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Direct Synthesis of 4-Fluoroisoxazoles through Gold-Catalyzed Cascade Cyclization−Fluorination of 2-Alkynone *O*-Methyl Oximes

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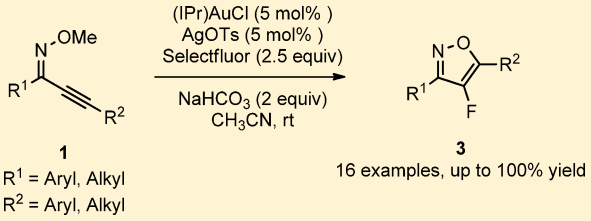
Supporting Information

ABSTRACT: A tandem protocol for the synthesis of fluorinated isoxazoles has been developed via catalytic intramolecular cyclizations of 2-alkynone *O*-methyl oximes and ensuing fluorination. The reactions proceed smoothly at room temperature in the presence of 5 mol % of (IPr)AuCl, 5 mol % of AgOTs, 2.5 equiv of Selectfluor, and 2 equiv of $NaHCO_3$. This process features an efficient one-pot cascade route to fluoroisoxazoles with high yields and high selectivity under mild reaction conditions.



INTRODUCTION

Isoxazole[1] is an important heteroaromatic scaffold exhibiting a broad range of biological activities such as analgesic,[2] antibiotic,[3] antidepressant,[4] and anticancer[5] activities. In particular, fluoroisoxazole[6] has drawn medicinal chemists' attention due to its pharmaceutical usefulness[7] and the unique role of fluorine in medicinal chemistry. Fluorine is the next smallest substituent to hydrogen and is the most electronegative element in the periodic table. Moreover, replacement of a C−H bond with a C−F bond entails only a modest steric perturbation, effectively blocks metabolic sites, and increases the lipophilicity of molecules. Therefore, fluorine can act as a bioisostere of hydrogen and thereby enhance the metabolic stability and cell-membrane permeability of therapeutic small molecules, which can ultimately lead to the improvement of pharmacokinetic and physicochemical properties.[8] For this reason, fluorine has been used as a remarkable tool for medicinal chemists to create new medicines. Despite such importance of organofluorine compounds, their synthetic routes are limited because of the difficulty of fluorination. In particular, the synthetic route for fluoroisoxazole has been very rarely reported. The representative synthetic route for fluoroisoxazole includes the condensation of 2-fluoro-1,3-diketone and hydroxylamine·HCl in $EtOH/H_2SO_4$,[9] which suffers from poor chemical yield and requires strongly acidic reaction conditions. Recently, a direct fluorination reaction of the isoxazole ring using electrophilic fluorinating reagents has been reported[10] as an alternate synthetic route, but it is also sluggish even in refluxing acetonitrile and requires harsher conditions such as reflux in sulfolane, resulting in low chemical yields (28−39%) and the formation of trifluorinated byproducts. In the past decade, the number of agrochemicals and pharmaceuticals containing fluorine has increased, and the need for new, direct, and practical synthetic route for variously substituted fluoroisoxazoles has continued to grow.

Although efficient C−F bond formation represents a major challenge in organic and organometallic chemistry, homogeneous gold catalysis has made rapid progress in C−F bond-forming reactions since Sadighi and co-workers reported the direct gold-catalyzed hydrofluorination of alkynes with the gold(I) fluoride complex and $Et_3N{\cdot}3HF$ in 2007.[11] While seeking gold-catalyzed C−F bond-forming reactions to construct fluoroisoxazole, we were particularly prompted to explore the feasibility of a gold-catalyzed tandem cyclization−fluorination sequence to give fluoroisoxazole. Tandem cyclization−fluorination of the C−C multiple bond allows an efficient and atom-economic route to assemble fluorinated heterocycles in one step. However, due to the scarcity of methods for the fluorination of C−Au bonds, gold-catalyzed tandem cyclization−fluorination of C−C multiple bond has been less investigated to date.[12] In 2008, Gouverneur and co-workers reported a gold-catalyzed alkoxyfluorination of β-hydroxy-α,α-difluoroynones, which featured a sequential alkoxyauration and oxidative fluorination of a transient vinyl gold species with Selectfluor.[13] Interestingly, α,α-difluorine substituents of the carbonyl group were essential for successful fluorination. More recently, Xu,[14] Fensterbank,[15] Wu,[16] and Michelet[17] independently developed gold-catalyzed intramolecular aminofluorinations of alkynes to afford fluoropyrazole, fluoropyrrolidine, fluoroimidazole, and fluoroindole, respectively. In these elegant tandem transformations, the initially formed aminoauration intermediates further reacted to afford the corresponding fluorinated *N*-heterocycles. In the course of our studies on gold-catalyzed tandem reactions to construct complex hetero-

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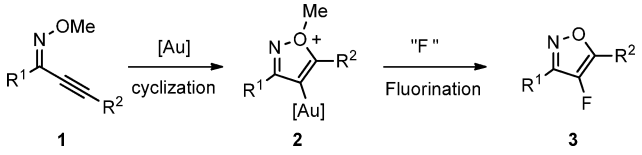
cycles, we have developed an efficient synthetic method for fluoroisoxazole. Herein, we report the first gold-catalyzed cascade cyclization−fluorination of 2-alkynone *O*-methyl oximes to give fluorinated isoxazoles at room temperature.

RESULTS AND DISCUSSION

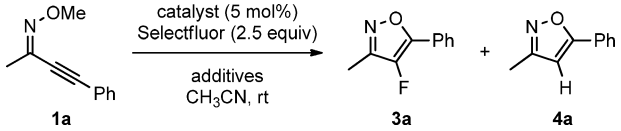
To develop a novel direct synthetic method for fluoroisoxazoles, we envisioned that π-acidic gold could catalyze the cyclization of 2-alkynone *O*-methyl oxime **1** leading to the cationic gold intermediate **2** and that subsequent fluorination might provide fluoroisoxazole **3** in a cascade manner (Scheme 1). This tandem transformation involves a gold-catalyzed cyclization reaction combined with oxidative and/or electrophilic fluorination in one pot, which allows direct access to highly functionalized isoxazoles.

Scheme 1. Strategy for Cyclization−Fluorination



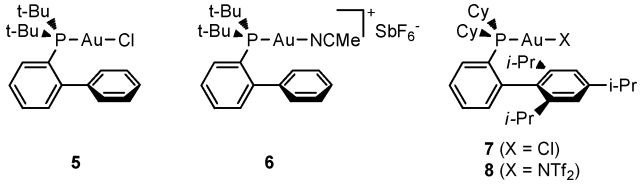
For the preliminary investigation, we chose (*Z*)-4-phenylbut-3-yn-2-one *O*-methyl oxime (**1a**) as a model substrate to optimize suitable conditions for the cascade reaction. First, we carried out the tandem cyclization−fluorination reaction in the presence of $(PPh_3)AuCl$ (5 mol %), Selectfluor (1.5 equiv), and $NaHCO_3$ (2 equiv) at room temperature. To our delight, $(PPh_3)AuCl$ produced the cyclization−fluorination product **3a** in 54% yield as well as the cyclization−protodeauration product **4a** in 3% yield after 120 h (Table 1, entry 1). When the amount of Selectfluor was increased from 1.5 to 2.5 equiv, the formation of **3a** and **4a** increased to 65% and 5%, respectively, in a shorter time (96 h, Table 1, entry 2). In some gold-catalyzed reactions, addition of H_2O sometimes accelerates the reaction progress by enhancing the solubility of reagents such as base and Selectfluor, which are poorly soluble in CH_3CN.[18] However, when the reaction was carried out in the presence of H_2O (10 equiv), protodeaurated isoxazole **4a** was obtained in increased yield (14%), and the reaction was completed in a much shorter time (68 h, Table 1, entry 3), suggesting that H_2O can accelerate protodeauration as well as the fluorination. Notably, the yield of **3a** and the selectivity of **3a**/**4a** were substantially reduced in the absence of base either with or without H_2O (Table 1, entries 4 and 5), indicating that the addition of a base was essential for the reaction. With the above

Table 1. Catalyst Screening and Optimization of Reaction Conditions for the Tandem Cyclization−Fluorination[a]



entry	catalyst	additives (equiv)	time (h)	yield (%)[b] 3a	4a
1[c]	$(PPh_3)AuCl$	$NaHCO_3$ (2)	120	54	3
2	$(PPh_3)AuCl$	$NaHCO_3$ (2)	96	65	5
3	$(PPh_3)AuCl$	$NaHCO_3$ (2)/H_2O (10)	68	66	14
4	$(PPh_3)AuCl$	H_2O (10)	85	47	22
5	$(PPh_3)AuCl$		120	46	10
6	$(PPh_3)AuNTf_2$	$NaHCO_3$ (2)	144	64	12
7[d]	$(PCy_3)AuCl$	$NaHCO_3$ (2)	120	49	11
8	$(PEt_3)AuCl$	$NaHCO_3$ (2)	98	75	4
9	$(PMe_3)AuCl$	$NaHCO_3$ (2)	98	65	6
10	$(PhO)_3PAuCl$	$NaHCO_3$ (2)	120	67	9
11	AuCl	$NaHCO_3$ (2)	72	77	2
12	$AuCl_3$	$NaHCO_3$ (2)	120	77	5
13	$NaAuCl_4{\cdot}2H_2O$	$NaHCO_3$ (2)	120	66	10
14	(IPr)AuCl	$NaHCO_3$ (2)	24	81	0
15	**5**	$NaHCO_3$ (2)	117	73	6
16	**6**	$NaHCO_3$ (2)	120	43	16
17	**7**	$NaHCO_3$ (2)	105	64	5
18	**8**	$NaHCO_3$ (2)	92	50	22
19			96	NR[e]	
20		$NaHCO_3$ (2)	144	NR[e]	

[a]Reaction conditions: **1a** (69.3 mg, 400 μmol), Au-catalyst (20.0 μmol), Selectfluor (354 mg, 1.00 mmol), $NaHCO_3$ (800 μmol), CH_3CN (4 mL). [b]Isolated yields. [c]1.5 equiv of Selectfluor was used. 16% of **1a** was recovered. [d]26% of **1a** was recovered. [e]No reaction.



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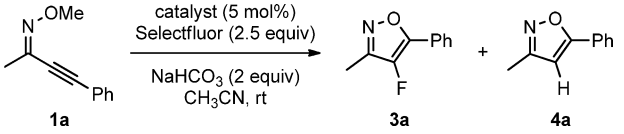
preliminary data in hand, we began a survey of catalysts to investigate various gold catalysts: $(PPh_3)AuNTf_2$, $(PCy_3)AuCl$, $(PEt_3)AuCl$, $(PMe_3)AuCl$, $(PhO)_3PAuCl$, AuCl, $AuCl_3$, $NaAuCl_4{\cdot}2H_2O$, (IPr)AuCl (IPr = *N*,*N*′-bis(2,6-diisopropylphenyl)imidazol-2-ylidene), and the gold(I) complexes **5**–**8** bearing bulky biphenyl-based phosphine ligands. After extensive optimization studies, (IPr)AuCl[19] (5 mol %) was identified as the best catalyst for the cascade cyclization–fluorination reaction (Table 1, entry 14). In the presence of (IPr)AuCl (5 mol %), fluoroisoxazole **3a** was isolated in 81% yield after 24 h at room temperature without the formation of **4a**. The tandem reaction did not happen without a gold catalyst (Table 1, entries 19 and 20) at room temperature under the standard conditions.

We further investigated the effect of silver cocatalysts on the cascade cyclization–fluorination reaction as shown in Table 2.

Table 2. Silver Salt Effect on the Tandem Cyclization–Fluorination Reaction[a]



1a 3a 4a

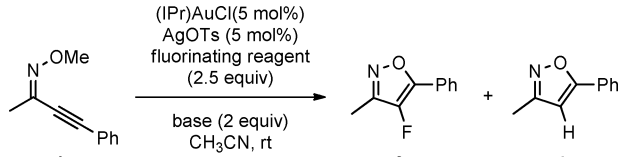
entry	catalyst	time (h)	yield (%)[b] 3a	4a
1	(IPr)AuCl/AgOTs	4.5	92	0
2	(IPr)AuCl/AgOTf	5.5	91	0
3	(IPr)AuCl/$AgNTf_2$	4.5	88	0
4	(IPr)AuCl/$AgSbF_6$	5.5	87	0
5	(IPr)AuCl/$AgNO_3$	4.5	88	0
6	(IPr)AuCl/$AgBF_4$	4.5	85	0
7	(IPr)AuCl/AgCl	28	88	0
8	AgOTs	96	NR[c]	
9[d]	(IPr)$AuCH_3$/TsOH	4.5	82	0
10[e]	(IPr)$AuCH_3$/TfOH	5.5	68	0

[a]Reaction conditions: **1a** (69.3 mg, 400 μmol), Au-catalyst (20.0 μmol), Ag-salt (20.0 μmol), Selectfluor (354 mg, 1.00 mmol), $NaHCO_3$ (800 μmol), CH_3CN (4 mL). [b]Isolated yields. [c]No reaction. [d]TsOH (20.0 μmol) was used instead of Ag-salt. [e]TfOH (20.0 μmol) was used instead of Ag-salt.

Addition of 5 mol % silver salts remarkably facilitated the tandem process. The tandem reactions were completed in 4.5–5.5 h in the presence of AgOTs, AgOTf, $AgNTf_2$, $AgSbF_6$, $AgNO_3$, or $AgBF_4$ and afforded **3a** as a sole product in 85–92% yield (Table 2, entries 1–6). Interestingly, the addition of AgCl did not speed up the tandem process at all (Table 2, entry 7). This dramatic silver salt effect[20] requires further mechanistic investigation. A control experiment revealed that silver salt alone did not provide the desired tandem product **3a** at room temperature after 96 h under the optimized reaction conditions (Table 2, entry 8). In addition, we also carried out the cascade cyclization–fluorination reaction with (IPr)AuOTs prepared by premixing (IPr)$AuCH_3$ and TsOH in the absence of silver salts, which provided fluoroisoxazole **3a** in 82% yield after 4.5 h (Table 2, entry 9). It was comparable to the reaction of (IPr)AuCl/AgOTs (92%, 4.5 h, Table 2, entry 1). Likewise, (IPr)AuOTf prepared via protonolysis of (IPr)$AuCH_3$ by TfOH also provided fluoroisoxazole **3a** in 68% yield after 5.5 h (Table 2, entry 10). Obviously, anion had a significant effect on the cascade cyclization–fluorination reaction as well. Therefore, it cannot be excluded that the apparent silver salt effect might be originated from the anion effect. We are currently further investigating the silver salt effect and the anion effect on the cascade cyclization–fluorination reaction.

