JOC The Journal of Organic Chemistry

pubs.acs.org/joc Note

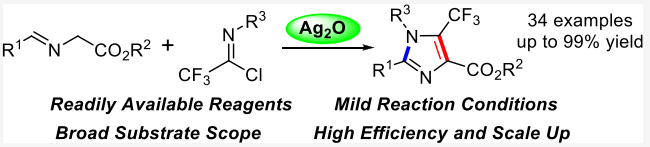
Silver-Mediated [3 + 2] Cycloaddition of Azomethine Ylides with Trifluoroacetimidoyl Chlorides for the Synthesis of 5-(Trifluoromethyl)imidazoles

Hefei Yang, Shu-Ning Lu, Zhengkai Chen,* and Xiao-Feng Wu*

Cite This: J. Org. Chem. 2021, 86, 4361−4370 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

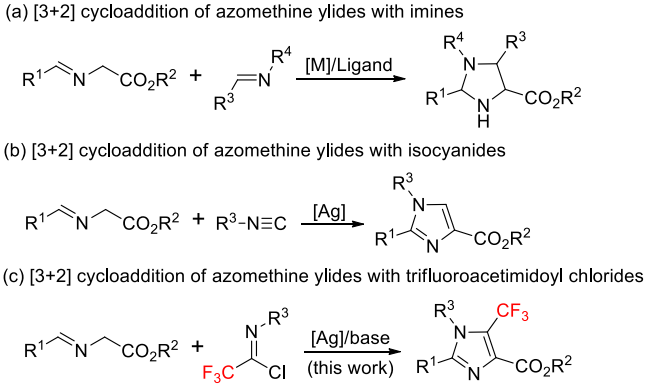
ABSTRACT: A silver-mediated [3 + 2] cycloaddition of azomethine ylides with trifluoroacetimidoyl chlorides for the rapid assembly of 5-(trifluoromethyl)imidazoles has been developed. Notable features of the reaction include readily accessible reagents, a broad substrate scope, and high efficiency. The protocol can be successfully applied to construct the analogue of the specific allosteric modulator of $GABA_A$ receptors. The silver species could be recycled by a simple operation.



Multisubstituted imidazoles are kinds of highly privileged structural cores that have found extensive application in the fields of biological and pharmaceutical chemistry, as ligands as well as functional materials.[1] Imidazole skeletons exist in several commercial drugs and bioactive compounds, such as losartan, eprosartan, econazole, clotrimazole, selective inhibitors of COX-2, and specific allosteric modulators of the $GABA_A$ receptor.[2] Due to their unique properties and wide application prospects, considerable synthetic approaches for the construction of imidazole scaffolds have been explored over the past decades.[3] Despite numerous elegant achievements regarding imidazole synthesis having been made, the general methods for the preparation of specifically functionalized imidazoles, such as trifluoromethyl-substituted imidazoles,[4] still remain underdeveloped. It is well-known that the incorporation of fluorine-containing groups into heterocycles could dramatically improve the chemical, physical, and biological properties of the parent molecule.[5] Therefore, the development of an efficient and straightforward route for producing valuable trifluoromethyl-substituted imidazoles is of great significance and will be particularly appealing.

Azomethine ylides are regarded as kinds of versatile building blocks and have been widely applied to 1,3-dipolar cycloaddition reactions with different dipolarophiles for the assembly of various five-membered heterocyclic compounds.[6] With respect to the synthesis of imidazole derivatives, a variety of literature reports involving catalytic asymmetric [3 + 2] cycloaddition of azomethine ylides with imines to construct chiral imidazolidines have been published (Scheme 1a).[7] It is noteworthy that fluorinated imidazolidines could be successfully assembled through 1,3-dipolar cycloaddition of azomethine ylides with fluorinated imines, which were completed by the groups of Wu[7c] and Wang.[7d,e] Bi and Xu independently demonstrated a silver-promoted [3 + 2] cycloaddition of azomethine ylides with isocyanides for the production of 1,2,4-trisubstituted imidazoles with good functional group tolerance (Scheme 1b).[8] Inspired by the unique property of silver in the construction of heterocycles[9] and our ongoing efforts on the synthesis of trifluoromethyl-containing N-heterocycles,[10] we herein describe a synthetic protocol for delivering 5-(trifluoromethyl)imidazoles via silver-mediated [3 + 2] cycloaddition of azomethine ylides with trifluoroacetimidoyl chlorides (Scheme 1c). It is notable that trifluoroacetimidoyl chloride can be easily obtained by simply mixing the parent amine with TFA, CCl_4, and PPh_3,[11] which is significantly cheaper than the preparation of the aforementioned fluori-

Scheme 1. Synthesis of Imidazolidines or Imidazoles from [3 + 2] Cycloaddition of Azomethine Ylides

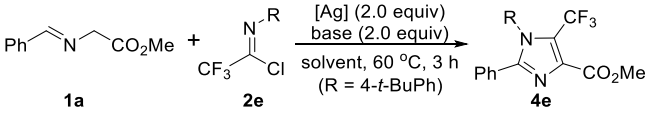


Received: January 18, 2021
Published: February 22, 2021

nated imine from expensive trifluoroacetaldehyde ethyl hemiacetal. Trifluoroacetimidoyl chlorides have been frequently utilized as versatile trifluoromethyl synthons for the construction of an array of important trifluoromethyl-containing molecules.[12]

The reaction conditions were optimized by using (*E*)-methyl 2-(benzylideneamino)acetate (**1a**) and *N*-(4-(*tert*-butyl)-phenyl)-2,2,2-trifluoroacetimidoyl chloride (**2e**) as benchmark substrates. The reaction was performed in the presence of 2.0 equiv of Ag_2CO_3, 2.0 equiv of DBU, and 4 Å MS in toluene at 60 °C under an N_2 atmosphere for 3 h. Gratifyingly, the [3 + 2] cycloaddition reaction occurred smoothly to deliver the desired imidazole product **4e** in 32% yield (Table 1, entry 1).

Table 1. Optimization of the Reaction Conditions[a]



1a **2e** **4e**

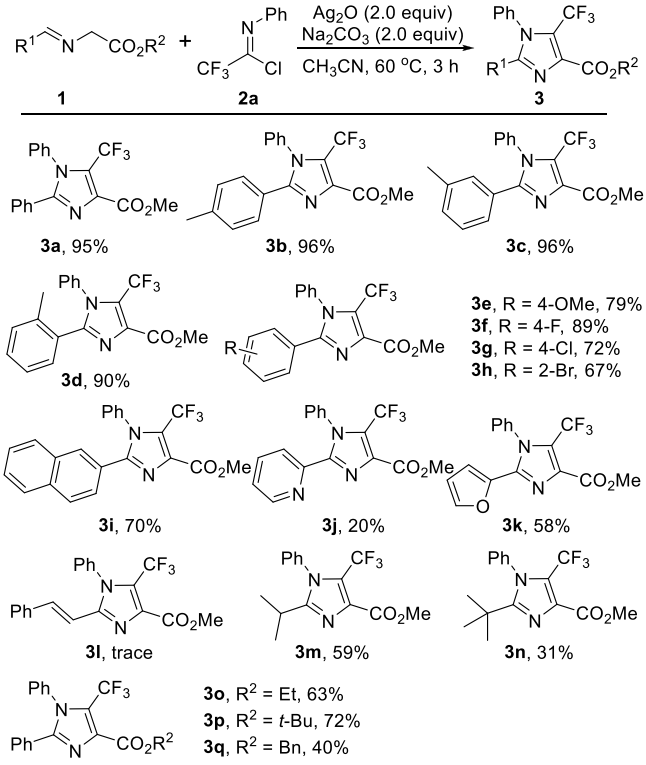
Entry	[Ag]	base	solvent	yield[b] (%)
1	Ag_2CO_3	DBU	toluene	32
2	Ag_2CO_3	DBU	DMF	15
3	Ag_2CO_3	DBU	DMSO	9
4	Ag_2CO_3	DBU	DCE	6
5	Ag_2CO_3	DBU	CH_3CN	36
6	Ag_2CO_3	Et_3N	CH_3CN	68
7	Ag_2CO_3	DIPEA	CH_3CN	70
8	Ag_2CO_3	$NaHCO_3$	CH_3CN	62
9	Ag_2CO_3	Na_2CO_3	CH_3CN	72
10	Ag_2CO_3	K_2CO_3	CH_3CN	69
11	Ag_2CO_3	K_3PO_4	CH_3CN	71
12	Ag_2O	Na_2CO_3	CH_3CN	91 (88)[c]
13	AgF	Na_2CO_3	CH_3CN	58
14	AgOAc	Na_2CO_3	CH_3CN	18
15	AgOTFA	Na_2CO_3	CH_3CN	60
16	**Ag_2O**	**Na_2CO_3**	**CH_3CN**	**99 (97)**[c,d]
17	Ag_2O	Na_2CO_3	CH_3CN	71−81[d,e]
18	Ag_2O	Na_2CO_3	CH_3CN	14−15[d,f]
19	Ag_2O	Na_2CO_3	CH_3CN	96[d,g]
20	Ag_2O	Na_2CO_3	CH_3CN	71[d,h]

[a]Reaction conditions unless specified otherwise: **1a** (0.2 mmol), **2e** (0.4 mmol), [Ag] (2.0 equiv), base (2.0 equiv), and 4 Å MS (40 mg) in solvent (2.0 mL) at 60 °C under N_2 atmosphere for 3 h. [b]Yields determined by GC analysis using dodecane as an internal standard. [c]Isolated yield. [d]**1a** (0.3 mmol), **2e** (0.2 mmol). [e]The reaction was performed in the presence of 1.5 equiv of Ag_2O (81%) or 1.0 equiv of Ag_2O (71%). [f]The reaction was performed in the presence of 0.3 equiv of Ag_2O under an air (14%) or O_2 (15%) atmosphere. [g]80 °C. [h]40 °C.

The solvent effect was next investigated by the employment of different solvents, and the result indicated that CH_3CN could lead to superior reactivity (Table 1, entries 2−5). Then, we screened a variety of other organic and inorganic bases, including Et_3N, DIPEA, $NaHCO_3$, Na_2CO_3, K_2CO_3, and K_3PO_4, which showed that Na_2CO_3 was the best choice to give the 5-(trifluoromethyl)imidazole product **4e** in 72% yield (Table 1, entries 6−11). The examination of other silver salts was also performed, and Ag_2O was the optimal promoter to improve the reaction yield to 91% (Table 1, entries 12−15). It was noteworthy that switching the ratio of the starting substrates **1a** and **2e** to 1.5/1 further facilitated the reaction and the product **4e** could be isolated in 97% yield (Table 1, entry 16). Further increasing the ratio of **1a** and **2e** to 2/1 or 2.5/1 caused a slight decrease in the reaction yield (see the Supporting Information for details). Reducing the amounts of Ag_2O to 1.5 or 1.0 equiv resulted in an obvious decrease in reaction efficiency (Table 1, entry 17). When the reaction was carried out in the presence of 0.3 equiv of Ag_2O under an air or O_2 atmosphere, the reaction yield was decreased to 14% or 15% (Table 1, entry 18). In the meantime, the hydrolysis and decomposition of trifluoroacetimidoyl chloride **2e** were observed. Elevating the reaction temperature to 80 °C enabled a comparable reactivity, whereas lowering the temperature had a harmful influence on the reaction (Table 1, entries 19 and 20).

Having established the optimal conditions, the scope of the reaction was investigated with a wide range of azomethine ylides, and the results are summarized in Scheme 2. Various

Scheme 2. Scope of the Imino Esters[a,b]



[a]Reaction conditions: **1** (0.3 mmol), **2a** (0.2 mmol), Ag_2O (2.0 equiv), Na_2CO_3 (2.0 equiv), and 4 Å MS (40 mg) in CH_3CN (2.0 mL) under an N_2 atmosphere at 60 °C for 3 h. [b]Isolated yields.

