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tert-Butyl Nitrite-Mediated Domino Synthesis of Isoxazolines and Isoxazoles from Terminal Aryl Alkenes and Alkynes

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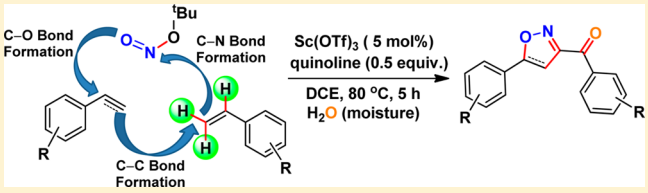
Supporting Information

ABSTRACT: A sequential construction of C−C, C−O, C═N, and C═O bonds from alkenes leading to the direct synthesis of isoxazolines in the presence of *tert*-butyl nitrite, quinoline, and the $Sc(OTf)_3$ catalyst in DCE at 80 °C has been accomplished. An unprecedented three consecutive C−H functionalizations of two styrenes are involved in this isoxazoline synthesis. In this radical-mediated reaction, one-half of the aryl alkene is converted into an intermediate 2-nitroketone, which serves as a 1,3-dipolarophile and undergoes cycloaddition with the other half of the unreacted aromatic terminal alkene. The use of an alkyne in lieu of an alkene leads to the formation of isoxazole under identical reaction conditions.

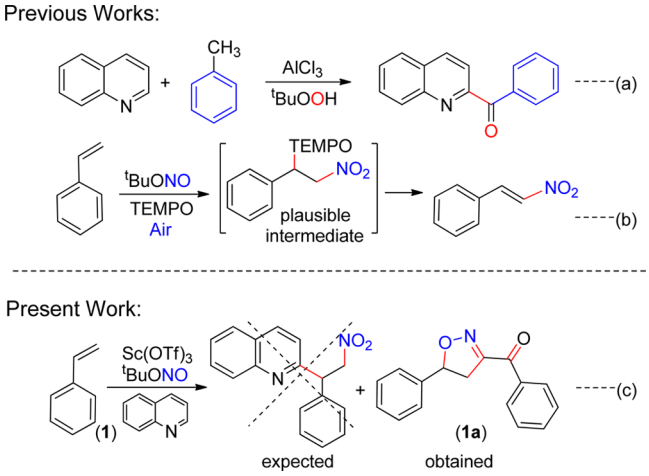


INTRODUCTION

Alkenes are simple organic molecules which have been widely applied in organic synthesis for the construction of a diverse array of complex molecules. One of the finest approaches to build such molecules in a single operation is via the direct 1,2-difunctionalization of alkenes. In this context, both intra- and intermolecular heterodifunctionalization of alkenes have acquired significant attention. In contrast to intermolecular processes, intramolecular difunctionalizations are more selective and thermodynamically favorable. Despite this, the transition-metal-catalyzed intermolecular difunctionalizations such as carbohalogenation,[1] dihydroxylation,[2] oxyarylation,[3] oxyamination,[4] aminofluorination,[5] aminocyanation,[6] hydroalkylation,[7] carboboration,[8] and other difunctionalizations[9] are still well explored. However, intermolecular difunctionalization of olefins using a C−H functionalization strategy remain fewer in numbers. In this context, an intermolecular Fe(II)-catalyzed carbonylation-peroxidation,[10] *p*-toluenesulfonic acid (*p*TsOH)-catalyzed oxidative keto-peroxidation,[11] copper- or cobalt-catalyzed alkylation-peroxidation,[12] and copper-catalyzed cycloalkylation-peroxidation[13] of olefins have been reported.

Recently, our group has developed a Lewis acid ($AlCl_3$)-catalyzed cross-dehydrogenative coupling between electron-deficient N-heterocycles (quinoline, isoquinoline, and quinoxaline) and alkylbenzenes for the synthesis of C1- or C2-aroylated N-heterocycles (Scheme 1a).[14] In the presence of an $AlCl_3$ catalyst, electron-deficient N-heterocycles act as radical acceptors, which trap the in situ-generated aroyl radical ($ArCO^{\bullet}$) obtained from alkyl benzene via peroxide (TBHP). During the nitration of alkenes using *tert*-butyl nitrite as a nitrating agent, a radical pathway follows where the in situ-generated alkyl radical is trapped by the radical scavenger TEMPO (Scheme 1b).[15a] A query arises if an alkene is treated with *tert*-butyl nitrite in the presence of quinoline in lieu of TEMPO: Will it offer a similar 1,2-difunctionalized product (Scheme 1)?

Scheme 1. C−H Functionalization of Alkene to Isoxazoline



RESULTS AND DISCUSSION

We treated styrene (**1**) with quinoline (1 equiv), *tert*-butyl nitrite (^tBuONO) (**a**, 2.0 equiv), and an $AlCl_3$ catalyst (5 mol %) in 1,2-dichloroethane (DCE) at 80 °C. A new product was isolated (55%), and spectroscopic analysis confirmed the structure to be phenyl(5-phenyl-4,5-dihydroisoxazol-3-yl)-methanone (**1a**) (Scheme 1c).[16a] The synthesis of isoxazolines involving three C−H functionalizations of two styrenes is unprecedented in the literature. The newly formed product is devoid of any quinoline moiety; however, in its absence the yield decreased to 12% (Table 1, entry 2), thereby suggesting its possible involement as a base. Isoxazolines are an important

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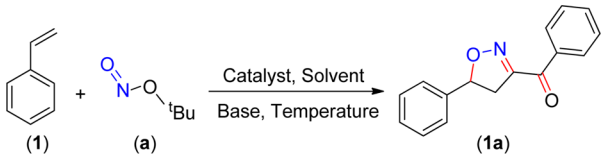
Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst (mol %)	solvent	base	yield %[b]
1	$AlCl_3$ (5.0)	DCE	quinoline	55
2	$AlCl_3$ (5.0)	DCE	-	12
3	$AlCl_3$ (5.0)	*p*-xylene	quinoline	45
4	$AlCl_3$ (5.0)	toluene	quinoline	43
5	$AlCl_3$ (5.0)	PhCl	quinoline	52
6	$AlCl_3$ (5.0)	cyclohexane	quinoline	50
7	$AlCl_3$ (5.0)	DMF	quinoline	34
8	$AlCl_3$ (5.0)	DMSO	quinoline	<5
9	$FeCl_3$ (5.0)	DCE	quinoline	51
10	$FeCl_2$ (5.0)	DCE	quinoline	55
11	$Cu(OTf)_2$ (5.0)	DCE	quinoline	0
12	$Sc(OTf)_3$ (5.0)	DCE	quinoline	66
13	$Sc(OTf)_3$ (10.0)	DCE	quinoline	68
14	$Sc(OTf)_3$ (5.0)	DCE	DBU	54
15	$Sc(OTf)_3$ (5.0)	DCE	DABCO	50
16	$Sc(OTf)_3$ (5.0)	DCE	Pyridine	41
17	$Sc(OTf)_3$ (5.0)	DCE	DMAP	30
18	-	DCE	quinoline	22
19	$Sc(OTf)_3$(5.0)	DCE	quinoline	39[c]
20	$Sc(OTf)_3$(5.0)	DCE	quinoline	56[d]
21	**$Sc(OTf)_3$(5.0)**	**DCE**	**quinoline**	**65**[e]

[a]Reaction conditions: styrene (**1**) (0.4 mmol) and *tert*-butylnitrite (**a**) (0.8 mmol) at 80 °C. [b]Yield after 5 h. [c]Temperature = 100 °C. [d]Temperature = 60 °C. [e]Quinoline, 0.5 equiv.

class of heterocycle that have attracted considerable attention in the field of anticancer research.[17] Some of the important isoxazoline scaffolds exhibiting potent anticancer properties are 3,5-diaryl-isoxazoline-linked 2,3-dihydroquinazolinone hybrids,[17a] arylisoxazoline-containing anthranilic diamides,[17b] 3,5-diaryl-isoxazoline-linked pyrrolo[2,1-*c*][1,4]benzodiazepine (PBD) conjugates,[17c] and dibenzo[b,f]azepinetethered isoxazoline[17d] (Figure 1).