It was also found that base had a significant effect on the outcome of the reaction. K_2CO_3, Li_2CO_3, Na_3PO_4, K_3PO_4, and KOH gave comparable results to $NaHCO_3$ (Table 3, entries 3, 5, 6, 7 and 9). However, the reaction in the presence of Na_2CO_3, $KHCO_3$, Cs_2CO_3, or NaOH required a prolonged reaction time (Table 3, entries 1, 2, 4, and 8), and Et_3N reversed the selectivity in favor of **4a** (Table 3, entry 10). Meanwhile, Selectfluor has been disclosed as the best fluorinating reagent for gold-catalyzed tandem cyclization–fluorination reaction. Other fluorinating reagent such as *N*-fluorobenzenesulfonimide (NFSI) or *N*-fluoropyridinium tetrafluoroborate (NFPY-BF_4) failed to give the desired product **3a** at room temperature after 48 h (Table 3, entries 12 and 13).

Table 3. Base Effect and Fluorinating Reagent Effect on the Tandem Cyclization–Fluorination Reaction[a]



1a 3a 4a

entry	base	fluorinating reagent	time (h)	yield (%)[b] 3a	4a
1	Na_2CO_3	Selectfluor	34	83	0
2	$KHCO_3$	Selectfluor	96	57	24
3	K_2CO_3	Selectfluor	5	87	0
4[c]	Cs_2CO_3	Selectfluor	120	17	0
5	Li_2CO_3	Selectfluor	4.5	90	0
6	Na_3PO_4	Selectfluor	4.5	85	0
7	K_3PO_4	Selectfluor	5.5	82	0
8	NaOH	Selectfluor	18.5	71	12
9	KOH	Selectfluor	5.5	85	0
10	Et_3N	Selectfluor	4.5	1	86
11	2,6-lutidine	Selectfluor	42	33	34
12[d]	$NaHCO_3$	NFSI[e]	48	0	0
13[f]	$NaHCO_3$	NFPY-BF_4[g]	48	0	62

[a]Reaction conditions: **1a** (69.3 mg, 400 μmol), (IPr)AuCl (20.0 μmol), AgOTs (20.0 μmol), fluorinating reagent (1.00 mmol), base (800 μmol), CH_3CN (4 mL). [b]Isolated yields. [c]79% of **1a** was recovered. [d]85% of **1a** was recovered. [e]NFSI = *N*-fluorobenzenesulfonimide. [f]25% of **1a** was recovered. [g]NFPY-BF_4 = *N*-fluoropyridinium tetrafluoroborate.

With the optimized reaction conditions in hand, we investigated the scope of this tandem cyclization–fluorination reaction with a variety of *O*-methyl oximes. As shown in Scheme 2, 1,3-disubstituted propynone oximes displayed a broad substrate scope and functional group compatibility. Substrates **1c**–**f** bearing electron-poor R^1 groups at the 1 position of propynone oximes underwent the tandem reaction very well and smoothly provided the corresponding fluoroisoxazoles **3c**–**f** at room temperature in good to excellent yields (79–96%). Substrates **1g**–**i** bearing electron-rich R^1 groups at the 1 position of propynone oximes also gave the desired products **3g**–**i** in slightly lower yields (62–96%). The electronic effects of R^2 group at the 3 position of propynone oximes were also investigated. Both electron-poor and electron-

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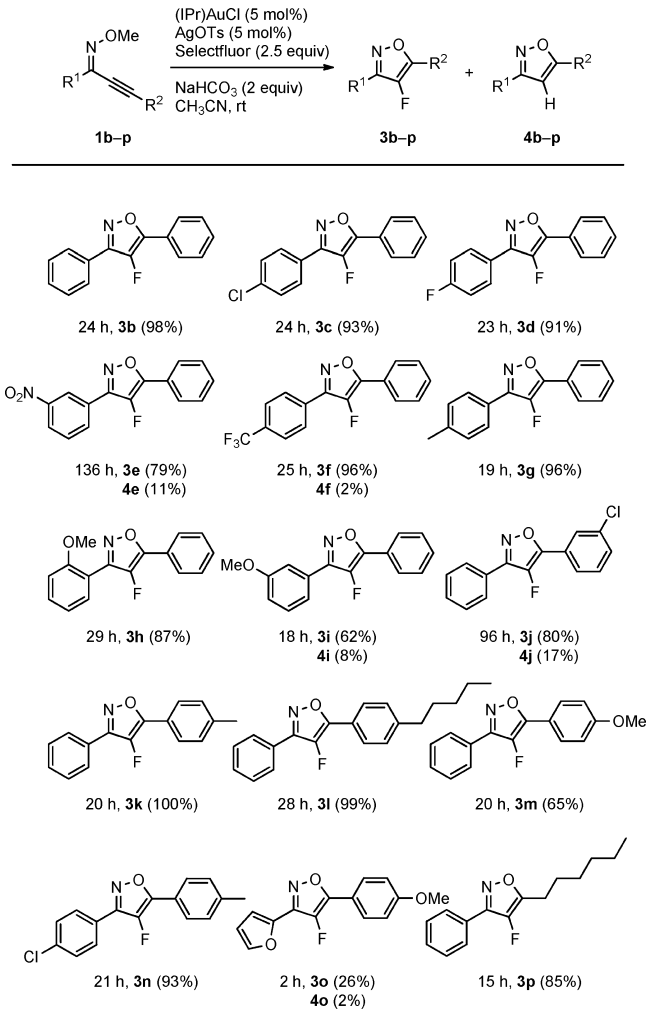
Scheme 2. Gold-Catalyzed Cascade Cyclization–Fluorination of Various *O*-Methyl Oximes[a]

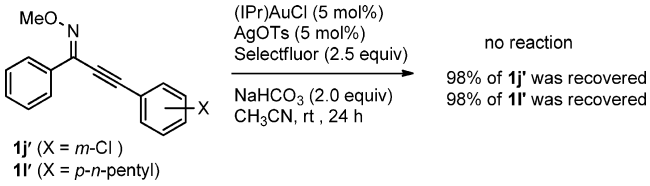


[a]Isolated yields are given. Reaction conditions: **1b–p** (200 μmol), (IPr)AuCl (6.2 mg, 10.0 μmol), AgOTs (2.8 mg, 10.0 μmol), Selectfluor (177 mg, 500 μmol), $NaHCO_3$ (33.6 mg, 400 μmol), CH_3CN (2 mL).

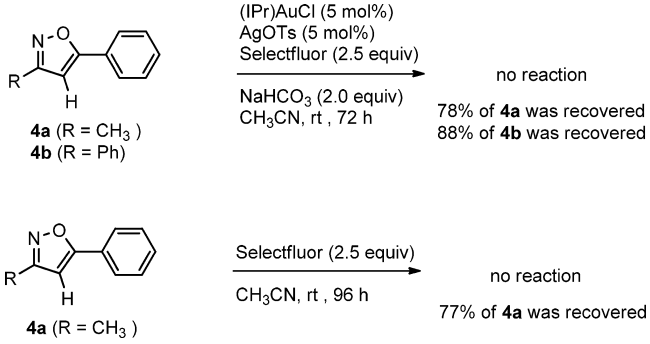
rich substrates **1j–m** produced the desired products **3j–m** in good yields (65–100%). However, the electron-poor substrate **1j** required a prolonged reaction time (96 h). Both modifications to the R^1 and R^2 groups at 1 and 3 positions did not change the reactivity (**3n**), while furan-substituted propynone oxime **1o** was rather unstable under the standard conditions, decomposed rapidly, and afforded **3o** in decreased yield (26%). The tandem reaction could also be applied to the synthesis of aliphatic fluoroisoxazole **3p**.

In order to obtain mechanistic insight, we carried out several experiments with (*E*)-*O*-methyl oximes (Scheme 3) and 3,5-disubstituted isoxazoles (Scheme 4). First, when (*E*)-*O*-methyl oximes were subjected to the standard reaction conditions, the starting (*E*)-*O*-methyl oximes **1j′** and **1l′** were recovered (Scheme 3) after 24 h, probably because (*E*)-*O*-methyl oximes could not meet the geometric requirements for the cyclization–fluorination reaction and the corresponding (*E*)- and (*Z*)-*O*-methyl oximes were not interconvertible at room temperature. Second, we also investigated direct fluorination of isoxazole under the standard conditions (Scheme 4). 3,5-Disubstituted isoxazoles **4a** and **4b** did not undergo direct fluorination

Scheme 3. Gold-Catalyzed Cascade Cyclization–Fluorination of (*E*)-*O*-Methyl Oximes



Scheme 4. Gold-Catalyzed Direct Fluorination of 3,5-Disubstituted Isoxazoles



reactions at room temperature under the standard conditions, and the isoxazole fluorination did not happen even in the presence of only Selectfluor. It has been also reported that the direct fluorinations of isoxazoles with only Selectfluor in refluxing acetonitrile were sluggish and gave only traces of the 4-fluoroisoxazoles.[10] Therefore, unlike pyrazole,[14] direct fluorination of isoxazole **4** was excluded from the possible mechanism. In addition, we carried out an *in situ* NMR experiment using a stoichiometric amount of **1a**, (IPr)AuCl, and AgOTs (1:1:1) and monitored reaction progress from intensity changes in substrate OMe resonance (Figure 1). In this NMR experiment, we observed the generation of CH_3OTs, which suggests that ^-OTs can act as a demethylating agent. After 24 h, the reaction produced an insoluble solid in the NMR tube, and broad NMR peaks were observed (e, Figure 1). The formed solid was isolated, crystallized, and characterized to be the isoxazolyl-gold intermediate $[(IPr)Au(C_{10}H_8NO)]$ (**9**) by X-ray crystallography (Figure 2). The resulting structure displays a nearly linear geometry at the gold(I) with C1–Au1–C2 bond angle of 177.84° and nearly equal Au–C bond distances (Au1–C1 = 2.026 Å, Au1–C2 = 2.020 Å). Further efforts to investigate detailed mechanism are ongoing in our laboratory.

On the basis of previous studies[14,15,21] and our own observation, a plausible mechanistic pathway can be proposed for the gold-catalyzed cyclization–fluorination of (*Z*)-2-alkynone *O*-methyl oxime (Scheme 5). The initial coordination of the gold(I) catalyst **A** to the alkyne of *O*-methyl oxime **1a** and subsequent cyclization would lead to the gold(I) complex **C**. After this, demethylation and oxidation by Selectfluor would afford the cationic gold(III) intermediate **E** bearing both isoxazole and fluoride; **E** readily decomposes to yield cross-coupled fluoroisoxazole **3a** and the cationic gold(I) catalyst **A** after reductive elimination. In the meanwhile, the protodeauration of **D** would generate isoxazole **4a**. This proposed mechanism involves a redox Au(I)/Au(III) catalytic cycle mediated by the external oxidant Selectfluor. However, the exact mechanistic pathway leading to **3a** is still unclear and

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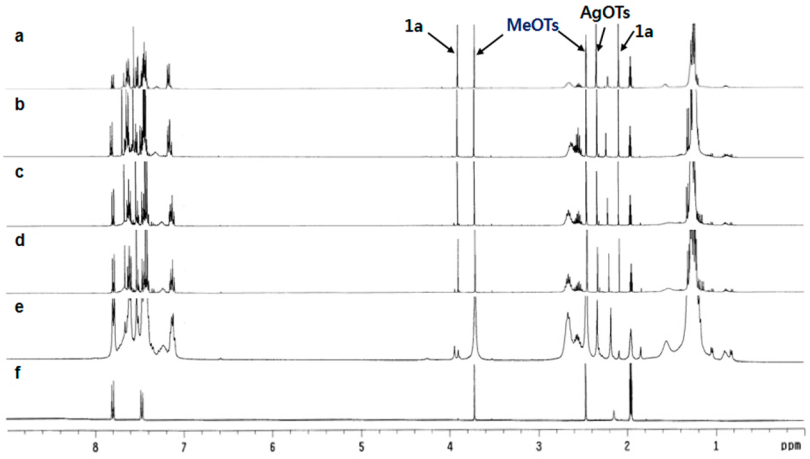


Figure 1. ^{1}H NMR monitoring of the stoichiometric reaction of **1a**, (IPr)AuCl, and AgOTs (1:1:1): (a) 0 h, (b) 2 h, (c) 4 h, (d) 6 h, (e) 24 h, (f) MeOTs.

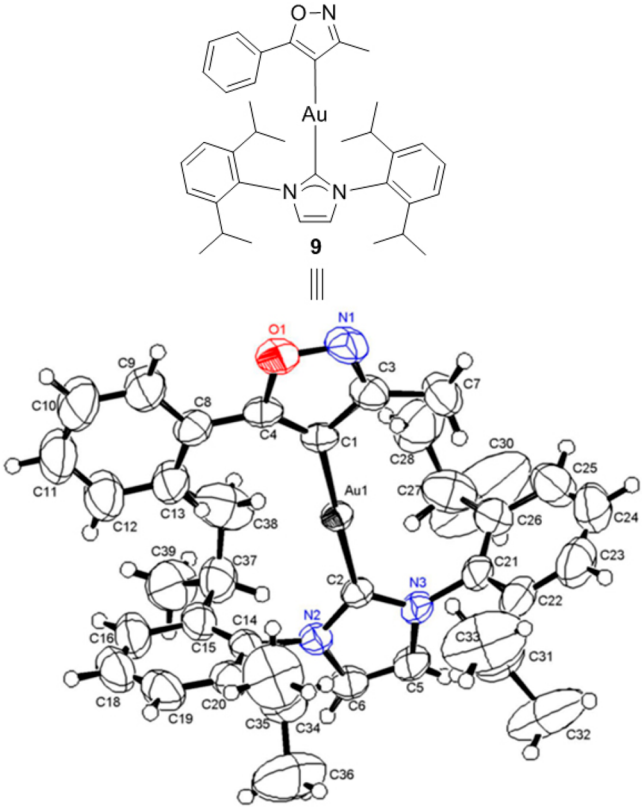
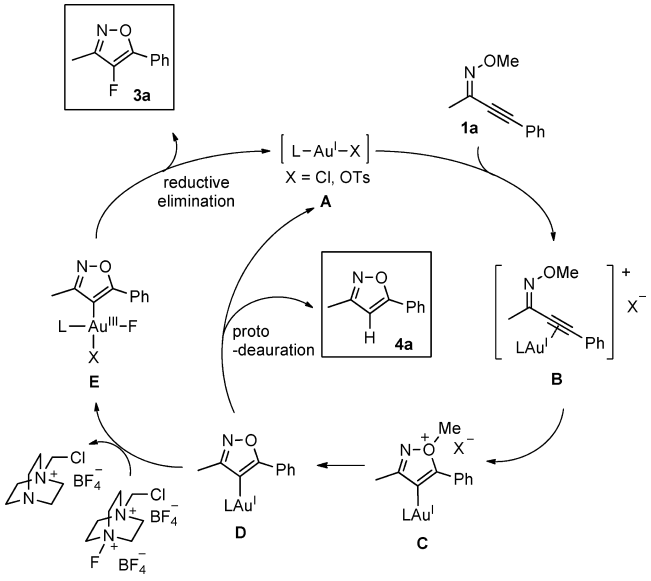


Figure 2. ORTEP drawing of the crystal structure for [(IPr)Au-($C_{10}H_8NO$)] (**9**). Selected bond lengths (Å) and angles (deg): Au1–C1 = 2.026(3), Au1–C2 = 2.020(3), C1–C4 = 1.363(4), C1–C3 = 1.432(4); C1–Au1–C2 = 177.84(10), Au1–C1–C4 = 132.8(2), Au1–C2–N3 = 127.31(18).

requires further investigation. An alternative possible mechanistic pathway is gold(III)-mediated cyclization. We carried out a ^{19}F NMR experiment in CD_3CN ((IPr)AuCl/AgOTs/Selectfluor = 1:1:2) and observed a small broad singlet peak at −179.3 ppm, which is characteristic of Au(III)$^{+}$XFL species. Formation of Au(III) species in analogous ^{19}F NMR experiments was previously observed and described in the literature.[15,21b] Additionally, $AuCl_3$ has been reported to cyclize acetylenic oximes.[21d] Thus, an alternative mechanism involving gold(III)-mediated cyclization cannot be ruled out.

