JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

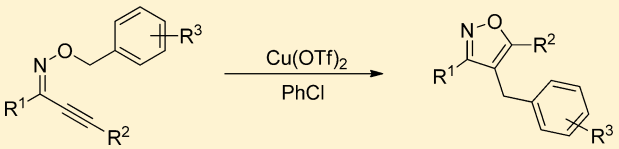
Copper-Catalyzed Synthesis of Trisubstituted Isoxazoles via a Cascade Cyclization−Migration Process

Masafumi Ueda, Shoichi Sugita, Aoi Sato, Tetsuya Miyoshi, and Okiko Miyata*

Kobe Pharmaceutical University, Motoyamakita, Higashinada, Kobe 658-8558, Japan

Supporting Information

ABSTRACT: An atom-economical, catalytic, and regioselective synthesis of 3,4,5-trisubstituted isoxazoles has been successfully developed. Treatment of *O*-arylmethyl alkynyl oxime ethers with 5 mol % of $Cu(OTf)_2$ in chlorobenzene at reflux gave 4-arylmethylisoxazoles in good to excellent yields via the sequential intramolecular addition of the oxime moiety to the alkyne with subsequent 1,3-migration of the arylmethyl group.



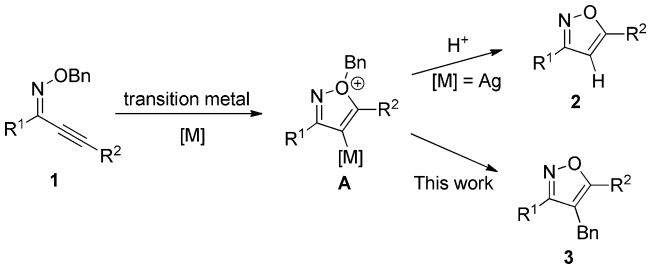
Heterocycles are well-known for their wide range of biological properties.[1] Of the various bioactive heterocycles, isoxazoles have attracted considerable interest because of their wide reaching applications in medicinal chemistry[2] and material science.[3] For this reason, considerable research efforts have been focused on the development of novel and efficient methods for the synthesis of isoxazoles **3**.[4]

Although isoxazoles are generally synthesized according to an intermolecular [3 + 2] cycloaddition reaction between an alkyne and a nitrile oxide,[5] the direct construction of trisubstituted isoxazoles via a cycloaddition reaction with an internal alkyne has not been reported as frequently in the literature.[6,7] Furthermore, these methods usually require harsh conditions and result in poor chemo- and regioselectivities. An alternative stepwise approach has also been reported for the selective and efficient construction of trisubstituted isoxazoles. This approach involves the preformation of an isoxazole ring bearing a functional group at the 4-position, such as a halogen,[8] silicon,[9] boronic ester[10] or aluminum,[11] which can be subsequently cross-coupled with an appropriate coupling partner to provide the desired substituted product. Using a more straightforward approach, Chen et al.[12] and Campagne et al.[13] independently reported the one-pot synthesis of trisubstituted isoxazoles using a domino sequence. This involved the construction of the isoxazole ring system through a palladium-catalyzed annulation of the corresponding acyclic precursor with subsequent cross-coupling of the resulting 4-isoxazolylpalladium intermediate.[14] However, these reactions were not atom-economical, as the loss of a functional group would result in generation of chemical waste in the course of the transformation.

From the perspective of atom economy alone, the direct synthesis of trisubstituted isoxazoles with high levels of chemo- and regioselectivity in a one-pot sequence is both highly desirable and challenging. Herein, we report the direct synthesis of trisubstituted isoxazoles using a domino process involving the transition metal catalyzed cyclization of an *O*-benzyl alkynyl oxime ether with subsequent 1,3-migration of the benzyl groups.

The π-acidic transition-metal-catalyzed intramolecular addition of a heteroatom to an alkyne with subsequent migration of the substituent initially attached to the heteroatom is one of the most powerful strategies for the synthesis of heterocyclic compounds.[15] Although the use of these transformations has effectively provided well-precedented access to benzofurans,[16] indoles,[17] benzothiophenes,[18] furans,[19] pyrans,[20] and pyrrolidine,[21] less is known about the synthesis of isoxazoles using this methodology.[22] Our working hypothesis for the current research is outlined in Scheme 1. We recently reported the

Scheme 1. Synthesis of Di- and Trisubstituted Isoxazoles



development of a silver-catalyzed synthesis of disubstituted isoxazoles via the generation of a vinyl metal intermediate **A** which was subsequently protonated under acidic conditions to give the desired disubstituted isoxazole **2**.[23] It was envisaged that the benzyl group could migrate from the oxygen of the oxonium ion in **A** to the 4-position of the isoxazole core, leading to the formation of trisubstituted isoxazoles under suitable conditions.

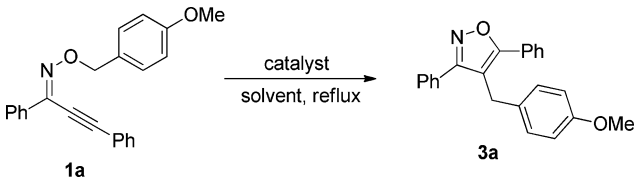
Alkynyl oxime ether **1a** bearing a *p*-methoxybenzyl group on the oxygen atom was selected as a model system for our initial screening work because it would generate a highly stabilized carbocation and enhance the migratory aptitude of the benzyl group. A series of alkynophilic catalysts were screened for their

Received: July 8, 2012

 © XXXX American Chemical Society

ability to catalyze the synthesis of the trisubstituted isoxazole **3a** (Table 1). When **1a** was treated with $AuCl_3$ in dichloroethane at reflux, the desired trisubstituted isoxazole **3a** was obtained, albeit in a low yield (Table 1, entries 1 and 2).[24] A survey of other catalysts revealed $Cu(OTf)_2$ as the most effective catalyst (Table 1, entries 3–5). This reaction was found to be strongly temperature dependent (Table 1, entries 6–10). Solvent polarity was also a significant factor for the efficiency of the reaction (Table 1, entries 8 and 9). It should be noted that *n*-butyl *p*-methoxybenzyl ether was obtained as a byproduct when the reaction was carried out in *n*-BuOH (Table 1, entry 10). This result indicated that the reaction proceeded via generation of *p*-methoxybenzyl cation. Following the screening process, the use of chlorobenzene at reflux was found to be optimal (Table 1, entries 6–9).

Table 1. Optimization of Cyclization–Migration Reaction



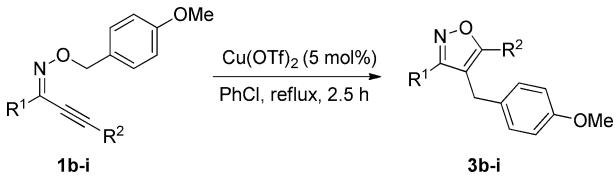
entry	catalyst (mol %)	solvent	bp (°C)	time (h)	yield (%)
1	$AuCl_3$ (5)	$(CH_2Cl)_2$	83	10	29
2	$AuCl_3$ (10)	$(CH_2Cl)_2$	83	8	23
3	$AgBF_4$ (5)	$(CH_2Cl)_2$	83	6	43
4	$CuCl_2$ (5)	$(CH_2Cl)_2$	83	10	NR
5	$Cu(OTf)_2$ (5)	$(CH_2Cl)_2$	83	2	57
6	$Cu(OTf)_2$ (5)	THF	65	2	NR
7	$Cu(OTf)_2$ (5)	toluene	110	2	47
8	$Cu(OTf)_2$ (5)	xylenes	137	2	47
9	$Cu(OTf)_2$ (5)	PhCl	132	2	70
10[a]	$Cu(OTf)_2$ (5)	*n*-BuOH	116	2	27

[a]*n*-Butyl *p*-methoxybenzyl ether was obtained in 11% yield.