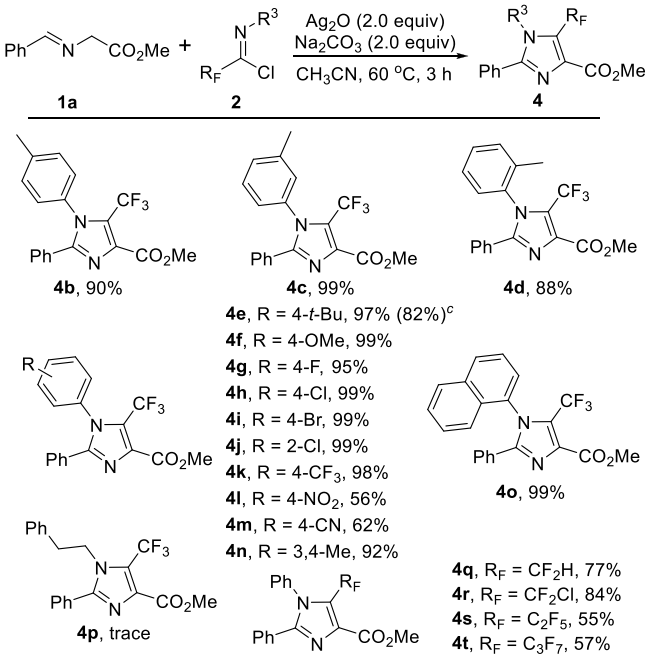
imino ester substrates with electron-donating or -withdrawing groups at the benzene ring could successfully participate in the reaction to furnish the highly substituted imidazoles **3a−h** in 67−96% yields. A slight steric effect was observed with regard to the products **3b−d**. The electron-rich substrates **3a−e** generally showed higher reactivity in comparison to that of electron-deficient substrates **3f−h**. The transformation was also tolerant of a naphthalene ring to deliver the imidazole product **3i** in 70% yield. Notably, azomethines containing a heterocyclic motif, such as pyridine or furan, were also compatible with the standard conditions, albeit with relatively lower yields (**3j**,**k**). The obtained imidazole products could possibly be utilized as bidentate ligands in metal-catalyzed cross-coupling reactions. The imino ester from cinnamalde-

https://dx.doi.org/10.1021/acs.joc.1c00131
J. Org. Chem. 2021, 86, 4361−4370

hyde was unstable under the optimal conditions and did not participate in the reaction (**3l**). The reaction was also amendable to imino esters from aliphatic aldehydes, and the corresponding alkyl-substituted imidazole products **3m**,**n** were afforded in acceptable yields. Other azomethines with diverse alkyl-substituted ester groups were applicable to the current reaction system, resulting in the formation of targeted products **3o**−**q** in acceptable yields.

The generality of the [3 + 2] cycloaddition reaction was further surveyed by using a library of fluorinated imidoyl chlorides (Scheme 3). To our surprise, the reaction proceeded

Scheme 3. Scope of Fluorinated Imidoyl Chlorides[a,b]

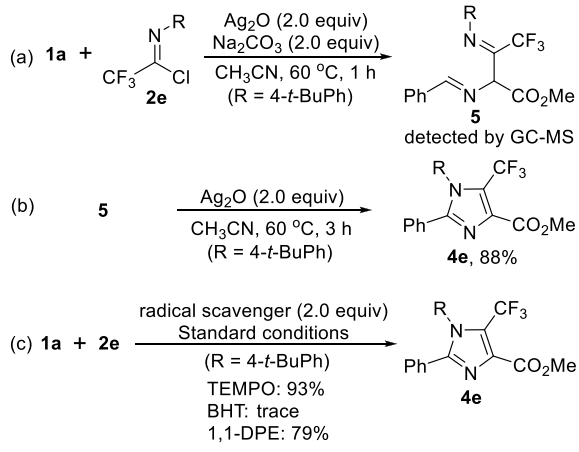


[a]Reaction conditions: **1a** (0.3 mmol), **2** (0.2 mmol), Ag_2O (2.0 equiv), Na_2CO_3 (2.0 equiv), and 4 Å MS (40 mg) in CH_3CN (2.0 mL) under an N_2 atmosphere at 60 °C for 3 h. [b]Isolated yields. [c]Two mmol scale.

with very high efficiency, as it was demonstrated that most of the *N*-aryl-trifluoroacetimidoyl chlorides bearing electron-donating or -withdrawing groups react smoothly with azomethine ylide **1a** to lead to the corresponding 5-(trifluoromethyl)imidazoles **4b**−**n** in almost quantitative yields. The electronic effect (**4b**−**n**) and steric hindrance (**4b**−**d**) of the aryl ring seemingly made little difference in the reaction due to the comparable yields obtained of these substrates. The good tolerance of the halogen atoms (F, Cl, and Br) on the aryl ring provided a synthetic handle for further derivatization (**4g**−**j**). Several strongly electron deficient groups, such as $-CF_3$, $-NO_2$, and −CN, were compatible with the optimized conditions (**4k**−**m**). More importantly, the reaction could be easily reproducible on a 2 mmol scale without any difficulty (**4e**). The naphthalene ring could also be incorporated into the desired imidazole product **4o** in 99% yield under the standard conditions. Unfortunately, the trifluoroacetimidoyl chlorides from heteroaryl amines could not be prepared and the trifluoroacetimidoyl chloride derived from an aliphatic amine was not a viable substrate for the transformation. The protocol was amenable to a range of other fluorinated imidoyl chlorides for the preparation of the corresponding fluoroalkyl-substituted imidazoles (**4q**−**t**) with moderate to good reactivity. The observation data indicated the excellent generality and compatibility of the reaction.

A series of control experiments were performed to help understand the reaction mechanism (Scheme 4). The coupling

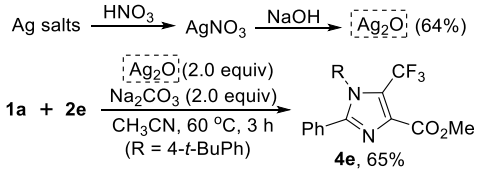
Scheme 4. Mechanistic Investigations



product **5** of azomethine ylide **1a** and trifluoroacetimidoyl chloride **2e** was successfully detected by GC-MS in the model reaction (Scheme 4a). We also synthesized intermediate **5** and treated it with 2.0 equiv of Ag_2O, and the imidazole product **4e** was afforded in 88% yield, suggesting the plausible intermediacy of **5** (Scheme 4b). Radical trapping experiments were conducted by the addition of 2.0 equiv of radical scavengers. A comparable yield was obtained when TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl) was added into the reaction, whereas a trace of the product was observed with BHT (2,4-di-*tert*-butyl-4-methylphenol). With regard to 1,1-DPE (1,1-diphenylethylene), a 73% yield of the product **4e** was achieved (Scheme 4c). Therefore, a single-electron-transfer (SET) process was likely not invoved in the reaction.

The serious problem of this reaction is the employment of stoichiometric Ag_2O. Although 2 equiv of Ag_2O enables the high efficiency of the reaction and Ag_2O is one of the cheapest silver sources, we still want to recycle the Ag_2O and reduce the cost.[13] As depicted in Scheme 5, excess Ag_2O and other silver

Scheme 5. Recovery Experiment of Ag Salts

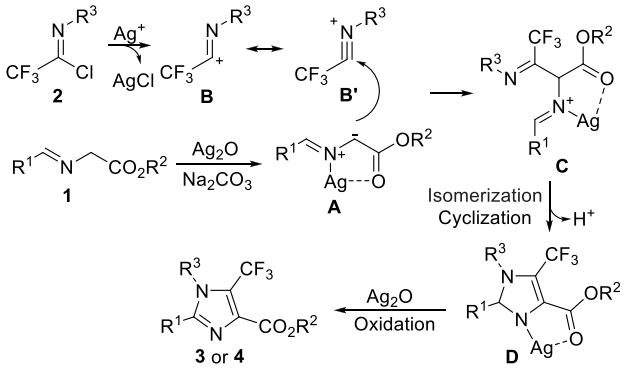


salts could be readily collected by simple filtration. The residue was treated with dilute nitric acid and filtrated to remove insoluble AgCl. Subsequently, an NaOH solution was added to the resulting $AgNO_3$ solution to precipitate Ag_2O in 64% yield. When the removal of 1 equiv of insoluble AgCl is considered, the actual recovery rate of Ag_2O is 85%. The obtained Ag_2O was recycled in the reaction to afford the imidazole product **4e** in 65% yield.

On the basis of the mechanistic studies and previous reports,[8] a plausible reaction pathway was proposed as depicted in Scheme 6. First, the interaction of azomethine

https://dx.doi.org/10.1021/acs.joc.1c00131
J. Org. Chem. 2021, 86, 4361−4370

Scheme 6. Plausible Reaction Mechanism



ylide **1** with silver and base formed dipole intermediate **A**.[6c,14] The reaction of trifluoroacetimidoyl chloride with silver gave the trifluoroacetimidoyl cation **B**, which could isomerize to complex **B′**. Then, the nucleophilic attack of intermediate **A** to complex **B′** led to the intermediate **C**, which underwent an isomerization and cyclization process to furnish the dihydroimidazole-silver complex **D**.[8a] Finally, the further oxidation of **D** with the aid of Ag_2O could deliver the desired imidazole product **3** or **4**.

Ethyl 2-(4-bromophenyl)-1-(2,4-dichlorophenyl)-1*H*-4-imidazolecarboxylate is regarded as a specific allosteric modulator of the $GABA_A$ receptor, which shows high potency and efficacy.[2d] The CF_3 analogue of this bioactive molecule **6** could be successfully assembled in 87% yield by using the developed protocol (Scheme 7). The positive result further highlights the huge synthetic utility of the present [3 + 2] cycloaddition reaction.

In conclusion, we have explored an efficient approach for the rapid construction of 5-(trifluoromethyl)imidazoles through the silver-mediated [3 + 2] cycloaddition of azomethine ylides with trifluoroacetimidoyl chlorides. The reaction features simple operation, readily available reagents, a broad substrate scope, high efficiency, and good application prospects and presents a rapid and straightforward pathway for the synthesis of biologically valuable imidazole molecules. The reaction could be scaled up to a 2 mmol scale and be successfully applied to construct the analogue of a specific allosteric modulator of $GABA_A$ receptors. Furthermore, the recycling of silver species could allow for more applications of this protocol in organic synthesis.

EXPERIMENTAL SECTION

General Information. Unless otherwise noted, all reactions were carried out under an N_2 atmosphere. All reagents were from commercial sources and were used as received without further purification. All solvents were dried by standard techniques and distilled prior to use. Column chromatography was performed on silica gel (200−300 mesh) using petroleum ether (bp 60−90 °C) and ethyl acetate as eluents. NMR spectra were recorded on a Bruker Avance instrument operating for ^{1}H NMR at 400 MHz, ^{13}C NMR at 100 MHz, and ^{19}F NMR at 377 MHz, and spectral data are reported in ppm relative to tetramethylsilane (TMS) as an internal standard and $CDCl_3$ (^{1}H NMR δ 7.26, ^{13}C NMR δ 77.16) as a solvent. All coupling constants (J) are reported in Hz. The following abbreviations were used to describe peak splitting patterns when appropriate: s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublets of doublets, t = triplet, dt = doublet of triplets, q = quadruplet, m = multiplet, br = broad. Gas chromatography (GC) analyses were performed on a Shimadzu GC-2014C chromatograph equipped with a FID detector. Mass spectra (MS) were measured on a spectrometer by direct inlet at 70 eV. Mass spectroscopy data of the products were collected on an HRMS-TOF instrument or a Waters TOFMS GCT Premier apparatus using EI or ESI ionization. Melting points were measured with a WRR digital point apparatus and were not corrected.