Scheme 5. Plausible Mechanism



CONCLUSIONS

We have successfully developed an efficient gold-catalyzed tandem cyclization–fluorination of (*Z*)-2-alkynone *O*-methyl oxime to furnish fluoroisoxazole under mild conditions (room temperature). This is the first report of construction of fluoroisoxazoles using one-pot gold(I)-catalyzed tandem cyclization–fluorination. This methodology may be useful in medicinal chemistry, and its application to the synthesis of bioactive fluorinated isoxazoles is currently underway in our laboratory.

EXPERIMENTAL SECTION

General Methods. All reactions were performed in flame-dried glassware fitted with a glass stopper under positive pressure of Ar with magnetic stirring, unless otherwise noted. Air- and moisture-sensitive liquids and solutions were transferred via syringe or stainless steel cannula. TLC was performed on commercial 0.25 mm plates and visualized under UV light (254 nm) or by staining with cerium ammonium molybdenate (CAM), potassium permanganate ($KMnO_4$), or *p*-anisaldehyde. Flash chromatography was performed on commercial 230–400 mesh silica gel 60. Reagents were purchased

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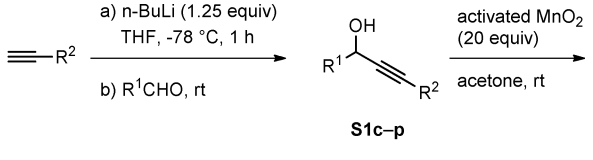
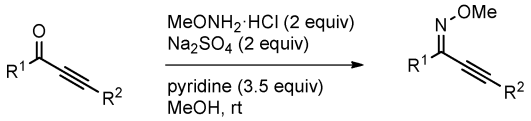
from commercial suppliers and used without further purification unless otherwise noted. Solvents were distilled from proper drying agents (CaH_2 or Na wire) under Ar atmosphere at 760 mmHg. All moisture- and/or oxygen-sensitive solids were handled and stored in a glovebox under N_2. NMR spectra were recorded at 24 °C. Chemical shifts are expressed in ppm relative to TMS (^{1}H, 0 ppm), $CDCl_3$ (^{1}H, 7.26 ppm; ^{13}C, 77.2 ppm), acetone-d_6 (^{1}H, 2.05 ppm; ^{13}C, 206.2, 29.9 ppm), and C_6H_5F (^{19}F, −113.15 ppm); coupling constants are expressed in Hz. High resolution mass spectra electrospray ionization (HRMS-ESI) was obtained on TOF LC−MS spectrometer. Infrared spectra were recorded with peaks reported in cm^{-1}.

Synthesis of Substrates.



S1c–p



S2c–p 1a–p

Representative Procedure for the Synthesis of Propargyl Alcohols S1c–p. To a 50 mL two-neck round-bottom flask were added phenylacetylene (625 mg, 6.00 mmol, 1.20 equiv) and anhydrous THF (15 mL). The mixture was cooled to −78 °C, and *n*-butyllithium (2.5 M in hexanes, 2.50 mL, 6.25 mmol, 1.25 equiv) was added slowly via syringe. The mixture was stirred at −78 °C for 1 h, then warmed to 0 °C, stirred for 1 h, and then recooled to −78 °C. *p*-Fluorobenzaldehyde (633 mg, 5.00 mmol) in THF (5 mL) was added dropwise via syringe, and the reaction was stirred at −78 °C for 1 h, warmed to rt, and stirred for an additional 30 min. Upon the completion of the reaction, the reaction was quenched with saturated aqueous NH_4Cl (30 mL) and extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed with brine (50 mL), then dried over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation. The residue was purified by column chromatography (10:1 hexanes/EtOAc) to afford **S1d** (947 mg, 84%) as a colorless liquid.

*1-(4-Chlorophenyl)-3-phenylprop-2-yn-1-ol (**S1c**).* Reaction time: 1 h. White solid (983 mg, 52%). TLC: R_f 0.43 (4:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (d, J = 8.4 Hz, 2H), 7.47 (m, 2H), 7.38 (d, J = 8.4 Hz, 2H), 7.35−7.32 (m, 3H), 5.68 (d, J = 6.0 Hz, 1H), 2.27 (d, J = 6.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.3, 134.5, 132.0, 129.0, 128.8, 128.6, 128.3, 122.4, 88.4, 87.2, 64.6. LRMS (EI) m/z (rel int): (pos) 242 ([M]$^+$, 46), 207 ([M − Cl]$^+$, 100). HRMS m/z calcd for $C_{15}H_{11}ClO$ 242.0498, found 242.0496. IR (KBr film): 3345, 1597, 1489, 837, 756, 691 cm^{-1}.

*1-(4-Fluorophenyl)-3-phenylprop-2-yn-1-ol (**S1d**).* Reaction time: 0.5 h. Colorless liquid (947 mg, 84%). TLC: R_f 0.25 (5:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (dd, J = 8.4, 5.2 Hz, 2H), 7.47 (m, 2H), 7.35−7.32 (m, 3H), 7.09 (t, J = 8.4 Hz, 2H), 5.68 (d, J = 6.0 Hz, 1H), 2.27 (d, J = 6.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.7 (d, J_{C-F} = 245.3 Hz), 136.5 (d, J_{C-F} = 3.8 Hz), 131.8, 128.7, 128.6 (d, J_{C-F} = 8.5 Hz), 128.4, 122.2, 115.5 (d, J_{C-F} = 21.6 Hz), 88.5, 86.9, 64.4. ^{19}F NMR (376 MHz, $CDCl_3$): δ −113.8 (m). HRMS (ESI) m/z calcd for $C_{15}H_{11}FO$ 226.0794, found 226.0797.

*1-(3-Nitrophenyl)-3-phenylprop-2-yn-1-ol (**S1e**).* Reaction time: 1 h. Orange solid (1.08 g, 85%). TLC: R_f 0.23 (4:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.51 (t, J = 1.6 Hz, 1H), 8.22 (dm, J = 8.0 Hz, 1H), 7.96 (dm, J = 8.0 Hz, 1H), 7.59 (t, J = 8.0 Hz, 1H), 7.48 (m, 2H), 7.39−7.32 (m, 3H), 5.81 (d, J = 5.6 Hz, 1H), 2.45 (d, J = 5.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.4, 142.7, 132.7, 131.8, 129.6, 129.1, 128.4, 123.3, 121.8, 121.7, 87.7, 87.4, 64.0. HRMS (ESI) m/z calcd for $C_{15}H_{11}NO_3$ 253.0739, found 253.0743.

*3-Phenyl-1-(4-(trifluoromethyl)phenyl)prop-2-yn-1-ol (**S1f**).* Reaction time: 0.5 h. Colorless liquid (1.19 g, 86%). TLC: R_f 0.48 (3:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, J = 8.4 Hz, 2H), 7.67 (d, J = 8.4 Hz, 2H), 7.47 (m, 2H), 7.36−7.32 (m, 3H), 5.76 (d, J = 6.0 Hz, 1H), 2.37 (d, J = 6.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.4, 131.8, 130.5 (q, J_{C-F} = 32.2 Hz), 128.9, 128.4, 127.0. 125.6 (q, J_{C-F} = 3.9 Hz), 124.1 (q, J_{C-F} = 271 Hz), 122.0, 87.9, 87.3, 64.4. ^{19}F NMR (376 MHz, $CDCl_3$): δ −62.6 (s). LRMS (EI) m/z (rel int): (pos) 276 ([M]$^+$, 100), 259 ([M − OH]$^+$,16), 207 ([M − CF_3]$^+$, 44). HRMS m/z calcd for $C_{16}H_{11}F_3O$ 276.0762, found 276.0768.

*3-Phenyl-1-(p-tolyl)prop-2-yn-1-ol (**S1g**).* Reaction time: 1 h. Pale violet solid (1.12 g, 75%). TLC: R_f 0.30 (4:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, J = 8.0 Hz, 2H), 7.47 (m, 2H), 7.33−7.31 (m, 3H), 7.22 (d, J = 8.0 Hz, 2H), 5.66 (d, J = 6.4 Hz, 1H), 2.37 (s, 3H), 2.19 (d, J = 6.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.5, 138.0, 131.9, 129.6, 128.8, 128.5, 126.9, 122.7, 89.1, 86.7, 65.2, 21.4. LRMS (EI) m/z (rel int): (pos) 222 ([M]$^+$, 72), 207 ([M − CH_3]$^+$, 100). HRMS m/z calcd for $C_{16}H_{14}O$ 222.1045, found 222.1046. IR (KBr film): 3346, 3054, 3023, 2921, 1597, 1489, 820, 757, 691 cm^{-1}.

*1-(2-Methoxyphenyl)-3-phenylprop-2-yn-1-ol (**S1h**).* Reaction time: 1 h. Milky oil (1.06 g, 89%). TLC: R_f 0.26 (4:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (dd, J = 7.6, 1.6 Hz, 1H), 7.48 (m, 2H), 7.36−7.30 (m, 4H), 7.01 (td, J = 7.6, 0.8 Hz, 1H), 6.95 (dd, J = 7.6, 0.8 Hz, 1H), 5.93 (d, J = 6.0 Hz, 1H), 3.93 (s, 3H), 3.05 (d, J = 6.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.9, 131.8, 129.8, 128.8, 128.4, 128.2, 128.1, 122.8, 120.9, 110.9, 88.3, 86.1, 61.7, 55.6. LRMS (EI) m/z (rel int): (pos) 238 ([M]$^+$, 66), 223 ([M − CH_3]$^+$, 100), 207 ([M − OCH_3]$^+$, 46). HRMS m/z calcd for $C_{16}H_{14}O_2$ 238.0994, found 238.0995.

*1-(3-Methoxyphenyl)-3-phenylprop-2-yn-1-ol (**S1i**).* Reaction time: 1 h. Milky oil (955 mg, 80%). TLC: R_f 0.08 (10:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49−7.46 (m, 2H), 7.34−7.31 (m, 4H), 7.21−7.18 (m, 2H), 6.89 (ddd, J = 8.4, 2.6, 1.0 Hz, 1H), 5.67 (d, J = 6.4 Hz, 1H), 3.84 (s, 3H), 2.26 (d, J = 6.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.9, 142.2, 131.8, 129.7, 128.6, 128.3, 122.4, 119.0, 114.1, 112.2, 88.6, 86.6, 65.0, 55.3. LRMS (EI) m/z (rel int): (pos) 238 ([M]$^+$, 100), 223 ([M − CH_3]$^+$, 25), 207 ([M − OCH_3]$^+$, 33). HRMS m/z calcd for $C_{16}H_{14}O_2$ 238.0994, found 238.0994.

*3-(3-Chlorophenyl)-1-phenylprop-2-yn-1-ol (**S1j**).* Reaction time: 1 h. Pale yellow oil (1.21 g, 82%). TLC: R_f 0.20 (10:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, J = 7.2 Hz, 2H), 7.50−7.28 (m, 7H), 5.72 (d, J = 6.0 Hz, 1H), 2.37 (d, J = 6.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.5, 134.4, 131.8, 130.1, 129.8, 129.1, 128.9, 128.8, 126.9, 124.3, 90.1, 85.4, 65.3. HRMS (EI) m/z calcd for $C_{15}H_{11}ClO$ 242.0498, found 242.0494.

*1-Phenyl-3-(p-tolyl)prop-2-yn-1-ol (**S1k**).* Reaction time: 1 h. Pale yellow oil (1.08 g, 71%). TLC: R_f 0.13 (10:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, J = 7.2 Hz, 2H), 7.45−7.35 (m, 5H), 7.15 (d, J = 8.0 Hz, 2H), 5.70 (d, J = 1.6 Hz, 1H), 2.73 (brs, 1H), 2.38 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.9, 138.9, 131.8, 129.2, 128.8, 128.5, 126.9, 119.5, 88.3, 86.9, 65.2, 21.6. HRMS (EI) m/z calcd for $C_{16}H_{14}O$ 222.1045, found 222.1049.

*3-(4-Pentylphenyl)-1-phenylprop-2-yn-1-ol (**S1l**).* Reaction time: 1 h. Pale yellow oil (1.13 g, 88%). TLC: R_f 0.20 (10:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, J = 6.8 Hz, 2H), 7.44−7.34 (m, 5H), 7.14 (d, J = 8.0 Hz, 2H), 5.70 (s, 1H), 2.61 (t, J = 7.6 Hz, 2H), 2.38 (brs, 1H), 1.62 (quintet, J = 7.6 Hz, 2H), 1.38−1.29 (m, 4H), 0.91 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.8, 140.8, 131.7, 128.6, 128.4, 128.3, 126.7, 119.5, 88.0, 86.9, 65.1, 35.8, 31.4, 30.9, 22.5, 14.0. HRMS (EI) m/z calcd for $C_{20}H_{22}O$ 278.1671, found 278.1673.

*3-(4-Methoxyphenyl)-1-phenylprop-2-yn-1-ol (**S1m**).* Reaction time: 1 h. Pale yellow oil (1.11 g, 77%). TLC: R_f 0.15 (10:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, J = 7.2 Hz, 2H), 7.44−7.35 (m, 5H), 6.85 (d, J = 9.2 Hz, 2H), 5.68 (d, J = 2.4 Hz, 1H), 3.80 (s, 3H), 2.59 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.0, 141.1, 133.4, 128.8, 128.5, 126.9, 114.7, 114.1, 87.6, 86.8, 65.3, 55.4. HRMS (ESI) m/z calcd for $C_{16}H_{14}O_2$ 238.0994, found 238.0991.

