

Synthesis of 3,4,5-Trisubstituted Isoxazoles through Gold-Catalyzed Cascade Cyclization–Oxidative Alkynylation and Cyclization-Fluorination of 2-Alkynone *O*-Methyloximes

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Gold-catalyzed tandem cyclization–oxidative alkynylation and cyclization-fluorination reactions of 2-alkynone *O*-methyloximes are described. The reactions proceed smoothly at room temperature in the presence of 10 mol % of (PPh₃)AuNTf₂, 2.5 equivalents of selectfluor, and 2 equivalents of K₃PO₄. 2-Alkynone *O*-methyloximes undergo intramolecular oxyauration/cyclization and ensuing oxidative cross-coupling and fluorination process to afford the corresponding 3,4,5-trisubstituted isoxazoles in a cascade manner.

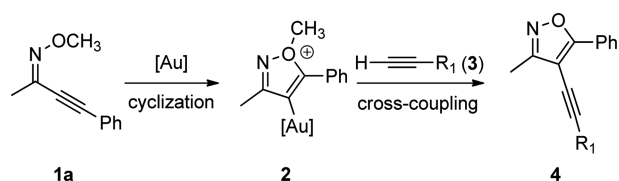
Key Words : Gold, Isoxazole, *O*-Methyloxime, Cross-coupling, Alkyne

Introduction

Isoxazole¹ is an important scaffold frequently found in many natural products and biologically active compounds such as analgesics,² antibiotics,³ antidepressants,⁴ and anti-cancer agent.⁵ It has also been used as a synthetic intermediate, building block and chiral ligand in organic synthesis.⁵ The prevailing methods for the synthesis of isoxazoles mostly involve the condensation between a hydroxylamine and a 1,3-dicarbonyl compound,⁶ the condensation between a hydroxylamine and α,β -unsaturated carbonyl compound,⁷ and the [3+2] cycloaddition reaction between an alkyne and a nitrile oxide.⁸ These methods usually require harsh conditions and suffer from poor chemo- and regioselectivities. Furthermore, they are unsuitable for the selective synthesis of fully substituted isoxazoles. So far, only a few methodologies for the selective synthesis of fully substituted isoxazoles have been reported. Larock and co-workers reported a stepwise synthesis of trisubstituted isoxazoles that featured the iodocyclization of 2-alkynone *O*-methyloximes and a subsequent palladium-catalyzed coupling reaction.⁹ Harrity and co-workers demonstrated a stepwise reaction involving [3+2] cycloaddition reaction of nitrile oxides and alkynylboronates to provide isoxazole boronic esters, followed by Suzuki coupling reaction.¹⁰ Denmark and co-workers also reported a [3+2] cycloaddition reaction between alkynyltrimethylsilyl ethers and nitrile oxides to produce isoxazolylsilanols, the cross-coupling reactions of which afforded 3,4,5-trisubstituted isoxazoles.¹¹ In these three cases, extra functionalization at the 4-position, such as iodination, borylation, or silylation, is required and is followed by cross-coupling reaction with a genuine substituent in a stepwise manner. Considering “atom economy”¹² to prevent wasting atoms and “pot economy”¹³ to target the inherent efficiency by avoiding intermediate isolation, the direct synthesis of trisubstituted isoxazoles in one sequence is highly desirable

and challenging. However, cycloaddition reactions with internal alkynes to afford trisubstituted isoxazoles are limited to a handful of highly activated alkynes (*e.g.*, acetylene dicarboxylate and related electron-deficient acetylenes) and suffer from poor regioselectivities¹⁴ as mentioned previously. Facile one-pot domino reactions have rarely been reported.¹⁵ The lack of direct synthetic methods for the fully substituted isoxazoles has become more acute due to increasing needs and applications in the pharmaceutical industry.

In recent years, gold catalysts have drawn significant attention due to their applicability in many organic transformations, which originates from their promising properties such as air- and moisture-stability, a broad range of functional group compatibilities, superior π -acidity, fine-tunable reactivity with various ligands, and mild reaction conditions.¹⁶ Interestingly, gold rarely changes oxidation state during the reaction. Hence, for a long time, gold-catalyzed cross-coupling reactions were not considered feasible although many organic transformations are catalyzed by gold. However, more recently, it was discovered that gold was able to undergo Au(I)/Au(III) redox cycles in the presence of an external oxidant such as Selectfluor, which enabled cross-coupling reactions.¹⁷ Therefore, to develop novel direct synthetic methods for the fully substituted isoxazoles, we envisioned cyclization of 2-alkynone *O*-methyloxime **1a** catalyzed by π -acidic gold, leading to the cationic gold intermediate **2**; the subsequent oxidative alkynylation might provide trisubstituted isoxazole **4** in a cascade manner



Scheme 1. Strategy for cascade cyclization–oxidative alkynylation.

(Scheme 1). This “pot economic” transformation involves gold-catalyzed cyclization reaction combined with oxidative cross-coupling in one-pot, which allows direct access to the highly functionalized isoxazoles.

Experimental

General Remarks. Reagents were purchased in Sigma-Aldrich Ltd. Alfa Aesar, Strem chemicals Inc. or Acros organics, and used without further purification. All solvents were distilled before used under dry Ar over appropriate drying agents (sodium benzophenone ketyl, metal hydride). Reactions were performed in an oven-dried glassware under positive Ar pressure with magnetic stirring. TLC was performed on 0.25 mm E. Merck silica gel 60 F254 plates and visualized under UV light (254 nm) or by staining with *p*-anisaldehyde or cerium ammonium molybdate (CAM). Flash chromatography was performed on E. Merck 230–400 mesh silica gel 60. NMR spectra were recorded on Varian Unity 400 instruments at 24 °C. Chemical shifts are expressed in ppm relative to TMS (¹H, 0 ppm), or CDCl₃ (¹H, 7.26 ppm; ¹³C, 77.2 ppm); coupling constants are expressed in Hz. High resolution mass spectra electrospray ionization (HRMS-ESI) were obtained on an Agilent technologies 6220 TOF LC/MS spectrometer.

Synthesis of (Z)-4-Phenylbut-3-yn-2-one O-methylloxime (1a). In an oven-dried roundbottom flask, NH₂OCH₃·HCl (263 mg, 3.20 mmol) and NaOAc (258 mg, 3.20 mmol) were dissolved in anhydrous EtOH (10.5 mL) under Ar atmosphere. 4-Phenyl-3-butyn-2-one (310 μL, 2.10 mmol) was added and the resulting suspension was stirred at rt. After 1.5 h, EtOH was evaporated. Then, the residue was diluted with H₂O (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried over anhydrous MgSO₄, filtered, and evaporated. Column chromatography (60:1 hexane/EtOAc) afforded **1a** (191 mg, 52%) as a colorless liquid. TLC: *R_f* 0.14 (14:1 hexane/EtOAc); IR (KBr film) 2936, 2223, 1599, 1490, 1375, 1313, 1170, 1061, 757, 690 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 7.54–7.51 (m, 2H), 7.40–7.32 (m, 3H), 3.97 (s, 3H), 2.13 (s, 3H); ¹³C-NMR (100 MHz, CDCl₃) δ 137.7, 132.3, 129.6, 128.6, 121.9, 99.3, 81.2, 62.5, 20.8; LRMS (ESI) *m/z* (rel int): 174 ([M + H]⁺, 100), 128 ([M – NOCH₃]⁺, 46); HRMS (ESI) *m/z* calcd for C₁₁H₁₁NO 173.0841, found 173.0840.

Representative Procedure for the Synthesis of 3-Methyl-5-phenyl-4-phenylethynylisoxazole (4a). To a stirring solution of K₃PO₄ (170 mg, 800 μmol), PPh₃AuNTf₂ (29.6 mg, 40.0 μmol) and Selectfluor (354 mg, 1.00 mmol) in MeCN (4 mL) were added (Z)-4-phenylbut-3-yn-2-one O-methylloxime (**1a**) (69.3 mg, 400 μmol), phenylacetylene (**3a**) (88.0 μL, 800 μmol) and H₂O (72.0 μL) sequentially under Ar atmosphere. The resulting suspension was stirred at rt for 17 h. After the completion of the reaction, the reaction mixture was diluted with H₂O (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried over anhydrous MgSO₄, filtered, and evaporated. Purification by column chromatography (35:1 hexane/EtOAc) afforded **4a**

(52 mg, 50%) as a yellow solid, **5** (12.6 mg, 20%) as a yellow solid, **6** (12.9 mg, 18%) as a yellow liquid, and **7a** (43.6 mg, 27%) as a white solid.

