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Iodine-Mediated Cyclization of Enamines to Imidazole-4-Carboxylic Derivatives with Sequential Removal of Nitrogen Atoms from $TMSN_3$

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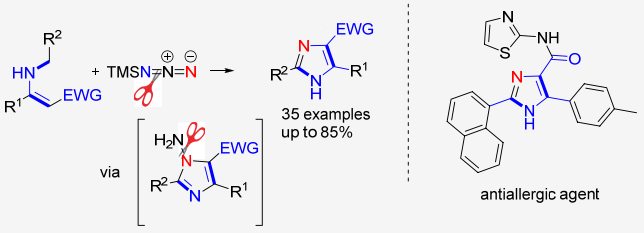
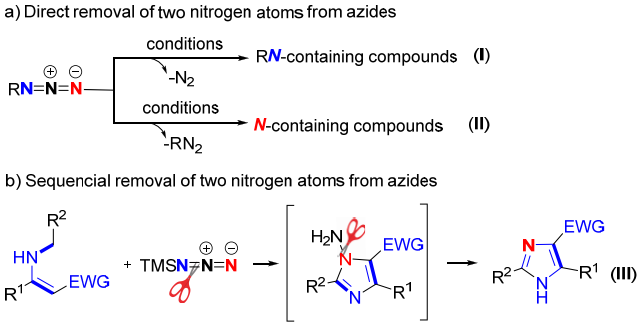
ABSTRACT: An iodine-mediated oxidative [4+1] cyclization of enamines with $TMSN_3$ for the synthesis of 2,5-disubstituted imidazole-4-carboxylic derivatives has been developed. The mechanistic studies revealed that the reaction proceeds through a sequential removal of two nitrogen atoms from $TMSN_3$. The synthetic utility was further demonstrated with a gram-scale reaction and various derivatization transformations of the products.



INTRODUCTION

Azides are important and versatile reagents in organic chemistry, particularly in the construction of functional nitrogen-containing molecules.[1,2] Among these reactions, the decomposition of azides to incorporate one nitrogen atom into the functional molecules is typically rationalized by extrusion of dinitrogen or diazo compounds to give amines,[3] amides,[4] amidines,[5] or *N*-containing heterocycles[6,7] (Scheme 1a).

Scheme 1. Reactions of the Decomposition of Azides to Remove Two Nitrogen Atoms



Different mechanisms may be operative in these aminations that involve transition metals catalysis,[2a] radical chemistry,[1c] or nitrene intermediates.[1d] A variety of classic methods have been established via this pathway, including the Curtius rearrangement,[2b] Schmidt reaction,[7] Staudinger reaction,[2c] et al., as well as the application in pharmaceutical chemistry,[8] materials science,[9] and biotechnology.[10] However, to the best of our knowledge, exceptions of this denitrogenative reaction of azides have been rarely described. Because of the significance of azides in organic synthesis and in continuation of our interest in developing novel methods for the synthesis of heterocycles,[11] herein, we report an iodine-mediated oxidative [4+1] cyclization of enamines with a sequential removal of two nitrogen atoms from $TMSN_3$ (Scheme 1b).

Imidazoles are privileged scaffolds in a variety of biologically active molecules and valuable synthetic building blocks (Figure 1).[12] Especially, the derivatives of 2,5-disubstituted imidazole-4-carboxylic acids are of continuing interest in drug discovery because many of them show vital activities on a large number of biological targets,[13] such as the inhibitor of mPGES-1,[13a] antiallergic[13b] and antituberculosis agents,[13c] inhibitor of allosteric B-Raf protein kinase,[13d] and antagonist of CCK2 receptor.[13e] Consequently, much effort has been devoted to the synthesis of this skeleton. The synthetic approaches to 2,5-disubstituted imidazole-4-carboxylic derivatives include multistep synthesis via condensation/substitution/cyclization,[14] transition-metal-catalyzed crossing-coupling based on available imidazoles,[15] or related variations of these reactions.[16] While effective, these methods suffer from limitations such as the use of prefunctionalized starting materials, requiring toxic transition metal catalysts, and finally, poor functional group compatibility. Recently, the synthesis of 2,5-disubstituted imidazole-4-carboxylic derivatives was further improved via oxidative cyclization of enamine compounds.[6a] Sharada reported a PIFA-mediated cycloaminative approach providing polysubstituted imidazoles via in situ generation of 3° enamino esters from aliphatic amines and acetylenedicarboxylate

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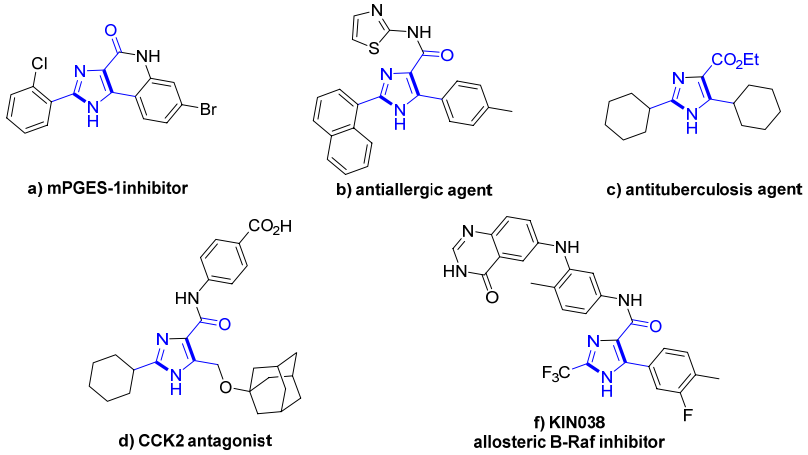


Figure 1. Representative 2,5-disubstituted imidazole-4-carboxylic derivatives.

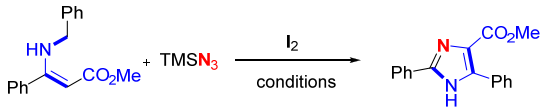
esters.[6a] Yu has developed a Cu-catalyzed cyclization of trifluoromethyl-substituted enaminoesters with $TMSN_3$ as the nitrogen source to prepare the imidazole compounds.[6b] However, because of the requirement of multiple electron-deficient groups (such as $-CO_2R$, $-CF_3$) on the substrates to reduce the byproducts, the reported systems are inefficient for the similar cyclization of the more general enamine compounds. Therefore, the exploration of novel and practical methods for the construction of 2,5-disubstituted imidazole-4-carboxylic derivatives is still highly desirable and of great significance.

RESULTS AND DISCUSSIONS

Initially, *N*-benzyl *β*-enamino ester **1a** and $TMSN_3$ were reacted in the presence of I_2 in *N*,*N*-dimethylformamide (DMF) at 80 °C for 12 h, providing the methyl-2,5-diphenyl 1*H*-imidazole-4-carboxylate **2a** in 13% yield (Table 1, entry 1). This result encouraged us to further optimize the reaction conditions. A screening of bases with different combinations and loadings showed that the addition of a base could enhance the reaction outcomes (Table 1, entries 2−10). The results revealed that the combination of K_2CO_3 and NaOAc was more effective, delivering product **2a** in 85% yield (Table 1, entry 6). Solvents such as EtOAc, 1,2-dimethoxyethane (DME), and dimethyl sulfoxide (DMSO) gave inferior results (Table 1, entries 11−14), which also indicated that DMF is a better choice for this transformation. In the absence of I_2, no desired product **2a** was observed (Table 1, entry 15). A further increase or decrease in the loading of I_2 did not help to improve the outcome of the reaction (Table 1, entries 16 and 17). Lowering the temperature to 60 °C led to a drop in the product yield (Table 1, entry18). The yield was decreased to 68% when NaN_3 was used as the nitrogen source (Table 1, entry 19). This might be due to the poor solubility of the inorganic salt in the reaction mixture. We then tried to reduce the reaction time; however, **2a** was obtained only in 67% for 6 h (entry 20).

Having established the optimized conditions, we aimed to define the substrate scope of this method. First, the reactivity of different *N*-benzyl *β*-enaminoesters was examined. As seen in Scheme 2, the substrates with different substituents on the phenyl ring, including electron-donating (−Me, −OMe) and electron-withdrawing groups (−F, −Cl, −Br, $-CF_3$), proceeded smoothly to afford the corresponding products (**2a**−**m**). In most cases, moderate to good yields of the desired products were obtained. The lower yield of **2d** might be due to the steric effect of the *o*-methyl group. Heterocyclic variants of substituted imidazole-4-carboxylic esters **2n** (2-thienyl) and **2o** (3-thienyl) could be accessed in 67% and 74% yields, respectively. In addition, bi- and fused aryl *N*-benzyl *β*-enaminoesters were also compatible, delivering the desired products in moderate yields (**2p** and **2q**). Further investigations on the ester group showed that **1r** bearing a $-CO_2Et$ group was also a suitable substrate to give the desired product in good yield (**2r**).

