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Article

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Synthesis of 4-Isoxazolines through Gold(I)-Catalyzed Cyclization of Propargylic *N*-Hydroxylamines

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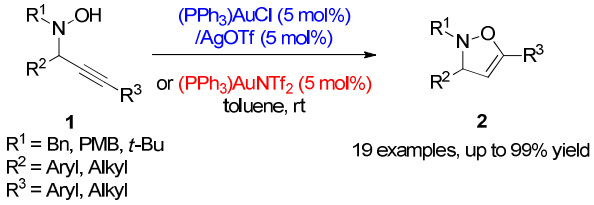


ABSTRACT: New catalytic methods for the synthesis of 4-isoxazolines have been developed via catalytic intramolecular cyclizations of propargylic *N*-hydroxylamines. The reactions proceed rapidly in less than one hour at room temperature in the presence of 5 mol% $(PPh_3)AuCl$/5 mol% AgOTf or 5 mol% $(PPh_3)AuNTf_2$. This process features an efficient route to 4-isoxazolines with high yields, short reaction times, and mild reaction conditions.

Introduction

4-Isoxazolines[1] (2,3-dihydroisoxazoles) are not only important scaffolds for various biologically active compounds, [2] but are also versatile synthetic intermediates for the preparation of interesting natural products.[3] The reductive opening of 4-isoxazolines provides access to building blocks such as β–amino ketones,[4] β–amino alcohols,[4] and β-lactams.[5] In addition, due to the thermal instability of the N-O bond associated with the π-system, 4-isoxazolines can be thermally or catalytically isomerized to various structures such as 2-acylaziridine,[6] 4-oxazoline,[7] and pyrrole[8] (Figure 1). Although their value in both chemistry and biology has been widely recognized, only a few methods to obtain such scaffolds have been described so far: the [3+2] cycloadditions between nitrones and alkynes,[9] cycloadditions between oxaziridines and alkynes,[10] and the cyclization of propargylic *N*-hydroxylamines. Among these, the 1,3-dipolar cycloaddition of nitrones to acetylenes is one of the most attractive approaches to the synthesis of 4-isoxazolines. However, this method often suffers from poor regioselectivity and limited substrate scope for alkynes (e.g., acetylene carboxylates and related electron-deficient acetylenes). Recently, the cyclization of propargylic *N*-hydroxylamines has emerged as an alternative pathway for the synthesis of 4-isoxazolines, and not surprisingly, only a few catalytic methods have been reported to date. Such a transformation can be accelerated by $Pd(OAc)_2$,[11] ZnI_2-DMAP,[12] $NaAuCl_4 \bullet 2H_2O$-DMAP,[13] $AgBF_4$,[14] or $ZnMe_2$.[15] Although these methods provide synthetic routes to 4-isoxazaolines with the desired regioselectivity, some of these methods require additional bases (Et_3N or DMAP), rather long reaction times (12–48 h for $Pd(OAc)_2$), high temperatures, or high loading of catalysts (10–300 mol%). Therefore, the development of mild and efficient catalytic conditions to facilitate access to synthetically useful 4-isoxazolines is still needed. In the course of our studies on gold-catalyzed reactions to construct complex heterocycles, we developed a highly efficient synthetic method, which can produce 4-isoxazolines in very short times. Herein, we report a mild gold(I)-catalyzed cyclization of propargylic *N*-hydroxylamines to yield 4-isoxazolines at room temperature in 5–60 minutes.

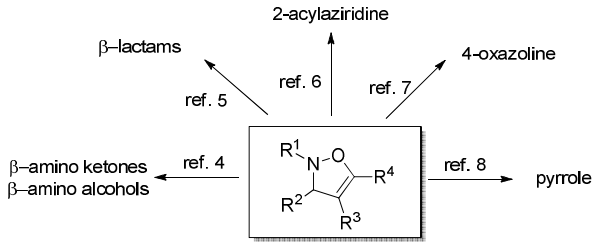


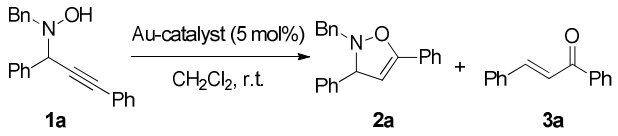
Figure 1. 4-Isoxazoline as a versatile synthetic intermediate.

Results and Discussion

Although gold(III) catalyzes the cyclization of propargylic *N*-hydroxylamines in the presence of 20 mol% of DMAP under refluxing CH_2Cl_2 conditions, gold(I)-catalyzed cyclization has long been elusive.[13] To assess the feasibility of gold(I)-catalyzed cyclization of propargylic *N*-hydroxylamine, we began to investigate the cycloisomerization of *N*-benzyl-*N*-(1,3-diphenylprop-2-yn-1-yl)hydroxylamine (**1a**) in the presence of various gold(I) and gold(III) catalysts in CH_2Cl_2 at room temperature (Table 1). First, we carried out cyclization reactions using cationic phosphine Au(I) chloride catalysts. $(PPh_3)AuCl$ produced the cyclization product **2a** in 33% yield after 48 h but 66% starting material was recovered (Table 1, entry 1). Unfortunately, this reaction was sluggish and other phosphine ligands such as PCy_3 and PMe_3 could not improve the result (entries 2 and 3). An NHC ligand such as IPr was not effective, either (entry 4). As expected, gold(III) catalysts such as $AuCl_3$ or $NaAuCl_4•2H_2O$ facilitated the reaction and afforded the cyclized product **2a** in 56% and 51% yields, respectively (entries 5 and 6). However, these catalysts also produced the undesired byproduct chalcone (**3a**), which was presumably generated from the addition of gold(III) catalyst to the already formed 4-isoxazoline **2a** during the reaction and the subsequent hydrolysis of **I-3** during workup (Scheme 1). Molecular sieve removal of H_2O and flash chromatography could not prevent the formation of **3a**. This might originate from the intrinsic properties of gold(III) catalysts to easily form a complex with 4-isoxazolines.[13] Indeed, the reaction of **2a** and $AuCl_3$ afforded **3a** in 30% yield with complicated unidentified byproducts after 48 h (eq 1). To our surprise, the gold(I) catalyst, AuCl afforded **2a** as a sole product in 15 min (entry 7). The reaction

was very rapid and no byproduct formation was observed. After a series of optimization studies, $(PPh_3)AuNTf_2$ (5 mol%) was identified as the best catalyst for the cyclization reaction (entry 8). In the presence of $(PPh_3)AuNTf_2$ (5 mol%), 4-isoxazoline **2a** was isolated in 91% yield after 15 min at room temperature without the formation of **3a**.

Table 1. Catalyst Screening and Optimization of Reaction Conditions.[a]

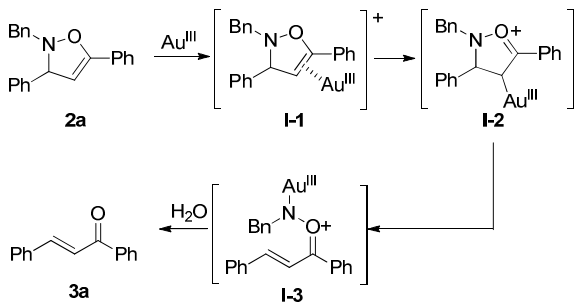


1a **2a** **3a**

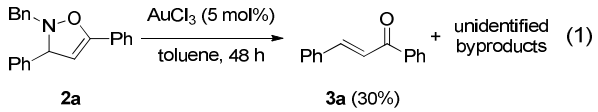
entry	Au-catalyst	time (h)	yield (%)[b]		
			2a	**3a**	Rec **1a**[c]
1	$(PPh_3)AuCl$	48	33	0	66
2	$(PCy_3)AuCl$	48	14	0	85
3	$(PMe_3)AuCl$	48	14	0	85
4	(IPr)AuCl	48	26	0	72
5	$AuCl_3$	0.1	56	24	0
6	$NaAuCl_4 \cdot 2H_2O$	0.2	51	29	0
7	AuCl	0.25	83	0	0
8	$(PPh_3)AuNTf_2$	0.25	91	0	0

[a] Reaction conditions: **1a** (62.6 mg, 200 μmol), Au-catalyst (10.0 μmol, 5 mol%), CH_2Cl_2 (2 mL). [b] Isolated yields after flash column chromatography. [c] Recovered **1a**.

Scheme 1. Plausible Mechanism for the Formation of **3a**.



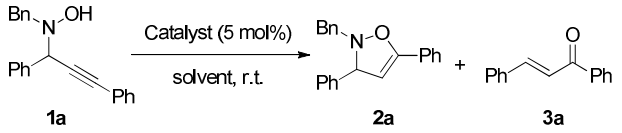
2a **I-1** **I-2** **3a** **I-3**



The significant difference in the reactivity of $(PPh_3)AuCl$ and $(PPh_3)AuNTf_2$ prompted us to further investigate the effect of anion and silver co-catalysts on the cyclization reaction as shown in Table 2. Interestingly, the addition of 5 mol% of silver salts to the $(PPh_3)AuCl$ reaction remarkably accelerated the cyclization process. The reactions were completed in 0.5–1 hours and afforded **2a** as the sole product in 79–90% yield (Table 2, entries 1–6). Particularly, the reaction using $(PPh_3)AuCl/AgNTf_2$ gave **2a** with a comparable yield to the reaction using $(PPh_3)AuNTf_2$ (1 h, 87%, Table 2, entry 4, vs 0.25 h, 91%, Table 1, entry 8). The best result was obtained with $(PPh_3)AuCl/AgOTf$, which afforded the 4-isoxazoline **2a** in 90% in 0.5 h. Meanwhile, the AuCl/AgOTf reaction was slower than the $(PPh_3)AuCl/AgOTf$ reaction and 3% of byproduct chalcone (**3a**) was isolated (Table 2, entry 7).

According to the previous literature,[14] $AgBF_4$ is known to catalyze the cyclization. However, AgOTf was not an effective catalyst. When it was employed alone, only 24% of **2a** was obtained after 48 h along with 54% of byproduct **3a** (Table 2, entry 8). Obviously, the $(PPh_3)AuCl/AgOTf$ system exhibited better activity than $(PPh_3)AuCl$ or AgOTf alone, which might be because of the silver salt effect[16] or anion effect. Therefore, in order to compare the silver salt effect and the anion effect, we carried out the cyclization reaction in the presence of $(PPh_3)AuOTf$ prepared by premixing $(PPh_3)AuCH_3$ and TfOH in the absence of silver salts, which provided 4-isoxazoline **2a** in 76% yield and **3a** in 5% yield respectively after 5 min (Table 2, entry 9). The reaction was rapid and comparably efficient. Therefore, the anion effect was evidently significant. Although AgOTf alone can catalyze the cyclization, the remarkable reactivity of the $(PPh_3)AuCl/AgOTf$ system must originate from the intrinsic activity of Au(I)-catalyst and its anion. As another evidence of this, $(PPh_3)AuNTf_2$ alone without any silver salt catalyzed the cyclization of propargylic *N*-hydroxylamines with comparable reactivity (*vide supra*). Interestingly, TfOH alone could not catalyze the cyclization and was unable to generate **2a** and **3a** (Table 2, entry 10).

