8531, Japan*

Riku Nishimura − *Department of Applied Chemistry, Graduate School of Engineering, Osaka Prefecture University, Osaka 599-8531, Japan*

Akihiro Nomoto − *Department of Applied Chemistry, Graduate School of Engineering, Osaka Prefecture University, Osaka 599-8531, Japan*

Michio Ueshima − *Department of Applied Chemistry, Graduate School of Engineering, Osaka Prefecture University, Osaka 599-8531, Japan*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.1c01128

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by Grant-in-Aid for Scientific Research on Scientific Research (19H02756, 19H02791) from The Japan Society for the Promotion of Science (JSPS) and the Nagoya Institute of Technology Nanotechnology Platform Program of MEXT, Grant Number JPMXP09 2021008. The authors also acknowledge the editor and reviewers for their suggestions.

■ DEDICATION

This work is dedicated to Emeritus Professor Noboru Sonoda (Osaka University) on the occasion of his 88th birthday.

■ REFERENCES

(1) (a) Sammes, P. G. Recent chemistry of the β-lactam antibiotics. *Chem. Rev.* **1976**, *76*, 113−155. (b) Ojima, I.; Habus, I.; Zhao, M.; Zucco, M.; Park, Y. H.; Sun, C. M.; Brigaud, T. New and efficient approaches to the semisynthesis of taxol and its C-13 side chain analogs by means of β-lactam synthon method. *Tetrahedron* **1992**, *48*, 6985−7012. (c) Hanessian, S.; Rozema, M. J. A Highly Stereoselective and Practical Total Synthesis of the Tricyclic β-Lactam Antibiotic GV104326 (4-Methoxytrinem). *J. Am. Chem. Soc.* **1996**, *118*, 9884−9891. (d) Turnidge, J. D. The Pharmacodynamics of β-Lactams. *Clin. Infect. Dis.* **1998**, *27*, 10−22. (e) Elander, R. P.

Industrial production of β-lactam antibiotics. *Appl. Microbiol. Biotechnol.* **2003**, *61*, 385−392. (f) Burnett, D. A. β-Lactam Cholesterol Absorption Inhibitors. *Curr. Med. Chem.* **2004**, *11*, 1873−1887. (g) da Silveira Pinto, L. S.; Alves Vascincelos, T. R.; Gomes, C. R. B.; de Souza, V. N. A Brief Review on the Development of Novel Potentially Active Azetidin-2-ones Against Cancer. *Curr. Org. Chem.* **2020**, *24*, 473−486.

(2) Gómez-Gallego, M.; Mancheño, M. J.; Sierra, M. A. Non-Classical Polycyclic β-Lactams. *Tetrahedron* **2000**, *56*, 5743−5774.

(3) Allen, M. P.; Blake, J. F.; Bryce, D. K.; Haggan, M. E.; Liras, S.; McLean, S.; Segelstein, B. E. Design, synthesis and biological evaluation of 3-amino-3-phenylpropionamide derivatives as novel μ opioid receptor ligands. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 523−526.

(4) Palomo, C.; Oiarbide, M.; Landa, A.; Esnal, A.; Linden, A. A β-Lactam-Based Stereoselective Access to β,γ-Dihydroxy α-Amino Acid-Derived Peptides with Either α,β-Like or Unlike Configurations. *J. Org. Chem.* **2001**, *66*, 4180−4186.

(5) Anderson, K. W.; Tepe, J. J. The First Intermolecular Friedel−Crafts Acylation with β-Lactams. *Org. Lett.* **2002**, *4*, 459−461.

(6) Alcaide, B.; Almendros, P.; Alonso, J. M.; Redondo, M. C. Asymmetric Synthesis of Unusual Fused Tricyclic β-Lactam Structures via Aza-Cycloadditions/Ring Closing Metathesis. *J. Org. Chem.* **2003**, *68*, 1426−1432.

(7) Alcaide, B.; Almendros, P. β-Lactams as Versatile Synthetic Intermediates for the Preparation of Heterocycles of Biological Interest. *Curr. Med. Chem.* **2004**, *11*, 1921−1949.

(8) Klapars, A.; Parris, S.; Anderson, K. W.; Buchwald, S. L. Synthesis of Medium Ring Nitrogen Heterocycles via a Tandem Copper-Catalyzed C−N Bond Formation−Ring-Expansion Process. *J. Am. Chem. Soc.* **2004**, *126*, 3529−3533.

