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Article

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Synthesis of Pyrrole via a Silver-catalyzed 1,3-Dipolar Cycloaddition / Oxidative Dehydrogenative Aromatization Tandem Reaction

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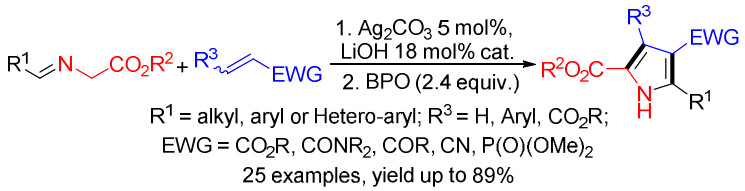


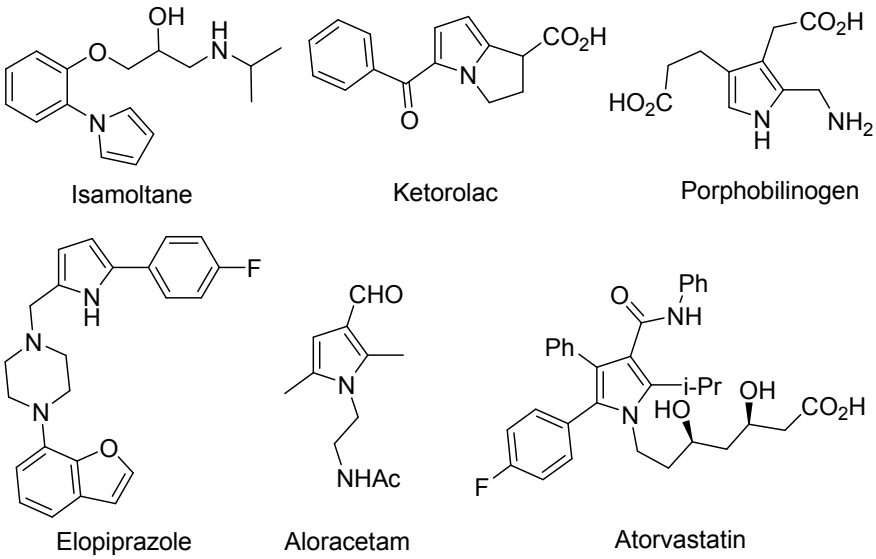
ABSTRACT: Pyrroles are an important group of heterocyclic compounds with a wide range of interesting properties, which have resulted in numerous applications in a variety of fields. Despite the importance of these compounds, there have been few reports in the literature pertaining to the synthesis of pyrroles from simple alkenes using a one-pot sequential 1,3-dipolar cycloaddition/aromatization reaction sequence. Herein, we report the development of a benzoyl peroxide-mediated oxidative

dehydrogenative aromatization reaction for the construction of pyrrolidines. We subsequently developed a one-pot tandem reaction that combined this new method with a well-defined silver-catalyzed 1,3-dipolar cycloaddition reaction, thereby providing a practical method for the synthesis of multi-substituted pyrroles. The mechanism of this oxidative dehydrogenative aromatization reaction was also examined in detail.

INTRODUCTION

Pyrroles are an important class of aromatic heterocyclic compounds that can be found in a large number of natural products.[1] Pyrrole derivatives play critical roles in numerous biologically important compounds, such in as chlorophyll, hemoglobin, and vitamin B_{12}. Furthermore, the pyrrole skeleton can be found in several marketed drugs, such as atorvastatin, aloracetam, elopiprazole, isamoltane, and ketorolac (Fig. 1).[2] A large number of synthetic pyrrole derivatives has also been prepared with a wide variety of interesting properties, and many of these systems have found important applications in biology, medicine, materials science, and the dye industry.[3] In light of their importance, pyrrole derivatives have attracted considerable attention from the organic chemistry community, culminating in the development of several new strategies for the synthesis of compounds belonging to this class. [4]

Figure 1. Pyrrole in some marketed drugs.

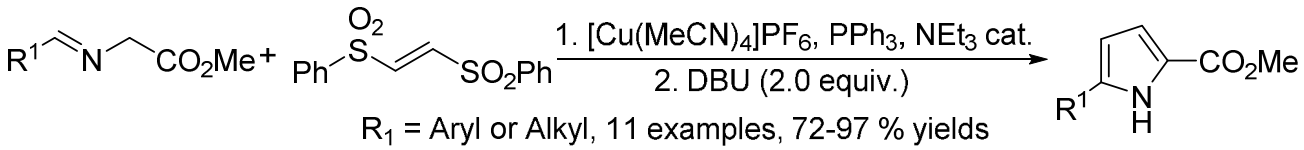


During the past three decades, 1,3-dipolar cycloaddition reactions have been used extensively to provide powerful synthetic methods for the construction of nitrogen-containing five-membered heterocycles, such as isoxazolidine, pyrazole, indolizine, and triazole.[5] This strategy has also been used prepare pyrrolidines.[6] However, despite considerable progress toward the synthesis of indolizines,[7] there have been very few reports pertaining to the synthesis of pyrroles using a one-pot 1,3-cycloaddition reaction. The few methods that have been reported in this area are generally limited by their requirement for electron-deficient alkyne substrates[8] and their analogs, such as (*E*)-1,2-bis(phenylsulfonyl)ethane,[9] ((1-bromovinyl)sulfonyl)benzene,[10] and (*E*)-4-ethoxy-1,1,1-trifluorobut-3-en-2-one,[11] which are expensive and difficult to access, as well as lacking in sufficient structural diversity. These limitations could be attributed in part to a lack of suitable methods for the oxidative dehydrogenative aromatization of pyrrolidines. Although 4,5-dichloro-3,6-dioxocyclohexa-1,4-diene-1,2-dicarbonitrile (DDQ),[12] *o*-iodoxybenzoic acid,[13] and manganese dioxide[14] have been used previously to promote the oxidative dehydrogenative aromatization reactions of isolated pyrrolidines, the overall synthetic efficiency of these reactions can be reduced considerably by their requirement to conducted as step-wise processes. Furthermore, DDQ is expensive and toxic, and its consumption during the course of these reactions results in the formation of toxic by-products. We recently reported a series of synthetic methods for the construction of indolizines using a tandem one-pot 1,3-dipolar cycloaddition/oxidative dehydrogenative aromatization reaction sequence.[15] As part of our ongoing research towards the oxidative dehydrogenative aromatization reactions of nitrogen-containing heterocycles, we report herein the development of a practical synthetic method for the construction of pyrroles via a tandem reaction sequence starting from simple alkenes (Scheme 1).

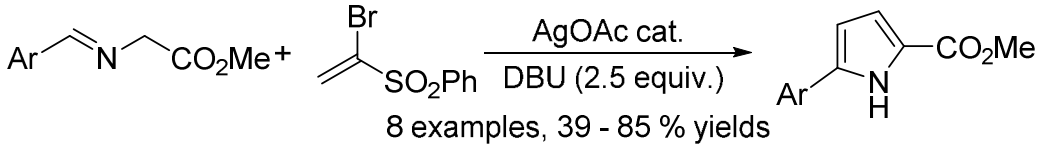
Scheme 1. Different one-pot synthetic pathways for the construction of pyrroles from alkenes using a 1,3-dipolar cycloaddition reaction.

Previous work

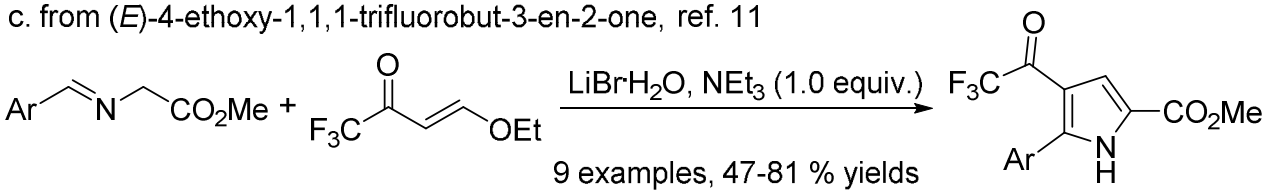
a. from (*E*)-1,2-bis(phenylsulfonyl)ethene, ref. 9



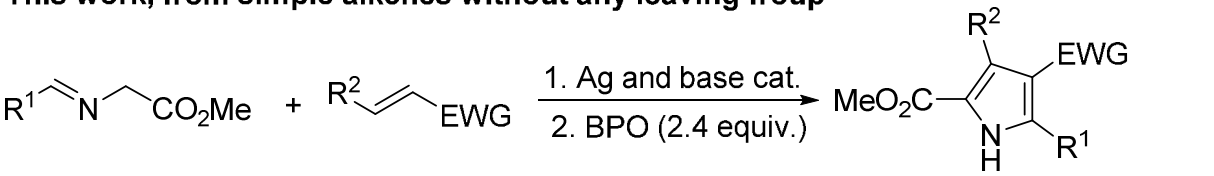
b. from ((1-bromovinyl)sulfonyl)benzene, ref. 10



c. from (*E*)-4-ethoxy-1,1,1-trifluorobut-3-en-2-one, ref. 11



This work, from simple alkenes without any leaving froup



R^1 = Aryl, alkyl; R^2 = H, aryl, alkyl, COR, CO_2R; EWG = CN, CO_2R, COR, $P(O)(OMe)_2$ etc.