Table 2. The Silver Salt and Solvent Effect on the Cyclization.[a]



1a 2a 3a

entry	catalyst	solvent	time (h)	yield (%)[b]	
				2a	**3a**
1	$(PPh_3)AuCl/AgOTs$	CH_2Cl_2	0.5	82	0
2	$(PPh_3)AuCl/AgSbF_6$	CH_2Cl_2	0.5	79	0
3	$(PPh_3)AuCl/AgBF_4$	CH_2Cl_2	0.75	82	0
4	$(PPh_3)AuCl/AgNTf_2$	CH_2Cl_2	1	87	0
5	$(PPh_3)AuCl/AgNO_3$	CH_2Cl_2	1	79	0
6	$(PPh_3)AuCl/AgOTf$	CH_2Cl_2	0.5	90	0
7	AuCl/AgOTf	CH_2Cl_2	4	76	3
8	AgOTf	CH_2Cl_2	48	24	54
9[c]	$(PPh_3)AuCH_3/TfOH$	CH_2Cl_2	0.1	76	5
10	TfOH	CH_2Cl_2	48	NR[d]	-
11	$(PPh_3)AuCl/AgOTf$	THF	0.5	90	0
12	$(PPh_3)AuCl/AgOTf$	CH_3CN	1.5	90	0
13	$(PPh_3)AuCl/AgOTf$	Toluene	0.25	94	0
14[c]	$(PPh_3)AuNTf_2$	Toluene	0.5	90	0

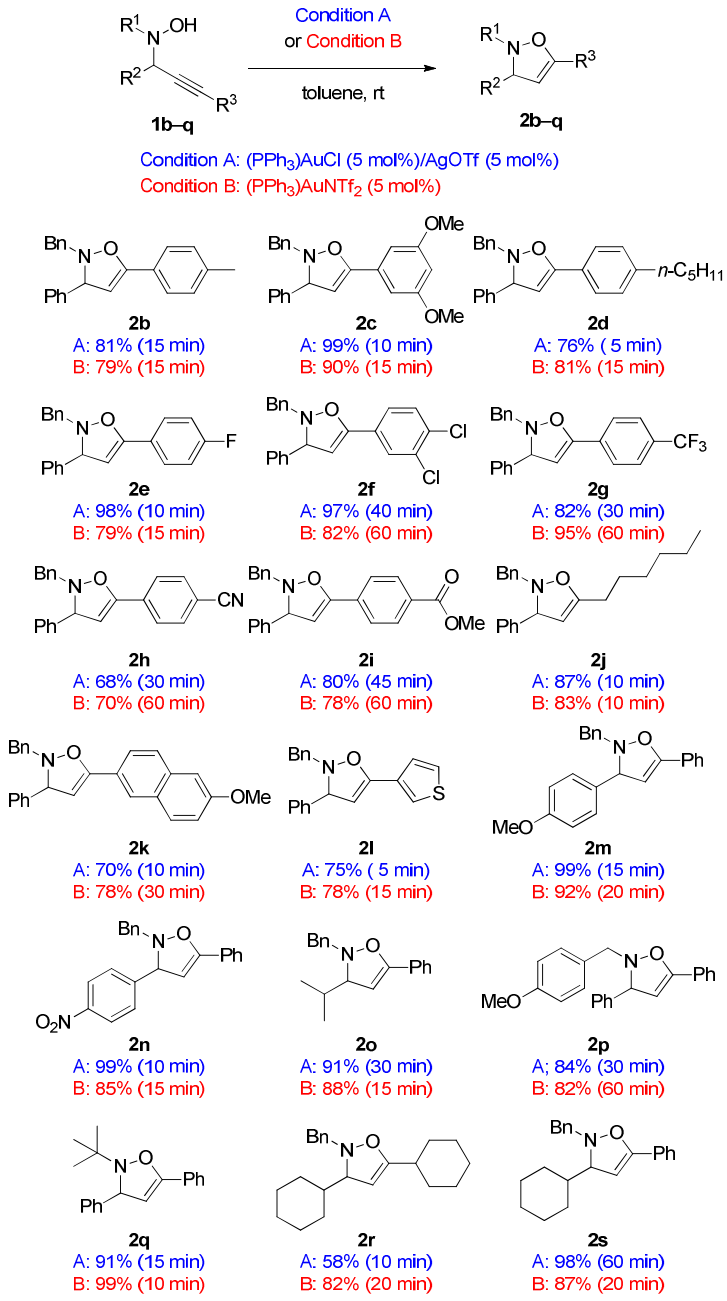
[a] Reaction conditions: **1a** (62.6 mg, 200 μmol), Au-catalyst (10.0 μmol, 5 mol%), Ag-salt (10.0 μmol, 5 mol%), CH_2Cl_2 (2 mL). [b] Isolated yields after flash column chromatography. [c] TfOH (10.0 μmol, 5 mol%) was used instead of Ag-salt. [d] No reaction.

Au(I)-catalyzed cyclization reactions of propargylic *N*-hydroxylamines showed a negligible solvent effect on the yield and the reaction time. The reactions were effective in various solvents such as CH_2Cl_2, THF, CH_3CN, and toluene (Table 2, entry 6 and entries 11–14). Based on table 2, we chosen the relatively non-polar solvent, toluene for further study (Table 2, entries 13 and 14).

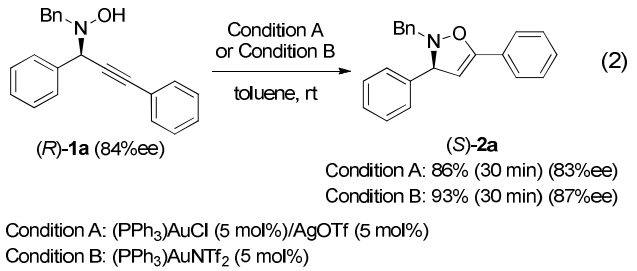
After we identified $(PPh_3)AuCl/AgOTf$ and $(PPh_3)AuNTf_2$ as the best catalysts, we investigated the scope of Au(I)-catalyzed cyclization reactions of propargylic *N*-hydroxylamines using

$(PPh_3)AuCl/AgOTf$ or $(PPh_3)AuNTf_2$ independently under optimized conditions (Scheme 2). Both the $(PPh_3)AuCl/AgOTf$ catalyst system and the $(PPh_3)AuNTf_2$ catalyst worked well with a wide variety of substrates and showed broad functional group compatibility. The cyclization yields are fully comparable and independent of the electronic nature. Substrates **1b–d** bearing electron-donating substituents as R^3 group underwent the cyclization reactions very smoothly and provided the corresponding 4-isoxazolines **2b–d** at room temperature in good to excellent yields (76–99%). Substrates **1e–i** bearing electron-withdrawing substituents as R^3 groups also provided the desired 4-isoxazolines **2e–i** in good yields (68–98%) under the same reaction conditions. Evidently, no reactivity difference between the $(PPh_3)AuCl/AgOTf$ catalyst system and the $(PPh_3)AuNTf_2$ was observed. The Au(I)-catalyzed cyclization reaction was also applicable to the substrates carrying aliphatic, naphthyl, thiophenyl substitutents as R^3 to deliver the corresponding 4-isoxazolines (**2j–l** and **2r**). Modifications to the R^1 and R^2 groups were carried out as well. The substrates bearing electron-donating *p*-methoxyphenyl, electron-withdrawing *p*-nitrophenyl and aliphatic groups in the R^2 underwent clean conversion to 4-isoxazolines (**2m–o**, **2r**, and **2s**). The benzyl group in R^1 could be replaced with a *p*-methoxybenzyl (PMB) group and a *t*-butyl group without loss of reactivity. Although bulky *t*-butyl substituted 4-isoxazoline **2q** was very unstable and decomposed to **3a** during column chromatography, **2q** was successfully isolated in over 90% yield by rapid flash chromatography.

Scheme 2. Synthesis of 4-Isoxazolines under Optimized Conditions.

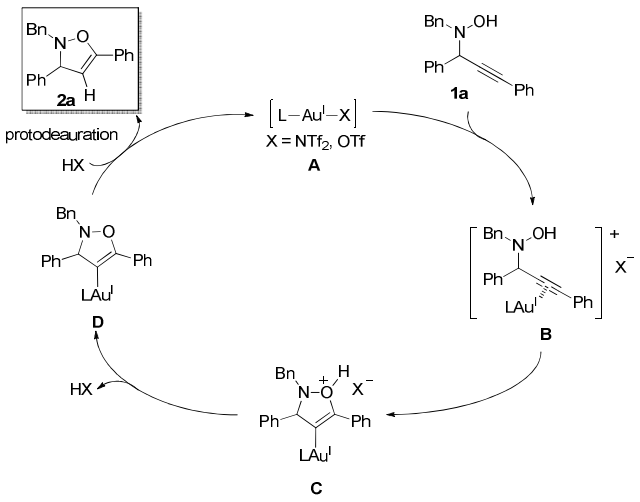


Moreover, the potential of this reaction was further proved by preliminary experiments using optically active propargylic *N*-hydroxylamine (eq 2). The enantioenriched propargylic *N*-hydroxylamine, (*R*)-**1a** can be cyclized without loss in enantiopurity, which suggests that this reaction is mild enough to allow 4-isoxazolines from enantiopure propargylic *N*-hydroxylamines under preservation of the stereochemical integrity. Therefore, it is applicable to the stereoselective synthesis of 4-isoxazolines when it is coupled to diastereoselective or enantioselective synthesis of propargylic *N*-hydroxylamine.



Mechanistically, we speculate that Au(I) catalyst **A** coordinates with the alkyne of **1a** and subsequent cyclization leads to the Au(I) complex **C**. Subsequent deprotonation generates the Au(I) complex **D**, which readily decomposes to yield protodeaurated 4-isoxazoline **2a** and regenerates the cationic gold(I) catalyst **A** (Scheme 3).

Scheme 3. Plausible Mechanism.



Conclusions

In conclusion, we have successfully developed an efficient gold-catalyzed cyclization of propargylic *N*-hydroxylamines to furnish synthetically valuable 4-isoxazolines under mild conditions (room temperature, 5 mol% catalyst loading) in short reaction times (5–60 minutes). This is the first report on the construction of 4-isoxazolines using gold(I)-catalyzed intramolecular cyclization. We believe that

this methodology will be very useful in synthetic organic chemistry and medicinal chemistry. Its application to the synthesis of bioactive natural products is currently underway in our laboratory.

Experimental Section

General Methods All reactions were performed in oven-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 0.25 mm E. Merck silica gel 60 F_{254} 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 E. Merck 230−400 mesh silica gel 60. Reagents were purchased 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 mm Hg. All moisture- and/or oxygen-sensitive solids were handled and stored in a glove box 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), C_6D_6 (^{1}H, 7.16 ppm; ^{13}C, 128.1 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 (HRMS) were obtained by electrospray ionization (ESI) or electron ionization (EI). Infrared spectra were recorded with peaks reported in cm^{-1}.

Procedure for the synthesis of nitrone S1a–f.

*(Z)-N-Benzylidene-benzylamine-N-oxide (**S1a**).*[17] *N*-Benzylhydroxylamine (2.00 g, 16.2 mmol, 1.00 equiv), benzaldehyde (1.65 mL, 16.2 mmol, 1.00 equiv) and anhydrous $MgSO_4$ (1.95 g, 16.2 mmol, 1.00 equiv) were suspended in anhydrous CH_2Cl_2 (80 mL). After stirring at room temperature for 15 h, the resulting suspension was filtered and washed with CH_2Cl_2 (100 mL). The filtrate was concentrated by rotary evaporation. The residue was purified by column chromatography (1:1 hexane/EtOAc) to afford *(Z)-N*-benzylidenebenzylamine-*N*-oxide (**S1a**) (3.40 g, 99%) as a white solid. TLC: R_f 0.45 (1:1

hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22–8.19 (m, 2H), 7.49–7.39 (m, 9H), 5.06 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 134.6, 133.3, 130.6, 130.5, 130.0, 129.3, 129.0, 128.8, 128.5, 71.3. HRMS (ESI) *m/z* calcd for $C_{14}H_{13}NNaO$ $[M+ Na]^+$ 234.0889, found 234.0896.

*(Z)-N-(4-Methoxybenzylidene)-1-phenylmethanamine oxide (**S1b**).*[18] *N*-Benzylhydroxylamine (493 mg, 4.00 mmol, 1.00 equiv), *p*-methoxybenzaldehyde (535 μL, 4.40 mmol, 1.10 equiv) and 4 Å molecular sieves (500 mg) were suspended in anhydrous toluene (12 mL). After stirring at room temperature for 12 h, the resulting suspension was filtered and washed with CH_2Cl_2 (20 mL). The filtrate was concentrated by rotary evaporation. Recrystallization from hexanes/EtOAc (4:1) afforded **S1b** (960 mg, 99%) as a white solid. TLC: R_f 0.35 (1:1 hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, J = 8.8 Hz, 2H), 7.46 (dd, J = 8.0 Hz, 2.0 Hz, 2H), 7.42–7.36 (m, 3H), 7.32 (s, 1H), 6.90 (d, J = 8.8 Hz, 2H), 5.01 (s, 2H), 3.84 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 161.3, 134.2, 133.6, 130.8, 129.3, 129.1, 129.0, 123.5, 113.9, 70.8, 55.5. HRMS (ESI) *m/z* calcd for $C_{15}H_{15}NNaO_2$ $[M+ Na]^+$ 264.0995, found 264.1001.