(9) Alcaide, B.; Almendros, P.; Aragoncillo, C. β-Lactams: Versatile Building Blocks for the Stereoselective Synthesis of Non-β-Lactam Products. *Chem. Rev.* **2007**, *107*, 4437−4492.

(10) Kamath, A.; Ojima, I. Advances in the chemistry of β-lactam and its medicinal applications. *Tetrahedron* **2012**, *68*, 10640−10664.

(11) Koch, V.; Lorion, M. M.; Barde, E.; Bräse, S.; Cossy, J. Cobalt-Catalyzed α-Arylation of Substituted α-Halogeno β-Lactams. *Org. Lett.* **2019**, *21*, 6241−6244.

(12) (a) Veinberg, G.; Potorocina, I.; Vorona, M. Recent Trends in the Design, Synthesis and Biological Exploration of β-Lactams. *Curr. Med. Chem.* **2013**, *21*, 393−416. (b) Llarrull, L. I.; Testero, S. A.; Fisher, J.; Mobashery, S. The future of the β-lactams. *Curr. Opin. Microbiol.* **2010**, *13*, 551−557.

(13) Townes, J. A.; Evans, M. A.; Queffelec, J.; Taylor, S. J.; Morken, J. P. Stereoselective Synthesis of *trans* β-Lactams through Iridium-Catalyzed Reductive Coupling of Imines and Acrylates. *Org. Lett.* **2002**, *4*, 2537−2540.

(14) Hevia, E.; Pérez, J.; Riera, V.; Miguel, D.; Campomanes, P.; Menéndez, I.; Sordo, T. L.; Garcia-Granda, S. Synthesis of β-Lactams from a *N*-Rhenaimine: Effect of the Transition Metal on the Energetic Profile of the Staudinger Reaction. *J. Am. Chem. Soc.* **2003**, *125*, 3706−3707.

(15) Nakamura, I.; Yamamoto, Y. Transition-Metal-Catalyzed Reactions in Heterocyclic Synthesis. *Chem. Rev.* **2004**, *104*, 2127−2198.

(16) Choi, M. K.-W.; Yu, W.-Y.; Che, C.-M. Ruthenium-Catalyzed Stereoselective Intramolecular Carbenoid C−H Insertion for β- and γ-Lactam Formations by Decomposition of α-Diazoacetamides. *Org. Lett.* **2005**, *7*, 1081−1084.

(17) Toyofuku, M.; Fujiwara, S.-i.; Shin-ike, T.; Kuniyasu, H.; Kambe, N. Palladium-Catalyzed Intramolecular Selenocarbamoylation of Alkynes with Carbamoselenoates: Formation of α-Alkylidene-β-lactam Framework. *J. Am. Chem. Soc.* **2005**, *127*, 9706−9707.

(18) Stanley, L. M.; Sibi, M. P. Enantioselective Copper-Catalyzed 1,3-Dipolar Cycloadditions. *Chem. Rev.* **2008**, *108*, 2887−2902.

(19) Arndtsen, B. A. Metal-Catalyzed One-Step Synthesis: Towards Direct Alternatives to Multistep Heterocycle and Amino Acid Derivative Formation. *Chem. Eur. J.* **2009**, *15*, 302−313.

(20) Tuba, R. Synthesis of β-lactams by transition metal promoted Staudinger reactions: alternative synthetic approaches from transition metal enhanced organocatalysis to in situ, highly reactive intermediate synthesis and catalytic tandem reactions. *Org. Biomol. Chem.* **2013**, *11*, 5976−5988.

(21) Wang, Z.; Ni, J.; Kuninobu, Y.; Kanai, M. Copper-Catalyzed Intramolecular C(sp^3)−H and C(sp^2)−H Amidation by Oxidative Cyclization. *Angew. Chem. Int. Ed.* **2014**, *53*, 3496−3499.

(22) Pedroni, J.; Boghi, M.; Saget, T.; Cramer, N. Access to β-Lactams by Enantioselective Palladium(0)-Catalyzed C(sp^3)−H Alkylation. *Angew. Chem. Int. Ed.* **2014**, *53*, 9064−9067.

(23) Xu, X.; Deng, Y.; Yim, D. N.; Zavalij, P. Y.; Doyle, M. P. Enantioselective *cis*-β-lactam synthesis by intramolecular C−H functionalization from enoldiazoacetamides and derivative donor−acceptor cyclopropenes. *Chem. Sci.* **2015**, *6*, 2196−2201.