4a: mp 67–69 °C (from EtOAc); TLC: *R_f* 0.20 (14:1 hexane/EtOAc); ¹H-NMR (400 MHz, CDCl₃) δ 8.20–8.17 (m, 2H), 7.57–7.55 (m, 2H), 7.53–7.47 (m, 3H), 7.40–7.39 (m, 3H), 2.44 (s, 3H); ¹³C-NMR (100 MHz, CDCl₃) δ 168.4, 162.0, 131.7, 130.8, 129.1, 129.0, 128.7, 127.5, 126.4, 122.9, 99.3, 96.3, 78.9, 10.8; LRMS (ESI) *m/z* (rel int): 260 ([M + H]⁺, 84), 219 ([M – CH₂CN]⁺, 100); HRMS (ESI) *m/z* calcd for C₁₈H₁₃NO 259.0997, found 259.0997.

5: mp 76–78 °C (from EtOAc) (Lit.,²⁵ 65–68 °C); TLC: *R_f* 0.13 (14:1 hexane/EtOAc); ¹H-NMR (400 MHz, CDCl₃) δ 7.77–7.75 (m, 2H), 7.48–7.42 (m, 3H), 6.36 (s, 1H), 2.36 (s, 3H); ¹³C-NMR (100 MHz, CDCl₃) δ 169.9, 160.6, 130.2, 129.1, 127.8, 126.0, 100.4, 11.7; LRMS (ESI) *m/z* (rel int): 160 ([M + H]⁺, 100); HRMS (ESI) *m/z* calcd for C₁₀H₉NO 159.0684, found 159.0682.

6: TLC: *R_f* 0.26 (14:1 hexane/EtOAc); ¹H-NMR (400 MHz, CDCl₃) δ 7.82–7.79 (m, 2H), 7.51–7.47 (m, 2H), 7.45–7.41 (m, 1H), 2.37 (s, 3H); ¹³C-NMR (100 MHz, CDCl₃) δ 152.3 (d, *J_{C-F}* = 9.4 Hz), 152.1 (d, *J_{C-F}* = 7.1 Hz), 142.5 (d, *J_{C-F}* = 253.9 Hz), 130.1, 129.2, 126.2 (d, *J_{C-F}* = 5.0 Hz), 125.4 (d, *J_{C-F}* = 3.4 Hz), 8.9 (d, *J_{C-F}* = 2.9 Hz); ¹F-NMR (376 MHz, CDCl₃) δ –180.5 (s, 1F); LRMS (ESI) *m/z* (rel int): 178 ([M + H]⁺, 2), 105 ([M – NCCH₃CF]⁺, 100). HRMS (ESI) *m/z* calcd for C₁₀H₈FNO 177.0590, found 177.0590.

7a: mp 85–87 °C (from EtOAc) (Lit.,²⁶ 82–85 °C); TLC: *R_f* 0.44 (14:1 hexane/EtOAc); ¹H-NMR (400 MHz, CDCl₃) δ 7.55–7.52 (m, 4H), 7.40–7.32 (m, 6H); ¹³C-NMR (100 MHz, CDCl₃) δ 132.7, 129.4, 128.6, 122.0, 81.8, 74.1; LRMS (ESI) *m/z* (rel int): 405 ([2M + H]⁺, 8), 203 ([M + H]⁺, 28); HRMS (ESI) *m/z* calcd for C₁₆H₁₀ 202.0783, found 202.0784.

Synthesis of 4-(2-Chlorophenylethynyl)-3-methyl-5-phenylisoxazole (4b). 1-Chloro-2-ethynylbenzene (**3b**) was used. The suspension was stirred for 25 h at rt. Column chromatography (50:1 hexane/EtOAc) afforded **4b** (55.0 mg, 47%) as a yellow solid, **5** (13.8 mg, 22%) as a yellow solid, **6** (16.5 mg, 23%) as a yellow liquid, and **7b** (47 mg, 22%) as a white solid.

4b: mp 71–73 °C (from EtOAc); TLC: *R_f* 0.15 (14:1 hexane/EtOAc); ¹H-NMR (400 MHz, CDCl₃) δ 8.27–8.25 (m, 2H), 7.59–7.57 (m, 1H), 7.53–7.46 (m, 4H), 7.34–7.26 (m, 2H), 2.47 (s, 3H); ¹³C-NMR (100 MHz, CDCl₃) δ 168.8, 162.1, 135.9, 133.3, 130.9, 129.9, 129.7, 129.0, 127.3, 126.8, 126.6, 123.0, 99.1, 93.2, 84.1, 10.8; LRMS (ESI) *m/z* (rel int): 294 ([M + H]⁺, 100), 253 ([M – CH₂CN]⁺, 53); HRMS (ESI) *m/z* calcd for C₁₈H₁₂ClNO 293.0607, found 293.0608.

7b: mp 142–144 °C (from EtOAc) (Lit.,²⁷ 138–140 °C); TLC: *R_f* 0.39 (14:1 hexane/EtOAc); ¹H-NMR (400 MHz, CDCl₃) δ 7.58 (ddd, 2H, *J* = 8.0, 1.6, 0.4 Hz), 7.42 (ddd, 2H, *J* = 8.0, 1.6, 0.4 Hz), 7.31 (td, 2H, *J* = 8.0, 1.6 Hz), 7.24 (td, 2H, *J* = 8.0, 1.6 Hz); ¹³C-NMR (100 MHz, CDCl₃) δ 137.2, 134.6, 130.5, 129.7, 126.8, 122.0, 79.6, 78.6; LRMS (ESI) *m/z* (rel int): 271 ([M + H]⁺, 100); HRMS (ESI) *m/z* calcd for C₁₆H₈Cl₂ 270.0003, found 270.0004.

Synthesis of 4-(3-Chlorophenylethynyl)-3-methyl-5-phenylisoxazole (4c). 1-Chloro-3-ethynylbenzene (**3c**) was used. The suspension was stirred for 17 h at rt. Column chromatography (40:1 hexane/EtOAc) afforded **4c** (40.0 mg, 34%) as a yellow solid, **5** (19.0 mg, 30%) as a yellow solid, **6** (15.0 mg, 21%) as a yellow liquid, and **7c** (23.0 mg, 11%) as a white solid.

4c: mp 81–83 °C (from EtOAc); TLC: R_f 0.25 (14:1 hexane/EtOAc); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 8.16–8.14 (m, 2H), 7.54–7.48 (m, 4H), 7.34 (dt, 1H, $J = 7.6, 2.0$ Hz), 7.38–7.30 (m, 2H), 2.43 (s, 3H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 168.9, 162.0, 134.6, 131.5, 131.0, 130.0, 129.8, 129.2, 129.1, 127.4, 126.5, 124.6, 98.8, 94.7, 80.1, 10.8; LRMS (ESI) m/z (rel int): 294 ($[\text{M} + \text{H}]^+$, 100), 253 ($[\text{M} - \text{CH}_2\text{CN}]^+$, 53); HRMS (ESI) m/z calcd for $\text{C}_{18}\text{H}_{12}\text{ClNO}$ 293.0607, found 293.0610.

7c: mp 78–80 °C (from EtOAc) (Lit.,²⁶ 73 °C); TLC: R_f 0.5 (14:1 hexane/EtOAc); IR (KBr film) 3066, 1583, 1557, 1470, 1455, 1401, 1261, 1164, 1093, 1076, 907, 890, 850, 793, 776, 675, 522 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.51 (m, 2H), 7.41 (d, 2H, $J = 8.0$ Hz), 7.38–7.32 (m, 2H), 7.28 (t, 2H, $J = 8.0$ Hz); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 134.6, 132.5, 130.9, 129.9, 129.4, 123.5, 80.8, 74.9.