*(Z)-N-(4-Nitrobenzylidene)-1-phenylmethanamine oxide (**S1c**).*[18] *N*-Benzylhydroxylamine (493 mg, 4.00 mmol, 1.00 equiv), *p*-nitrobenzaldehyde (664 mg, 4.40 mmol, 1.10 equiv) and 4 Å molecular sieves (500 mg) were suspended in anhydrous toluene (12 mL). After stirring at room temperature for 12 h, the resulting suspension was filtered and washed with CH_2Cl_2 (20 mL). The filtrate was concentrated by rotary evaporation. The residue was purified by column chromatography (1:1 hexane/EtOAc) to afford **S1c** (830 mg, 81 %) as a yellow solid. TLC: R_f 0.55 (1:1 hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 (d, J = 9.2 Hz, 2H), 8.23 (d, J = 9.2 Hz, 2H), 7.52 (s, 1H), 7.50–7.48 (m, 2H), 7.45–7.43 (m, 3H), 5.11 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 148.0, 136.2, 132.7, 132.3, 129.6, 129.5, 129.3, 129.0, 123.9, 72.2. HRMS (ESI) *m/z* calcd for $C_{14}H_{13}N_2O_3$ $[M+ H]^+$ 257.0921, found 257.0925.

*(Z)-N-(2-Methylpropylidene)benzylamine-N-oxide (**S1d**).*[17] *N*-Benzylhydroxylamine (247 mg, 2.00 mmol, 1.00 equiv), 2-methylpropionaldehyde (183 μL, 2.00 mmol, 1.00 equiv) and anhydrous $MgSO_4$ (240 mg, 2.00 mmol, 1.00 equiv) were suspended in anhydrous Et_2O (10 mL). After Stirring at room

temperature for 15 h, the resulting suspension was filtered and washed with CH_2Cl_2 (20 mL). The filtrate was concentrated by rotary evaporation. Recrystallization from hexanes/EtOAc (4:1) afforded **S1b** (230 mg, 65%) as a white solid. TLC: R_f 0.15 (3:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.4–7.35 (m, 5H), 6.47 (d, J = 7.2 Hz, 1H), 4.86 (s, 2H), 3.16 (sept, J = 6.4 Hz, 1H), 1.08 (d, J = 6.4 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): 144.7, 133.2, 129.2, 129.0, 128.9, 69.4, 26.1, 18.9. HRMS (ESI) *m/z* calcd for $C_{11}H_{15}NNaO$ $[M+ Na]^+$ 200.1046, found 200.1055.

(Z)-N-Benzylidene-1-(4-methoxyphenyl)methanamine oxide ***(S1e)***.[19] *N*-(4-Methoxybenzyl)hydroxylamine (766 mg, 5.00 mmol, 1.00 equiv), benzaldehyde (508 μL, 5.00 mmol, 1.00 equiv) and anhydrous $MgSO_4$ (600 mg, 5.00 mmol, 1.00 equiv) were suspended in anhydrous CH_2Cl_2 (25 mL). After stirring for 12 h at room temperature, the resulting suspension was filtered and washed with CH_2Cl_2 (20 mL). The filtrate was concentrated by rotary evaporation. The residue was purified by column chromatography (1:1 hexane/EtOAc) to afford **S1e** (1.16 g, 96%) as a white solid. TLC: R_f 0.48 (1:2 hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21–8.18 (m, 2H), 7.41–7.38 (m, 5H), 7.33 (s, 1H), 6.93 (d, J = 8.8 Hz, 2H), 4.99 (s, 2H), 3.82 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.3, 134.1, 131.1, 130.6, 128.8, 128.6, 125.3, 114.5, 70.8, 55.5. HRMS (ESI) *m/z* calcd for $C_{15}H_{16}NO_2$ $[M+ H]^+$ 242.1176, found 242.1177.

(Z)-N-(Cyclohexylmethylene)-1-phenylmethanamine oxide ***(S1f)***.[4] *N*-(4-Methoxybenzyl)hydroxylamine (493 mg, 4.00 mmol, 1.00 equiv), cyclohexylaldehyde (550 μL, 4.40 mmol, 1.10 equiv) and anhydrous $MgSO_4$ (530 mg, 4.40 mmol, 1.10 equiv) were suspended in anhydrous toluene (12 mL). After stirring for 16.5 h at room temperature, the resulting suspension was filtered and washed with CH_2Cl_2 (20 mL). The filtrate was concentrated by rotary evaporation. The residue was recrystallized from hexane/EtOAc, and the mother liquor was further purified by column chromatography (1:1 hexane/EtOAc) to afford **S1f** (858 mg, 99%) as a white solid. TLC: R_f 0.22 (1:2 hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (m, 5H), 6.45 (d, J = 7.2 Hz, 1H), 4.84 (s, 2H),

2.97 (m, 1H), 1.85–1.82 (m, 2H), 1.68–1.64 (m, 3H), 1.40–1.29 (m, 2H), 1.25–1.06 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.2, 133.4, 129.2, 129.0, 128.9, 69.5, 35.2, 28.9, 26.1, 25.4.

General procedure for the synthesis of propargylic *N*-hydroxylamines 1a–s.[20]

To an oven-dried, 25-mL one-arm roundbottom flask, anhydrous Et_2O (12.0 mL), nitrone (1.20 mmol, 1.20 equiv), $ZnBr_2$ (45.0 mg, 0.20 mmol, 0.20 equiv), alkyne (1.00 mmol, 1.00 equiv), *i*-Pr_2NEt (226 μL, 1.30 mmol, 1.30 equiv) and TMSOTf (217 μL, 1.20 mmol, 1.20 equiv) were added sequentially at room temperature. The heterogeneous mixture was stirred at room temperature for indicated time. The resulting suspension was filtered through a plug of silica gel (1 cm × 5 cm), washed with Et_2O (50 mL), and concentrated by rotary evaporation. The crude product of the reaction was dissolved in MeOH (10 mL) with magnetic stirring, and treated with a *p*-toluenesulfonic acid (19.0 mg, 0.1 mmol). After completion of the TMS deprotection, the resulting mixture was concentrated by rotary evaporation. The residue was purified by column chromatography (hexanes/EtOAc) to afford propargylic *N*-hydroxylamines **1a–s**.

*N-Benzyl-N-(1,3-diphenylprop-2-yn-1-yl)hydroxylamine (**1a**).*[4] **1a** was prepared from phenylacetylene (110 μL, 1.00 mmol) and the *(Z)-N*-benzylidenebenzylamine-*N*-oxide (**S1a**) (253 mg, 1.20 mmol). Reaction time: 16 h. Then, the reaction mixture was stirred for an additional 2 h after the addition of *p*-toluenesulfonic acid. White solid (260 mg, 84%). TLC: R_f 0.25 (9:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, J = 7.2 Hz, 2H), 7.59–7.56 (m, 2H), 7.42–7.27 (m, 11H), 5.00 (s, 1H), 4.96 (brs, 1H), 4.07 (d, J = 13.2 Hz, 1H), 4.00 (d, J = 13.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.5, 137.1, 132.2, 129.9, 129.2, 128.7, 128.6, 128.5, 128.4, 128.3, 127.8, 122.9, 88.9, 84.6, 63.2, 60.6. HRMS (ESI) *m/z* calcd for $C_{22}H_{20}NO$ $[M+H]^+$ 314.1539, found 314.1542. IR (KBr film): 3229, 3062, 3030, 2905, 1489, 1453 cm^{-1}.

*N-benzyl-N-(1-phenyl-3-(p-tolyl)prop-2-yn-1-yl)hydroxylamine (**1b**).*[21] **1b** was prepared from 4-ethynyltoluene (127 μL, 1.00 mmol) and the *(Z)-N*-benzylidene-benzylamine-*N*-oxide (**S1a**) (253 mg, 1.20 mmol). Reaction time: 16 h. Then, the reaction mixture was stirred for an additional 1 h after the

addition of *p*-toluenesulfonic acid. White solid (220 mg, 67%). TLC: R_f 0.37 (9:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, *J* = 7.6 Hz, 2H), 7.47 (d, *J* = 7.6 Hz, 2H), 7.42–7.27 (m, 8H), 7.16 (d, *J* = 8.0 Hz, 2H), 5.00 (s, 1H), 4.88 (brs, 1H), 4.08 (d, *J* = 13.2 Hz, 1H), 4.00 (d, *J* = 13.2 Hz, 1H), 2.37 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.8, 137.7, 137.4, 132.1, 129.9, 129.3, 129.1, 128.6, 128.5, 128.3, 127.7, 119.9, 89.2, 83.9, 63.4, 60.7, 21.7. HRMS (ESI) *m/z* calculated for $C_{23}H_{22}NO$ $[M+H]^+$ 328.1696, found 328.1702. IR (KBr film): 3229, 3062, 3029, 2918, 1509, 1452 cm^{-1}.

*N-Benzyl-N-(3-(3,5-dimethoxyphenyl)-1-phenylprop-2-yn-1-yl)hydroxylamine (**1c**).* **1c** was prepared from 1-ethynyl-3,5-dimethoxybenzene (162 mg, 1.00 mmol) and the *(Z)-N*-benzylidene-benzylamine-*N*-oxide (**S1a**) (253 mg, 1.20 mmol). Reaction time: 2 h. Then, the reaction mixture was stirred for an additional 2 h after the addition of *p*-toluenesulfonic acid. White solid (373 mg, quantitative yield). TLC: R_f 0.37 (5:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (dd, *J* = 8.8 Hz, 1.2 Hz, 2H), 7.38–7.26 (m, 8H), 6.72 (d, *J* = 2.4 Hz, 2H), 6.48 (t, *J* = 2.4, 1H), 5.16 (brs, 1H), 4.96 (s, 1H), 4.03 (d, *J* = 12.8 Hz, 1H), 3.98 (d, *J* = 12.8, 1H), 3.80 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.7, 137.4, 137.1, 129.9, 129.2, 128.6, 128.5, 128.4, 127.8, 124.2, 110.0, 102.1, 88.9, 84.3, 63.3, 61.4, 55.7. HRMS (ESI) *m/z* calculated for $C_{24}H_{23}NNaO_3$ $[M+Na]^+$: 396.1570, found 396.1563. IR (KBr film): 3228, 3029, 2360, 1588, 1453, 1205 cm^{-1}. mp: 134–135 °C.

*N-Benzyl-N-(3-(4-pentylphenyl)-1-phenylprop-2-yn-1-yl)hydroxylamine (**1d**).*[22] **1d** was prepared from 1-ethynyl-4-pentylbenzene (195 μL, 1.00 mmol) and the *(Z)-N*-benzylidenebenzylamine-*N*-oxide (**S1a**) (253 mg, 1.20 mmol). Reaction time: 4 h. Then, the reaction mixture was stirred for an additional 1 h after the addition of *p*-toluenesulfonic acid. White solid (360 mg, 94%). TLC: R_f 0.43 (9:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, *J* = 7.6 Hz, 2H), 7.49 (d, *J* = 8.0 Hz, 2H), 7.42–7.27 (m, 8H), 7.17 (d, *J* = 8.0 Hz, 2H), 5.03 (s, 1H), 4.75 (brs, 1H), 4.11 (d, *J* = 13.2 Hz, 1H), 4.00 (d, *J* = 13.2 Hz, 1H), 2.62 (t, *J* = 7.6 Hz, 2H), 1.62 (quintet, *J* = 7.6 Hz, 2H), 1.37–1.29 (m, 4H), 0.90 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.9, 137.7, 137.3, 132.1, 129.9, 129.1, 128.7, 128.6, 128.5, 128.3, 127.7, 120.1, 89.3, 83.8, 63.4, 60.8, 36.1, 31.6, 31.2, 22.7, 14.2. HRMS (ESI) *m/z*

calculated for $C_{27}H_{29}NNaO$ $[M+Na]^+$ 406.2141, found 406.2136. IR (KBr film): 2954, 2927, 2856, 1509, 1453 cm^{-1}.

