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Synthesis of Substituted Oxazoles from *N*-Benzyl Propargyl Amines and Acid Chlorides

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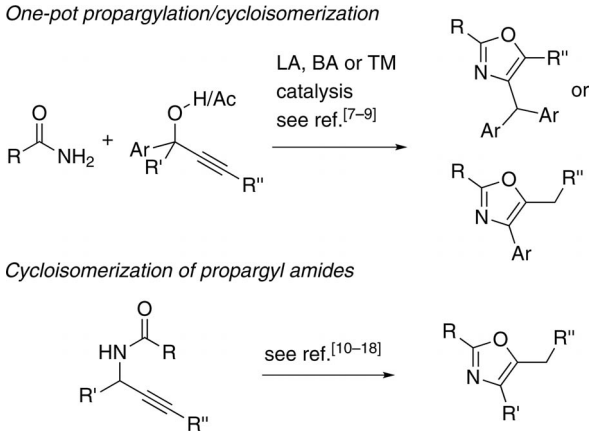
The reaction between *N*-benzylpropargylamines and acid chlorides at elevated temperatures provides efficient, direct access to a variety of di- and tri-substituted oxazoles. The versatility of this reaction is explored and 21 examples are demonstrated. The usefulness of the methodology is showcased through the short and efficient formal syntheses of medicinally relevant drugs aleglitazar and romazarit.

Introduction

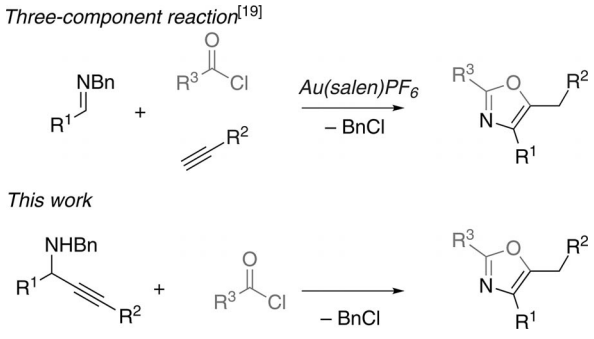
Synthetic methods for the preparation of oxazoles continues to attract interest owing to the increasing importance of such structures as subunits in functional molecules with applications ranging from materials,[1] to detectors,[2] peptide mimetics,[3] amino-alcohol precursors,[4] and drugs.[5] Classical methods for oxazole synthesis include dehydration of *N*-2-keto amides, often under forcing conditions.[6] More recently, Lewis[7] or Brønsted[8] catalysis has been used to form propargyl amides from acylamides and propargyl alcohols/acetates with concomitant cycloisomerization to give oxazole products (Scheme 1). A mild version of this reaction is a one-pot procedure with sequential addition of ruthenium and gold.[9]



Scheme 1. Previous work.

Catalytic cycloisomerization of propargyl amides has received significant attention, and the topic has recently been reviewed.[10] Examples of such processes include the gold-catalyzed cycloisomerization of propargyl amides with both terminal and internal alkynes.[11] The latter are interesting because such cycloisomerization reactions have previously been limited to terminal alkynes.[12] Additional protocols for cycloisomerization of propargyl amides to oxazoles include the use of mercury,[13] palladium,[14] hypervalent iodine,[15] cerium,[16] silica gel,[17] and bases.[18]

We recently disclosed a gold-catalyzed, three-component reaction for the formation of oxazoles by merging imine-alkyne couplings with a cycloisomerization manifold.[19] The overall process is enabled by the loss of a sacrificial benzyl group on the imine nitrogen in the form of benzyl chloride (Scheme 2). As part of a mechanistic investigation into this reaction, an *N*-benzylpropargylamine was treated with an acid chloride, resulting in the clean formation of the corresponding oxazole product. The operational convenience, ease of access to starting materials (*N*-Bn-propargylamines and acid chlorides), and efficiency of the reaction suggested that it might be an attractive procedure in its own



Scheme 2. The present study.

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right. Herein, we report the optimization and substrate scope of this reaction as well as a mechanistic investigation of the cyclization step. The reaction produces di- and trisubstituted oxazole products in up to 99% yield, is general with respect to functional group tolerance (aryl, alkyl, heterocyclic and silyl), proceeds to completion within minutes, and does not require solvent, catalyst, or additives. The usefulness of the methodology in an applied context is demonstrated by short and, in principle, modular, formal syntheses of the drugs romazarit and aleglitazar.

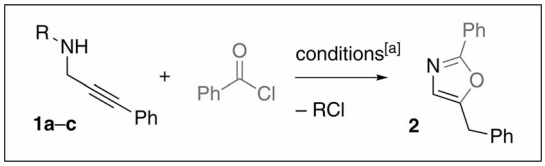
An attractive feature is also that the *N*-benzylpropargylamine starting materials are conveniently accessed, typically in a single step, using catalytic protocols such as iridium-catalyzed addition of alkynes to imines,[21] or three-component coupling of aldehydes, alkynes and benzylamine (A^3-coupling).[22] Alternative methods include stoichiometric acetylide addition to imines.[20]

Results and Discussion

The reaction was optimized by using propargylamines **1a**–**c** as substrates. Oxazole formation was found to proceed efficiently in polar as well as nonpolar solvents (Table 1, entries 1–5). More importantly, the yields were also retained under solvent-free conditions. At 150 °C, using microwave irradiation, the reaction time could be reduced to 15 min.

Addition of additives such as Bu_4NCl, NaI, NaBr, or HCl (1.0 M in dioxane) did not have a significant impact on the yield of the reaction. Use of pyridine as the solvent inhibited oxazole formation completely. Exchange of the Bn sacrificial group for an electron-rich *p*MeOBn substituent (**1b**) gave a lower yield of oxazole **2** (47%). Because an excess of *p*MeOBnCl (78%) compared to **2** was observed after the complete consumption of starting materials, and prolonged heating of the reaction mixture did not cause observable decomposition of the product, the reduced yield in this case is attributed to debenzylation side-reactions occurring prior the cyclization step. Use of a methyl substituent as the leaving group[23] (**1c**) also gave oxazole **2**, albeit in lower yield (23%). It is noteworthy that 3-phenylpropargylamine (**1b**) under the optimized conditions only gave 4% yield of oxazole **2** (Table 1, entry 8). As one equivalent of HCl is released in this process, 50% conversion should, in principle, be possible.