Synthesis of 4-(3,5-Difluorophenylethynyl)-3-methyl-5-phenylisoxazole (4d). K_3PO_4 (85.0 mg, 400 μmol), $\text{PPh}_3\text{AuNTf}_2$ (14.8 mg, 20.0 μmol), Selectfluor (177 mg, 500 μmol), MeCN (2 mL), (*Z*)-4-phenylbut-3-yn-2-one *O*-methyloxime (**1a**) (34.6 mg, 200 μmol), 1-ethynyl-3,5-difluorobenzene (**3d**) (48.0 μL , 400 μmol) and H_2O (36.0 μL) were used. The suspension was stirred for 22 h at rt. Column chromatography (40:1 hexane/EtOAc) afforded **4d** (26.8 mg, 45%) as a yellow solid, **5** (6.8 mg, 21%) as a yellow solid, **6** (9.2 mg, 26%) as a yellow liquid, and **7d** (17.0 mg, 16%) as a white solid.

4d: mp 99–101 °C (from EtOAc); TLC: R_f 0.24 (14:1 hexane/EtOAc); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 8.14–8.12 (m, 2H), 7.54–7.48 (m, 3H), 7.07–7.04 (m, 2H), 6.86 (tt, 1H, $J = 8.8, 2.0$ Hz), 2.43 (s, 3H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 169.3, 163.0 (dd, $J_{\text{C-F}} = 243.5, 11.7$ Hz), 132.3, 131.1, 129.6, 129.2, 128.6, 127.3, 126.5, 114.7 (dd, $J_{\text{C-F}} = 19.0, 7.2$ Hz), 105.1 (t, $J_{\text{C-F}} = 25.6$ Hz), 81.0, 62.5, 20.8; LRMS (ESI) m/z (rel int): 296 ($[\text{M} + \text{H}]^+$, 100), 255 ($[\text{M} - \text{CH}_2\text{CN}]^+$, 35); HRMS (ESI) m/z calcd for $\text{C}_{18}\text{H}_{11}\text{F}_2\text{NO}$ 295.0809, found 295.0809.

7d: mp 87–89 °C (from EtOAc); TLC: R_f 0.62 (14:1 hexane/EtOAc); IR (KBr film) 3100, 1610, 1583, 1456, 1402, 1094, 1077, 960, 890, 794, 681 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.07–7.02 (m, 4H), 6.90–6.84 (tt, 2H, $J = 8.8, 2.0$ Hz); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 162.9 (dd, $J_{\text{C-F}} = 250, 13.5$ Hz), 124.1 (t, $J_{\text{C-F}} = 11.9$ Hz), 115.8 (dd, $J_{\text{C-F}} = 19.1, 8.0$ Hz), 106.2 (t, $J_{\text{C-F}} = 25.4$ Hz), 80.2 (d, $J_{\text{C-F}} = 4.0$ Hz), 75.2; $^{19}\text{F-NMR}$ (376 MHz, CDCl_3) δ –108.7 (t, 4F, $J = 8.3$ Hz).

Synthesis of 4-(3-Fluorophenylethynyl)-3-methyl-5-phenylisoxazole (4e). K_3PO_4 (85.0 mg, 400 μmol), $\text{PPh}_3\text{AuNTf}_2$ (14.8 mg, 20.0 μmol), Selectfluor (177 mg, 500 μmol), MeCN (2 mL), (*Z*)-4-phenylbut-3-yn-2-one *O*-methyloxime (**1a**)

(34.6 mg, 200 μmol), 1-ethynyl-3-fluorobenzene (**3e**) (46.0 μL , 400 μmol) and H_2O (36.0 μL) were used. The suspension was stirred for 20 h at 60 °C. Column chromatography (40:1 hexane/EtOAc) afforded **4e** (23.0 mg, 41%) as a yellow solid, **5** (8.7 mg, 27%) as a yellow solid, **6** (9.1 mg, 26%) as a yellow liquid, and **7e** (18.2 mg, 19%) as a white solid.

4e: mp 79–81 °C (from EtOAc); TLC: R_f 0.22 (14:1 hexane/EtOAc); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 8.17–8.14 (m, 2H), 7.54–7.47 (m, 3H), 7.39–7.32 (m, 2H), 7.27–7.23 (m, 1H), 7.12–7.07 (m, 1H), 2.44 (s, 3H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 168.9, 162.7 (d, $J_{\text{C-F}} = 246.0$ Hz), 162.0, 131.0, 130.4 (d, $J_{\text{C-F}} = 8.7$ Hz), 129.1, 127.6 (d, $J_{\text{C-F}} = 2.9$ Hz), 127.4, 126.5, 124.7 (d, $J_{\text{C-F}} = 9.4$ Hz), 118.5 (d, $J_{\text{C-F}} = 22.9$ Hz), 116.4 (d, $J_{\text{C-F}} = 21.6$ Hz), 98.9, 94.9, 79.9, 10.8. LRMS (ESI) m/z (rel int): 278 ($[\text{M} + \text{H}]^+$, 100), 237 ($[\text{M} - \text{CH}_2\text{CN}]^+$, 62); HRMS (ESI) m/z calcd for $\text{C}_{18}\text{H}_{12}\text{FNO}$ 277.0903, found 277.0903.

7e: mp 122–124 °C (from EtOAc) (Lit.,²⁸ 122–123 °C); TLC: R_f 0.40 (14:1 hexane/EtOAc); IR (KBr film) 3030, 1604, 1583, 1482, 1461, 1428, 1265, 1130, 1078, 933, 868, 782 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.33–7.30 (m, 4H), 7.21–7.20 (m, 2H), 7.12–7.07 (m, 2H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 162.5 (d, $J_{\text{C-F}} = 240.8$ Hz), 130.4 (d, $J_{\text{C-F}} = 8.7$ Hz), 128.7 (d, $J_{\text{C-F}} = 3.6$ Hz), 123.6 (d, $J_{\text{C-F}} = 9.4$ Hz), 119.5 (d, $J_{\text{C-F}} = 23.0$ Hz), 117.1 (d, $J_{\text{C-F}} = 21.6$ Hz), 80.8 (d, $J_{\text{C-F}} = 2.8$ Hz), 74.6; $^{19}\text{F-NMR}$ (376 MHz, CDCl_3) δ –112.2––112.3 (m, 2F).

Synthesis of 4-(2,4-Difluorophenylethynyl)-3-methyl-5-phenylisoxazole (4f). K_3PO_4 (85.0 mg, 400 μmol), $\text{PPh}_3\text{AuNTf}_2$ (14.8 mg, 20 μmol), Selectfluor (177 mg, 500 μmol), MeCN (2 mL), (*Z*)-4-phenylbut-3-yn-2-one *O*-methyloxime (**1a**) (34.6 mg, 200 μmol), 1-ethynyl-2,4-difluorobenzene (**3f**) (55.0 μL , 400 μmol) and H_2O (36.0 μL) were used. The suspension was stirred for 24 h at 60 °C. Column chromatography (40:1 hexane/EtOAc) afforded **4f** (17.0 mg, 30%) as a yellow solid, **5** (2.7 mg, 8%) as a yellow solid, **6** (8.4 mg, 24%) as a yellow liquid, and **7f** (9.1 mg, 8%) as a yellow solid.

4f: mp 87–89 °C (from EtOAc); TLC: R_f 0.36 (14:1 hexane/EtOAc); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 8.21–8.18 (m, 2H), 7.54–7.48 (m, 4H), 6.95–6.90 (m, 2H), 2.44 (s, 3H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 168.9, 164.5 (d, $J_{\text{C-F}} = 11.2$ Hz), 163.3 (dd, $J_{\text{C-F}} = 240.0, 19.0$ Hz), 161.9, 134.1 (dd, $J_{\text{C-F}} = 9.9, 2.8$ Hz), 131.0, 129.1, 127.3, 126.5, 118.8, 112.0 (dd, $J_{\text{C-F}} = 21.8, 3.5$ Hz), 104.7 (t, $J_{\text{C-F}} = 25.0$ Hz), 98.9, 88.7, 83.9, 10.8; LRMS (ESI) m/z (rel int): 296 ($[\text{M} + \text{H}]^+$, 100), 255 ($[\text{M} - \text{CH}_2\text{CN}]^+$, 63); HRMS (ESI) m/z calcd for $\text{C}_{18}\text{H}_{11}\text{F}_2\text{NO}$ 295.0809, found 295.0811.