The general scope of the reaction was then examined under the optimized conditions (Table 1, entry 9). A variety of different *O*-*p*-methoxybenzyl alkynyl oxime ethers **1b–i** were treated with $Cu(OTf)_2$ in refluxing chlorobenzene, affording the corresponding trisubstituted isoxazole **3b–i** in good to high yields (Table 2). Electron-rich and electron-poor aryl groups and an alkyl group were well tolerated at the R^1 position, affording the corresponding trisubstituted isoxazoles **3b–d** (Table 2, entries 1–3) in good yields. Furthermore, the ester moiety on oxime ether **1e** was compatible with the reaction conditions, providing isoxazole carboxylate **3e** (Table 2, entry 4) in good yield and demonstrating the mild nature of the current transformation. The substituent at the R^2 position on the triple bond terminus could also be varied without any discernible issue under the optimized reaction conditions. For example, substrates **1f** and **1g** bearing aliphatic substituents performed well under the current reaction conditions providing the desired trisubstituted isoxazoles in high yields (Table 2, entries 5 and 6). It is noteworthy that the acidic proton of the terminal alkyne in oxime **1h** did not have an adverse impact on the transformation and the desired product was obtained in high chemical yield (Table 2, entry 7). Unfortunately, when the silyl-protected substrate **1i** was subjected to the current reaction conditions, partial desilylation was observed. Consequently, upon completion of the copper-catalyzed cyclization, the crude product was treated with TBAF to afford 4-(hydroxymethyl)-isoxazole **3i** in 65% yield (Table 2, entry 8). Additionally, this method for the synthesis of trisubstituted isoxazoles can be applied to a gram scale synthesis; thus, the copper-catalyzed reaction of **1b** (1 g) afforded **3b** in 63% yield (entry 9).

We then proceeded to investigate the scope for changing the substituents on the migrating group (Table 3). The *p*-silyloxybenzyl group in oxime ether **4a** successfully migrated to give the corresponding trisubstituted isoxazole **5a** in high yield (Table 3, entry 1). Remarkably, the introduction of a dimethylamino group in oxime ether **4b** enhanced the efficiency of the domino reaction, which proceeded even at a lower temperature in refluxing dichloroethane (Table 3, entry 2). The substrate **4c** bearing an *o*-methoxy group gave **5c** in relatively lower yield, likely because of steric repulsion (Table 3, entry 3). The introduction of an electron-withdrawing group such as an ester moiety completely inhibited the cyclization reaction and only the oxime ether **4d** was recovered (Table 3, entry 4). This result indicated that the rate-determining step involved the generation of the benzyl cation by C–O bond

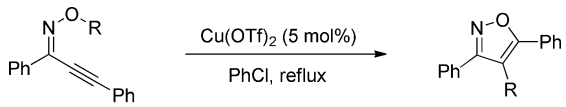
Table 2. Copper-Catalyzed Synthesis of Trisubstituted Isoxazoles



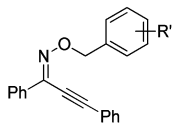
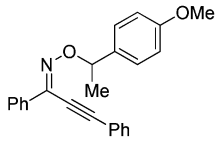
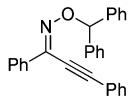
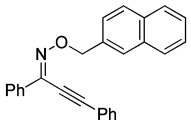
entry	substrate	R^1	R^2	product	yield[a] (%)
1	**1b**	4-$CF_3C_6H_4$	Ph	**3b**	85
2	**1c**	4-$MeOC_6H_4$	Ph	**3c**	78
3	**1d**	cyclohexyl	Ph	**3d**	73
4	**1e**	CO_2Me	Ph	**3e**	70
5	**1f**	Ph	*n*-Bu	**3f**	66
6	**1g**	Ph	cyclohexyl	**3g**	93
7	**1h**	Ph	H	**3h**	80
8[b]	**1i**	Ph	CH_2OTBS	**3i** (R^2= CH_2OH)	65
9[c]	**1b**	4-$CF_3C_6H_4$	Ph	**3b**	63

[a]Isolated yields. [b]Reaction was carried out with $Cu(OTf)_2$ (5 mol %) followed by treatment with TBAF (1 equiv). [c]Reaction was carried out with 1 g of **1b**.

Table 3. Substitution Effect of the Migrating Group

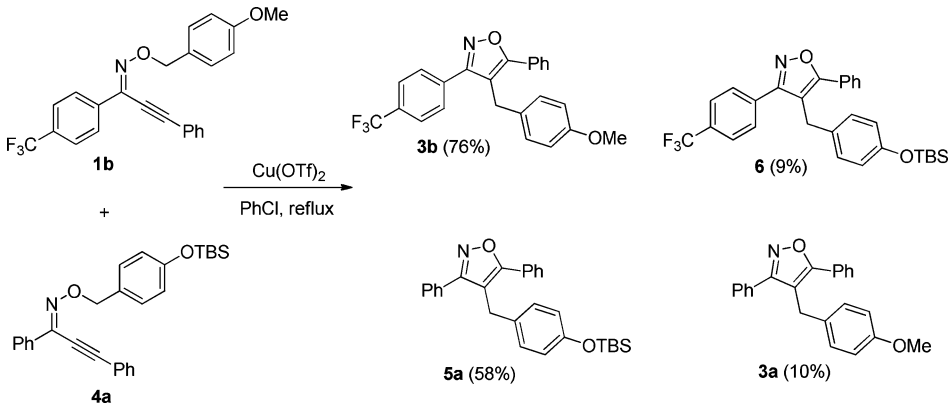


4a-g **5a-g**

entry	substrate		time (h)	product	yield (%)
1		**4a** (R' = 4-OTBS)	2	**5a**	87
2[a]		**4b** (R' = 4-NMe_2)	2	**5b**	83
3		**4c** (R' = 2-OMe)	9	**5c**	57
4		**4d** (R' = 4-CO_2Me)	10	**5d**	NR
5		**4e**	2	**5e**	54
6		**4f**	3	**5f**	76
7		**4g**	2	**5g**	49

[a]Reaction was carried out in $(CH_2Cl)_2$ at 83 °C.

Scheme 2. Crossover Reaction between 1b and 4a

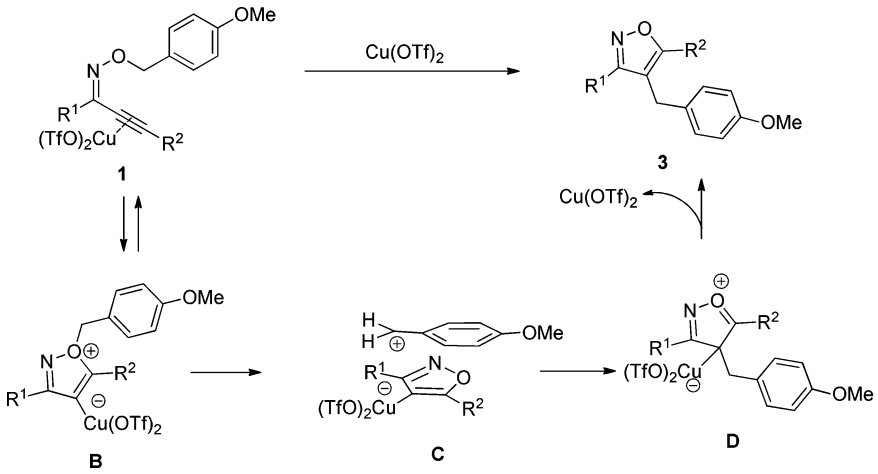


cleavage. Pleasingly, the substituted benzyl groups and 2-naphthylmethyl group in substrates **4e–g** were well tolerated under the current conditions, affording **5e–g** (Table 3, entries 5–7) in moderate yields.