Table 1. Optimization of the Reaction Conditions[a]



1a **2a**

entry	base, ratio	solvent	yield (%)
1		DMF	13
2	Na_2CO_3	DMF	39[b]
3	K_2CO_3	DMF	66[b]
4	NaOAc	DMF	31[b]
5	K_2CO_3/NaOAc, 2.5:1	DMF	72[b]
6	K_2CO_3/NaOAc, 3:1	DMF	85
7	K_2CO_3/KOAc, 3:1	DMF	78
8	Na_2CO_3/NaOAc, 3:1	DMF	77
9	Cs_2CO_3/NaOAc, 3:1	DMF	66
10	NaOH/NaOAc, 3:1	DMF	47
11	K_2CO_3/NaOAc, 3:1	EtOAc	68
12	K_2CO_3/NaOAc, 3:1	DME	42
13	K_2CO_3/NaOAc, 3:1	CH_3CN	67
14	K_2CO_3/NaOAc, 3:1	DMSO	66
15	K_2CO_3/NaOAc, 3:1	DMF	0[c]
16	K_2CO_3/NaOAc, 3:1	DMF	79[d]
17	K_2CO_3/NaOAc, 3:1	DMF	75[e]
18	K_2CO_3/NaOAc, 3:1	DMF	56[f]
19	K_2CO_3/NaOAc, 3:1	DMF	68[g]
20	K_2CO_3/NaOAc, 3:1	DMF	67[h]

[a]Reaction conditions: **1a** (0.3 mmol), $TMSN_3$ (0.9 mmol), I_2 (0.9 mmol), base (4 equiv) in solvent (6 mL) at 80 °C for 12 h. [b]3.5 equiv base was used. [c]I_2 was not used. [d]2.5 equiv of I_2 was used. [e]3.5 equiv of I_2 was used. [f]60 °C. [g]NaN_3 was used instead of $TMSN_3$. [h]6 h.

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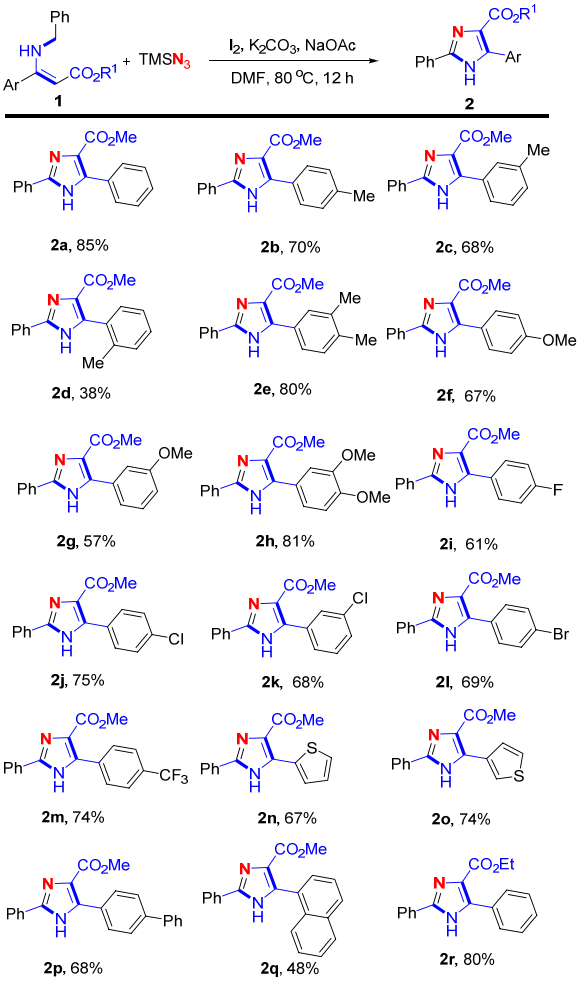
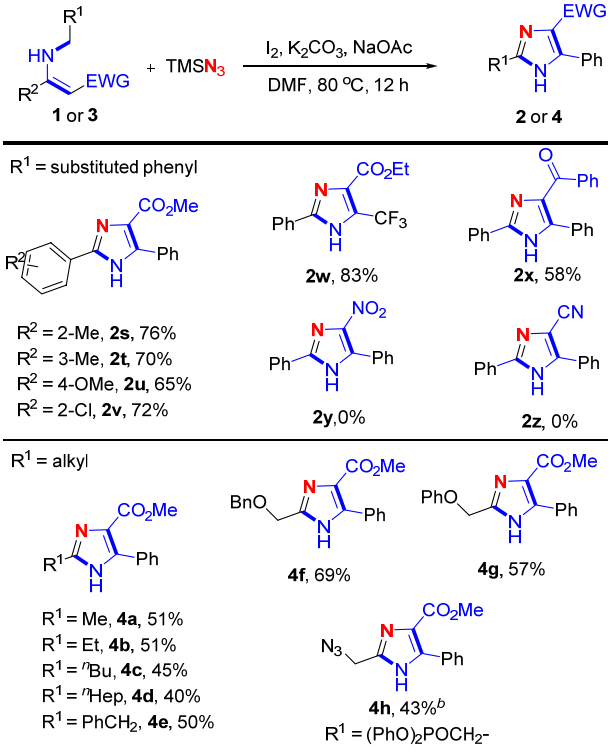
Scheme 2. Scope of *N*-Benzyl Enaminoesters[a]



[a]Reaction conditions: **1** (0.3 mmol), $TMSN_3$ (3 equiv), I_2 (3 equiv), K_2CO_3 (3 equiv), and NaOAc (1 equiv) in DMF (6 mL) at 80 °C for 12 h.

Scheme 3. Scope of *N*-Substituted Enamines[a]



[a]Reaction conditions: **1** or **3** (0.3 mmol), $TMSN_3$ (3 equiv), I_2 (3 equiv), K_2CO_3 (3 equiv), and NaOAc (1 equiv) in DMF (6 mL) at 80 °C for 12 h. [b]The reaction was carried out in CH_3CN.

Further assessment of the substrate scope for this reaction was performed by treating more types of enamines with $TMSN_3$ (Scheme 3). To our delight, substrates with *N*-substituted benzyl were participated well in this cyclization process to give the desired products in 65−76% yields (**2s**−**v**). Notably, the reaction of sterically hindered 2-methyl- or 2-chloro-benzyl-substituted substrates proceeded well under the optimized conditions, leading to the corresponding imidazole products **2s** or **2v** in 76% and 72% yields, respectively. Enaminoester **1w** bearing a *β*-trifluoromethyl performed well and afforded the substituted imidazole in 83%. Delightfully, enaminone **1x** was also tolerant, thereby furnishing the diaryl ketone **2x** in 58% yield. However, when $-NO_2$- and −CN-substituted enamines **1y** and **1z** were subjected to the current conditions, no desired products were obtained. Extension of the method to *N*-alkyl-substituted enaminoesters gave the target imidazoles in moderate yields (**4a**−**h**). Notably, the length of alkyl chains had little influence on the reaction. Enaminoesters **3** possessing C2, C3, C5, and C8 *N*-alkyl chains afforded the corresponding products in yields arranging from 40−51% (**4a**−**d**). Moreover, the substrates with functional groups such as −OBn and −OPh on the alkyl substituents were well tolerated, and the desired 2,5-disubstituted 1*H*-imidazole-4-carboxylic esters were obtained in 69% and 57% yields (**4f** and **g**), respectively. Interestingly, the reaction of enaminoester **3h** containing a diphenyl phosphate group with $TMSN_3$ produced a 2-azidomethyl imidazole compound in 43% yield, which could be further employed to generate more diversity through click reactions. The structure of **4h** had been further determined by crystallography analysis.

To demonstrate the practical applicability of this methodology, a gram-scale reaction of **1a** with $TMSN_3$ was conducted in an open flask, and the desired substituted imidazole-4-carboxylic ester was isolated in 62% yield (Scheme 4a). Furthermore, fused heteroaryl compound **2y** (Scheme 4b), which is a bioactive compound in the 1-*H* tautomeric form,[13f] was effectively prepared under the standard reaction conditions. Finally, hydrolysis of substituted imidazole-4-carboxylic ester **2z**, followed by condensation with 2-aminothiazole, concisely produced the antiallergic agent **5**[13b] (Scheme 4c).