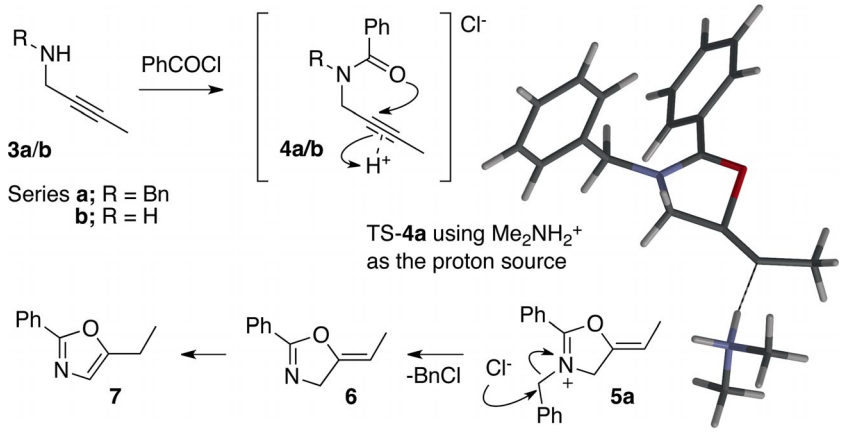
Table 1. Optimization of oxazole formation in the reaction between **1a**–**c** and BzCl.[a]



Entry	Propargylamine (R)	BzCl [equiv.]	Solvent	Temp. [°C]	Time	Yield [%][b]
1[c]	**1a** (Bn)	1.3	toluene	90	16 h	15
2[c]	**1a** (Bn)	1.3	toluene	150	16 h	60
3[c]	**1a** (Bn)	1.3	dioxane	110	16 h	63
4[c]	**1a** (Bn)	1.3	MeCN	110	16 h	53
5[c]	**1a** (Bn)	1.3	DMF	110	16 h	15
6	**1a** (Bn)	1.3	–	110	16 h	50
7[d]	**1a (Bn)**	**1.4**	**–**	**150**	**15 min**	**62**
8[d]	**1b** (H)	1.4	–	150	15 min	4
9[d]	**1c** (Me)	1.4	–	150	15 min	23

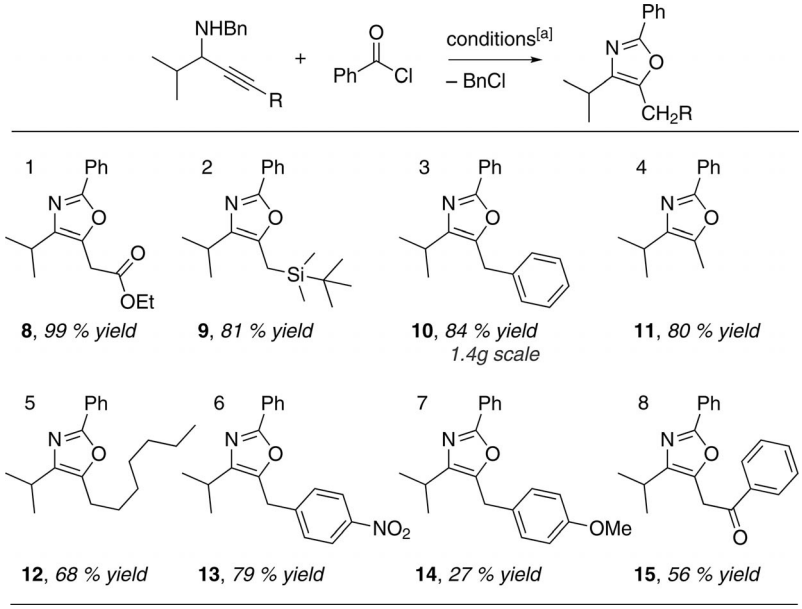
[a] Reaction run on 1.0 mmol scale (amine). [b] Measured by NMR spectroscopic analysis with methyl transcinnamate as internal standard. [c] Concentration 1.0 M (amine). [d] Microwave heating.

Mechanistically, an HCl salt of **3** is presumed to be the proton source that activates the alkyne for nucleophilic attack by the carbonyl (Scheme 3). When modeling the proposed reaction pathway at the B3LYP/6-31G+* level, the inductive effect of the benzyl substituent on **4a** was found to stabilize the transition state of the carbonyl addition to the alkyne by 2.5 kcal compared with the corresponding TS of the secondary propargyl amide **4b**.[24] It is also noteworthy that the *N*-Bn substituent stabilizes the positive charge on **5a**, thus lowering the relative energy of this intermediate by 6.4 kcal compared with **5b**. Moreover, the calculations indicate that, in contrast to the cyclization of **4a**, the cyclization of **4b** is actually a slightly endothermic process (2.5 kcal). These results are in line with earlier observations by Ohno that the reaction time for an *N*-Bn carbamate to



Scheme 3. Proposed mechanism for oxazole formation.

Table 2. Oxazole formation with varying substituents on the distal alkyne position.



[a] Reaction conditions: amine (1 mmol), BzCl (1.4 equiv.), microwave heating (150 °C, 15 min).