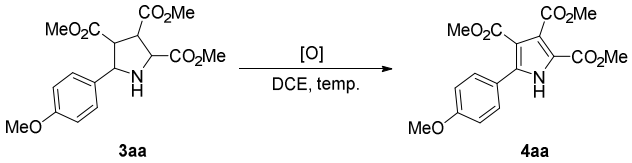
25 examples, yields up to 89%

RESULTS AND DISCUSSION

We initially investigated the reaction of trimethyl-5-(4-methoxyphenyl)pyrrolidine-2,3,4-tricarboxylate (**3aa**, 0.20 mmol) in 1,2-dichloroethane (DCE, 2.0 mL) as a model system. The results showed that the addition of benzoyl peroxide (BPO) to the reaction mixture resulted in the formation of the desired pyrrole product **4aa** in 70% yield (Table 1, entry 1). Several other oxidants were also evaluated, including *t*-butyl benzoperoxoate (TBPB), *t*-butyl hydroperoxide (TBHP), and potassium peroxydisulfate, but were all found to be much less efficient than BPO. Furthermore, di-*t*-butyl peroxide (DTBP), *m*-chloroperbenzoic acid (*m*CBPA), and dicumyl peroxide (DCP) failed to afford any of the desired product (Table 1, entries 2–9). We also investigated the effect of the temperature on the outcome of this reaction. The results revealed that reducing the temperature to 90 °C led to a decrease in the yield of **4aa** to 56% (Table 1, entry 10). Notably,

increasing the concentration of the reaction mixture to 0.2 M led to an increase in the yield of the desired product to 79% (Table 1, entry 11).

Table 1. Optimization of oxidative dehydrogenative aromatization reaction conditions.



3aa 4aa

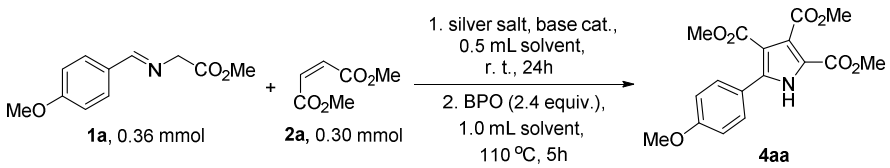
Entry	Oxidant	Amount (equiv.)	Temperature (°C)	Yield of **4aa** (%) [b]
1	BPO	2.4	110	70
2	TBPB	2.4	110	58
3	*m*CBPA	2.4	110	Trace
4	DTBP	2.4	110	Trace
5	TBHP	2.4	110	54
6	$K_2S_2O_8$	2.4	110	22
7	DCP	2.4	110	Trace
8	BPO	2.0	110	56
9	BPO	2.6	110	50
10	BPO	2.4	90	56
11 [c]	BPO	2.4	110	79
12 [d]	BPO	2.4	110	72

[a] Reaction conditions: 0.20 mmol **3aa** and 2.0 mL each of DCE and oxidant were heated in a sealed tube for 5 h. [b] Yields were determined by ^{1}H-NMR using *N*,*N*-dimethylacetamide (DMA) as an internal standard. [c] 1.0 mL of DCE solvent. [d] 0.5 mL of DCE solvent.

Having identified BPO as the best oxidant for the conversion of pyrrolidines to the corresponding pyrroles, we proceeded to optimize the conditions for the one-pot reaction. Methyl (*E*)-2-((4-methoxybenzylidene)amino)acetate (**1a**) [16] and dimethyl maleate (**2a**) were chosen as model substrates for this reaction (Table 2). Several silver salts were screened as catalysts for this 1,3-dipolar

cycloaddition reaction because silver catalyst systems are generally inexpensive, provide highly efficient catalysis under mild reaction conditions, and do not require the addition of a ligand.[17] The silver salts were tested using triethylamine (18 mol %) and DCE as the base and solvent, respectively. All of the silver salts evaluated in the current study exhibited similar catalytic activities, except for silver carbonate, which showed much higher activity, most likely because of its strong alkalinity (Table 2, entries 1–6). Several bases were evaluated using silver acetate as a catalyst, and the results revealed that lithium hydroxide was the best base in terms of the yield of the desired product (Table 2, entries 7–17). Notably, the use of silver carbonate in combination with lithium hydroxide produced **4aa** in 83% yield (Table 2, entry 18). We also evaluated a variety of solvents and found that the highest yield of **4aa** (89%) was achieved when the cyclohexane was used as the solvent (Table 2, entry 25). Further studies confirmed that the optimized reaction conditions were as follows: **1a** (1.2 equiv.), **2a** (0.30 mmol, 1.0 equiv.), silver carbonate (5 mol %), and lithium hydroxide (18 mol %) in cyclohexane (0.50 mL) at room temperature for 24 h in a test tube, followed by the addition of BPO (2.4 equiv.) and cyclohexane (1 mL) and heating at 110 °C for 5 h.

Table 2. Optimization of one-pot reaction conditions.



Entry	Silver salt (10 mol %) [b]	Base (18 mol %)	Solvent	Yield (%) [c]
1	AgOAc	NEt_3	DCE	57
2	$AgNO_3$	NEt_3	DCE	59
3	Ag_2O	NEt_3	DCE	51
4	AgF	NEt_3	DCE	58
5	$AgSbF_6$	NEt_3	DCE	64
6	Ag_2CO_3	N. A. [d]	DCE	75
7	AgOAc	N. A.	DCE	60

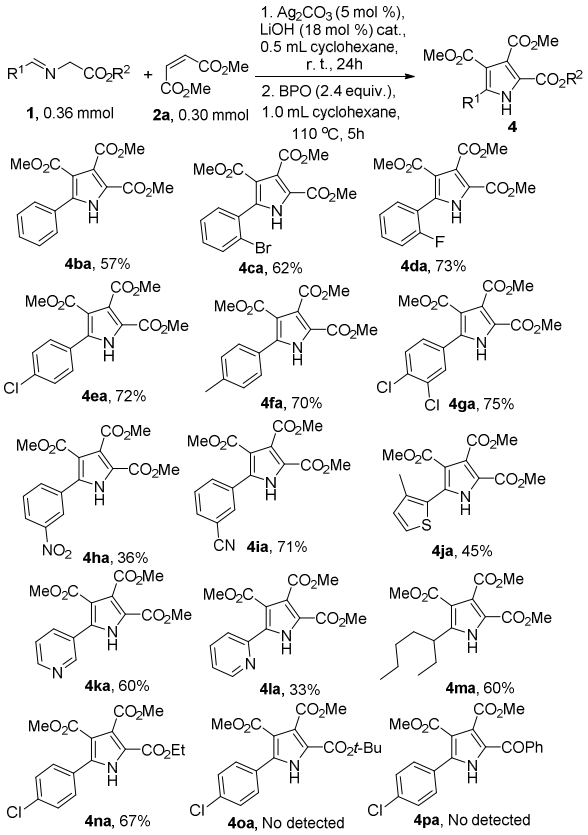
8	AgOAc	Na_2CO_3	DCE	55
9	AgOAc	K_2CO_3	DCE	63
10	AgOAc	Cs_2CO_3	DCE	66
11	AgOAc	KOH	DCE	62
12	AgOAc	NaOH	DCE	66
13	AgOAc	LiOH	DCE	71
14	AgOAc	*t*-BuOK	DCE	62
15	AgOAc	*t*-BuONa	DCE	40
16	AgOAc	*t*-BuOLi	DCE	69
17	AgOAc	Pyridine	DCE	58
18	Ag_2CO_3	LiOH	DCE	83
19	Ag_2CO_3 [e]	LiOH	DCE	69
20	Ag_2CO_3 [f]	LiOH	DCE	73
21	Ag_2CO_3	LiOH [g]	DCE	78
22	Ag_2CO_3	LiOH [h]	DCE	67
23	Ag_2CO_3	LiOH	Toluene	78
24	Ag_2CO_3	LiOH	1,4-dioxane	58
25	Ag_2CO_3	LiOH	cyclohexane	89
26	Ag_2CO_3	LiOH	DMC [i]	75
27	Ag_2CO_3	LiOH	DMF [j]	48

[a] Reaction conditions: **1a** (0.36 mmol, 1.2 equiv.), **2a** (0.30 mmol, 1.0 equiv.), silver salt (10 mol %), and base (18 mol %) in and solvent (0.50 mL) were stirred at room temperature for 24 h in a test tube. BPO (2.4 equiv.) and solvent (1.0 mL) were then added, and the resulting mixture was heated at 110 °C for 5 h in a sealed tube. [b] Based on the amounts of silver atoms. [c] Isolated yield. [d] No addition. [e] 5 mol % based on silver abundance. [f] 20 mol % based on silver. [g] 9 mol % LiOH. [h] 36 mol % LiOH. [i] Dimethyl carbonate. [j] *N*,*N*-dimethylformamide.

A series of imines were synthesized from the corresponding aldehydes using amino methyl acetate hydrochloride according to a reported procedure.[16] Each of these imines was then reacted with **2a** under the standard reaction conditions described above to explore the substrate scope of this reaction (Scheme 2). This transformation tolerated a variety of substituents on the phenyl ring of the imine substrate, including electron-donating and electron-withdrawing groups (**1b**–**1i**). However, the inclusion of a nitro

group was not tolerated because we were unable to prepare the corresponding imines from 2- and 4-nitro-benzaldehyde. Methyl (*E*)-2-((3-nitrobenzylidene)amino)acetate (**1h**) was successfully isolated but only produced the corresponding pyrrole in a low yield of 36%. These poor results could be attributed to the high oxidative potential of nitro compounds. Aromatic heterocycles, such as thiophene and pyridine, were also tolerated under the standard reaction conditions, affording the corresponding pyrroles in moderate yields (**1j**–**1l**). It is noteworthy that the imine prepared from alkyl aldehyde **1m** also afforded the corresponding pyrrole in a comparable yield to that of the aromatic aldehydes.

Scheme 2. Scope of imine component.