In order to gain insights into the reaction mechanism, a sequence of control experiments was performed in Scheme 5. Reducing the reaction time to 5 min, besides the formation of **2a**, hydrazine **6a** was also isolated in 26% yield (Scheme 5a). The structure of **6a** was verified by single-crystal X-ray diffraction analysis. To our surprise, without $TMSN_3$, oxidation of **6a** also could give the target product **2a** in 85% yield (Scheme 5b). These observations indicated that **6a** is a key intermediate in the transformation. We further tested if **6a** was produced from diazo compounds, which could be easily formed via ring-opening of the products from 1,3-dipolar cycloaddition between enamines and azides (Scheme 5c). However, the diazo **7** did not work under the reaction

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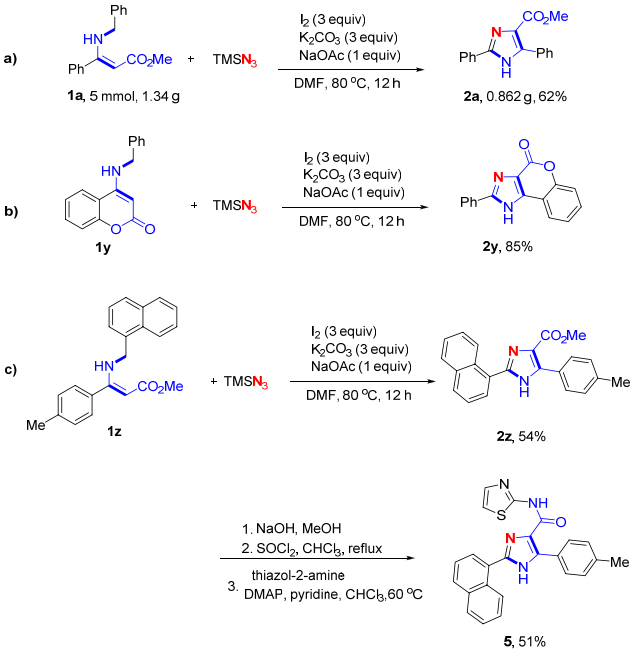
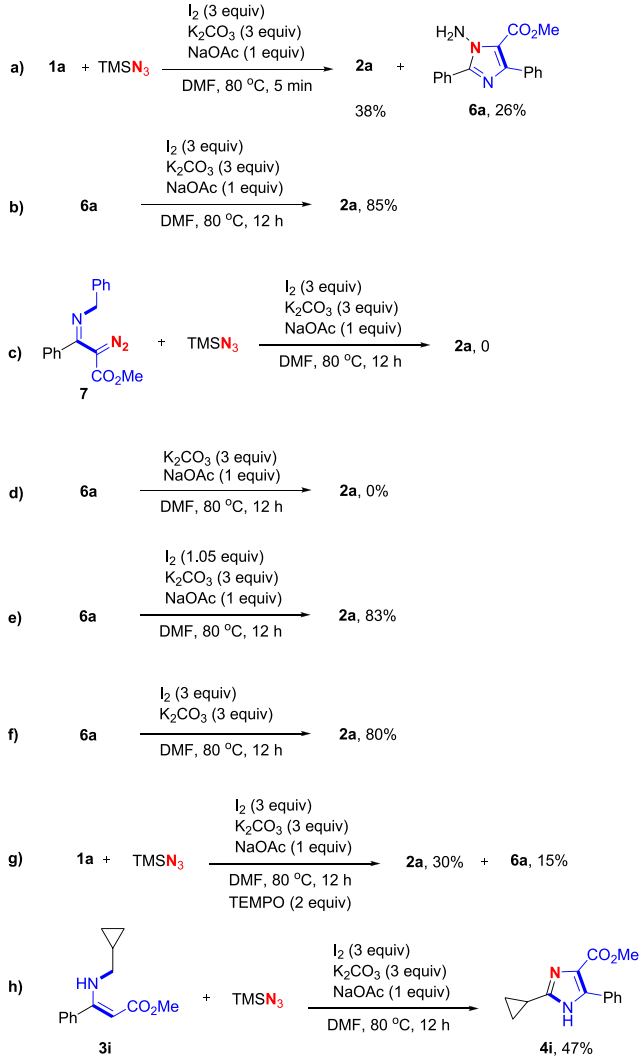
Scheme 4. Synthetic Applications



Scheme 5. Control Experiments



conditions, demonstrating that diazo compounds might not be generated in the procedure. The reaction of **6a** to **2a** was completely suppressed in the absence of iodine (Scheme 5d), while 1.05 equiv of iodine could afford 83% yield of **2a** (Scheme 5e). The results indicated that iodine also played a key role in this step. Compound **2a** was produced in a good yield from **6a** in the absence of NaOAc, which revealed that NaOAc might play an important role in the transformation of **1a** to **6a** (Scheme 5f). The addition of a radical scavenger, 2 equiv of TEMPO to the reaction system, gave **2a** and **6a** in 30% and 15% yields, respectively (Scheme 5g). Furthermore, a radical clock experiment of enaminoester **3i** was carried out, and no ring-opening product was observed (Scheme 5h). These results suggested that a radical pathway could be ruled out in this transformation.

According to our experimental outcomes and previous works,[6,7] a proposed mechanism is presented in Scheme 6. The initial 1,3-dipolar cycloaddition of enamine compounds **1** or **3** with $TMSN_3$ generates 1,2,3-triazoline intermediate **I**.[5b,5,17] Then, ring-opening of **I** gives α-azido enamine **II**.[18] Further base-induced intramolecular addition of N−N double bond forms 2,3-dihydro-imidazol **III**, which is further oxidized by iodine to give the hydrazine **6**. Subsequent **6** is oxidized under this I_2/base system to couple with another molecule **6**, providing the 1,1′-azoimidazole **IV**.[19] At last, hydrolysis of **IV** produces the product **2** or **4**.[19] The role of iodine may be versatile, besides the oxidant in the aromatization and formation of **III**, as well as the useful catalyst in the steps of 1,3-dipolar cycloaddition and nucleophilic addition.

CONCLUSION

In conclusion, we have developed an oxidative [4+1] cyclization between enamines and $TMSN_3$ under transition-metal-free conditions, and a series of 2,5-disubstituted 1*H*-imidazole-4-carboxylic derivatives bearing different substituents were synthesized efficiently. Moreover, the mechanistic studies revealed that the reaction proceeds through an unexpected sequential removal of the two nitrogen atoms from $TMSN_3$. The gram-scale reaction and derivatization of the products may have potential applications in future organic synthesis. Further investigations of the detailed reaction mechanism are ongoing in our laboratory.

EXPERIMENTAL SECTION

General Information. All solvents and reagents were obtained from commercial sources and used without further purification. ^1H NMR spectra obtained with tetramethylsilane (TMS, δ = 0 ppm) as an internal standard in $CDCl_3$ using an Agilent DD2 400-MR spectrometer (400 MHz). Data were reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad), coupling constant (J), and integration. ^{13}C NMR spectra were recorded on an Agilent DD2 400-MR spectrometer (100 MHz). The chemical shifts were determined on the δ-scale relative to $CDCl_3$ (δ = 77.0 ppm). High-resolution mass spectrometry was recorded on an AB SCIEX TOFTM 4600 MS equipped with an electrospray ionization time-of-flight (ESI-TOF) probe operating in the positive ion mode. The single-crystal X-ray experiment was performed on an Agilent Xcalibur Eos Gemini diffractometer equipped with graphite-monochromatized Cu Kα radiation (λ = 1.5418 Å). Silica gel (200−300 mesh) was used for column chromatographic separations and purifications. Petroleum ether (PE) refers to the fraction boiling at 60−90 °C. Enamine compounds **1** and **3** were known compounds and prepared by

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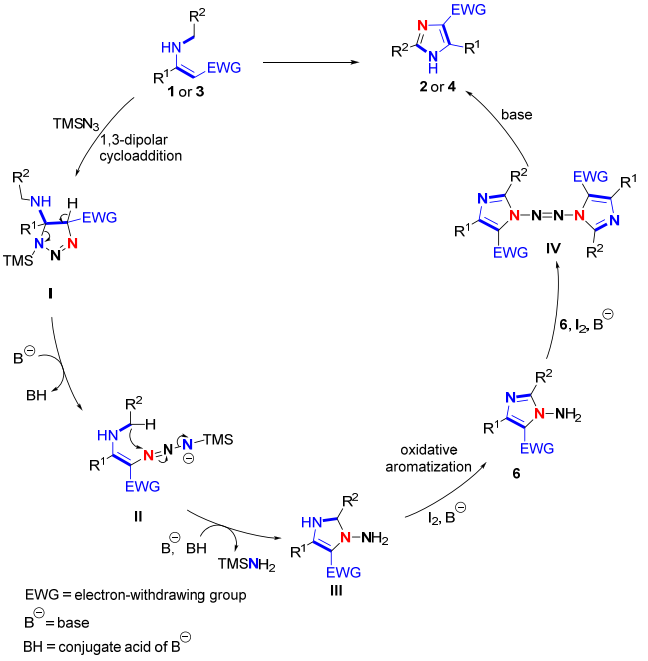
Scheme 6. Possible Reaction Mechanism



literatures,[6b,11] and the spectra data were matched with the data reported.

Experimental Procedures for the Synthesis of 2 or 4. A sealed tube was charged with *N*-benzyl *β*-enamino esters **1** or **3** (0.3 mmol), DMF (6 mL), then K_2CO_3 (128 mg, 0.9 mmol, 3 equiv, 21.3 mg/mL), NaOAc (24.6 mg, 0.3 mmol, 1 equiv, 4.1 mg/mL), I_2 (228 mg, 0.9 mmol, 3 equiv, 38 mg/L), and $TMSN_3$ (104 mg, 0.9 mmol, 3 equiv, 17.3 mg/mL). The reaction mixture was stirred in an oil bath at 80 °C for 12 h. After the solution cooled to room temperature, saturated brine (50 mL) was added to the mixture, and the solution was extracted by EtOAc (40 mL × 3). The combined organic layer was washed with water (50 mL × 2) and dried with anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the residue was separated by flash column chromatography to afford the pure product **2** or **4**.