To investigate the migration step in the current reaction, a crossover experiment was performed in which an equimolar mixture of two different alkynyl oxime ethers, **1b** and **4a**,was subjected to the domino reaction under the optimized conditions (Scheme 2). As a result, the noncrossover products **3b** and **5a** were obtained in 76 and 58% yields, respectively, together with small amounts of the crossover products **6** and **3a**. This result demonstrated that the benzyl cation could partially dissociate and exchange with the other cations following the initial cyclization, as a consequence of the high reaction temperature.

Although the precise mechanism of the reaction could not be fully elucidated, a possible reaction pathway was proposed and is depicted in Scheme 3. Initially, the oxygen atom of the oxime ether adds to the Cu(II)-activated C–C triple bond in a 5-*endo-dig* fashion, generating an oxonium intermediate **B**. The irreversible generation and 1,3-migration of the benzyl cation via the formation of ion-pair **C** would lead to the generation of

Scheme 3. Possible Reaction Pathway



intermediate **D**. The interaction of benzyl cation and the π-electron of the isoxazole core would lead to an intramolecular 1,3-migration, although partial separation of the ion-pair could occur at high temperatures.[18a] However, an alternative pathway for the formation of crossover product, in which the intermediate **B** acted as an electrophile causing the intermolecular benzylation without the generation of the cation species, would not be excluded. In the final step, aromatization of **D** would afford the trisubstituted isoxazole **3** and liberate the copper catalyst.

In conclusion, we have successfully developed a copper-catalyzed synthesis of trisubstituted isoxazoles from alkynyl oxime ethers via the intermolecular addition of the oxime oxygen atom to the alkyne group with subsequent 1,3-migration of the substituted benzyl group. The current synthetic method represents a typical atom-economical synthesis in that all of the atoms in starting substrate were incorporated in the final product without the loss of any atoms.

■ EXPERIMENTAL SECTION

General Procedure for Prepatarion of Alkynyl Oxime Ether 1a−g and 7. To a solution of alkynyl ketone (6.53 mmol) in EtOH (65 mL) were added *O*-(*p*-methoxybenzyl)hydroxylamine (1.0 g, 6.53 mmol) and PPTS (163 mg, 0.65 mmol). The reaction mixture was stirred at reflux for 12 h, then concentrated under reduced pressure, diluted with H_2O, and extracted with $CHCl_3$. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography on SiO_2 (hexane/AcOEt = 30:1−10:1) afforded the corresponding oxime ether **1a−g** and **7**. The geometry of C═N was deduced by NOESY experiments.

*(1Z)-1,3-Diphenyl-2-propyn-1-one O-[(4-Methoxyphenyl)-methyl]oxime (**1a**).* 1,3-Diphenyl-2-propyn-1-one was used for ketone. Isolated yield 75% (1.67 g). Colorless oil. IR (neat): 2935, 2213 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.92−7.89 (2H, m), 7.60−7.57 (2H, m), 7.43−7.36 (8H, m), 6.91 (2H, dt, J = 8.5, 2.0 Hz), 5.30 (2H, s), 3.81 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 159.3, 140.1, 133.7, 132.1, 129.9, 129.6, 129.6, 129.4, 128.4, 128.3, 126.5, 121.9, 113.7, 101.1, 79.7, 76.9, 55.2. HRMS (Orbitrap-ESI): calcd for $C_{23}H_{20}NO_2$ [M + H]$^+$ 342.1489, found 342.1490.

*(1Z)-1-[4-(Trifluoromethyl)phenyl]-3-phenyl-2-propyn-1-one O-[(4-Methoxyphenyl)methyl]oxime (**1b**).* 3-Phenyl-1-[4-(trifluoromethyl)phenyl]-2-propyn-1-one was used for ketone. Isolated yield 41% (1.09 g). Colorless crystals. Mp: 69−71 °C (Et_2O−hexane). IR (neat): 2937, 2213 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.01 (2H, dd, J = 8.0, 0.5 Hz), 7.63 (2H, dd, J = 8.0, 0.5), 7.60−7.56 (2H, m), 7.42−7.37 (5H, m), 6.91 (2H, dt, J = 8.5, 2.0 Hz), 5.32 (2H, s), 3.81 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 159.5, 138.9, 137.1, 132.1, 131.4, 131.0, 130.0, 129.7, 129.3, 121.5, 113.8, 101.9, 79.1, 77.3, 55.2. HRMS (Orbitrap-ESI): calcd for $C_{24}H_{19}NO_2F_3$ [M + H]$^+$ 410.1362, found 410.1362.

*(1Z)-1-(4-Methoxyphenyl)-3-phenyl-2-propyn-1-one O-[(4-Methoxyphenyl)methyl]oxime (**1c**).* 1-(4-Methoxyphenyl)-3-phenyl-2-propyn-1-one was used for ketone. Isolated yield 36% (0.87 g). Colorless oil. IR (neat): 2934, 2213 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.84 (2H, dt, J = 8.5, 2.0), 7.58−7.55 (2H, m), 7.41−7.32 (5H, m), 6.90 (2H, dt, J = 9.0, 2.0 Hz), 6.89 (2H, dt, J = 8.5, 2.0 Hz), 5.27 (2H, s), 3.81 (3H, s), 3.78 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 160.8, 159.3, 139.8, 132.1, 129.8, 129.3, 128.4, 127.9, 126.4, 122.0, 113.7, 113.7, 100.7, 79.8, 76.7, 55.3, 55.2. HRMS (Orbitrap-ESI): calcd for $C_{24}H_{22}NO_3$ [M + H]$^+$ 372.1594, found 372.1591.

*(1Z)-1-Cyclohexyl-3-phenyl-2-propyn-1-one O-[(4-Methoxyphenyl)methyl]oxime (**1d**).* 1-Cyclohexyl-3-phenyl-2-propyn-1-one was used for ketone. Isolated yield 72% (1.63 g). Colorless crystals. Mp: 78−80 °C (Et_2O−hexane). IR (neat): 2930, 2212 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.51−7.47 (2H, m), 7.35−7.29 (5H, m), 6.87 (2H, dt, J = 8.5, 2.0 Hz), 5.12 (2H, s), 3.78 (3H, s), 2.41 (1H, tt, J = 11.5, 3.5 Hz), 1.89−1.17 (10H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 159.2, 146.6, 132.0, 131.9, 129.9, 129.7, 129.6, 129.1, 128.3, 122.1, 113.7, 113.6, 100.0, 79.9, 76.3, 75.9, 55.2, 42.9, 37.0, 30.7, 29.4, 25.8, 25.7. HRMS (Orbitrap-ESI): calcd for $C_{23}H_{26}NO_2$ [M + H]$^+$ 348.1958, found 348.1958.

*(2E)-2-[[(4-Methoxyphenyl)methyloxy]imino]-4-phenyl-3-butynoic Acid Methyl Ester (**1e**).* Methyl 2-oxo-4-phenyl-3-butynoate was used for ketone. Isolated yield 77% (1.62 g). Colorless oil. IR (neat): 2954, 2209, 1739 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.53−7.50 (2H, m), 7.39−7.28 (5H, m), 6.89 (2H, dt, J = 8.5, 2.0 Hz), 5.36 (2H, s), 3.89 (3H, s), 3.78 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 161.4, 159.7, 133.7, 132.1, 130.0, 129.7, 128.3, 128.1, 121.2, 113.8, 102.7, 78.5, 77.9, 77.2, 55.1, 53.0. HRMS (Orbitrap-ESI): calcd for $C_{19}H_{18}NO_4$ [M + H]$^+$ 324.1230, found 324.1232.

*(1Z)-1-Phenyl-2-heptyn-1-one O-[(4-Methoxyphenyl)methyl]-oxime (**1f**).* 1-Phenyl-2-heptyn-1-one was used for ketone. Isolated yield 99% (2.07 g). Colorless oil. IR (neat): 2958, 2217 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.84−7.81 (2H, m), 7.39−7.33 (5H, m), 6.89 (2H, dt, J = 8.5, 2.0 Hz), 5.24 (2H, s), 3.80 (3H, s), 2.52 (2H, t, J = 7.0 Hz), 1.67−1.44 (4H, m,), 0.92 (3H, t, J = 7.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 159.3, 140.4, 134.0, 129.9, 129.7, 129.3, 128.2, 126.4, 113.6, 103.8, 76.6, 71.7, 55.1, 30.3, 21.9, 19.4, 13.5. HRMS (Orbitrap-ESI): calcd for $C_{21}H_{24}NO_2$ [M + H]$^+$ 322.1802, found 322.1804.