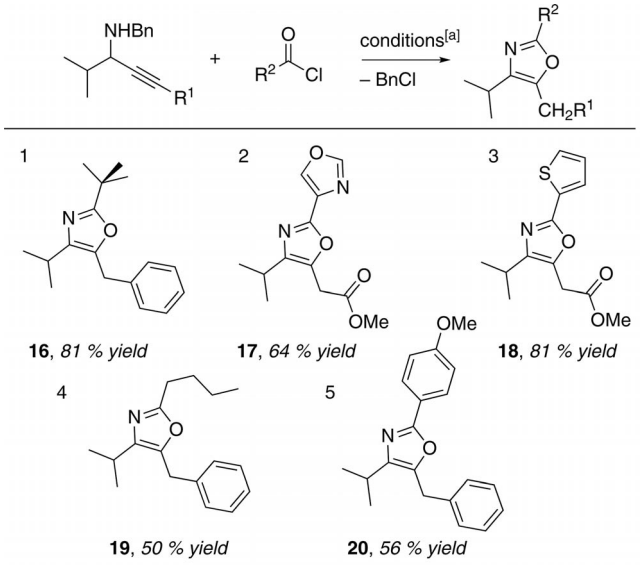
cyclize in an iodocarbamation reaction is an order of magnitude shorter than that of the corresponding N-H substrate.[25] We cannot exclude the possibility that preorganization as a result of steric effects also plays a part in the cyclization, but it is clear that the *N*-Bn group serves not only as a chloride trap, but also facilitates cyclization under the mildly acidic conditions.

Using the optimized protocol, the substrate scope of the reaction was explored. A series of functionalities including alkyl, aryl, ester, ketone, and silyl groups were found to be well-tolerated at the distal alkyne position (Table 2). In particular, oxazole **8** formed in essentially quantitative yield from the corresponding ester. The reaction could be run on more than a gram scale with a slightly improved efficiency (Table 2, entry 3). For cases in which lower yields were obtained, particularly for substrates containing an electron-donating group (Table 2, entry 7), the starting alkyne was consumed and the remaining mass was comprised of a complex mixture.

Aryl-, heterocyclic-, and aliphatic acyl chlorides were well-tolerated in the reaction (Table 3). However, electron-deficient *p*NO_2BzCl failed to form the corresponding oxazole.

Oxazoles with aliphatic as well as aromatic substituents at the C4-position were readily formed from the corresponding starting materials (Table 4). Under the standard conditions, unisomerized 2-oxazoline **21** was formed in good yield from the corresponding alkyne. This compound could, however, be isomerized to oxazole **22** in the presence of acid. Using a *gem*-dimethyl-substituted propargylamine, the corresponding nonaromatic 5-benzylidene-2-oxazoline **26** was isolated as a single geometric isomer, albeit in moderate yield (Table 4, entry 6).

Table 3. Oxazole formation with acyl chlorides.

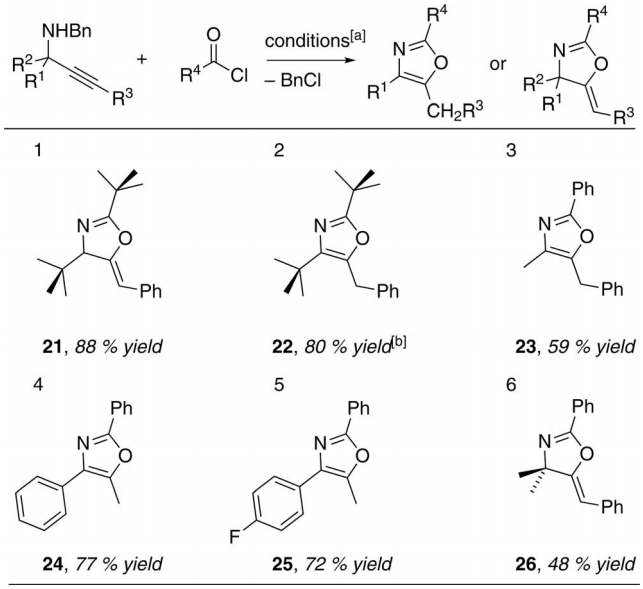


[a] Reaction conditions: amine (1 mmol), acyl chloride (1.4 equiv.), microwave heating (150 °C, 15 min).

The acylation–cycloisomerization protocol was applied to short formal syntheses of the medicinally relevant structures romazarit[26] (**30**) and aleglitazar[27] (**34**).

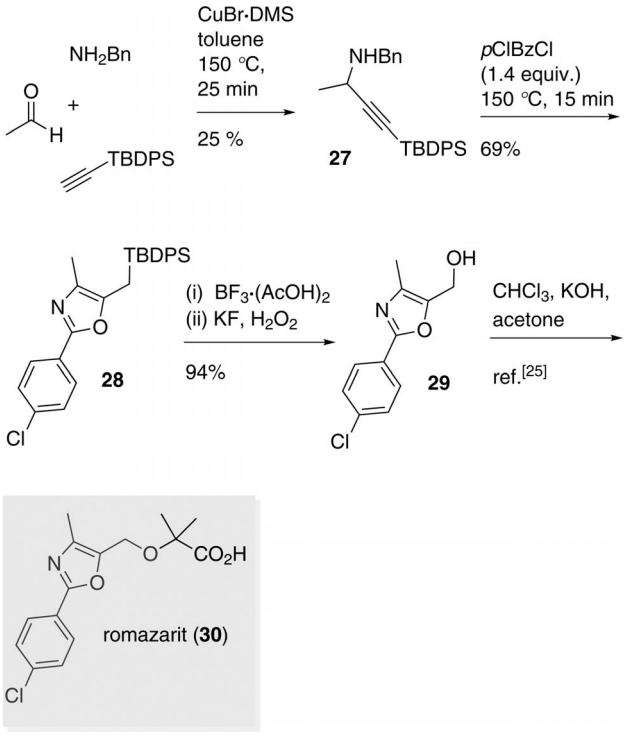
The synthesis of romazarit (**30**) commenced with the assembly of *N*-Bn-propargylamine **27** by using an A^3-coupling (Scheme 4). From propargylamine **27**, oxazole **28** was formed in good yield by reaction with *p*ClPhCOCl under standard conditions. Conversion of the silyl group of **28** into the desired primary alcohol **29** was accomplished un-

Table 4. Cyclization with varying substituents at the proximal propargylic position.