Gram-Scale Synthesis of 2a. A 100 mL round-bottom flask was charged with *N*-benzyl *β*-enamino esters **1** (1.34 g, 5 mmol, 26.8 mg/mL), DMF (50 mL), then K_2CO_3 (2.07 g, 15 mmol, 3 equiv, 41.5 mg/mL), NaOAc (410 mg, 5 mmol, 1 equiv, 8.2 mg/mL), I_2 (3.81 g, 15 mmol, 3 equiv, 76.1 mg/mL), and $TMSN_3$ (1.73 g, 15 mmol, 3 equiv, 34.5 mg/mL). The reaction mixture was stirred in an oil bath at 80 °C for 12 h. After the solution cooled to room temperature, saturated brine (200 mL) was added to the mixture, and the solution was extracted by EtOAc (100 mL × 3). The combined organic layer was washed with water (100 mL × 2) and dried with anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the residue was separated by flash column chromatography to afford the pure product **2a** (862 mg, 62%) (eluent: PE/EtOAc = 3:1).

*Methyl 2,5-Diphenyl-1H-imidazole-4-carboxylate (**2a**).*[14a] The product was obtained as a light yellow solid (71 mg, 85%) (eluent: PE/EtOAc = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.92−7.95 (m, 2H), 7.84−7.86 (m, 2H), 7.36−7.45 (m, 6H), 3.84 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): *δ* 161.5, 147.5, 129.9, 129.2, 128.9, 128.8, 128.7, 128.0, 126.0, 51.8. HRMS (ESI-TOF) *m*/*z*: calcd for $C_{17}H_{15}N_2O_2$ $[M + H]^+$, 279.1128; found, 279.1131.

*Methyl 2-Phenyl-5-(p-tolyl)-1H-imidazole-4-carboxylate (**2b**).* The product was obtained as a light yellow solid (61 mg, 70%) (eluent: PE/EtOAc = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.92−7.95 (m, 2H), 7.74−7.76 (m, 2H), 7.40−7.45 (m, 3H), 7.20−7.22 (m, 2H), 3.84 (s, 3H), 2.37 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): *δ* 161.5, 147.2, 138.8, 130.2, 129.9, 129.2, 129.1, 128.9, 128.7, 128.6, 126.0, 51.8, 21.4. HRMS (ESI-TOF) *m*/*z*: calcd for $C_{18}H_{17}N_2O_2$ $[M + H]^+$, 293.1285; found, 293.1291.

*Methyl 2-Phenyl-5-(m-tolyl)-1H-imidazole-4-carboxylate (**2c**).* The product was obtained as a light yellow solid (60 mg, 68%) (eluent: PE/EtOAc = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.89−7.92 (m, 2H), 7.50−7.53 (m, 2H), 7.35−7.37 (m, 3H), 7.19−7.23 (m, 1H), 7.10−7.13 (m, 1H), 3.76 (s, 3.H), 2.3 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): *δ* 162.1, 147.5, 137.5, 131.4, 129.8, 129.7, 129.5, 128.8, 128.7, 127.7,126.5, 126.1, 51.7, 21.4. HRMS (ESI-TOF) *m*/*z*: calcd for $C_{18}H_{17}N_2O_2$ $[M + H]^+$, 293.1285; found ,293.1281.

*Methyl 2-Phenyl-5-(o-tolyl)-1H-imidazole-4-carboxylate (**2d**).* The product was obtained as a white solid (33 mg, 38%) (eluent: PE/EtOAc = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.87−7.89 (m, 2H), 7.35−7.37 (m, 3H), 7.14−7.2 (m, 3H), 7.06−7.10 (m, 1H), 3.65 (m, 3H), 2.13 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): *δ* 162.3, 147.2, 137.4, 130.1, 129.9, 129.6, 128.9, 128.8, 126.0, 125.1, 51.6, 19.8. HRMS (ESI-TOF) *m*/*z*: calcd for $C_{18}H_{17}N_2O_2$ $[M + H]^+$, 293.1285; found, 293.1297.

*Methyl 4-(3,4-Dimethylphenyl)-2-phenyl-1H-imidazole-5-carboxylate (**2e**).* The product was obtained as a light yellow solid (73 mg, 80%) (eluent: PE/EtOAc = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.90−7.93 (m, 2H), 7.50−7.55 (m, 2H), 7.38−7.41 (m, 3H), 7.11−7.13 (m, 1H), 3.81 (s, 3H), 2.25 (s, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): *δ* 161.7, 147.2, 137.4, 136.2, 130.2, 129.7, 129.2, 128.8, 126.7, 126.0, 51.7, 19.7, 19.6. HRMS (ESI-TOF) *m*/*z*: calcd for $C_{19}H_{19}N_2O_2$ $[M + H]^+$, 307.1441; found, 307.1452.

*Methyl 4-(4-Methoxyphenyl)-2-phenyl-1H-imidazole-5-carboxylate (**2f**).* The product was obtained as a light yellow solid (62 mg, 67%) (eluent: PE/EtOAc = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.94−7.97 (m, 2H), 7.84−7.87 (m, 2H), 7.41−7.44 (m, 3H), 6.93−6.95 (m, 2H), 3.86 (s, 3H), 3.83 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): *δ*160.1, 147.1, 132.2, 132.1, 130.7, 130.0, 129.0, 128.6, 128.5, 126.0, 113.7, 113.5, 55.3, 51.8. HRMS (ESI-TOF) *m*/*z*: calcd for $C_{18}H_{17}N_2O_3$ $[M + H]^+$, 309.1233; found, 309.1240.

*Methyl 4-(3-Methoxyphenyl)-2-phenyl-1H-imidazole-5-carboxylate (**2g**).* The product was obtained as a light yellow solid (53 mg, 57%) (eluent: PE/EtOAc = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.93−7.96 (m, 2H), 7.41−7.47 (m, 5H), 7.28−7.32 (m, 1H), 6.90−6.93 (m, 1H), 3.84 (s, 3H), 3.83 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): *δ* 161.3, 159.2, 147.4, 133.3, 130.0, 129.0, 128.9, 128.5, 126.0, 121.7, 114.9, 114.5, 55.3, 51.9. HRMS (ESI-TOF): *m*/*z* calcd for $C_{18}H_{17}N_2O_3$ $[M + H]^+$, 309.1233; found, 309.1241.

*Methyl 4-(3,4-Dimethoxyphenyl)-2-phenyl-1H-imidazole-5-carboxylate (**2h**).* The product was obtained as a light yellow solid (82 mg, 81%) (eluent: PE/EtOAc = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.94−7.97 (m, 2H), 7.51−7.57 (m, 2H),7.40−7.45 (m, 3H), 6.88−6.90 (m, 1H), 3.91 (s, 3H), 3.89 (s, 3H), 3.85 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): *δ* 161.3, 149.5, 148.3, 147.2, 130.0, 128.9, 128.6, 126.0, 122.1, 112.6, 110.6, 55.9, 55.8, 51.8. HRMS (ESI-TOF): *m*/*z* calcd for $C_{19}H_{19}N_2O_4$ $[M + H]^+$, 339.1339; found, 339.1356.

*Methyl 4-(4-Fluorophenyl)-2-phenyl-1H-imidazole-5-carboxylate (**2i**).* The product was obtained as a white solid (54 mg, 61%) (eluent: PE/EtOAc = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.92−7.96 (m, 4H), 7.43−7.49 (m, 3H), 7.08−7.13 (m, 2H), 7.87 (s, 3H), 3.87 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): *δ* 163.1 (d, J_{C-F} = 247 Hz), 160.8, 147.5, 131.2 (d, J_{C-F} = 8 Hz), 130.1, 129.0, 128.4, 126.0, 114.9 (d, J_{C-F} = 21 Hz), 51.9. HRMS (ESI-TOF): *m*/*z* calcd for $C_{17}H_{14}FN_2O_2$ $[M + H]^+$, 297.1033; found, 297.1052.

*Methyl 4-(4-Chlorophenyl)-2-phenyl-1H-imidazole-5-carboxylate (**2j**).* The product was obtained as a light yellow solid (70 mg, 75%) (eluent: PE/EtOAc = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.93−7.95 (m, 4H), 7.43−7.47 (m, 3H), 7.37−7.40 (m, 2H), 3.87 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): *δ* 134.6, 130.6, 130.1, 129.0, 128.6, 128.2, 125.9, 52.1. HRMS (ESI-TOF): *m*/*z* calcd for $C_{17}H_{14}ClN_2O_2$ $[M + H]^+$, 313.0738; found, 313.0747.