*(1Z)-3-Cyclohexyl-1-phenyl-2-propyn-1-one O-[(4-Methoxyphenyl)methyl]oxime (**1g**).* 3-Cyclohexyl-1-phenyl-2-propyn-1-one was used for ketone. Isolated yield 50% (1.13 g). Colorless oil. IR (neat): 2932, 2215 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.85−7.81 (2H, m), 7.39−7.33 (5H, m), 6.89 (2H, dt, J = 8.5, 2.0 Hz), 5.24 (2H, s), 3.81 (3H, s), 2.73 (1H, m), 1.89−1.33 (10H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 159.2, 140.5, 134.1, 129.7, 129.3, 128.1, 126.4, 113.6,

107.5, 76.5, 71.7, 55.1, 32.0, 29.7, 25.7, 24.4. HRMS (Orbitrap-ESI): calcd for $C_{23}H_{26}NO_2$ [M + H]$^+$ 348.1958, found 348.1948.

*(1Z)-3-(Trimethylsilyl)-1-phenyl-2-propyn-1-one O-[(4-Methoxyphenyl)methyl]oxime (**7**).* 1-Phenyl-3-trimethylsilyl-2-propyn-1-one was used for ketone. Isolated yield 68% (1.49 g). Colorless oil. IR (neat): 2959, 2157, 1614. cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.86−7.82 (2H, m), 7.42−7.36 (5H, m), 6.91 (2H, d, *J* = 8.5 Hz), 5.28 (2H, s), 3.82 (3H, s), 0.31 (9H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 159.5, 140.3, 133.6, 130.0, 129.85, 129.75, 128.6, 128.5, 126.7, 113.9, 108.4, 94.4, 77.7, 55.4, −0.1. HRMS (Orbitrap-ESI): calcd for $C_{20}H_{24}NO_2Si$ [M + H]$^+$ 338.1571, found 338.1571.

Prepatarion of Alkynyl Oxime Ether 1h,i. *(1E)-1-Phenyl-2-propyn-1-one O-[(4-Methoxyphenyl)methyl]oxime (**1h**).* To a solution of **7** (525 mg, 1.56 mmol) in THF (50 mL) was added dropwise TBAF (3.1 mL, 3.11 mmol, 1.0 M in THF) under N_2 atmosphere at 0 °C. After being stirred at the same temperature for 30 min, the reaction mixture was diluted with H_2O and extracted with $CHCl_3$. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by FCC (hexane/AcOEt = 30:1) afforded **1h** (413 mg, 99%). Colorless crystals. Mp: 72−74 °C (Et_2O-hexane). IR (neat): 2938, 2346, 1615 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.85−7.82 (2H, m), 7.39−7.34 (5H, m), 6.88 (2H, d, *J* = 8.5 Hz), 5.26 (2H, s), 3.79 (3H, s), 3.73 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 159.4, 139.3, 133.0, 130.0, 129.7, 129.3, 128.3, 126.3, 113.7, 89.3, 77.1, 73.6, 55.2. HRMS (Orbitrap-ESI): calcd for $C_{17}H_{16}NO_2$ [M + H]$^+$ 266.1176, found 266.1176.

*(1Z)-4-Hydroxy-1-phenyl-2-butyn-1-one O-[(4-Methoxyphenyl)-methyl]oxime (**8**).* To a solution of **1h** (200 mg, 0.75 mmol) in THF (11 mL) was added dropwise *n*-BuLi (0.71 mL, 1.13 mmol, 1.6 M in hexane) under Ar atmosphere at −40 °C. After the reaction mixture was stirred for 5 min, paraformaldehyde (33 mg, 1.13 mmol) was added. The reaction mixture was stirred for 15 min and then allowed to warm to room temperature. The reaction was quenched with satd NH_4Cl and extracted with AcOEt. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by PTLC (hexane/AcOEt = 5:1) afforded **8** (194 mg, 88%).

*(1Z)-4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-1-phenyl-2-butyn-1-one O-[(4-Methoxyphenyl)methyl]oxime (**1i**).* To a solution of **8** (50 mg, 0.17 mmol) in CH_2Cl_2 (2 mL) were added TBSCl (31 mg, 0.20 mmol) and imidazole (25 mg, 0.37 mmol) at room temperature. After being stirred for 2 h under N_2 atmosphere at room temperature, the reaction mixture was diluted with H_2O and extracted with $CHCl_3$. The organic layers dried over $MgSO_4$ and concentrated in vacuo. Purification by PTLC (hexane/AcOEt = 10:1) afforded **1i** (62 mg, 89%). Colorless oil. IR (neat): 2931, 2215 1613 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.84−7.80 (2H, m), 7.38−7.33 (5H, m), 6.88 (2H, dt, *J* = 8.5, 2.0 Hz), 5.23 (2H, s), 4.60 (2H, d, *J* = 1.0 Hz), 3.80 (3H, s), 0.91 (9H, s), 0.12 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 159.4, 139.6, 133.4, 130.1, 129.5, 128.2, 126.4, 113.7, 100.4 76.9, 75.4, 55.2, 52.1, 25.7, 18.2, −5.2. HRMS (Orbitrap-ESI): calcd for $C_{24}H_{32}NO_3Si$ [M + H]$^+$ 410.2146, found 410.2145.

General Procedure for Cu(OTf)$_2$-Catalyzed Synthesis of Trisubstituted Isoxazoles (3a−h). To a solution of alkynyl oxime ether (30 mg) in chlorobenzene (15 mL) was added Cu(OTf)$_2$ (5 mol %) under an Ar atmosphere at room temperature. The reaction mixture was stirred at reflux for 2.5 h and then concentrated under reduced pressure. Purification by PTLC (hexane/EtOAc) afforded the corresponding trisubstituted isoxazole **3a−h**.

*3,5-Diphenyl-4-[(4-methoxyphenyl)methyl]isoxazole (**3a**).* Isolated yield 70% (21.0 mg). Colorless solid. Mp: 98−101 °C (Et_2O−hexane). IR (neat): 2931, 1610 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.70−7.67 (2H, m), 7.55−7.52 (2H, m), 7.44−7.37 (6H, m), 7.09 (2H, dt, *J* = 8.5, 2.0 Hz), 6.86 (2H, dt, *J* = 8.5, 2.0 Hz), 4.04 (2H, s), 3.79 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 167.0, 164.2, 158.3, 130.8, 129.8, 129.5, 129.3, 128.9, 128.8, 128.7, 128.3, 128.1, 126.8, 114.3, 111.2, 55.2, 27.9. HRMS (Orbitrap-ESI): calcd for $C_{23}H_{20}NO_2$ [M + H]$^+$ 342.1489, found 342.1489.

*3-[4-(Trifluoromethyl)phenyl]-4-[(4-methoxyphenyl)methyl]-5-phenylisoxazole (**3b**).* Isolated yield 85% (25.5 mg). Colorless oil. IR (neat): 2935, 1613 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.71−7.68 (2H, m), 7.64 (4H, s), 7.45−7.43 (3H, m), 7.08 (2H, d, *J* = 8.5 Hz), 6.87 (2H, dt, *J* = 8.5, 2.0 Hz), 4.04 (2H, s), 3.80 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 167.7, 163.0, 158.5, 132.9, 130.3, 130.1, 129.0, 128.8, 128.7, 127.8, 126.9, 125.7, 125.6, 114.4, 111.2, 55.3, 27.9. HRMS (Orbitrap-ESI): calcd for $C_{24}H_{19}NO_2F_3$ [M + H]$^+$ 410.1362, found 410.1353.