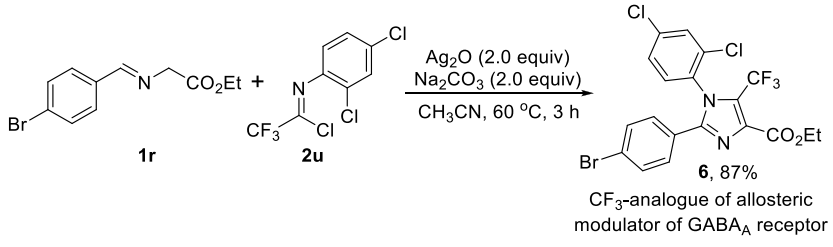
Preparation of Imino Esters 1.[15] To a stirred methanolic suspension (1.0 M) of glycine cooled to 0 °C was added $SOCl_2$ (1.2 equiv) dropwise (note: a vigorous exotherm with concomitant evolution of HCl is observed). The resulting clear solution was warmed to room temperature and stirred until complete conversion of the amino acid as indicated by TLC (ninhydrin stain, 5% MeOH/CH_2Cl_2). The mixture was concentrated under vacuum to afford the glycine methyl ester hydrochlorides. Workup: the volatiles were removed in vacuo, and the residue was further concentrated under high vacuum to afford the amino acid methyl ester hydrochlorides in all cases as off-white or white solids. The obtained amino acid methyl ester hydrochlorides could be directly used in the next step without further purification.

To a suspension of the glycine ester hydrochloride salt (1.5 equiv) were added anhydrous $MgSO_4$ (1.5 equiv) in CH_2Cl_2 (25 mL) and Et_3N (1.5 equiv) under an N_2 atmosphere. The mixture was stirred at room temperature for 1 h before the aldehyde (1.0 equiv) was added. After the mixture was stirred at room temperature for 24 h, $MgSO_4$ was removed by filtration and the filtrate was washed sequentially with brine, saturated aqueous $NaHCO_3$ solution, and water. The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated under vacuum to afford the glycine imino ester.

Preparation of Fluorinated Imidoyl Chlorides 2.[11] A 200 mL two-necked flask equipped with a septum cap, a condenser, and a Teflon-coated magnetic stir bar was charged with PPh_3 (34.5 g, 132 mmol), Et_3N (7.3 mL, 53 mmol), CCl_4 (21.1 mL, 220 mmol), and TFA (3.4 mL, 44 mmol). After the solution was stirred for about 10 min (ice bath), an amine (53 mmol) dissolved in CCl_4 (21.1 mL, 220 mmol) was added. The mixture was then refluxed with stirring (3 h). After the reaction was completed, residual solid Ph_3PO, PPh_3, and Et_3N-HCl were washed with hexane several times. Then the hexane was filtered and concentrated under vacuum. The crude product was purified by column chromatography on silica gel or neutral alumina to afford the corresponding product.

General Procedure for the Synthesis of 5-(Trifluoromethyl)-imidazoles (3 or 4). Ag_2O (92.7 mg, 0.4 mmol), Na_2CO_3 (42.4 mg, 0.4 mmol), and 4 Å MS (40 mg) were added to a solution of azomethine ylide **1** (0.3 mmol) and trifluoroacetimidoyl chloride **2** (0.2 mmol) in CH_3CN (2 mL). The mixture was stirred at 60 °C

Scheme 7. Synthetic Utility



https://dx.doi.org/10.1021/acs.joc.1c00131
J. Org. Chem. 2021, 86, 4361−4370

under an N_2 atmosphere for 3 h. After the reaction was completed, the mixture was slowly cooled to room temperature and extracted three times with EtOAc (3 × 10 mL). The extracts were combined and concentrated under vacuum. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc) to yield the product **3** or **4**.

Scale-up Reaction. Ag_2O (927 mg, 4 mmol), Na_2CO_3 (424 mg, 4 mmol), and 4 Å MS (400 mg) were added to a solution of azomethine ylide **1a** (3 mmol, 1.5 equiv) and trifluoroacetimidoyl chloride **2e** (2 mmol, 1.0 equiv) in CH_3CN (20 mL). The mixture was stirred at 60 °C under an N_2 atmosphere for 3 h. After the reaction was completed, the mixture was slowly cooled to room temperature and extracted three times with EtOAc (3 × 50 mL). The extracts were combined and concentrated under vacuum. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc) to yield the product **4e** as a white solid (659 mg, 82%).

*Methyl 1,2-Diphenyl-5-(trifluoromethyl)-1H-imidazole-4-carboxylate (**3a**).* Upon completion of the reaction the mixture was concentrated and purified via flash column chromatography (petroleum ether/ethyl acetate 5/1, R_f = 0.4) to give the title product **3a** as a white solid (65.7 mg, 95%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52−7.42 (m, 3H), 7.33 (d, *J* = 7.1 Hz, 2H), 7.28 (t, *J* = 6.5 Hz, 3H), 7.21 (t, *J* = 7.4 Hz, 2H), 3.99 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 162.1, 149.9, 135.6, 134.1, 130.1, 129.7, 129.5, 129.2, 128.2, 127.9, 125.4 (C−F, q, $^2J_{C-F}$ = 39.7 Hz), 119.6 (C−F, q, $^1J_{C-F}$ = 270.1 Hz), 52.6. ^{19}F NMR (377 MHz, $CDCl_3$): δ −54.7. Mp: 112.4−113.5 °C. HRMS (ESI): [M + H]$^+$ calcd for $C_{18}H_{14}F_3N_2O_2$ 347.1002; found 347.1018.

*Methyl 1-Phenyl-2-(p-tolyl)-5-(trifluoromethyl)-1H-imidazole-4-carboxylate (**3b**).* Upon completion of the reaction the mixture was concentrated and purified via flash column chromatography (petroleum ether/ethyl acetate 5/1, R_f = 0.3) to give the title product **3b** as a white solid (69.1 mg, 96%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52−7.41 (m, 3H), 7.27 (d, *J* = 6.9 Hz, 2H), 7.21 (d, *J* = 8.2 Hz, 2H), 7.02 (d, *J* = 8.1 Hz, 2H), 3.99 (s, 3H), 2.27 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 162.2, 150.0, 139.9, 135.7, 134.0, 130.0, 129.5, 129.1, 128.9, 127.9, 125.4, 125.2 (C−F, q, $^2J_{C-F}$ = 39.6 Hz), 119.7 (C−F, q, $^1J_{C-F}$ = 270.0 Hz), 52.6, 21.3. ^{19}F NMR (377 MHz, $CDCl_3$): δ −54.6. Mp: 135.3−136.2 °C. HRMS (ESI): [M + H]$^+$ calcd for $C_{19}H_{16}F_3N_2O_2$ 361.1158; found 361.1177.

*Methyl 1-Phenyl-2-(m-tolyl)-5-(trifluoromethyl)-1H-imidazole-4-carboxylate (**3c**).* Upon completion of the reaction the mixture was concentrated and purified via flash column chromatography (petroleum ether/ethyl acetate 5/1, R_f = 0.4) to give the title product **3c** as a white solid (69.1 mg, 96%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53−7.41 (m, 3H), 7.29 (d, *J* = 12.0 Hz, 3H), 7.10 (d, *J* = 7.6 Hz, 1H), 7.05 (t, *J* = 7.6 Hz, 1H), 6.95 (d, *J* = 7.7 Hz, 1H), 3.99 (s, 3H), 2.23 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 162.2, 150.0, 138.1, 135.8, 134.1, 130.4, 130.2, 130.0, 129.5, 128.1, 127.9, 127.9, 126.0, 125.3 (C−F, q, $^2J_{C-F}$ = 39.5 Hz), 119.7 (C−F, q, $^1J_{C-F}$ = 270.2 Hz), 52.6, 21.2. ^{19}F NMR (377 MHz, $CDCl_3$): δ −54.6. Mp: 134.2−135.7 °C. HRMS (ESI): [M + H]$^+$ calcd for $C_{19}H_{16}F_3N_2O_2$ 361.1158; found 361.1182.

*Methyl 1-Phenyl-2-(o-tolyl)-5-(trifluoromethyl)-1H-imidazole-4-carboxylate (**3d**).* Upon completion of the reaction the mixture was concentrated and purified via flash column chromatography (petroleum ether/ethyl acetate 5/1, R_f = 0.4) to give the title product **3d** as a white solid (64.8 mg, 90%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37−7.29 (m, 3H), 7.21−7.14 (m, 3H), 7.09 (t, 2H), 7.03 (t, *J* = 7.4 Hz, 1H), 3.98 (s, 3H), 2.17 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 162.0, 150.3, 138.1, 135.0, 133.7, 130.7, 130.1, 129.9, 129.7, 129.1, 128.1, 127.2, 125.2, 124.9 (C−F, q, $^2J_{C-F}$ = 40.0 Hz), 119.7 (C−F, q, $^1J_{C-F}$ = 270.1 Hz), 52.5, 20.0. ^{19}F NMR (377 MHz, $CDCl_3$): δ −54.7. Mp: 136.8−137.4 °C. HRMS (ESI): [M + H]$^+$ calcd for $C_{19}H_{16}F_3N_2O_2$ 361.1158; found 361.1176.

*Methyl 2-(4-Methoxyphenyl)-1-phenyl-5-(trifluoromethyl)-1H-imidazole-4-carboxylate (**3e**).* Upon completion of the reaction the mixture was concentrated and purified via flash column chromatography (petroleum ether/ethyl acetate 5/1, R_f = 0.4) to give the title product **3e** as a white solid (59.4 mg, 79%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53−7.43 (m, 3H), 7.29−7.23 (m, 4H), 6.73 (d, *J* = 8.9 Hz, 2H), 3.99 (s, 3H), 3.75 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 162.2, 160.6, 149.9, 135.8, 134.0, 130.7, 130.0, 129.5, 127.9, 125.1 (C−F, q, $^2J_{C-F}$ = 39.7 Hz), 120.6, 119.7 (C−F, q, $^1J_{C-F}$ = 269.9 Hz), 113.6, 55.2, 52.6. ^{19}F NMR (377 MHz, $CDCl_3$): δ −54.6. Mp: 124.8−125.3 °C. HRMS (ESI): [M + H]$^+$ calcd for $C_{19}H_{16}F_3N_2O_3$ 377.1108; found 377.1119.

*Methyl 2-(4-Fluorophenyl)-1-phenyl-5-(trifluoromethyl)-1H-imidazole-4-carboxylate (**3f**).* Upon completion of the reaction the mixture was concentrated and purified via flash column chromatography (petroleum ether/ethyl acetate 5/1, R_f = 0.3) to give the title product **3f** as a yellow oily liquid (64.8 mg, 89%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54−7.45 (m, 3H), 7.34−7.30 (m, 2H), 7.27 (d, *J* = 8.3 Hz, 2H), 6.91 (t, *J* = 8.6 Hz, 2H), 3.99 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 163.4 (C−F, d, $^1J_{C-F}$ = 251.2 Hz), 162.0, 148.9, 135.4, 134.1, 131.3 (C−F, d, $^3J_{C-F}$ = 8.6 Hz), 130.3, 129.7, 127.8, 125.5 (C−F, q, $^2J_{C-F}$ = 40 Hz), 124.4 (C−F, d, $^4J_{C-F}$ = 3.2 Hz), 120.9 (C−F, q, $^1J_{C-F}$ = 270.1 Hz), 115.5 (C−F, d, $^2J_{C-F}$ = 21.9 Hz), 52.7. ^{19}F NMR (377 MHz, $CDCl_3$): δ −54.7, −110.0. HRMS (ESI): [M + H]$^+$ calcd for $C_{18}H_{13}F_4N_2O_2$ 365.0908; found 365.0923.

*Methyl 2-(4-Chlorophenyl)-1-phenyl-5-(trifluoromethyl)-1H-imidazole-4-carboxylate (**3g**).* Upon completion of the reaction the mixture was concentrated and purified via flash column chromatography (petroleum ether/ethyl acetate 5/1, R_f = 0.3) to give the title product **3g** as a white solid (54.7 mg, 72%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55−7.45 (m, 3H), 7.29−7.25 (m, 4H), 7.20 (d, *J* = 8.7 Hz, 2H), 4.00 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 162.0, 148.7, 136.0, 135.4, 134.2, 130.4, 130.4, 129.7, 128.6, 127.8, 126.7, 125.6 (C−F, q, $^2J_{C-F}$ = 39.9 Hz), 119.5 (C−F, q, $^1J_{C-F}$ = 270.2 Hz), 52.7. ^{19}F NMR (377 MHz, $CDCl_3$): δ −54.7. Mp: 109.2−111.3 °C. HRMS (ESI): [M + H]$^+$ calcd for $C_{18}H_{13}ClF_3N_2O_2$ 381.0612; found 381.0628.