*N-Benzyl-N-(3-(4-fluorophenyl)-1-phenylprop-2-yn-1-yl)hydroxylamine (**1e**).* **1e** was prepared from *p*-fluorophenylacetylene (115 μL, 1.00 mmol) and the *(Z)-N*-benzylidenebenzylamine-*N*-oxide (**S1a**) (253 mg, 1.20 mmol). Reaction time: 2 h. Then, the reaction mixture was stirred for an additional 1 h after the addition of *p*-toluenesulfonic acid. White solid (330 mg, quantitative yield). TLC: R_f 0.49 (5:1 hexanes/EtOAc). ^1H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, J = 8.8 Hz, 2H), 7.55 (dd, J = 8.8 Hz, 5.6 Hz, 2H), 7.41–7.28 (m, 8H), 7.05 (t, J = 8.8 Hz, 2H), 4.98 (s, 1H), 4.05 (d, J = 12.8 Hz, 1H), 4.00 (d, J = 12.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.8 (d, J_{C-F} = 248.4 Hz), 137.5, 137.2, 134.1 (d, J_{C-F} = 8.5 Hz), 129.9, 129.1, 128.6 128.5, 128.4, 127.8, 119.1 (d, J_{C-F} = 3.1 Hz), 115.8 (d, J_{C-F} = 21.6 Hz), 87.8, 84.4, 63.2, 60.6. ^{19}F NMR (376 MHz, $CDCl_3$): δ –110.8. HRMS (EI TOF) *m/z* calculated for $C_{22}H_{19}FNO$ $[M+H]^+$ 332.1445, found 332.1443. IR (KBr film): 3240, 2903, 1600, 1505, 1229, 835, 697 cm^{-1}. mp: 134–136 ^oC.

*N-Benzyl-N-(3-(3,4-dichlorophenyl)-1-phenylprop-2-yn-1-yl)hydroxylamine (**1f**).* **1f** was prepared from 3,4-dichlorophenylacetylene (171 mg, 1.00 mmol) and the *(Z)-N*-benzylidenebenzylamine-*N*-oxide (**S1a**) (253 mg, 1.20 mmol). Reaction time: 2 h. Then, the reaction mixture was stirred for an additional 1 h after the addition of *p*-toluenesulfonic acid. White solid (330 mg, 86%). TLC: R_f 0.43 (9:1 hexanes/EtOAc). ^1H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, J = 1.6 Hz, 1H), 7.60 (d, J = 7.2 Hz, 2H), 7.44–7.26 (m, 10H), 5.05 (brs, 1H), 4.97 (brs, 1H), 4.03 (d, J = 13.2 Hz, 1H), 3.97 (d, J = 13.2 Hz, 1H). ^{13}C NMR (100 MHz, Acetone-d_6): δ 139.6, 139.2, 134.2, 133.0, 132.9, 132.5, 131.7, 130.1, 129.8, 129.1, 129.0, 128.7, 127.9, 124.7, 89.9, 85.9, 64.4, 61.7. HRMS (ESI) *m/z* calculated for $C_{22}H_{18}Cl_2NO$ $[M+H]^+$ 382.0760, found 382.0759. IR (KBr film): 3233, 3029, 1738, 1473, 1217, 736, 697 cm^{-1}. mp: 133–136 ^oC.

*N-benzyl-N-(1-phenyl-3-(4-(trifluoromethyl)phenyl)prop-2-yn-1-yl)hydroxylamine (**1g**).* **1g** was prepared from *p*-(trifluoromethyl)phenyl acetylene (163 μL, 1.00 mmol) and the *(Z)-N*-benzylidenebenzylamine-*N*-oxide (**S1a**) (253 mg, 1.20 mmol). Reaction time: 6 h. Then, the reaction

mixture was stirred for an additional 1 h after the addition of *p*-toluenesulfonic acid. White solid (267 mg, 70%). TLC: R_f 0.37 (9:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, J = 8.0 Hz, 2H), 7.64–7.60 (m, 4H), 7.42–7.28 (m, 8H), 5.03 (s, 1H), 4.95 (brs, 1H), 4.09 (d, J = 13.2 Hz, 1H), 4.00 (d, J = 13.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.1, 137.0, 132.4, 130.5 (q, J_{C-F} = 32.5 Hz), 129.8, 129.1, 128.7, 128.6, 128.5, 127.9, 126.8, 125.5 (q, J_{C-F} = 3.9 Hz), 124.1 (q, J_{C-F} = 270.1 Hz), 87.5, 87.4, 63.3, 60.9. ^{19}F NMR (376 MHz, $CDCl_3$): δ –63.2. HRMS (ESI) *m/z* calcd for $C_{23}H_{19}F_3NO$ $[M+H]^+$ 382.1413, found 382.1411. IR (KBr film): 3031, 2905, 1613, 1452, 758, 698 cm^{-1}. mp: 146–148 °C.

*4-(3-(Benzyl(hydroxy)amino)-3-phenylprop-1-yn-1-yl)benzonitrile (**1h**).* **1k** was prepared from 4-ethynylbenzonitrile (127 mg, 1.00 mmol) and the *(Z)-N*-benzylidenebenzylamine-*N*-oxide (**S1a**) (253 mg, 1.20 mmol). Reaction time: 2 h. Then, the reaction mixture was stirred for an additional 1 h after the addition of *p*-toluenesulfonic acid. Yellow solid (180 mg, 53%). TLC: R_f 0.36 (4:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (s, 4H), 7.61 (d, J = 7.2 Hz, 2H), 7.42–7.28 (m, 8H), 5.02 (s, 1H), 4.05 (d, J = 13.2 Hz, 1H), 4.01 (d, J = 13.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.9, 132.7, 132.3, 129.8, 129.1, 128.8, 128.7, 128.6, 128.5, 127.9, 127.8, 118.6, 112.1, 89.7, 87.2, 63.4, 60.9. HRMS (ESI) *m/z* calculated for $C_{23}H_{19}N_2O$ $[M+H]^+$ 339.1492, found 339.1498. IR (KBr film): 3220, 2227, 1599, 1452, 846, 736 cm^{-1}. mp: 170–172 °C.

*Methyl 4-(3-(benzyl(hydroxy)amino)-3-phenylprop-1-yn-1-yl)benzoate (**1i**).* **1i** was prepared from Methyl 4-ethynylbenzoate (160 mg, 1.00 mmol) and the *(Z)-N*-benzylidenebenzylamine-*N*-oxide (**S1a**) (253 mg, 1.20 mmol). Reaction time: 16 h. Then, the reaction mixture was stirred for an additional 1 h after the addition of *p*-toluenesulfonic acid. White solid (278 mg, 75%). TLC: R_f 0.31 (9:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, J = 8.4 Hz, 2H), 7.64–7.62 (m, 4H), 7.41–7.28 (m, 8H), 5.02 (s, 1H), 4.99 (brs, 1H), 4.06 (d, J = 13.2 Hz, 1H), 4.00 (d, J = 13.2 Hz, 1H), 3.93 (s, 3H). ^{13}C NMR (100 MHz, Acetone-d_6): δ 166.8, 139.6, 139.3, 132.8, 130.8, 130.4, 130.1, 129.8, 129.1, 129.0, 128.9, 128.7, 127.9, 90.7, 87.6, 64.5, 61.7, 52.6. HRMS (ESI) *m/z* calculated for $C_{24}H_{21}NNaO_3$

$[M+Na]^+$ 394.1414, found 394.1415. IR (KBr film): 3452, 2951, 1722, 1276, 769, 697 cm^{-1}. mp: 145–147 °C.

*N-benzyl-N-(1-phenylnon-2-yn-1-yl)hydroxylamine (**1j**).*[6a] **1j** was prepared from 1-octyne (148 uL, 1.00 mmol) and the *(Z)-N*-benzylidenebenzylamine-*N*-oxide (**S1a**) (253 mg, 1.20 mmol). Reaction time: 2 h. Then, the reaction mixture was stirred for an additional 1 h after the addition of *p*-toluenesulfonic acid. Colorless oil (260 mg, 81%). TLC: R_f 0.51 (5:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, J = 8.8 Hz, 2H), 7.36–7.25 (m, 8H), 4.69 (s, 1H), 3.88 (s, 2H), 2.38 (td, J = 7.2 Hz, 2.0 Hz, 2H), 1.63 (quintet, J = 7.2 Hz, 2H), 1.48 (m, 2H), 1.36–1.30 (m, 4H), 0.91 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.0, 137.3, 129.9, 129.1, 128.5, 128.4, 128.0, 127.6, 89.7, 74.9, 62.7, 60.5, 31.5, 29.1, 28.9, 22.8, 19.2, 14.3. HRMS (ESI) *m/z* calcd for $C_{22}H_{28}NO$ $[M+H]^+$ 322.2165, found 322.2168. IR (KBr film): 3200, 2954, 2929, 2857, 1453 cm^{-1}.

*N-Benzyl-N-(3-(6-methoxynaphthalen-2-yl)-1-phenylprop-2-yn-1-yl)hydroxylamine (**1k**).* **1k** was prepared from 2-ethynyl-6-methoxynaphthalene (182 mg, 1.00 mmol) and the *(Z)-N*-benzylidenebenzylamine-*N*-oxide (**S1a**) (253 mg, 1.20 mmol). Reaction time: 1 h. Then, the reaction mixture was stirred for an additional 1 h after the addition of *p*-toluenesulfonic acid. White solid (225 mg, 57%). TLC: R_f 0.37 (9:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (s, 1H), 7.73–7.68 (m, 4H), 7.58 (dd, J = 8.4 Hz, 1.2 Hz, 1H), 7.45–7.25 (m, 8H), 7.16 (dd, J = 9.2 Hz, 2.8 Hz, 1H), 7.13 (d, J = 2.8 Hz, 1H), 5.07 (s, 1H), 4.84 (s, 1H), 4.16 (d, J = 13.2 Hz, 1H), 4.07 (d, J = 13.2 Hz, 1H), 3.93 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6): δ 159.3, 139.3, 138.9, 135.2, 132.6, 130.4, 130.2, 130.1, 129.9, 129.5, 129.0, 128.6, 128.3, 128.0, 127.6, 120.3, 118.9, 106.6, 89.8, 64.4, 61.8, 55.2. HRMS (ESI) *m/z* calculated for $C_{27}H_{24}NO_2$ $[M+H]^+$ 394.1802, found 394.1797. IR (KBr film): 3234, 3060, 3029, 1628, 1601, 759, 737 cm^{-1}. mp: 148–150 °C.

*N-Benzyl-N-(1-phenyl-3-(thiophen-3-yl)prop-2-yn-1-yl)hydroxylamine (**1l**).* **1l** was prepared from 3-ethynylthiophene (99 μL, 1.00 mmol) and the *(Z)-N*-benzylidenebenzylamine-*N*-oxide (**S1a**) (253 mg, 1.20 mmol). Reaction time: 16 h. Then, the reaction mixture was stirred for an additional 1 h after the addition of *p*-toluenesulfonic acid. White solid (278 mg, 87%). TLC: R_f 0.29 (9:1 hexanes/EtOAc). ^{1}H

NMR (400 MHz, $CDCl_3$): δ 7.63–7.61 (m, 2H), 7.55 (dd, *J* = 2.8 Hz, 1.2 Hz, 1H), 7.40–7.37 (m, 3H), 7.36–7.27 (m, 6H), 7.21 (dd, *J* = 5.2 Hz, 1.2 Hz, 1H), 4.96 (s, 1H), 4.04 (d, *J* = 13.2 Hz, 1H), 3.99 (d, *J* = 13.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.5, 137.2, 130.4, 129.9, 129.4, 129.2, 128.6, 128.5, 128.3, 127.8, 125.5, 121.9, 84.3, 83.9, 63.3, 60.3. HRMS (ESI) *m/z* calculated for $C_{20}H_{18}NOS$ $[M+H]^+$ 320.1104, found 320.1100. IR (KBr film): 3231, 3106, 3029, 2904, 1453, 1357 cm^{-1}. mp: 139–141 °C.