(24) Zhang, S.-J.; Sun, W.-W.; Cao, P.; Dong, X.-P.; Liu, J.-K.; Wu, B. Stereoselective Synthesis of Diazabicyclic β-Lactams through Intramolecular Amination of Unactivated C(sp^3)−H Bonds of Carboxamides by Palladium Catalysis. *J. Org. Chem.* **2016**, *81*, 956−968.

(25) Kong, W.-J.; Liu, Y.-J.; Xu, H.; Chen, Y.-Q.; Dai, H.-X.; Yu, J.-Q. Pd-Catalyzed α-Selective C−H Functionalization of Olefins: En Route to 4-Imino-β-Lactams. *J. Am. Chem. Soc.* **2016**, *138*, 2146−2149.

(26) Zhang, M.; Wang, Q.; Peng, Y.; Chen, Z.; Wan, C.; Chen, J.; Zhao, Y.; Zhang, R.; Zhang, A. Q. Transition metal-catalyzed sp^3 C−H activation and intramolecular C−N coupling to construct nitrogen heterocyclic scaffolds. *Chem. Commun.* **2019**, *55*, 13048−13065.

(27) Chen, L.; Wang, K.; Shao, Y.; Sun, J. Stereoselective Synthesis of Fully Substituted β-Lactams via Metal−Organo Relay Catalysis. *Org. Lett.* **2019**, *21*, 3804−3807.

(28) Solé, D.; Pérez-Janer, F.; Amenta, A.; Bennasar, M.-L.; Fernández, I. Site Selectivity in Pd-Catalyzed Reactions of α-Diazo-α-(methoxycarbonyl)acetamides: Effects of Catalysts and Substrate Substitution in the Synthesis of Oxindoles and β-Lactams. *Molecules* **2019**, *24*, No. 3551.

(29) Tong, H.-R.; Zheng, W.; Lv, X.; He, G.; Liu, P.; Chen, G. Asymmetric Synthesis of β-Lactam via Palladium-Catalyzed Enantioselective Intramolecular C(sp^3)−H Amidation. *ACS Catal.* **2020**, *10*, 114−120.

(30) Nozawa-Kumada, K.; Saga, S.; Matsuzawa, Y.; Hayashi, M.; Shigeno, M.; Kondo, Y. Copper-Catalyzed Oxidative Benzylic C(sp^3)−H Cyclization for the Synthesis of β-Lactams. *Chem. Eur. J.* **2020**, *26*, 4496−4499.

(31) Faltracco, M.; Sukowski, V.; Druenen, M. v.; Hamlin, T. A.; Bickelhaupt, F. M.; Ruijter, E. Diastereoselective Synthesis of β-Lactams by Ligand-Controlled Stereodivergent Intramolecular Tsuji−Trost Allylation. *J. Org. Chem.* **2020**, *85*, 9566−9584.

(32) Zhang, H.; Lv; Xiaoyan, Yu. H.; Bai, Z.; Chen, G.; He, G. β-Lactam Synthesis via Copper-Catalyzed Directed Aminoalkylation of Unactivated Alkenes with Cyclobutanone *O*-Benzoyloximes. *Org. Lett.* **2021**, *23*, 3620−3625.

(33) (a) Zhang, Z.; Liu, Y.; Ling, L.; Li, Y.; Dong, Y.; Gong, M.; Zhao, X.; Zhang, Y.; Wang, J. Pd-Catalyzed Carbonylation of Diazo Compounds at Atmospheric Pressure: A Catalytic Approach to Ketenes. *J. Am. Chem. Soc.* **2011**, *133*, 4330−4341. (b) Li, W.; Liu, C.; Zhang, H.; Ye, K.; Zhang, G.; Zhang, W.; Duan, Z.; You, S.; Lei, A. Palladium-Catalyzed Oxidative Carbonylation of *N*-Allylamines for the Synthesis of β-Lactams. *Angew. Chem. Int. Ed.* **2014**, *53*, 2443−2446. (c) Willcox, D.; Chappell, B. G. N.; Hogg, K. F.; Calleja, J.; Smalley, A. P.; Gaunt, M. J. A general catalytic β-C−H carbonylation of aliphatic amines to β-lactams. *Science* **2016**, *354*, 851−857. (d) Piens, N.; D'hooghe, M. Carbonylation of Aziridines as a Powerful Tool for the Synthesis of Functionalized β-Lactams. *Eur. J. Org. Chem.* **2017**, *2017*, 5943−5960. (e) Piens, N.; Hecke, K. V.; Vogt, D.; D'hooghe, M. Cobalt carbonyl-catalyzed carbonylation of functionalized aziridines to versatile β-lactam building blocks. *Org. Biomol. Chem.* **2017**, *15*, 4816−4821.