*Methyl 5-(3-Chlorophenyl)-2-phenyl-1H-imidazole-4-carboxylate (**2k**).* The product was obtained as a light yellow solid (64 mg, 68%) (eluent: PE/EtOAc = 3:1).^{1}H NMR (400 MHz, $CDCl_3$): *δ* 10.20 (b, 1H), 7.94−8.00 (m, 3H), 7.86−7.90 (m, 1H), 7.44−7.48

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(m, 3H), 7.33−7.35 (m, 2H), 3.88 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 160.5, 148.0, 146.9, 134.9, 133.8, 130.2, 129.3, 129.2, 129.1, 128.5, 127.4, 126.0, 118.5, 52.1. HRMS (ESI-TOF): *m/z* calcd for $C_{17}H_{14}ClN_2O_2$ $[M + H]^+$, 313.0738; found, 313.0742.

*Methyl 5-(4-Bromophenyl)-2-phenyl-1H-imidazole-4-carboxylate (**2l**).* The product was obtained as a light yellow solid (74 mg, 69%) (eluent: PE/EtOAc = 3:1). ^1H NMR (400 MHz, $CDCl_3$): δ 7.94−7.97 (m, 2H), 7.84−7.86 (m, 2H), 7.54−7.56 (m, 2H), 7.45−7.49 (m, 3H), 3.88 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 160.6, 147.6, 131.2, 130.9, 130.4, 129.1, 127.9, 126.1, 123.2, 52.1. HRMS (ESI-TOF): *m/z* calcd for $C_{17}H_{13}NaBrN_2O_2$ $[M + Na]^+$, 379.0052; found, 379.0059.

*Methyl 2-Phenyl-4-(4-(trifluoromethyl)phenyl)-1H-imidazole-5-carboxylate (**2m**).* The product was obtained as a white solid 77 mg, 74%) (eluent: PE/EtOAc = 3:1). ^1H NMR (400 MHz, $CDCl_3$): δ 8.08−8.10 (m, 2H), 7.95−7.97 (m, 2H), 7.66−7.69 (m, 2H), 7.45−7.49 (m, 3H), 3.88 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 160.6, 147.9, 130.5, 130.3, 130.2, 129.6, 129.1, 128.4, 126.2, 126.0, 125.5, 124.9 (q, J_{C-F} = 3.81 Hz), 122.8, 52.1. HRMS (ESI-TOF): *m/z* calcd for $C_{18}H_{14}F_3N_2O_2$ $[M + H]^+$, 347.1001; found, 347.1004.

*Methyl 2-Phenyl-4-(thiophen-2-yl)-1H-imidazole-5-carboxylate (**2n**).* The product was obtained as a light yellow solid (57 mg, 67%) (eluent: PE/EtOAc = 3:1). ^1H NMR (400 MHz, $CDCl_3$): δ 10.47 (b. 1H), 7.95−8.05 (m, 3H), 7.36−7.40 (m, 4H), 7.06−7.09 (m, 1H), 3.90 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 160.6, 148.1, 142.5, 136.3, 130.1, 128.9, 128.5, 128.3, 127.5, 127.1, 126.2, 116.8, 52.0. HRMS (ESI-TOF): *m/z* calcd for $C_{15}H_{13}N_2O_2S$ $[M + H]^+$, 285.0692; found, 285.0712.

*Methyl 2-Phenyl-5-(thiophen-3-yl)-1H-imidazole-4-carboxylate (**2o**).* The product was obtained as a light yellow solid (63 mg, 74%) (eluent: PE/EtOAc = 3:1). ^1H NMR (400 MHz, $CDCl_3$): δ 8.17−8.18 (m, 1H), 7.92−7.94 (m, 2H), 7.18−7.80 (m, 1 H), 7.41−7.45 (m, 3H), 7.32−7.34 (m, 1H), 3.90 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 161.0, 147.3, 130.0, 128.9, 128.8, 128.6, 128.4, 127.9, 126.0, 125.9, 124.8, 51.9. HRMS (ESI-TOF): *m/z* calcd for $C_{15}H_{13}N_2O_2S$ $[M + H]^+$, 285.0692; found, 285.0707.

*Methyl 4-([1,1′-Biphenyl]-4-yl)-2-phenyl-1H-imidazole-5-carboxylate (**2p**).* The product was obtained as a light yellow solid (72 mg, 68%) (eluent: PE/EtOAc = 3:1). ^1H NMR (400 MHz, $CDCl_3$): δ 7.97−8.01 (m, 4H), 7.61−7.67 (m, 4H), 7.42−7.47 (m, 5H), 7.33−7.37 (m, 1H), 3.89 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 161.2, 147.4, 141.5, 140.7, 130.7, 130.2, 129.7, 129.0, 128.9, 128.8, 128.3, 127.5, 127.3, 127.1, 126.7, 126.1, 52.0. HRMS (ESI-TOF): *m/z* calcd for $C_{23}H_{19}N_2O_2$ $[M + H]^+$, 355.1441; found, 355.1454.

*Methyl 4-(Naphthalen-1-yl)-2-phenyl-1H-imidazole-5-carboxylate (**2q**).* The product was obtained as a light yellow solid (47 mg, 48%) (eluent: PE/EtOAc = 3:1). ^1H NMR (400 MHz, $CDCl_3$): δ 7.91-7.93 (m, 2H), 7.85−7.89 (m, 2H), 7.77 (m, 1H), 7.52−7.53 (m, 1H), 7.44−7.49 (m, 2H), 7.38−7.43 (m, 4H), 3.61 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 133.5, 132.0, 129.8, 129.3, 129.0, 128.8, 128.5, 128.3, 126.3, 125.9, 125.6, 124.9, 51.7. HRMS (ESI-TOF): *m/z* calcd for $C_{21}H_{17}N_2O_2$ $[M + H]^+$, 329.1284; found, 329.1293.

*Ethyl 2,4-diphenyl-1H-imidazole-5-carboxylate (**2r**).*[6b] The product was obtained as a white solid (70 mg, 80%) (eluent: PE/EtOAc = 3:1). ^1H NMR (400 MHz, $CDCl_3$): δ 7.94−7.96 (m, 2H), 7.83−7.85 (m, 2H), 7.32−7.44 (m, 6H), 4.27−4.34 (m, 2H), 1.24−1.30 (m, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 161.1, 147.6, 132.3, 129.8, 129.4, 128.9, 128.6, 127.8, 126.1, 61.0, 14.2. HRMS (ESI-TOF): *m/z* calcd for $C_{18}H_{17}N_2O_2$ $[M + H]^+$, 293.1284; found, 293.1289.

*Methyl 5-Phenyl-2-(o-tolyl)-1H-imidazole-4-carboxylate (**2s**).* The product was obtained as yellow oil (67 mg, 76%) (eluent: PE/EtOAc = 3:1). ^1H NMR (400 MHz, $CDCl_3$): δ 7.83−7.86 (m, 2H), 7.45 (d, *J* = 7.6 Hz, 1H), 7.29−7.40 (m, 5H), 7.15−7.19 (m, 1H), 3.78 (s, 3H), 2.47 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 161.5, 148.0, 146.5, 138.2, 136.9, 134.0, 131.1, 129.6, 129.2, 129.1, 128.6, 127.9, 127.7, 125.9, 51.7, 20.7. HRMS (ESI-TOF): *m/z* calcd for $C_{18}H_{17}N_2O_2$ $[M + H]^+$, 293.1290; found, 293.1287.

*Methyl 5-Phenyl-2-(m-tolyl)-1H-imidazole-4-carboxylate (**2t**).* The product was obtained as a yellow solid (61 mg, 70%) (eluent: PE/EtOAc = 3:1). ^1H NMR (400 MHz, $CDCl_3$): δ 7.67−7.81 (m, 4H), 7.32−7.38 (m, 3H), 7.18−7.20 (m, 2H), 3.78 (s, 3H), 2.36 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 161.8, 147.8, 140.0, 131.9, 129.5, 129.2, 128.6, 127.9, 126.1, 126.0, 51.7, 21.4. HRMS (ESI-TOF): *m/z* calcd for $C_{18}H_{17}N_2O_2$ $[M + H]^+$, 293.1285; found, 293.1287.

*Methyl 2-(4-Methoxyphenyl)-5-phenyl-1H-imidazole-4-carboxylate (**2u**).* The product was obtained as a yellow solid (60 mg, 65%) (eluent: PE/EtOAc = 3:1). ^1H NMR (400 MHz, $CDCl_3$): δ 7.83−7.88 (m, 4H), 7.35−7.42 (m, 3H), 6.92−6.95 (m, 2H), 3.83 (s, 3H), 3.82 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 161.5, 161.0, 147.6, 132.3, 129.2, 128.6, 128.3, 127.9, 127.5, 127.0, 121.5, 114.3, 55.4, 51.7. HRMS (ESI-TOF): *m/z* calcd for $C_{18}H_{17}N_2O_3$ $[M + H]^+$, 309.1234; found, 309.1228.