Next we sought to improve the self-coupling of aryl alkene via C−H functionalization leading to the formation of isoxazoline by varying other reaction parameters. Nonpolar solvents such as *p*-xylene (45%), toluene (43%), chlorobenzene (52%), cyclohexane (50%), and polar aprotic solvents such as DMF (34%) and DMSO (<5%), were all found to be less efficient compared to DCE (55%) (Table 1, entries 3−8). Other Lewis acid catalysts, such as $FeCl_3$ (51%) and $FeCl_2$ (55%), provided a comparable yield of (**1a**), but $Cu(OTf)_2$ completely failed to give the desired product (Table 1, entries 9−11). When $Sc(OTf)_3$ (5 mol %) was employed in lieu of other catalysts under otherwise identical conditions, it gave the best yield of 66% (Table 1, entry 12). No substantial improvement in the yield (68%) was observed when the catalyst-loading was increased up to 10 mol % (Table 1, entry 13). Replacing the base quinoline with DBU (54%), DABCO (50%), pyridine (41%), and DMAP (30%) all gave lower yields of (**1a**) (Table 1, entries 14−17). The presence of $Sc(OTf)_3$ is essential for this transformation, which is perhaps serving the role of a Lewis acid catalyst to enhance the reactivity of alkene, because in its absence the reaction just provided a 22% yield of (**1a**) (Table 1, entry 18). Both increasing (110 °C) and decreasing the temperature (60 °C) reduced the product yield (Table 1, entries 19 and 20). The product yield remained unaltered even when the quantity of quinoline was reduced to 0.5 equiv. After screening various reaction conditions, it was observed that the use of styrene (0.4 mmol), ^{t}BuONO (2.0 equiv), $Sc(OTf)_3$ (5 mol %), and quinoline (0.5 equiv) gave the best yield for this transformation (Table 1, entry 21).

Encouraged by this unprecedented self-coupling of styrenes, we further implemented this strategy to other substrates. Styrenes containing moderately electron-donating groups such as *p*-Me (**2**), *m*-Me (**3**), *p*-^{t}Bu (**4**), *p*-Ph (**5**), and *p*-CH_2Cl (**6**) all provided their corresponding isoxazolines (**2a**, 60%), (**3a**, 58%), (**4a**, 58%), (**5a**, 54%), and (**6a**, 58%) in moderate yields (Scheme 2). Styrenes having moderately electron-withdrawing substituents such as *p*-Cl (**7**), *m*-Cl (**8**), *o*-Cl (**9**), *p*-Br (**10**) *o*-Br (**11**) *p*-F (**12**), and *m*-F (**13**), yielded their corresponding isoxazolines (**7a**), (**8a**), (**9a**), (**10a**), (**11a**), (**12a**), and (**13a**) in the range of 61−70% (Scheme 2).

However, styrene-containing strongly electron-withdrawing substituents such as *m*-nitro (**14**) and *p*-CO_2Et (**15**) both provided their desired product in similar yields (**14a**, 72%) and (**15a**, 68%). 2,4-Dimethyl (**16**)- and 2,4,6-trimethyl (**17**)-substituted styrenes also reacted successfully, affording their corresponding isoxazolines (**16a**, 55%) and (**17a**, 49%),

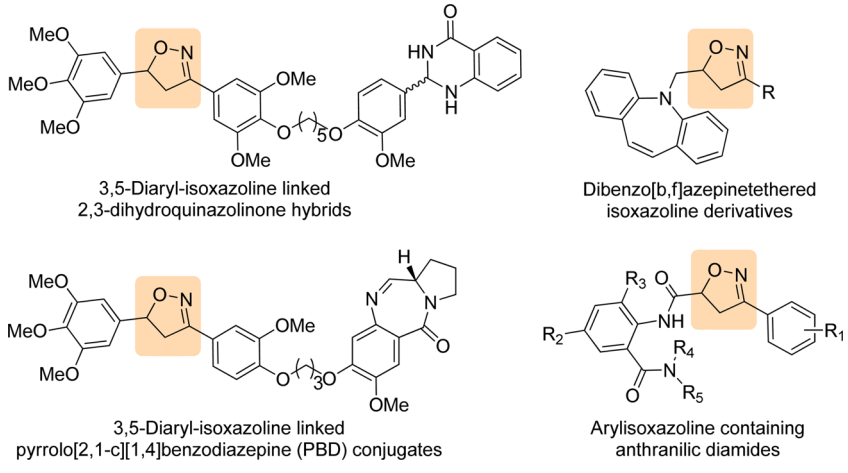


Figure 1. Representative Anticancer Isoxazolines.

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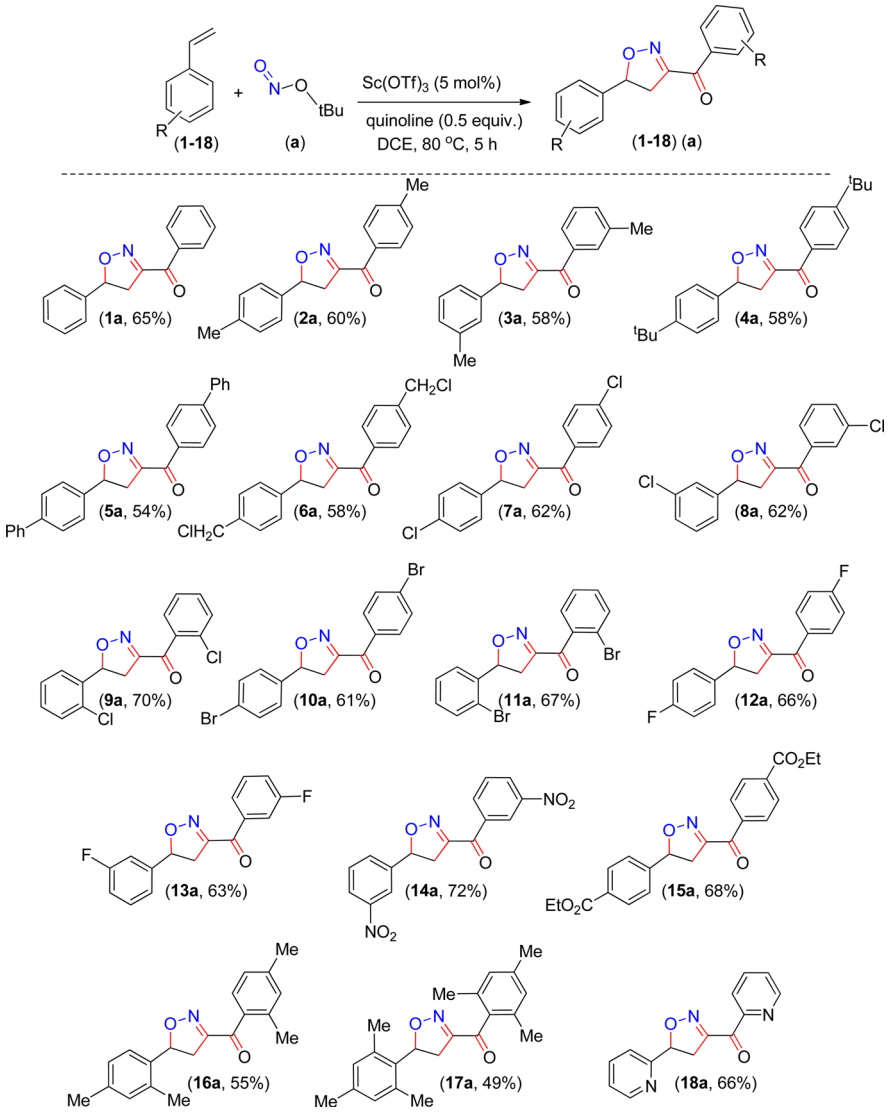
Scheme 2. Substrate Scope for Synthesis of Isoxazolines[a,b]



[a]Reaction conditions: alkene (**1**–**18**) (0.4 mmol), quinoline (0.2 mmol), and *tert*-butyl nitrite (**a**) (0.8 mmol) at 80 °C in DCE. [b]Yield after 5 h.

respectively. Heteroaromatic olefin (**18**) was tolerated well in this transformation, giving its product **18a** in 66% yield. No substantial differences in the yield of the products were observed for substrates possessing either electron-donating or electron-withdrawing substituents. This may be because of the high reactivity of the reaction intermediates leading to product in this multistep process.