7f: mp 168–170 °C (from EtOAc) (Lit.,²⁹ 187–188 °C); TLC: R_f 0.48 (14:1 hexane/EtOAc); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.53–7.48 (m, 2H), 6.91–6.84 (m, 4H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 164.6 (dd, $J_{\text{C-F}} = 205.0, 11.0$ Hz), 163.7 (dd, $J_{\text{C-F}} = 202.0, 9.1$ Hz), 135.5 (dd, $J_{\text{C-F}} = 7.9, 1.8$ Hz), 112.2 (dd, $J_{\text{C-F}} = 17.6, 3.0$ Hz), 107.0 (dd, $J_{\text{C-F}} = 12.8, 3.7$ Hz), 104.8 (t, $J_{\text{C-F}} = 20.6$ Hz), 78.3, 75.1; LRMS (ESI) m/z (rel int): 275 ($[\text{M} + \text{H}]^+$, 100); HRMS (ESI) m/z calcd for

$C_{16}H_6F_4$ 274.0406, found 274.0404.

Synthesis of 4-(2-Fluorophenylethynyl)-3-methyl-5-phenylisoxazole (4g). 1-Ethynyl-2-fluorobenzene (**3g**) was used. The suspension was stirred for 20 h at rt. Column chromatography (50:1 hexane/EtOAc) afforded **4g** (40.3 mg, 36%) as a yellow solid, **5** (11.9 mg, 19%) as a yellow solid, **6** (3.7 mg, 5%) as a yellow liquid, and **7g** (49.9 mg, 26%) as a yellow solid.

4g: mp 68–70 °C (from EtOAc); TLC: R_f 0.33 (14:1 hexane/EtOAc); 1H -NMR (400 MHz, $CDCl_3$) δ 8.23–8.20 (m, 2H), 7.55–7.46 (m, 4H), 7.40–7.34 (m, 1H), 7.17 (td, 1H, $J = 7.6, 1.2$ Hz), 7.16–7.13 (m, 1H), 2.45 (s, 3H); ^{13}C -NMR (100 MHz, $CDCl_3$) δ 168.8, 162.9 (d, $J_{C-F} = 250.3$ Hz), 162.0, 133.2, 130.9, 130.7 (d, $J_{C-F} = 7.6$ Hz), 129.1, 127.4, 126.5, 124.3 (d, $J_{C-F} = 3.1$ Hz), 115.9 (d, $J_{C-F} = 20.6$ Hz), 111.7 (d, $J_{C-F} = 16.0$ Hz), 99.1, 89.9, 84.1 (d, $J_{C-F} = 3.8$ Hz), 10.8; LRMS (ESI) m/z (rel int): 278 ($[M + H]^+$, 100), 236 ($[M - CH_3CN]^+$, 80); HRMS (ESI) m/z calcd for $C_{18}H_{12}FNO$ 277.0903, found 277.0904.

7g: mp 144–146 °C (from EtOAc); TLC: R_f 0.42 (14:1 hexane/EtOAc); 1H -NMR (400 MHz, $CDCl_3$) δ 7.52 (td, 2H, $J = 7.6, 2.0$ Hz), 7.39–7.34 (m, 2H), 7.13 (td, 2H, $J = 7.6, 1.2$ Hz), 7.11–7.08 (m, 2H); ^{13}C -NMR (100 MHz, $CDCl_3$) δ 164.0 (d, $J_{C-F} = 251.8$ Hz), 134.5, 131.3 (d, $J_{C-F} = 7.6$ Hz), 124.3 (d, $J_{C-F} = 3.1$ Hz), 115.9 (d, $J_{C-F} = 20.6$ Hz), 110.7 (d, $J_{C-F} = 15.3$ Hz), 78.6, 76.1; LRMS (ESI) m/z (rel int): 477 ($[2M + H]^+$, 6), 239 ($[M + H]^+$, 100). HRMS (ESI) m/z calcd for $C_{16}H_8F_2$ 238.0594, found 238.0591.

Synthesis of 4-(3,5-Bis(trifluoromethyl)phenylethynyl)-3-methyl-5-phenylisoxazole (4h). 1-Ethynyl-3,5-bis(trifluoromethyl)benzene (**3h**) was used. The suspension was stirred for 18 h at rt. Column chromatography (50:1 hexane/EtOAc) afforded **4h** (48.2 mg, 30%) as a white solid, **5** (12.4 mg, 19%) as a yellow solid, **6** (10 mg, 14%) as a yellow liquid, and **7h** (36.2 mg, 10%) as a brown solid.

4h: mp 124–126 °C (from EtOAc); TLC: R_f 0.19 (14:1 hexane/EtOAc); 1H -NMR (400 MHz, $CDCl_3$) δ 8.14–8.11 (m, 2H), 7.95 (s, 2H), 7.87 (s, 1H), 7.57–7.48 (m, 3H), 2.46 (s, 3H); ^{13}C -NMR (100 MHz, $CDCl_3$) δ 169.8, 161.9, 132.3 (q, $J_{C-F} = 33.0$ Hz), 131.5 (d, $J_{C-F} = 3.5$ Hz), 131.3, 129.3, 127.1, 126.6, 125.3, 123.1 (q, $J_{C-F} = 270.0$ Hz), 122.3 (m), 98.1, 92.9, 82.6, 10.8; LRMS (ESI) m/z (rel int): 396 ($[M + H]^+$, 91); HRMS (ESI) m/z calcd for $C_{20}H_{11}F_6NO$ 395.0745, found 395.0746.

7h: mp 146–148 °C (from EtOAc) (Lit.,³⁰ 158.7–161.0 °C); TLC: R_f 0.55 (14:1 hexane/EtOAc); IR (KBr film) 3095, 2219, 1615, 1463, 1281, 1262, 1167, 1107, 1022, 899, 801, 699, 684 cm^{-1} ; 1H -NMR (400 MHz, $CDCl_3$) δ 7.55–7.52 (m, 4H), 7.40–7.32 (m, 2H); ^{13}C -NMR (100 MHz, $CDCl_3$) δ 132.5 (q, $J_{C-F} = 33.7$ Hz), 132.6 (d, $J_{C-F} = 2.9$ Hz), 123.8, 123.3 (t, $J_{C-F} = 3.6$ Hz), 121.6, 118.8, 79.9, 76.3; ^{19}F -NMR (376 MHz, $CDCl_3$): δ –63.3 (s, 12F).

Synthesis of 4-(2-(3-Methyl-5-phenylisoxazol-4-yl)ethynyl)benzonitrile (4i). 4-Ethynylbenzonitrile (**3i**) was used. The suspension was stirred for 40 h at rt. Column chromatography (40:1 hexane/EtOAc) afforded **4i** (36.7 mg, 32%) as a yellow solid, **5** (10 mg, 16%) as a yellow solid, **6** (15.4 mg,

22%) as a yellow liquid.

4i: mp 138–140 °C (from EtOAc); TLC: R_f 0.16 (14:1 hexane/EtOAc); 1H -NMR (400 MHz, $CDCl_3$) δ 8.15–8.13 (m, 2H), 7.70–7.67 (m, 2H), 7.64–7.61 (m, 2H), 7.55–7.50 (m, 3H), 2.44 (s, 3H); ^{13}C -NMR (100 MHz, $CDCl_3$) δ 169.5, 161.8, 132.4, 132.1, 131.2, 129.2, 127.8, 127.2, 126.6, 118.5, 112.3, 98.5, 94.4, 83.4, 10.8; LRMS (ESI) m/z (rel int): 285 ($[M + H]^+$, 92), 244 ($[M - CH_2CN]^+$, 32); HRMS (ESI) m/z calcd for $C_{19}H_{12}N_2O$ 284.0950, found 284.0950.