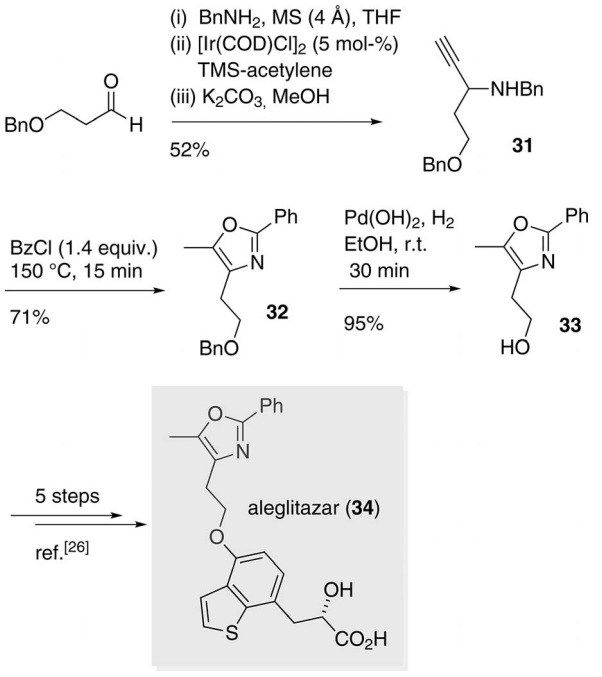
[a] Reaction conditions: amine (1 mmol), acyl chloride (1.4 equiv.), microwave heating (150 °C, 15 min). [b] Formed from **21** with a catalytic amount of *p*TSA.

der modified Tamao–Fleming conditions.[28] Alcohol **29** can then be converted into the final structure **30** in a single step by using known methodology.[26]



Scheme 4. Formal synthesis of romazarit (**30**).

The synthesis of the oxazole building block of aleglitazar (**34**) started with formation of *N*-Bn-propargylamine **31** by using a one-pot procedure (Scheme 5). Imine formation followed by Ir-catalyzed addition of TMS-acetylene to the enolizable imine proceeded smoothly[21] and quenching the reaction by addition of a mixture of carbonate and methanol removed the TMS group to give **31** in 52% isolated yield. Oxazole **32** was then formed by the reaction of *N*-Bn-propargylamine **31** with benzoyl chloride using the standard protocol. The completion of building block **33** was accomplished by hydrogenolysis of the benzyl group of **32** using Pearlmans catalyst.[29]



Scheme 5. Formal synthesis of aleglitazar (**34**).

Conclusions

The reaction between *N*-Bn-propargylamines and acid chlorides at elevated temperatures was investigated and found to be a general method that can be used to rapidly and conveniently assemble diversely substituted oxazoles from readily available starting materials. The cyclization step was investigated in silico and a benzyl group on the propargylic nitrogen was found to facilitate the cyclization by 2.5 kcal compared with a proton, which may, at least in part, account for the superior efficiency of such substrates in the reaction. The usefulness of the reaction in an applied context was demonstrated through the short formal syntheses of aleglitazar (**34**) and romazarit (**30**) by routes involving three and four isolated intermediates, respectively. The step-economical access to starting materials, short reaction times, and operational convenience of the cycloisomerization step should be of particular value for library generation.

Experimental Section

General Experimental Methods: All reactions were carried out in oven-dried glassware under an atmosphere of nitrogen. Microwave

reactions were preformed with a Biotage Initiator. Mixtures were concentrated by using a Heidolph rotary evaporator. NMR spectra were recorded with a Bruker Ultrashield 400 plus (^{1}H at 400 MHz and ^{13}C at 101 MHz). Spectra were processed using MestReNova. Chemical shifts are reported in ppm downfield from $SiMe_4$ using the residual peak of $CDCl_3$ as reference (δ = 7.26 for ^{1}H and δ = 77.2 for ^{13}C). ^{1}H NMR spectra are reported as follows: chemical shifts (δ, ppm), multiplicity (s = singlet, br. s = broad singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, m = multiplet, app. = apparent), coupling constant [Hz] and integration. ^{13}C NMR spectra are reported as chemical shifts (δ, ppm). The ^{13}C NMR spectra for **31** contain signal overlaps in the aromatic region. For known compounds (references given), only ^{1}H NMR data are reported. HRMS were recorded with a Micromass Q-TOF spectrometer (ESI). IR spectra were recorded with a Bruker ALPHA-P and reported as follows: wavenumbers (cm^{-1}), description (w = weak, m = medium, s = strong, br = broad). Melting points were measured with an Electrothermal 9100 melting point apparatus and are uncorrected. Reactions were followed by TLC using aluminum-backed plates (Merck $60F_{254}$ silica gel) and visualized with UV (252 nm) and/or $KMnO_4$. Preparative chromatography was preformed using silica gel (Acros 40–60 μm, 60 Å) columns or a flash-purification system (Biotage Isolera One). All other solvents and reagents were purchased from commercial suppliers and used as received.

General Procedure for the Preparation of Oxazoles: Under an atmosphere of nitrogen, acyl chloride (1.4 equiv.) was added to *N*-benzylpropargylamine (1 equiv.) in a microwave vial. The resulting mixture was heated under microwave irradiation with a ceiling temperature of 150 °C for 15 min. After cooling to ambient temperature, the mixture was diluted with CH_2Cl_2. A small amount of silica was added to the reaction mixture and the resulting slurry was concentrated under reduced pressure. The concentrate was added to a silica gel column and eluted with a mixture of ethyl acetate and petroleum ether. The product-containing fractions were pooled and concentrated under reduced pressure to give the corresponding oxazoles.

Ethyl 2-(4-Isopropyl-2-phenyloxazol-5-yl)acetate (8): Yield 99% {>95% pure by NMR spectroscopic analysis and a single spot by TLC [R_f = 0.37 (EtOAc/petroleum ether, 1:10)]}; white solid; m.p. 72.5–73.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06–7.93 (m, 2 H), 7.47–7.32 (m, 3 H), 4.19 (q, J = 7.1 Hz, 2 H), 3.73 (s, 2 H), 2.95–2.85 (m, 1 H), 1.37–1.21 (m, 9 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.0, 160.2, 144.2, 138.1, 129.9, 128.6, 127.8, 126.2, 61.4, 31.3, 25.7, 22.0, 14.1 ppm. IR ($CHCl_3$ film): $\tilde{\nu}$ = 2966 (m), 2871 (w), 1727 (s), 1552 (m) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{16}H_{20}NO_3$ $[M + H]^+$ 274.144; found 274.140.