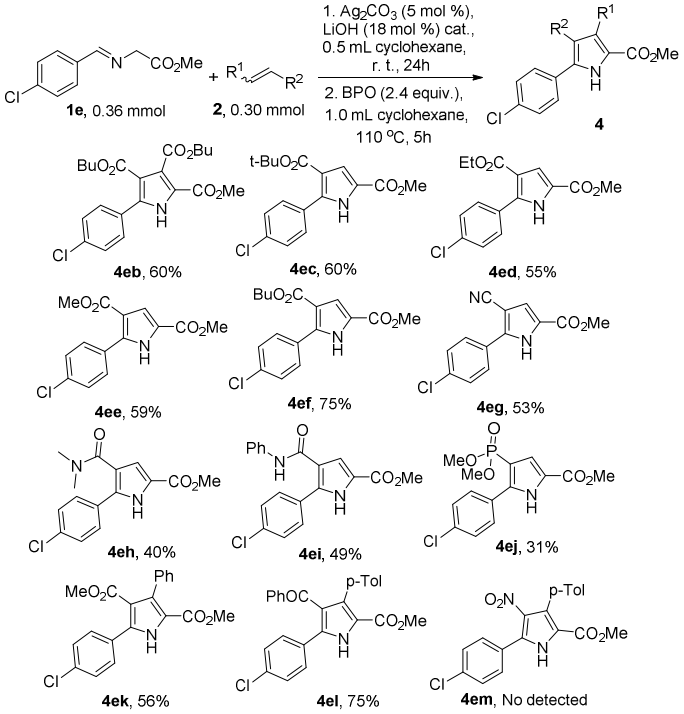


[a] Isolated yield.

The scope of the alkene substrate was also studied by reacting a broad range of alkenes bearing various electron-withdrawing groups with **1e** under the standard reaction conditions (Scheme 3). Several acrylic acid derivatives, including acrylates (**2c**–**2f**), acrylonitrile (**2g**), and acrylamides (**2h** and **2i**) reacted smoothly with **1e** under the standard reaction conditions to give the corresponding pyrroles in

moderate to good yields. Several other electron-deficient alkenes, including dimethyl vinylphosphonate (**2j**), methyl cinnamate (**2k**), and chalcone (**2l**) also reacted well to afford the corresponding pyrroles in moderate to good yields. However, once again, the nitro compound **2m** failed to yield the desired pyrrole.

Scheme 3. The scope of the alkene component

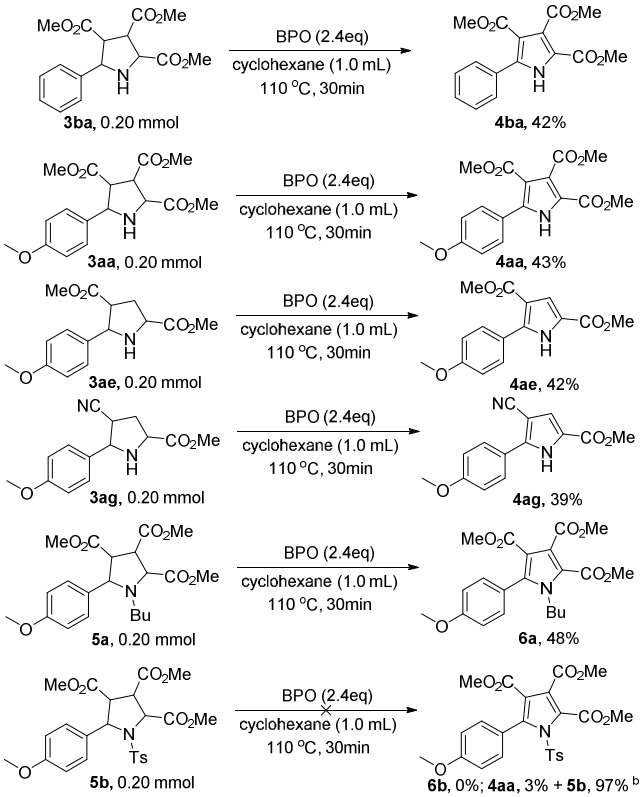


[a] Isolated yield.

The mechanism of this oxidative dehydrogenative aromatization reaction was examined using a series of kinetic and control experiments. Several pyrrolidines with different substitution groups at various positions were synthesized and heated in the presence of BPO (2.4 equiv.) at 110 °C for 30 min using cyclohexane as the solvent. The isolated yields of the corresponding pyrroles are shown in Scheme 4. Most of these pyrrolidines produced pyrroles in similar yields, even when there was a bulky butyl substituent on the nitrogen of the pyrrolidine ring (**5a**). However, the reaction was inhibited by pyrroles bearing a *p*-toluenesulfonyl group on their nitrogen atom (**5b)**. These experiments confirmed that **5b**

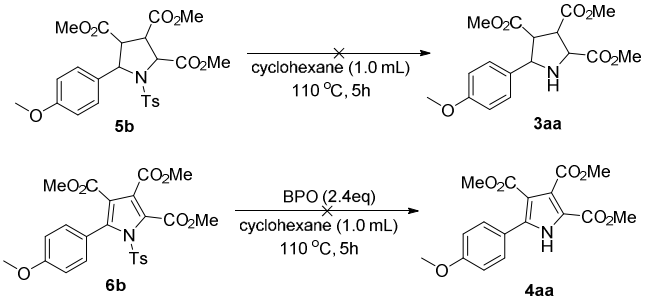
was stable in the absence of BPO and that **6b** was stable under the standard reaction conditions (Scheme 5), despite *N*-*p*-toluenesulfonyl substituted pyrrolidines having been reported to be unstable under basic conditions.[18]

Scheme 4. Kinetic experiments



[a] Isolated yield. [b] Yields were determined by ^{1}H NMR using DMA as an internal standard.

Scheme 5. Control experiments.

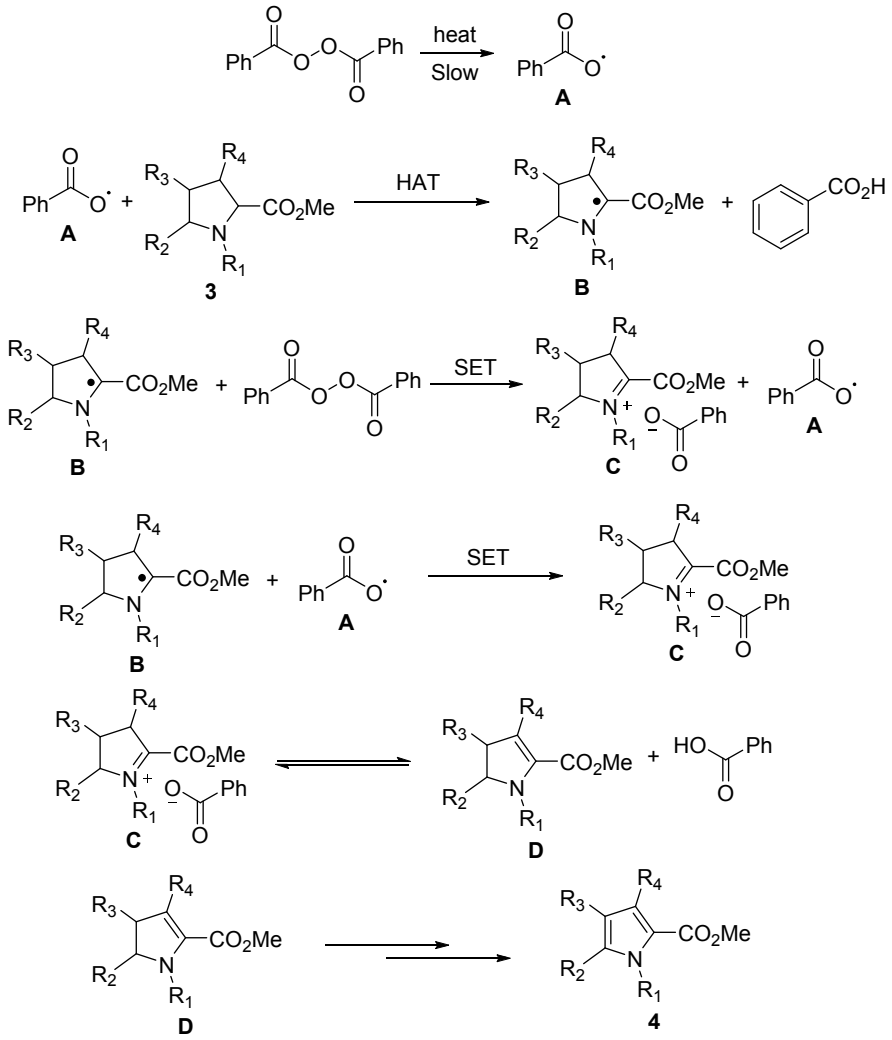


[a] Starting material recovered.

Based on the broad substrate scope of this transformation and the results of the kinetic and control experiments, we proposed a plausible mechanism for this reaction, which is shown in Scheme 6. The

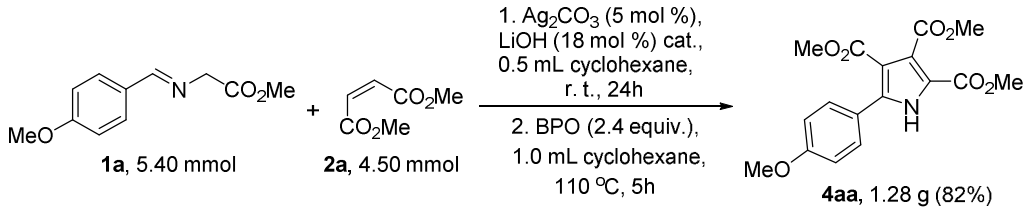
initial thermal decomposition of BPO would lead to the formation of radical **A**, which would undergo a hydrogen-atom transfer reaction with **3** to give radical intermediate **B** Radical **B** would then react with BPO or **A** to form intermediate **C** through a single electron-transfer reaction. Intermediate **C** would be converted to benzoic acid and intermediate **D**, which would be oxidized to pyrrole **4**. The overall reaction rate would be dependent on the rate of BPO decomposition.