We envisaged that the reaction of terminal alkyenes with *tert*-butyl nitrite was expected to give a similar 2-nitroketone intermediate (Supporting Information, Scheme S1), which was expected to undergo a 1,3-dipolar cycloaddition with the unreacted alkyne, serving as the dienophile. This strategy was tested with different alkynes such as phenylacetylene (**19**), 3-methylphenylacetylene (**20**), 4-*tert*-butylphenylacetylene (**21**), 4-methoxyphenylacetylene (**22**), 3-fluorophenylacetylene (**23**), and 4-fluorophenylacetylene (**24**) under the exact experimental conditions to that of styrene (Scheme 2). Interestingly, all the substrates yielded their corresponding isoxazoles (**19a**), (**20a**), (**21a**), (**22a**), (**23a**), and (**24a**) in the range of 34–53% (Scheme 3) rather than isoxazoline derivatives. This result is not surprising because in the case of terminal aryl alkyne, the unreacted part served as the dienophile while the other half forms the 2-nitroketone intermediate, which acts as the 1,3-dipolarophile (see Supporting Information, Scheme S1). This method is not successful for aliphatic alkenes and alkynes as the intermediate radicals obtained are not stable. This protocol is not successful with internal alkenes or alkynes because during the formation of product, loss of both the terminal protons in alkene and one proton in alkyne are necessary.

To ascertain the source of keto oxygen in product (**1a**), the reaction of styrene (**1**) was performed in the presence of H_2O^{18} under otherwise identical conditions. The incorporation of an ^{18}O-labeled product suggests that water might be the source of oxygen in the keto group (see Supporting Information). When the reaction was performed in the presence of the radical scavenger 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO, 1 equiv), no desired product was observed. However, it formed a TEMPO adduct and *β*-nitrostyrene. This result is consistent with the finding of Maiti et al.,[15a] thereby confirming the radical nature of the reaction. To ascertain the intermolecular nature of the coupling, an equimolar mixture of two different styrenes (*p*-Me (**2**) and *p*-Cl (**7**)) were reacted under the present

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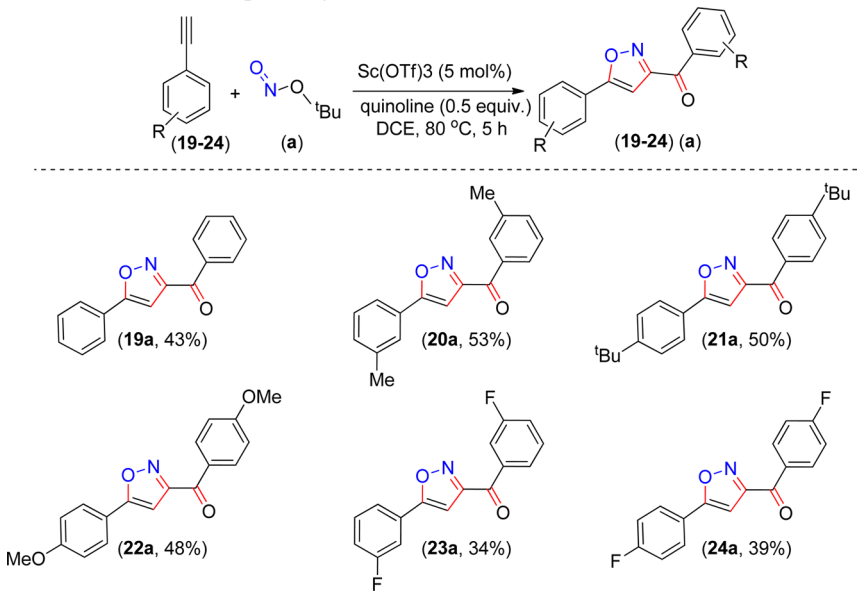
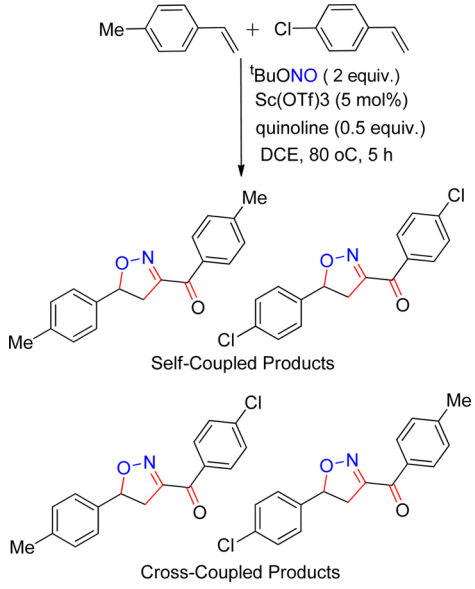
Scheme 3. Substrate Scope for Synthesis of Isoxazoles[a,b]



[a]Reaction conditions: alkyne (**19**–**23**) (0.5 mmol), quinoline (0.5 equiv), and *tert*-butyl nitrite (**a**) (1 mmol) at 80 °C in DCE. [b]Yield after 5 h.

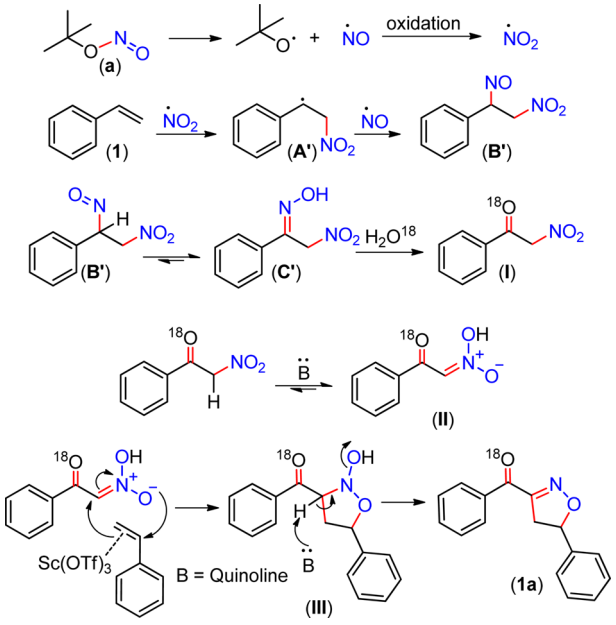
experimental conditions. The detection of four different isoxazolines (Scheme 4) from the ^{1}H NMR and HRMS analyses confirms the intermolecular cross-coupling of the process (see Supporting Information).