https://doi.org/10.1021/acs.joc.1c01128
J. Org. Chem. XXXX, XXX, XXX−XXX

(34) Hart, D. J.; Ha, D. C. The Ester Enolate-Imine Condensation Route to β-Lactams. *Chem. Rev.* **1989**, *89*, 1447−1465.
(35) Podlech, J.; Linder, M. R. Cycloadditions of Ketenes Generated in the Wolff Rearrangement. Stereoselective Synthesis of Aminoalkyl-Substituted β-Lactams from α-Amino Acids. *J. Org. Chem.* **1997**, *62*, 5873−5883.
(36) France, S.; Wack, H.; Hafez, A. M.; Taggi, A. E.; Witsil, D. R.; Lectka, T. Bifunctional Asymmetric Catalysis: A Tandem Nucleophile/Lewis Acid Promoted Synthesis of β-Lactams. *Org. Lett.* **2002**, *4*, 1603−1605.
(37) Pirrung, M. C.; Sarma, K. D. β-Lactam Synthesis by Ugi Reaction of β-Keto Acids in Aqueous Solution. *Synlett* **2004**, 1425−1427.
(38) France, S.; Weatherwax, A.; Taggi, A. E.; Lectka, T. Advances in the Catalytic, Asymmetric Synthesis of β-Lactams. *Acc. Chem. Res.* **2004**, *37*, 592−600.
(39) Donati, D.; Morelli, C.; Porcheddu, A.; Taddei, M. A New Polymer-Supported Reagent for the Synthesis of β-Lactams in Solution. *J. Org. Chem.* **2004**, *69*, 9316−9318.
(40) France, S.; Shah, M. H.; Weatherwax, A.; Wack, H.; Roth, J. P.; Lectka, T. Bifunctional Lewis Acid-Nucleophile-Based Asymmetric Catalysis: Mechanistic Evidence for Imine Activation Working in Tandem with Chiral Enolate Formation in the Synthesis of β-Lactams. *J. Am. Chem. Soc.* **2005**, *127*, 1206−1215.
(41) Dohi, T.; Maruyama, A.; Minamitsuji, Y.; Takenaga, N.; Kita, Y. First hypervalent iodine(III)-catalyzed C−N bond forming reaction: catalytic spirocyclization of amides to *N*-fused spirolactams. *Chem. Commun.* **2007**, 1224−1226.
(42) Pitts, C. R.; Lectka, T. Chemical Synthesis of β-Lactams: Asymmetric Catalysis and Other Recent Advances. *Chem. Rev.* **2014**, *114*, 7930−7953.
(43) Gomes, L. F. R.; Veiros, L. F.; Maulide, N.; Afonso, C. A. M. Diazo- and Transition-Metal-Free C−H Insertion: A Direct Synthesis of β-Lactams. *Chem. Eur. J.* **2015**, *21*, 1449−1453.
(44) Huang, Z.; Wang, C.; Tokunaga, E.; Shibata, N. Stereoselective Synthesis of β-Lactam-triflones under Catalyst-Free Conditions. *Org. Lett.* **2015**, *17*, 5610−5613.
(45) Hosseyni, S.; Jarrahpour, A. Recent advances in β-lactam synthesis. *Org. Biomol. Chem.* **2018**, *16*, 6840−6852.
(46) (a) Staudinger, H. Zur Kenntniss der Ketene. Diphenylketen. *Justus Liebigs Ann. Chem.* **1907**, *356*, 51−123. (b) Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Ferraris, D.; Lectka, T. The Development of the First Catalyzed Reaction of Ketenes and Imines: Catalytic, Asymmetric Synthesis of beta-Lactams. *J. Am. Chem. Soc.* **2002**, *124*, 6626−6635. (c) Zhang, Y.-R.; He, L.; Wu, X.; Shao, P.-L.; Ye, S. *N*-Heterocyclic Carbene Catalyzed Staudinger Reaction of Ketenes with Imines: Highly Enantioselective Synthesis of *N*-Boc β-Lactams. *Org. Lett.* **2008**, *10*, 277−280. (d) Todorov, A. R.; Kurteva, V. B.; Bontchev, R. P.; Vassilev, N. G. Chiral amine-induced stereoselectivity in *trans*-β-lactam formation via Staudinger cycloaddition. *Tetrahedron* **2009**, *65*, 10339−10347. (e) Lall, M. S.; Tao, Y.; Arcari, J. T.; Boyles, D. C.; Brown, M. F.; Damon, D. B.; Lilley, S. C.; Mitton-Fry, M. J.; Starr, J.; Stewart, A. M., III; Sun, J. Process Development for the Synthesis of Monocyclic β-Lactam Core 17. *Org. Process. Res. Dev.* **2018**, *22*, 212−218. (f) Chen, L.; Zhang, L.; Shao, Y.; Xu, G.; Zhang, X.; Tang, S.; Sun, J. Rhodium-Catalyzed C═N Bond Formation through a Rebound Hydrolysis Mechanism and Application in β-Lactam Synthesis. *Org. Lett.* **2019**, *21*, 4124−4127. (g) Synofzik, J.; Bakulina, O.; Balabas, O.; Dar'in, D.; Krasavin, M. Catalyst-Free Synthesis of Diastereomerically Pure 3-Sulfonylazetidin-2-ones via Microwave-Assisted Tandem Wolff Rearrangement−Staudinger Cycloaddition. *Synthesis* **2020**, *52*, 3029−3035.
(47) (a) Mehta, V. P.; Punji, B. Recent advances in transition-metal-free direct C−C and C−heteroatom bond forming reactions. *RSC Adv.* **2013**, *3*, 11957−11986. (b) Kumari, S.; Kishore, D.; Paliwal, S.; Chauhan, R.; Dwivedi, J.; Mishra, A. Transition metal-free one-pot synthesis of nitrogen-containing heterocycles. *Mol. Divers.* **2016**, *20*, 185−232. (c) Khan, I.; Zaib, S.; Ibrar, A. New frontiers in the transition-metal-free synthesis of heterocycles from alkynoates: an overview and current status. *Org. Chem. Front.* **2020**, *7*, 3734−3791.