*Methyl 2-(2-bromophenyl)-1-phenyl-5-(trifluoromethyl)-1H-imidazole-4-carboxylate (**3h**).* Upon completion of the reaction the mixture was concentrated and purified via flash column chromatography (petroleum ether/ethyl acetate 5/1, R_f = 0.3) to give the title product **3h** as a white solid (56.8 mg, 67%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (d, *J* = 9.0 Hz, 1H), 7.38−7.30 (m, 3H), 7.29−7.25 (m, 3H), 7.24−7.15 (m, 2H), 3.99 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 161.7, 149.0, 134.7, 133.6, 132.6, 132.5, 131.5, 130.3, 129.9, 129.0, 127.3, 126.8, 125.2 (C−F, q, $^2J_{C-F}$ = 40.0 Hz), 124.3, 119.6 (C−F, q, $^1J_{C-F}$ = 270.3 Hz), 52.6. ^{19}F NMR (377 MHz, $CDCl_3$): δ −54.8. Mp: 116.6−117.6 °C. HRMS (ESI): [M + H]$^+$ calcd for $C_{18}H_{13}BrF_3N_2O_2$ 425.0107; found 425.0114.

*Methyl 2-(Naphthalen-2-yl)-1-phenyl-5-(trifluoromethyl)-1H-imidazole-4-carboxylate (**3i**).* Upon completion of the reaction the mixture was concentrated and purified via flash column chromatography (petroleum ether/ethyl acetate 5/1, R_f = 0.3) to give the title product **3i** as a white solid (55.5 mg, 70%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (s, 1H), 7.74 (d, *J* = 7.9 Hz, 1H), 7.65 (d, *J* = 8.5 Hz, 2H), 7.53−7.41 (m, 5H), 7.38 (d, *J* = 10.2 Hz, 1H), 7.31 (d, *J* = 7.6 Hz, 2H), 4.02 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 162.2, 149.8, 135.7, 134.3, 133.3, 132.5, 130.2, 129.7, 129.6, 128.6, 127.9, 127.9, 127.6, 127.4, 126.6, 125.6 (C−F, q, $^2J_{C-F}$ = 39.7 Hz), 125.6, 125.5, 119.7 (C−F, q, $^1J_{C-F}$ = 270.0 Hz), 52.7. ^{19}F NMR (377 MHz, $CDCl_3$): δ −54.6. Mp: 135.7−136.6 °C. HRMS (ESI): [M + H]$^+$ calcd for $C_{22}H_{16}F_3N_2O_2$ 397.1158; found 397.1174.

*Methyl 1-Phenyl-2-(pyridin-2-yl)-5-(trifluoromethyl)-1H-imidazole-4-carboxylate (**3j**).* Upon completion of the reaction the mixture was concentrated and purified via flash column chromatography (petroleum ether/ethyl acetate 5/1, R_f = 0.2) to give the title product **3j** as a white solid (13.9 mg, 20%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (d, *J* = 4.7 Hz, 1H), 7.91 (d, *J* = 7.9 Hz, 1H), 7.68 (t, *J* = 8.6 Hz, 1H), 7.49−7.38 (m, 3H), 7.30 (d, *J* = 7.4 Hz, 2H), 7.17 (t, 1H), 4.00 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz,

https://dx.doi.org/10.1021/acs.joc.1c00131
J. Org. Chem. 2021, 86, 4361−4370

$CDCl_3$): δ 162.0, 148.8, 148.1, 147.7, 136.4, 136.1, 133.9, 129.5, 128.7, 127.8, 126.2 (C−F, q, $^2J_{C-F}$ = 39.3 Hz), 124.7, 119.5 (C−F, q, $^1J_{C-F}$ = 270.3 Hz), 52.6. ^{19}F NMR (377 MHz, $CDCl_3$): δ −54.8. Mp: 102.8−103.4 °C. HRMS (ESI): $[M + H]^+$ calcd for $C_{17}H_{13}F_3N_3O_2$ 348.0954; found 348.0976.

*Methyl 2-(Furan-2-yl)-1-phenyl-5-(trifluoromethyl)-1H-imidazole-4-carboxylate (**3k**).* Upon completion of the reaction the mixture was concentrated and purified via flash column chromatography (petroleum ether/ethyl acetate 5/1, R_f = 0.2) to give the title product **3k** as a white solid (39.0 mg, 58%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66−7.53 (m, 3H), 7.40 (d, J = 1.2 Hz, 1H), 7.36 (d, J = 7.5 Hz, 2H), 6.29−6.24 (m, 1H), 5.76 (d, J = 3.5 Hz, 1H), 3.99 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 161.7, 144.2, 142.5, 142.0, 135.1, 134.3, 130.7, 129.7, 127.8, 125.1 (C−F, q, $^2J_{C-F}$ = 40.1 Hz), 119.5 (C−F, q, $^1J_{C-F}$ = 270.1 Hz), 112.1, 111.3, 52.6. ^{19}F NMR (377 MHz, $CDCl_3$): δ −54.9. Mp: 103.4−105.2 °C. HRMS (ESI): $[M + H]^+$ calcd for $C_{16}H_{12}F_3N_2O_3$ 337.0795; found 337.0814.

*Methyl 2-Isobutyl-1-phenyl-5-(trifluoromethyl)-1H-imidazole-4-carboxylate (**3m**).* Upon completion of the reaction the mixture was concentrated and purified via flash column chromatography (petroleum ether/ethyl acetate 5/1, R_f = 0.4) to give the title product **3m** as a white solid (38.5 mg, 59%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60−7.51 (m, 3H), 7.31−7.26 (m, 2H), 3.97 (s, 3H), 2.74−2.62 (m, 1H), 1.24 (d, J = 6.9 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 162.3, 156.8, 134.9, 133.3, 130.2, 129.6, 127.6, 124.3 (C−F, q, $^2J_{C-F}$ = 39.6 Hz), 119.7 (C−F, q, $^1J_{C-F}$ = 269.8 Hz), 52.6, 26.2, 21.5. ^{19}F NMR (377 MHz, $CDCl_3$): δ −54.8. Mp: 97.8−98.3 °C. HRMS (ESI): $[M + H]^+$ calcd for $C_{15}H_{16}F_3N_2O_2$ 313.1158; found 313.1175.

*Methyl 2-(tert-Butyl)-1-phenyl-5-(trifluoromethyl)-1H-imidazole-4-carboxylate (**3n**).* Upon completion of the reaction the mixture was concentrated and purified via flash column chromatography (petroleum ether/ethyl acetate 5/1, R_f = 0.2) to give the title product **3n** as a white solid (20.2 mg, 31%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (t, J = 7.4 Hz, 1H), 7.48 (t, J = 7.5 Hz, 2H), 7.34 (d, J = 7.6 Hz, 2H), 3.94 (s, 3H), 1.20 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 162.7, 158.0, 136.0, 132.2, 130.4, 129.2, 128.8, 125.3 (C−F, q, $^2J_{C-F}$ = 39.0 Hz), 119.6 (C−F, q, $^1J_{C-F}$ = 269.9 Hz), 52.6, 35.0, 30.1. ^{19}F NMR (377 MHz, $CDCl_3$): δ −55.0. Mp: 122.3−123.8 °C. HRMS (ESI): $[M + H]^+$ calcd for $C_{16}H_{18}F_3N_2O_2$ 327.1315; found 327.1332.

*Ethyl 1,2-Diphenyl-5-(trifluoromethyl)-1H-imidazole-4-carboxylate (**3o**).* Upon completion of the reaction the mixture was concentrated and purified via flash column chromatography (petroleum ether/ethyl acetate 5/1, R_f = 0.3) to give the title product **3o** as a white solid (45.4 mg, 63%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52−7.42 (m, 3H), 7.33 (d, J = 7.1 Hz, 2H), 7.28 (t, J = 6.6 Hz, 3H), 7.21 (t, J = 7.4 Hz, 2H), 4.47 (q, J = 7.1 Hz, 2H), 1.43 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 161.9, 149.8, 135.6, 134.6, 130.1, 129.6, 129.5, 129.2, 128.3, 128.2, 127.9, 125.0 (C−F, q, $^2J_{C-F}$ = 39.6 Hz), 119.7 (C−F, q, $^1J_{C-F}$ = 269.9 Hz), 61.8, 14.1. ^{19}F NMR (377 MHz, $CDCl_3$): δ −54.5. Mp: 105.8−106.3 °C. HRMS (ESI): $[M + H]^+$ calcd for $C_{19}H_{16}F_3N_2O_2$ 361.1158; found 361.1176.

*tert-Butyl 1,2-Diphenyl-5-(trifluoromethyl)-1H-imidazole-4-carboxylate (**3p**).* Upon completion of the reaction the mixture was concentrated and purified via flash column chromatography (petroleum ether/ethyl acetate 5/1, R_f = 0.3) to give the title product **3p** as a white solid (55.9 mg, 72%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52−7.41 (m, 3H), 7.33 (d, J = 7.1 Hz, 2H), 7.26 (t, J = 6.3 Hz, 3H), 7.20 (t, J = 7.4 Hz, 2H), 1.63 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 161.4, 149.6, 136.2, 135.8, 129.9, 129.5, 129.2, 128.5, 128.2, 127.9, 123.9 (C−F, q, $^2J_{C-F}$ = 39.2 Hz), 119.9 (C−F, q, $^1J_{C-F}$ = 269.7 Hz), 82.8, 27.9. ^{19}F NMR (377 MHz, $CDCl_3$): δ −54.2. Mp: 132.6−133.2 °C. HRMS (ESI): $[M + H]^+$ calcd for $C_{21}H_{20}F_3N_2O_2$ 389.1471; found 389.1480.

*Benzyl 1,2-Diphenyl-5-(trifluoromethyl)-1H-imidazole-4-carboxylate (**3q**).* Upon completion of the reaction the mixture was concentrated and purified via flash column chromatography (petroleum ether/ethyl acetate 5/1, R_f = 0.3) to give the title product **3q** as a yellow oily liquid (33.8 mg, 40%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51−7.41 (m, 5H), 7.40−7.30 (m, 5H), 7.29−7.18 (m, 5H), 5.45 (s, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 161.8, 149.9, 135.6, 135.5, 134.3, 130.1, 129.7, 129.5, 129.2, 128.6, 128.5, 128.3, 128.2, 127.9, 125.2 (C−F, q, $^2J_{C-F}$ = 39.6 Hz), 119.7 (C−F, q, $^1J_{C-F}$ = 269.9 Hz), 67.4. ^{19}F NMR (377 MHz, $CDCl_3$): δ −54.5. HRMS (ESI): $[M + H]^+$ calcd for $C_{24}H_{18}F_3N_2O_2$ 423.1315; found 423.1328.

*Methyl 2-Phenyl-1-(p-tolyl)-5-(trifluoromethyl)-1H-imidazole-4-carboxylate (**4b**).* Upon completion of the reaction the mixture was concentrated and purified via flash column chromatography (petroleum ether/ethyl acetate 5/1, R_f = 0.4) to give the title product **4b** as a yellow oily liquid (64.8 mg, 90%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (d, J = 7.1 Hz, 2H), 7.29−7.26 (m, 1H), 7.24−7.19 (m, 4H), 7.13 (d, J = 8.3 Hz, 2H), 3.98 (s, 3H), 2.41 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 162.2, 149.9, 140.3, 134.0, 132.9, 130.1, 129.6, 129.2, 128.3, 128.2, 127.5, 125.4 (q, $J_{(C-F)}$ = 39.6 Hz), 119.7 (q, $J_{(C-F)}$ = 269.9 Hz), 52.6, 21.3. ^{19}F NMR (377 MHz, $CDCl_3$): δ −54.8. HRMS (ESI): $[M + H]^+$ calcd for $C_{19}H_{16}F_3N_2O_2$ 361.1158; found 361.1172.