Scheme 4. Crossover Experiment



On the basis of the literature reports, intermediates detected by HRMS analysis, and from the controlled experiments we conducted, a plausible mechanism has been proposed (Scheme 5). The heterolytic cleavage of *tert*-butyl nitrite produces a NO$^\bullet$ radical which converts to a $NO_2^\bullet$ radical under aerobic reaction conditions.[18] The nitro radical ($NO_2^\cdot$) then attacks the terminal carbon of the olefin to generate a nitroalkane-radical intermediate (**A′**). The nitroalkane radical (**A′**) couples with another NO$^\bullet$ radical to give a C-nitroso intermediate (**B′**). In the presence of base, the C-nitroso intermediate (**B′**) rearranges to an α-nitrooxime (**C′**), which is hydrolyzed to 2-

Scheme 5. Proposed Mechanism for Isoxazoline Synthesis



nitroacetophenon (**I**) using the moisture present in the solvent/open atmosphere.[19] The intermediate 2-nitroacetophenone tautomerized to a 1,3-dipolar intermediate (**II**) in the presence of base. The unreacted styrene serves as the dienophile and undergoes cycloaddition with the 1,3-dipolar intermediate (**II**) to give intermediate (**III**).[16] Here $Sc(OTf)_3$ acts as a Lewis acid catalyst to enhance the reactivity of the alkene toward a cycloaddition reaction.[21] Finally, loss of a water molecule from the intermediate (**III**) leads to the formation of the final isoxazoline product (**1a**). Here, quinoline serves as a base[16b,c] to facilitate tautomerization and the dehydration step of the reaction. Intermediates (**C′**), (**I**), (**II**), and (**III**) have been detected by HRMS analysis of the reaction mixture at various time intervals (see Supporting Information). This mechanism successfully accounts for the formation of all four

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isoxazololine products (Scheme 4). Two independent 1,3-dipolar intermediates were generated from two different styrenes (**2** and **7**). Each of these 1,3-dipolar intermediates coupled with the unreacted styrenes (**2** and **7**) independently to give four possible products (Scheme 4). A similar mechanism for the formation of isoxazole from a terminal alkyne can be proposed. (see Supporting Information)

In conclusion, *tert*-butyl nitrite serves as a convenient N−O source to convert alkenes or alkynes into intermediate 2-nitroketone in DCE. The generated intermediate reacts with the unreacted alkenes or alkynes via a 1,3-dipolar cycloaddition to afford isoxazolines or isoxazoles in the presence of quinoline and the $Sc(OTf)_3$ catalyst. In this domino process, C−C, C−O, C═N, and C═O bonds are constructed simultaneously. A radical mechanism has been proposed, where the cleavage of *tert*-butyl nitrite produces an NO$^{\bullet}$ radical. The NO$^{\bullet}$ radical is oxidized to an $NO_2^{\bullet}$ radical and a sequential addition of these radicals to styrene produces a C-nitroso intermediate which is hydrolyzed to a 2-nitroacetophenone. The generated 2-nitroacetophenone tautomerizes to a 1,3-dipolar intermediate which undergoes cycloaddition with the unreacted alkene to generate isoxazoline via loss of a water molecule. An analogous mechanism has been proposed involving alkynes for the generation of isoxazoles.

EXPERIMENTAL SECTION

General Information. All of the reagents were commercial grade and purified according to the established procedures. Organic extracts were dried over anhydrous sodium sulfate. Solvents were removed in a rotary evaporator under reduced pressure. Silica gel (60−120 mesh size) was used for the column chromatography. Reactions were monitored by TLC on silica gel 60 F_{254} (0.25 mm). NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^{1}H NMR (400 and 600 MHz), and for ^{13}C NMR (100 and 150 MHz), $CDCl_3$ was the internal standard. MS spectra were recorded using ESI mode. IR spectra were recorded in KBr or neat.

General Procedure for the Synthesis of Phenyl(5-phenyl-4,5-dihydroisoxazol-3-yl)methanone (1a) from Styrene (1) and *tert*-Butyl nitrite (a). To an oven-dried 10 mL round-bottom flask fitted with a reflux condenser was added styrene (**1**) (42 mg, 0.4 mmol), quinoline (26 mg, 0.2 mmol), *tert*-butyl nitrite (**a**) (82 mg, 0.8 mmol), $Sc(OTf)_3$ (9.8 mg, 0.02 mmol), and 1, 2-dichloroethane (1.5 mL). The reaction mixture was refluxed in an oil bath that was preheated to 80 °C for 5 h. The reaction mixture was cooled to room temperature, admixed with ethyl acetate (25 mL), and the organic layer was washed with saturated sodium bicarbonate solution (1 × 5 mL). The organic layer was dried over anhydrous sodium sulfate (Na_2SO_4), and the solvent was evaporated under reduced pressure. The obtained crude product was purified over a column of silica gel (hexane/ethyl acetate, 9.9:0.1) to give pure phenyl(5-phenyl-4,5-dihydroisoxazol-3-yl)methanone (**1a**) (33 mg, yield 65%). The identity and purity of the product were confirmed by spectroscopic analysis.

*Phenyl(5-phenyl-4,5-dihydroisoxazol-3-yl)methanone (**1a**).*[16a] Gummy; yield = 33 mg, 65%: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.24 (d, 2H, J = 7.2 Hz), 7.62 (t, 1H, J = 7.4 Hz), 7.49 (t, 2H, J = 7.8 Hz), 7.42−7.35 (m, 5H), 5.79 (dd, 1H, J_1 = 8.8 Hz, J_2 = 2.8 Hz), 3.80 (dd, 1H, J_1 = 11.6 Hz, J_2 = 6.4 Hz), 3.40 (dd, 1H, J_1 = 8.8 Hz, J_2 = 9.2 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 186.4, 157.6, 139.8, 135.9, 133.9, 130.5, 129.1, 128.8, 128.6, 126.1, 84.4, 42.0; IR (KBr, cm^{-1}) 3063, 3029, 2957, 2926, 2851, 1651, 1598, 1580, 1572, 1494, 1448, 1360, 1250, 1154, 1077, 901, 851, 791, 756; HRMS (ESI/Q-TOF) m/z: [M + H]$^+$ calcd for $C_{16}H_{14}NO_2$ 252.1019, found 252.1025.

*p-Tolyl(5-(p-tolyl)-4,5-dihydroisoxazol-3-yl)methanone (**2a**).* Gummy; yield = 33 mg, 60%: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.16 (d, 2H, J = 8.0 Hz), 7.29 (d, 2H, J = 8.6 Hz), 7.27−7.25 (m, 2H), 7.20 (d, 2H, J = 8.0 Hz), 5.74 (dd, 1H, J_1 = 8.8 Hz, J_2 = 2.4 Hz), 3.75 (dd, 1H, J_1 = 11.6 Hz, J_2 = 6.0 Hz), 3.38 (dd, 1H, J_1 = 8.8 Hz, J_2 = 8.8 Hz), 2.43 (s, 3H), 2.36 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 186.1, 157.7, 144.9, 138.7, 136.9, 133.4, 130.7, 129.7, 129.4, 126.2, 84.4, 42.0, 21.9, 21.4; IR (KBr, cm^{-1}) 3025, 2952, 2923, 2856, 1647, 1606, 1577, 1516, 1450, 1358, 1253, 1185, 1118, 1036, 902, 852, 831, 813, 788, 741; HRMS (ESI/Q-TOF) m/z: [M + H]$^+$ calcd for $C_{18}H_{18}NO_2$ 280.1332, found 280.1330.

*m-Tolyl(5-(m-tolyl)-4,5-dihydroisoxazol-3-yl)methanone (**3a**).* Gummy; yield = 31.5 mg, 58%: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.05−8.03 (m, 2H), 7.43 (d, 1H, J = 7.2 Hz), 7.38 (t, 1H, J = 7.5 Hz), 7.29 (t, 1H, J = 7.5 Hz), 7.18−7.15 (m, 3H), 5.74 (dd, 1H, J_1 = 9.0 Hz, J_2 = 2.4 Hz), 3.77 (dd, 1H, J_1 = 11.4 Hz, J_2 = 6.0 Hz), 3.39 (dd, 1H, J_1 = 9.0 Hz, J_2 = 9.0 Hz), 2.43 (s, 3H), 2.37 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 186.7, 157.7, 139.8, 138.9, 138.4, 136.0, 134.7, 130.9, 129.6, 128.9, 128.5, 127.9, 126.8, 123.2, 84.5, 42.1, 21.6, 21.5; IR (KBr, cm^{-1}) 3023, 2957, 2924, 2855, 1650, 1601, 1575, 1488, 1459, 1426, 1358, 1259, 1213, 1134, 1040, 921, 787, 732, 699, 670; HRMS (ESI/Q-TOF) m/z: [M + H]$^+$ calcd for $C_{18}H_{18}NO_2$ 280.1332, found 280.1342.