*3-(4-Methoxyphenyl)-4-[(4-methoxyphenyl)methyl]-5-phenylisoxazole (**3c**).* Isolated yield 78% (23.4 mg). Colorless oil. IR (neat): 2935, 1612 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.69−7.65 (2H, m), 7.47 (2H, dt, *J* = 9.0, 2.5 Hz) 7.43−7.39 (3H, m), 7.10 (2H, dt, *J* = 9.0, 2.5 Hz) 6.89 (2H, dt, *J* = 9.0, 2.5 Hz), 6.86 (2H, dt, *J* = 9.0, 2.5 Hz), 4.02 (2H, s), 3.80 (3H, s), 3.79 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.9, 163.8, 160.6, 158.3, 130.8, 129.7, 129.6, 128.9, 128.8, 128.2, 126.8, 121.6, 114.3, 114.2, 111.0, 55.24, 55.21, 28.0. HRMS (Orbitrap-ESI): calcd for $C_{24}H_{22}NO_3$ [M + H]$^+$ 372.1594, found 372.1591.

*3-Cyclohexyl-4-[(4-methoxyphenyl)methyl]-5-phenylisoxazole (**3d**).* Isolated yield 73% (21.9 mg). Colorless crystals. Mp: 128−130 °C (EtOAc−hexane). IR (neat): 2927, 1615 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.64−7.60 (2H, m), 7.41−7.37 (3H, m), 7.05 (2H, dt, *J* = 8.5, 2.0 Hz), 6.83 (2H, dt, *J* = 8.5, 2.0 Hz), 3.93 (2H, s), 3.78 (3H, s), 2.49 (1H, tt, *J* = 13.5, 3.0 Hz), 1.86−1.52 (7H, m), 1.29−1.21 (3H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 168.5, 165.5, 158.3, 130.7, 129.4, 128.8, 128.4, 126.8, 114.1, 111.2, 55.2, 35.6, 31.6, 27.5, 26.3, 25.9; HRMS (Orbitrap-ESI): calcd for $C_{23}H_{26}NO_2$ [M + H]$^+$ 348.1958, found 348.1957.

*4-[(4-Methoxyphenyl)methyl]-5-phenyl-3-isoxazolecarboxylic Acid Methyl Ester (**3e**).* Isolated yield 70% (21.0 mg). Colorless crystals. Mp: 84−86 °C (Et_2O−hexane). IR (neat): 2953, 1740, 1613 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.69−7.66 (2H, m), 7.47−7.44 (3H, m), 7.05 (2H, d, *J* = 8.5 Hz), 6.83 (2H, dt, *J* = 8.5, 2.0 Hz), 4.21 (2H, s), 3.91 (3H, s), 3.77 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 168.6, 160.8, 158.2, 155.4, 130.6, 130.3, 129.0, 128.8, 127.2, 127.1, 114.4, 114.0, 55.2, 52.6, 27.2. HRMS (Orbitrap-ESI): calcd for $C_{19}H_{18}NO_4$ [M + H]$^+$ 324.1230, found 324.1227.

*5-Butyl-4-[(4-methoxyphenyl)methyl]-3-phenylisoxazole (**3f**).* Isolated yield 66% (19.8 mg). Colorless oil. IR (neat): 2957, 1613 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.52−7.49 (2H, m), 7.38−7.36 (3H, m), 6.98 (2H, dt, *J* = 8.5, 2.0 Hz), 6.80 (2H, dt, *J* = 8.5, 2.0 Hz), 3.79 (2H, s), 3.77 (3H, s), 2.67 (2H, t, *J* = 7.5 Hz), 1.65 (2H, quint, *J* = 7.5 Hz), 1.35 (2H, m), 0.90 (3H, t, *J* = 7.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.9, 162.8, 158.1, 131.2, 129.7, 129.2, 128.8, 128.6, 128.2, 114.0, 111.2, 55.2, 29.5, 27.2, 25.5, 22.3, 13.6. HRMS (Orbitrap-ESI): calcd for $C_{21}H_{24}NO_2$ [M + H]$^+$ 322.1802, found 322.1800.

*5-Cyclohexyl-4-[(4-methoxyphenyl)methyl]-3-phenylisoxazole (**3g**).* Isolated yield 93% (27.9 mg). Colorless crystals. Mp: 134−136 °C (EtOAc−hexane). IR (neat): 2926, 1615 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49−7.46 (2H, m), 7.38−7.34 (3H, m), 6.98 (2H, dt, *J* = 8.5, 2.0 Hz), 6.80 (2H, dt, *J* = 8.5, 2.0 Hz,), 3.80 (2H, s), 3.77 (3H, s), 2.71 (1H, tt, *J* = 11.5, 3.0 Hz), 1.83−1.64 (7H, m), 1.30−1.26 (3H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 162.8, 158.1, 131.4, 129.7, 129.1, 128.8, 128.5, 128.2, 114.0, 109.8, 55.2, 36.2, 30.8, 27.1, 26.1, 25.6. HRMS (Orbitrap-ESI): calcd for $C_{23}H_{26}NO_2$ [M + H]$^+$ 348.1958, found 348.1949.

*4-[(4-Methoxyphenyl)methyl]-3-phenylisoxazole (**3h**).* Isolated yield 80% (24.0 mg). Colorless oil. IR (neat): 2935, 1611 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.06 (1H, m), 7.63−7.60 (2H, m), 7.45−7.42 (3H, m), 7.09 (2H, dt, *J* = 8.5, 2.0 Hz), 6.84 (2H, dt, *J* = 8.5, 2.0 Hz), 3.83 (2H, s), 3.79 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 161.3, 158.3, 157.2, 130.7, 129.5, 129.4, 129.0, 128.7, 128.2, 118.2, 114.1, 55.2, 28.0. HRMS (Orbitrap-ESI): calcd for $C_{17}H_{16}NO_2$ [M + H]$^+$ 266.1176, found 266.1176.

*4-[(4-Methoxyphenyl)methyl]-3-phenyl-5-isoxazolemethanol (**3i**).* Cu(OTf)$_2$ (4 mg, 0.01 mmol) was added to a solution of alkynyl oxime ether **1i** (100 mg, 0.24 mmol) in chlorobenzene (41 mL) under an Ar atmosphere at room temperature. The reaction mixture was stirred at reflux for 2 h and then filtered. The filter cake was then washed with THF, and the filtrates were combined. A solution of TBAF (0.24 mL, 0.24 mmol, 1 M in THF) was then added to the mixture in a dropwise manner under a N_2 atmosphere at 0 °C.

Following a 30 min period of stirring at the same temperature, the reaction mixture was diluted with H_2O and extracted with $CHCl_3$. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by PTLC (toluene/EtOAc = 4:1) to give **3i** (46 mg, 65%). Colorless crystals. Mp: 73−75 °C (Et_2O−hexane). IR (neat): 3380, 2933, 1612 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.50−7.47 (2H, m), 7.41−7.37 (3H, m), 6.99 (2H, dt, *J* = 8.5, 2.0 Hz), 6.78 (2H, dt, *J* = 8.5, 2.0 Hz), 4.62 (2H, s), 3.85 (2H, s), 3.75 (3H, s), 2.75 (1H, br s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 168.0, 163.1, 158.2, 130.8, 129.5, 129.0, 128.7, 128.3, 114.1, 113.8, 55.2, 54.9, 27.1; HRMS (Orbitrap-ESI): calcd for $C_{18}H_{18}NO_3$ [M + H]$^+$ 296.1281, found 296.1275.

General Procedure for Preparation of Alkynyl Oxime Ethers 4a,c−g. To a solution of 1,3-diphenyl-2-propyn-1-one (1.0 g, 4.85 mmol) in EtOH (50 mL) were added alkoxyamine (4.85 mmol) and PPTS (121 mg, 0.49 mmol). The reaction mixture was stirred at reflux for 12 h, then concentrated under reduced pressure, diluted with H_2O and extracted with $CHCl_3$. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography on SiO_2 (hexane/AcOEt = 30:1−10:1) afforded the corresponding oxime ethers **4a,c−g**.