5-[(*tert*-Butyldimethylsilyl)methyl]-4-isopropyl-2-phenyloxazole (9): Yield 81% {>95% pure by NMR spectroscopic analysis and a single spot by TLC [R_f = 0.21 (EtOAc/petroleum ether, 1:40)]}; pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02–7.90 (m, 2 H), 7.47–7.30 (m, 3 H), 2.88–2.76 (m, 1 H), 2.08 (s, 2 H), 1.27 (d, J = 6.9 Hz, 6 H), 0.93 (s, 9 H), 0.06 (s, 6 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.6, 144.6, 139.9, 129.3, 128.7, 128.4, 125.8, 26.5, 25.7, 22.4, 16.8, 11.0, –5.6 ppm. IR ($CHCl_3$ film): $\tilde{\nu}$ = 2956 (s), 2928 (s), 2858 (m), 1556 (w), 1463 (m), 1256 (s) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{19}H_{30}NOSi$ $[M + H]^+$ 316.210; found 316.213.

5-Benzyl-4-isopropyl-2-phenyloxazole (10): Yield 84% {>95% pure by NMR spectroscopic analysis and a single spot by TLC [R_f = 0.33 (EtOAc/petroleum ether, 1:40)]}; white solid; m.p. 70.7–72.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03–7.89 (m, 2 H), 7.44–7.35 (m, 3 H), 7.35–7.28 (m, 2 H), 7.27–7.20 (m, 3 H), 4.05 (s, 2 H), 3.04–2.84 (m, 1 H), 1.29 (d, J = 6.9 Hz, 6 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.0, 143.9, 142.7, 138.1, 129.9, 128.8, 128.7, 128.5, 128.1, 126.8, 126.3, 31.3, 25.8, 22.5 ppm. IR ($CHCl_3$ film): $\tilde{\nu}$ = 2968 (m), 1553 (m), 1450 (m), 1053 (m) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{19}H_{20}NO$ $[M + H]^+$ 278.152; found 278.150.

4-Isopropyl-5-methyl-2-phenyloxazole (11): Yield 80% {>95% pure by NMR spectroscopic analysis and a single spot by TLC [R_f = 0.28 (EtOAc/petroleum ether, 1:40)]}; pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06–7.91 (m, 2 H), 7.48–7.33 (m, 3 H), 2.95–2.82 (m, 1 H), 2.34 (s, 3 H), 1.28 (d, J = 6.9 Hz, 6 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.2, 141.9, 141.7, 129.6, 128.7, 128.3, 126.1, 25.9, 22.3, 10.6 ppm. IR ($CHCl_3$ film): $\tilde{\nu}$ = 2965 (m), 2871 (w), 1555 (m), 1449 (m) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{13}H_{16}NO$ $[M + H]^+$ 202.123; found 202.118.

5-Heptyl-4-isopropyl-2-phenyloxazole (12): Yield 68% {>95% pure by NMR spectroscopic analysis and a single spot by TLC [R_f = 0.76 (EtOAc/petroleum ether, 1:10)]}; pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01–7.97 (m, 2 H), 7.45–7.32 (m, 3 H), 2.93–2.83 (m, 1 H), 2.66 (t, J = 7.4 Hz, 2 H), 1.71–1.61 (m, 2 H), 1.39–1.22 (m, 14 H), 0.88 (t, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.3, 146.1, 141.6, 129.6, 128.7, 128.4, 126.2, 32.0, 29.3, 29.2, 28.9, 25.8, 25.0, 22.8, 22.5, 14.3 ppm. IR ($CHCl_3$ film): $\tilde{\nu}$ = 2958 (s), 2924 (s), 2857 (m), 1555 (m), 1450 (s) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{19}H_{28}NO$ $[M + H]^+$ 286.217; found 286.213.

4-Isopropyl-5-(4-nitrobenzyl)-2-phenyloxazole (13): Yield 79% {>95% pure by NMR spectroscopic analysis and a single spot by TLC [R_f = 0.39 (EtOAc/petroleum ether, 1:10)]}; white solid; m.p. 100.0–101.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.29–8.09 (m, 2 H), 8.06–7.90 (m, 2 H), 7.48–7.32 (m, 5 H), 4.15 (s, 2 H), 3.00–2.87 (m, 1 H), 1.30 (d, J = 6.9 Hz, 6 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.5, 145.6, 143.6, 141.9, 130.2, 129.3, 128.8, 127.8, 126.3, 124.1, 100.1, 31.1, 25.9, 22.4 ppm. IR ($CHCl_3$ film): $\tilde{\nu}$ = 2964 (m), 2927 (w), 2871 (w), 1599 (m), 1554 (w), 1518 (s), 1486 (m), 1449 (m), 1343 (s) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{19}H_{19}N_2O_3$ $[M + H]^+$ 323.140; found 323.139.

4-Isopropyl-5-(4-methoxybenzyl)-2-phenyloxazole (14): Yield 27% {>95% pure by NMR spectroscopic analysis and a single spot by TLC [R_f = 0.50 (EtOAc/petroleum ether, 1:10)]}; white solid; m.p. 96.1–97.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03–7.93 (m, 2 H), 7.46–7.34 (m, 3 H), 7.21–7.11 (m, 2 H), 6.91–6.81 (m, 2 H), 3.99 (s, 2 H), 3.79 (s, 3 H), 2.95 (hept, J = 6.9 Hz, 1 H), 1.30 (d, J = 6.9 Hz, 6 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.9, 158.5, 144.3, 142.5, 130.2, 129.8, 129.4, 128.7, 128.2, 126.3, 114.2, 55.4, 30.34, 25.8, 22.5 ppm. IR ($CHCl_3$ film): $\tilde{\nu}$ = 3011 (w), 2967 (m), 2831 (w), 1611 (m), 1551 (m), 1510 (s), 1485 (w), 1461 (m) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{20}H_{22}NO_2$ $[M + H]^+$ 308.165; found 308.164.