*1-(4-Chlorophenyl)-3-(p-tolyl)prop-2-yn-1-ol (**S1n**).* Reaction time: 1 h. White solid (1.22 g, 95%). TLC: R_f 0.33 (5:1 hexanes/

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EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 7.13 (d, J = 8.0 Hz, 2H), 5.66 (d, J = 6.0 Hz, 1H), 2.36 (s, 3H), 2.27 (d, J = 6.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.4, 139.2, 134.4, 131.8, 129.3, 128.9, 128.3, 119.2, 87.8, 87.3, 64.6, 21.7. LRMS (EI) m/z (rel int): (pos) 256 ([M]$^+$, 52), 241 ([M − CH_3]$^+$, 55), 221 ([M − Cl]$^+$, 100). HRMS m/z calcd for $C_{16}H_{13}ClO$ 256.0655, found 256.0660.

1-(Furan-2-yl)-3-(4-methoxyphenyl)prop-2-yn-1-ol (**S1o**). Reaction time: 0.33 h. White solid (1.04 g, 91%). TLC: R_f 0.22 (3:1 hexanes/EtOAc). Mp: 56−58 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (dd, J = 1.6, 0.8 Hz, 1H), 7.42 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 8.8 Hz, 2H), 6.52 (dt, J = 3.6, 0.8 Hz, 1H), 6.38 (dd, J = 3.6, 1.6 Hz, 1H), 5.68 (d, J = 7.2 Hz, 1H), 3.82 (s, 3H), 2.33 (d, J = 7.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.0, 153.2, 143.0, 133.3, 114.2, 114.0, 110.4, 107.8, 85.8, 84.9, 58.7, 55.3. LRMS (EI) m/z (rel int): (pos) 228 ([M]$^+$, 100), 211 ([M − OH]$^+$, 50). HRMS m/z calcd for $C_{14}H_{12}O_3$ 228.0786, found 228.0787. IR (KBr film): 3404, 2839, 2232, 1606, 1510, 1464, 1249, 1032, 833 cm^{-1}.

1-Phenylnon-2-yn-1-ol (**S1p**). Reaction time: 1 h. Pale yellow oil (1.36 g, 87%). TLC: R_f 0.15 (10:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (d, J = 7.2 Hz, 2H), 7.40−7.30 (m, 3H), 5.46 (dt, J = 6.4, 2.0 Hz, 1H), 2.27 (td, J = 7.2, 2.0 Hz, 2H), 2.10 (d, J = 6.4 Hz, 1H), 1.55 (quintet, J = 7.2 Hz, 2H), 1.44−1.37 (m, 2H), 1.35−1.26 (m, 4H), 0.89 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.5, 128.7, 128.4, 126.8, 88.0, 80.1, 65.1, 31.5, 28.8, 28.7, 22.7, 19.0, 14.2. HRMS (EI) m/z calcd for $C_{15}H_{20}O$ 216.1514, found 216.1509.

Representative Procedure for the Synthesis of Alkynones S2c−p. In a 50 mL two-neck round-bottom flask, propargyl alcohol **S1c** (850 mg, 3.50 mmol) was dissolved in acetone (25 mL). Activated MnO_2 (6.09 g, 70.0 mmol, 20 equiv) was added, and the mixture was stirred at rt for 30 min. Upon the completion of the reaction, the resulting suspension was filtered through a plug of Celite, and the filtrate was concentrated by rotary evaporation. Purification of the residue by column chromatography (10:1 hexanes/EtOAc) afforded alkynone **S2c** (598 mg, 71%) as a white solid.

1-(4-Chlorophenyl)-3-phenylprop-2-yn-1-one (**S2c**). Reaction time: 0.5 h. White solid (598 mg, 71%). TLC: R_f 0.65 (4:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (d, J = 8.8 Hz, 2H), 7.69 (dm, J = 7.2 Hz, 2H), 7.51 (m, 1H), 7.50 (d, J = 8.8 Hz, 2H), 7.44 (tm, J = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.7, 140.7, 135.3, 133.1, 131.0, 130.9, 129.1, 128.7, 119.9, 93.6, 86.6. HRMS (ESI) m/z calcd for $C_{15}H_9ClO$ 240.0342, found 240.0343. IR (KBr film): 2199, 1654, 847, 751, 681 cm^{-1}.

1-(4-Fluorophenyl)-3-phenylprop-2-yn-1-one (**S2d**). Reaction time: 0.5 h. White solid (761 mg, 95%). TLC: R_f 0.42 (5:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (dd, J = 8.4, 5.2 Hz, 2H), 7.69 (m, 2H), 7.50 (m, 1H), 7.43 (m, 2H), 7.20 (t, J = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.4, 166.5 (d, J_{C-F} = 255.4 Hz), 133.4 (d, J_{C-F} = 3.1 Hz), 133.1, 132.2 (d, J_{C-F} = 10.1 Hz), 130.9, 128.7, 120.0, 115.8 (d, J_{C-F} = 21.7 Hz), 93.4, 86.6. ^{19}F NMR (376 MHz, $CDCl_3$): δ −103.3 (m). HRMS (ESI) m/z calcd for $C_{15}H_9FO$ 224.0637, found 224.0634.

1-(3-Nitrophenyl)-3-phenylprop-2-yn-1-one (**S2e**). Reaction time: 0.5 h. Lemon yellow solid (798 mg, 89%). TLC: R_f 0.44 (4:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.07 (t, J = 2.0 Hz, 1H), 8.53 (dt, J = 7.6, 1.2 Hz, 1H), 8.49 (ddd, J = 7.6, 2.0, 1.2 Hz, 1H), 7.77−7.73 (m, 3H), 7.54 (m, 1H), 7.46 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.4, 148.5, 138.1, 134.6, 133.4, 131.5, 129.9, 128.9, 128.2, 124.6, 119.4, 95.4, 86.2. HRMS (ESI) m/z calcd for $C_{15}H_9NO_3$ 251.0582, found 251.0582.

3-Phenyl-1-(4-(trifluoromethyl)phenyl)prop-2-yn-1-one (**S2f**). Reaction time: 0.5 h. White solid (780 mg, 91%). TLC: R_f 0.43 (10:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (d, J = 8.0 Hz, 2H), 7.80 (d, J = 8.0 Hz, 2H), 7.70 (m, 2H), 7.52 (m, 1H), 7.45 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.7, 139.4, 135.2 (q, J_{C-F} = 32.5 Hz), 133.2, 131.2, 129.8, 128.8, 125.7 (q, J_{C-F} = 3.9 Hz), 123.6 (q, J_{C-F} = 270.9 Hz), 119.7, 94.5, 86.6. ^{19}F NMR (376 MHz, $CDCl_3$): δ −63.2 (s). HRMS (ESI) m/z calcd for $C_{16}H_9F_3O$ 274.0605, found 274.0606.

3-Phenyl-1-(p-tolyl)prop-2-yn-1-one (**S2g**). Reaction time: 0.5 h. Yellowish orange solid (796 mg, 80%). TLC: R_f 0.69 (10:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, J = 8.0 Hz, 2H), 7.69 (dm, J = 7.2 Hz, 2H), 7.49 (tm, J = 7.2 Hz, 1H), 7.42 (tm, J = 7.2 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 2.45 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.7, 145.2, 134.6, 133.0, 130.7, 129.7, 129.3, 128.6, 120.3, 92.6, 87.0, 21.8. HRMS (ESI) m/z calcd for $C_{16}H_{12}O$ 220.0888, found 220.0891. IR (KBr film): 3062, 3025, 2921, 2203, 1637, 1489, 833, 760, 690 cm^{-1}.

1-(2-Methoxyphenyl)-3-phenylprop-2-yn-1-one (**S2h**). Reaction time: 0.5 h. Yellow oil (1.00 g, 97%). TLC: R_f 0.41 (4:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (dd, J = 8.0, 2.0 Hz, 1H), 7.64 (dt, J = 6.8, 2.0 Hz, 2H), 7.53 (m, 1H), 7.44 (m, 1H), 7.38 (tm, J = 6.8, 2H), 7.07 (td, J = 8.0, 0.8 Hz, 1H), 7.01 (dm, J = 8.0 Hz, 1H), 3.95 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.7, 159.8, 135.0, 133.0, 132.6, 130.5, 128.6, 126.8, 120.7, 120.3, 112.2, 91.6, 89.2, 55.9. HRMS (ESI) m/z calcd for $C_{16}H_{12}O_2$ 236.0837, found 236.0839.

1-(3-Methoxyphenyl)-3-phenylprop-2-yn-1-one (**S2i**). Reaction time: 0.5 h. Pale yellow solid (797 mg, 96%). TLC: R_f 0.52 (5:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (ddd, J = 8.0, 1.6, 0.8 Hz, 1H), 7.22−7.68 (m, 3H), 7.50 (m, 1H), 7.46−7.41 (m, 3H), 7.19 (ddd, J = 8.0, 2.8, 0.8 Hz, 1H), 3.90 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.8, 159.8, 138.3, 133.1, 130.8, 129.7, 128.7, 122.9, 121.0, 120.1, 112.9, 93.0, 87.0, 55.5. HRMS (ESI) m/z calcd for $C_{16}H_{12}O_2$ 236.0837, found 236.0838.

3-(3-Chlorophenyl)-1-phenylprop-2-yn-1-one (**S2j**). Reaction time: 0.5 h. Yellow solid (954 mg, 95%). TLC: R_f 0.26 (10:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, J = 8.0 Hz, 2H), 7.67 (t, J = 1.6 Hz, 1H), 7.64 (dt, J = 7.6, 1.6 Hz, 1H), 7.57 (dt, J = 7.6, 1.6 Hz, 1H), 7.53 (tm, J = 8.0 Hz, 2H), 7.47 (m, 1H), 7.37 (t, J = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.9, 136.9, 134.9, 134.6, 132.9, 131.3, 131.2, 130.2, 129.8, 128.9, 122.1, 91.1, 87.6. HRMS (ESI) m/z calcd for $C_{15}H_9ClO$ 240.0342, found 240.0344.

1-Phenyl-3-(p-tolyl)prop-2-yn-1-one (**S2k**). Reaction time: 0.5 h. Yellow solid (930 mg, 95%). TLC: R_f 0.30 (10:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (dd, J = 7.6, 1.2 Hz, 2H), 7.63 (tt, J = 7.6, 1.2 Hz, 1H), 7.59 (d, J = 8.0 Hz, 2H), 7.52 (t, J = 7.6 Hz, 2H), 7.23 (d, J = 8.0 Hz, 2H), 2.41 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.3, 141.8, 137.2, 134.2, 133.3, 129.8, 129.7, 128.8, 117.2, 94.0, 87.0, 22.0. HRMS (ESI) m/z calcd for $C_{16}H_{12}O$ 220.0888, found 220.0891.

3-(4-Pentylphenyl)-1-phenylprop-2-yn-1-one (**S2l**). Reaction time: 0.5 h. Yellow solid (1.01 g, 97%). TLC: R_f 0.39 (10:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (dd, J = 7.6, 1.2 Hz, 2H), 7.63 (tt, J = 7.6, 1.2 Hz, 1H), 7.61 (d, J = 8.0 Hz, 2H), 7.52 (t, J = 7.6 Hz, 2H), 7.24 (d, J = 8.0 Hz, 2H), 2.64 (t, J = 7.6 Hz, 2H), 1.64 (quintet, J = 7.6 Hz, 2H), 1.38−1.25 (m, 4H), 0.90 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.3, 146.8, 137.3, 134.2, 133.4, 129.8, 129.1, 128.8, 117.4, 94.1, 87.0, 36.3, 31.6, 31.0, 22.7, 14.2. HRMS (ESI) m/z calcd for $C_{20}H_{20}O$ 276.1514, found 276.1517. IR (KBr film): 3030, 2929, 2195, 1644, 1598, 1449, 823, 700 cm^{-1}

3-(4-Methoxyphenyl)-1-phenylprop-2-yn-1-one (**S2m**). Reaction time: 0.5 h. Yellow solid (1.21 g, 82%). TLC: R_f 0.27 (10:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, J = 7.6 Hz, 2H), 7.65 (d, J = 8.8 Hz, 2H), 7.62 (m, 1H), 7.52 (t, J = 7.6 Hz, 2H), 6.94 (d, J = 8.8 Hz, 2H), 3.86 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.3, 162.0, 137.3, 135.4, 134.1, 129.7, 128.8, 114.7, 112.2, 94.5, 87.1, 55.7. HRMS (ESI) m/z calcd for $C_{16}H_{12}O_2$ 236.0837, found 236.0839.

1-(4-Chlorophenyl)-3-(p-tolyl)prop-2-yn-1-one (**S2n**). Reaction time: 0.5 h. White solid (848 mg, 81%). TLC: R_f 0.62 (5:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (d, J = 8.8 Hz, 2H), 7.59 (d, J = 8.0 Hz, 2H), 7.50 (d, J = 8.8 Hz, 2H), 7.25 (d, J = 8.0 Hz, 2H), 2.42 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.7, 141.8, 140.6, 135.4, 133.2, 130.9, 129.6, 129.0, 116.8, 94.4, 86.5, 21.8. HRMS (ESI) m/z calcd for $C_{16}H_{11}ClO$ 254.0498, found 254.0495.

1-(Furan-2-yl)-3-(4-methoxyphenyl)prop-2-yn-1-one (**S2o**). Reaction time: 0.5 h. Pale yellow solid (815 mg, 88%). TLC: R_f 0.36 (3:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (dd, J = 1.6, 0.8 Hz, 1H), 7.61 (d, J = 8.8 Hz, 2H), 7.41 (dd, J = 3.6, 0.8 Hz, 1H), 6.93 (d, J = 8.8 Hz, 2H), 6.60 (dd, J = 3.6, 1.6 Hz, 1H), 3.86 (s, 3H).

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^{13}C NMR (100 MHz, $CDCl_3$): δ 165.0, 161.8, 153.4, 147.8, 135.1, 120.5, 114.5, 112.6, 111.7, 93.2, 86.2, 55.5. HRMS (ESI) m/z calcd for $C_{14}H_{10}O_3$ 226.0630, found 226.0629.

*1-Phenylnon-2-yn-1-one (**S2p**).* Reaction time: 0.5 h. Pale yellow oil (1.20 g, 92%). TLC: R_f 0.35 (10:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (dd, J = 7.6, 1.2 Hz, 2H), 7.59 (tt, J = 7.6, 1.2 Hz, 1H), 7.47 (t, J = 7.6 Hz, 2H), 2.50 (t, J = 7.2 Hz, 2H), 1.68 (quintet, J = 7.2 Hz, 2H), 1.50−1.44 (m, 2H), 1.34−1.31 (m, 4H), 0.91 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.4, 137.2, 134.0, 129.7, 128.7, 97.1, 79.9, 31.4, 28.8, 28.0, 22.7, 19.4, 14.2. HRMS (ESI) m/z calcd for $C_{15}H_{18}O$ 214.1358, found 214.1359.