Synthesis of 3-Methyl-4-(4-nitrophenylethynyl)-5-phenylisoxazole (4j). 1-Ethynyl-4-nitrobenzene (**3j**) was used. The suspension was stirred for 19 h at rt. Column chromatography (40:1 hexane/EtOAc) afforded **4j** (44 mg, 36%) as a white solid, **5** (10 mg, 16%) as a yellow solid, **6** (16.7 mg, 24%) as a yellow liquid.

4j: mp 144–146 °C (from EtOAc); TLC: R_f 0.15 (14:1 hexane/EtOAc); 1H -NMR (400 MHz, $CDCl_3$) δ 8.27 (dt, 2H, $J = 6.8, 2.0$ Hz), 8.16–8.13 (m, 2H), 7.69 (dt, 2H, $J = 6.8, 2.0$ Hz), 7.54–7.52 (m, 3H), 2.46 (s, 3H); ^{13}C -NMR (100 MHz, $CDCl_3$) δ 169.7, 161.8, 147.5, 132.4, 131.3, 129.7, 129.2, 127.2, 126.6, 124.0, 98.4, 94.2, 84.3, 10.8; LRMS (ESI) m/z (rel int): 305 ($[M + H]^+$, 77), 264 ($[M - CH_2CN]^+$, 100); HRMS (ESI) m/z calcd for $C_{18}H_{12}F_2O_3$ 304.0848, found 304.0848.

Synthesis of 4-(3,4-Dichlorophenylethynyl)-3-methyl-5-phenylisoxazole (4k). 1,2-dichloro-4-ethynylbenzene (**3k**) was used. The suspension was stirred for 17 h at 60 °C. Column chromatography (40:1 hexane/EtOAc) afforded **4k** (45.0 mg, 34%) as a yellow solid, **5** (9.7 mg, 15%) as a yellow solid, **6** (34.5 mg, 48%) as a yellow liquid, and **7k** (38.0 mg, 14%) as a yellow solid.

4k: mp 135–137 °C (from EtOAc); TLC: R_f 0.30 (14:1 hexane/EtOAc); 1H -NMR (400 MHz, $CDCl_3$) δ 8.14–8.12 (m, 2H), 7.63 (d, 1H, $J = 2.0$ Hz), 7.54–7.49 (m, 3H), 7.47 (d, 1H, $J = 8.4$ Hz), 7.37 (dd, 1H, $J = 8.4, 2.0$ Hz), 2.43 (s, 3H); ^{13}C -NMR (100 MHz, $CDCl_3$) δ 168.9, 161.7, 133.3, 133.0, 132.8, 131.6, 130.9, 130.6, 129.0, 127.1, 126.3, 122.6, 98.5, 93.6, 80.8, 10.6; LRMS (ESI) m/z (rel int): 328 ($[M + H]^+$, 100); HRMS (ESI) m/z calcd for $C_{18}H_{11}Cl_2NO$ 327.0218, found 327.0218.

7k: mp 194–196 °C (from EtOAc); TLC: R_f 0.50 (14:1 hexane/EtOAc); IR (KBr film) 3405, 2306, 1655, 1261, 1026, 999, 827, 766, 669 cm^{-1} ; 1H -NMR (400 MHz, $CDCl_3$) δ 7.61 (d, 2H, $J = 2.0$ Hz), 7.43 (d, 2H, $J = 8.4$ Hz), 7.35 (dd, 2H, $J = 8.4, 2.0$ Hz); ^{13}C -NMR (500 MHz, CD_3OD) δ 131.2, 130.9, 128.7, 95.0, 68.0, 66.1, 65.8, 53.6.

Synthesis of 3-Methyl-4-(4-methylphenylethynyl)-5-phenylisoxazole (4l). 1-Ethynyl-4-methylbenzene (**3l**) and K_3PO_4 were used. The suspension was stirred for 19 h at rt. Column chromatography (40:1 hexane/EtOAc) afforded **4l** (26.8 mg, 25%) as a yellow solid, **5** (32.2 mg, 51%) as a yellow solid, **6** (10.0 mg, 14%) as a yellow liquid, and **7l** (36.7 mg, 20%) as a yellow solid.

4l: mp 73–75 °C (from EtOAc); TLC: R_f 0.20 (14:1 hexane/EtOAc); 1H -NMR (400 MHz, $CDCl_3$) δ 8.19–8.17 (m, 2H), 7.52–7.47 (m, 3H), 7.45 (d, 2H, $J = 8.0$ Hz), 7.20 (d, 2H, $J = 8.0$ Hz), 2.43 (s, 3H), 2.40 (s, 3H); ^{13}C -NMR

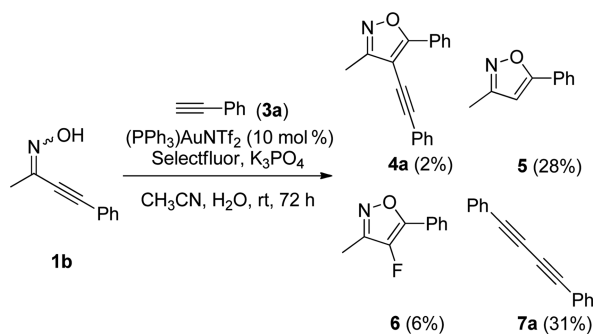
(100 MHz, CDCl₃) δ 168.2, 162.0, 139.2, 131.6, 130.7, 129.5, 129.0, 127.6, 126.4, 119.9, 99.5, 96.5, 78.2, 21.8, 10.8; LRMS (ESI) m/z (rel int): 274 ([M + H]⁺, 89), 233 ([M - CH₂CN]⁺, 100); HRMS (ESI) m/z calcd for C₁₉H₁₅NO 273.1154, found 273.1158.

7l: mp 140–142 °C (from EtOAc) (Lit.,²⁷ 137–138 °C); TLC: R_f 0.45 (14:1 hexane/EtOAc); ¹H-NMR (400 MHz, CDCl₃) δ 7.43–7.41 (m, 4H), 7.15–7.13 (m, 4H), 2.37 (s, 6H); ¹³C-NMR (100 MHz, CDCl₃) δ 139.7, 132.6, 129.4, 119.0, 81.8, 73.7, 21.8; LRMS (ESI) m/z (rel int): 231 ([M + H]⁺, 100); HRMS (ESI) m/z calcd for C₁₈H₁₄ 230.1096, found 230.1096.

Results and Discussion

Recently, α,β -acetylenic oximes of hydroxylamine have been cyclized to the corresponding isoxazoles in the presence of gold catalyst.¹⁸ Thus, we initially thought that the α,β -acetylenic oximes of hydroxylamine could serve as substrates for a one-pot cyclization–oxidative cross-coupling reaction. However, when 4-phenylbut-3-yn-2-one oxime (**1b**) was used as a substrate, it provided mainly isoxazole **5** from a cyclization–protodeauration and a trace of oxidative cross-coupling product **4a** (Scheme 2). (*Z*)-4-Phenylbut-3-yn-2-one oxime was equilibrated with (*E*) at room temperature and cyclized into the corresponding isoxazole even without gold catalyst. This uncatalyzed cyclization was rapid and was a potential problem for one-pot cyclization–oxidative cross-coupling reaction because it could not generate gold-complexed intermediate **2**. Therefore, we considered *O*-methyloximes as substrates, which were not cyclized spontaneously at room temperature and could be readily synthesized from commercially available ynones and methoxyamine hydrochloride in the presence of sodium acetate at room temperature using ethanol as the solvent. A mixture of *E-Z* isomers sometimes resulted and the desired *Z* isomer could be separated by column chromatography.

With the desired (*Z*)-4-phenylbut-3-yn-2-one *O*-methyloxime (**1a**) in hand, we began to investigate various gold catalysts and combinations with silver salts: (PPh₃)AuCl, (PCy₃)AuCl, (PhO)₃PAuCl, AuCl, AuCl₃, (PPh₃)AuNTf₂, (IPr)AuCl (IPr = *N,N'*-bis(2,6-diisopropylphenyl)imidazol-2-ylidene), along with AgOTf, AgNTf₂, or AgSbF₆ (Table



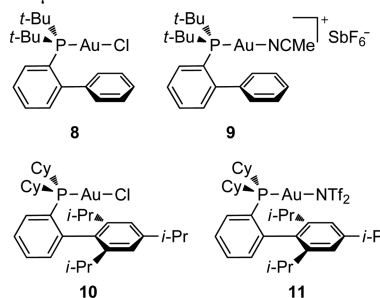
Scheme 2. Gold-catalyzed cyclization–oxidative alkylation and cyclization–fluorination of oxime **1b**.