*Methyl 2-(2-Chlorophenyl)-5-phenyl-1H-imidazole-4-carboxylate (**2v**).*[13a] The product was obtained as a yellow solid (63 mg, 72%) (eluent: PE/EtOAc = 3:1). ^1H NMR (400 MHz, $CDCl_3$): δ 7.70 (dd, *J* = 8.1, 1.6 Hz, 2H), 7.54 (dd, *J* = 7.4, 1.9 Hz, 1H), 7.49 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.35−7.45 (m, 6H), 3.81 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 161.9, 147.9, 146.6, 134.5, 133.9, 132.3, 131.2, 129.5, 129.4, 129.2, 128.9, 128.3, 127.7, 126.9, 117.7, 51.6. HRMS (ESI-TOF): *m/z* calcd for $C_{17}H_{14}ClN_2O_2$ $[M + H]^+$, 313.0744; found, 313.0739.

*Ethyl 2-Phenyl-5-(trifluoromethyl)-1H-imidazole-4-carboxylate (**2w**).*[6b] The product was obtained as a white solid (71 mg, 83%) (eluent: PE/EtOAc = 3:1). ^1H NMR (400 MHz, $CDCl_3$): δ 7.94−7.97 (m, 2H), 7.44−7.47 (m, 3H), 4.41 (q, *J* = 7.1 Hz, 2H), 1.39 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 159.4, 148.1, 136.1 (q, J_{C-F} = 39.3 Hz), 130.5, 128.9, 128.0, 126.4, 121.7 (q, J_{C-F} = 2.3 Hz), 120.7 (q, J_{C-F} = 268 Hz), 62.3, 13.8. HRMS (ESI-TOF): *m/z* calcd for $C_{13}H_{12}F_3N_2O_2$ $[M + H]^+$, 285.0845; found, 285.0847.

*(2,4-Diphenyl-1H-imidazol-5-yl)(phenyl)methanone (**2x**).*[16b] The product was obtained as a light yellow solid (56 mg, 58%) (eluent: PE/EtOAc = 3:1). ^1H NMR (400 MHz, $CDCl_3$): δ 12.00 (b, 1H), 8.19−8.21 (m, 2H), 7.57−7.60 (m, 2H), 7.29−7.42 (m, 3H), 7.12−8.15 (m, 3H), 7.05−7.09 (m, 5H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 187.7, 150.8, 149.9, 137.2, 133.7, 132.3, 130.1,129.9, 129.6, 128.8, 128.0, 127.9, 127.8, 127.6, 126.7. HRMS (ESI-TOF): *m/z* calcd for $C_{22}H_{17}N_2O$ $[M + H]^+$, 325.1341; found, 325.1351.

*2-Phenylchromeno[3,4-d]imidazol-4(1H)-one (**2y**).*[13f] The product was obtained as a light yellow solid (67 mg, 85% yield) (eluent: PE/EtOAc = 3:1). ^1H NMR (400 MHz, DMSO-d_6): δ 13.81 (b, 1H), 8.07−8.17 (m, 3H), 7.38−7.55 (m, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ 169.5, 152.3, 140.0, 130.7, 130.0, 129.4, 128.7, 127.7, 127.1, 126.9, 125.0, 122.7, 117.4. HRMS (ESI-TOF): *m/z* calcd for $C_{16}H_{10}N_2O_2$ $[M + H]^+$, 263.0815; found, 263.0811.

*Methyl 2-(Naphthalen-1-yl)-5-(p-tolyl)-1H-imidazole-4-carboxylate (**2z**).*[13b] The product was obtained as a yellow solid (55 mg, 54%) (eluent: PE/EtOAc = 3:1). ^1H NMR (400 MHz, $CDCl_3$): δ 8.55−8.57 (m, 1H), 7.83−7.93 (m, 4H), 7.68−7.70 (m, 1H), 7.51−7.55 (m, 2H), 7.45−7.49 (m, 1H), −7.26 (m, 1H), 7.23−7.24 (m, 1H), 3.82 (s, 3H), 2.39 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 161.5, 147.1, 138.8, 133.8, 130.9, 130.5, 129.2, 128.8, 128.5, 127.4, 126.5, 126.4, 125.5, 124.9, 51.8, 21.4. HRMS (ESI-TOF): *m/z* calcd for $C_{22}H_{18}N_2O_2$ $[M + H]^+$, 343.1441; found, 343.1441.

*Methyl 2-methyl-5-phenyl-1H-imidazole-4-carboxylate (**4a**).*[16c] The product was obtained as a light yellow oil (33 mg, 51%) (eluent: PE/EtOAc = 3:1). ^1H NMR (400 MHz, $CDCl_3$): δ 10.27 (b, 1H), 7.67 (dd, *J* = 7.6, 2.1 Hz, 2H)), 7.29−7.33 (m, 3H), 3.74 (s, 3H), 2.25 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 162.2, 146.3, 142.8, 131.2, 129.1, 128.6, 128.0, 121.3, 51.6, 13.6. HRMS (ESI-TOF): *m/z* calcd for $C_{12}H_{13}N_2O_2$ $[M + H]^+$, 217.0971; found, 217.0967.

*Methyl 2-Ethyl-5-phenyl-1H-imidazole-4-carboxylate (**4b**).* The product was obtained as a light yellow oil (35 mg, 51%) (eluent: PE/EtOAc = 3:1). ^1H NMR (400 MHz, $CDCl_3$): δ 7.73 (dd, *J* = 8.1, 1.6 Hz, 2H), 7.31−7.37 (m, 3H), 3.78 (s, 3H), 2.71 (q, *J* = 7.6 Hz, 1H), 1.27 (t, *J* = 7.7 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 161.8, 151.4, 131.9, 129.1, 128.5, 127.5, 120.2, 51.6, 21.7, 12.3. HRMS (ESI-TOF): *m/z* calcd for $C_{13}H_{15}N_2O_2$ $[M + H]^+$, 231.1128; found, 231.1127.

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*Methyl 2-Butyl-5-phenyl-1H-imidazole-4-carboxylate (**4c**).*[16c] The product was obtained as a light yellow oil (35 mg, 45%) (eluent: PE/EtOAc = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.72 (b, 1H), 7.68−7.70 (m, 2H), 7.29−7.34 (m, 3H), 3.75 (s, 3H), 2.58 (t, J = 7.9 Hz, 2H), 1.53−1.61 (m, 2H), 1.19−1.29 (m, 2H), 0.81 (t, J = 7.47 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 162.1, 150.6, 143.3, 131.6, 129.1, 128.5, 127.9, 120.8, 51.6, 30.4, 28.0, 22.3, 13.7. HRMS (ESI-TOF): m/z calcd for $C_{15}H_{19}N_2O_2$ [M + H]$^+$, 259.1441; found, 259.1458.

*Methyl 2-Heptyl-5-phenyl-1H-imidazole-4-carboxylate (**4d**).* The product was obtained as a light yellow oil (36 mg, 40%) (eluent: PE/EtOAc = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74−7.76 (m, 2H), 7.33−7.39 (m, 3H), 3.80 (s, 3H), 2.67 (t, J = 7.9 Hz, 2H), 1.64−1.71 (m, 2H), 1.21−1.28 (m, 8H), 0.84 (t, J = 6.7 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 161.7, 150.6, 132.9, 131.8, 130.0, 129.1, 128.3, 128.0, 51.7, 31.6, 29.3, 28.9, 28.5, 28.3, 22.6, 14.1. HRMS (ESI-TOF): m/z calcd for $C_{18}H_{25}N_2O_2$ [M + H]$^+$, 301.1910; found, 301.1897.

*Methyl 2-Benzyl-5-phenyl-1H-imidazole-4-carboxylate (**4e**).* The product was obtained as a light yellow oil (44 mg, 50%) (eluent: PE/EtOAc = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70−7.72 (m, 2H), 7.31−7.37 (m, 3H), 7.22−7.29 (m, 3H), 7.15−7.18 (m, 2H), 4.01 (s, 2H), 3.74 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 161.8, 148.6, 136.1, 131.5, 129.3, 129.1, 128.9, 128.8, 128.6, 128.0, 127.9, 127.2, 51.6, 34.8. HRMS (ESI-TOF): m/z calcd for $C_{18}H_{17}N_2O_2$ [M + H]$^+$, 293.1284; found, 293.1279.

*Methyl 2-((Benzyloxy)methyl)-5-phenyl-1H-imidazole-4-carboxylate (**4f**).* The product was obtained as a light yellow oil (67 mg, 69%) (eluent: PE/EtOAc = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73−7.76 (m, 2H), 7.29−7.40 (m, 8H), 4.63 (s, 2H), 4.57 (s, 2H), 3.81 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 161.6, 146.5, 136.9, 129.4, 129.1, 128.7, 128.6, 128.2, 128.1, 127.7, 73.4, 65.3, 51.7. HRMS (ESI-TOF): m/z calcd for $C_{19}H_{19}N_2O_3$ [M + H]$^+$, 323.1390; found, 323.1379.