(48) Rajamäki, S. H. M.; Luca, L. D.; Capitta, F.; Porcheddu, A. A telescopic one-pot synthesis of β-lactam rings using amines as a convenient source of imines. *RSC Adv.* **2016**, *6*, 38553−38557.
(49) Dong, C.-p.; Higashiura, Y.; Marui, K.; Kumazawa, S.; Nomoto, A.; Ueshima, M.; Ogawa, A. Metal-Free Oxidative Coupling of Benzylamines to Imines under an Oxygen Atmosphere Promoted Using Salicylic Acid Derivatives as Organocatalysts. *ACS Omega* **2016**, *1*, 799−807.
(50) (a) Dong, C.-p.; Kodama, S.; Uematsu, A.; Nomoto, A.; Ueshima, M.; Ogawa, A. Metal-Free Blue Dye Synthesis: Oxidative Coupling of Benzylamines and *N*,*N*-Dimethylanilines to Yield 4,4′-Diaminotriarylmethanes in the Presence of Salicylic Acid as a Co-oxidant. *J. Org. Chem.* **2017**, *82*, 12530−12538. (b) Kumazawa, S.; Uematsu, A.; Dong, C-p.; Kodama, S.; Nomoto, A.; Ueshima, M.; Ogawa, A. Metal-free synthesis of *N*-containing heterocycles from *O*-substituted aniline derivatives via 2,4,6-trihydroxybenzoic acid-catalyzed oxidative dehydrogenation of benzylamines under oxygen atmosphere. *Heterocycles* **2018**, *97*, 842−853. (c) Dong, C.-p.; Uematsu, A.; Kumazawa, S.; Yamamoto, Y.; Kodama, S.; Nomoto, A.; Ueshima, M.; Ogawa, A. 2,4,6-Trihydroxybenzoic Acid-Catalyzed Oxidative Ugi Reactions with Molecular Oxygen via Homo- and Cross-Coupling of Amines. *J. Org. Chem.* **2019**, *84*, 11562−11571. (d) Dong, C.-p.; Kodama, S.; Nomoto, A.; Ueshima, M.; Ogawa, A. 4,6-Dihydroxysalicylic Acid-Catalyzed Oxidative Condensation of Benzylic Amines and Aromatic Ketones for the Preparation of 2,4,6-Trisubstituted Pyridines and Its Application to Metal-Free Synthesis of G-Quadruplex Binding Ligands. *ACS Omega* **2019**, *4*, 9029−9040.
(51) (a) Ojima, I.; Delaloge, F. Asymmetric synthesis of building-blocks for peptides and peptidomimetics by means of the β-lactam synthon method. *Chem. Soc. Rev.* **1997**, *26*, 377−386. (b) Bolm, C.; Schiffers, I.; Dinter, C. L.; Defrère, L.; Gerlach, A.; Raabe, G. Efficient Asymmetric Synthesis of Unnatural β-Amino Acids. *Synthesis* **2001**, *11*, 1719−1730. (c) Hafez, A. M.; Dudding, T.; Wagerle, T. R.; Shah, M. H.; Taggi, A. E.; Lectka, T. A Multistage, One-Pot Procedure Mediated by a Single Catalyst: A New Approach to the Catalytic Asymmetric Synthesis of β-Amino Acids. *J. Org. Chem.* **2003**, *68*, 5819−5825. (d) Maruoka, K.; Ooi, T.; Kano, T. Design of chiral organocatalysts for practical asymmetric synthesis of amino acid derivatives. *Chem. Commun.* **2007**, 1487−1495. (e) Patzelt, C.; Pöthig, A.; Gulder, T. Iodine(III)-Catalyzed Cascade Reactions Enabling a Direct Access to β-Lactams and α-Hydroxy-β-amino Acids. *Org. Lett.* **2016**, *18*, 3466−3469.
(52) Generally, the ^{1}H NMR coupling constants of C_3 and C_4 protons show relative stereochemistry (*cis* isomer = 4−8 Hz, *trans* isomer = 0−2 Hz). Therefore, the stereochemistry of the β-lactams synthesized in this work was determined by the coupling constants. General characteristics of *cis*- and *trans*-β-lactams are shown in the following article, see (a) Barrow, K. D.; Spotswood, T. M. Stereochemistry and P. M. R. spectra of β-lactams. *Tetrahedron Lett.* **1965**, *6*, 3325−3335.
(53) (a) Cossío, F. P.; Arrieta, A.; Sierra, M. A. The Mechanism of the Ketene−Imine (Staudinger) Reaction in Its Centennial: Still an Unsolved Problem? *Acc. Chem. Res.* **2008**, *41*, 925−936. (b) Domingo, L. R.; Ríos-Gutiérrez, M.; Sáez, J. A. Unravelling the mechanism of the ketene-imine Staudinger reaction. An ELF quantum topological analysis. *RSC Adv.* **2015**, *5*, 37119−37129.
(54) (a) Wang, Y.; Liang, Y.; Jiao, L.; Du, D.-M.; Xu, J. Do Reaction Conditions Affect the Stereoselectivity in the Staudinger Reaction? *J. Org. Chem.* **2006**, *71*, 6983−6990. (b) Jiao, L.; Liang, Y.; Xu, J. Origin of the Relative Stereoselectivity of the β-Lactam Formation in the Staudinger Reaction. *J. Am. Chem. Soc.* **2006**, *128*, 6060−6069. (c) Ábrányi-Balogh, P.; Mucsi, Z.; Csizmadia, I. G.; Dancsó, A.; Keglevich, G.; Milen, M. Heteroatom effect on potential energy topology. A novel reaction mechanism of stereospecific Staudinger synthesis. *Tetrahedron* **2014**, *70*, 9682−9694. (d) Cassú, D. Computational Insight into the Scope of the Staudinger Cyclo-