*N-Benzyl-N-(1-(4-methoxyphenyl)-3-phenylprop-2-yn-1-yl)hydroxylamine (**1m**).*[23] **1m** was prepared from phenylacetylene (110 μL, 1.00 mmol) and the (*Z*)-*N*-(4-methoxybenzylidene)-1-phenylmethanamine oxide (**S1b**) (290 mg, 1.20 mmol). Reaction time: 16 h. Then, the reaction mixture was stirred for an additional 1 h after the addition of *p*-toluenesulfonic acid. White solid (210 mg, 61%). TLC: R_f 0.45 (9:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59–7.57 (m, 2H), 7.55 (d, *J* = 8.8 Hz, 2H), 7.40 (d, *J* = 7.2 Hz, 2H), 7.37–7.32 (m, 5H), 7.29 (d, *J* = 7.2 Hz, 1H), 6.92 (d, *J* = 8.8 Hz, 2H), 4.95 (brs, 1H), 4.02 (s, 2H), 3.81 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.7, 137.2, 132.1, 130.4, 130.0, 129.5, 128.6, 128.5, 128.4, 127.7, 123.0, 113.9, 88.7, 85.0, 62.7, 60.4, 55.5. HRMS (ESI) *m/z* calcd for $C_{23}H_{22}NO_2$ $[M+H]^+$ 344.1651, found 344.1649. IR (KBr film): 3231, 3062, 3030, 1511, 1251 cm^{-1}.

*N-Benzyl-N-(1-(4-nitrophenyl)-3-phenylprop-2-yn-1-yl)hydroxylamine (**1n**).*[21] **1n** was prepared from phenylacetylene (110 μL, 1.00 mmol) and the (*Z*)-*N*-(4-nitrobenzylidene)-1-phenylmethanamine oxide (**S1c**) (308 mg, 1.20 mmol). Reaction time: 4 h. Then, the reaction mixture was stirred for an additional 1 h after the addition of *p*-toluenesulfonic acid. White solid (295 mg, 82%). TLC: R_f 0.40 (9:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (dt, *J* = 8.8 Hz, 2.0 Hz, 2H), 7.83 (dt, *J* = 8.8 Hz, 2.0 Hz, 2H), 7.60–7.58 (m, 2H), 7.45–7.30 (m, 8H), 5.06, (s, 1H), 4.19 (d, *J* = 12.8 Hz, 1H), 4.13 (d, *J* = 12.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.2, 145.0, 136.5, 132.2, 129.9, 129.8, 129.2, 128.8, 128.7, 128.1, 123.7, 122.3, 90.3, 82.9, 62.6, 61.8. HRMS (ESI) *m/z* calcd for $C_{22}H_{19}N_2O_3$ $[M+H]^+$ 359.1390, found 359.1386. IR (KBr film): 3238, 3030, 1597, 1489 cm^{-1}.

*N-Benzyl-N-(4-methyl-1-phenylpent-1-yn-3-yl)hydroxylamine (**1o**).*[21] **1o** was prepared from phenylacetylene (55.0 μL, 500 μmol), (*Z*)-*N*-(2-methylpropylidene)-1-phenylmethanamine oxide (**S1d**) (106 mg, 600 μmol). Reaction time: 16 h. Then, the reaction mixture was stirred for an additional 4 h after the addition of *p*-toluenesulfonic acid. White solid (115 mg, 82%). TLC: R_f 0.40 (9:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52–7.49 (m, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.34–7.25 (m, 6H), 4.42 (s, 1H), 4.23 (d, *J* = 12.8 Hz, 1H), 3.89 (d, *J* = 12.8 Hz, 1H), 3.39 (d, *J* = 8.8 Hz, 1H), 2.14 (m, 1H), 1.13 (d, *J* = 6.8 Hz, 3H), 1.09 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.7, 132.1, 129.6, 128.6, 128.5, 128.4, 127.6, 123.2, 88.0, 85.4, 66.5, 62.5, 31.1, 20.2, 20.0. HRMS (ESI) *m/z* calcd for $C_{19}H_{22}NO$ $[M+H]^+$ 280.1696, found 280.1697. IR (KBr film): 3453, 2960, 1489, 1384 cm^{-1}.

*N-(1,3-Diphenylprop-2-yn-1-yl)-N-(4-methoxybenzyl)hydroxylamine (**1p**).*[21] **1p** was prepared from phenylacetylene (110 μL, 1.00 mmol) and the (*Z*)-*N*-benzylidene-1-(4-methoxyphenyl)methanamine oxide (**S1e**) (290 mg, 1.20 mmol). Reaction time: 16 h. Then, the reaction mixture was stirred for an additional 12 h after the addition of *p*-toluenesulfonic acid. White solid (355 mg, quantitative yield). TLC: R_f 0.30 (5:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, *J* = 6.8 Hz, 2H), 7.59–7.57 (m, 2H), 7.41–7.31 (m, 8H), 6.82 (dt, *J* = 8.8 Hz, 2.8 Hz, 2H), 5.02 (s, 1H), 4.06 (d, *J* = 13.2 Hz, 1H), 4.00 (d, *J* = 13.2 Hz, 1H), 3.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.3, 137.7, 132.2, 131.0, 129.2, 129.1, 128.7, 128.6, 128.5, 128.3, 122.9, 114.0, 89.0, 84.6, 63.1, 60.5, 55.5. HRMS (ESI) *m/z* calcd for $C_{23}H_{22}NO_2$ $[M+H]^+$ 344.1645, found 344.1650. IR (KBr film): 3231, 3061, 2906, 1489, 1301 cm^{-1}.

*N-(tert-Butyl)-N-(1,3-diphenylprop-2-yn-1-yl)hydroxylamine (**1q**).* **1q** was prepared from phenylacetylene (550 μL, 5.00 mmol) and *N-tert*-butylphenylnitrone (1.06 g, 6.00 mmol). Reaction time: 16 h. Then, the reaction mixture was stirred for an additional 12 h after the addition of *p*-toluenesulfonic acid. Light yellow solid (1.10 g, 79%). TLC: R_f 0.47 (9:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, *J* = 8.8 Hz, 2H), 7.51–7.48 (m, 2H), 7.39–7.29 (m, 6H), 5.20 (s, 1H), 4.34

(brs, 1H), 1.36 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.4, 131.7, 128.5, 128.4, 128.3 (2C), 127.6, 123.3, 88.7, 87.2, 60.2, 56.8, 26.8. HRMS (ESI) *m/z* calcd for $C_{19}H_{22}NO$ $[M+H]^+$ 280.1696, found 280.1698. IR (KBr film): 3532, 3457, 2971, 1597, 1490, 720, 650 cm^{-1}. mp: 76–79 °C.

*N-Benzyl-N-(1,3-dicyclohexylprop-2-yn-1-yl)hydroxylamine (**1r**).* **1r** was prepared from cyclohexylacetylene 95% (230 μL, 1.00 mmol) and (*Z*)-*N*-(cyclohexylmethylene)-1-phenylmethanamine oxide (**S1f**) (261 mg, 1.20 mmol). Reaction time: 24 h. Then, the reaction mixture was stirred for an additional 2 h after the addition of *p*-toluenesulfonic acid. White solid (323 mg, 99%). TLC: R_f 0.25 (6:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40–7.25 (m, 5H), 4.39 (s, 1H), 4.11 (d, *J* = 12.8 Hz, 1H), 3.79 (d, *J* = 12.8 Hz, 1H), 3.22 (d, *J* = 4.0 Hz, 1H), 2.55–2.51 (m, 1H), 2.09–0.86 (m, 21H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.8, 129.5, 128.5, 127.4, 93.3, 74.8, 64.9, 62.5, 40.3, 33.3, 33.2, 30.6 (2C), 29.3, 26.8, 26.3, 26.1, 25.0. HRMS (ESI) *m/z* calcd for $C_{22}H_{32}NO$ $[M+H]^+$ 326.2478, found 326.2483.

IR (KBr film): 3534, 3462, 2927, 1604, 1495, 743, 699 cm^{-1}. mp: 76–78 °C.

*N-benzyl-N-(1-cyclohexyl-3-phenylprop-2-yn-1-yl)hydroxylamine (**1s**).*[4] **1s** was prepared from phenylacetylene (110 μL, 1.00 mmol) and (*Z*)-*N*-(cyclohexylmethylene)-1-phenylmethanamine oxide (**S1f**) (261 mg, 1.20 mmol). Reaction time: 16.5 h. Then, the reaction mixture was stirred for an additional 2.5 h after the addition of *p*-toluenesulfonic acid. White solid (272 mg, 85%). TLC: R_f 0.5 (7:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (dd, *J* = 6.8 Hz, 2.8 Hz, 2H), 7.42 (d, J = 6.8 Hz, 2H), 7.35–7.29 (m, 6H), 4.60 (brs, 1H), 4.20 (d, *J* = 13.2 Hz, 1H), 3.92 (d, *J* = 13.2 Hz, 1H), 3.47 (d, *J* = 8.8 Hz, 1H), 2.14–2.12 (m, 2H), 1.88–1.67 (m, 4H), 1.36–0.97 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.8, 132.1, 129.5, 128.6, 128.5, 128.4, 127.5, 123.2, 88.3, 85.3, 65.3, 62.5, 40.3, 30.8, 30.7, 26.8, 26.3, 26.1. HRMS (ESI) *m/z* calcd for $C_{22}H_{26}NO$ $[M+H]^+$ 320.2009, found 320.2015. IR (KBr film): 3535, 3457, 2925, 1598, 1489, 756, 691 cm^{-1}. mp: 126–128°C. (Lit.[4] 126–128°C.)

General procedure for the synthesis of 4-isoxazoline 2a–s.

(PPh_3)AuCl/AgOTf: In a 25 mL one-arm roundbottom flask, propargylic *N*-hydroxylamine (200 μmol), (PPh_3)AuCl (5.0 mg, 10.0 μmol, 5 mol%), and AgOTf (2.6 mg, 10.0 μmol, 5 mol%) were dissolved in anhydrous toluene (4 mL) under Ar atmosphere. The resulting suspension was stirred at room temperature (as shown in table 2). Upon completion of the reaction, the reaction mixture was filtered through a plug of Celite, and rinsed with ether (20 mL). The filtrate was concentrated by rotary evaporation. The residue was purified by column chromatography (19:1 hexanes/EtOAc).

(PPh_3)AuNTf$_2$: In a 25 mL one-arm roundbottom flask, propargylic *N*-hydroxylamine (200 μmol) and (PPh_3)AuNTf$_2$ (7.4 mg, 10.0 μmol, 5 mol%) were dissolved in anhydrous toluene (4 mL) under Ar atmosphere. The resulting suspension was stirred at room temperature (as shown in table 2). Upon completion of the reaction, the reaction mixture was filtered through a plug of Celite, and rinsed with ether (20 mL). The filtrate was concentrated by rotary evaporation. The residue was purified by column chromatography (hexanes/EtOAc).

*2-Benzyl-3,5-diphenyl-2,3-dihydroisoxazole (**2a**).*[4,21] **2a** was prepared from *N*-benzyl-*N*-(1,3-diphenylprop-2-yn-1-yl)hydroxylamine (**1a**) (62.6 mg, 200 μmol). Purification by column chromatography (98:2 hexanes/EtOAc) afforded **2a** as a yellow solid. Reaction time: 15 min, yield: 59.0 mg (94%) for (PPh_3)AuCl/AgOTf. Reaction time: 30 min, yield: 56.3 mg (90 %) for (PPh_3)AuNTf$_2$. TLC: R_f 0.65 (9:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58–7.56 (m, 2H), 7.43 (d, J = 8.4 Hz, 2H), 7.37–7.23 (m, 11H), 5.42 (d, J = 2.4 Hz, 1H), 5.05 (d, J = 2.4 Hz, 1H), 4.43 (d, J = 12.8 Hz, 1H), 4.11 (d, J = 12.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.1, 142.3, 136.6, 129.8, 129.3, 128.9, 128.7, 128.6, 128.5, 127.8 (2C), 127.3, 125.9, 95.9, 73.8, 63.6. HRMS (ESI) *m/z* calcd for $C_{22}H_{20}NO$ $[M+H]^+$ 314.1539, found 314.1526. IR (KBr film): 3061, 1600, 1493, 771, 697 cm^{-1}. mp: 105–108 °C. (Lit.[4] 102–104 °C).