*(1Z)-1,3-Diphenyl-2-propyn-1-one O-[[4-[[(1,1-Dimethylethyl)-dimethylsilyl]oxy]phenyl]methyl]oxime (**4a**).* *O*-[[4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]phenyl]methyl]hydroxylamine was used for alkoxyamine. Isolated yield 71% (1.51 g). Colorless oil. IR (neat): 2930, 2214, 1610 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.01−7.98 (2H, m), 7.66−7.63 (2H, m), 7.47−7.39 (8H, m), 6.92 (2H, dt, *J* = 8.5, 2.0 Hz), 5.38 (2H, s), 1.06 (9H, s), 0.28 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 155.4, 140.1, 133.7, 132.1, 130.3, 129.7, 129.6, 129.4, 128.4, 128.3, 126.5, 121.9, 119.9, 101.1, 79.7, 76.9, 25.6, 18.1, −4.5. HRMS (Orbitrap-ESI): calcd for $C_{28}H_{32}NO_2Si$ [M + H]$^+$ 442.2197, found 442.2198.

*(1Z)-1,3-Diphenyl-2-propyn-1-one O-[(2-Methoxyphenyl)-methyl]oxime (**4c**).* *O*-[(2-Methoxyphenyl)methyl]hydroxylamine was used for alkoxyamine. Isolated yield 7% (0.115 g). Colorless oil. IR (neat): 2939, 2214, 1604 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.94−7.90 (2H, m), 7.62−7.59 (2H, m), 7.49 (1H, dd, *J* = 8.0, 2.0 Hz), 7.41−7.35 (6H, m), 7.28 (1H, td, *J* = 8.0, 2.0 Hz), 6.97 (1H, td, *J* = 8.0, 2.0 Hz), 6.89 (1H, d, *J* = 8.0 Hz), 5.46 (2H, s), 3.86 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 157.0, 140.2, 133.7, 132.1, 129.5, 129.4, 128.9, 128.7, 128.4, 128.3, 126.5, 126.3, 122.0, 120.4, 110.3, 101.2, 79.8, 72.1, 55.4. HRMS (Orbitrap-ESI): calcd for $C_{23}H_{20}NO_2$ [M + H]$^+$ 342.1489, found 342.1487.

*4-[[(Z)-(1,3-Diphenyl-2-propyn-1-ylidene)amino]oxymethyl]-benzoic Acid Methyl Ester (**4d**).* Methyl 4-[(aminooxy)methyl]-benzoate was used for alkoxyamine. Isolated yield 32% (0.572 g). Colorless crystals. Mp: 64−68 °C (AcOEt−hexane). IR (neat): 2951, 2215, 1716, 1615 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.04 (2H, dt, *J* = 8.5, 2.0 Hz) 7.91−7.88 (2H, m), 7.62−7.59 (2H, m), 7.52 (2H, d, *J* = 8.5 Hz), 7.40−7.36 (6H, m), 5.41 (2H, s), 3.90 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.9, 142.9, 140.9, 133.3, 132.1, 129.8, 129.7, 129.6, 129.5, 128.5, 128.4, 127.5, 126.5, 121.7, 101.6, 79.4, 76.2, 52.0. HRMS (Orbitrap-ESI): calcd for $C_{24}H_{20}NO_3$ [M + H]$^+$ 370.1438, found 370.1437.

*(1Z)-1,3-Diphenyl-2-propyn-1-one O-[1-(4-Methoxyphenyl)-ethyl]oxime (**4e**).* *O*-[1-(4-Methoxyphenyl)ethyl]hydroxylamine was used for alkoxyamine. Isolated yield 39% (0.671 g). Colorless oil. IR (neat): 2939, 2207, 1613 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.89−7.86 (2H, m), 7.62−7.58 (2H, m), 7.40−7.35 (8H, m), 6.89 (2H, dt, *J* = 8.5, 2.0 Hz), 5.44 (1H, q, *J* = 6.5 Hz), 3.79 (3H, s), 1.68 (3H, d, *J* = 6.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 159.0, 139.9, 135.2, 133.9, 132.1, 129.5, 129.4, 128.4, 128.3, 127.6, 126.5, 122.2, 113.7, 100.9, 82.0, 77.2, 55.2, 22.0. HRMS (Orbitrap-ESI): calcd for $C_{24}H_{22}NO_2$ [M + H]$^+$ 356.1645, found 356.1643.

*(1Z)-1,3-Diphenyl-2-propyn-1-one O-(Diphenylmethyl)oxime (**4f**).* *O*-(Diphenylmethyl)hydroxylamine was used for alkoxyamine. Isolated yield 64% (1.20 g). Colorless crystals. Mp: 135−138 °C (AcOEt/hexane). IR (neat): 3062, 2213, 1599 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.88−7.85 (2H, m), 7.62−7.59 (2H, m), 7.47 (4H, d, *J* = 8.0 Hz), 7.37−7.22 (12H, m), 6.46 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 141.4, 141.0, 133.4, 132.1, 129.7, 129.5, 128.5, 128.3, 127.6, 127.3, 126.6, 122.0, 101.5, 87.7, 80.0, 77.2. HRMS (Orbitrap-ESI): calcd for $C_{28}H_{22}NO$ [M + H]$^+$ 388.1696, found: 388.1692.

*(1Z)-1,3-Diphenyl-2-propyn-1-one O-(2-naphthylmethyl)oxime (**4g**).* *O*-(2-Naphthalenylmethyl)hydroxylamine was used for alkoxyamine. Isolated yield 60% (1.05 g). Colorless solid. IR (neat): 3061, 2210, 1601 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.93−7.90 (3H, m), 7.87−7.82 (3H, m), 7.63−7.59 (3H, m), 7.49−7.46 (2H, m), 7.41−7.37 (6H, m), 5.54 (2H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 140.6, 135.1, 133.7, 133.3, 133.0, 129.7, 129.5, 128.7, 128.42, 128.37, 128.1, 128.0, 127.7, 127.1, 127.0, 126.5, 126.03, 126.01, 125.9, 121.9, 101.4, 79.7, 77.2. HRMS (Orbitrap-ESI): calcd for $C_{26}H_{20}NO$ [M + H]$^+$ 362.1539, found 362.1538.

*Preparation of (1Z)-1,3-Diphenyl-2-propyn-1-one O-[[4-(Dimethylamino)phenyl]methyl]oxime (**4b**).* To a solution of *O*-[(4-dimethylaminophenyl)methyl]hydroxylamine hydrochloride (0.84 mmol) in MeOH (6 mL) were added 1,3-diphenyl-2-propyn-1-one (173 mg, 0.84 mmol), Na_2SO_4 (239 mg, 1.68 mmol), and pyridine (0.6 mL) under N_2 atmosphere at room temperature. After being stirred at the same temperature for 6 h, the reaction mixture was diluted with H_2O and extracted with $CHCl_3$. The organic phase was washed with H_2O, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography on SiO_2 (hexane/AcOEt = 15:1) afforded **4b** (98 mg, 34%). Colorless solid. Mp: 83−87 °C (Et_2O−hexane). IR (neat): 2927, 2211, 1615 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.92−7.89 (2H, m), 7.60−7.56 (2H, m), 7.40−7.36 (8H, m), 6.74 (2H, dt, *J* = 9.0, 2.0 Hz), 5.27 (2H, s), 2.95 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 150.4, 139.7, 133.9, 132.1, 129.9, 129.4, 129.3, 128.3, 128.3, 126.4, 125.1, 122.0, 112.2, 100.9, 79.9, 77.4, 40.5. HRMS (Orbitrap-ESI): calcd for $C_{24}H_{23}N_2O$ [M + H]$^+$ 355.1805, found 355.1806.