1). To our delight, most Au catalysts produced cyclization–oxidative cross-coupling product **4a** except (IPr)AuCl (Table 1, entry 18). Under the standard reaction conditions, (PPh₃)AuCl afforded **4a** in 29% yield as well as cyclized isoxazole **5**, fluorinated isoxazole **6**, and alkyne dimer **7**

Table 1. Optimization of gold-catalyzed cyclization–oxidative alkylation and cyclization–fluorination of (*Z*)-2-alkynone *O*-methyloxime **1a**^a

Entry	Catalyst/Additive	<i>T</i> (°C)	Time (h)	Yield (%) ^b			
				4a	5	6	7 ^c
1 ^d	(PPh ₃)AuCl	rt	17	29	1	20	19
2 ^d	(PPh ₃)AuCl/AgOTf	90	21	15	52	20	7
3	(PPh ₃)AuCl/AgSbF ₆	60	15	23	13	36	5
4	(PCy ₃)AuCl	60	16	15	25	28	8
5	(PCy ₃)AuCl/AgNTf ₂	60	15	7	39	8	4
6	(PEt ₃)AuCl	rt	22	35	19	33	12
7	(PEt ₃)AuCl/AgNTf ₂	rt	18	22	25	46	15
8	(PMe ₃)AuCl	60	23	28	19	10	8
9	8	rt	17	19	22	34	19
10	8 /AgNTf ₂	60	15	2	25	10	4
11	9	90	24	9	51	15	6
12	10	60	21	30	40	21	13
13	11	90	20	20	29	9	14
14	(PhO) ₃ PAuCl	rt	18	27	7	30	15
15	(PhO) ₃ PAuNTf ₂	rt	20	18	19	28	12
16 ^d	AuCl	rt	95	2	22	2	2
17 ^d	AuCl ₃	60	63	16	2	21	8
18 ^d	(IPr)AuCl	60	15	0	0	19	0
19	(PPh ₃)AuNTf ₂	rt	17	50	20	18	27
20 ^d	(PPh ₃)AuNTf ₂	rt	17	42	28	4	33
21 ^e	(PPh ₃)AuNTf ₂	rt	17	19	2	5	16

^aReaction conditions: **1a** (400 μ mol), **3a** (800 μ mol), Au-catalyst (40.0 μ mol), Ag-salt (40.0 μ mol), Selectfluor (1.00 mmol), K₃PO₄ (80.0 μ mol), H₂O (4.00 mmol), CH₃CN (4 mL). ^bIsolated yields. ^cIsolated yields based on **3a**. ^d600 μ mol of **3a** was used. ^e1.20 mmol of **3a** was used.

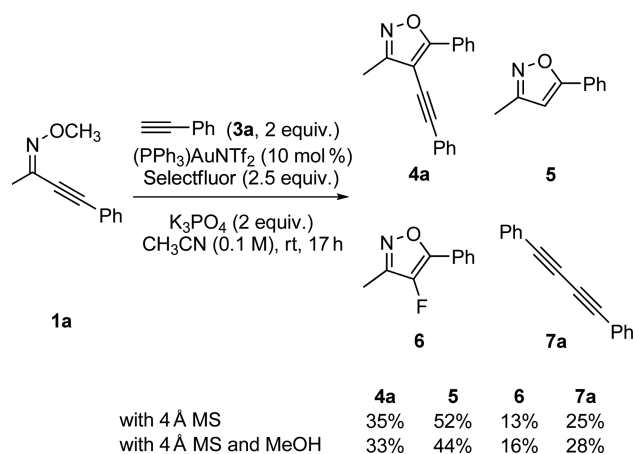


(Table 1, entry 1). Notably, no homocoupling product of **1a** was observed. The addition of AgOTf or AgSbF₆ made the reaction slower at room temperature and increased the formation of cyclized isoxazole **5** (entries 2 and 3). The gold(I) complex (PEt₃)AuCl afforded **4a** in 35% yield with increased formation of **5** (entry 6). Among the gold(I) complexes **8–11** bearing bulky biphenyl-based phosphine ligands, which have been shown to be excellent ligands for Pd-catalyzed reactions,¹⁹ only **10** yielded comparable results and produced **4a** and **5** in 30% and 40% yields, respectively (entry 12). After extensive optimization studies, (PPh₃)AuNTf₂ (10 mol %) was identified as the best catalyst for one-pot cyclization–oxidative cross-coupling reaction (entry 19). Under this condition, cross-coupling product **4a** and fluorinated product **6** were isolated in 50% and 18% yield, respectively. Furthermore, when 2 equivalents of alkyne **3a** were used, a better result was obtained than when 1.5 or 3 equivalents of alkyne **3a** were used (entry 19 vs. entries 20 and 21).

The role of H₂O in gold-catalyzed reactions is still unclear and under investigation. Recently, it has been reported that the addition of H₂O enhances the solubility of the reagents such as base and Selectfluor, which are poorly soluble in CH₃CN.²⁰ Indeed, when the reaction was carried out in the presence of 4 Å molecular sieves without the addition of H₂O, **4a** was obtained in decreased yield (35%, Scheme 3). Using MeOH instead of H₂O did not improve the yield of **4a** (33%, Scheme 3).

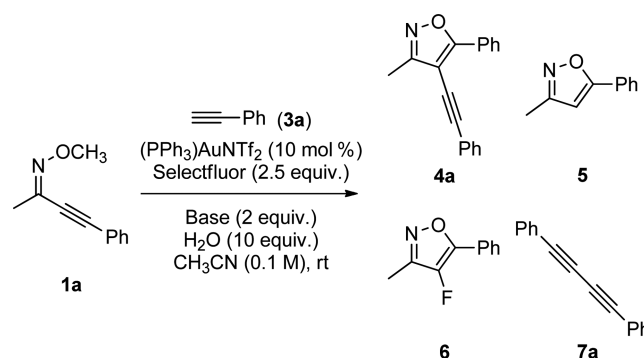
The base effect has also been extensively studied as shown in Table 2. Increasing the amount of potassium phosphate tribasic did not improve the yield of **4a** (3 equiv., entry 2). Interestingly, the reactions of carbonate bases provided comparable results, except that of Cs₂CO₃, which was sluggish even at 60 °C and afforded **5** as a sole product in 28% yield (entries 4–9). Meanwhile, usage of amine bases such as Et₃N and 2,6-lutidine increased the formation of **5** instead of **4a** (entries 12 and 13).

Selectfluor has been known as the best external oxidant for gold-catalyzed cross-coupling reactions.²¹ When the



Scheme 3. Gold-catalyzed cyclization–oxidative alkynylation and cyclization–fluorination in the absence of H₂O.