*Methyl 2-Phenyl-1-(m-tolyl)-5-(trifluoromethyl)-1H-imidazole-4-carboxylate (**4c**).* Upon completion of the reaction the mixture was concentrated and purified via flash column chromatography (petroleum ether/ethyl acetate 5/1, R_f = 0.4) to give the title product **4c** as a white solid (71.3 mg, 99%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36−7.26 (m, 5H), 7.21 (t, J = 7.4 Hz, 2H), 7.06 (d, J = 7.5 Hz, 2H), 3.98 (s, 3H), 2.35 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 162.1 149.7, 139.7, 135.4, 134.0, 130.8, 129.6, 129.2, 129.1, 128.3, 128.2, 128.1, 125.4 (C−F, q, $^2J_{C-F}$ = 39.8 Hz), 124.9, 119.6 (C−F, q, $^1J_{C-F}$ = 270.0 Hz), 52.6, 21.2. ^{19}F NMR (377 MHz, $CDCl_3$): δ −54.7. Mp: 140.3−141.4 °C. HRMS (ESI): $[M + H]^+$ calcd for $C_{19}H_{16}F_3N_2O_2$ 361.1158; found 361.1176.

*Methyl 2-Phenyl-1-(o-tolyl)-5-(trifluoromethyl)-1H-imidazole-4-carboxylate (**4d**).* Upon completion of the reaction the mixture was concentrated and purified via flash column chromatography (petroleum ether/ethyl acetate = 20:1, R_f = 0.3) to give the title product **4d** as a yellow oily liquid (63.4 mg, 88%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (t, 1H), 7.40−7.33 (m, 4H), 7.32−7.28 (m, 2H), 7.25−7.20 (m, 2H), 4.01 (s, 3H), 1.91 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 162.1, 149.5, 135.7, 134.7, 134.1, 131.3, 130.5, 129.8, 128.7, 128.4, 128.3, 127.0, 125.1 (C−F, q, $^2J_{C-F}$ = 39.6 Hz), 119.6 (C−F, q, $^1J_{C-F}$ = 270.1 Hz), 52.6, 17.1. ^{19}F NMR (377 MHz, $CDCl_3$): δ −55.8. HRMS (ESI): $[M + H]^+$ calcd for $C_{19}H_{16}F_3N_2O_2$ 361.1158; found 361.1176.

*Methyl 1-(4-(tert-Butyl)phenyl)-2-phenyl-5-(trifluoromethyl)-1H-imidazole-4-carboxylate (**4e**).* Upon completion of the reaction the mixture was concentrated and purified via flash column chromatography (petroleum ether/ethyl acetate 5/1, R_f = 0.3) to give the title product **4e** as a white solid (78.0 mg, 97%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, J = 8.6 Hz, 2H), 7.36−7.27 (m, 3H), 7.23−7.15 (m, 4H), 3.99 (s, 3H), 1.34 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 162.2, 153.5, 149.9, 134.0, 132.8, 129.6, 129.2, 128.4, 128.1, 127.3, 126.4, 125.4 (C−F, q, $^2J_{C-F}$ = 39.7 Hz), 119.7 (C−F, q, $^1J_{C-F)}$ = 270.1 Hz), 52.6, 34.9, 31.2. ^{19}F NMR (377 MHz, $CDCl_3$): δ −54.7. Mp: 137.6−138.2 °C. HRMS (ESI): $[M + H]^+$ calcd for $C_{22}H_{22}F_3N_2O_2$ 403.1628; found 403.1646.

*Methyl 1-(4-Methoxyphenyl)-2-phenyl-5-(trifluoromethyl)-1H-imidazole-4-carboxylate (**4f**).* Upon completion of the reaction the mixture was concentrated and purified via flash column chromatography (petroleum ether/ethyl acetate 5/1, R_f = 0.3) to give the title product **4f** as a yellow oily liquid (76.3 mg, 99%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38−7.33 (m, 2H), 7.30 (t, J = 7.4 Hz, 1H), 7.23 (t, J = 7.3 Hz, 2H), 7.18 (d, J = 8.9 Hz, 2H), 6.93 (d, J = 8.9 Hz, 2H), 3.98 (s, 3H), 3.84 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 162.1, 160.4, 150.0, 133.9, 129.6, 129.2, 128.9, 128.3, 128.2, 128.0, 125.4 (C−F, q, $^2J_{C-F}$ = 39.3 Hz), 119.6 (C−F, q, $^1J_{C-F}$ = 270.1 Hz), 114.5, 55.5, 52.6. ^{19}F NMR (377 MHz, $CDCl_3$): δ −54.9. HRMS (ESI): $[M + H]^+$ calcd for $C_{19}H_{16}F_3N_2O_3$ 377.1108; found 377.1121.

https://dx.doi.org/10.1021/acs.joc.1c00131
J. Org. Chem. 2021, 86, 4361−4370

*Methyl 1-(4-Fluorophenyl)-2-phenyl-5-(trifluoromethyl)-1H-imidazole-4-carboxylate (**4g**).* Upon completion of the reaction the mixture was concentrated and purified via flash column chromatography (petroleum ether/ethyl acetate = 20:1, R_f = 0.3) to give the title product **4g** as a yellow oily liquid (68.5 mg, 95%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35−7.30 (m, 3H), 7.29−7.23 (m, 4H), 7.14 (t, J = 8.4 Hz, 2H), 3.99 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 163.1 (C−F, d, $^1J_{C-F}$ = 251.7 Hz), 162.0, 150.0, 134.2, 131.5, (C−F, d, $^4J_{C-F}$ = 3.1 Hz), 129.8, 129.8 (C−F, d, $^3J_{C-F}$ = 10.0 Hz), 129.2, 128.3, 128.0, 125.4 (C−F, q, $^2J_{C-F}$ = 39.6 Hz), 119.6 (C−F, q, $^1J_{C-F}$ = 270.1 Hz), 116.7 (C−F, d, $^2J_{C-F}$ = 23.2 Hz), 52.7. ^{19}F NMR (377 MHz, $CDCl_3$): δ −54.7, −109.3. HRMS (ESI): $[M + H]^+$ calcd for $C_{18}H_{13}F_4N_2O_2$ 365.0908; found 365.0925.

*Methyl 1-(4-Chlorophenyl)-2-phenyl-5-(trifluoromethyl)-1H-imidazole-4-carboxylate (**4h**).* Upon completion of the reaction the mixture was concentrated and purified via flash column chromatography (petroleum ether/ethyl acetate 5/1, R_f = 0.4) to give the title product **4h** as a yellow oily liquid (81 mg, 99%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (d, J = 8.6 Hz, 2H), 7.36−7.30 (m, 3H), 7.26 (t, 2H), 7.22 (d, J = 8.6 Hz, 2H), 3.99 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 161.9, 149.9, 136.3, 134.4, 134.0, 129.9, 129.9, 129.2, 129.2, 128.4, 127.9, 125.3 (C−F, q, $^2J_{C-F}$ = 39.6 Hz), 119.6 (C−F, q, $^1J_{C-F}$ = 270.2 Hz), 52.7. ^{19}F NMR (377 MHz, $CDCl_3$): δ −54.6. HRMS (ESI): $[M + H]^+$ calcd for $C_{18}H_{13}ClF_3N_2O_2$ 381.0612; found 381.0632.

*Methyl 1-(4-Bromophenyl)-2-phenyl-5-(trifluoromethyl)-1H-imidazole-4-carboxylate (**4i**).* Upon completion of the reaction the mixture was concentrated and purified via flash column chromatography (petroleum ether/ethyl acetate 5/1, R_f = 0.3) to give the title product **4i** as a yellow oily liquid (84.8 mg, 99%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, J = 8.6 Hz, 2H), 7.36−7.31 (m, 3H), 7.27 (d, J = 7.1 Hz, 2H), 7.15 (d, J = 8.6 Hz, 2H), 3.99 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 161.9, 149.8, 134.5, 134.3, 132.8, 129.9, 129.4, 129.2, 128.3, 127.9, 125.2 (C−F, q, $^2J_{C-F}$ = 39.8 Hz), 124.3, 119.5 (C−F, q, $^1J_{C-F}$ = 270.0 Hz), 52.6. ^{19}F NMR (377 MHz, $CDCl_3$): δ −54.5. HRMS (ESI): $[M + H]^+$ calcd for $C_{18}H_{13}BrF_3N_2O_2$ 425.0107; found 425.0119.

*Methyl 1-(2-Chlorophenyl)-2-phenyl-5-(trifluoromethyl)-1H-imidazole-4-carboxylate (**4j**).* Upon completion of the reaction the mixture was concentrated and purified via flash column chromatography (petroleum ether/ethyl acetate 5/1, R_f = 0.4) to give the title product **4j** as a yellow oily liquid (75.6 mg, 99%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48−7.42 (m, 2H), 7.41−7.34 (m, 4H), 7.29 (t, J = 7.4 Hz, 1H), 7.21 (t, J = 7.4 Hz, 2H), 3.97 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 161.8, 150.0, 134.2, 133.5, 132.9, 131.7, 130.5, 130.0, 128.9, 128.3, 128.1, 127.8, 125.6 (C−F, q, $^2J_{C-F}$ = 40.0 Hz), 119.5 (C−F, q, $^1J_{C-F}$ = 270.2 Hz), 52.6. ^{19}F NMR (377 MHz, $CDCl_3$): δ −56.0. HRMS (ESI): $[M + H]^+$ calcd for $C_{18}H_{13}ClF_3N_2O_2$ 381.0612; found 381.0624.

*Methyl 2-Phenyl-5-(trifluoromethyl)-1-(4-(trifluoromethyl)-phenyl)-1H-imidazole-4-carboxylate (**4k**).* Upon completion of the reaction the mixture was concentrated and purified via flash column chromatography (petroleum ether/ethyl acetate 5/1, R_f = 0.4) to give the title product **4k** as a white solid (80.7 mg, 98%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.2 Hz, 2H), 7.35−7.23 (m, 5H), 4.00 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 161.8, 149.9, 138.6, 134.6, 132.3 (C−F, q, $^2J_{C-F}$ = 33.2 Hz), 130.1, 129.3, 128.5, 128.5, 127.7, 126.8 (C−F, q, $^3J_{C-F}$ = 3.5 Hz), 125.3 (C−F, q, $^2J_{C-F}$ = 40.0 Hz), 123.2 (C−F, q, $^1J_{C-F}$ = 272.7 Hz), 119.5 (C−F, q, $^1J_{C-F}$ = 270.0 Hz), 52.7. ^{19}F NMR (377 MHz, $CDCl_3$): δ −54.4, −62.8. Mp: 114.6−115.7 °C. HRMS (ESI): $[M + H]^+$ calcd for $C_{19}H_{13}F_6N_2O_2$ 415.0876; found 415.0890.

*Methyl 1-(4-Nitrophenyl)-2-phenyl-5-(trifluoromethyl)-1H-imidazole-4-carboxylate (**4l**).* Upon completion of the reaction the mixture was concentrated and purified via flash column chromatography (petroleum ether/ethyl acetate 5/1, R_f = 0.2) to give the title product **4l** as a white solid (43.8 mg, 56%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (d, J = 8.5 Hz, 2H), 7.50 (d, J = 8.7 Hz, 2H), 7.38−7.33 (m, 1H), 7.30−7.25 (m, 4H), 4.01 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 161.7, 149.9, 148.4, 140.8, 134.9, 130.3, 129.3, 129.2, 128.6, 127.4, 125.3 (C−F, q, $^2J_{C-F}$ = 40.4 Hz), 125.0, 119.5 (C−F, q, $^1J_{C-F}$ = 270.2 Hz), 52.9. ^{19}F NMR (377 MHz, $CDCl_3$): δ −54.2. Mp: 163.4−164.7 °C. HRMS (ESI): $[M + H]^+$ calcd for $C_{18}H_{13}F_3N_3O_4$ 392.0853; found 392.0869.