https://doi.org/10.1021/acs.joc.1c01128
J. Org. Chem. XXXX, XXX, XXX−XXX

addition Reaction for the Preparation of β-Lactams. *ChemistrySelect* **2020**, *5*, 3278−3282.
(55) Bose, A. K.; Banik, B. K.; Manhas, M. S. Stereocontrol of β-lactam formation using microwave irradiation. *Tetrahedron Lett.* **1995**, *36*, 213−216.
(56) Synofzik, J.; Dar'in, D.; Novikov, M. S.; Kantin, G.; Bakulina, O.; Krasavin, M. α-Acyl-α-diazoacetates in Transition-Metal-Free β-Lactam Synthesis. *J. Org. Chem.* **2019**, *84*, 12101−12110.
(57) Zarei, M. One-Pot Sequence Synthesis of Azetidin-2-one Using Diethyl Chlorophosphate. *J. Chem. Res.* **2012**, *36*, 118−120.
(58) Mihovilovic, M. D.; Feicht, A.; Kayser, M. M. An Efficient and Simple Procedure for the Preparation of α-Keto-β-lactams. *J. Prakt. Chem.* **2000**, *342*, 585−590.

https://doi.org/10.1021/acs.joc.1c01128
J. Org. Chem. XXXX, XXX, XXX−XXX