*Methyl 2-(Phenoxymethyl)-5-phenyl-1H-imidazole-4-carboxylate (**4g**).* The product was obtained as a light yellow solid (53 mg, 57%) (eluent: PE/EtOAc = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (dd, J = 8.1, 1.6 Hz, 2H), 7.38−7.44 (m, 3H), 7.28−7.32 (m, 2H), 6.95−7.03 (m, 3H), 5.22 (s, 2H), 3.84 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 157.5, 129.8, 129.1, 129.0, 128.2, 122.1, 114.6, 63.4, 51.9. HRMS (ESI-TOF): m/z calcd for $C_{18}H_{17}N_2O_3$ [M + H]$^+$, 309.1233; found, 309.1227.

*Methyl 2-(Azidomethyl)-5-phenyl-1H-imidazole-4-carboxylate (**4h**).* The product was obtained as a light yellow oil (33 mg, 43%) (eluent: PE/EtOAc = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (dd, J = 7.5, 2.2 Hz, 2H), 7.34−7.39 (m, 3H), 4.41 (s, 2H), 3.79 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 161.8, 143.8, 130.9, 129.1, 128.9, 128.8, 128.1, 120.0, 51.8, 47.5. HRMS (ESI-TOF): m/z calcd for $C_{12}H_{12}N_5O_2$ [M + H]$^+$, 258.0985; found, 258.0973.

*Methyl 2-Cyclopropyl-5-phenyl-1H-imidazole-4-carboxylate (**4i**).* The product was obtained as a light yellow oil (34 mg, 47%) (eluent: PE/EtOAc = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (dd, J = 8.1, 1.6 Hz, 2H), 7.32−7.37 (m, 3H), 3.78 (s, 3H), 1.90−1.97 (m, 1H), 1.02−1.07 (m, 2H), 0.97−1.01 (m, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 161.4, 151.8, 132.0, 129.2, 128.5, 127.9, 119.2, 51.6, 29.7, 9.0, 8.2. HRMS (ESI-TOF): m/z calcd for $C_{14}H_{14}N_2O_2$ [M + H]$^+$, 243.1128; found, 243.1122.

*Methyl 1-Amino-2,4-diphenyl-1H-imidazole-5-carboxylate (**6a**).* The product was obtained as a light yellow solid (23 mg, 26%) (eluent: PE/EtOAc = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (dd, J = 7.5, 2.2 Hz, 2H), 7.67 (dd, J = 8.0, 1.6 Hz, 2H), 7.35−7.45 (m, 6H), 5.64 (s, 2H), 3.77 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 161.7, 148.7, 146.9, 129.7, 129.5, 129.3, 128.3, 128.2, 127.7, 118.1, 65.5, 60.4, 51.5. HRMS (ESI-TOF): m/z calcd for $C_{17}H_{15}N_3O_2$ [M + H]$^+$, 294.1237; found, 294.1241.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c01145.

Copies of NMR spectra and X-ray structures (PDF)

Accession Codes

CCDC 2054878−2054879 and 2054889 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Fu, J.; Zanoni, G.; Anderson, E. A.; Bi, X. α-Substituted vinyl azides: an emerging functionalized alkene. *Chem. Soc. Rev.* **2017**, *46*, 7208−7228. (b) Wang, F.; Chen, P.; Liu, G. Copper-Catalyzed Radical Relay for Asymmetric Radical Transformations. *Acc. Chem. Res.* **2018**, *51*, 2036−2046. (c) Hema, K.; Sureshan, K. M. Topochemical Azide-Alkyne Cycloaddition Reaction. *Acc. Chem. Res.* **2019**, *52*, 3149−3163. (d) Ye, L. W.; Zhu, X. Q.; Sahani, R. L.; Xu, Y.; Qian, P. C.; Liu, R. S. Nitrene Transfer and Carbene Transfer in Gold Catalysis. *Chem. Rev.* **2020**, .

(2) (a) Park, Y.; Kim, Y.; Chang, S. Transition Metal-Catalyzed C-H Amination: Scope, Mechanism, and Applications. *Chem. Rev.* **2017**, *117*, 9247−9301. (b) Zhao, W.; Wurz, R. P.; Peters, J. C.; Fu, G. C. Photoinduced, Copper-Catalyzed Decarboxylative C-N Coupling to Generate Protected Amines: An Alternative to the Curtius Rearrangement. *J. Am. Chem. Soc.* **2017**, *139*, 12153−12156. (c) Bednarek, C.; Wehl, I.; Jung, N.; Schepers, U.; Bräse, S. The Staudinger Ligation. *Chem. Rev.* **2020**, *120*, 4301−4354.

(3) (a) Chakrabarti, K.; Mishra, A.; Panja, D.; Paul, B.; Kundu, S. Selective Synthesis of Mono- and Di-methylated Amines Using Methanol and Sodium Azide as C1 and N1 Sources. *Green Chem.* **2018**, *20*, 3339−3345. (b) Liu, J.; Qiu, X.; Huang, X.; Luo, X.; Zhang, C.; Wei, J.; Pan, J.; Liang, Y.; Zhu, Y.; Qin, Q.; Song, S.; Jiao, N. From Alkylarenes to Anilines via Site-Directed Carbon-Carbon Amination. *Nat. Chem.* **2019**, *11*, 71−77.

(4) (a) Ghosh, T.; Maity, P.; Ranu, B. C. $Cu(OAc)_2$-Promoted *ortho* $C(sp^2)$-H Amidation of 8-Aminoquinoline Benzamide with Acyl Azide: Selective Formation of Aroyl or Acetyl Amide Based on Catalyst Loading. *J. Org. Chem.* **2018**, *83*, 11758−11767. (b) Han, M.; Yang, M.; Wu, R.; Li, Y.; Jia, T.; Gao, Y.; Ni, H. L.; Hu, P.; Wang, B. Q.; Cao, P. Highly Enantioselective Iridium-Catalyzed Coupling Reaction of Vinyl Azides and Racemic Allylic Carbonates. *J. Am. Chem. Soc.* **2020**, *142*, 13398−13405.

(5) (a) Xu, X.; Ge, Z.; Cheng, D.; Ma, L.; Lu, C.; Zhang, Q.; Yao, N.; Li, X. $CuCl/CCl_4$-Promoted Convenient Synthesis of Sulfonyl Amidines from Tertiary Amines and Sulfonyl Azides. *Org. Lett.* **2010**, *12*, 897−899. (b) Liu, B.; Ning, Y.; Virelli, M.; Zanoni, G.; Anderson, E. A.; Bi, X. Direct Transformation of Terminal Alkynes into Amidines by a Silver-Catalyzed Four-Component Reaction. *J. Am. Chem. Soc.* **2019**, *141*, 1593−1598.

(6) (a) Arepally, S.; Babu, V. N.; Bakthadoss, M.; Sharada, D. S. A Direct Cycloaminative Approach to Imidazole Derivatives via Dual C-H Functionalization. *Org. Lett.* **2017**, *19*, 5014−5017. (b) Ma, H.; Zhang, X.; Chen, L.; Yu, W. A Domino Azidation/C-H Amination Approach toward Trifluoromethyl Substituted Imidazoles. *J. Org. Chem.* **2017**, *82*, 11841−11847. (c) Patel, S. M.; Prasad, P. E.; Bakthadoss, M.; Sharada, D. S. Photocatalytic Visible-Light-Induced Nitrogen Insertion via Dual $C(sp^3)$-H and $C(sp^2)$-H Bond Functionalization: Access to Privileged Imidazole-based Scaffolds. *Org. Lett.* **2021**, *23*, 257−261. (d) Yugandar, S.; Konda, S.; Parameshwarappa, G.; Ila, H. One-Pot Synthesis of 2,4,5-Trisubstituted Imidazoles via [2 + 2 + 1] Cycloannulation of 1,3-Bishet(aryl)-monothio-1,3-diketones, α-Substituted Methylamines and Sodium Nitrite through α-Nitrosation of Enaminones. *J. Org. Chem.* **2016**, *81*, 5606−5622.

(7) (a) Foley, C.; Shaw, A.; Hulme, C. Aza-Riley Oxidation of Ugi-Azide and Ugi-3CR Products toward Vicinal Tricarbonyl Amides: Two-Step MCR-Oxidation Methodology Accessing Functionalized α,β-Diketoamides and α,β-Diketotetrazoles. *Org. Lett.* **2018**, *20*, 1275−1278. (b) Charaschanya, M.; Li, K.; Motiwala, H. F.; Aubé, J. An Interrupted Schmidt Reaction: C-C Bond Formation Arising from Nitrilium Ion Capture. *Org. Lett.* **2018**, *20*, 6354−6358.

(8) Ghosh, A. K.; Brindisi, M.; Sarkar, A. The Curtius Rearrangement: Applications in Modern Drug Discovery and Medicinal Chemistry. *ChemMedChem* **2018**, *13*, 2351−2373.