*Methyl 1-(4-Cyanophenyl)-2-phenyl-5-(trifluoromethyl)-1H-imidazole-4-carboxylate (**4m**).* Upon completion of the reaction the mixture was concentrated and purified via flash column chromatography (petroleum ether/ethyl acetate 5/1, R_f = 0.2) to give the title product **4m** as a white solid (46.1 mg, 62%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, J = 8.4 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H), 7.38−7.33 (m, 1H), 7.27 (d, J = 4.4 Hz, 4H), 4.00 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 161.7, 149.8, 139.3, 134.8, 133.5, 130.3, 129.3, 129.0, 128.6, 127.5, 125.2 (C−F, q, $^2J_{C-F}$ = 39.9 Hz), 119.5 (C−F, q, $^1J_{C-F}$ = 270.2 Hz), 117.2, 114.4, 52.8. ^{19}F NMR (377 MHz, $CDCl_3$): δ −54.2. Mp: 130.7−131.5 °C. HRMS (ESI): $[M + H]^+$ calcd for $C_{19}H_{13}F_3N_3O_2$ 372.0954; found 372.0971.

*Methyl 1-(3,4-Dimethylphenyl)-2-phenyl-5-(trifluoromethyl)-1H-imidazole-4-carboxylate (**4n**).* Upon completion of the reaction the mixture was concentrated and purified via flash column chromatography (petroleum ether/ethyl acetate 5/1, R_f = 0.3) to give the title product **4n** as a white solid (68.5 mg, 92%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39−7.34 (m, 2H), 7.28 (d, J = 6.6 Hz, 1H), 7.22 (t, J = 7.4 Hz, 2H), 7.17 (d, J = 8.0 Hz, 1H), 7.02 (s, 1H), 6.99 (d, J = 8.0 Hz, 1H), 3.98 (s, 3H), 2.31 (s, 3H), 2.25 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 162.2, 149.7, 138.9, 138.1, 133.8, 133.0, 130.4, 129.5, 129.1, 128.4, 128.1, 125.4 (C−F, q, $^2J_{C-F}$ = 39.5 Hz), 125.0, 119.6 (C−F, q, $^1J_{C-F}$ = 270.1 Hz), 52.5, 19.7, 19.5. ^{19}F NMR (377 MHz, $CDCl_3$): δ −54.8. Mp: 87.8−89.0 °C. HRMS (ESI): $[M + H]^+$ calcd for $C_{20}H_{18}F_3N_2O_2$ 375.1315; found 375.1331.

*Methyl 1-(Naphthalen-1-yl)-2-phenyl-5-(trifluoromethyl)-1H-imidazole-4-carboxylate (**4o**).* Upon completion of the reaction the mixture was concentrated and purified via flash column chromatography (petroleum ether/ethyl acetate 5/1, R_f = 0.3) to give the title product **4o** as a yellow oily liquid (83.5 mg, 99%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, J = 9.0 Hz, 1H), 7.91 (d, J = 7.5 Hz, 1H), 7.55−7.45 (m, 4H), 7.30−7.26 (m, 3H), 7.17 (t, J = 7.4 Hz, 1H), 7.06 (t, J = 7.6 Hz, 2H), 4.03 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 162.1, 150.6, 134.2, 133.8, 132.0, 130.9, 130.3, 129.8, 128.6, 128.5, 128.3, 128.2, 128.1, 127.2, 126.5, 126.5 (C−F, q, $^2J_{C-F}$ = 39.9 Hz), 125.0, 121.6, 119.6 (C−F, q, $^1J_{C-F}$ = 270.3 Hz), 52.7. ^{19}F NMR (377 MHz, $CDCl_3$): δ −55.6. HRMS (ESI): $[M + H]^+$ calcd for $C_{22}H_{16}F_3N_2O_2$ 397.1158; found 397.1171.

*Methyl 5-(Difluoromethyl)-1,2-diphenyl-1H-imidazole-4-carboxylate (**4q**).* Upon completion of the reaction the mixture was concentrated and purified via flash column chromatography (petroleum ether/ethyl acetate 5/1, R_f = 0.4) to give the title product **4q** as a white solid (50.0 mg, 77%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (t, J = 52.4 Hz, 1H), 7.48−7.40 (m, 3H), 7.38−7.30 (m, 4H), 7.28 (d, J = 7.3 Hz, 1H), 7.25−7.18 (m, 2H), 4.00 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 163.0, 150.1, 136.0, 133.0, 131.5 (C−F, t, $^2J_{C-F}$ = 22.5 Hz), 129.8, 129.5, 129.3, 129.2, 128.4, 128.2, 128.0, 108.3 (C−F, t, $^1J_{C-F}$ = 235.4 Hz), 52.4. ^{19}F NMR (377 MHz, $CDCl_3$): δ −111.8. Mp: 149.8−150.5 °C. HRMS (ESI): $[M + H]^+$ calcd for $C_{18}H_{15}F_2N_2O_2$ 329.1096; found 329.1113.

*Methyl 5-(Chlorodifluoromethyl)-1,2-diphenyl-1H-imidazole-4-carboxylate (**4r**).* Upon completion of the reaction the mixture was concentrated and purified via flash column chromatography (petroleum ether/ethyl acetate 5/1, R_f = 0.3) to give the title product **4r** as a white solid (60.2 mg, 84%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52−7.42 (m, 3H), 7.35−7.27 (m, 5H), 7.21 (t, J = 7.4 Hz, 2H), 3.99 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 162.3, 149.6, 135.7, 132.3, 131.5 (C−F, t, $^2J_{C-F}$ = 32.4 Hz), 130.1, 129.6, 129.4, 129.2, 128.2, 128.2, 120.4 (C−F, t, $^1J_{C-F}$ = 288.8 Hz), 52.6. ^{19}F NMR (377 MHz, $CDCl_3$): δ −43.4. Mp: 104.8−105.2 °C. HRMS (ESI): $[M + H]^+$ calcd for $C_{18}H_{14}ClF_2N_2O_2$ 363.0706; found 363.0728.

*Methyl 5-(Perfluoroethyl)-1,2-diphenyl-1H-imidazole-4-carboxylate (**4s**).* Upon completion of the reaction the mixture was concentrated and purified via flash column chromatography

https://dx.doi.org/10.1021/acs.joc.1c00131
J. Org. Chem. 2021, 86, 4361−4370

(petroleum ether/ethyl acetate 5/1, R_f = 0.3) to give the title product **4s** as a white solid (43.1 mg, 55%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (d, J = 7.2 Hz, 1H), 7.42 (t, J = 7.5 Hz, 2H), 7.31 (d, J = 7.3 Hz, 2H), 7.28−7.25 (m, 3H), 7.20 (t, J = 7.5 Hz, 2H), 3.98 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 161.8, 151.3, 136.1, 135.7, 130.1, 129.7, 129.3, 129.1, 128.6, 128.3, 128.1, 123.4 (C−F, t, $^3J_{C-F}$ = 29.3 Hz), 118.6 (C−F, qt, $^1J_{C-F}$ = 287.4 Hz, 39.0 Hz), 110.4 (C−F, qt, $^2J_{C-F}$ = 238.1 Hz, 41.6 Hz), 52.6. ^{19}F NMR (377 MHz, $CDCl_3$): δ −83.1, −105.3. Mp: 75.2−77.6 °C. HRMS (ESI): [M + H]$^+$ calcd for $C_{19}H_{14}F_5N_2O_2$ 397.0970; found 397.0986.

*Methyl 5-(Perfluoropropyl)-1,2-diphenyl-1H-imidazole-4-carboxylate (**4t**).* Upon completion of the reaction the mixture was concentrated and purified via flash column chromatography (petroleum ether/ethyl acetate 5/1, R_f = 0.3) to give the title product **4t** as a yellow oily liquid (50.0 mg, 57%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48−7.39 (m, 3H), 7.32 (d, J = 7.1 Hz, 2H), 7.27 (t, J = 5.7 Hz, 3H), 7.23−7.17 (m, 2H), 3.98 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 161.8, 151.4, 136.5, 135.7, 135.0, 130.1, 129.3, 129.1, 128.6, 128.1, 127.0, 123.3 (C−F, t, $^4J_{C-F}$ = 29.8 Hz), 117.7 (C−F, qt, $^1J_{C-F}$ = 288.3 Hz, 34.1 Hz), 112.6 (C−F, tt, $^2J_{C-F}$ = 258.5 Hz, 34.0 Hz), 108.5 (C−F, tm, $^3J_{C-F}$ = 266.64 Hz), 52.6. ^{19}F NMR (377 MHz, $CDCl_3$): δ −80.2, −102.0, −123.1. HRMS (ESI): [M + H]$^+$ calcd for $C_{20}H_{14}F_7N_2O_2$ 447.0938; found 447.0950.

Procedure for Control Experiments (Scheme 4, eq a). Under a nitrogen atmosphere, Ag_2O (0.092 g, 0.4 mmol, 2.0 equiv), Na_2CO_3 (0.0424 g, 0.4 mmol, 2.0 equiv), **1a** (0.3 mmol, 1.5 equiv), **2e** (0.2 mmol, 1.0 equiv), 4 Å MS (40 mg), and MeCN (2 mL) (extra dry) were placed in an oven-dried 15 mL *In-Ex* tube. Then the tube was sealed and the mixture was stirred at 60 °C (oil bath) for 1 h. The sample of the reaction was tested by GC-MS, and the coupling product **5** was successfully detected by GC-MS.

Preparation of Intermediate 5. Under a nitrogen atmosphere, KO-*t*-Bu (0.0896g, 0.8 mmol, 2.0 equiv), **1a** (0.6 mmol, 1.5 equiv), **2e** (0.4 mmol, 1.0 equiv), and MeCN (3 mL) (extra dry) were placed in an oven-dried 15 mL *In-Ex* tube. Then the tube was sealed and the mixture was stirred at 60 °C (oil bath) for 1 h. After the reaction was complete, the mixture was slowly cooled to room temperature and extracted three times with EtOAc (3 × 10 mL). The extracts were combined and concentrated under vacuum. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc) to yield the product **5** as a yellow oily liquid (89.2 mg, 55%).

*methyl (Z)-2-(((E)-benzylidene)amino)-3-((4-(tert-butyl)phenyl)-imino)-4,4,4-trifluorobutanoate (**5**).* Upon completion of the reaction the mixture was concentrated and purified via flash column chromatography (petroleum ether/ethyl acetate 5/1, R_f = 0.4) to give the title product **5** as a yellow oily liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, J = 7.3 Hz, 2H), 7.48−7.35 (m, 3H), 7.32 (d, J = 8.9 Hz, 2H), 6.70 (d, J = 8.8 Hz, 2H), 6.68 (d, J = 2.5 Hz, 1H), 5.70−5.60 (m, 1H), 3.96 (s, 3H), 1.29 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 160.8, 156.6, 143.4, 142.8, 137.0, 129.0, 128.9, 126.8, 126.5, 123.6 (C−F, q, $^1J_{C-F}$ = 284.7 Hz), 113.1, 95.5, 69.6 (C−F, q, $^2J_{C-F}$ = 33.6 Hz), 53.5, 34.0, 31.4. ^{19}F NMR (377 MHz, $CDCl_3$): δ −69.0. HRMS (ESI): [M + H]$^+$ calcd for $C_{22}H_{24}F_3N_2O_2$ 405.1784; found 405.1798.

Procedure for Control Experiments (Scheme 4, eq b). Under a nitrogen atmosphere, Ag_2O (0.0927 g, 0.4 mmol, 2 equiv), Na_2CO_3 (0.0424 g, 0.4 mmol, 2 equiv), **5** (0.0808 g, 0.2 mmol, 1 equiv), 4 Å MS (40 mg), and MeCN (2 mL) (extra dry) were placed in an oven-dried 15 mL *In-Ex* tube. Then the tube was sealed and the mixture was stirred at 60 °C (oil bath) for 3 h. After the reaction was complete, the mixture was slowly cooled to room temperature and extracted three times with EtOAc (3 × 10 mL). The extracts were combined and concentrated under vacuum. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc) to yield the product **4e** as a white solid (70.8 mg, 88%).