Table 2. Base effect on the cyclization–oxidative alkynylation and cyclization–fluorination reactions of (*Z*)-2-alkynone *O*-methyloxime **1a**^a

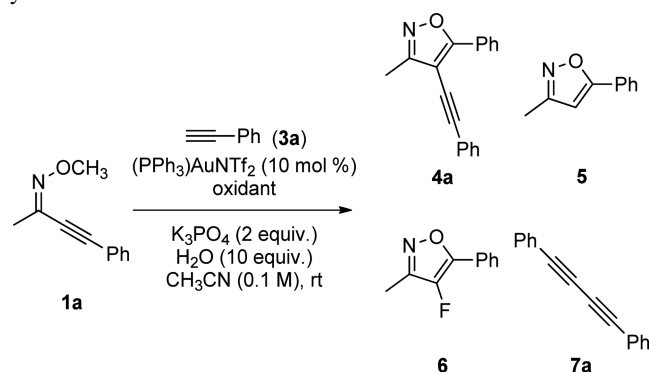


Entry	Bases	Time (h)	Yield (%) ^b			
			4a	5	6	7a ^c
1	K ₃ PO ₄	17	50	20	18	27
2 ^d	K ₃ PO ₄	15	38	15	17	17
3	Na ₃ PO ₄	26	43	12	31	28
4 ^e	Cs ₂ CO ₃	17	0	28	0	0
5	K ₂ CO ₃	27	43	16	21	8
6	Na ₂ CO ₃	22	42	8	30	30
7	Li ₂ CO ₃	17	47	13	10	40
8	KHCO ₃	42	18	31	15	16
9	NaHCO ₃	20	44	15	17	31
10	KOH	23	40	31	17	13
11	NaOH	18	37	51	16	20
12	Et ₃ N	19	30	59	1	16
13	2,6-Lutidine	20	10	85	2	6

^aReaction conditions: **1a** (400 μmol), **3a** (800 μmol), Au-catalyst (40.0 μmol), Selectfluor (1.00 mmol), Base (800 μmol), H₂O (4.00 mmol), CH₃CN (4 mL). ^bIsolated yields. ^cIsolated yields based on **3a**. ^d3 equivalents of base were used. ^eThe reaction was carried out at 60 °C and 72% of starting **1a** was recovered.

reaction was carried out in the presence of 1.5 equivalents of Selectfluor, **4a** was isolated in 15% yield and 61% of starting (*Z*)-2-alkynone *O*-methyloxime **1a** was recovered after 2 days (Table 3, entry 1). The best yield was observed with 2.5 equivalents of Selectfluor (Table 1, entry 19). Using more than 2.5 equivalents of Selectfluor decreased the yield of **4a** from 50% to 48% (Table 3, entry 3). Meanwhile, when the amount of Selectfluor was increased from 1.5 to 3.0 equivalents, the formation of fluorinated isoxazole **6** increased from 3% to 20%. As expected, other oxidants such as PhI(OAc)₂, oxone, and *t*-BuOOH did not generate fluorinated isoxazole **6** (entries 4–7), neither did *N*-fluorobenzene-sulfonimide (NFSI), even carrying fluorine source (entries 8 and 9). The reactions of these oxidants were very sluggish in the formation of **4a** even at 80 °C. Interestingly, oxone afforded cyclized isoxazole **5** in 71% yield as a major product at 60 °C (entry 6).

Current cyclization–oxidative alkynylation and cyclization–fluorination reactions showed profound concentration effect and solvent effect on the yield of the desired product. Upon increasing the reaction concentration from 0.1 to 0.5 M (Table 1, entry 19 vs. Table 4, entry 1), the yield of **4a** decreased

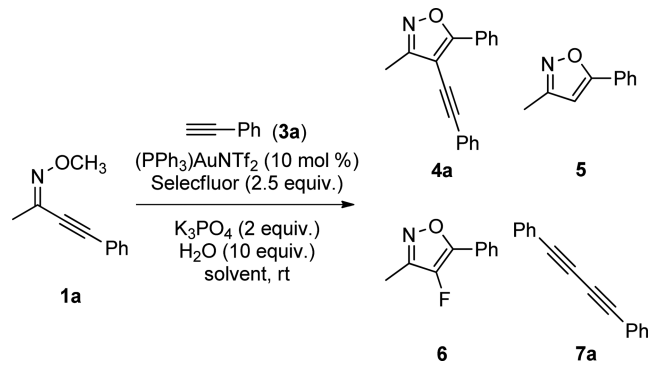
Table 3. Oxidant effect on the cyclization–oxidative alkylation and cyclization–fluorination reactions of (*Z*)-2-alkynone *O*-methyloxime **1a**^a

Entry	Oxidants/ Equivalents	Time (h)	Yield (%) ^b				
			4a	5	6	7a ^c	1a ^d
1	Selectfluor/1.5	48	15	21	3	12	61
2	Selectfluor/2.0	45	36	39	8	19	17
3	Selectfluor/3.0	19	48	31	20	22	0
4	PhI(OAc) ₂ /2.5	19	2	4	0	6	77
5 ^e	PhI(OAc) ₂ /2.5	19	0	14	0	9	80
6	Oxone/2.5	16	6	71	0	4	0
7 ^e	<i>t</i> -BuOOH/2.5	18	no reaction				
8 ^f	NFSI/2.5	19	13	0	0	11	85
9 ^e	NFSI/2.5	30	15	7	0	8	79

^aReaction conditions: **1a** (400 μmol), **3a** (800 μmol), (PPh₃)AuNTf₂ (40.0 μmol), oxidant, K₃PO₄ (800 μmol), H₂O (4.00 mmol), CH₃CN (4 mL). ^bIsolated yields. ^cIsolated yields based on **3a**. ^d% of recovered **1a**. ^e80 °C. ^f60 °C

from 50% to 8%, and 30% of starting (*Z*)-2-alkynone *O*-methyloxime **1a** was recovered. In contrast, upon lowering the reaction concentration from 0.1 to 0.02 M (Table 1, entry 19 vs. Table 4, entry 2), **4a** was isolated in 40% yield after the extended reaction time (93 h). Alternative solvent such as DMF was less effective even at 80 °C, leading to the formation of cyclized isoxazole **5** in 43% as a major product and **4a** in 16% (entry 3). In less polar solvent 1,4-dioxane, the yield was far below the predictions: only 2% yield of **4a** was obtained at 60 °C (entry 4). In particular, no conversion was observed in the relatively non-polar solvents, DCE and toluene (entries 5 and 6).

Under the standard reaction conditions, the reaction scope with respect to various alkyne coupling partners was probed as shown in Table 5. The reaction proceeded smoothly with alkynes bearing electron-withdrawing groups on the phenyl ring (entries 1–10). The reaction with alkyne **3b**, which has Cl on the phenyl ring, led to **4b** in 47% yield with the formation of **5**, **6** and **7** at ambient temperature (entry 1). On the other hand, the reactions with alkynes bearing electron-donating groups on the phenyl ring were sluggish and did not provide the coupling products (entries 12 and 13), except for the reaction of alkyne **3i** (entry 11). Instead, the reactions with these electron-rich alkynes afforded cyclized isoxazole **5** as a major product. Current observations are consistent with those of the Sonogashira cross-coupling

Table 4. Solvent effect on the cyclization–oxidative alkylation and cyclization–fluorination reactions of (*Z*)-2-alkynone *O*-methyloxime **1a**^a

Entry	Solvent/Conc. (M)	Time (h)	Yield (%) ^b				
			4a	5	6	7a ^c	1a ^d
1	CH ₃ CN/0.5	24	8	34	6	10	30
2	CH ₃ CN/0.02	93	40	22	29	17	9
3 ^e	DMF/0.1	20	16	43	3	13	25
4 ^f	1,4-Dioxane/0.1	14	2	29	4	12	61
5 ^f	DCE/0.1	15	No reaction				
6 ^f	Toluene/0.1	15	No reaction				

^aReaction conditions: **1a** (400 μmol), **3a** (800 μmol), (PPh₃)AuNTf₂ (40.0 μmol), Selectfluor (1.00 mmol), K₃PO₄ (800 μmol), H₂O (4.00 mmol), Solvent. ^bIsolated yields. ^cIsolated yields based on **3a**. ^d% of recovered **1a**. ^e80 °C. ^f60 °C

process: The reaction proceeds more rapidly with more electron-poor alkynes.²² K₃PO₄ is supposed to abstract the acetylenic proton of the terminal alkyne, thus forming a gold-acetylide species (vide infra).²³ It should be pointed out that the employed bases are usually not basic enough to deprotonate the alkyne in order to generate the anionic nucleophile leading to the gold-acetylide species. Therefore, electron-withdrawing substituents on the phenyl ring that make the alkyne proton more acidic would lead to easier abstraction of the acetylenic proton.