Scheme 6. Proposed mechanism for the oxidative dehydrogenative aromatization reaction



This reaction sequence was also conducted on 4.5-mmol scale to highlight the synthetic utility of this new transformation. As shown in Scheme 7, we successfully isolated 1.28 g of **4aa** (82%), demonstrating the robust nature of this process.

Scheme 7. The gram scale experiments.



CONCLUSION

In summary, we have developed a new BPO-mediated oxidative dehydrogenative aromatization reaction for the construction of pyrrolidines. The results of a series of control experiments revealed that this reaction proceeds via a radical-based mechanism. This reaction was subsequently combined with a silver-catalyzed 1,3-dipolar cycloaddition reaction in one pot to afford a practical synthetic method for preparation of multi-substituted pyrroles. This tandem reaction is simple and uses readily available starting materials under mild reaction conditions.

EXPERIMENTAL SECTION

General Methods. Unless otherwise noted, all commercial reagents and solvents were obtained from the commercial provider and used without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded on 400 MHz spectrometers. Flash column chromatography was performed on 300-400 mesh silica gels. Analytical thin layer chromatography was performed with pre-coated glass baked plates (250 μ) and visualized by fluorescence. HRMS were recorded on TOF-Q spectrometer. Imines were synthesized according to the literature.

General procedure for synthesis of α-iminoesters 1 [16]:

A suspension of methyl/ethyl glycinate hydrochloride (12 mmol, 1.2 equiv.), excess $MgSO_4$, and Et_3N (12 mmol, 1.2 equiv.) in CH_2Cl_2 (10 ml) was stirred at r.t. for 1 h. Aldehyde (10 mmol, 1.0 equiv.) was added and the mixture was stirred at r.t. overnight. The reaction was monitored by TLC. After the reaction finish, $MgSO_4$ was removed by filtration and the filtrate was washed with H_2O (30 ml). The aqueous phase was extracted with CH_2Cl_2 (10 ml × 3) and the combined organic layers were washed with brine. The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuous. Products obtained were sufficiently pure, but were purified by re-crystallization if necessary.

General procedure for synthesis of Pyrrolidines 3 [16c]:

A solution of Et_3N (1.53 ml, 11 mmol) in 5.0 ml of toluene was added drop wise to the mixture of imine **1** (10 mmol), AgOAc (0.17 g, 1.1 mmol), electron-deficient olefin **2** (11 mmol) in 15 ml of toluene. Reaction mixture was stirred at room temperature for 12-48 h. Then toluene was removed by evaporation. The solid residue was suspended in 50 ml $CHCl_3$ and the precipitate was removed by filtration. Organic phase was washed with 100 ml of water, 100 ml of brine and dried over Na_2SO_4, filtered and volatiles were evaporated. The product was purified by column chromatography on silica gel (petroleum ether/ ethyl acetate).

*Dimethyl 5-(4-methoxyphenyl)pyrrolidine-2,4-dicarboxylate (**3ae**)*: PE/ EA = 2/ 1; white solid; m. p. 49-51 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 7.25 (d, J = 8.4 Hz, 2H), 6.85 (d, J = 8.4 Hz, 2H), 4.50 (d, J = 7.9 Hz, 1H), 3.97 (t, J = 8.2 Hz, 1H), 3.83

(s, 3H), 3.79 (s, 3H), 3.31-3.27 (m, 4H), 2.60 - 2.40 (m, 1H), 2.41 (t, J = 7.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): 173.8, 173.1, 159.0, 131.2, 127.9, 113.6, 65.4, 59.9, 55.2, 52.2, 51.3, 49.7, 33.3 cm^{-1}; IR (NaCl) v: 3360, 2998, 2952, 2838, 1737, 1613, 1585, 1514, 1436, 1378 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{15}H_{19}NO_5Na$ 316.1155; Found 316.1174.

*Methyl 4-cyano-5-(4-methoxyphenyl)pyrrolidine-2-carboxylate (**3ag**)*: PE/ EA = 2/ 1; white solid; m. p. 60-62 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz): 7.4 (d, J = 8.4 Hz, 2H), 6.9 (d, J = 8.6 Hz, 2H), 4.3 (d, J = 9.2 Hz, 1H), 4.1 (dd, J = 8.9, 5.0 Hz, 1H), 3.8 (ds, 6H), 2.8 (q, J = 9.1 Hz, 1H), 2.6 - 2.5 (m, 2H), 1.72 - 1.55 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): 173.8, 159.9, 130.6, 127.8, 119.7, 114.3, 67.0, 58.5, 55.3, 52.5, 36.5, 34.3; IR (NaCl) v: 3349, 3002, 2954, 2839, 2242, 1738, 1613, 1585, 1515, 1457, 1436, 1374, 1339 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{14}H_{17}N_2O_3$ 261.1234; Found 261.1234.

General procedure for synthesis of Pyrroles 4:

Imine substrate **1** (0.36 mmol), LiOH (1.3 mg, 0.054 mmol), Ag_2CO_3 (8.3 mg, 0.015 mmol), electron-deficient olefin **2** (0.3 mmol, 1.0 equiv.) and cyclohexane (0.50 ml) were added to a tube. Then the mixture was stirred at r.t. for 12-24 h. Benz peroxide (BPO) (174.4 mg, 0.72 mmol) was added follow by another 1.0 ml cyclohexane. The tube was sealed and then the mixture was stirred at 110 ^{o}C for 5 h. After the reaction finished, the reaction mixture was cooled down to room temperature, poured into saturated sodium bicarbonate (20 ml) and extracted with $CHCl_3$ (10 ml x 3). The organic layers were combined, dried with Na_2SO_4 and filtered. Then the mixture was evaporated under vacuum and the crude mixture was purified by flash chromatography (silica gel, petroleum ether/ ethyl acetate).

Procedure for the gram scale experiment:

Iminoesters **1a** (1.20 g, 5.4 mmol), LiOH (19.5 mg, 0.81 mmol), Ag_2CO_3 (124.5 mg, 0.225 mmol), dimethyl maleate **2a** (575 µl, 4.5 mmol) and cyclohexane (7.5 ml) were added to a neat. Then the mixture was stirred at r.t. for 24 h. Benzoperoxide (BPO) (2.61 g, 10.8 mmol) was added follow by another 15.0 ml cyclohexane and then the mixture was stirred at 110 ^{o}C for 5 h. When the reaction finished, the mixture was cooled down to room temperature, poured into saturated sodium bicarbonate (20 ml) and extracted with $CHCl_3$ (30 ml x 3). The organic layers were combined, dried with Na_2SO_4 and filtered. Then the mixture was evaporated under vacuum and the crude mixture was purified by flash chromatography (silica gel, petroleum ether/ ethyl acetate). The pyrrole **4aa** was isolated as a white solid in the yield of 82% (1.28 g).

Characteristic data of Pyrroles:

*Trimethyl 5-(4-methoxyphenyl)-1H-pyrrole-2,3,4-tricarboxylate (**4aa**)*: 93.1 mg (89%, PE/ EA = 1/ 1); yellow solid; ^{1}H NMR ($CDCl_3$, 400 MHz): 9.69 (s, 1H), 7.50 (d, J = 6.9 Hz, 1H), 6.93 (dd, J = 8.8, 2.7 Hz, 2H), 3.94 (s, 2H), 3.83 (s, 2H), 3.78 (s, 2H), 3.71 (s, 2H). [19]

*Trimethyl 5-phenyl-1H-pyrrole-2,3,4-tricarboxylate (**4ba**)*: 54.4 mg (57 %, PE/ EA = 2/1); white solid; ^{1}H NMR($CDCl_3$, 400 MHz): 10.10 (s, 1H), 7.54 (dd, J = 6.7, 3.0 Hz, 2H), 7.44 - 7.36 (m, 3H), 3.93 (s, 3H), 3.69 (s, 6H). [19]

*Trimethyl 5-(2-bromophenyl)-1H-pyrrole-2,3,4-tricarboxylate (**4ca**)*: 73.4 mg (62 %, PE/ EA = 3/1); white solid; m. p. 144-146 ^{o}C; ^{1}H NMR($CDCl_3$, 400 MHz): 10.29 (s, 1H), 7.64 (d, J = 7.9 Hz, 1H), 7.38-7.27 (m, 3H), 3.94 (s, 3H), 3.68 (s, 3H), 3.64 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 165.8, 162.8, 160.4, 138.2, 132.7, 132.1, 131.9, 130.8, 126.9, 123.9, 123.8, 119.5, 113.9, 52.8, 52.4, 51.6; IR (NaCl) v: 3261, 3001, 2952, 1717, 1574, 1525, 1474, 1446, 1419, 1360 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{16}H_{14}BrNO_6Na$ 417.9897; Found 417.9895.

*Trimethyl 5-(2-fluorophenyl)-1H-pyrrole-2,3,4-tricarboxylate (**4da**)*: 73.0 mg (73 %, PE/ EA = 2/1); white solid; m. p. 158-159 ^{o}C; ^{1}H NMR($CDCl_3$, 400 MHz): 10.31 (s, 1H), 7.49-7.42 (m, 1H), 7.42-7.35 (m, 1H), 7.14 (dt, J = 23.0, 8.3 Hz, 2H), 3.92 (s, 3H), 3.68 (d, J = 8.9 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): 165.8, 162.9, 160.3, 160.0 (d, J=248.6 Hz), 133.5, 131.7 (d, J = 2.1 Hz), 131.4 (d, J = 8.3 Hz), 124.4, 123.8 (d, J = 3.7 Hz), 120.0, 118.2 (d, J = 14.4 Hz), 115.7 (d, J = 21.8 Hz), 113.9, 52.7, 52.3, 51.6; IR (NaCl) v: 3268, 2954, 1716, 1651, 1622, 1575, 1525, 1489, 1456, 1361 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{16}H_{14}FNO_6Na$ 358.0697; Found 358.0697.