*(4-(tert-Butyl)phenyl)(5-(4-(tert-butyl)phenyl)-4,5-dihydroisoxazol-3-yl)methanone (**4a**).* Gummy; yield = 42 mg, 58%: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.18 (d, 2H, J = 8.4 Hz), 7.50 (d, 2H, J = 8.4 Hz), 7.42 (d, 2H, J = 8.4 Hz), 7.30 (d, 2H, J = 8.4 Hz), 5.75 (dd, 1H, J_1 = 9.0 Hz, J_2 = 2.4 Hz), 3.75 (dd, 1H, J_1 = 11.4 Hz, J_2 = 6.0 Hz), 3.40 (dd, 1H, J_1 = 8.4 Hz, J_2 = 9.0 Hz), 1.35 (s, 9H), 1.32 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ 186.2, 157.74, 157.72, 151.9, 136.8, 133.4, 130.5, 126.0, 125.7, 84.3, 41.9, 35.4, 34.8, 31.5, 31.3; IR (KBr, cm^{-1}) 2963, 2926, 2899, 2868, 1647, 1605, 1577, 1559, 1462, 1410, 1363, 1268, 1254, 1198, 1108, 1017, 905, 851, 763, 724; HRMS (ESI/Q-TOF) m/z: [M + H]$^+$ calcd for $C_{24}H_{30}NO_2$ 364.2271, found 364.2270.

*[1,1′-Biphenyl]-4-yl(5-([1,1′-biphenyl]-4-yl)-4,5-dihydroisoxazol-3-yl)methanone (**5a**).* White solid; yield = 43 mg, 54%: mp 193.4−195.5 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.37 (d, 2H, J = 8.4 Hz), 7.73 (d, 2H, J = 8.4 Hz), 7.65 (dd, 4H, J_1 = 7.8 Hz, J_2 = 4.2 Hz), 7.60 (d, 2H, J = 7.8 Hz), 7.50 (d, 2H, J = 7.2 Hz), 7.46 (q, 4H, J = 6.4 Hz), 7.42 (t, 1H, J = 7.5 Hz), 7.37 (t, 1H, J = 7.5 Hz), 5.85 (dd, 1H, J_1 = 9.0 Hz, J_2 = 2.4 Hz), 3.85 (dd, 1H, J_1 = 11.4 Hz, J_2 = 6.0 Hz), 3.48 (dd, 1H, J_1 = 9.0 Hz, J_2 = 8.4 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ 185.9, 157.8, 146.6, 141.9, 140.7, 140.0, 138.8, 134.7, 131.2, 129.2, 129.1, 128.6, 127.9, 127.8, 127.5, 127.34, 127.3, 126.7, 84.3, 42.1; IR (KBr, cm^{-1}) 3054, 3029, 2919, 2851, 1647, 1603, 1578, 1559, 1485, 1405, 1157, 1006, 905, 851, 836, 763, 753, 738, 689; HRMS (ESI/Q-TOF) m/z: [M + H]$^+$ calcd for $C_{28}H_{22}NO_2$ 404.1645, found 404.1650.

*(4-(Chloromethyl)phenyl)(5-(4-(chloromethyl)phenyl)-4,5-dihydroisoxazol-3-yl)methanone (**6a**).* White solid; yield = 40 mg, 58%: mp. 109.6−112.8 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.25 (d, 2H, J = 8.4 Hz), 7.51 (d, 2H, J = 7.8 Hz), 7.43 (d, 2H, J = 8.4 Hz), 7.36 (d, 2H, J = 8.4 Hz), 5.79 (dd, 1H, J_1 = 8.4 Hz, J_2 = 3.0 Hz), 4.63 (s, 2H), 4.59 (s, 2H), 3.79 (dd, 1H, J_1 = 11.4 Hz, J_2 = 6.0 Hz), 3.38 (dd, 1H, J_1 = 9.0 Hz, J_2 = 9.0 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ 185.6, 157.6, 143.2, 140.0, 138.2, 135.7, 131.0, 129.4, 128.7, 126.5, 84.1, 45.8, 45.5, 42.0; IR (KBr, cm^{-1}) 2965, 2923, 2851, 1640, 1607, 1578, 1564, 1444, 1357, 1286, 1256, 1109, 941, 919, 834, 765, 704, 668, 576, 530; HRMS (ESI/Q-TOF) m/z: [M + H]$^+$ calcd for $C_{18}H_{16}Cl_2NO_2$ 348.0553, found 348.0559.

*(4-Chlorophenyl)(5-(4-chlorophenyl)-4,5-dihydroisoxazol-3-yl)-methanone (**7a**).* Gummy; yield = 40 mg, 62%: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.21 (d, 2H, J = 8.9 Hz), 7.46 (d, 2H, J = 8.9 Hz), 7.37 (d, 2H, J = 8.2 Hz), 7.29 (d, 2H, J = 8.6 Hz), 5.76 (dd, 1H, J_1 = 8.8 Hz, J_2 = 2.4 Hz), 3.78 (dd, 1H, J_1 = 11.6 Hz, J_2 = 6.4 Hz), 3.34 (dd, 1H, J_1 = 8.8 Hz, J_2 = 8.8 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 184.8, 157.5, 140.6, 138.2, 134.8, 131.9, 129.7, 129.3, 129.0, 127.5, 83.8, 41.9; IR (KBr, cm^{-1}) 2952, 2924, 2851, 1646, 1584, 1493, 1433, 1401, 1367, 1293, 1274, 1258, 1157, 1039, 1014, 937, 902, 845, 829, 807, 745, 719, 684; HRMS (ESI/Q-TOF) m/z: [M + H]$^+$ calcd for $C_{16}H_{12}Cl_2NO_2$ 320.0240, found 320.0242.

*(3-Chlorophenyl)(5-(3-chlorophenyl)-4,5-dihydroisoxazol-3-yl)-methanone (**8a**).* Gummy; yield = 40 mg, 62%: ^{1}H NMR ($CDCl_3$,

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J. Org. Chem. 2017, 82, 6358−6365

600 MHz) δ 8.22 (s, 1H), 8.15 (d, 1H, J = 7.8 Hz), 7.59 (d, 1H, J = 8.4 Hz), 7.44 (t, 1H, J = 7.8 Hz), 7.36−7.33 (m, 3H), 7.24−7.23 (m, 1H), 5.77 (dd, 1H, J_1 = 8.4 Hz, J_2 = 3.0 Hz), 3.79 (dd, 1H, J_1 = 11.4 Hz, J_2 = 6.0 Hz), 3.36 (dd, 1H, J_1 = 8.4 Hz, J_2 = 9.0 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 184.8, 157.4, 141.7, 137.2, 135.1, 134.9, 133.9, 130.5, 130.4, 129.9, 129.1, 128.7, 126.2, 124.2, 83.7, 41.9; IR (KBr, cm^{-1}) 3068, 2952, 2925, 2854, 1653, 1576, 1566, 1479, 1426, 1361, 1276, 1248, 1094, 1160, 1079, 919, 784, 733, 692; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{16}H_{12}Cl_2NO_2$ 320.0240, found 320.0247.