General Procedure for $Cu(OTf)_2$-Catalyzed Synthesis of Trisubstituted Isoxazoles (5a−c,e−g). To a solution of alkynyl oxime ether (30 mg) in chlorobenzene or dichloroethane (15 mL) was added $Cu(OTf)_2$ (5 mol %) under an Ar atmosphere at room temperature. The reaction mixture was stirred at reflux for 2−10 h and then concentrated under reduced pressure. Purification by PTLC (hexane/EtOAc) afforded the corresponding trisubstituted isoxazole **5a−c,e−g**.

*4-[4-[[(1,1-Dimethylethyl)dimethylsilyloxy]phenyl]methyl]-3,5-diphenylisoxazole (**5a**).* Isolated yield 87% (26.1 mg). Colorless crystals. Mp: 98−101 °C (Et_2O−hexane). IR (neat) 2931, 1609 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.70−7.67 (2H, m), 7.53−7.49 (2H, m), 7.44−7.33 (6H, m), 7.01 (2H, d, *J* = 8.0 Hz), 6.78 (2H, dt, *J* = 8.0, 2.5 Hz), 4.02 (2H, s), 0.97 (9H, s), 0.19 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 167.0, 164.2, 154.2, 131.5, 129.8, 129.5, 129.3, 128.9, 128.8, 128.6, 128.4, 128.1, 126.9, 120.4, 111.4, 28.1, 25.7, 18.2, −4.4. HRMS (Orbitrap-ESI): calcd for $C_{28}H_{32}NO_2Si$ [M + H]$^+$ 442.2197, found 442.2194.

*4-[[4-(Dimethylamino)phenyl]methyl]-3,5-diphenylisoxazole (**5b**).* Isolated yield 83% (24.9 mg). Colorless crystals. Mp: 118−120 °C (Et_2O−hexane). IR (neat): 3008, 1616 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.73−7.69 (2H, m), 7.58−7.55 (2H, m), 7.43−7.36 (6H, m), 7.05 (2H, d, *J* = 8.5), 6.70 (2H, dt, *J* = 8.5, 2.0 Hz), 4.00 (2H, s), 2.93 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.9, 164.2, 149.3, 129.6, 129.4, 129.3, 128.9, 128.6, 128.4, 128.3, 128.1, 126.8, 126.5, 113.0, 111.5, 40.6, 27.7. HRMS (Orbitrap-ESI): calcd for $C_{24}H_{23}N_2O$ [M + H]$^+$ 355.1805, found 355.1798.

*4-[(2-Methoxyphenyl)methyl]-3,5-diphenylisoxazole (**5c**).* Isolated yield 57% (17.1 mg). Colorless crystals. Mp: 152−155 °C (EtOAc−hexane). IR (neat) 3011, 1600 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.67−7.64 (2H, m), 7.54−7.52 (2H, m), 7.42−7.32 (6H, m), 7.27−7.21 (1H, m), 6.99 (1H, d, *J* = 7.5 Hz), 6.91 (1H, d, *J* = 7.5 Hz), 6.85 (1H, t, *J* = 7.5 Hz), 4.02 (2H, s), 3.82 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 167.1, 164.3, 157.1, 129.6, 129.4, 128.8, 128.6, 128.4, 128.3, 127.7, 127.1, 126.8, 120.7, 110.8, 110.0, 55.2, 23.3. HRMS (Orbitrap-ESI): calcd for $C_{23}H_{20}NO_2$ [M + H]$^+$ 342.1489, found 342.1504.

*4-[1-(4-Methoxyphenyl)ethyl]-3,5-diphenylisoxazole (**5e**).* Isolated yield 54% (16.2 mg). Colorless oil. IR (neat): 2973, 1612 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.60−7.57 (2H, m), 7.43−7.30 (8H, m),

7.13 (2H, d, J = 8.5 Hz), 6.84 (2H, dt, J = 8.5 Hz), 4.35 (1H, q, J = 7.0 Hz), 3.81 (3H, s), 1.42 (3H, d, J = 7.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.5, 164.1, 158.0, 136.1, 129.9, 129.8, 129.2, 129.0, 128.6, 128.5, 128.3, 128.1, 128.0, 117.8, 113.8, 55.2, 32.1, 19.4. HRMS (Orbitrap-ESI): calcd for $C_{24}H_{22}NO_2$ $[M + H]^+$ 356.1645, found 356.1641.

*3,5-Diphenyl-4-(diphenylmethyl)isoxazole (**5f**).* Isolated yield 76% (22.8 mg). Colorless solid. IR (neat): 3062, 1594 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.40−7.13 (16H, m), 7.03−7.00 (4H, m), 5.69 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 167.6, 164.6, 141.3, 129.6, 129.5, 129.2, 129.1, 128.3, 128.2, 128.1, 128.0, 126.6, 116.1, 45.7. HRMS (Orbitrap-ESI): calcd for $C_{28}H_{22}NO$ $[M + H]^+$ 388.1696, found 388.1691.

*3,5-Diphenyl-4-(2-naphthylmethyl)isoxazole (**5g**).* Isolated yield 49% (14.7 mg). Colorless oil. IR ($CHCl_3$): 3060, 1600 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.85 (2H, d, J = 8.0 Hz), 7.74−7.68 (3H, m), 7.58−7.53 (3H, m), 7.50−7.44 (2H, m), 7.42−7.30 (7H, m), 4.26 (2H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 167.4, 164.3, 136.5, 133.7, 132.3, 129.9, 129.6, 129.2, 129.0, 128.8, 128.7, 128.3, 128.0, 127.8, 127.6, 126.8, 126.5, 126.3, 126.1, 125.7, 110.5, 29.1; HRMS (Orbitrap-ESI): calcd for $C_{26}H_{20}NO$ $[M + H]^+$ 362.1539, found 362.1541.

Crossover Reaction. To a solution of alkynyl oxime ether **1b** (45 mg, 0.11 mmol) and **4a** (48.5 mg, 0.11 mmol) in chlorobenzene (38 mL) was added $Cu(OTf)_2$ (4.1 mg, 0.01 mmol) under Ar atmosphere at room temperature. The reaction mixture was stirred for 2 h at reflux and then concentrated. Purification by PTLC hexane/EtOAc = 15/1) afforded **3b** (35 mg, 76%), **5a** (30 mg, 58%), **3a** (4 mg, 10%), and **6** (5 mg, 9%).

3-[4-(Trifluoromethyl)phenyl]-4-[4-[[(1,1-dimethylethyl)-dimethylsilyloxy]phenyl]methyl]-5-phenylisoxazole (6). Colorless solid. IR (neat): 2931, 1609 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.71−7.68 (2H, m), 7.63 (4H, s), 7.46−7.44 (3H, m), 7.01 (2H, d, J = 8.5 Hz), 6.79 (2H, dt, J = 8.5, 2.0 Hz), 4.02 (2H, s), 0.98 (9H, s), 0.19 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 167.6, 163.1, 154.4, 131.0, 130.1, 129.0, 128.8, 128.7, 127.8, 126.9, 125.63, 125.58, 120.6, 111.3, 28.0, 25.6, 18.2, −4.4. HRMS (Orbitrap-ESI): calcd for $C_{29}H_{31}NO_2F_3Si$ $[M + H]^+$ 510.2071, found 510.2069.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: miyata@kobepharma-u.ac.jp.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by Grants-in Aid from the Ministry of Education, Culture, Sports, Science and Technology of Japan (MEXT), the MEXT-Supported Program for the Strategic Research Foundation at Private Universities, and the Research Foundation for Pharmaceutical Sciences. M.U. is grateful to the Mitsubishi Chemical Award in Synthetic Organic Chemistry, Japan.

■ REFERENCES

(1) Katritzky, A. R.; Ramsden, C. A.; Scriven, E. F. V.; Taylor, R. J. K.; Joule, J. *Comprehensive Heterocyclic Chemistry III*; Elsevier: Oxford, 2008.