*Trimethyl 5-(4-chlorophenyl)-1H-pyrrole-2,3,4-tricarboxylate (**4ea**)*: 75.6 mg (72%, PE/ EA = 3/ 1); white solid; ^{1}H NMR ($CDCl_3$, 400 MHz): 10.23 (s, 1H), 7.47 (dd, J = 6.5, 4.5 Hz, 2H), 7.36 (d, J = 8.6 Hz, 2H), 3.92 (s, 3H), 3.72 (s, 3H), 3.69 (s, 3H). [19]

*Trimethyl 5-(p-tolyl)-1H-pyrrole-2,3,4-tricarboxylate (**4fa**)*: 69.6 mg (70%, PE/ EA = 3/ 1); yellow solid; ^{1}H NMR ($CDCl_3$, 400 MHz): 10.04 (s, 1H), 7.42 (d, J = 8.1 Hz, 2H), 7.19 (d, J = 7.7 Hz, 2H), 3.92 (s, 3H), 3.71 (s, 2H), 3.69 (s, 2H), 2.36 (s, 3H). [19]

*Trimethyl 5-(3,4-dichlorophenyl)-1H-pyrrole-2,3,4-tricarboxylate (**4ga**)*: 84.6 mg (75%, PE/ EA = 3/ 1); white solid; m. p. 138-140 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 10.48 (s, 1H), 7.67 (s, 1H), 7.47 (d, J = 8.3 Hz, 1H), 7.41 (d, J = 8.4 Hz, 1H), 3.94 (s, 3H), 3.73 (d, J = 6.5 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): 165.7, 162.9, 160.3, 137.4, 133.7, 132.3, 131.2, 130.0, 129.8, 129.0, 125.0, 120.1, 112.7, 52.8, 52.4, 51.7; IR (NaCl) *v*: 3261, 2953, 1717, 1575, 1555, 1521, 1472, 1447, 1381, 1351 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{16}H_{13}Cl_2NO_6Na$ 408.0012; Found 408.0008.

*Trimethyl 5-(3-nitrophenyl)-1H-pyrrole-2,3,4-tricarboxylate (**4ha**)*: 38.7 mg (36 %, PE/ EA = 2/1); yellow sticky oil; ^{1}H NMR($CDCl_3$, 400 MHz): 10.39 (s, 1H), 8.45 (s, 1H), 8.26 (d, J = 7.2 Hz, 1H), 7.93 (d, J = 7.7 Hz, 1H), 7.61 (t, J = 7.9 Hz, 1H), 3.95 (s, 3H), 3.78 (s, 3H), 3.73 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 165.6, 162.8, 160.1, 147.9, 137.0, 135.6, 131.5, 129.2, 124.9, 124.5, 124.0, 120.5, 113.0, 52.9, 52.5, 51.8; IR (NaCl) *v*: 3262, 3004, 2954, 1717, 1575, 1521, 1449, 1349 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{16}H_{14}N_2O_8Na$ 385.0642; Found 385.0641.

*Trimethyl 5-(3-cyanophenyl)-1H-pyrrole-2,3,4-tricarboxylate (**4ia**)*: 73.1 mg (71 %, PE/ EA = 2/1); yellow solid; m. p. 126-129 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 10.54 (s, 1H), 7.81 (s, 1H), 7.75 (d, J = 7.9 Hz, 1H), 7.61 (d, J = 8.3 Hz, 1H), 7.46 (t, J = 8.0 Hz, 1H), 3.86 (s, 3H), 3.69 (s, 3H), 3.64 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 165.7, 162.9, 160.1, 137.4, 134.1, 133.0, 132.6, 131.3, 129.0, 124.9, 120.4, 118.1, 112.7, 112.4, 52.8, 52.5, 51.8; IR (KBr) *v*: 3282, 3075, 2995, 2961, 2232, 1470, 1717, 1682, 1617, 1589, 1561, 1519, 1466, 1432, 1409, 1357, 1308 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{17}H_{14}N_2O_6Na$ 365.0744; Found 365.0739.

*Trimethyl 5-(3-methylthiophen-2-yl)-1H-pyrrole-2,3,4-tricarboxylate (**4ja**)*: 45.9 mg (45%, PE/ EA = 3/ 1); yellow solid; m. p. 112-115 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 9.79 (s, 1H), 7.33 (d, J = 5.0 Hz, 1H), 6.91 (d, J = 5.0 Hz, 1H), 3.95 (s, 3H), 3.79 (s, 3H), 3.71 (s, 3H), 2.17 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 165.8, 162.7, 160.1, 139.3, 132.4, 129.8, 126.6, 124.4, 124.3, 119.9, 114.5, 52.8, 52.4, 51.6, 14.8; IR (NaCl) *v*: 3255, 3000, 2953, 1717, 1585, 1555, 1508, 1456, 1398, 1353 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{15}H_{15}NO_6SNa$ 360.0512; Found 360.0509.

*Trimethyl 5-(pyridin-3-yl)-1H-pyrrole-2,3,4-tricarboxylate (**4ka**)*: 57.6 mg (60%, PE/ EA = 1/ 3); white solid; m. p. 169-172 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 11.47 (s, 1H), 8.59 (d, J = 2.3 Hz, 1H), 8.58 – 8.53 (m, 1H), 7.97 (dt, J = 7.9, 2.0 Hz, 1H), 7.34 (dd, J = 8.0, 4.9 Hz, 1H), 3.94 (s, 3H), 3.80 (s, 3H), 3.69 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 165.9, 162.9, 160.2, 149.7, 149.3, 138.0, 136.6, 126.8, 125.0, 123.0, 120.7, 112.9, 52.8, 52.5, 51.7; IR (NaCl) *v*: 3253, 2954, 1716, 1646, 1575, 1556, 1520, 1456, 1409, 1360, 1338 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{15}H_{14}N_2O_6Na$ 341.0744; Found 341.0742.

*Trimethyl 5-(pyridin-2-yl)-1H-pyrrole-2,3,4-tricarboxylate (**4la**)*: 31.0 mg (33%, PE/ EA = 1/ 3); white solid; m. p. 156-159 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 11.32 (s, 1H), 8.72-8.55 (m, 2H), 8.01 (d, J = 8.0 Hz, 1H), 7.39 (dd, J = 8.0, 4.8 Hz, 1H), 3.96 (s, 3H), 3.83 (s, 3H), 3.72 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 165.8, 162.9, 160.2, 149.7, 149.2, 138.0, 136.5, 126.8, 125.0, 123.0, 120.8, 112.9, 52.8, 52.5, 51.7; IR (NaCl) *v*: 3254, 2954, 1716, 1576, 1520, 1450, 1409, 1358, 1334 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{15}H_{14}N_2O_6Na$ 341.0744; Found 341.0742.

*Trimethyl 5-(heptan-3-yl)-1H-pyrrole-2,3,4-tricarboxylate (**4ma**)*: 60.6 mg (60%, PE/ EA = 6/ 1); yellow sticky oil; ^{1}H NMR ($CDCl_3$, 400 MHz): 9.55 (s, 1H), 3.93 (s, 3H), 3.86 (s, 3H), 3.79 (s, 3H), 3.60 (qq, J = 11.8, 6.2, 4.8 Hz, 1H), 1.80-1.54 (m, 4H), 1.30-1.11 (m, 4H), 0.83 (q, J = 7.2, 6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): 166.4, 163.7, 146.8, 118.4, 112.6, 52.6, 52.3, 51.3, 38.2, 34.2, 29.4, 27.9, 22.5, 13.8, 11.8; IR (NaCl) *v*: 3293, 2957, 2932, 2873, 1716, 1575, 1519, 1463, 1376, 1344 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{17}H_{25}NO_6Na$ 362.1574; Found 362.1580.

*2-Ethyl 3,4-dimethyl 5-(4-chlorophenyl)-1H-pyrrole-2,3,4-tricarboxylate (**4na**)*: 73.8 mg (67%, PE/ EA = 5/ 1); yellow solid; m. p. 147-149 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 10.44 (s, 1H), 7.49 (d, J = 8.1 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), 4.08 (q, J = 7.1 Hz, 2H), 3.92 (s, 3H), 3.70 (s, 3H), 1.25 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 165.8, 163.1, 160.1, 139.0, 135.5, 130.9, 128.6, 128.3, 124.9, 120.0, 112.2, 61.6, 52.6, 51.6, 13.9; IR (KBr) *v*: 3284, 2982, 1751, 1742, 1728, 1694, 1654, 1560, 1483, 1458, 1446, 1428, 1351 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{17}H_{16}ClNO_6Na$ 388.0558; Found 388.0555.

*3,4-Dibutyl 2-methyl 5-(4-chlorophenyl)-1H-pyrrole-2,3,4-tricarboxylate (**4eb**)*: 79.0 mg (60%, PE/ EA = 6/ 1); yellow solid; m. p. 72-75 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 10.18 (s, 1H), 7.48 (d, J = 8.3 Hz, 2H), 7.36 (d, J = 8.4 Hz, 2H), 4.33 (t, J = 6.7 Hz, 2H), 4.11 (t, J = 6.6 Hz, 2H), 3.70 (s, 3H), 1.73 (p, J = 6.9 Hz, 2H), 1.52 (dt, J = 14.7, 6.8 Hz, 2H), 1.44 (p, J = 7.5 Hz, 2H), 1.24 (h, J = 7.4 Hz, 2H), 0.96 (t, J = 7.4 Hz, 3H), 0.86 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 165.4, 162.7, 160.5, 138.9, 135.5, 130.9, 128.7, 128.2, 125.3, 119.5, 112.7, 65.7, 64.5, 52.2, 30.6, 30.5, 19.1, 19.0, 13.7, 13.6; IR (KBr) *v*: 3172, 2956, 2870, 1728, 1702, 1654, 1577, 1486, 1450, 1428, 1356 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{22}H_{26}ClNO_6Na$ 458.1341; Found 458.1339.