*(Z)-4-Phenylbut-3-yn-2-one O-Methyl Oxime (**1a**) and (E)-4-Phenylbut-3-yn-2-one O-Methyl Oxime (**1a′**).* In a 250 mL round-bottom flask, 4-phenylbut-3-yn-2-one (**S2a**, 2.48 g, 16.5 mmol), $MeONH_2$·HCl (2.15 g, 25.8 mmol), and NaOAc (2.11 g, 25.8 mmol) were dissolved in EtOH (69 mL), and the mixture was stirred at rt for 2 h. Upon the completion of the reaction, the reaction was quenched with H_2O (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation. The residue was purified by column chromatography (100:1 hexanes/EtOAc) to afford (*Z*)-*O*-methyl oxime **1a** as a colorless liquid (1.74 g, 61%) and (*E*)-*O*-methyl oxime **1a′** as a colorless liquid (1.12 g, 39%). The configurations of the oximes were determined by comparing their ^{1}H NMR spectra with reported values.[22]

1a. TLC: R_f 0.42 (20:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (m, 2H), 7.38−7.33 (m, 3H), 3.97 (s, 3H), 2.13 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.7, 132.3, 129.6, 128.6, 121.9, 99.3, 81.2, 62.5, 20.8. HRMS (ESI) m/z calcd for $C_{11}H_{11}NO$ 173.0841, found 173.0840. IR (KBr film) 2936, 2223, 1599, 1490, 1375, 1313, 1170, 1061, 757, 690 cm^{-1}.

1a′. TLC: R_f 0.48 (20:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (m, 2H), 7.36−7.31 (m, 3H), 3.98 (s, 3H), 2.09 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.4, 131.9, 129.0, 128.4, 122.0, 90.2, 85.5, 62.4, 16.6. HRMS (ESI) m/z calcd for $C_{11}H_{11}NO$ 173.0841, found 173.0839.

Representative Procedure for the Synthesis of *O*-Methyl Oximes 1b−p. In a 50 mL round-bottom flask, 4-phenylbut-3-yn-2-one (**S2b**, 206 mg, 1.00 mmol), $MeONH_2$·HCl (167 mg, 2.00 mmol), and Na_2SO_4 (284 mg, 2.00 mmol) were dissolved in anhydrous MeOH (3 mL). Pyridine (0.3 mL) was added via syringe, and the mixture was stirred at rt for 17 h. Upon the completion of the reaction, the reaction was quenched with H_2O (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), then dried over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation. The residue was purified by column chromatography (6:1 hexanes/$CHCl_3$) to afford (*Z*)-*O*-methyl oxime **1b** as a pale yellow oil (181 mg, 77%) and (*E*)-*O*-methyl oxime **1b′** as a colorless oil (9.4 mg, 4%).

*(Z)-1,3-Diphenylprop-2-yn-1-one O-Methyl Oxime (**1b**) and (E)-1,3-Diphenylprop-2-yn-1-one O-Methyl Oxime (**1b′**).* The configurations of the oximes were determined by comparing their ^{1}H NMR spectra with reported values.[22]

1b. TLC: R_f 0.29 (50:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93−7.90 (m, 2H), 7.64−7.60 (m, 2H), 7.43−7.36 (m, 6H), 4.14 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.1, 133.8, 132.4, 129.9, 129.7, 128.7, 128.6, 126.7, 122.0, 101.4, 79.7, 63.3. HRMS (ESI) m/z calcd for $C_{16}H_{13}NO$ 235.0997, found 235.0996. IR (KBr film): 3059, 2935, 2211, 1597, 1443, 755, 689 cm^{-1}.

1b′. TLC: R_f 0.21 (50:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92−7.90 (m, 2H), 7.57−7.55 (m, 2H), 7.45−7.39 (m, 3H), 7.37−7.32 (m, 3H), 4.06 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.4, 132.2, 131.9, 130.1, 129.7, 129.3, 128.5, 128.3, 122.2, 90.8, 85.4, 63.4. HRMS (ESI) m/z calcd for $C_{16}H_{13}NO$ 235.0997, found 235.0997. IR (KBr film): 3055, 2936, 2210, 1597, 1444, 756, 690 cm^{-1}.

*(Z)-1-(4-Chlorophenyl)-3-phenylprop-2-yn-1-one O-Methyl Oxime (**1c**).* The configuration of the oxime was determined by comparing its ^{1}H NMR spectra with reported values.[22] Reaction time: 44 h. White solid (322 mg, 48%). TLC: R_f 0.61 (10:1 hexanes/EtOAc). Mp: 53−55 °C. (lit.[22] 52−54 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, J = 8.8 Hz, 2H), 7.61 (m, 2H), 7.42−7.36 (m, 3H), 7.37 (d, J = 8.8 Hz, 2H), 4.14 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.9, 135.6, 132.2, 132.1, 129.7, 128.6, 128.5, 127.7, 121.6, 101.5, 79.0, 63.2. HRMS (ESI) m/z calcd for $C_{16}H_{12}ClNO$ 269.0607, found 269.0610. IR (KBr film): 2935, 2212, 1597, 1489, 833, 756, 689 cm^{-1}.

*(Z)-1-(4-Fluorophenyl)-3-phenylprop-2-yn-1-one O-Methyl Oxime (**1d**) and (E)-1-(4-Fluorophenyl)-3-phenylprop-2-yn-1-one O-Methyl Oxime (**1d′**).* The configurations of the *E*/*Z*-oximes were determined by comparing NOE spectra. Reaction time: 24 h.

1d. Colorless liquid (403 mg, 56%). TLC: R_f 0.27 (6:1 hexanes/$CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (dd, J = 8.8, 5.2 Hz, 2H), 7.61 (m, 2H), 7.42−7.36 (m, 3H), 7.09 (t, J = 8.8 Hz, 2H), 4.13 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.7 (d, J_{C-F} = 248.6 Hz), 138.9, 132.2, 129.8 (d, J_{C-F} = 3.1 Hz), 129.6, 128.4 (d, J_{C-F} = 6.9 Hz), 128.3, 121.6, 115.5 (d, J_{C-F} = 21.7 Hz), 101.4, 79.2, 63.1. ^{19}F NMR (376 MHz, $CDCl_3$): δ −111.4 (m). HRMS (ESI) m/z calcd for $C_{16}H_{12}FNO$ 253.0903, found 253.0903. IR (KBr film): 3064, 2937, 2214, 1509, 1489, 1233, 1157, 1053, 840, 756, 689 cm^{-1}.

1d′. Milky oil (29.0 mg, 4%). TLC: R_f 0.18 (6:1 hexanes/$CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (dd, J = 8.8, 5.2 Hz, 2H), 7.56 (m, 2H), 7.40−7.33 (m, 3H), 7.11 (t, J = 8.8 Hz, 2H), 4.06 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.2 (d, J_{C-F} = 250.0 Hz), 141.0, 132.0, 131.9 (d, J_{C-F} = 7.7 Hz), 129.2, 128.4, 127.8 (d, J_{C-F} = 3.1 Hz), 121.8, 115.2 (d, J_{C-F} = 21.7 Hz), 90.7, 85.0, 63.3. ^{19}F NMR (376 MHz, $CDCl_3$): δ −109.5 (m). HRMS (ESI) m/z calcd for $C_{16}H_{12}FNO$ 253.0903, found 253.0903.

*(Z)-1-(3-Nitrophenyl)-3-phenylprop-2-yn-1-one O-Methyl Oxime (**1e**).* The NOE spectra of the *E*/*Z*-oximes were not clear, and their configurations were determined by Larock's ICl reaction,[22] which has shown that only (*Z*)-*O*-methyl oximes afford iodoisoxazoles. Reaction time: rt, 19 h; 40 °C, 3 h; 60 °C, 21 h. White solid (158 mg, 20%). TLC: R_f 0.38 (10:1 hexanes/EtOAc). Mp: 86−88 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.78 (m, 1H), 8.26 (d, J = 8.0 Hz, 1H), 8.25 (d, J = 8.0 Hz, 1H), 7.64 (m, 2H), 7.59 (t, J = 8.0 Hz, 1H), 7.45−7.39 (m, 3H), 4.19 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.6, 138.0, 135.6, 132.5, 132.2, 130.2, 129.6, 128.8, 124.3, 121.6, 121.4, 102.6, 78.7, 63.8. LRMS (EI) m/z (rel int): (pos) 280 ([M]$^+$, 100), 203 ([M − C_6H_5]$^+$, 14). HRMS m/z calcd for $C_{16}H_{12}N_2O_3$ 280.0848, found 280.0846. IR (KBr film): 3083, 2937, 2204, 1532, 1489, 1050, 892, 757, 741, 719, 681 cm^{-1}.

*(Z)-3-Phenyl-1-(4-(trifluoromethyl)phenyl)prop-2-yn-1-one O-Methyl Oxime (**1f**).* The configuration of the oxime was determined by comparing its ^{1}H NMR spectra with reported values.[22] Reaction time: 36 h. White solid (277 mg, 41%). TLC: R_f 0.56 (10:1 hexanes/EtOAc). Mp: 44−46 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, J = 8.0 Hz, 2H), 7.66 (d, J = 8.0 Hz, 2H), 7.62 (m, 2H), 7.43−7.37 (m, 3H), 4.17 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.7, 137.0 (q, J_{C-F} = 1.6 Hz), 132.2, 131.4 (q, J_{C-F} = 32.5 Hz), 129.8, 128.5, 126.8, 125.4 (q, J_{C-F} = 3.9 Hz), 124.0 (q, J_{C-F} = 270.1 Hz), 121.5, 101.9, 78.9, 63.4. ^{19}F NMR (376 MHz, $CDCl_3$): δ −62.8 (s). HRMS (ESI) m/z calcd for $C_{17}H_{12}F_3NO$ 303.0871, found 303.0872. IR (KBr film): 2938, 2899, 2213, 1619, 1599, 1489, 1324, 1127, 1053, 847, 756, 689 cm^{-1}.

*(Z)-3-Phenyl-1-(p-tolyl)prop-2-yn-1-one O-Methyl Oxime (**1g**).* The configuration of the oxime was determined by comparing its ^{1}H NMR spectra with reported values.[23] Reaction time: rt, 19 h; 60 °C, 23 h. Yellow oil (579 mg, 75%). TLC: R_f 0.73 (10:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, J = 8.0 Hz, 2H), 7.61 (m, 2H), 7.40−7.35 (m, 3H), 7.20 (d, J = 8.0 Hz, 2H), 4.12 (s, 3H), 2.38 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.1, 140.0, 132.3, 131.1, 129.7, 129.3, 128.6, 126.6, 122.1, 101.1, 79.8, 63.2, 21.6. HRMS (ESI) m/z calcd for $C_{17}H_{15}NO$ 249.1154, found 249.1156. IR (KBr film): 2935, 2897, 2212, 1611, 1489, 822, 756, 690 cm^{-1}.

*(E)-1-(2-Methoxyphenyl)-3-phenylprop-2-yn-1-one O-Methyl Oxime (**1h**).* The NOE spectra of the *E*/*Z*-oximes were not clear, and their configurations were determined by Larock's ICl reaction,[22] which has shown that only (*Z*)-*O*-methyl oximes afford iodoisoxazoles. Reaction time: 14 h. White solid (950 mg, 99%). TLC: R_f 0.43 (10:1 hexanes/EtOAc). Mp: 48−50 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ

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7.53 (m, 2H), 7.49 (dd, J = 7.6, 1.6 Hz, 1H), 7.38 (m, 1H), 7.35−7.31 (m, 3H), 7.00 (td, J = 7.6, 1.2 Hz, 1H), 6.97 (d, J = 7.6 Hz, 1H), 4.12 (s, 3H), 3.89 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.9, 139.0, 132.2, 131.0, 130.3, 129.4, 128.5, 123.7, 122.4, 120.8, 112.0, 100.3, 81.0, 63.1, 56.0. HRMS (ESI) m/z calcd for $C_{17}H_{15}NO_2$ 265.1103, found 265.1102. IR (KBr film): 2936, 2211, 1599, 1488, 1251, 1047, 755, 691 cm^{-1}.

*(Z)-1-(3-Methoxyphenyl)-3-phenylprop-2-yn-1-one O-Methyl Oxime (**1i**).* The configuration of the oxime was determined by comparing its ^{1}H NMR spectra with reported values.[24] Reaction time: 26 h. Colorless liquid (566 mg, 74%). TLC: R_f 0.32 (6:1 hexanes/$CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (m, 2H), 7.51 (dm, J = 8.0 Hz, 1H), 7.47 (dd, J = 2.4, 1.6 Hz, 1H), 7.41−7.36 (m, 3H), 7.32 (t, J = 8.0 Hz, 1H), 6.95 (ddd, J = 8.0, 2.4, 0.8 Hz, 1H), 4.14 (s, 3H), 3.86 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.6, 139.8, 134.9, 132.2, 129.5, 129.4, 128.4, 121.8, 119.3, 115.7, 111.5, 131.1, 79.4, 63.2, 55.3. HRMS (ESI) m/z calcd for $C_{17}H_{15}NO_2$ 265.1103, found 265.1104. IR (KBr film): 3057, 2936, 2201, 1600, 1486, 1255, 1048, 890, 790, 757, 690 cm^{-1}.

*(Z)-3-(3-Chlorophenyl)-1-phenylprop-2-yn-1-one O-Methyl Oxime (**1j**) and (E)-3-(3-Chlorophenyl)-1-phenylprop-2-yn-1-one O-Methyl Oxime (**1j′**).* The configurations of the E/Z-oximes were determined by comparing NOE spectra. Reaction time: 25 h.

1j. Pale yellow oil (622 mg, 60%). TLC: R_f 0.37 (10:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90−7.87 (m, 2H), 7.60 (t, J = 1.6 Hz, 1H), 7.49 (dt, J = 7.6 Hz, 1.6 Hz, 1H), 7.42−7.36 (m, 4H), 7.32 (t, J = 7.6 Hz, 1H), 4.14 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.8, 134.6, 133.5, 132.1, 130.5, 130.0, 129.9, 128.7, 126.7, 123.7, 99.6, 80.6, 77.4, 63.4. HRMS (ESI) m/z calcd for $C_{16}H_{12}ClNO$ 269.0607, found 269.0611. IR (KBr film): 3063, 2935, 2214, 1591, 1473, 1182, 767, 690 cm^{-1}.

1j′. Yellow oil (28.2 mg, 3%). TLC: R_f 0.29 (10:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90−7.87 (m, 2H), 7.54 (t, J = 2.0 Hz, 1H), 7.45−7.41 (m, 4H), 7.35 (dm, J = 8.0 Hz,1H), 7.28 (t, J = 8.0 Hz, 1H), 4.06 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.1, 134.5, 132.0, 131.7, 130.3, 130.2, 129.9, 129.7, 129.6, 128.4, 123.9, 89.0, 86.5, 63.5. HRMS (ESI) m/z calcd for $C_{16}H_{12}ClNO$ 269.0607, found 269.0607. IR (KBr film): 3023, 2930, 2208, 1609, 1465, 1192, 760, 699 cm^{-1}.