2-(4-Isopropyl-2-phenyloxazol-5-yl)-1-phenylethanone (15): Yield 56% {>95% pure by NMR spectroscopic analysis and a single spot by TLC [R_f = 0.33 (EtOAc/petroleum ether, 1:10)]}; yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10–8.02 (m, 2 H), 8.02–7.92 (m, 2 H), 7.66–7.56 (m, 1 H), 7.56–7.47 (m, 2 H), 7.47–7.35 (m, 3 H), 4.37 (s, 2 H), 2.98–2.86 (m, 1 H), 1.28 (d, J = 6.9 Hz, 6 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 194.6, 160.6, 144.7, 138.5, 136.2, 133.8, 130.0, 128.9, 128.74, 128.72, 128.0, 126.4, 35.8, 26.0, 22.2 ppm. IR ($CHCl_3$ film): $\tilde{\nu}$ = 2966 (m), 2927 (w), 2872 (w), 1689 (s), 1554 (w), 1449 (m), 1212 (m) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{20}H_{20}NO_2$ $[M + H]^+$ 306.149; found 306.146.

5-Benzyl-2-(*tert*-butyl)-4-isopropyloxazole (16): Yield 81% {>95% pure by NMR spectroscopic analysis and a single spot by TLC

[R_f = 0.59 (EtOAc/petroleum ether, 1:10)]}; white solid; m.p. 62.7–63.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.26 (m, 2 H), 7.25–7.18 (m, 1 H), 7.18–7.12 (m, 2 H), 3.94 (s, 2 H), 2.92–2.78 (m, 1 H), 1.32 (s, 9 H), 1.21 (d, J = 6.9 Hz, 6 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.2, 142.4, 140.6, 138.7, 128.7, 128.3, 126.5, 33.7, 31.2, 28.9, 26.0, 22.4 ppm. IR ($CHCl_3$ film): $\tilde{\nu}$ = 2966 (s), 2870 (w), 1567 (m), 1495 (w), 1455 (m), 1053 (m) cm^{-1}. HRMS (ESI): m/z calcd. for $C_{17}H_{24}NO$ [M + H]$^+$ 258.186; found 258.182.

Methyl 2-(4-Isopropyl-[2,4′-bioxazol]-5-yl)acetate (17): Yield 64% {>95% pure by NMR spectroscopic analysis and a single spot by TLC [R_f = 0.39 (EtOAc/petroleum ether, 1:1)]}; pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.21 (dd, J = 6.9, 1.0 Hz, 1 H), 7.93 (t, J = 3.6 Hz, 1 H), 3.72 (s, 2 H), 3.70 (s, 3 H), 2.93–2.80 (m, 1 H), 1.25 (d, J = 6.9 Hz, 6 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.3, 153.6, 151.7, 144.4, 138.4, 138.3, 130.7, 52.6, 30.9, 25.8, 22.0 ppm. IR ($CHCl_3$ film): $\tilde{\nu}$ = 2966 (m), 2874 (w), 1740 (s), 1537 (w) cm^{-1}. HRMS (ESI): m/z calcd. for $C_{12}H_{15}N_2O_4$ [M + H]$^+$ 251.103; found 251.107.

Methyl 2-[4-Isopropyl-2-(thiophen-2-yl)oxazol-5-yl]acetate (18): Yield 81% {>95% pure by NMR spectroscopic analysis and a single spot by TLC [R_f = 0.19 (EtOAc/petroleum ether, 1:10)]}; white solid; m.p. 55.8–57.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61 (dt, J = 5.6, 2.8 Hz, 1 H), 7.37 (dd, J = 5.0, 1.2 Hz, 1 H), 7.07 (dd, J = 5.0, 3.7 Hz, 1 H), 3.73 (s, 3 H), 3.72 (s, 2 H), 2.94–2.79 (m, 1 H), 1.27 (d, J = 6.9 Hz, 6 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.5, 156.6, 144.4, 137.6, 130.5, 127.9, 127.8, 127.5, 52.6, 31.1, 25.9, 22.1 ppm. IR ($CHCl_3$ film): $\tilde{\nu}$ = 2967 (m), 2946 (w), 2873 (w), 1736 (s), 1574 (m) cm^{-1}. HRMS (ESI): m/z calcd. for $C_{12}H_{15}N_2O_4$ [M + H]$^+$ 266.085; found 266.080.

5-Benzyl-2-butyl-4-isopropyloxazole (19): Yield 50% {>95% pure by NMR spectroscopic analysis and a single spot by TLC [R_f = 0.43 (EtOAc/petroleum ether, 1:10)]}; pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30 (ddd, J = 7.5, 4.5, 1.2 Hz, 2 H), 7.25–7.19 (m, 1 H), 7.17 (dd, J = 7.8, 1.0 Hz, 2 H), 3.92 (s, 2 H), 2.93–2.77 (m, 1 H), 2.66 (dd, J = 8.0, 8.0 Hz, 2 H), 1.74–1.62 (m, 2 H), 1.41–1.28 (m, 2 H), 1.22 (d, J = 6.9 Hz, 6 H), 0.90 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 163.4, 142.9, 140.8, 138.4, 128.7, 128.4, 126.6, 31.1, 29.6, 28.3, 25.5, 22.5, 22.4, 13.9 ppm. IR ($CHCl_3$ film): $\tilde{\nu}$ = 2961 (m), 2872 (w), 1572 (m), 1460 (m) cm^{-1}. HRMS (ESI): m/z calcd. for $C_{17}H_{24}NO$ [M + H]$^+$ 258.186; found 258.183.