*(E)-Chalcone (**3a**).* TLC: R_f 0.62 (9:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (dt, J = 1.2 Hz, 6.8 Hz, 2H), 7.81 (d, J = 16.0 Hz, 1H), 7.66–7.64 (m, 2H), 7.61–7.56 (m, 2H), 7.53–7.49 (m, 2H), 7.44–7.42 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.7, 145.0, 138.4, 135.1, 133.0, 130.7,

129.2, 128.8, 128.7, 128.6, 122.3. HRMS (ESI) *m/z* calcd for $C_{15}H_{13}O$ $[M+H]^+$ 209.0961, found 209.0964. IR (KBr film): 3059, 1664, 1606, 1215, 746, 688 cm^{-1}.

*2-Benzyl-3-phenyl-5-(p-tolyl)-2,3-dihydroisoxazole (**2b**).* **2b** was prepared from *N*-benzyl-*N*-(1-phenyl-3-(*p*-tolyl)prop-2-yn-1-yl)hydroxylamine (**1b**) (65.4 mg, 200 μmol). Purification by column chromatography (98:2 hexanes/EtOAc) afforded **2b** as a yellow solid. Reaction time: 15 min, yield: 53.0 mg (81%) for $(PPh_3)AuCl/AgOTf$. Reaction time: 15 min, yield: 52.7 mg (79 %) for $(PPh_3)AuNTf_2$. TLC: R_f 0.74 (9:1 hexanes/EtOAc). ^1H NMR (400 MHz, C_6D_6): δ 7.47 (dt, *J* = 8.0 Hz, 2.0 Hz, 2H), 7.40 (dm, *J* = 8.0 Hz, 2H), 7.36 (dm, *J* = 8.0 Hz, 2H), 7.17–7.12 (m, 4H), 7.09–7.05 (m, 2H), 6.88 (d, *J* = 8.0 Hz, 2H), 5.11 (d, *J* = 2.8 Hz, 1H), 4.87 (d, *J* = 2.8 Hz, 1H), 4.33 (d, *J* = 13.2 Hz, 1H), 3.92 (d, *J* = 13.2 Hz, 1H), 2.01 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.7, 143.6, 139.5, 138.0, 130.1, 129.8, 129.2, 129.0, 128.2, 128.1, 128.0, 127.2, 126.6, 96.1, 75.0, 64.2, 21.7. HRMS (EI) *m/z* calcd for $C_{23}H_{21}NO$ $[M]^+$ 327.1623, found 327.1625. IR (KBr film): 3028, 1653, 1510, 759, 731 cm^{-1}.

*2-Benzyl-5-(3,5-dimethoxyphenyl)-3-phenyl-2,3-dihydroisoxazole (**2c**).* **2c** was prepared from *N*-benzyl-*N*-(3-(3,5-dimethoxyphenyl)-1-phenylprop-2-yn-1-yl)hydroxylamine (**1c**) (74.6 mg, 200 μmol). Purification by column chromatography (95:5 hexanes/EtOAc) afforded **2c** as a pale yellow solid. Reaction time: 10 min, yield: 74.6 mg (99%) for $(PPh_3)AuCl/AgOTf$. Reaction time: 15 min, yield: 67.1 mg (90%) for $(PPh_3)AuNTf_2$. TLC: R_f 0.54 (5:1 hexanes/EtOAc). ^1H NMR (400 MHz, C_6D_6): δ 7.39–7.36 (m, 4H), 7.17–7.01 (m, 6H), 6.92 (d, *J* = 2.4 Hz, 2H), 6.54 (t, *J* = 2.4 Hz, 1H), 5.13 (d, *J* = 3.2 Hz, 1H), 4.86 (d, *J* = 3.2 Hz, 1H), 4.34 (d, *J* = 13.2 Hz, 1H), 3.93 (d, *J* = 13.2 Hz, 1H), 3.25 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.9, 153.7, 143.4, 137.8, 131.8, 130.2, 129.2, 128.9, 128.2, 128.1, 127.9, 104.8, 102.6, 97.6, 74.8, 64.1, 55.3. HRMS (ESI) *m/z* calculated for $C_{24}H_{24}NO_3$ $[M+H]^+$ 374.1751, found 374.1758. IR (KBr film): 3017, 2360, 1592, 1215, 698, 668 cm^{-1}.

*2-Benzyl-5-(4-pentylphenyl)-3-phenyl-2,3-dihydroisoxazole (**2d**).*[15] **2d** was prepared from *N*-benzyl-*N*-(3-(4-pentylphenyl)-1-phenylprop-2-yn-1-yl)hydroxylamine (**1d**) (76.6 mg, 200 μmol). Purification by column chromatography (98:2 hexanes/EtOAc) afforded **2d** as a yellow syrup. Reaction time: 5 min, yield: 58.0 mg (76%) for $(PPh_3)AuCl/AgOTf$. Reaction time: 15 min, yield: 62.0 mg (81 %) for

$(PPh_3)AuNTf_2$. TLC: R_f 0.60 (9:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, C_6D_6): δ 7.50 (dt, J = 8.4 Hz, 1.6 Hz, 2H), 7.41–7.35 (m, 4H), 7.17–7.02 (m, 6H), 6.95 (d, J = 8.4 Hz, 2H), 5.13 (d, J = 3.2 Hz, 1H), 4.87 (d, J = 3.2 Hz, 1H), 4.34 (d, J = 13.2 Hz, 1H), 3.92 (d, J = 13.2 Hz, 1H), 2.38 (t, J = 7.6 Hz, 2H), 1.45 (quintet, J = 7.6 Hz, 2H), 1.25–1.13 (m, 4H), 0.83 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.7, 144.6, 143.6, 138.0, 130.1, 129.2, 129.1, 129.0, 128.2, 128.1, 128.0, 127.5, 126.7, 96.2, 74.9, 64.2, 36.4, 32.1, 31.8, 23.3, 14.7. HRMS (ESI) *m/z* calcd for $C_{27}H_{30}NO$ $[M+H]^+$ 384.2322, found 384.2329. IR (KBr film): 3061, 2928, 1652, 770, 733 cm^{-1}.

*2-Benzyl-5-(4-fluorophenyl)-3-phenyl-2,3-dihydroisoxazole (**2e**).* **2e** was prepared from *N*-benzyl-*N*-(3-(4-fluorophenyl)-1-phenylprop-2-yn-1-yl)hydroxylamine (**1e**) (66.2 mg, 200 μmol). Purification by column chromatography (98:2 hexanes/EtOAc) afforded **2e** as a yellow oil. Reaction time: 10 min, yield: 65.0 mg (98%) for $(PPh_3)AuCl/AgOTf$. Reaction time: 15 min, yield: 52.3 mg (79 %) for $(PPh_3)AuNTf_2$. TLC: R_f 0.65 (9:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, C_6D_6): δ 7.38 (dd, J = 8.8 Hz, 1.2 Hz, 2H), 7.34 (dd, J = 8.8 Hz, 1.2 Hz, 2H), 7.24 (dd, J = 8.8 Hz, 5.2 Hz, 2H), 7.18–7.13 (m, 4H), 7.10–7.05 (m, 2H), 6.65 (tt, J = 8.8 Hz, 2.0 Hz, 2H), 4.96 (d, J = 2.8 Hz, 1H), 4.83 (d, J = 2.8 Hz, 1H), 4.27 (d, J = 13.2 Hz, 1H), 3.89 (d, J = 13.2 Hz, 1H). ^{13}C NMR (100 MHz, C_6D_6): δ 163.8 (d, J_{CF} = 247.6 Hz), 152.6, 143.3, 137.8, 130.0, 129.2, 129.1, 128.5, 128.5, 128.5, 128.2, 127.9, 126.0 (d, J_{CF} = 3.9 Hz), 116.0 (d, J_{CF} = 21.6 Hz), 96.7 (d, J_{CF} = 1.6 Hz), 96.7, 75.0, 64.1. ^{19}F NMR (376 MHz, $CDCl_3$): δ –111.9. HRMS (EI) *m/z* calcd for $C_{22}H_{18}FNO$ $[M]^+$ 331.1372, found 331.1367. IR (KBr film): 3029, 1602, 1510, 733, 697 cm^{-1}.

*2-Benzyl-5-(3,4-dichlorophenyl)-3-phenyl-2,3-dihydroisoxazole (**2f**).* **2f** was prepared from *N*-benzyl-*N*-(3-(3,4-dichlorophenyl)-1-phenylprop-2-yn-1-yl)hydroxylamine (**1f**) (76.4 mg, 200 μmol). Purification by column chromatography (98:2 hexanes/EtOAc) afforded **2f** as a pale yellow solid. Reaction time: 40 min, yield: 74.0 mg (97%) for $(PPh_3)AuCl/AgOTf$. Reaction time: 60 min, yield: 62.6 mg (82%) for $(PPh_3)AuNTf_2$. TLC: R_f 0.61 (9:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, C_6D_6): δ 7.46 (d, J = 2.0 Hz, 1H), 7.33 (dt, J = 8.0 Hz, 1.6 Hz, 2H), 7.29 (dt, J = 8.0 Hz, 1.6 Hz, 2H), 7.18–7.06 (m, 6H), 6.93 (dd, J = 8.0 Hz, 2.0 Hz, 1H), 6.87 (d, J = 8.0 Hz, 1H), 4.83 (d, J = 2.8 Hz, 1H), 4.77 (d, J =

2.8 Hz, 1H), 4.20 (d, *J* =13.2 Hz, 1H), 3.84 (d, *J* =13.2 Hz, 1H). ^{13}C NMR (100 MHz, CDCl3): δ 151.0, 141.7, 136.3, 133.1, 132.9, 130.6, 129.7, 128.9, 128.8, 128.6, 128.0, 127.9, 127.8, 127.2, 125.1, 97.8, 73.9, 63.6. HRMS (EI) *m/z* calcd for $C_{22}H_{17}Cl_2NO$ $[M]^+$ 381.0687, found 381.0683. IR (KBr film): 3062, 1651, 1468, 1046, 732, 676 cm^{-1}. mp: 88–89 °C.

*2-Benzyl-3-phenyl-5-(4-(trifluoromethyl)phenyl)-2,3-dihydroisoxazole (**2g**)*. **2g** was prepared from *N*-benzyl-*N*-(1-phenyl-3-(4-(trifluoromethyl)phenyl)prop-2-yn-1-yl)hydroxylamine (**1g**) (76.2 mg, 200 μmol). Purification by column chromatography (98:2 hexanes/EtOAc) afforded **2g** as a white solid. Reaction time: 30 min, yield: 62.2 mg (82%) for $(PPh_3)AuCl/AgOTf$. Reaction time: 60 min, yield: 72.4 mg (95 %) for $(PPh_3)AuNTf_2$. TLC: R_f 0.68 (9:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, C_6D_6): δ 7.36 (dt, *J* = 8.0 Hz, 1.6 Hz, 2H), 7.33 (dt, *J* = 8.0 Hz, 1.6 Hz, 2H), 7.24–7.14 (m, 8H), 7.11–7.06 (m, 2H), 5.03 (d, *J* = 2.8 Hz, 1H), 4.82 (d, *J* = 2.8 Hz, 1H), 4.24 (d, *J* = 13.2 Hz, 1H), 3.86 (d, *J* = 13.2 Hz, 1H). ^{13}C NMR (100 MHz, C_6D_6): δ 152.1, 142.9, 137.6, 132.9 (q. J_{CF} = 1.6 Hz), 131.3, 130.9, 130.0, 129.3, 129.1, 128.3 (q. J_{CF} = 20.9 Hz), 127.9, 126.7, 126.0 (q. J_{CF} = 3.9 Hz), 125.2 (q. J_{CF} = 270.9 Hz), 99.3, 74.9, 64.1. ^{19}F NMR (376 MHz, $CDCl_3$): δ –62.8 HRMS (ESI) *m/z* calcd for $C_{23}H_{19}F_3NO$ $[M+H]^+$ 382.1413, found 382.1414. IR (KBr film): 3063, 1494, 1125, 731, 697 cm^{-1}. mp: 124–127 °C.