*(2-Chlorophenyl)(5-(2-chlorophenyl)-4,5-dihydroisoxazol-3-yl)-methanone (**9a**).* Gummy; yield = 45 mg, 70%: ^1H NMR ($CDCl_3$, 600 MHz) δ 7.54 (d, 1H, J = 7.8 Hz), 7.47−7.43 (m, 3H), 7.42 (d, 1H, J = 7.5 Hz), 7.38−7.36 (m, 1H), 7.32−7.28 (m, 2H), 6.15 (dd, 1H, J_1 = 7.8 Hz, J_2 = 3.6 Hz), 3.90 (dd, 1H, J_1 = 12.0 Hz, J_2 = 6.0 Hz), 3.23 (dd, 1H, J_1 = 7.8 Hz, J_2 = 10.2 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz) δ 188.2, 158.1, 137.8, 137.3, 132.5, 132.4, 132.0, 131.5, 130.5, 130.0, 129.8, 127.5, 126.8, 126.6, 82.8, 40.4; IR (KBr, cm^{-1}) 3066, 2923, 2849, 1672, 1651, 1578, 1471, 1435, 1369, 1310, 1273, 1245, 1161, 1128, 1056, 1036, 933, 910, 882, 855, 755, 742, 691; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{16}H_{12}Cl_2NO_2$ 320.0240, found 320.0236.

*(4-Bromophenyl)(5-(4-bromophenyl)-4,5-dihydroisoxazol-3-yl)-methanone (**10a**).* Gummy; yield = 50 mg, 61%: ^1H NMR ($CDCl_3$, 400 MHz) δ 8.13 (d, 2H, J = 8.0 Hz), 7.64 (d, 2H, J = 8.6 Hz), 7.53 (d, 2H, J = 8.0 Hz), 7.23 (d, 2H, J = 8.6 Hz), 5.74 (dd, 1H, J_1 = 8.8 Hz, J_2 = 2.8 Hz), 3.78 (dd, 1H, J_1 = 11.6 Hz, J_2 = 6.0 Hz), 3.34 (dd, 1H, J_1 = 8.8 Hz, J_2 = 9.4 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 185.0, 157.5, 138.7, 134.5, 132.3, 132.03, 132.0, 129.5, 127.8, 122.9, 83.8, 41.9; IR (KBr, cm^{-1}) 2952, 2924, 2853, 1640, 1578, 1559, 1489, 1409, 1396, 1361, 1274, 1256, 1153, 1104, 1072, 1010, 941, 919, 904, 842, 824, 793, 744, 679; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{16}H_{12}Br_2NO_2$ 409.9210, found 409.9215.

*(2-Bromophenyl)(5-(2-bromophenyl)-4,5-dihydroisoxazol-3-yl)-methanone (**11a**).* Gummy; yield = 55 mg, 67%: ^1H NMR ($CDCl_3$, 600 MHz) δ 7.64 (d, 1H, J = 7.8 Hz), 7.60 (d, 1H, J = 7.5 Hz), 7.50 (d, 1H, J = 7.5 Hz), 7.45 (d, 1H, J = 7.8 Hz), 7.42 (t, 1H, J = 7.2 Hz), 7.36 (q, 2H, J = 7.0 Hz), 7.21 (t, 1H, J = 7.7 Hz), 6.11 (dd, 1H, J_1 = 7.2 Hz, J_2 = 4.2 Hz), 3.93 (dd, 1H, J_1 = 12.0 Hz, J_2 = 6.0 Hz), 3.21 (dd, 1H, J_1 = 7.8 Hz, J_2 = 9.6 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz) δ 188.9, 157.8, 139.5, 139.3, 133.6, 133.2, 132.4, 130.0, 129.9, 128.1, 127.4, 126.8, 121.1, 120.2, 84.8, 40.6; IR (KBr, cm^{-1}) 2956, 2924, 2853, 1672, 1576, 1467, 1434, 1368, 1307, 1270, 1243, 1162, 1119, 1047, 1026, 930, 909, 858, 745, 739, 681, 668, 644; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{16}H_{12}Br_2NO_2$ 409.9210, found 409.9220.

*(4-Fluorophenyl)(5-(4-fluorophenyl)-4,5-dihydroisoxazol-3-yl)-methanone (**12a**).* Gummy; yield = 38 mg, 66%: ^1H NMR ($CDCl_3$, 600 MHz) δ 8.33−8.31 (m, 2H), 7.35−7.33 (m, 2H), 7.16 (t, 2H, J = 8.7 Hz), 7.09 (t, 2H, J = 8.7 Hz), 5.76 (dd, 1H, J_1 = 9.0 Hz, J_2 = 2.4 Hz), 3.77 (dd, 1H, J_1 = 11.4 Hz, J_2 = 6.0 Hz), 3.36 (dd, 1H, J_1 = 9.0 Hz, J_2 = 8.4 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz) δ 184.6, 167.3, 165.6, 163.9, 162.2, 157.6, 135.57, 135.55, 133.41, 133.35, 132.2, 132.18, 128.1, 128.0, 116.2, 116.1, 115.9, 115.8, 83.9, 42.1; IR (KBr, cm^{-1}) 3073, 2957, 2924, 2846, 1642, 1598, 1559, 1511, 1439, 1411, 1358, 1299, 1287, 1239, 1156, 1098, 1013, 939, 902, 853, 816, 754; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{16}H_{12}F_2NO_2$ 288.0831, found 288.0825.

*(3-Fluorophenyl)(5-(3-fluorophenyl)-4,5-dihydroisoxazol-3-yl)-methanone (**13a**).* Gummy; yield = 36 mg, 63%: ^1H NMR ($CDCl_3$, 600 MHz) δ 8.07 (d, 1H, J = 7.8 Hz), 7.95 (d, 1H, J = 9.4 Hz), 7.50−7.46 (m, 1H), 7.39−7.36 (m, 1H), 7.34−7.31 (m, 1H), 7.13 (d, 1H, J = 7.8 Hz), 7.09−7.04 (m, 2H), 5.79 (dd, 1H, J_1 = 8.4 Hz, J_2 = 3.0 Hz), 3.80 (dd, 1H, J_1 = 12.0 Hz, J_2 = 6.0 Hz), 3.37 (dd, 1H, J_1 = 8.4 Hz, J_2 = 9.6 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz) δ 184.8, 164.1, 163.6, 162.5, 161.9, 157.4, 142.4, 137.6, 130.9, 130.8, 130.4, 130.3, 126.5, 126.4, 121.63, 121.61, 121.1, 120.9, 117.4, 117.2, 115.9, 115.8, 113.2, 113.0, 83.7, 42.0; IR (KBr, cm^{-1}) 2958, 2923, 2851, 1653, 1587, 1484, 1444, 1362, 1260, 1214, 927, 893, 807, 741, 692, 672, 522; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{16}H_{12}F_2NO_2$ 288.0831, found 288.0836.

*(3-Nitrophenyl)(5-(3-nitrophenyl)-4,5-dihydroisoxazol-3-yl)-methanone (**14a**).* Gray solid; yield = 49 mg, 72%: mp 92.3−95.9 °C; ^1H NMR ($CDCl_3$, 600 MHz) δ 9.08 (s, 1H), 8.60 (d, 1H, J = 7.8 Hz), 8.47 (d, 1H, J = 7.8 Hz), 8.25−8.22 (m, 2H), 7.72 (t, 2H, J = 7.8 Hz), 7.62 (t, 1H, J = 7.8 Hz), 5.94 (dd, 1H, J_1 = 9.0 Hz, J_2 = 2.4 Hz), 3.91 (dd, 1H, J_1 = 11.4 Hz, J_2 = 6.6 Hz), 3.43 (dd, 1H, J_1 = 8.4 Hz, J_2 = 9.0 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz) δ 183.7, 157.4, 148.8, 141.7, 136.8, 136.1, 132.0, 130.4, 129.9, 128.1, 125.5, 123.9, 122.5, 121.2, 83.4, 41.8; IR (KBr, cm^{-1}) 3124, 3083, 3043, 1653, 1612, 1590, 1534, 1477, 1346, 1256, 1094, 1002, 930, 906, 886, 834, 811, 737, 706, 684, 652; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{16}H_{12}N_3O_6$ 342.0721, found 342.0719.