*4-(tert-Butyl) 2-methyl 5-(4-chlorophenyl)-1H-pyrrole-2,4-dicarboxylate (**4ec**)*: 60.1 mg (60%, PE/ EA = 8/ 1); yellow solid; m. p. 146-148 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 10.07 (s, 1H), 7.53 (d, J = 8.5 Hz, 2H), 7.36 (d, J = 8.5 Hz, 2H), 7.31

(d, J = 2.8 Hz, 1H), 3.74 (s, 3H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): 163.2, 161.6 (d, J = 3.2 Hz), 139.2 (d, J = 4.9 Hz), 134.9, 130.7 (d, J = 2.1 Hz), 129.6, 128.2, 121.8, 118.8 (d, J = 1.7 Hz), 116.2, 80.5, 51.8, 28.2; IR (NaCl) v: 3278, 2978, 1687, 1576, 1514, 1470, 1438, 1417, 1392, 1367, 1344 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{17}H_{18}ClNO_4Na$ 358.0817; Found 358.0817.

*4-Ethyl 2-methyl 5-(4-chlorophenyl)-1H-pyrrole-2,4-dicarboxylate (**4ed**)*: 51.1 mg (55%, PE/ EA = 6/ 1); yellow solid; m. p. 124-126 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 10.02 (s, 1H), 7.56 (d, J = 8.6 Hz, 2H), 7.41 – 7.33 (m, 3H), 4.22 (q, J = 7.1 Hz, 2H), 3.77 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 163.8, 161.5, 139.6, 135.1, 130.7, 129.2, 128.2, 122.1, 118.7, 114.5, 60.1, 51.8, 14.2; IR (KBr) v: 3309, 3288, 2980, 1719, 1694, 1577, 1560, 1474, 1437, 1420, 1347 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{15}H_{14}ClNO_4Na$ 330.0504; Found 330.0512.

*Dimethyl 5-(4-chlorophenyl)-1H-pyrrole-2,4-dicarboxylate (**4ee**)*: 52.2 mg (59%, PE/ EA = 6/ 1); yellow solid; m. p. 182-183 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 9.71 (s, 1H), 7.57 (d, J = 8.4 Hz, 2H), 7.43 – 7.36 (m, 3H), 3.82 (s, 3H), 3.76 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 164.2, 161.3, 139.5, 135.3, 130.5, 129.1, 128.5, 122.2, 118.5, 114.1, 51.9, 51.3; IR (KBr) v: 3283, 3141, 3001, 2955, 1718, 1694, 1605, 1577, 1560, 1474, 1438, 1415, 1400, 1350, 1312 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{14}H_{12}ClNO_4Na$ 316.0347; Found 316.0349.

*4-Butyl 2-methyl 5-(4-chlorophenyl)-1H-pyrrole-2,4-dicarboxylate (**4ef**)*: 75.2 mg (75%, PE/ EA = 12/ 1); yellow solid; m. p. 107-109 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 10.22 (s, 1H), 7.55 (d, J = 8.1 Hz, 2H), 7.39-7.32 (m, 3H), 4.15 (t, J = 6.5 Hz, 2H), 3.73 (s, 3H), 1.60 (p, J = 6.8 Hz, 2H), 1.33 (h, J = 7.3 Hz, 2H), 0.91 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 164.0, 161.6, 139.7, 135.1, 130.8, 129.3, 128.2, 122.1, 118.7, 114.5, 64.1, 51.8, 30.7, 19.2, 13.7; IR (KBr) v: 3305, 2994, 2969, 2950, 2873, 1720, 1695, 1605, 1577, 1560, 1467, 1437, 1401, 1384, 1351 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{17}H_{18}ClNO_4Na$ 358.0817; Found 358.0814.

*Methyl 5-(4-chlorophenyl)-4-cyano-1H-pyrrole-2-carboxylate (**4eg**)*: 41.1 mg (53%, PE/ EA = 6/ 1); yellow solid; m. p. 214-217 °C; ^{1}H NMR (DMSO, 400 MHz): 13.13 (s, 1H), 7.82 (d, J = 8.4 Hz, 2H), 7.57 (d, J = 8.5 Hz, 2H), 7.29 (s, 1H), 3.81 (s, 3H); ^{13}C NMR (DMSO, 100 MHz): 160.2, 141.5, 134.7, 129.4, 129.4, 127.9, 124.5, 120.0, 116.7, 91.7, 52.3; IR (KBr) v: 3283, 3160, 2959, 2227, 1724, 1695, 1676, 1654, 1577, 1560, 1473, 1433, 1343, 1333 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{13}H_9ClN_2O_2Na$ 283.0245; Found 283.0257.

*Methyl 5-(4-chlorophenyl)-4-(dimethylcarbamoyl)-1H-pyrrole-2-carboxylate (**4eh**)*: 36.8 mg (40%, PE/ EA = 1/ 1); orange-red solid; m. p. 149-151 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 10.25 (s, 1H), 7.44 (d, J = 8.5 Hz, 2H), 7.32 (d, J = 8.5 Hz, 2H), 6.94 (d, J = 2.6 Hz, 1H), 3.83 (s, 3H), 3.04 (s, 3H), 2.75 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 167.5, 161.4, 134.4, 133.6, 129.3, 129.1, 128.1, 122.7, 118.5, 116.2, 51.8, 38.7, 35.1; IR (NaCl) v: 3191, 2950, 1713, 1612, 1578, 1561, 1509, 1465, 1437, 1401, 1385, 1330 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{15}H_{15}ClN_2O_3Na$ 329.0663; Found 329.0663.

*Methyl 5-(4-chlorophenyl)-4-(phenylcarbamoyl)-1H-pyrrole-2-carboxylate (**4ei**)*: 51.9 mg (49%, PE/ EA = 4/ 1); light-red solid; m. p. 196-198 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 9.79 (s, 1H), 7.59 (d, J = 8.2 Hz, 2H), 7.47 – 7.39 (m, 5H), 7.33 – 7.29 (m, 3H), 7.10 (t, J = 7.4 Hz, 1H), 3.85 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 162.1, 161.2, 137.9, 136.4, 135.6, 130.3, 129.1, 129.0, 128.9, 124.3, 122.5, 119.8, 118.8, 116.2, 52.0; IR (KBr) v: 3284, 2952, 1694, 1644, 1618, 1597, 1577, 1560, 1545, 1500, 1467, 1439, 1315 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{19}H_{15}ClN_2O_3Na$ 377.0663; Found 377.0662.

*Dimethyl 5-(4-chlorophenyl)-3-phenyl-1H-pyrrole-2,4-dicarboxylate (**4ek**)*: 61.6 mg (56%, PE/ EA = 4/ 1); yellow solid; m. p. 199-201 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 9.63 (s, 1H), 7.54 (d, J = 8.5 Hz, 2H), 7.43 (d, J = 8.5 Hz, 2H), 7.37 (td, J = 7.8, 7.0, 4.5 Hz, 5H), 3.63 (s, 3H), 3.49 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 164.8, 161.4, 137.8, 135.2, 133.9, 133.6, 130.2, 129.9, 129.6, 128.6, 127.3, 127.2, 119.6, 114.8, 51.6, 51.0; IR (KBr) v: 3287, 3091, 3061, 2948, 2849, 1718, 1672, 1602, 1577, 1570, 1556, 1494, 1465, 1445, 1416, 1400, 1307 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{20}H_{16}ClNO_4Na$ 392.0660; Found 392.0656.

*Methyl 5-(4-chlorophenyl)-4-(dimethoxyphosphoryl)-1H-pyrrole-2- carboxylate (**4ej**)*: 32.1 mg (31%, PE/ EA = 1/ 1); yellow sticky oil; ^{1}H NMR ($CDCl_3$, 400 MHz): 10.37 (s, 1H), 7.66 (d, J = 8.6 Hz, 2H), 7.36 (d, J = 8.6 Hz, 2H), 7.28 – 7.21 (m, 1H), 3.81 (s, 3H), 3.65 (s, 3H), 3.63 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 161.1 (d, J = 2.0 Hz), 140.7 (d, J = 23.0 Hz), 135.2, 129.8, 129.0, 128.6, 123.4 (d, J = 15.8 Hz), 121.9 (d, J = 11.6 Hz), 107.5 (d, J = 216.6 Hz), 52.5 (d, J = 5.7 Hz), 51.8; IR (KBr) v: 3147, 3069, 2955, 2926, 2853, 2756, 1718, 1575, 1469, 1440, 1413, 1389, 1324, 1312 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{14}H_{15}ClNO_5PNa$ 366.0269; Found 366.0268.

*Methyl 4-benzoyl-5-(4-chlorophenyl)-3-(p-tolyl)-1H-pyrrole-2- carboxylate (**4el**)*: 60.2 mg (47%, PE/ EA = 8/ 1); yellow solid; m. p. 230-231 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 9.52 (s, 1H), 7.65 (d, J = 8.1 Hz, 2H), 7.40 (d, J = 8.5 Hz, 2H), 7.34 (t, J = 7.4 Hz, 1H), 7.28 (d, J = 3.9 Hz, 2H), 7.19 (dt, J = 8.0, 3.7 Hz, 4H), 7.00 (d, J = 7.7 Hz, 2H), 3.76 (s, 3H), 2.26 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 193.8, 161.4, 138.0, 137.0, 135.1, 134.8, 133.0, 132.7, 130.1, 129.8, 129.7, 129.1, 129.0, 129.0, 128.2, 128.0, 123.6, 118.9, 51.6, 21.2; IR (KBr) v: 3270, 3065, 3024, 2953, 2919, 2854, 1679, 1638, 1598, 1575,

1556, 1530, 1498, 1448, 1419, 1394, 1335 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{26}H_{20}ClNO_3Na$ 452.1024; Found 452.1019.