*(Z)-1-Phenyl-3-(p-tolyl)prop-2-yn-1-one O-Methyl Oxime (**1k**) and (E)-1-Phenyl-3-(p-tolyl)prop-2-yn-1-one O-Methyl Oxime (**1k′**).* The NOE spectra of the E/Z-oximes were not clear and their configurations were determined by Larock's ICl reaction,[22] which has shown that only (Z)-O-methyl oximes afford iodoisoxazoles. Reaction time: 24 h.

1k. Pale yellow oil (690 mg, 71%). TLC: R_f 0.57 (10:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01(d, J = 7.2 Hz, 2H), 7.63 (d, J = 8.0 Hz, 2H), 7.53−7.48 (m, 3H), 7.24 (d, J = 8.0 Hz, 2H), 4.26 (s, 3H), 2.41 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.2, 140.1, 133.9, 132.3, 129.8, 129.4, 128.6, 126.7, 118.9, 101.8, 79.2, 63.3, 21.8. HRMS (ESI) m/z calcd for $C_{17}H_{15}NO$ 249.1154, found 249.1156. IR (KBr film): 3029, 2935, 2210, 1606, 1444, 816, 766, 692 cm^{-1}.

1k′. Pale yellow oil (38.7 mg, 4%). TLC: R_f 0.49 (10:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, J = 7.6 Hz, 2H), 7.45−7.40 (m, 5H), 7.15 (d, J = 7.6 Hz, 2H), 4.05 (s, 3H), 2.40 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ142.6, 139.6, 132.1, 132.0, 130.1, 129.8, 129.4, 128.3, 119.1, 91.2, 84.9, 63.4, 21.8. HRMS (ESI) m/z calcd for $C_{17}H_{15}NO$ 249.1154, found 249.1156. IR (KBr film): 3029, 2935, 2208, 1606, 1445, 816, 772, 692 cm^{-1}.

*(Z)-3-(4-Pentylphenyl)-1-phenylprop-2-yn-1-one O-Methyl Oxime (**1l**) and (E)-3-(4-Pentylphenyl)-1-phenylprop-2-yn-1-one O-Methyl Oxime (**1l′**).* The NOE spectra of the E/Z-oximes were not clear and their configurations were determined by Larock's ICl reaction,[22] which has shown that only (Z)-O-methyl oximes afford iodoisoxazoles. Reaction time: 26 h

1l. Pale yellow oil (676 mg, 80%). TLC: R_f 0.60 (10:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92−7.90 (m, 2H), 7.52 (d, J = 8.0 Hz, 2H), 7.41−7.37 (m, 3H), 7.19 (d, J = 8.0 Hz, 2H), 4.13 (s, 3H), 2.62 (t, J = 7.6 Hz, 2H), 1.66 (quintet, J = 7.6 Hz, 2H), 1.36−1.28 (m, 4H), 0.89 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.1, 140.2, 133.9, 132.3, 129.8, 128.8, 128.6, 126.7, 119.1, 101.8, 79.2, 63.3, 36.1, 31.6, 31.0, 22.7, 14.2. HRMS (ESI) m/z calcd for $C_{21}H_{23}NO$ 305.1780, found 305.1785. IR (KBr film): 3027, 2931, 2210, 1588, 1464, 834, 766, 692 cm^{-1}.

1l′. Pale yellow oil (30.2 mg, 4%).TLC: R_f 0.46 (10:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91−7.89 (m, 2H), 7.46 (d, J = 8.0 Hz, 2H), 7.44−7.40 (m, 3H), 7.15 (d, J = 8.0 Hz, 2H), 4.05 (s, 3H), 2.60 (t, J = 7.6 Hz, 2H), 1.61 (quintet, J = 7.6 Hz, 2H), 1.36−1.29 (m, 4H), 0.89 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.6, 142.6, 132.2, 132.1, 130.1, 129.8, 128.7, 128.3, 119.3, 91.3, 84.9, 63.3, 36.1, 31.6, 31.0, 22.7, 14.2. HRMS (ESI) m/z calcd for $C_{21}H_{23}NO$ 305.1780, found 305.1778. IR (KBr film): 2927, 2208, 1509, 1461, 838, 816, 690 cm^{-1}.

*(Z)-3-(4-Methoxyphenyl)-1-phenylprop-2-yn-1-one O-Methyl Oxime (**1m**).* The NOE spectra of the E/Z-oximes were not clear, and their configurations were determined by Larock's ICl reaction,[22] which has shown that only (Z)-O-methyl oximes afford iodoisoxazoles. Reaction time: 24 h. Pale yellow oil (926 mg, 80%). TLC: R_f 0.55 (10:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00−7.97 (m, 2H), 7.60 (d, J = 8.8 Hz, 2H), 7.46−7.42 (m, 3H), 6.92 (d, J = 8.8 Hz, 2H), 4.18 (s, 3H), 3.81 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.7, 140.2, 133.9, 133.8, 129.7, 128.5, 126.6, 114.2, 113.8, 101.8, 78.8, 63.1, 55.3. HRMS (ESI) m/z calcd for $C_{17}H_{15}NO_2$ 265.1103, found 265.1104. IR (KBr film): 3003, 2935, 2208, 1584, 1463, 832, 766, 692 cm^{-1}.

*(Z)-1-(4-Chlorophenyl)-3-(p-tolyl)prop-2-yn-1-one O-Methyl Oxime (**1n**).* The NOE spectra of the E/Z-oximes were not clear, and their configurations were determined by Larock's ICl reaction,[22] which has shown that only (Z)-O-methyl oximes afford iodoisoxazoles. Reaction time: 52 h. White solid (183 mg, 57%). TLC: R_f 0.55 (10:1 hexanes/EtOAc). Mp: 46−48 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, J = 8.8 Hz, 2H), 7.50 (d, J = 8.0 Hz, 2H), 7.37 (d, J = 8.8 Hz, 2H), 7.19 (d, J = 8.0 Hz, 2H), 4.13 (s, 3H), 2.39 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.3, 139.2, 135.8, 132.4, 132.3, 129.5, 128.8, 127.9, 118.7, 102.2, 78.8, 63.4, 21.8. HRMS (ESI) m/z calcd for $C_{17}H_{14}ClNO$ 283.0764, found 283.0767. IR (KBr film): 2935, 2210, 1594, 1490, 1049, 833, 815 cm^{-1}.

*(E)-1-(Furan-2-yl)-3-(4-methoxyphenyl)prop-2-yn-1-one O-Methyl Oxime (**1o**).* The NOE spectra of the E/Z-oximes were not clear, and their configurations were determined by Larock's ICl reaction,[22] which has shown that only (Z)-O-methyl oximes afford iodoisoxazoles. Reaction time: 22 h. Pale yellow oil (348 mg, 46%). TLC: R_f 0.24 (10:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, J = 8.8 Hz, 2H), 7.50 (dd, J = 1.6, 0.8 Hz, 1H), 6.90 (d, J = 8.8 Hz, 2H), 6.82 (dd, J = 3.6, 0.8 Hz, 1H), 6.48 (dd, J = 3.6, 1.6 Hz, 1H), 4.13 (s, 3H), 3.84 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ160.8, 148.3, 144.0, 133.9, 132.3, 144.2, 133.4, 112.2, 111.5, 99.8, 77.1, 63.3, 55.3. HRMS (ESI) m/z calcd for $C_{15}H_{13}NO_3$ 255.0895, found 255.0896. IR (KBr film): 2936, 2205, 1605, 1485, 1253, 1050, 832 cm^{-1}.

*(Z)-1-Phenylnon-2-yn-1-one O-Methyl Oxime (**1p**) and (E)-1-Phenylnon-2-yn-1-one O-Methyl Oxime (**1p′**).* The NOE spectra of the E/Z-oximes were not clear and their configurations were determined by Larock's ICl reaction,[22] which has shown that only (Z)-O-methyl oximes afford iodoisoxazoles. Reaction time: 23 h.

1p. Pale yellow oil (915 mg, 72%). TLC: R_f 0.37 (10:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85−7.83 (m, 2H), 7.38−7.35 (m, 3H), 4.01 (s, 3H), 2.54 (t, J = 7.2 Hz, 2H), 1.62 (quintet, J = 7.2 Hz, 2H), 1.51−1.47 (m, 2H), 1.35−1.31 (m, 4H), 0.91 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.4, 134.1, 129.6, 128.4, 126.6, 104.1, 71.7, 63.1, 31.4, 28.8, 28.4, 22.7, 20.0, 14.2. HRMS (ESI) m/z calcd for $C_{16}H_{21}NO$ 243.1623, found 243.1623. IR (KBr film): 3061, 2933, 2217, 1585, 1444, 767, 692 cm^{-1}.

1p′. Pale yellow oil (38.3 mg, 3%).TLC: R_f 0.32 (10:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84−7.82 (m, 2H), 7.41−7.37 (m, 3H), 3.99 (s, 3H), 2.40 (t, J = 7.2 Hz, 2H), 1.61 (quintet, J = 7.2 Hz, 2H), 1.54−1.41 (m, 2H), 1.33−1.29 (m, 4H), 0.89 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.5, 132.3, 129.9, 129.7, 128.1, 93.0, 77.0, 63.1, 31.5, 28.9, 28.4, 22.7, 19.6, 14.2. HRMS (ESI) m/z calcd for $C_{16}H_{21}NO$ 243.1623, found 243.1626. IR (KBr film): 3061, 2931, 2217, 1632, 1465, 767, 692 cm^{-1}.

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Representative Procedure for Direct Synthesis of 4-Fluoroisoxazoles through Gold-Catalyzed Cascade Cyclization−Fluorination. In a 25 mL one-arm round-bottom flask, (*Z*)-4-phenylbut-3-yn-2-one *O*-methyl oxime (**1b**, 47.0 mg, 200 μmol), Selectfluor (177 mg, 500 μmol), $NaHCO_3$ (33.6 mg, 400 μmol), (IPr)AuCl (6.2 mg, 10.0 μmol), and AgOTs (2.8 mg, 10.0 μmol) were dissolved in anhydrous CH_3CN (2 mL) under Ar atmosphere. The resulting suspension was stirred at rt for 24 h. Upon the completion of the reaction, the reaction mixture was diluted with CH_2Cl_2 (20 mL), filtered through a plug of Celite, and rinsed with CH_2Cl_2 (20 mL). The filtrate was dried over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation. The residue was purified by column chromatography (10:1 hexanes/EtOAc) to afford 4-fluoroisoxazole **3b** as a white solid (47.2 mg, 98%).

*4-Fluoro-3-methyl-5-phenylisoxazole (**3a**).* This reaction was carried out in 0.4 mmol scale. Purification by column chromatography (40:1 hexanes/EtOAc) afforded 4-fluoroisoxazole **3a** as a colorless crystal (65.0 mg, 92%). TLC: R_f 0.51 (20:1 hexanes/EtOAc (×2)). Mp: 31−33 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (dm, *J* = 7.2 Hz, 2H), 7.49 (tm, *J* = 7.2 Hz, 2H), 7.43 (tm, *J* = 7.2 Hz, 1H), 2.37 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.1 (d, J_{C-F} = 10.0 Hz), 151.9 (d, J_{C-F} = 6.9 Hz), 142.3 (d, J_{C-F} = 254.7 Hz), 129.9 (d, J_{C-F} = 1.5 Hz), 129.0, 126.0 (d, J_{C-F} = 5.5 Hz), 125.2 (d, J_{C-F} = 4.6 Hz), 8.7 (d, J_{C-F} = 3.1 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ −180.6 (s). HRMS (ESI) *m*/*z* calcd for $C_{10}H_8FNO$ 177.0590, found 177.0590. IR (KBr film): 3062, 2931, 1657, 1510, 1470, 1194, 766, 691 cm^{-1}.

*4-Fluoro-3,5-diphenylisoxazole (**3b**).* Purification by column chromatography (30:1 hexanes/EtOAc) afforded **3b** (47.2 mg, 98%) as a white solid. TLC: R_f 0.25 (50:1 hexanes/EtOAc). Mp: 102−104 °C (lit.[10] 101−103 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96−7.94 (m, 2H), 7.89 (d, *J* = 7.2 Hz, 2H), 7.56−7.45 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.8 (d, J_{C-F} = 19.3 Hz), 153.4 (d, J_{C-F} = 10.8 Hz), 141.8 (d, J_{C-F} = 258 Hz), 130.7, 130.4, 129.3, 129.2, 127.3 (d, J_{C-F} = 3.1 Hz), 127.0 (d, J_{C-F} = 3.9 Hz), 126.1 (d, J_{C-F} = 5.4 Hz), 125.5 (d, J_{C-F} = 5.4 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ −177.7 (s). HRMS (ESI) *m*/*z* calcd for $C_{15}H_{10}FNO$ 239.0746, found 239.0746. IR (KBr film): 3065, 1647, 1466, 1214, 772, 691 cm^{-1}.

*3-(4-Chlorophenyl)-4-fluoro-5-phenylisoxazole (**3c**).* Purification by column chromatography (40:1 hexanes/EtOAc) afforded **3c** (50.8 mg, 93%) as a white solid. TLC: R_f 0.50 (20:1 hexanes/EtOAc). Mp: 133−134 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91−7.87 (m, 4H), 7.56−7.48 (m, 3H), 7.50 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.9 (d, J_{C-F} = 19.3 Hz), 152.3 (d, J_{C-F} = 10.0 Hz), 141.4 (d, J_{C-F} = 257.7 Hz), 136.7, 130.3 (d, J_{C-F} = 1.6 Hz), 129.4, 129.1, 128.3 (d, J_{C-F} = 3.9 Hz), 125.7 (d, J_{C-F} = 4.7 Hz), 125.3 (d, J_{C-F} = 4.7 Hz), 125.2. ^{19}F NMR (376 MHz, $CDCl_3$): δ −177.7 (s). HRMS (ESI) *m*/*z* calcd for $C_{15}H_9ClFNO$ 273.0357, found 273.0356. IR (KBr film): 1447, 1265, 1093, 836, 739, 688 cm^{-1}.

*4-Fluoro-3-(4-fluorophenyl)-5-phenylisoxazole (**3d**).* Purification by column chromatography (40:1 hexanes/EtOAc) afforded **3d** (46.6 mg, 91%) as a white solid. TLC: R_f 0.40 (15:1 hexanes/EtOAc). Mp: 121−123 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (dd, *J* = 8.8, 5.2 Hz, 2H), 7.88 (m, 2H), 7.54 (m, 2H), 7.48 (m, 1H), 7.21 (t, *J* = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.0 (d, J_{C-F} = 250.0 Hz), 153.7 (d, J_{C-F} = 19.3 Hz), 152.3 (d, J_{C-F} = 10.9 Hz), 141.3 (d, J_{C-F} = 256.9 Hz), 130.3, 129.1 (dd, J_{C-F} = 8.5, 3.8 Hz), 129.1, 125.8 (d, J_{C-F} = 5.4 Hz), 125.3 (d, J_{C-F} = 5.5 Hz), 123.0 (dd, J_{C-F} = 3.9, 3.1 Hz), 116.2 (d, J_{C-F} = 21.6 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ −178.0 (s), −109.3 (m). HRMS (ESI) *m*/*z* calcd for $C_{15}H_9F_2NO$ 257.0652, found 257.0651. IR (KBr film): 1650, 1447, 1265, 1215, 1100, 848, 739, 689 cm^{-1}.