Procedure for Control Experiments (Scheme 4, eq c). Under a nitrogen atmosphere, Ag_2O (0.0927 g , 0.4 mmol, 2.0 equiv), Na_2CO_3 (0.0424 g, 0.4 mmol, 2.0 equiv), **1a** (0.3 mmol, 1.5 equiv), **2e** (0.2 mmol, 1.0 equiv), 4 Å MS (40 mg), TEMPO (62.5 mg, 0.4 mmol, 2.0 equiv), BHT (88.1 mg, 0.4 mmol, 2.0 equiv), or 1,1-DPE (72.1 mg, 0.4 mmol, 2.0 equiv), and MeCN (2 mL) (extra dry) were placed in an oven-dried 15 mL *In-Ex* tube. Then the tube was sealed and the mixture was stirred at 60 °C (oil bath) for 3 h. After the reaction was complete, the mixture was slowly cooled to room temperature and extracted three times with EtOAc (3 × 10 mL). The extracts were combined and concentrated under vacuum. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc) to yield the product **4e** as a white solid in 93%, trace or 79% yield.

Recovery Experiment of Ag Salts (Scheme 5). Under a nitrogen atmosphere, Ag_2O (0.2317 g, 1.0 mmol, 2.0 equiv), Na_2CO_3 (0.1060 g, 1.0 mmol, 2.0 equiv), **1a** (0.75 mmol, 1.5 equiv), **2e** (0.5 mmol, 1.0 equiv), 4 Å MS (100 mg), and MeCN (5 mL) (extra dry) were placed in an oven-dried 15 mL *In-Ex* tube. Then the tube was sealed and the mixture was stirred at 60 °C (oil bath) for 3 h. After the reaction was complete, the mixture was slowly cooled to room temperature and concentrated under reduced pressure. The residue was washed three times with CH_2Cl_2 (3 × 5 mL), and the solid was dissolved in 25 mL of HNO_3 (10%, v/v in H_2O). After it was stirred for 1 h, the reaction mixture was filtered to remove the insoluble AgCl. To the filtrate was added 25 mL of NaOH (10%, v/v in H_2O). The suspension was filtered and the solid residue washed with water (3 × 5 mL) to afford 0.148 g of Ag_2O (64%) as a brown powder.

Standard Reaction by Using Recycled Ag_2O. Under a nitrogen atmosphere, Ag_2O (0.0927 g, 0.4 mmol, 2.0 equiv), Na_2CO_3 (0.0424 g, 0.4 mmol, 2.0 equiv), **1a** (0.3 mmol, 1.5 equiv), **2e** (0.2 mmol, 1.0 equiv), 4 Å MS (40 mg), and MeCN (2 mL) (extra dry) were placed in an oven-dried 15 mL *In-Ex* tube. Then the tube was sealed and the mixture was stirred at 60 °C (oil bath) for 3 h. After the reaction was complete, the mixture was slowly cooled to room temperature and extracted three times with EtOAc (3 × 10 mL). The extracts were combined and concentrated under vacuum. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc) to yield the product **4e** as a white solid in 65% yield.

Synthetic Utility (Scheme 7). Under a nitrogen atmosphere, Ag_2O (0.0927 g, 0.4 mmol, 2.0 equiv), Na_2CO_3 (0.0424 g, 0.4 mmol, 2.0 equiv), **1r** (0.3 mmol, 1.5 equiv), **2u** (0.2 mmol, 1.0 equiv), 4 Å MS (40 mg), MeCN (2 mL) (extra dry) were placed in an oven-dried 15 mL *In-Ex* tube. Then the tube was sealed and the mixture was stirred at 60 °C (oil bath) for 3 h. After the reaction was complete, the mixture was slowly cooled to room temperature and extracted three times with EtOAc (3 × 10 mL). The extracts were combined and concentrated under vacuum. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc) to yield the product **6**.

*Ethyl 2-(4-Bromophenyl)-1-(2,4-dichlorophenyl)-5-(trifluoromethyl)-1H-imidazole-4-carboxylate (**6**).* Upon completion of the reaction the mixture was concentrated and purified via flash column chromatography (petroleum ether/ethyl acetate 5/1, R_f = 0.4) to give the title product **6** as a yellow oily liquid (88.1 mg, 87%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (d, J = 2.0 Hz, 1H), 7.45−7.34 (m, 4H), 7.23 (d, J = 8.6 Hz, 2H), 4.46 (q, J = 7.1 Hz, 2H), 1.42 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 161.2, 149.0, 137.5, 135.0, 133.8, 132.0, 131.8, 130.6, 130.3, 128.4, 126.8, 125.3 (C−F, q, $^2J_{C-F}$ = 39.7 Hz), 124.9, 119.4 (C−F, q, $^1J_{C-F}$ = 270.3 Hz), 61.9, 14.1. ^{19}F NMR (377 MHz, $CDCl_3$): δ −55.7. HRMS (ESI): [M + H]$^+$ calcd for $C_{19}H_{13}BrCl_2F_3N_2O_2$ 506.9484; found 506.9492.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00131.

Details of the experimental conditions and ^{1}H, ^{13}C, and ^{19}F NMR spectra for all isolated compounds (PDF)

https://dx.doi.org/10.1021/acs.joc.1c00131
J. Org. Chem. 2021, 86, 4361−4370

AUTHOR INFORMATION

Corresponding Authors

Zhengkai Chen − *Department of Chemistry, Zhejiang Sci-Tech University, Hangzhou 310018, People's Republic of China*; orcid.org/0000-0002-5556-6461; Email: zkchen@zstu.edu.cn

Xiao-Feng Wu − *Dalian National Laboratory for Clean Energy, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, 116023 Dalian, Liaoning, People's Republic of China; Leibniz-Institut für Katalyse e. V, Universität Rostock, 18059 Rostock, Germany*; orcid.org/0000-0001-6622-3328; Email: xiao-feng.wu@catalysis.de

Authors

Hefei Yang − *Department of Chemistry, Zhejiang Sci-Tech University, Hangzhou 310018, People's Republic of China*

Shu-Ning Lu − *Department of Chemistry, Zhejiang Sci-Tech University, Hangzhou 310018, People's Republic of China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.1c00131

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We acknowledge financial support from the Natural Science Foundation of Zhejiang Province (LY19B020016).

REFERENCES

(1) (a) Zhang, L.; Peng, X.-M.; Damu, G. L. V.; Geng, R.-X.; Zhou, C.-H. Comprehensive Review in Current Developments of Imidazole-Based Medicinal Chemistry. *Med. Res. Rev.* **2014**, *34*, 340−437. (b) Wang, G.; Peng, Z.; Wang, J.; Li, J.; Li, X. Synthesis and biological evaluation of novel 2,4,5-triarylimidazole−1,2,3-triazole derivatives via click chemistry as α-glucosidase inhibitors. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 5719−5723. (c) Janssen-Müller, D.; Schlepphorst, C.; Glorius, F. Privileged chiral N-heterocyclic carbene ligands for asymmetric transition-metal catalysis. *Chem. Soc. Rev.* **2017**, *46*, 4845−4854. (d) Goossens, K.; Lava, K.; Bielawski, C. W.; Binnemans, K. Ionic Liquid Crystals: Versatile Materials. *Chem. Rev.* **2016**, *116*, 4643−4807. (e) Leclercq, L.; Nardello-Rataj, V. Pickering emulsions based on cyclodextrins: A smart solution for antifungal azole derivatives topical delivery. *Eur. J. Pharm. Sci.* **2016**, *82*, 126−137. (f) Zarnowska, E. D.; Rodgers, F. C.; Oh, I.; Rau, V.; Lor, C.; Laha, K. T.; Jurd, R.; Rudolph, U.; Eger, E. I.; Pearce, R. A. Etomidate blocks LTP and impairs learning but does not enhance tonic inhibition in mice carrying the N265M point mutation in the beta3 subunit of the GABAA receptor. *Neuropharmacology* **2015**, *93*, 171−178. (g) Koch, P.; Bäuerlein, C.; Jank, H.; Laufer, S. Targeting the Ribose and Phosphate Binding Site of p38 Mitogen-Activated Protein (MAP) Kinase: Synthesis and Biological Testing of 2-Alkylsulfanyl-, 4(5)-Aryl-, 5(4)-Heteroaryl-Substituted Imidazoles. *J. Med. Chem.* **2008**, *51*, 5630−5640. (h) Laufer, S. A.; Zimmermann, W.; Ruff, K. J. Tetrasubstituted Imidazole Inhibitors of Cytokine Release: Probing Substituents in the N-1 Position. *J. Med. Chem.* **2004**, *47*, 6311−6325.

(2) (a) Habashi, J. P.; Judge, D. P.; Holm, T. M.; Cohn, R. D.; Loeys, B. L.; Cooper, T. K.; Myers, L.; Klein, E. C.; Liu, G.; Calvi, C.; Podowski, M.; Neptune, E. R.; Halushka, M. K.; Bedja, D.; Gabrielson, K.; Rifkin, D. B.; Carta, L.; Ramirez, F.; Huso, D. L.; Dietz, H. C. Losartan, an AT1 Antagonist, Prevents Aortic Aneurysm in a Mouse Model of Marfan Syndrome. *Science* **2006**, *312*, 117−121. (b) Ruilope, L.; Jager, B. Eprosartan for the treatment of hypertension. *Expert Opin. Pharmacother.* **2003**, *4*, 107−114. (c) Khanna, I. K.; Yu, Y.; Huff, R. M.; Weier, R. M.; Xu, X.; Koszyk, F. J.; Collins, P. W.; Cogburn, J. N.; Isakson, P. C.; Koboldt, C. M.; Masferrer, J. L.; Perkins, W. E.; Seibert, K.; Veenhuizen, A. W.; Yuan, J.; Yang, D.-C.; Zhang, Y. Y. Selective Cyclooxygenase-2 Inhibitors: Heteroaryl Modified 1,2-Diarylimidazoles Are Potent, Orally Active Antiinflammatory Agents. *J. Med. Chem.* **2000**, *43*, 3168−3185. (d) Asproni, B.; Talani, G.; Busonero, F.; Pau, A.; Sanna, S.; Cerri, R.; Mascia, M. P.; Sanna, E.; Biggio, G. Synthesis, Structure-Activity Relationships at the GABAA Receptor in Rat Brain, and Differential Electrophysiological Profile at the Recombinant Human GABAA Receptor of a Series of Substituted 1,2-Diphenylimidazoles. *J. Med. Chem.* **2005**, *48*, 2638−2645.

(3) (a) Kamijo, S.; Yamamoto, Y. Recent Progress in the Catalytic Synthesis of Imidazoles. *Chem. - Asian J.* **2007**, *2*, 568−578. (b) Gulevich, A. V.; Dudnik, A. S.; Chernyak, N.; Gevorgyan, V. Transition Metal-Mediated Synthesis of Monocyclic Aromatic Heterocycles. *Chem. Rev.* **2013**, *113*, 3084−3213. (c) Guo, X.-X.; Gu, D.-W.; Wu, Z.; Zhang, W. Copper-Catalyzed C−H Functionalization Reactions: Efficient Synthesis of Heterocycles. *Chem. Rev.* **2015**, *115*, 1622−1651. (d) Bellina, F.; Rossi, R. Regioselective Functionalization of the Imidazole Ring via Transition Metal-Catalyzed C-N and C-C Bond Forming Reactions. *Adv. Synth. Catal.* **2010**, *352*, 1223−1276.