5-Benzyl-4-isopropyl-2-(4-methoxyphenyl)oxazole (20): Yield 56% {>95% pure by NMR spectroscopic analysis and a single spot by TLC [R_f = 0.54 (EtOAc/petroleum ether, 1:10)]}; white solid; m.p. 66.0–66.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00–7.89 (m, 2 H), 7.39–7.31 (m, 2 H), 7.31–7.22 (m, 3 H), 7.02–6.90 (m, 2 H), 4.06 (s, 2 H), 3.86 (s, 3 H), 3.05–2.88 (m, 1 H), 1.32 (d, J = 6.9 Hz, 6 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.0, 160.1, 143.2, 142.5, 138.3, 128.8, 128.5, 127.9, 126.7, 121.1, 114.1, 55.5, 31.2, 25.8, 22.5 ppm. IR ($CHCl_3$ film): $\tilde{\nu}$ = 2964 (m), 2934 (w), 2837 (w), 1613 (m), 1560 (w), 1500 (s), 1251 (s) cm^{-1}. HRMS (ESI): m/z calcd. for $C_{20}H_{22}NO_2^+$ [M + H]$^+$ 308.165; found 308.165.

5-Benzyl-4-methyl-2-phenyloxazole (21): Yield 59% {>95% pure by NMR spectroscopic analysis and a single spot by TLC [R_f = 0.25 (EtOAc/petroleum ether, 1:10)]}; pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07–7.86 (m, 2 H), 7.45–7.37 (m, 3 H), 7.35–7.29 (m, 2 H), 7.28–7.21 (m, 3 H), 4.03 (s, 2 H), 2.21 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.9, 145.6, 137.8, 133.1, 130.0, 128.84, 128.82, 128.5, 127.9, 126.9, 126.2, 31.2, 11.6 ppm. IR ($CHCl_3$ film): $\tilde{\nu}$ = 3006 (w), 2925 (w), 2834 (w), 1553 (m), 1493 (m), 1450 (m) cm^{-1}. HRMS (ESI): m/z calcd. for $C_{17}H_{16}NO$ [M + H]$^+$ 250.123; found 250.122.

5-Methyl-2,4-diphenyloxazole (22): Yield 77% {>95% pure by NMR spectroscopic analysis and a single spot by TLC [R_f = 0.48 (EtOAc/petroleum ether, 1:10)]}; white solid; m.p. 66.8–68.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.22–8.05 (m, 2 H), 7.87–7.73 (m, 2 H), 7.55–7.45 (m, 5 H), 7.37 (t, J = 7.4 Hz, 1 H), 2.64 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.5, 144.1, 136.1, 132.5, 130.1, 128.8, 128.7, 127.8, 127.4, 126.9, 126.3, 12.1 ppm. IR ($CHCl_3$ film): $\tilde{\nu}$ = 3057 (m), 2938 (w), 1557 (m), 1206 (m) cm^{-1}. HRMS (ESI): m/z calcd. for $C_{16}H_{14}NO$ [M + H]$^+$ 236.108; found 236.107.

4-(4-Fluorophenyl)-5-methyl-2-phenyloxazole (25): Yield 72% {>95% pure by NMR spectroscopic analysis and a single spot by TLC [R_f = 0.48 (EtOAc/petroleum ether, 1:10)]}; white solid; m.p. 69.2–70.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.17–8.04 (m, 2 H), 7.80–7.66 (m, 2 H), 7.56–7.41 (m, 3 H), 7.25–7.09 (m, 2 H), 2.59 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 162.2 (d, $^1J_{C,F}$ = 246.7 Hz), 159.5, 143.7 (d, $^4J_{C,F}$ = 1.1 Hz), 135.3, 130.1, 128.8, 128.7, 128.6 (d, $^3J_{C,F}$ = 8.1 Hz), 127.7, 126.2, 115.6 (d, $^2J_{C,F}$ = 21.6 Hz), 12.0 ppm. IR ($CHCl_3$ film): $\tilde{\nu}$ = 3063 (w), 2992 (w), 2926 (w), 1556 (m), 1506 (s) cm^{-1}. HRMS (ESI): m/z calcd. for $C_{16}H_{13}FNO$ [M + H]$^+$ 254.098; found 254.100.

5-[(*tert*-Butyldiphenylsilyl)methyl]-2-(4-chlorophenyl)-4-methyloxazole (28): Yield 67% {>95% pure by NMR spectroscopic analysis and a single spot by TLC [R_f = 0.41 (EtOAc/petroleum ether, 1:10)]}; pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63–7.56 (m, 4 H), 7.53–7.46 (m, 2 H), 7.44–7.38 (m, 2 H), 7.38–7.32 (m, 4 H), 7.29–7.25 (m, 2 H), 2.67 (s, 2 H), 1.92 (s, 3 H), 1.09 (s, 9 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.6, 145.3, 136.1, 135.4, 134.0, 131.3, 129.6, 128.9, 127.8, 127.0, 126.3, 27.8, 18.5, 11.4, 9.8 ppm. IR ($CHCl_3$ film): $\tilde{\nu}$ = 2960 (w), 2930 (m), 2857 (m), 1624 (w), 1547 (w), 1483 (m), 1427 (m), 1105 (s), 1092 (s) cm^{-1}. HRMS (ESI): m/z calcd. for $C_{27}H_{29}ClNOSi$ [M + H]$^+$ 446.171; found 446.170.

4-[2-(Benzyloxy)ethyl]-5-methyl-2-phenyloxazole (32): Yield 71% {>95% pure by NMR spectroscopic analysis and a single spot by TLC [R_f = 0.26 (EtOAc/petroleum ether, 1:10)]}; pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00–7.94 (m, 2 H), 7.46–7.37 (m, 3 H), 7.36–7.30 (m, 4 H), 7.29–7.25 (m, 1 H), 4.54 (s, 2 H), 3.77 (t, J = 7.0 Hz, 2 H), 2.82 (t, J = 6.9 Hz, 2 H), 2.34 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.5, 144.8, 138.6, 133.4, 129.82, 128.78, 128.5, 128.0, 127.73, 127.65, 126.0, 73.2, 69.4, 27.0, 10.4 ppm. IR ($CHCl_3$ film): $\tilde{\nu}$ = 2952 (w), 2921 (m), 2864 (m), 1553 (w), 1485 (w), 1450 (m), 1098 (s) cm^{-1}. HRMS (ESI): m/z calcd. for $C_{19}H_{20}NO_2$ [M + H]$^+$ 294.149; found 294.147.