*4-(2-Benzyl-3-phenyl-2,3-dihydroisoxazol-5-yl)benzonitrile (**2h**)*. **2h** was prepared from 4-(3-(benzyl(hydroxy)amino)-3-phenylprop-1-yn-1-yl)benzonitrile (**1h**) (67.6 mg, 200 μmol). Purification by column chromatography (95:5 hexanes/EtOAc) afforded **2h** as a white solid. Reaction time: 30 min, yield: 46.0 mg (68%) for $(PPh_3)AuCl/AgOTf$. Reaction time: 60 min, yield: 47.3 mg (70 %) for $(PPh_3)AuNTf_2$. TLC: R_f 0.65 (4:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, C_6D_6): δ 7.33 (dt, *J* = 8.0 Hz, 1.6 Hz, 2H), 7.29 (dt, *J* = 8.0 Hz, 1.6 Hz, 2H), 7.18–7.13 (m, 4H), 7.10–7.03 (m, 2H), 7.02 (dt, *J* = 8.8 Hz, 2.0 Hz, 2H), 6.87 (dt, *J* = 8.8 Hz, 2.0 Hz, 2H), 4.97 (d, *J* = 2.8 Hz, 1H), 4.78 (d, *J* = 2.8 Hz, 1H), 4.18 (d, *J* = 13.2 Hz, 1H), 3.82 (d, *J* = 13.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.4, 141.4, 136.2, 133.1, 132.4, 129.7, 128.8, 128.6, 128.0, 127.9, 127.2, 126.4, 118.7, 112.5, 99.7, 74.0, 63.6. HRMS (ESI) *m/z* calcd for $C_{23}H_{19}N_2O$ $[M+H]^+$ 339.1492, found 339.1497. IR (KBr film): 3061, 3029, 2226, 1607, 738, 697 cm^{-1}. mp: 118–120 °C.

*Methyl 4-(2-benzyl-3-phenyl-2,3-dihydroisoxazol-5-yl)benzoate (**2i**).* **2i** was prepared from methyl 4-(3-(benzyl(hydroxy)amino)-3-phenylprop-1-yn-1-yl)benzoate (**1i**) (74.2 mg, 200 μmol). Purification by column chromatography (95:5 hexanes/EtOAc) afforded **2i** as a white solid. Reaction time: 45 min, yield: 59.0 mg (80%) for $(PPh_3)AuCl/AgOTf$. Reaction time: 60 min, yield: 57.9 mg (78 %) for $(PPh_3)AuNTf_2$. TLC: R_f 0.50 (9:1 hexanes/EtOAc). ^1H NMR (400 MHz, C_6D_6): δ 8.02 (dt, J = 8.8 Hz, 1.6 Hz, 2H), 7.41 (dt, J = 8.8 Hz, 1.6 Hz, 2H), 7.36 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 7.17–7.12 (m, 4H), 7.10–7.05 (m, 2H), 5.08 (d, J = 2.8 Hz, 1H), 4.82 (d, J = 2.8 Hz, 1H), 4.25 (d, J = 13.2 Hz, 1H), 3.85 (d, J = 13.2 Hz, 1H), 3.44 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6): δ 166.6, 152.6, 142.9, 137.7, 133.8, 131.4, 130.5, 130.0, 129.2, 129.1, 128.3, 128.2, 127.9, 126.4, 99.5, 74.9, 64.1, 52.1. HRMS (EI) *m/z* calcd for $C_{24}H_{21}NO_3$ $[M]^+$ 371.1521, found 371.1516. IR (KBr film): 3061, 3028, 2950, 1720, 1242, 772, 697 cm^{-1}. mp: 146–147 °C.

*2-Benzyl-5-hexyl-3-phenyl-2,3-dihydroisoxazole (**2j**).*[14] **2j** was prepared from *N*-benzyl-*N*-(1-phenylnon-2-yn-1-yl)hydroxylamine (**1j**) (64.2 mg, 200 μmol). Purification by column chromatography (98:2 hexanes/EtOAc) afforded **2j** as a yellow oil. Reaction time: 10 min, yield: 56.0 mg (87%) for $(PPh_3)AuCl/AgOTf$. Reaction time: 10 min, yield: 53.3 mg (83 %) for $(PPh_3)AuNTf_2$. TLC: R_f 0.57 (9:1 hexanes/EtOAc). ^1H NMR (400 MHz, C_6D_6): δ 7.38 (d, J = 8.0 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), 7.21–7.17 (m, 2H), 7.13–7.04 (m, 4H), 4.76 (s, 1H), 4.49 (m, 1H), 4.28 (d, J = 13.2 Hz, 1H), 3.89 (d, J = 13.2 Hz, 1H), 2.03 (t, J = 7.6 Hz, 2H), 1.40 (quintet, J = 7.6 Hz, 2H), 1.23–1.09 (m, 6H), 0.85 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, C_6D_6): δ 156.2, 144.3, 138.2, 129.9, 129.1, 128.9, 128.0, 127.9, 127.8, 96.0, 74.4, 64.3, 32.3, 29.6, 27.7, 26.8, 23.4, 14.7. HRMS (ESI) *m/z* calcd for $C_{22}H_{28}NO$ $[M+H]^+$ 322.2165, found 322.2169. IR (KBr film): 3062, 2954, 2927, 1453, 771, 669 cm^{-1}.

*2-Benzyl-5-(6-methoxynaphthalen-2-yl)-3-phenyl-2,3-dihydroisoxazole (**2k**).* **2k** was prepared from *N*-benzyl-*N*-(3-(6-methoxynaphthalen-2-yl)-1-phenylprop-2-yn-1-yl)hydroxylamine (**1k**) (78.6 mg, 200 μmol). Purification by column chromatography (95:5 hexanes/EtOAc) afforded **2k** as a yellow solid. Reaction time: 10 min, yield: 55.0 mg (70%) for $(PPh_3)AuCl/AgOTf$. Reaction time: 30 min, yield: 61.0 mg (78%) for $(PPh_3)AuNTf_2$. TLC: R_f 0.54 (9:1 hexanes/EtOAc). ^1H NMR (400 MHz, C_6D_6): δ 8.05 (s,

1H), 7.59 (dd, *J* = 8.8 Hz, 1.2 Hz, 1H), 7.49 (d, *J* = 8.8 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 4H), 7.33 (d, *J* = 8.8 Hz, 1H), 7.20–7.16 (m, 3H), 7.11–7.01 (m, 4H), 6.85 (d, *J* = 1.2 Hz, 1H), 5.25 (d, *J* = 2.4 Hz, 1H), 4.94 (d, *J* = 2.4 Hz, 1H), 4.41 (d, *J* = 13.2 Hz, 1H), 3.98 (d, *J* = 13.2 Hz, 1H), 3.34 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6): δ 159.3, 153.9, 143.6, 138.0, 135.8, 130.8, 130.1, 129.5, 129.2, 129.1, 129.0, 128.1, 128.0, 127.6, 125.9, 125.1, 125.0, 120.1, 106.7, 96.9, 75.1, 64.2, 55.2. HRMS (ESI) *m/z* calcd for $C_{27}H_{24}NO_2$ $[M+H]^+$ 394.1802, found 394.1806. IR (KBr film): 3060, 3028, 2360, 1625, 751, 697 cm^{-1}. mp: 121–123 °C.

*2-Benzyl-3-phenyl-5-(thiophen-3-yl)-2,3-dihydroisoxazole (**2l**).* **2l** was prepared from *N*-benzyl-*N*-(1-phenyl-3-(thiophen-3-yl)prop-2-yn-1-yl)hydroxylamine (**1l**) (63.8 mg, 200 μmol). Purification by column chromatography (98:2 hexanes/EtOAc) afforded **2l** as a white solid. Reaction time: 5 min, yield: 48.0 mg (75%) for $(PPh_3)AuCl/AgOTf$. Reaction time: 15 min, yield: 50.0 mg (78%) for $(PPh_3)AuNTf_2$. TLC: R_f 0.72 (9:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, C_6D_6): δ 7.37 (d, *J* = 7.2 Hz, 2H), 7.33 (d, *J* = 7.2 Hz, 2H), 7.17–7.12 (m, 5H), 7.10–7.04 (m, 2H), 6.93 (dd, *J* = 5.2 Hz, 1.2 Hz, 1H), 6.72 (dd, *J* = 5.2 Hz, 3.2 Hz, 1H), 4.92 (d, *J* = 2.8 Hz, 1H), 4.81 (d, *J* = 2.8 Hz, 1H), 4.29 (d, *J* = 13.2 Hz, 1H), 3.87 (d, *J* = 13.2 Hz, 1H). ^{13}C NMR (100 MHz, C_6D_6): δ 150.0, 143.4, 137.9, 131.0, 130.1, 129.2, 129.0, 128.2, 128.1, 127.9, 126.6, 126.4, 123.7, 96.7, 74.8, 64.2. HRMS (ESI) *m/z* calcd for $C_{20}H_{18}NOS$ $[M+H]^+$ 320.1104, found 320.1108. IR (KBr film): 3107, 3028, 1659, 1453, 787, 657 cm^{-1}. mp: 85–88 °C.

*2-Benzyl-3-(4-methoxyphenyl)-5-phenyl-2,3-dihydroisoxazole (**2m**).* **2m** was prepared from *N*-benzyl-*N*-(1-(4-methoxyphenyl)-3-phenylprop-2-yn-1-yl)hydroxylamine (**1m**) (68.6 mg, 200 μmol). Purification by column chromatography (95:5 hexanes/EtOAc) afforded **2m** as a yellow solid. Reaction time: 15 min, yield: 68.0 mg (99%)for $(PPh_3)AuCl/AgOTf$. Reaction time: 20 min, yield: 63.0 mg (92%) for $(PPh_3)AuNTf_2$. TLC: R_f 0.52 (9:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, C_6D_6): δ 7.53–7.51 (m, 2H), 7.41 (d, *J* = 6.8 Hz, 2H), 7.26 (dt, *J* = 8.8 Hz, 2.4 Hz, 2H), 7.18–7.14 (m, 2H), 7.10 (dt, *J* = 7.6 Hz, 1.2 Hz, 1H), 7.04–7.00 (m, 3H), 6.78 (dt, *J* = 8.8 Hz, 2.4 Hz), 5.14 (d, *J* = 2.8 Hz, 1H), 4.87 (d, *J* = 2.8 Hz, 1H), 4.33 (d, *J* = 13.2 Hz, 1H), 3.94 (d, *J* = 13.2 Hz, 1H), 3.27 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6): δ 160.2, 153.5, 138.0, 135.4, 130.1, 130.0, 129.5, 129.3, 129.1, 129.0, 128.1, 126.6, 114.7, 97.2, 74.6,

64.0, 55.3. HRMS (EI) *m/z* calcd for $C_{23}H_{21}NO_2$ $[M]^+$ 343.1572, found 343.1564. IR (KBr film): 3062, 3029, 2836, 1653, 1608, 763, 698 cm^{-1}. mp: 68–70 °C.

*2-Benzyl-3-(4-nitrophenyl)-5-phenyl-2,3-dihydroisoxazole (**2n**).* **2n** was prepared from *N*-benzyl-*N*-(1-(4-nitrophenyl)-3-phenylprop-2-yn-1-yl)hydroxylamine (**1n**) (71.6 mg, 200 μmol). Purification by column chromatography (97:3 hexanes/EtOAc) afforded **2n** as a brown solid. Reaction time: 10 min, yield: 71.0 mg (99%) for $(PPh_3)AuCl/AgOTf$. Reaction time: 15 min, yield: 61.0 mg (85%) for $(PPh_3)AuNTf_2$. TLC: R_f 0.60 (9:1 hexanes/EtOAc). ^1H NMR (400 MHz, C_6D_6): δ 7.81 (dt, *J* = 8.8 Hz, 2.0 Hz, 2H), 7.49–7.47 (m, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.14–7.03 (m, 6H), 6.99 (dt, *J* = 8.0 Hz, 2.0 Hz, 2H), 4.91 (d, *J* = 2.8 Hz, 1H), 4.63 (d, *J* = 2.8 Hz, 1H), 4.28 (d, *J* = 12.8 Hz, 1H), 3.77 (d, *J* = 12.8 Hz, 1H). ^{13}C NMR (100 MHz, C_6D_6): δ 154.3, 149.9, 148.1, 137.1, 130.8, 130.1, 130.0, 129.3, 129.2, 129.1, 128.1, 126.6, 124.2, 95.3, 73.5, 63.9. HRMS (EI) *m/z* calcd for $C_{22}H_{18}N_2O_3$ $[M]^+$ 358.1317, found 358.1318. IR (KBr film): 3062, 3030, 1519, 734, 696 cm^{-1}. mp: 120–122 °C.