(4) (a) Bunev, A. S.; Vasiliev, M. A.; Statsyuk, V. E.; Ostapenko, G. I.; Peregudov, A. S. Synthesis of 1-aryl-4-tosyl-5-(trifluoromethyl)-1*H*-imidazoles. *J. Fluorine Chem.* **2014**, *163*, 34−37. (b) Bunev, A. S.; Varakina, E. V.; Khochenkov, D. A.; Peregudov, A. S. 1-Imidoyl-1,2,3-benzotriazoles-Novel Reagents for the Synthesis of 1-Aryl-5-trifluoromethylimidazoles. *Russ. Russ. J. Org. Chem.* **2019**, *55*, 493−497. (c) Hu, S.; Yang, H.; Chen, Z.; Wu, X.-F. Base-mediated [3 + 2] annulation of trifluoroacetimidoyl chlorides and isocyanides: An improved approach for regioselective synthesis of 5-trifluoromethyl-imidazoles. *Tetrahedron* **2020**, *76*, 131168.

(5) (a) Müller, K.; Faeh, C.; Diederich, F. Fluorine in Pharmaceuticals: Looking Beyond Intuition. *Science* **2007**, *317*, 1881−1886. (b) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. Fluorine in medicinal chemistry. *Chem. Soc. Rev.* **2008**, *37*, 320−330. (c) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. Applications of Fluorine in Medicinal Chemistry. *J. Med. Chem.* **2015**, *58*, 8315−8359. (d) Meyer, F. Trifluoromethyl nitrogen heterocycles: synthetic aspects and potential biological targets. *Chem. Commun.* **2016**, *52*, 3077−3094.

(6) (a) Pandey, G.; Banerjee, P.; Gadre, S. R. Construction of Enantiopure Pyrrolidine Ring System via Asymmetric [3 + 2]-Cycloaddition of Azomethine Ylides. *Chem. Rev.* **2006**, *106*, 4484−4517. (b) Adrio, J.; Carretero, J. C. Novel dipolarophiles and dipoles in the metal-catalyzed enantioselective 1,3-dipolar cycloaddition of azomethine ylides. *Chem. Commun.* **2011**, *47*, 6784−6794. (c) Adrio, J.; Carretero, J. C. Recent advances in the catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides. *Chem. Commun.* **2014**, *50*, 12434−12446. (d) Pascual-Escudero, A.; de Cózar, A.; Cossío, F. P.; Adrio, J.; Carretero, J. C. Alkenyl Arenes as Dipolarophiles in Catalytic Asymmetric 1,3-Dipolar Cycloaddition Reactions of Azomethine Ylides. *Angew. Chem., Int. Ed.* **2016**, *55*, 15334−15338. (e) Xu, B.; Zhang, Z.-M.; Xu, S.; Liu, B.; Xiao, Y.; Zhang, J. Copper(I)/Ming-Phos-Catalyzed Asymmetric Intermolecular [3 + 2] Cycloaddition of Azomethine Ylides with α-Trifluoromethyl α, β-Unsaturated Esters. *ACS Catal.* **2017**, *7*, 210−214. (f) Fang, X.; Wang, C.-J. Catalytic asymmetric construction of spiropyrrolidines via 1,3-dipolar cycloaddition of azomethine ylides. *Org. Biomol. Chem.* **2018**, *16*, 2591−2601. (g) Adrio, J.; Carretero, J. C. Stereochemical diversity in pyrrolidine synthesis by catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides. *Chem. Commun.* **2019**, *55*, 11979−11991. (h) Cheng, F.; Kalita, S. J.; Zhao, Z. N.; Yang, X.; Zhao, Y.; Schneider, U.; Shibata, N.; Huang, Y. Y. Diastereodivergent Asymmetric 1,3-Dipolar Cycloaddition of Azomethine Ylides and beta-Fluoroalkyl Vinylsulfones: Low Copper(II) Catalyst Loading and Theoretical Studies. *Angew. Chem., Int. Ed.* **2019**, *58*, 16637−16643. (i) Liang, L.; Niu, H.-Y.; Wang, D.-C.; Yang, X.-H.; Qu, G.-R.; Guo, H.-M. Facile synthesis of chiral [2,3]-fused hydrobenzofuran via asymmetric Cu(i)-catalyzed dearomative 1,3-dipolar cycloaddition. *Chem. Commun.* **2019**, *55*, 553−556. (j) Xiong, Y.; Du, Z.; Chen, H.;

Yang, Z.; Tan, Q.; Zhang, C.; Zhu, L.; Lan, Y.; Zhang, M. Well-Designed Phosphine−Urea Ligand for Highly Diastereo- and Enantioselective 1,3-Dipolar Cycloaddition of Methacrylonitrile: A Combined Experimental and Theoretical Study. *J. Am. Chem. Soc.* **2019**, *141*, 961−971. (k) Wei, L.; Chang, X.; Wang, C.-J. Catalytic Asymmetric Reactions with *N*-Metallated Azomethine Ylides. *Acc. Chem. Res.* **2020**, *53*, 1084−1100.

(7) (a) Viso, A.; Fernández de la Pradilla, R.; García, A.; Guerrero-Strachan, C.; Alonso, M.; Tortosa, M.; Flores, A.; Martínez-Ripoll, M.; Fonseca, I.; André, I.; Rodríguez, A. Highly Diastereoselective [3 + 2] Cycloadditions between Nonracemic p-Tolylsulfinimines and Iminoesters: An Efficient Entry to Enantiopure Imidazolidines and Vicinal Diaminoalcohols. *Chem. - Eur. J.* **2003**, *9*, 2867−2876. (b) Liu, W.-J.; Chen, X.-H.; Gong, L.-Z. Direct Assembly of Aldehydes, Amino Esters, and Anilines into Chiral Imidazolidines via Brønsted Acid Catalyzed Asymmetric 1,3-Dipolar Cycloadditions. *Org. Lett.* **2008**, *10*, 5357−5360. (c) Xie, H.; Zhu, J.; Chen, Z.; Li, S.; Wu, Y. Diastereoselective silver-catalyzed 1,3-dipolar cycloaddition of azomethine ylides with fluorinated imine. *J. Org. Chem.* **2010**, *75*, 7468−7471. (d) Li, Q.-H.; Wei, L.; Chen, X.; Wang, C.-J. Asymmetric construction of fluorinated imidazolidines via Cu(i)-catalyzed exo'-selective 1,3-dipolar cycloaddition of azomethine ylides with fluorinated imines. *Chem. Commun.* **2013**, *49*, 6277−6279. (e) Wei, L.; Li, Q.-H.; Wang, C.-J. Copper(I)-Catalyzed Asymmetric 1,3-Dipolar Cycloaddition of Azomethine Ylides with Fluorinated Imines: The Expanded Scope and Mechanism Insights. *J. Org. Chem.* **2018**, *83*, 11814−11824. (f) Yu, B.; Yang, K.-F.; Bai, X.-F.; Cao, J.; Zheng, Z.-J.; Cui, Y.-M.; Xu, Z.; Li, L.; Xu, L.-W. Ligand-Controlled Inversion of Diastereo- and Enantioselectivity in Silver-Catalyzed Azomethine Ylide−Imine Cycloaddition of Glycine Aldimino Esters with Imines. *Org. Lett.* **2018**, *20*, 2551−2554. (g) Molina, A.; Díaz-Tendero, S.; Adrio, J.; Carretero, J. C. Catalytic asymmetric synthesis of diazabicyclo[3.1.0]hexanes by 1,3-dipolar cycloaddition of azomethine ylides with azirines. *Chem. Commun.* **2020**, *56*, 5050−5053.

(8) (a) Huang, X.; Cong, X.; Mi, P.; Bi, X. Azomethine-isocyanide [3 + 2] cycloaddition to imidazoles promoted by silver and DBU. *Chem. Commun.* **2017**, *53*, 3858−3861. (b) Hu, Z.; Dong, J.; Xu, X. Silver-Catalyzed [3 + 2] Cycloaddition of Azomethine Ylides with Isocyanides for Imidazole Synthesis. *Adv. Synth. Catal.* **2017**, *359*, 3585−3591.

(9) (a) Fang, G.; Bi, X. Silver-catalysed reactions of alkynes: recent advances. *Chem. Soc. Rev.* **2015**, *44*, 8124−8173. (b) Sivaguru, P.; Cao, S.; Babu, K. R.; Bi, X. Silver-Catalyzed Activation of Terminal Alkynes for Synthesizing Nitrogen-Containing Molecules. *Acc. Chem. Res.* **2020**, *53*, 662−675.

(10) (a) Hu, S.; Yang, Z.; Chen, Z.; Wu, X.-F. Metal-Free Synthesis of 5-Trifluoromethyl-1,2,4-Triazoles from Iodine-Mediated Annulation of Trifluoroacetimidoyl Chlorides and Hydrazones. *Adv. Synth. Catal.* **2019**, *361*, 4949−4954. (b) Chen, Z.; Wang, W.-F.; Yang, H.; Wu, X.-F. Palladium-Catalyzed Four-Component Carbonylative Cyclization Reaction of Trifluoroacetimidoyl Chlorides, Propargyl Amines, and Diaryliodonium Salts: Access to Trifluoromethyl-Containing Trisubstituted Imidazoles. *Org. Lett.* **2020**, *22*, 1980−1984. (c) Wang, L.-C.; Du, S.; Chen, Z.; Wu, X.-F. $FeCl_3$-Mediated Synthesis of 2-(Trifluoromethyl)quinazolin-4(3*H*)-ones from Isatins and Trifluoroacetimidoyl Chlorides. *Org. Lett.* **2020**, *22*, 5567−5571. (d) Chen, Z.; Wang, L.-C.; Zhang, J.; Wu, X.-F. Palladium-catalyzed three-component carbonylative synthesis of 2-(trifluoromethyl)-quinazolin-4(3*H*)-ones from trifluoroacetimidoyl chlorides and amines. *Org. Chem. Front.* **2020**, *7*, 2499−2504. (e) Yang, H.; Wang, L.-C.; Wang, W.-F.; Chen, Z.; Wu, X.-F. Palladium-Catalyzed Cascade Carbonylative Cyclization Reaction of Trifluoroacetimidoyl Chlorides and 2-Iodoanilines: Toward 2-(Trifluoromethyl)-quinazolin-4(3*H*)-ones Synthesis. *ChemistrySelect* **2020**, *5*, 11072−11076. (f) Du, S.; Wang, L.-C.; Yang, Z.; Chen, Z.; Wu, X.-F. A Convenient $FeCl_3$-Mediated Synthesis of 5-Trifluoromethyl-1,2,4-triazoles from Trifluoroacetimidoyl Chlorides and Hydrazides. *Adv. Synth. Catal.* **2020**, *362*, 5130−5134.

(11) Tamura, K.; Mizukami, H.; Maeda, K.; Watanabe, H.; Uneyama, K. One-pot synthesis of trifluoroacetimidoyl halides. *J. Org. Chem.* **1993**, *58*, 32−35.

(12) Chen, Z.; Hu, S.; Wu, X.-F. Trifluoroacetimidoyl halides: a potent synthetic origin. *Org. Chem. Front.* **2020**, *7*, 223−254.

(13) Tang, P.; Ritter, T. Silver-mediated fluorination of aryl silanes. *Tetrahedron* **2011**, *67*, 4449−4454.

(14) (a) Liu, H.; Wu, Y.; Zhao, Y.; Li, Z.; Zhang, L.; Yang, W.; Jiang, H.; Jing, C.; Yu, H.; Wang, B.; Xiao, Y.; Guo, H. Metal-Catalyzed [6 + 3] Cycloaddition of Tropone with Azomethine Ylides: A Practical Access to Piperidine-Fused Bicyclic Heterocycles. *J. Am. Chem. Soc.* **2014**, *136*, 2625−2629. (b) Zeng, W.; Zhou, Y.-G. Bifunctional AgOAc-Catalyzed Asymmetric [3 + 2] Cycloaddition of Azomethine Ylides. *Org. Lett.* **2005**, *7*, 5055−5058.

(15) Zhang, C.; Yang, J.; Zhou, W.; Tan, Q.; Yang, Z.; He, L.; Zhang, M. Enantioselective Mannich Reaction of Glycine Iminoesters with *N*-Phosphinoyl Imines: A Bifunctional Approach. *Org. Lett.* **2019**, *21*, 8620−8624.

https://dx.doi.org/10.1021/acs.joc.1c00131
J. Org. Chem. 2021, 86, 4361−4370