Synthetic procedure for 5a:

A mixture of 1-bromobutane (0.47 ml, 4.4 mmol), pyrrolidine **3aa** (0.70 g, 2 mmol), potassium carbonate (0.33 g, 2.4 mmol), and potassium iodide (66.4 mg, 0.40 mmol) in acetonitrile (2.0 mL) was stirred at 100 °C for 8 h, and the reaction mixture was added a saturated $NaHCO_3$ aqueous solution and then extracted with ethyl acetate (15 mL) for three times. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash column chromatography on silica gel (PE/EA = 2/1) to give the title compound (0.57 g, 70%) as a yellow sticky oil.

*Trimethyl 1-butyl-5-(4-methoxyphenyl)pyrrolidine-2,3,4-tricarboxylate (**5a**)*: yellow sticky oil; ^1H NMR ($CDCl_3$, 400 MHz): 7.33 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 4.21 (d, *J* = 9.9 Hz, 1H), 3.92 (t, *J* = 9.2 Hz, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 3.72 (s, 3H), 3.66 (d, *J* = 9.2 Hz, 1H), 3.57 (t, *J* = 9.6 Hz, 1H), 3.24 (s, 3H), 2.68 - 2.52 (m, 2H), 1.30 - 1.11 (m, 4H), 0.75 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 172.8, 172.1, 170.6, 159.1, 132.1, 129.1, 113.2, 68.8, 68.0, 55.2, 53.0, 52.4, 52.3, 51.6, 51.5, 48.5, 28.8, 20.3, 13.8; IR (KBr) *v*: 2954, 2871, 1741, 1611, 1585, 1511, 1436, 1339 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{21}H_{29}NO_7Na$ 430.1836; Found 430.1844.

Synthetic procedure for 5b:

The compound **3aa** (351.4 mg, 1.0 mmol) was dissolved in 5.0 mL of methylene chloride, *p*-toluenesulfonyl chloride (286.0 mg, 1.5 mmol) and triethyl amine (405 μL, 2.5 mmol) were added subsequently and the resulting mixture was stirred for 42 hours at room temperature. The reaction mixture was added a saturated brine, extracted with $CHCl_3$ (15 ml) for three times, dried over Na_2SO_4, filtered and volatiles were evaporated. The crude product was purified by column chromatography on silica gel (PE/EA = 3/2) to afford the compound **5b** (414.7 mg, 82%).

*Trimethyl 5-(4-methoxyphenyl)-1-tosylpyrrolidine-2,3,4-tricarboxylate (**5b**)*: white solid; m. p. 140-142 °C; ^1H NMR ($CDCl_3$, 400 MHz): 7.54 (d, *J* = 8.0 Hz, 2H), 7.12 (dd, *J* = 16.3, 8.1 Hz, 4H), 6.64 (d, *J* = 8.3 Hz, 2H), 5.29 (d, *J* = 8.9 Hz, 1H), 5.09 (d, *J* = 7.6 Hz, 1H), 3.83 (s, 3H), 3.77 (s, 3H), 3.75 (s, 3H), 3.46 (t, *J* = 7.0 Hz, 1H), 3.37 (dd, *J* = 9.0, 6.4 Hz, 1H), 3.19 (s, 3H), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 170.0, 169.8, 168.2, 159.2, 143.7, 135.5, 129.1, 129.0, 128.2, 127.3, 113.1, 65.5, 61.7, 55.2, 52.7, 52.3, 51.6, 51.5, 48.1, 21.5; IR (KBr) *v*: 3449, 2999, 2950, 2843, 1743, 1615, 1598, 1588, 1516, 1439, 1402, 1365, 1331 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{24}H_{27}NO_9SNa$ 528.1299; Found 528.1298.

Procedure of kinetic experiments:

Pyrrolidine **3** or **5** (0.20 mmol), BPO (0.48 mmol) and 1.0 mL of cyclohexane was added to a tube. Then the tube was sealed and heated for 30 min in a preheated oil bath at 110 °C. The reaction mixture was cooled down to room temperature, poured into saturated sodium bicarbonate (20 ml) and extracted with $CHCl_3$ (10 ml x 3). The organic layers were combined, dried with Na_2SO_4 and filtered. Then the mixture was evaporated under vacuum and the crude mixture was purified by flash chromatography (silica gel, petroleum ether/ ethyl acetate) to afford **4** or **6**.

*Dimethyl 5-(4-methoxyphenyl)-1H-pyrrole-2,4-dicarboxylate (**4ae**)*: PE/ EA = 5/ 1; white solid; m. p. 169-171 °C; ^1H NMR ($CDCl_3$, 400 MHz): 9.55 (s, 1H), 7.59 (d, *J* = 8.7 Hz, 2H), 7.39 (d, *J* = 2.8 Hz, 1H), 6.97 (d, *J* = 8.8 Hz, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 3.78 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 164.5, 161.4, 160.4, 141.0, 130.5, 123.1, 121.6, 118.6, 113.7, 113.3, 55.3, 51.8, 51.1; IR (KBr) *v*: 3310, 3001, 2953, 1726, 1701, 1616, 1586, 1567, 1484, 1467, 1414, 1349, 1315 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{15}H_{15}NO_5Na$ 312.0842; Found 312.0842.

*Methyl 4-cyano-5-(4-methoxyphenyl)-1H-pyrrole-2-carboxylate (**4ag**)*: PE/ EA = 3/ 1; white solid; m. p. 222-223 °C; ^1H NMR (DMSO, 400 MHz): 12.97 (s, 1H), 7.83 (d, *J* = 9.1 Hz, 2H), 7.33 (s, 1H), 7.13 (d, *J* = 9.1 Hz, 2H), 3.86 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): 160.7, 160.3, 143.1, 129.2, 123.7, 121.5, 119.9, 117.2, 114.8, 90.5, 55.8, 52.2; IR (KBr) *v*: 3288, 3137, 3006, 2951, 2845, 2221, 1698, 1615, 1584, 1569, 1513, 1480, 1457, 1438,1414, 1343,1302 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{14}H_{12}N_2O_3Na$ 279.0740; Found 279.0745.

*Trimethyl 1-butyl-5-(4-methoxyphenyl)-1H-pyrrole-2,3,4-tricarboxylate (**6a**)*: PE/ EA = 2/ 1; colorless sticky oil; ^1H NMR ($CDCl_3$, 400 MHz): 7.22 (d, *J* = 8.3 Hz, 2H), 6.99 (d, *J* = 8.3 Hz, 2H), 4.11 (t, *J* = 7.8 Hz, 2H), 3.96 (s, 3H), 3.87 (s, 3H), 3.85 (s, 3H), 3.61 (s, 3H), 1.53 (p, *J* = 7.6 Hz, 2H), 1.14 (h, *J* = 7.3 Hz, 2H), 0.76 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 167.0, 163.1, 160.2, 160.1, 143.1, 131.6, 126.1, 122.1, 119.0, 113.7, 111.9, 55.3, 52.7, 51.9, 51.4, 46.1, 33.4, 19.7, 13.4; IR (NaCl) *v*: 2955, 2874, 1744, 1714, 1612, 1575, 1550, 1526, 1488, 1456, 1404 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{21}H_{25}NO_7Na$ 426.1523; Found 426.1524.

Synthetic procedure for 6b:

To a solution of the pyrrole **4aa** (347.3 mg, 1.0 mmol) in CH_2Cl_2 (1.0 mL) was added 4-*N*,*N*-dimethylaminopyridine (12.2 mg, 0.10 mmol) and *p*-TsCl (286.0 mg, 1.5 mmol). The solution was stirred for 5 min at room temperature and NaH (60% in mineral oil, 4.0 mmol) was added. Then the mixture was stirred for 12 h at 60°C. The solution was diluted with CH_2Cl_2, washed with H_2O and brine, dried over Na_2SO_4, and concentrated in vacuum. The crude product was purified by column chromatography on silica gel (PE/EA = 2/1) to afford **6b** (319.2 mg, 64%).

*Trimethyl 5-(4-methoxyphenyl)-1-tosyl-1H-pyrrole-2,3,4-tricarboxylate (**6b**)*: pale yellow solid; m. p. 106-108 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 7.37 (d, *J* = 8.1 Hz, 2H), 7.18 (d, *J* = 8.1 Hz, 2H), 7.01 (d, *J* = 8.3 Hz, 2H), 6.81 (d, *J* = 8.3 Hz, 2H), 4.04 (s, 3H), 3.87 (s, 3H), 3.86 (s, 3H), 3.59 (s, 3H), 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 163.5, 162.6, 161.8, 160.6, 146.3, 137.4, 134.4, 133.4, 129.8, 129.7, 128.3, 119.5, 118.7, 117.8, 112.7, 55.3, 53.5, 52.5, 52.2, 21.8; IR (KBr) *v*: 3449, 3002, 2953, 2840, 1736, 1612, 1595, 1577, 1541, 1499, 1443, 1389, 1354, 1301 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{24}H_{23}NO_9SNa$ 524.0986; Found 524.0986.

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Supporting Information Available. The experiment procedures, NMR spectra for all new compounds and ^{1}H NMR spectra for known compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

REFERENCES.

(1) Selected books and reviews about pyrrole: (a) Gossauer, A. in *Organic Chemistry in Monographs*, Springer-Verlag, New York, **1974**, *V15*, 1. (b) Jones, R. A.; Bean, G. P. in *Organic Chemistry*, Academic Press, London, **1974**, *V34*, 1. (c) In *Chem. Heterocycl. Compd.*, Jones, R. A. eds., John Wiley & Sons, Inc., New York, **1992**, *49*, 1. (d) Nisha; Kumar, K.; Kumar, V. *RSC Adv.* **2015**, *5*, 10899.