*2-Benzyl-3-isopropyl-5-phenyl-2,3-dihydroisoxazole (**2o**).*[4, 12] **2o** was prepared from *N*-benzyl-*N*-(4-methyl-1-phenylpent-1-yn-3-yl)hydroxylamine (**1o**) (55.8 mg, 200 μmol). Purification by column chromatography (98:2 hexanes/EtOAc) afforded **2o** as a colorless oil. Reaction time: 30 min, yield: 50.7 mg (91%) for $(PPh_3)AuCl/AgOTf$. Reaction time: 15 min, yield: 49.0 mg (88%) for $(PPh_3)AuNTf_2$. TLC: R_f 0.62 (9:1 hexanes/EtOAc). ^1H NMR (400 MHz, C_6D_6): δ 7.50 (dt, *J* = 7.6 Hz, 1.6 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.19 (d, *J* = 8.4 Hz, 2H), 7.10 (tt, *J* = 7.6 Hz, 1.6 Hz, 1H), 7.06–6.95 (m, 3H), 5.02 (d, *J* = 2.8 Hz, 1H), 4.20 (d, *J* = 13.2 Hz, 1H), 3.68 (d, *J* = 13.2 Hz, 1H), 3.51 (dd, *J* = 6.4 Hz, 2.8 Hz, 1H), 1.66 (octet, *J* = 6.4 Hz, 1H), 0.91 (d, *J* = 6.4 Hz, 3H), 0.88 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.8, 138.2, 130.3, 130.2, 129.3, 129.0, 128.9, 128.0, 126.5, 93.9, 77.2, 64.7, 34.6, 19.0, 18.9. HRMS (ESI) *m/z* calcd for $C_{19}H_{22}NO$ $[M+H]^+$ 280.1696, found 280.1699. IR (KBr film): 3062, 3029, 2957, 2360, 1653, 1494, 1295, 1070, 696 cm^{-1}.

*2-(4-Methoxybenzyl)-3,5-diphenyl-2,3-dihydroisoxazole (**2p**).* **2p** was prepared from *N*-(1,3-diphenylprop-2-yn-1-yl)-*N*-(4-methoxybenzyl)hydroxylamine (**1p**) (68.6 mg, 200 μmol). Purification by column chromatography (95:5 hexanes/EtOAc) afforded **2o** as a yellow solid. Reaction time: 30 min,

yield: 57.3 mg (84%) for (PPh_3)AuCl/AgOTf. Reaction time: 60 min, yield: 56.0 mg (82%) for (PPh_3)AuNTf$_2$. TLC: R_f 0.57 (5:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59–7.56 (m, 2H), 7.39–7.22 (m, 10H), 6.88 (dt, *J* = 8.8 Hz, 2.8 Hz, 2H), 5.42 (d, *J* = 2.8 Hz, 1H), 5.05 (d, *J* = 2.8 Hz, 1H), 4.38 (d, *J* = 12.8 Hz, 1H), 4.06 (d, *J* = 12.8 Hz, 1H), 3.82 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.3, 153.0, 142.3, 131.1, 129.2, 129.0, 128.7, 128.6, 128.5 127.7, 127.3, 125.9, 113.9, 95.8, 73.4, 62.9, 55.4. HRMS (ESI) *m/z* calcd for $C_{23}H_{22}NO_2$ $[M+H]^+$ 344.1645, found 344.1647. IR (KBr film): 2360, 1611, 1512, 1248, 697 cm^{-1}. mp: 77–79 °C.

*2-(tert-Butyl)-3,5-diphenyl-2,3-dihydroisoxazole (**2q**).*[10] **2q** was prepared from *N*-(*tert*-butyl)-*N*-(1,3-diphenylprop-2-yn-1-yl)hydroxylamine (**1q**) (56.0 mg, 200 μmol). Purification by column chromatography (98:2 hexanes/EtOAc) afforded **2q** as a colorless oil. Reaction time: 15 min, yield: 51.0 mg (91%) for (PPh_3)AuCl/AgOTf. Reaction time: 10 min, yield: 55.4 mg (99%) for (PPh_3)AuNTf$_2$. TLC: R_f 0.75 (9:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, C_6D_6): δ 7.52 (dd, *J* = 8.0 Hz, 1.6 Hz, 2H), 7.47 (dd, *J* = 8.0 Hz, 1.6 Hz, 2H), 7.20 (t, J = 7.6 Hz, 2H), 7.11–7.01 (m, 4H), 5.14 (d, *J* = 2.8 Hz, 1H), 5.01 (d, *J* = 2.8 Hz, 1H), 1.15 (s, 9H). ^{13}C NMR (100 MHz, C_6D_6): δ 153.4, 145.9, 129.8, 129.4, 129.2, 129.1, 128.1, 127.8, 126.4, 98.3, 69.6, 61.1, 25.7. HRMS (ESI) *m/z* calcd for $C_{19}H_{22}NO$ $[M+H]^+$ 280.1696, found 280.1697. IR (KBr film): 3027, 2973, 1656, 1493, 1449 cm^{-1}.

*2-Benzyl-3,5-dicyclohexyl-2,3-dihydroisoxazole (**2r**).* **2r** was prepared from *N*-benzyl-*N*-(1,3-dicyclohexylprop-2-yn-1-yl)hydroxylamine (**1r**) (65.1 mg, 200 μmol). Purification by column chromatography (15:1 hexanes/EtOAc) afforded **2r** as a yellow solid. Reaction time: 10 min, yield: 37.3 mg (58%) for (PPh_3)AuCl/AgOTf. Reaction time: 20 min, yield: 53.0 mg (82%) for (PPh_3)AuNTf$_2$. TLC: R_f 0.57 (15:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39–7.26 (m, 5H), 4.46 (d, *J* = 1.6 Hz, 1H), 4.08 (d, *J* = 12.8 Hz, 1H), 3.71 (d, *J* = 12.8 Hz, 1H), 3.44 (dd, *J* = 6.8 Hz, 1.6 Hz, 1H), 2.11–1.54 (m, 11H), 1.26–0.69 (m, 11H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.5, 137.4, 129.9, 128.4, 127.5, 90.5, 75.1, 64.1, 43.8, 35.6, 31.2, 31.0, 29.3, 29.1, 26.8, 26.4, 26.2, 26.1. HRMS (ESI) *m/z* calcd for $C_{22}H_{32}NO$ $[M+H]^+$ 326.2478, found 326.2483. IR (KBr film): 3030, 2925, 1668, 1496, 1450 cm^{-1}. mp: 60–62 °C.

*2-Benzyl-3-cyclohexyl-5-phenyl-2,3-dihydroisoxazole (**2s**).*[4] **2s** was prepared from *N*-(benzyl)-*N*-(1-cyclohexyl-3-phenylprop-2-yn-1-yl)hydroxylamine (**1s**) (63.9 mg, 200 μmol). Purification by column chromatography (60:1 hexanes/EtOAc) afforded **2s** as a yellow solid. Reaction time: 60 min, yield: 62.8 mg (98%) for $(PPh_3)AuCl/AgOTf$. Reaction time: 20 min, yield: 55.5 mg (87%) for $(PPh_3)AuNTf_2$. ^1H NMR (400 MHz, $CDCl_3$): δ .53 (d, J = 7.2 Hz, 2H), 7.43(d, J = 7.2 Hz, 2H), 7.38–7.28 (m, 6H), 5.32 (d, J = 2.8 Hz, 1H), 4.25 (d, J = 12.8 Hz, 1H), 3.84 (d, J = 12.8 Hz, 1H), 3.68 (dd, J = 6.8 Hz, 2.8 Hz, 2H), 1.90–1.87 (m, 1H), 1.76–1.62 (m, 4H), 1.46–1.37 (m, 1H), 1.30–0.94 (m, 4H) 0.87–0.76 (m,1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.4, 137.0, 130.1, 129.4, 128.9, 128.5, 128.4, 127.6, 125.8, 94.1, 75.8, 64.1, 43.7, 29.5, 29.2, 26.7, 26.3, 26.2. HRMS (ESI) *m/z* calcd for $C_{22}H_{26}NO$ $[M+H]^+$ 320.2009, found 320.2014. IR (KBr film): 3062, 2923, 1652, 1494, 1448 cm^{-1}. mp: 90–92°C. (Lit.[4] 88–91 °C).

Synthesis of chiral 4-isoxazoline (*S*)-2a.

*(R)-N-Benzyl-N-(1,3-diphenylprop-2-yn-1-yl)hydroxylamine (R-**1a**).* [23,24] (*R*)-**1a** was prepared according to the previously reported procedure.[23,24] A solution of dimethylzinc (1.2 M) in toluene (1.3 mL, 1.6 mmol) was added dropwise to a solution of di-(*t*-butyl) (*R,R*)-tartrate [(*R,R*)-DTBT] (52.5 mg, 0.2 mmol) in toluene (6 mL) at 0 °C under an Ar atmosphere. After the reaction mixture was stirred for 10 min, a solution of racemic *N*-benzyl-*N*-(1-(4-methoxyphenyl)-3-phenylprop-2-yn-1-yl)hydroxylamine (**1m**) (68.7 mg, 0.1 mmol) in toluene (6 mL) was added dropwise. The mixture was stirred for 10 min, and a solution of nitrone **S1a** (121 mg, 1.0 mmol) in toluene (8 mL) and phenylacetylene (112 uL, 1.0 mmol) were added dropwise. After stirred for 18 h at 0 °C, the mixture was quenched with NH_4Cl (pH = 4-5) at 0 °C. The organic layer was separated and extracted with EtOAc (4 × 50 mL), dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated by rotary evaporation. The residue was purified by column chromatography (9:1 hexanes/EtOAc) to afford (*R*)-**1a** as a white solid (213 mg, 68%). The spectral data matched to those of **1a**. Chiral HPLC Method: Phenomenex Lux 5 μ Cellulose-1 column 250 × 4.6 mm; Injection volume, 5 μL; Flow rate, 1.0 mL/min; Elution method, *i*-PrOH/hexane 2.4/97.6 isocratic (0–45 min); UV detection at 254 nm; t_1 = 11.2 min (major isomer), t_2 = 12.4 min (minor isomer): $[\alpha]_D^{20.0}$ +41.2 (c 0.6, MeOH), 84% ee.

*(S)-2-Benzyl-3,5-diphenyl-2,3-dihydroisoxazole (S-**2a**).*[15] (*S*)-**2a** was prepared from *N*-benzyl-*N*-(1,3-diphenylprop-2-yn-1-yl)hydroxylamine (*R*)-**1a** (62.6 mg, 0.20 mmol). Purification by column chromatography (98:2 hexanes/EtOAc) afforded (*S*)-**2a** as a yellow solid. Reaction time: 30 min, yield: 54.0 mg (86%) for $(PPh_3)AuCl/AgOTf$. Reaction time: 30 min, yield: 58.4 mg (93%) for $(PPh_3)AuNTf_2$. The obtained spectral data matched to those of **2a**. Chiral HPLC Method: Phenomenex Lux 5 μ Cellulose-1 column 250 × 4.60 mm; Injection volume, 5 μL; Flow rate, 1.0 mL/min; Elution method, *i*-PrOH/hexane = 1/99 isocratic (0–45 min); UV detection at 254 nm; t_1 = 9.9 min (major isomer), t_2 = 10.9 min (minor isomer): $[\alpha]_D^{20.0}$ −118.9 (c 0.5, MeOH), 87% ee for $(PPh_3)AuNTf_2$, 83% ee for $(PPh_3)AuCl/AgOTf$.

ASSOCIATED CONTENT

Supporting Information

Copies of ^1H and ^{13}C NMR spectra and HPLC chromatograms. 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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