(2) (a) Carlsen, L.; Döpp, D.; Döpp, H.; Duus, F.; Hartmann, H.; Lang-Fugmann, S.; Schulze, B.; Smalley, R. K.; Wakefield, B. J. In *Houben-Weyl Methods in Organic Chemistry*; Schaumann, E., Ed.; Georg Thieme Verlag: Stuttgart, 1992; Vol. *E8a*, p 45. (b) Sperry, J.; Wright, D. *Curr. Opin. Drug Discov. Devel.* **2005**, *8*, 723.

(3) (a) Burrows, A. D.; Frost, C. G.; Mahon, M. F.; Raithby, P. R.; Richardson, C.; Stevenson, A. J. *Chem. Commun.* **2010**, *46*, 5064. (b) Lee, Y.; Koyama, Y.; Yonekawa, M.; Tanaka, T. *Macromolecules* **2009**, *42*, 7709.

(4) Wakefield, B. J. In *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*; Shaumann, E., Ed.; Georg Thieme Verlag: Stuttgart, 2001; Vol. *11*, p 229.

(5) Jäger, V.; Colinas, P. A. In *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Ed.; Wiley: Hoboken, 2002; Vol. *59*, p 361.

(6) For recent examples, see: (a) Sanders, B. C.; Friscourt, F.; Ledin, P. A.; Mbua, N. E.; Arumugam, S.; Guo, J.; Boltje, T. J.; Popik, V. V.; Boons, G.-J. *J. Am. Chem. Soc.* **2011**, *133*, 949. (b) Budzik, B. W.; Evans, K. A.; Wisnoski, D. D.; Jin, J.; Rivero, R. A.; Szewczyk, G. R.; Jayawickreme, C.; Moncol, D. L.; Yu, H. *Bioorg. Med. Lett.* **2010**, *20*, 1363.

(7) For recent study on the synthesis of disubstituted isoxazole, see: (a) Wang, L.; Yu, X.; Feng, X.; Bao, M. *Org. Lett.* **2012**, *14*, 2418. (b) Dadiboyena, S.; Nefzi, A. *Tetrahedron Lett.* **2012**, *53*, 2096. (c) Dissanayake, A. A.; Odom, A. L. *Tetrahedron* **2012**, *68*, 807. (d) Burhard, J. A.; Tchitchanov, B. H.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 5379.

(8) (a) Waldo, J. P.; Larock, R. C. *J. Org. Chem.* **2007**, *72*, 9643. (b) Okitsu, T.; Potewar, T. M.; Wada, A. *J. Org. Chem.* **2011**, *76*, 3438.

(9) Denmark, S. E.; Kallemeyn, J. M. *J. Org. Chem.* **2005**, *70*, 2839.

(10) (a) Kumar, J. S. D.; Ho, M. M.; Leung, J. M.; Toyokuni, T. *Adv. Synth. Catal.* **2002**, *344*, 1146. (b) Moore, J. E.; Davies, M. W.; Goodenough, K. M.; Wybrow, R. A. J.; York, M.; Johnson, C. N.; Harrity, J. P. A. *Tetrahedron* **2005**, *61*, 6707.

(11) Jackowski, O.; Lecourt, T.; Micouin, L. *Org. Lett.* **2011**, *13*, 5664.

(12) She, Z.; Niu, D.; Chen, L.; Gunawan, M. A.; Shanja, X.; Hersh, W. H.; Chen, Y. *J. Org. Chem.* **2012**, *77*, 3627.

(13) Gayon, E.; Quinonero, O.; Lemouzy, S.; Vrancken, E.; Campagne, J.-M. *Org. Lett.* **2011**, *13*, 6418.

(14) For other recently reported methods for the synthesis of trisubstituted isoxazoles, see: (a) Nishiwaki, N.; Kobiro, K.; Hirao, S.; Sawayama, J.; Saigo, K.; Ise, Y.; Nishizawa, M.; Ariga, M. *Org. Biomol. Chem.* **2012**, *10*, 1987. (b) Kawai, H.; Sugita, Y.; Tokunaga, E.; Shibata, N. *Eur. J. Org. Chem.* **2012**, 1295. (c) Xiang, D.; Xin, X.; Liu, X.; Zhang, R.; Yang, J.; Dong, D. *Org. Lett.* **2012**, *14*, 644. (d) Hashimoto, Y.; Takada, A.; Takikawa, H.; Suzuki, K. *Org. Biomol. Chem.* **2012**, *10*, 6003.

(15) (a) Lipshutz, B. H., Yamamoto, Y., Eds. *Chem. Rev.* **2008**, *108*, 3239. (b) Kirsch, S. F. *Synthesis* **2008**, 3183. (c) Krause, N.; Winter, C. *Chem. Rev.* **2011**, *111*, 1994. (d) Corma, C.; Leyva-Pérez, A.; Sabater, M. J. *Chem. Rev.* **2011**, *111*, 1657.

(16) (a) Manarin, F.; Roehr, J. A.; Gay, R. M.; Brandao, R.; Menezes, P. H.; Nogueira, C. W.; Zeni, G. *J. Org. Chem.* **2009**, *74*, 2153. (b) Fürstner, A.; Heilmann, E. K.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 4760. (c) Nakamura, I.; Mizushima, Y.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 15022. (d) Fürstner, A.; Davies, P. W. *J. Am. Chem. Soc.* **2005**, *127*, 15024.

(17) (a) Takaya, J.; Udagawa, S.; Kusama, H.; Iwasawa, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 4906. (b) Li, G.; Huang, X.; Zhang, L. *Angew. Chem., Int. Ed.* **2008**, *47*, 346. (c) Nakamura, I.; Yamagishi, U.; Song, D.; Konta, S.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 2284. (d) Cariou, K.; Ronan, B.; Mignani, S.; Fensterbank, L.; Malacria, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1881. (e) Shimada, T.; Nakamura, I.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 10546.

(18) (a) Nakamura, I.; Sato, T.; Terada, M.; Yamamoto, Y. *Org. Lett.* **2008**, *10*, 2649. (b) Nakamura, I.; Sato, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 4473.

(19) (a) Cheong, J. Y.; Im, D.; Lee, M.; Lim, W.; Rhee, Y. H. *J. Org. Chem.* **2011**, *76*, 324. (b) Nakamura, I.; Chan, C. S.; Araki, T.; Terada, M.; Yamamoto, Y. *Adv. Synth. Catal.* **2009**, *351*, 1089. (c) Peng, L.; Zhang, X.; Ma, M.; Wang, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 1905.

(d) Fürstner, A.; Stelzer, F.; Szillat, H. *J. Am. Chem. Soc.* **2001**, *123*, 11863.
(20) (a) Wang, Y.-M.; Kuzniewski, C. N.; Rauniyar, V.; Hoong, C.; Toste, F. D. *J. Am. Chem. Soc.* **2011**, *133*, 12972. (b) Komeyama, K.; Takahashi, K.; Takai, K. *Org. Lett.* **2008**, *10*, 5119.
(21) Istrate, F. M.; Gagosz, F. *Org. Lett.* **2007**, *9*, 3181.
(22) For the related gold-catalyzed synthesis of isoxazoles, see: Nakamura, I.; Okamoto, M.; Terada, M. *Org. Lett.* **2010**, *12*, 2453.
(23) Ueda, M.; Ikeda, Y.; Sato, A.; Ito, Y.; Kakiuchi, M.; Shono, H.; Miyoshi, T.; Naito, T.; Miyata, O. *Tetrahedron* **2011**, *67*, 4612.
(24) Those conditions were previously used in a domino reaction involving a cyclization and Claisen-type [3,3]-sigmatropic rearrangement; see: Ueda, M.; Sato, A.; Ikeda, Y.; Miyoshi, T.; Naito, T.; Miyata, O. *Org. Lett.* **2010**, *12*, 2594.