*Ethyl 4-(3-(4-(ethoxycarbonyl)benzoyl)-4,5-dihydroisoxazol-5-yl)-benzoate (**15a**).* Gummy; yield = 54 mg, 68%: ^1H NMR ($CDCl_3$, 600 MHz) δ 8.28 (d, 2H, J = 8.4 Hz), 8.14 (d, 2H, J = 8.4 Hz), 8.07 (d, 2H, J = 8.4 Hz), 7.43 (d, 2H, J = 7.8 Hz), 5.85 (dd, 1H, J_1 = 8.4 Hz, J_2 = 3.0 Hz), 4.41 (q, 2H, J = 6.4 Hz), 4.38 (q, 2H, J = 6.4.Hz), 3.83 (dd, 1H, J_1 = 12.0 Hz, J_2 = 6.0 Hz), 3.37 (dd, 1H, J_1 = 9.0 Hz, J_2 = 9.0 Hz), 1.42 (t, 3H, J = 6.9 Hz), 1.39 (t, 3H, J = 7.2 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz) δ 185.5, 166.2, 165.9, 157.5, 144.5, 139.0, 134.9, 131.0, 130.4, 129.7, 125.9, 84.0, 61.7, 61.4, 42.0, 14.5, 14.47; IR (KBr, cm^{-1}) 3064, 2995, 2979, 2928, 2900, 2848, 1718, 1653, 1613, 1572, 1475, 1444, 1409, 1367, 1284, 1255, 1194, 1126, 1112, 1019, 945, 872, 863, 762, 727; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{22}H_{22}NO_6$ 396.1442, found 396.1451.

*(2,4-Dimethylphenyl)(5-(2,4-dimethylphenyl)-4,5-dihydroisoxazol-3-yl)methanone (**16a**).* Gummy; yield = 34 mg, 55%: ^1H NMR ($CDCl_3$, 600 MHz) δ 7.65 (d, 1H, J = 8.4 Hz), 7.02−7.01 (m, 2H), 6.99−6.96 (m, 3H), 5.87 (dd, 1H, J_1 = 9.0 Hz, J_2 = 2.4 Hz), 3.67 (dd, 1H, J_1 = 12.0 Hz, J_2 = 5.4 Hz), 3.15 (dd, 1H, J_1 = 8.4 Hz, J_2 = 9.0 Hz), 2.36 (s, 3H), 2.30 (s, 3H), 2.25 (s, 6H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz) δ 189.8, 158.5, 142.6, 138.8, 138.3, 135.1, 134.6, 132.5, 131.8, 131.3, 127.3, 126.2, 125.2, 82.8, 40.6, 21.7, 21.2, 20.9, 19.4; IR (KBr, cm^{-1}) 3020, 2955, 2924, 2855, 1653, 1612, 1578, 1559, 1500, 1452, 1379, 1311, 1288, 1252, 1236, 1036, 929, 879, 843, 821, 757; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{22}NO_2$ 308.1645, found 308.1647.

*Mesityl(5-mesityl-4,5-dihydroisoxazol-3-yl)methanone (**17a**).* Gummy; yield = 33 mg, 49%: ^1H NMR ($CDCl_3$, 600 MHz) δ 6.89 (s, 4H), 6.27 (t, 1H, J = 12.6 Hz), 3.66 (dd, 1H, J_1 = 12.6 Hz, J_2 = 5.4 Hz), 3.29 (dd, 1H, J_1 = 12.0 Hz, J_2 = 5.4 Hz), 2.31 (s, 6H), 2.29 (s, 3H), 2.28 (s, 3H), 2.27 (s, 3H), 2.25 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz) δ 167.5, 156.2, 140.7, 138.8, 136.9, 135.3, 135.2, 130.8, 130.6, 128.6, 128.5, 126.9, 84.3, 37.7, 21.4, 21.0, 20.2, 19.98, 19.85; IR (KBr, cm^{-1}) 3008, 2960, 2923, 2854, 1612, 1579, 1452, 1379, 1311, 1251, 1036, 978, 953, 934, 878, 850, 834; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{22}H_{26}NO_2$ 336.1958, found 336.1968.

*Pyridin-2-yl(5-(pyridin-2-yl)-4,5-dihydroisoxazol-3-yl)methanone (**18a**).* Gummy; yield = 33 mg, 66%: ^1H NMR ($CDCl_3$, 600 MHz) δ 8.60−8.57 (m, 2H), 8.41−8.39 (m, 1H), 7.94 (t, 1H, J = 8.1 Hz), 7.73 (t, 1H, J = 7.8 Hz), 7.52 (d, 1H, J = 7.8 Hz), 7.47 (t, 1H, J = 6.3 Hz), 7.25−7.23 (m, 1H), 5.78 (dd, 1H, J_1 = 7.2 Hz, J_2 = 4.2 Hz), 3.95 (dd, 1H, J_1 = 11.4 Hz, J_2 = 6.6 Hz), 3.81 (dd, 1H, J_1 = 7.2 Hz, J_2 = 10.2 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz) δ 159.7, 156.9, 150.3, 149.6, 146.2, 144.4, 138.3, 137.5, 125.32, 125.28, 123.3, 120.9, 82.3, 42.5; IR (KBr, cm^{-1}) 2924, 2853, 1640, 1591, 1569, 1468, 1436, 1384, 1287, 1262, 1152, 1095, 1049, 1006, 894, 849, 790, 749, 668; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{12}N_3O_2$ 254.0924, found 254.0934.

General Procedure for the Synthesis of Phenyl(5-phenylisoxazol-3-yl)methanone (19a) from Phenylacetylene (19) and *tert*-Butyl Nitrite (a). To an oven-dried 10 mL round-bottom flask fitted with a reflux condenser was added phenyl acetylene (**19**) (51 mg, 0.5 mmol), quinoline (33 mg, 0.25 mmol), *tert*-butyl nitrite (**a**) (103 mg, 1 mmol), $Sc(OTf)_3$ (12 mg, 0.025 mmol), and 1,2-dichloroethane (1.5 mL). The reaction mixture was refluxed in an oil bath that was preheated to 80 °C for 5 h. The reaction mixture was cooled to room temperature, admixed with ethyl acetate (25 mL), and

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J. Org. Chem. 2017, 82, 6358−6365

the organic layer was washed with saturated sodium bicarbonate solution (1 × 5 mL). The organic layer was dried over anhydrous sodium sulfate (Na_2SO_4), and the solvent was evaporated under reduced pressure. The obtained crude product was purified over a column of silica gel (hexane/ethyl acetate, 9.9:0.1) to give pure phenyl(5-phenylisoxazol-3-yl)methanone (**19a**) (27 mg, yield 43%). The identity and purity of the product were confirmed by spectroscopic analysis.

*Phenyl(5-phenylisoxazol-3-yl)methanone (**19a**).*[16a] White solid; yield = 27 mg, 43%: mp 78.4−82.9 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.36−8.34 (m, 2H), 7.87−7.85 (m, 2H), 7.68−7.66 (m, 1H), 7.56−7.50 (m, 5H), 7.06 (s, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ 186.1, 171.0, 162.7, 135.9, 134.3, 130.96, 130.92, 129.4, 128.8, 126.9, 126.2, 100.5; IR (KBr, cm^{-1}) 2953, 2923, 2853, 1655, 1577, 1449, 1244, 1146, 1041, 1028, 848, 894, 824, 769, 681, 676, 617; HRMS (ESI/Q-TOF) m/z: [M + H]$^+$ calcd for $C_{16}H_{12}NO_2$ 250.0863, found 250.0860.