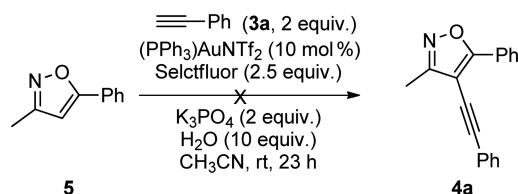
To discriminate the cyclization–oxidative alkylation mechanism from the alkylation through direct C–H activation of *in situ* formed isoxazole **5**, the isoxazole **5** was prepared independently and treated with (PPh₃)AuNTf₂ (10 mol %) in the presence of Selectfluor, K₃PO₄, and H₂O (Scheme 4). This experiment led to recovery of the starting material **5** and formation of alkyne dimer **7** with no detectable trace of the alkylation product **4a** and fluorinated isoxazole **6**, which suggests that the alkylation mechanism does not operate through direct C–H activation of isoxazole **5**. Therefore, the product **4a** would be formed through oxidative coupling before the protodeauration of the gold(I) complex.

On the basis of previous literature and our observation, two plausible mechanistic pathways can be suggested for the gold-catalyzed cyclization–oxidative alkylation of (*Z*)-2-alkynone *O*-methyloxime (Scheme 5). Initial coordination of the gold(I) catalyst **A** to the terminal alkyne **3a** would form a π-coordinated alkyne adduct **B**, which transforms into the σ-

Table 5. Synthesis of 3,4,5-trisubstituted isoxazoles by gold-catalyzed cascade cyclization–oxidative alkylation and cyclization–fluorination of (*Z*)-2-alkynone *O*-methyloximes^a

Entry	HC≡CAr	Time (h)	Yield (%) ^b			
			4	5	6	7 ^c
1		25	47(4b)	22	23	22(7b)
2		17	34(4c)	30	21	11(7c)
3		22	45(4d)	21	26	16(7d)
4 ^d		20	41(4e)	27	26	19(7e)
5 ^d		24	30(4f)	8	24	8(7f)
6		20	36(4g)	19	5	26(7g)
7		18	30(4h)	19	14	10(7h)
8		40	32(4i)	16	22	0(7i)
9		19	36(4j)	16	24	0(7j)
10 ^d		17	34(4k)	15	48	14(7k)
11		19	25(4l)	51	14	20(7l)
12 ^e		40	0(4m)	47	0	0(7m)
13 ^{d,f}		50	0(4n)	8	0	0(7n)

^aReaction conditions: **1a** (400 μmol), **3b–n** (800 μmol), (PPh₃)AuNTf₂ (40.0 μmol), Selectfluor (1.00 mmol), K₃PO₄ (800 μmol), H₂O (4.00 mmol), CH₃CN (4 mL). ^bIsolated yields. ^cIsolated yields based on **3b–n**. ^d60 °C. ^e45% of starting **1a** was recovered. ^f80% of starting **1a** was recovered.

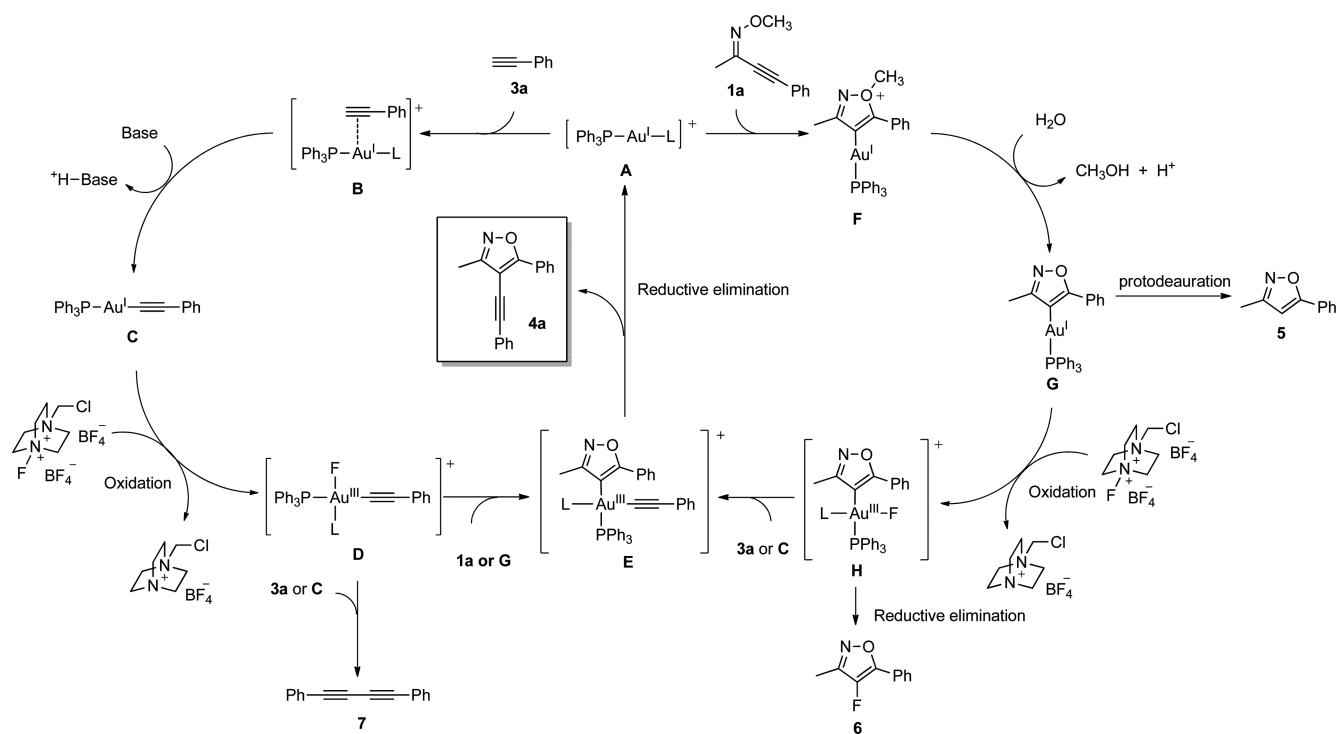
**Scheme 4.** Gold-catalyzed alkylation of isoxazole **5**.

acetylide gold(I) complex **C** in the presence of base. Then, oxidation by Selectfluor would afford the cationic gold(III) intermediate **D**, which reacts with the second molecule of **C** and gives the homo-coupled product **7**. This mechanism has been well documented recently.²⁴ On the other hand, the coordination of gold(III) intermediate **D** to the alkyne of *O*-methyloxime **1a** and subsequent cyclization would lead to the gold(III) complex **E** bearing both isoxazole and alkyne substituents; **E** readily decomposes to yield cross-coupled product **4a** and the cationic gold(I) catalyst **A** after reductive elimination. In the other possible mechanistic pathway, the gold(I)-catalyzed cyclization of *O*-methyloxime **1a** may occur before the formation of σ -acetylide gold(I) complex **C**. The gold(I) complex **G**, which is formed after the demethylation of the cyclized gold(I) complex **F**, may give the proto-deauration product **5**. Otherwise, Selectfluor would oxidize the gold(I) complex **G** to the cationic gold(III) intermediate **H**, the reductive elimination of which would afford the fluorinated isoxazole **6**, or the fluoride-acetylide ligand exchange of which would give the gold(III) complex **E**. As mentioned previously, **E** undergoes reductive elimination to provide cross-coupled product **4a** and to regenerate the cationic gold(I) catalyst **A**. This suggested mechanism involves a redox Au(I)/Au(III) catalytic cycle mediated by the external oxidant Selectfluor.

Conclusion

In conclusion, we have developed a novel one-pot method to synthesize trisubstituted isoxazoles from (*Z*)-2-alkynone *O*-methyloxime. This gold-catalyzed cascade reaction proceeds under mild conditions (room temperature) *via* the intermolecular addition of the oxime oxygen atom to the tethered triple bond and subsequent alkylation or fluorination. Mechanistically, gold-catalyzed cycloisomerization has been combined with the gold-catalyzed oxidative cross-coupling or fluorination process. The current synthetic method is straightforward and represents a typical pot-economical synthesis in that no intermediate purification operations are needed. This is the first example to synthesize various alkynyl isoxazoles from structurally simple *O*-methyloxime in a tandem manner, and offers the efficient construction of functionalized isoxazoles.

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Scheme 5. Plausible mechanism for gold-catalyzed cyclization–oxidative alkynylation of (*Z*)-2-alkynone *O*-methoxyime.

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