(2) Bhardwaj, V.; Gumber, D.; Abbot, V.; Dhimana, S.; Sharma, P. *RSC Adv.* **2015**, *5*, 15233.

(3) Selected recent reviews: (a) Alfonso, M.; Tárraga, A.; Molina, P. *Tetrahedron Lett.* **2016**, *57*, 3053. (b) Patel, R. V.; Park, S. W. *Bioorg. & Med. Chem.* **2015**, *23*, 5247. (c) Saha, I.; Lee, J. T.; Lee, C.-H. *Eur. J. Org. Chem.* **2015**, 3859. (d) Labuta, Jan; Hill, J. P.; Ishihara, S.; Hanyková, L.; Ariga K. *Acc. Chem. Res.* **2015**, *48*, 521. (e) Kim, S. K.; Sessler, J. L. *Acc. Chem. Res.* **2014**, *47*, 2525. (f) Ding, Y.; Tang, Y.; Zhu, W.; Xie, Y. *Chem. Soc. Rev.* **2015**, *44*, 1101. (g) Lakshmi, V.; Rao, M. R.; Ravikanth, M. *Org. Biomol. Chem.* **2015**, *13*, 2501.

(4) Several recent reviews and selected recent papers: (a) Odom, A. L.; McDaniel, T. J. *Acc. Chem. Res.* **2015**, *48*, 2822. (b) Este´vez, V.; Villacampa, M.; Mene´ndez, J. C. *Chem. Soc. Rev.* **2014**, *43*, 4633. (c) Esmail Vessally *RSC Adv.* **2016**, *6*, 18619. (d) Khajuria, R.; Dham, S.; Kapoor K. K. *RSC Adv.* **2016**, *6*, 37039. (e) Sharma, A.; Piplani, P. *J. Heterocyclic Chem.* **2017**, *54*, 27.

(5) Selected books and recent reviews about 1,3-dipolar cycloaddition: (a) Suga, H.; Itoh, K. in *Methods and Applications of Cycloaddition Reactions in Organic Syntheses* Nishiwaki, N. eds., John Wiley & Sons, Inc., Hoboken, N. J, **2014**, 175. (b) Hashimoto, T.; Maruoka, K. *Handbook of Cyclization Reactions* Ma, S. eds., Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, **2010**, *1*, 87. (c) Singh, M. S.; Chowdhury, S.; Koley, S. *Tetrahedron* **2016**, *72*, 1603. (d) Najera, C.; Sansano, J. M.; Yus, M. *Org. & Biomol. Chem.* **2015**, *13*, 8596. (e) Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2015**, *115*, 5366. (f) Adrio, J.; Carretero, J. C. *Chem. Commun.* **2014**, *50*, 12434.

(6) Selected recent examples: (a) Cayuelas, A.; Larranaga, O.; Najera, C.; Sansano, J. M.; de Cozar, A.; Cossio, F. P. *Tetrahedron* **2016**, *72*, 6043. (b) Arpa, E. M.; Gonzalez-Esguevillas, M.; Pascual-Escudero, A.; Adrio, J.; Carretero, J. C. *J. Org. Chem.* **2016**, *81*, 6128. (c) Xu, H.; Golz, C.; Strohmann, C.; Antonchick, A. P.; Waldmann, H. *Angew. Chem. Int.*

Ed. **2016**, *55*, 7761. (d) Bai, X.; Li, L.; Xu, Z.; Zheng, Z.; Xia, C.; Cui, Y.; Xu, L. *Chem. Eur. J.* **2016**, *22*, 10399. (e) Zhang, Z.; Xu, B.; Xu, S.; Wu, H.; Zhang, J. *Angew. Chem., Int. Ed.* **2016**, *55*, 6324.

(7) Selected recent examples: (a) Bakshi, D.; Singh, A. *Asian J. Org. Chem.* **2016**, *5*, 70. (b) Li, F.; Chen, J.; Hou, Y.; Li, Y.; Wu, X.-Y.; Tong, X. *Org. Lett.* **2015**, *17*, 5376. (c) Gomha, S. M.; Dawood, K. M. *J. Chem. Res.* **2014**, *38*, 515. (d) Allgaeuer, D. S.; Mayer, P.; Mayr, H. *J. Am. Chem. Soc.* **2013**, *135*, 15216. (e) Yu, C.; Zhang, Y.; Zhang, S.; Li, H.; Wang, W. *Chem. Commun.* **2011**, *47*, 1036.

(8) Wang, Z.; Shi, Y.; Luo, X.; Han, D.; Deng, W. *New J. Chem.* **2013**, *37*, 1742.

(9) (a) Lopez-Perez, A.; Robles-Machin, R.; Adrio, J.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2007**, *46*, 9261. (b) Robles-Machin, R.; Lopez-Perez, A.; Gonzalez-Esguevillas, M.; Adrio, J.; Carretero, J. C. *Chem. Eur. J.* **2010**, *16*, 9864.

(10) Kudryavtsev, K. V.; Ivantcova, P. M.; Churakov, A. V.; Vasin, V. A. *Tetrahedron Lett.* **2012**, *53*, 4300.

(11) Xin, Y.; Zhao, J.; Han, J.; Zhu, S. *J. Fluorine Chem.* **2010**, *131*, 642.

(12) (a) Liu, H.; Tao, H.; Cong, H.; Wang, C. *J. Org. Chem.* **2016**, *81*, 3752. (b) Liu, H.; Liu, K.; Xue, Z.; He, Z.; Wang, C. *Org. Lett.* **2015**, *17*, 5440. (c) Das, T.; Saha, P.; Singh, V. K. *Org. Lett.* **2015**, *17*, 5088. (d) Arrieta, A.; Otaegui, D.; Zubia, A.; Cossío, F. P.; Díaz-Ortiz, A.; de la Hoz, A.; Herrero, M. A.; Prieto, P.; Foces-Foces, C.; Pizarro, J. L.; Arriortua, M. I. *J. Org. Chem.* **2007**, *72*, 4313.

(13) Murthy, S. N.; Nageswar, Y. V. D. *Tetrahedron Lett.* **2011**, *52*, 4481.

(14) (a) Fejes, I.; Toke, L.; Blasko, G.; Nyergesa, M.; Pak, C. S. *Tetrahedron* **2000**, *56*, 8545. (b) Oussaid, B.; Garrigues, B.; Soufiaoui, M. *Can. J. Chem.* **1994**, *72*, 2483. (c) Baumann, M.; Baxendale, I. R.; Kirschning, A.; Ley, S. V.; Wegner, J. *Heterocycles* **2011**, *82*, 1297.

(15) (a) Liu, Y.; Hu, H.-Y.; Zhang, Y.; Hu, H.-W.; Xu, J.-H. *Org. Biomol. Chem.* **2010**, *8*, 4921. (b) Hu, H.; Feng, J.; Zhu, Y.; Gu, N.; Kan, Y. *RSC Adv.* **2012**, *2*, 8637. (c) Liu, Y.; Hu, H.-Y.; Su, X.-B.; Sun, J.-W.; Cao, C.-S.; Shi, Y.-H. *Eur. J. Org. Chem.* **2013**, 2020; (d) Wang, F.; Shen, Y.; Hu, H.; Wang, X.; Wu, H.; Liu, Y. *J. Org. Chem.* **2014**, *79*, 9556; (e) Shi, F.; Zhang, Y.; Lu, Z.; Zhu, X.; Kan, W.; Wang, X.; Hu, H. *Synthesis* **2016**, *48*, 413; (f) Hu, H.; Li, G.; Gu, N.; Ji, M. *Chin. J. Org. Chem.* **2016**, *36*, 330; (g) Xu, J; Hu, H., Liu, Y.; Wang, X.; Kan, Y.; Wang, C. *Eur. J. Org. Chem.* **2017**, 257.

(16) (a) Zhao, Y.; Chen, K.; Fan, J.; Okamura, T.; Lu, Y.; Luo, L.; Sun, W. *Dalton Trans.* **2014**, *43*, 2252. (b) Gu, X.; Xu, Z.; Lo, V.; Che, C. *Synthesis* **2012**, *44*, 3307. (c) Nájera, C.; Retamosa, M. G.; Sansano, J. M. *Tetrahedron: Asymmetry* **2006**, *17*, 1985.

(17) Selected silver-catalyzed 1,3-dipolar cycloaddition reactions for synthesizing pyrrolidines from alkenes: (a) Paetzel, M.; Galley, G. *Tetrahedron Lett.* **1993**, *34*, 5707. (b) Cooper, D. M.; Grigg, R.; Hargreaves, S.; Kennewell, P.; Redpath, J. *Tetrahedron* **1995**, *51*, 7791. (c) Ayerbe, M.; Arrieta, A.; Cossio, F. P.; Linden, A. *J. Org. Chem.* **1998**, *63*, 1795. (d) Grigg, R.; Hargreves, S.; Redpath, J.; Turchi, S.; Yoganathan, G. *Synthesis* **1999**, 441. (e) Zubia, A.; Mendoza, L.; Vivanco, S.; Aldaba, E.; Carrascal, T.; Lecea, B.; Arrieta, A.; Zimmerman, T.; Vidal-Vana-clocha, F.; Cossio, F. P. *Angew. Chem., Int. Ed.* **2005**, *44*, 2903. (f) Kudryavtsev, K. V.; Mantsyzov, A. B.; Ivantcova, P. M.; Sokolov, M. N.; Churakov, A. V.; Brase, S.; Zefirov, N. S.; Polshakov, V. I. *Org. Lett.* **2016**, *18*, 4698.

(18) Lee, H. S.; Kim, J. M.; Kim, J. N. *Tetrahedron Lett.* **2007**, *48*, 4119.

(19) Yavari, I.; Bayat, M. J. *Synlett* **2013**, *24*, 2279.