*m-Tolyl(5-(m-tolyl)isoxazol-3-yl)methanone (**20a**).* Gummy; yield = 37 mg, 53%: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.15 (d, 1H, J = 7.8 Hz), 8.13 (s, 1H), 7.67 (s, 1H), 7.65 (d, 1H, J = 7.8 Hz), 7.47 (d, 1H, J = 7.8 Hz), 7.43 (t, 1H, J = 7.5 Hz), 7.39 (t, 1H, J = 7.5 Hz), 7.30 (d, 1H, J = 7.8 Hz), 7.02 (s, 1H), 2.46 (s, 3H), 2.45 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ 186.3, 171.2, 162.7, 135.1, 131.7, 131.2, 129.3, 128.7, 128.2, 126.8, 123.4, 100.4, 21.64, 21.61; IR (KBr, cm^{-1}) 2923, 2853, 1665, 1602, 1574, 1444, 1378, 1319, 1290, 1262, 1207, 1158, 1140, 1095, 1055, 941, 841, 811, 793, 751, 701, 678; HRMS (ESI/Q-TOF) m/z: [M + H]$^+$ calcd for $C_{18}H_{16}NO_2$ 278.1176, found 278.1180.

*(4-(tert-Butyl)phenyl)(5-(4-(tert-butyl)phenyl)isoxazol-3-yl)-methanone (**21a**).* Gummy; yield = 45 mg, 50%: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.29 (d, 2H, J = 8.4 Hz), 7.79 (d, 2H, J = 8.8 Hz), 7.57−7.52 (m, 4H), 7.00 (s, 1H), 1.372 (s, 9H), 1.365 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 185.7, 171.0, 162.7, 158.1, 154.4, 133.4, 130.9, 126.30, 126.29, 126.0, 125.8, 124.2, 99.9, 35.5, 35.2, 31.3, 31.2; IR (KBr, cm^{-1}) 2958, 2923, 2853, 1659, 1606, 1465, 1444, 1363, 1255, 1106, 1017, 897, 856, 777; HRMS (ESI/Q-TOF) m/z: [M + H]$^+$ calcd for $C_{24}H_{28}NO_2$ 362.2115, found 362.2111.

*(4-Methoxyphenyl)(5-(4-methoxyphenyl)isoxazol-3-yl)-methanone (**22a**).*[20] White solid; yield = 37 mg, 48%: mp 127.8−130.5 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.37 (d, 2H, J = 8.8 Hz), 7.78 (d, 2H, J = 8.8 Hz), 7.01−6.99 (m, 4H), 6.89 (s, 1H), 3.90 (s, 3H), 3.87 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 184.4, 170.7, 164.6, 162.9, 161.6, 133.4, 128.9, 127.8, 119.8, 114.7, 114.1, 99.2, 55.8, 55.6; IR (KBr, cm^{-1}) 2940, 2837, 1658, 1580, 1469, 1190, 895, 737; HRMS (ESI/Q-TOF) m/z: [M + H]$^+$ calcd for $C_{18}H_{16}NO_4$ 310.1074, found 310.1070.

*(3-Fluorophenyl)(5-(3-fluorophenyl)isoxazol-3-yl)methanone (**23a**).* Gummy; yield = 24 mg, 34%: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.19 (d, 1H, J = 7.8 Hz), 8.07−8.05 (m, 1H), 7.64 (d, 1H, J = 7.8 Hz), 7.57−7.48 (m, 3H), 7.39−7.36 (m, 1H), 7.22−7.19 (m, 1H), 7.08 (s, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 183.1, 169.9, 164.4, 164.1, 162.5, 161.9, 161.6, 131.3, 131.2, 130.6, 130.5, 128.6, 126.84, 126.81, 122.04, 122.0, 121.6, 121.3, 118.2, 117.9, 117.7, 117.5, 113.4, 113.2, 101.2; IR (KBr, cm^{-1}) 3145, 1655, 1610, 1506, 1450, 1190, 895, 750, 680; HRMS (ESI/Q-TOF) m/z: [M + H]$^+$ calcd for $C_{16}H_{10}F_2NO_2$ 286.0674, found 286.0670.

*(4-Fluorophenyl)(5-(4-fluorophenyl)isoxazol-3-yl)methanone (**24a**).* Gummy; yield = 28 mg, 39%: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.44−8.41 (m, 2H), 7.86−7.82 (m, 2H), 7.23−7.18 (m, 4H), 6.99 (s, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 184.1, 170.1, 167.9, 165.6, 165.4, 163.1, 162.6, 133.8, 133.7, 133.6, 132.22, 132.19, 128.4, 128.3, 123.2, 123.1, 116.8, 116.6, 116.5, 116.2, 115.9, 100.27, 100.25; IR (KBr, cm^{-1}) 3135, 2924, 2850, 1654, 1613, 1507, 1446, 1253, 1240, 1162, 942, 838, 771; HRMS (ESI/Q-TOF) m/z: [M + H]$^+$ calcd for $C_{16}H_{10}F_2NO_2$ 286.0674, found 286.0680.

Crossover Experiment Using Two Styrenes. To an oven-dried 10 mL round-bottom flask fitted with a reflux condenser was added *p*-Me styrene (**2**) (24 mg, 0.2 mmol), *p*-Cl styrene (**7**) (28 mg, 0.2 mmol), quinoline (26 mg, 0.2 mmol), *tert*-butyl nitrite (**a**) (82 mg, 0.8 mmol), $Sc(OTf)_3$ (9.8 mg, 0.02 mmol), and 1,2-dichloroethane (1.5 mL). The reaction mixture was refluxed in an oil bath that was preheated to 80 °C for 5 h. The reaction mixture was cooled to room temperature, admixed with ethyl acetate (25 mL), and the organic layer was washed with saturated sodium bicarbonate solution (1 × 5 mL). The organic layer was dried over anhydrous sodium sulfate (Na_2SO_4), and the solvent was evaporated under reduced pressure. The obtained crude product was purified over a column of silica gel (hexane/ethyl acetate, 9.9:0.1) to get rid of the nonpolar impurities. The identities of the products were confirmed by ^{1}H NMR (see Supporting Information, Figure S4) and HRMS (see Supporting Information, Figure S5).

H_2O^{18}-Labeling Experiment for the Formation of Isoxazoline (1a) From Styrene. To an oven-dried 10 mL round-bottom flask fitted with a reflux condenser was added, sequentially, styrene (**1**) (42 mg, 0.4 mmol), quinoline (26 mg, 0.2 mmol), *tert*-butyl nitrite (**a**) (82 mg, 0.8 mmol), $Sc(OTf)_3$ (9.8 mg, 0.02 mmol), H_2O^{18} (8 mg, 0.4 mmol), and 1,2-dichloroethane (1.5 mL). The reaction mixture was refluxed in an oil bath that was preheated to 80 °C. After completion of the reaction (5 h), the crude product was admixed with ethyl acetate (25 mL). The organic layer was washed with saturated sodium bicarbonate solution (1 × 5 mL), dried over anhydrous sodium sulfate (Na_2SO_4), and evaporated under reduced pressure. The identity of the ^{18}O-labeled product was confirmed by HRMS (see Supporting Information, Figure S6) and ^{13}C{^{1}H} NMR (see Supporting Information, Figure S7).

H_2O^{18}-Labeling Experiment for the Formation of Isoxazole (19a) From Phenylacetylene. To an oven-dried 10 mL round-bottom flask fitted with a reflux condenser was added, sequentially, phenyl acetylene (41 mg, 0.4 mmol), quinoline (26 mg, 0.2 mmol), *tert*-butyl nitrite (82 mg, 0.8 mmol), $Sc(OTf)_3$ (9.8 mg, 0.02 mmol), H_2O^{18} (8 mg, 0.4 mmol), and 1,2-dichloroethane (1.5 mL). The reaction mixture was refluxed in an oil bath that was preheated to 80 °C. After completion of the reaction (5 h), the crude product was admixed with ethyl acetate (25 mL). The organic layer was washed with saturated sodium bicarbonate solution (1 × 5 mL), dried over anhydrous sodium sulfate (Na_2SO_4), and evaporated under reduced pressure. The identity of the ^{18}O-labeled product was confirmed by HRMS (see Supporting Information, Figure S8).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00946.

Mechanistic investigation, spectral, and analytical data of all products (PDF)

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Notes

The authors declare no competing financial interest.

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