*4-Fluoro-3-(3-nitrophenyl)-5-phenylisoxazole (**3e**) and 3-(3-Nitrophenyl)-5-phenylisoxazole (**4e**).* Purification by column chromatography (100:1 hexanes/EtOAc) afforded **3e** (44.8 mg, 79%) as a white solid and **4e** (5.6 mg, 11%) as a white solid.

3e. TLC: R_f 0.29 (10:1 hexanes/EtOAc (×2)). Mp: 144−146 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.82 (t, *J* = 2.0 Hz, 1H), 8.37 (ddd, *J* = 8.0, 2.0, 1.2 Hz, 1H), 8.30 (d, *J* = 8.0 Hz, 1H), 7.90 (dm, *J* = 7.2 Hz, 2H), 7.73 (t, *J* = 8.0 Hz, 1H), 7.58−7.48 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.6 (d, J_{C-F} = 19.3 Hz), 151.3 (d, J_{C-F} = 10.1 Hz), 148.7, 141.2 (d, J_{C-F} = 257.7 Hz), 132.6 (d, J_{C-F} = 3.1 Hz), 130.6, 130.2, 129.2, 128.5 (d, J_{C-F} = 3.9 Hz), 125.5, 125.4 (d, J_{C-F} = 4.7 Hz), 125.1, 122.0 (d, J_{C-F} = 3.8 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ −177.7 (s). HRMS (ESI) *m*/*z* calcd for $C_{15}H_9FN_2O_3$ 284.0597, found 284.0597. IR (neat): 1640, 1536, 1467, 1345, 1098, 947, 770, 752, 698, 689 cm^{-1}.

4e. TLC: R_f 0.12 (10:1 hexanes/EtOAc (×2)). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.70 (t, *J* = 2.0 Hz, 1H), 8.34 (ddd, *J* = 8.0, 2.0, 1.2 Hz, 1H), 8.30 (dm, *J* = 8.0 Hz, 1H), 7.87 (m, 2H), 7.70 (t, *J* = 8.0 Hz, 1H), 7.56−7.48 (m, 3H), 6.93 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.5, 161.1, 148.7, 132.5, 131.0, 130.7, 130.1, 129.2, 127.0, 125.9, 124.6, 121.9, 97.3. HRMS (ESI) *m*/*z* calcd for $C_{15}H_{10}N_2O_3$ 266.0691, found 266.0691. IR (KBr film): 2917, 2849, 1737, 1533, 1462, 1349, 1242, 806, 765, 741, 686 cm^{-1}.

*4-Fluoro-5-phenyl-3-(4-(trifluoromethyl)phenyl)isoxazole (**3f**) and 5-Phenyl-3-(4-(trifluoromethyl)phenyl)isoxazole (**4f**).* Purification by column chromatography (40:1 hexanes/EtOAc) afforded **3f** (59.2 mg, 96%) as a white solid and **4f** (1.0 mg, 2%) as a white solid.

3f. TLC: R_f 0.47 (20:1 hexanes/EtOAc). Mp: 121−123 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (d, *J* = 8.4 Hz, 2H), 7.90 (m, 2H), 7.79 (d, *J* = 8.4 Hz, 2H), 7.57−7.47 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.3 (d, J_{C-F} = 18.6 Hz), 152.1 (d, J_{C-F} = 10.8 Hz), 141.4 (d, J_{C-F} = 257.7 Hz), 132.3 (q, J_{C-F} = 32.5 Hz), 130.5 (d, J_{C-F} = 1.5 Hz), 130.3 (dq, J_{C-F} = 4.0, 1.0 Hz), 129.2, 127.4 (d, J_{C-F} = 3.9 Hz), 126.0 (q, J_{C-F} = 3.1 Hz), 125.6 (d, J_{C-F} = 4.7 Hz), 125.3 (d, J_{C-F} = 5.4 Hz), 123.8 (q, J_{C-F} = 270.8 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ −177.7 (s), −63.1 (s). HRMS (ESI) *m*/*z* calcd for $C_{16}H_9F_4NO$ 307.0620, found 307.0620. IR (KBr film): 3055, 1644, 1450, 1327, 1265, 1115, 850, 740, 696 cm^{-1}.

4f. TLC: R_f 0.29 (20:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, *J* = 8.4 Hz, 2H), 7.86 (m, 2H), 7.76 (d, *J* = 8.4 Hz, 2H), 7.54−7.48 (m, 3H), 6.87 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1, 161.9, 132.6 (q, J_{C-F} = 1.1 Hz), 131.9 (q, J_{C-F} = 32.5 Hz), 130.5, 129.1, 127.2, 127.1, 126.0 (q, J_{C-F} = 3.1 Hz), 125.9, 123.9 (q, J_{C-F} = 270.9 Hz), 97.4. HRMS (ESI) *m*/*z* calcd for $C_{16}H_{10}F_3NO$ 289.0714, found 289.0713. IR (KBr film): 2923, 2852, 1736, 1450, 1258, 1113, 851, 769, 693 cm^{-1}.

*4-Fluoro-5-phenyl-3-(p-tolyl)isoxazole (**3g**).* Purification by column chromatography (40:1 hexanes/EtOAc) afforded **3g** (48.7 mg, 96%) as a white solid. TLC: R_f 0.28 (40:1 hexanes/EtOAc). Mp: 119−121 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (m, 2H), 7.84 (d, *J* = 8.0 Hz, 2H), 7.53 (m, 2H), 7.46 (m, 1H), 7.33 (d, *J* = 8.0 Hz, 2H), 2.44 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.4 (d, J_{C-F} = 19.3 Hz), 153.2 (d, J_{C-F} = 10.8 Hz), 141.5 (d, J_{C-F} = 256.9 Hz), 140.7, 130.1 (d, J_{C-F} = 1.5 Hz), 129.7, 129.0, 126.9 (d, J_{C-F} = 3.9 Hz), 126.0 (d, J_{C-F} = 4.7 Hz), 125.3 (d, J_{C-F} = 4.7 Hz), 123.9 (d, J_{C-F} = 3.9 Hz), 21.5. ^{19}F NMR (376 MHz, $CDCl_3$): δ −177.7 (s). HRMS (ESI) *m*/*z* calcd for $C_{16}H_{12}FNO$ 253.0903, found 253.0905. IR (neat): 2923, 2854, 1649, 1446, 1218, 1116, 818, 761, 682 cm^{-1}.

*4-Fluoro-3-(2-methoxyphenyl)-5-phenylisoxazole (**3h**).* Purification by column chromatography (40:1 hexanes/EtOAc) afforded **3h** (46.6 mg, 87%) as a white solid. TLC: R_f 0.39 (10:1 hexanes/EtOAc). Mp: 92−93 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (m, 2H), 7.58 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.54−7.45 (m, 4H), 7.10 (td, *J* = 7.6, 1.2 Hz, 1H), 7.06 (d, *J* = 7.6 Hz, 1H), 3.91 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.6, 153.0 (d, J_{C-F} = 13.9 Hz), 152.6 (d, J_{C-F} = 19.3 Hz), 142.0 (d, J_{C-F} = 256.9 Hz), 131.9, 130.7 (d, J_{C-F} = 1.6 Hz), 129.9, 129.0, 126.2 (d, J_{C-F} = 5.4 Hz), 125.3 (d, J_{C-F} = 4.7 Hz), 120.9, 115.7 (d, J_{C-F} = 3.1 Hz), 111.4, 55.8. ^{19}F NMR (376 MHz, $CDCl_3$): δ −173.9 (s). HRMS (ESI) *m*/*z* calcd for $C_{16}H_{12}FNO_2$ 269.0852, found 269.0854. IR (KBr film): 3065, 2939, 1477, 1273, 1252, 1118, 1027, 758, 757, 691 cm^{-1}.

*4-Fluoro-3-(3-methoxyphenyl)-5-phenylisoxazole (**3i**) and 3-(3-Methoxyphenyl)-5-phenylisoxazole (**4i**).* Purification by column chromatography (100:1 hexanes/EtOAc) afforded **3i** (33.4 mg, 62%) as a white solid and **4i** (2.9 mg, 6%) as a colorless oil.

3i. TLC: R_f 0.28 (20:1 hexanes/EtOAc). Mp: 71−73 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (dm, *J* = 6.8 Hz, 2H), 7.55−7.47 (m, 5H), 7.43 (t, *J* = 8.0 Hz, 1H), 7.06 (ddd, *J* = 8.0, 2.8, 1.2 Hz, 1H), 3.89 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.0, 153.6 (d, J_{C-F} = 19.4

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Hz), 153.1 (d, J_{C-F} = 10.1 Hz), 141.5 (d, J_{C-F} = 257.0 Hz), 132.2, 130.1 (d, J_{C-F} = 6.2 Hz), 129.1 (d, J_{C-F} = 3.1 Hz), 127.9 (d, J_{C-F} = 3.9 Hz), 125.9 (d, J_{C-F} = 5.4 Hz), 125.3 (d, J_{C-F} = 4.6 Hz), 119.6 (d, J_{C-F} = 4.7 Hz), 116.7, 111.9 (d, J_{C-F} = 3.1 Hz), 55.4. ^{19}F NMR (376 MHz, $CDCl_3$): δ −177.4 (s). HRMS (ESI) m/z calcd for $C_{16}H_{12}FNO_2$ 269.0852, found 269.0852. IR (KBr film): 1648, 1593, 1481, 1255, 1206, 1041, 862, 714, 688 cm^{-1}.

4i. TLC: R_f 0.13 (20:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (dm, J = 6.4 Hz, 2H), 7.52−7.41 (m, 5H), 7. 39 (t, J = 7.6 Hz, 1H), 7.06 (ddd, J = 7.6, 2.4, 1.6 Hz, 1H), 6.82 (s, 1H), 3.89 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 162.9, 160.0, 130.4, 130.3, 130.0, 129.0, 127.4, 125.8, 119.3, 116.2, 111.7, 97.6, 55.4. HRMS (ESI) m/z calcd for $C_{16}H_{13}NO_2$ 251.0946, found 251.0946. IR (KBr film): 2924, 2852, 1735, 1573, 1473, 1259, 1041, 839, 787, 764, 689 cm^{-1}.

*5-(3-Chlorophenyl)-4-fluoro-3-phenylisoxazole (**3j**) and 5-(3-Chlorophenyl)-3-phenylisoxazole (**4j**).* Purification by column chromatography (30:1 hexanes/EtOAc) afforded **3j** (44.8 mg, 80%) as a white solid and **4j** (8.9 mg, 17%) as a white solid.

3j. TLC: R_f 0.27 (50:1 hexanes/EtOAc). Mp: 109−111 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95−7.93 (m, 2H), 7.87 (m, 1H), 7.77 (dt, J = 7.2, 1.6 Hz, 1H), 7.54−7.51 (m, 3H), 7.49−7.43 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.6 (d, J_{C-F} = 10.0 Hz), 152.4 (d, J_{C-F} = 19.4 Hz), 142.2 (d, J_{C-F} = 258.8 Hz), 135.5, 130.9, 130.7, 130.4, 129.3, 127.6 (d, J_{C-F} = 5.5 Hz), 127.3 (d, J_{C-F} = 3.8 Hz), 126.7 (d, J_{C-F} = 3.8 Hz), 125.5 (d, J_{C-F} = 5.5 Hz), 123.5 (d, J_{C-F} = 5.4 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ −176.2 (s). HRMS (ESI) m/z calcd for $C_{15}H_9ClFNO$ 273.0357, found 273.0360. IR (KBr film): 1650, 1463, 1165, 933, 792, 772, 701, 690 cm^{-1}.

4j. TLC: R_f 0.08 (50:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88−7.83 (m, 3H), 7.74 (m, 1H), 7.52−7.47 (m, 3H), 7.44 (d, J = 5.2 Hz, 2H), 6.86 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.2, 163.3, 135.4, 130.6, 130.5, 130.4, 129.3, 129.2, 129.1, 127.0, 126.1, 124.1, 98.5. HRMS (ESI) m/z calcd for $C_{15}H_{10}ClNO$ 255.0451, found 255.0449. IR (KBr film): 3071, 1601, 1453, 934, 810, 708 cm^{-1}.

*4-Fluoro-3-phenyl-5-(p-tolyl)isoxazole (**3k**).* Purification by column chromatography (30:1 hexanes/EtOAc) afforded **3k** (50.0 mg, 100%) as a white solid. TLC: R_f 0.25 (50:1 hexanes/EtOAc). Mp: 89−91 °C (lit.[10] 96−97 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95−7.93 (m, 2H), 7.78 (d, J = 8.0 Hz, 2H), 7.53−7.50 (m, 3H), 7.33 (d, J = 8.0 Hz, 2H), 2.43 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.0 (d, J_{C-F} = 19.3 Hz), 153.3 (d, J_{C-F} = 10 Hz), 141.3 (d, J = 256.2 Hz), 140.7, 130.6, 130.0, 129.2, 127.3 (d, J_{C-F} = 3.8 Hz), 127.1 (d, J_{C-F} = 3.9 Hz), 125.4 (d, J_{C-F} = 4.6 Hz), 123.4 (d, J_{C-F} = 5.4 Hz), 21.8. ^{19}F NMR (376 MHz, $CDCl_3$): δ −178.4 (s). HRMS (ESI) m/z calcd for $C_{16}H_{12}FNO$ 253.0903, found 253.0905. IR (KBr film): 2922, 1648, 1468, 819, 770, 691 cm^{-1}.

*4-Fluoro-5-(4-pentylphenyl)-3-phenylisoxazole (**3l**).* Purification by column chromatography (30:1 hexanes/EtOAc) afforded **3l** (62.2 mg, 99%) as a white solid. TLC: R_f 0.39 (50:1 hexanes/EtOAc). Mp: 56−58 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96−7.93 (m, 2H), 7.79 (d, J = 8.0 Hz, 2H), 7.54−7.50 (m, 3H), 7.33 (d, J = 8.0 Hz, 2H), 2.67 (t, J = 7.6 Hz, 2H), 1.66 (quintet, J = 7.6 Hz, 2H), 1.39−1.30 (m, 4H), 0.91 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.1 (d, J_{C-F} = 19.3 Hz), 153.3 (d, J_{C-F} = 10.8 Hz), 145.7, 141.4 (d, J_{C-F} = 256.2 Hz), 130.6, 129.3, 129.2, 127.3 (d, J_{C-F} = 3.9 Hz), 127.1 (d, J_{C-F} = 3.9 Hz), 125.4 (d, J_{C-F} = 4.7 Hz), 123.6 (d, J_{C-F} = 4.7 Hz), 36.1, 31.7, 31.1, 22.7, 14.2. ^{19}F NMR (376 MHz, $CDCl_3$): δ −178.5 (s). HRMS (ESI) m/z calcd for $C_{20}H_{20}FNO$ 309.1529, found 309.1534. IR (KBr film): 3055, 2951, 1645, 1462, 1212, 812, 769, 692 cm^{-1}.