(9) Yue, Q.; Gao, E. Q. Azide and Carboxylate as Simultaneous Coupler for Magnetic Coordination Polymers. *Coord. Chem. Rev.* **2019**, *382*, 1−31.

(10) Sasmal, P. K.; Carregal-Romero, S.; Han, A. A.; Streu, C. N.; Lin, Z.; Namikawa, K.; Elliott, S. L.; Köster, R. W.; Parak, W. J.; Meggers, E. Catalytic Azide Reduction in Biological Environments. *ChemBioChem* **2012**, *13*, 1116−1120.

(11) (a) Gao, P.; Chen, H.-J.; Bai, Z.-J.; Zhao, M.-N.; Yang, D.; Wang, J.; Wang, N.; Du, L.; Guan, Z.-H. IBX-Promoted Oxidative Cyclization of N-Hydroxyalkyl Enamines: A Metal-Free Approach toward 2,3-Disubstituted Pyrroles and Pyridines. *J. Org. Chem.* **2020**, *85*, 7939−7951. (b) Gao, P.; Wang, J.; Bai, Z.; Fan, M.-J.; Yang, D.-S.; Guan, Z.-H. $K_2S_2O_8$/TEMPO-Induced Cascade Oxidative Cyclization/1,2-Migration of Electron-Deficient Groups: Strategy for the Construction of 1*H*-Pyrrol-2(3*H*)-ones. *Org. Lett.* **2018**, *20*, 3627−3630. (c) Gao, P.; Wang, J.; Bai, Z.; Shen, L.; Yan, Y.−Y.; Yang, D.-S.; Fan, M.-J.; Guan, Z. Synthesis of Polycarbonyl Pyrroles via $K_2S_2O_8$-Mediated Oxidative Cyclization of Enamines. *Org. Lett.* **2016**, *18*, 6074−6077.

(12) (a) Zhang, F. M.; Dong, L. Z.; Qin, J. S.; Guan, W.; Liu, J.; Li, S. L.; Lu, M.; Lan, Y. Q.; Su, Z. M.; Zhou, H. C. Effect of Imidazole Arrangements on Proton-Conductivity in Metal-Organic Frameworks. *J. Am. Chem. Soc.* **2017**, *139*, 6183−6189. (b) Yu, Z.; Pandian, G. N.; Hidaka, T.; Sugiyama, H. Therapeutic Gene Regulation Using Pyrrole-imidazole Polyamides. *Adv. Drug Delivery Rev.* **2019**, *147*, 66−85.

(13) (a) Shiro, T.; Kakiguchi, K.; Takahashi, H.; Nagata, H.; Tobe, M. Synthesis and Biological Evaluation of Substituted Imidazoquinoline Derivatives as mPGES-1 Inhibitors. *Bioorg. Med. Chem.* **2013**, *21*, 2068−2078. (b) Sueoka, H.; Yasuoka, J.; Nishiyama, A.; Kiuchi, M.; Yamamoto, K.; Sugahara, K.; Ehara, S.; Sakata, K. Imidazole Derivatives. Patent US. US6288061(B1). Welfide Corp: Japan, 2001. (c) Gupta, P.; Hameed, S.; Jain, R. Ring-Substituted Imidazoles as a New Class of Anti-tuberculosis Agents. *Eur. J. Med. Chem.* **2004**, *39*, 805−814. (d) Dietrich, J.; Gokhale, V.; Wang, X.; Hurley, L. H.; Flynn, G. A. Application of a Novel [3 + 2] Cycloaddition Reaction to Prepare Substituted Imidazoles and Their Use in the Design of Potent DFG-out Allosteric B-Raf Inhibitors. *Bioorg. Med. Chem.* **2010**, *18*, 292−304. (e) Low, C. M. R.; Buck, I. M.; Cooke, T.; Cushnir, J. R.; Kalindjian, S. B.; Kotecha, A.; Pether, M. J.; Shankley, N. P.; Vinter, J. G.; Wright, L. Scaffold Hopping with Molecular Field Points: Identification of a Cholecystokinin-2 (CCK2) Receptor Pharmacophore and Its use in the Design of a Prototypical Series of Pyrrole- and Imidazole-based CCK2 Antagonists. *J. Med. Chem.* **2005**, *48*, 6790−6802. (f) Colotta, V.; Catarzi, D.; Varano, F.; Cecchi, L.; Filacchioni, G.; Martini, C.; Giusti, L.; Lucacchini, A. *Il.* Tricyclic Heteroaromatic Systems. Synthesis and Benzodiazepine Receptor Affinity of 2-Substituted-1-Benzopyrano[3,4-d]Oxazol-4-Ones, -Thiazol-4-Ones, and -Imidazol-4-Ones. *Farmaco* **1998**, *53*, 375−381.

(14) (a) Rolfs, A.; Liebscher, J. Versatile Novel Syntheses of Imidazoles. *J. Org. Chem.* **1997**, *62*, 3480−3487. (b) Mukhopadhyay, S.; Batra, S. Applications of Sodium Nitrite in Organic Synthesis. *Eur. J. Org. Chem.* **2019**, *2019*, 6424−6451.

(15) Wang, Y. X.; Qi, S. L.; Luan, Y. X.; Han, X. W.; Wang, S.; Chen, H.; Ye, M. Enantioselective Ni-Al Bimetallic Catalyzed *exo*-Selective C-H Cyclization of Imidazoles with Alkenes. *J. Am. Chem. Soc.* **2018**, *140*, 5360−5364.

(16) (a) Huang, Y.; Zu, X.; Wu, F.; Xu, J.; Wu, X.; Yao, H. Highly Efficient Oxidation of 2-Imidazoline-5-carboxylic Derivatives to

https://doi.org/10.1021/acs.joc.1c01145
J. Org. Chem. 2021, 86, 10492−10500

Imidazole-5-carboxylic Derivatives by Dioxygen. *Tetrahedron* **2012**, *68*, 3123−3128. (b) Wu, P.; Zhang, X.; Chen, B. Direct Synthesis of 2,4,5-Trisubstituted Imidazoles and di/tri-Substituted Pyrimidines via Cycloadditions of α,β-Unsaturated Ketones/Aldehydes and *N*′-Hydroxyl Imidamides. *Tetrahedron Lett.* **2019**, *60*, 1103−1107. (c) Xu, K.; Yang, R.; Yang, S.; Jiang, C.; Ding, Z. Hypervalent Iodane Mediated Reactions of *N*-Acetyl Enamines for the Synthesis of Oxazoles and Imidazoles. *Org. Biomol. Chem.* **2019**, *17*, 8977−8981. (d) Li, S.; Li, Z.; Yuan, Y.; Li, Y.; Zhang, L.; Wu, Y. Gold(I)-Catalyzed Aminohalogenation of Fluorinated *N*′-Aryl-*N*-Propargyl Amidines for the Synthesis of Imidazole Derivatives under Mild Conditions. *Chem. - Eur. J.* **2013**, *19*, 1496−1501.

(17) Cheng, G.; Zeng, X.; Shen, J.; Wang, X.; Cui, X. A Metal-free Multicomponent Cascade Reaction for the Regiospecific Synthesis of 1,5-Disubstituted 1,2,3-Triazoles. *Angew. Chem.* **2013**, *125*, 13507−13510.

(18) (a) Bakulev, V. A.; Beryozkina, T.; Thomas, J.; Dehaen, W. The Rich Chemistry Resulting from the 1,3-Dipolar Cycloaddition Reactions of Enamines and Azides. *Eur. J. Org. Chem.* **2018**, *2018*, 262−294. (b) Zheng, X.; Wan, J.-P. The C═C Bond Decomposition Initiated by Enamine-Azide Cycloaddition for Catalyst- and Additive-Free Synthesis of N-Sulfonyl Amidines. *Adv. Synth. Catal.* **2019**, *361*, 5690−5694.

(19) (a) Kuźmenko, V. V.; Nanavyan, I. M.; Pozharskii, A. F. 2,2′-Dialkoxy, 2,2′-Dihydroxy, and 2,2′-Diamino Derivatives of 1,1′-Azobenzimidazole. The First Synthesis of Heterocyclic Tetrazenes by Nucleophilic Substitution Reactions. *Chem. Heterocycl. Compd.* **1992**, *28*, 154−157. (b) Pozharskii, A. F.; Nanavyan, I. M.; Kuz'menko, V. V.; Chernyshev, A. I.; Orlov, Y.. V.; Klyuev, N. A. Oxidation of 1-Aminobenzimidazoles. Synthesis and Properties of 1, 1′-Azobenzimidazoles. *Chem. Heterocycl. Compd.* **1989**, *25*, 1241−1253. (c) Stevens, M. Y.; Sawant, R. T.; Odell, L. R. Synthesis of Sulfonyl Azides via Diazotransfer using an Imidazole-1-sulfonyl Azide Salt: Scope and ^{15}N NMR Labeling Experiments. *J. Org. Chem.* **2014**, *79*, 4826−4831.

https://doi.org/10.1021/acs.joc.1c01145
J. Org. Chem. 2021, 86, 10492−10500