*4-Fluoro-5-(4-methoxyphenyl)-3-phenylisoxazole (**3m**).* Purification by column chromatography (30:1 hexanes/EtOAc) afforded **3m** (34.9 mg, 65%) as a white solid. TLC: R_f 0.20 (50:1 hexanes/EtOAc). Mp: 97−99 °C (lit.[10] 103−104 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95−7.92 (m, 2H), 7.83 (d, J = 8.8 Hz, 2H), 7.53−7.50 (m, 3H), 7.04 (d, J = 8.8 Hz, 2H), 3.89 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.2, 154.0 (d, J_{C-F} = 19.4 Hz), 153.3 (d, J_{C-F} = 10.1 Hz), 140.8 (d, J_{C-F} = 255.4 Hz), 130.6, 129.2, 128.9, 127.2 (m, 2C), 119.0, 114.8, 55.6. ^{19}F NMR (376 MHz, $CDCl_3$): δ −179.7 (s). HRMS (ESI) m/z calcd for $C_{16}H_{12}FNO_2$ 269.0852, found 269.0855. IR (KBr film): 2937, 1647, 1461, 1255, 832, 772, 692 cm^{-1}.

*3-(4-Chlorophenyl)-4-fluoro-5-(p-tolyl)isoxazole (**3n**).* Purification by column chromatography (40:1 hexanes/EtOAc) afforded **3n** (53.6 mg, 93%) as a white solid. TLC: R_f 0.44 (20:1 hexanes/EtOAc (×2)). Mp: 143−145 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (d, J = 8.0 Hz, 2H), 7.76 (d, J = 8.4 Hz, 2H), 7.49 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 2.43 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.1 (d, J_{C-F} = 19.3 Hz), 152.1 (d, J_{C-F} = 10.9 Hz), 140.9 (d, J_{C-F} = 256.2 Hz), 140.6, 136.6, 129.8, 129.3, 128.3 (d, J_{C-F} = 3.1 Hz), 125.4 (d, J_{C-F} = 3.9 Hz), 125.2 (d, J_{C-F} = 4.7 Hz), 123.0 (d, J_{C-F} = 5.4 Hz), 21.6. ^{19}F NMR (376 MHz, $CDCl_3$): δ −178.5 (s). HRMS (ESI) m/z calcd for $C_{16}H_{11}ClFNO$ 287.0513, found 287.0512. IR (KBr film): 1651, 1602, 1455, 1264, 1213, 1110, 1092, 1045, 836, 819 cm^{-1}.

*4-Fluoro-3-(furan-2-yl)-5-(4-methoxyphenyl)isoxazole (**3o**) and 3-(Furan-2-yl)-5-(4-methoxyphenyl)isoxazole (**4o**).* Purification by column chromatography (20:1 hexanes/EtOAc) afforded **3o** (13.5 mg, 26%) as a white solid and **4o** (2.8 mg, 6%) as a white solid.

3o. TLC: R_f 0.44 (5:1 hexanes/EtOAc). Mp: 119−120 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, J = 8.8 Hz, 2H), 7.64 (d, J = 1.6 Hz, 1H), 7.04 (d, J = 8.8 Hz, 2H), 7.02 (m, 1H), 6.59 (dd, J = 3.6, 1.6 Hz, 1H), 3.88 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.1 (d, J_{C-F} = 1.6 Hz), 153.3 (d, J_{C-F} = 17.8 Hz), 146.2 (d, J_{C-F} = 21.6 Hz), 144.5, 141.4 (d, J_{C-F} = 4.6 Hz), 138.9 (d, J_{C-F} = 256.2 Hz), 127.0 (d, J_{C-F} = 4.6 Hz), 118.4 (d, J_{C-F} = 5.4 Hz), 114.6, 112.5 (d, J_{C-F} = 1.8 Hz), 111.6, 55.4. ^{19}F NMR (376 MHz, $CDCl_3$): δ −179.9 (s). HRMS (ESI) m/z calcd for $C_{14}H_{10}FNO_3$ 259.0645, found 259.0644. IR (KBr film): 1655, 1605, 1474, 1263, 1113, 1012, 828, 766 cm^{-1}.

4o. TLC: R_f 0.35 (5:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, J = 8.8 Hz, 2H), 7.57 (dd, J = 1.8, 0.8 Hz, 1H), 7.00 (d, J = 8.8 Hz, 2H), 6.94 (dd, J = 3.2, 0.8 Hz, 1H), 6.66 (s, 1H), 6.54 (dd, J = 3.2, 1.8 Hz, 1H), 3.87 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1, 161.3, 155.4, 144.5, 143.8, 127.5, 120.0, 114.4, 111.7, 110.0, 95.6, 55.4. HRMS (ESI) m/z calcd for $C_{14}H_{11}NO_3$ 241.0739, found 241.0736. IR (KBr film): 1736, 1619, 1440, 1257, 1027, 837 cm^{-1}.

*4-Fluoro-5-hexyl-3-phenylisoxazole (**3p**).* Purification by column chromatography (30:1 hexanes/EtOAc) afforded **3p** (42.2 mg, 85%) as a pale yellow oil. TLC: R_f 0.50 (10:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89−7.87 (m, 2H), 7.51−7.47 (m, 3H), 2.82 (td, J = 7.6, 1.2 Hz, 2H), 1.76 (quintet, J = 7.2 Hz, 2H), 1.42−1.30 (m, 6H), 0.9 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.8 (d, J_{C-F} = 24.7 Hz), 152.5 (d, J_{C-F} = 10.8 Hz), 142.0 (d, J_{C-F} = 250.0 Hz), 130.4, 129.1, 127.3 (d, J_{C-F} = 3.9 Hz), 127.2 (d, J_{C-F} = 3.9 Hz), 31.5, 28.9, 26.7, 24.8, 22.7, 14.2. ^{19}F NMR (376 MHz, $CDCl_3$): δ −184.5 (s). HRMS (ESI) m/z calcd for $C_{15}H_{18}FNO$ 247.1372, found 247.1377. IR (KBr film): 3069, 2930, 1657, 1462, 1263, 771, 693 cm^{-1}.

*Stoichiometric Reaction of **1a**, (IPr)AuCl, and AgOTs.* (IPr)AuCl (46.6 mg, 75.0 μmol) and AgOTs (20.9 mg, 75.0 μmol) were placed in a J. Young NMR tube under Ar atmosphere, and a solution of (*Z*)-4-phenylbut-3-yn-2-one *O*-methyl oxime (**1a**) in acetonitrile-d_3 (0.75 mL) was added. The ensuing formation of the gold intermediate was monitored at room temperature by ^{1}H NMR spectroscopy. Upon the completion of the reaction, the resulting suspension was filtered and washed with anhydrous CH_3CN (3 mL). Then, the solid was dissolved in anhydrous CH_2Cl_2 (3 mL), and the insoluble powder was filtered off. The filtrate was concentrated by rotary evaporation. Recrystallization from CH_3CN afforded **9** as a colorless crystal (32.0 mg, 57%). TLC: R_f 0.18 (4:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, acetone-d_6): δ 7.80 (s, 2H), 7.73 (dm, J = 7.2 Hz, 2H), 7.64 (t, J = 8.0 Hz, 2H), 7.47 (d, J = 8.0 Hz, 4H), 7.14 (tm, J = 7.2 Hz, 1H), 7.08 (tm, J = 7.2 Hz, 2H), 2.76 (septet, J = 7.2 Hz, 4H), 1.57 (s, 3H), 1.34 (d, J = 7.2 Hz, 12H), 1.26 (d, J = 7.2 Hz, 12H). ^{13}C NMR (100 MHz, acetone-d_6): δ 195.9, 173.2, 168.6, 147.0, 135.9, 134.4, 132.7, 131.3, 129.0, 128.1, 126.0, 125.0, 124.9, 29.7, 24.8, 24.3, 14.7. HRMS (ESI) m/z calcd for $C_{37}H_{44}AuN_3O$ 743.3150, found 743.3144.

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■ ASSOCIATED CONTENT

Supporting Information

The ORTEP structure and CIF file of compound **9** and copies of NMR spectra of compounds **S1c−p**, **S2c−p**, **1a−p**, **1a′**, **1b′**, **1d′**, **1j′**, **1k′**, **1l′**, **3a−p**, **4e**, **4f**, **4i**, **4j**, **4o**, and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Pinho, e M.; Teresa, M. V. D. *Curr. Org. Chem.* **2005**, *9*, 925−958.
(2) Daidone, G.; Raffa, D.; Maggio, B.; Plescia, F.; Cutuli, V. M. C.; Mangano, N. G.; Caruso, A. *Arch. Pharm.* **1999**, *332*, 50−54.
(3) Cali, P.; Nærum, L.; Mukhija, S.; Hjelmencrantz, A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5997−6000.
(4) Liu, J.; Yu, L.-F.; Eaton, J. B.; Caldarone, B.; Cavino, K.; Ruiz, C.; Terry, M.; Fedolak, A.; Wang, D.; Ghavami, A.; Lowe, D. A.; Brunner, D.; Lukas, R. J.; Kozikowski, A. P. *J. Med. Chem.* **2011**, *54*, 7280−7288.
(5) Kumbhare, R. M.; Kosurkar, U. B.; Janaki Ramaiah, M.; Dadmal, T. L.; Pushpavalli, S. N.; Pal-Bhadra, M. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 5424−5427.
(6) Pace, A.; Buscemi, S.; Vivona, N. *Org. Prep. Proced. Int.* **2007**, *39*, 1−70.
(7) Palin, R.; Abernethy, L.; Ansari, N.; Cameron, K.; Clarkson, T.; Dempster, M.; Dunn, D.; Easson, A.-M.; Edwards, D.; Maclean, J.; Everett, K.; Feilden, H.; Ho, K.-K.; Kultgen, S.; Littlewood, P.; McArthur, D.; McGregor, D.; McLuskey, H.; Neagu, I.; Neale, S.; Nisbet, L.-A.; Ohlmeyer, M.; Pham, Q.; Ratcliffe, P.; Rong, Y.; Roughton, A.; Sammons, M.; Swanson, R.; Tracey, H.; Walker, G. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 892−898.
(8) For review, see: (a) St. Jean, D. J., Jr.; Fotsch, C. *J. Med. Chem.* **2012**, *55*, 6002−6020. (b) Hodgetts, K. J.; Combs, K. J.; Elder, A. M.; Harriman, G. C. *Annu. Rep. Med. Chem.* **2010**, *45*, 429−448. (c) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320−330. (d) Shah, P.; Westwell, A. D. *J. Enzyme. Inhib. Med. Chem.* **2007**, *22*, 527−540.
(9) Bumgardner, C. L.; Sloop, J. C. *J. Fluorine Chem.* **1992**, *56*, 141−146.
(10) Stephens, C. E.; Blake, J. A. *J. Fluorine Chem.* **2004**, *125*, 1939−1945.
(11) Akana, J. A.; Bhattacharyya, K. X.; Müller, P.; Sadighi, J. P. *J. Am. Chem. Soc.* **2007**, *129*, 7736−7737.
(12) Liu, G. *Org. Biomol. Chem.* **2012**, *10*, 6243−6248.
(13) Schuler, M.; Silva, F.; Bobbio, C.; Tessier, A.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2008**, *47*, 7927−7930.
(14) Qian, J.; Liu, Y.; Zhu, J.; Jiang, B.; Xu, Z. *Org. Lett.* **2011**, *13*, 4220−4223.
(15) Simonneau, A.; Garcia, P.; Goddard, J.-P.; Mouriès-Mansuy, V.; Malacria, M.; Fensterbank, L. *Beilstein J. Org. Chem.* **2011**, *7*, 1379−1386.
(16) Li, S.; Li, Z.; Yuan, Y.; Li, Y.; Zhang, L.; Wu, Y. *Chem.—Eur. J.* **2013**, *19*, 1496−1501.
(17) Arcadi, A.; Pietropaolo, E.; Alvino, A.; Michelet, V. *Org. Lett.* **2013**, *15*, 2766−2769.
(18) (a) Zhang, G.; Luo, Y.; Wang, Y.; Zhang, L. *Angew. Chem., Int. Ed.* **2011**, *50*, 4450−4454. (b) Hopkinson, M. N.; Ross, J. E.; Giuffredi, G. T.; Gee, A. D.; Gouverneur, V. *Org. Lett.* **2010**, *12*, 4904−4907.
(19) For a recent review on NHC ligands in gold catalysis, see: Gatineau, D.; Goddard, J.-P.; Mouriès-Mansuy, V.; Fensterbank, L. *Isr. J. Chem.* **2013**, *53*, 892−900.
(20) Wang, D.; Cai, R.; Sharma, S.; Jirak, J.; Thummanapelli, S. K.; Akhmedov, N. G.; Zhang, H.; Liu, X.; Petersen, J. L.; Shi, X. *J. Am. Chem. Soc.* **2012**, *134*, 9012−9019.
(21) (a) Mankad, N. P.; Toste, F. D. *Chem. Sci.* **2012**, *3*, 72−76. (b) Wang, W.; Jasinski, J.; Hammond, G. B.; Xu, B. *Angew. Chem., Int. Ed.* **2010**, *49*, 7247−7252. (c) Mankad, N. P.; Toste, F. D. *J. Am. Chem. Soc.* **2010**, *132*, 12859−12861. (d) Praveen, C.; Kalyanasundaram, A.; Perumal, P. T. *Synlett* **2010**, 777−781.
(22) Waldo, J. P.; Larock, R. C. *J. Org. Chem.* **2007**, *72*, 9643−9647.
(23) Dolliver, D. D.; Bhattarai, B. T.; Pandey, A.; Lanier, M. L.; Bordelon, A. S.; Adhikari, S.; Dinser, J. A.; Flowers, P. F.; Wills, V. S.; Schneider, C. L.; Shaughnessy, K. H.; Moore, J. N.; Raders, S. M.; Snowden, T. S.; McKim, A. S.; Fronczek, F. R. *J. Org. Chem.* **2013**, *78*, 3676−3687.
(24) She, Z.; Niu, D.; Chen, L.; Gunawan, M. A.; Shanja, X.; Hersh, W. H.; Chen, Y. *J. Org. Chem.* **2012**, *77*, 3627−3633.