General Procedure for the Preparation of Oxazolines 21 and 26: Under an atmosphere of nitrogen, acyl chloride (1.4 equiv.) was added to *N*-benzylpropargylamine (1 equiv.) in a microwave vial. The resulting mixture was heated under microwave irradiation with a ceiling temperature of 150 °C for 15 min. After cooling to ambient temperature, the mixture was diluted with CH_2Cl_2. A small amount of silica was added to the reaction mixture and the resulting slurry was concentrated under reduced pressure. The concentrate was added to a silica gel column and eluted with a mixture of ethyl acetate and petroleum ether. The product-containing fractions were pooled and concentrated under reduced pressure to give the corresponding oxazoline.

(*Z*)-5-Benzylidene-2,4-di-*tert*-butyl-4,5-dihydrooxazole (21): Yield 80%; white solid; m.p. 66.9–67.9 °C; R_f = 0.63 (EtOAc/petroleum ether, 1:10). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54 (d, J = 7.2 Hz, 2 H), 7.38–7.29 (m, 2 H), 7.18 (t, J = 7.4 Hz, 1 H), 5.57 (d, J = 1.9 Hz, 1 H), 4.32 (d, J = 1.9 Hz, 1 H), 1.33 (s, 9 H), 0.98 (s, 9 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.7, 154.8, 135.4, 128.6, 128.1, 126.1, 103.3, 78.6, 36.0, 33.6, 27.9, 25.8 ppm. IR

($CHCl_3$ film): $\tilde{\nu}$ = 2972 (m), 2903 (w), 2870 (w), 1691 (s), 1667 (m), 1600 (w) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{18}H_{26}NO$ $[M + H]^+$ 272.201; found 272.201.

(*Z*)-5-Benzylidene-4,4-dimethyl-2-phenyl-4,5-dihydrooxazole (26): Yield 48% {>95% pure by NMR spectroscopic analysis and a single spot by TLC [R_f = 0.57 (EtOAc/petroleum ether, 1:10)]}; pale-yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.19–8.06 (m, 2 H), 7.70–7.65 (m, 2 H), 7.62–7.48 (m, 3 H), 7.47–7.37 (m, 2 H), 7.27–7.22 (m, 1 H), 5.57 (s, 1 H), 1.56 (s, 6 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.8, 160.0, 135.2, 132.0, 128.8, 128.7, 128.4, 128.1, 127.0, 126.3, 99.5, 71.1, 29.8 ppm. IR ($CHCl_3$ film): $\tilde{\nu}$ = 2973 (m), 2929 (w), 2857 (w), 1695 (m), 1651 (s), 1454 (m), 1448 (m) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{18}H_{18}NO$ $[M + H]^+$ 264.139; found 264.135.

Isomerization of 21 to 5-Benzyl-2,4-di-*tert*-butyloxazole (22): To a solution of **21** (1.48 g, 5.45 mmol) in toluene (25 mL) was added *p*-toluenesulfonic acid monohydrate (200 mg, 1.05 mmol) and the mixture was heated to reflux. After 24 h the mixture was cooled to ambient temperature and $NaHCO_3$ (0.5 g, 5.95 mmol) was added. The mixture was filtered and concentrated under reduced pressure. Purification by silica gel chromatography (EtOAc/petroleum ether, 1:20) gave **22**, yield 1.30 g (88%); >95% pure by NMR spectroscopic analysis and a single spot by TLC [R_f = 0.74 (EtOAc/petroleum ether, 1:10)]; white solid; m.p. 47.7–48.5 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.26 (m, 2 H), 7.25–7.19 (m, 1 H), 7.16–7.09 (m, 2 H), 4.08 (s, 2 H), 1.32 (s, 9 H), 1.28 (s, 9 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 142.9, 141.8, 139.2, 129.2, 128.6, 128.1, 126.3, 33.5, 32.4, 31.9, 30.4, 28.8 ppm. IR ($CHCl_3$ film): $\tilde{\nu}$ = 2967 (s), 2869 (w), 1573 (m), 1495 (m), 1455 (m), 1160 (s) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{18}H_{26}NO$ $[M + H]^+$ 272.201; found 272.201.

Procedure for the Preparation of *N*-Benzyl-4-(*tert*-butyldiphenylsilyl)but-3-yn-2-amine (27): Under an atmosphere of nitrogen, alkyne (1.6 equiv.), benzylamine (1.3 equiv.) and aldehyde (1 equiv.) were added to a suspension of $CuBr{\cdot}SMe_2$ (0.2 equiv.) in toluene (1 M). The mixture was heated under microwave irradiation for 25 min at 150 °C. After cooling to ambient temperature a small amount of silica was added and the resulting slurry was concentrated under reduced pressure. The concentrate was added to a silica gel column and eluted with ethyl acetate and petroleum ether. Fractions containing the product were pooled and concentrated under reduced pressure, yield 25% {>95% pure by NMR spectroscopic analysis and a single spot by TLC [R_f = 0.28 (EtOAc/petroleum ether, 1:10)]}; pale-yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.96–7.77 (m, 4 H), 7.54–7.25 (m, 11 H), 4.16 (d, *J* = 12.6 Hz, 1 H), 3.95 (d, *J* = 12.6 Hz, 1 H), 3.69 (q, *J* = 6.9 Hz, 1 H), 1.51 (d, *J* = 6.9 Hz, 3 H), 1.40 (br. s, 1 H), 1.14 (s, 9 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 140.0, 135.8, 133.7, 129.7, 128.69, 128.65, 127.9, 127.3, 113.3, 82.4, 51.8, 45.6, 27.2, 22.6, 18.6 ppm. IR ($CHCl_3$ film): $\tilde{\nu}$ = 2956 (w), 2928 (m), 2856 (m), 2156 (m), 1428 (m), 1108 (s) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{27}H_{32}NSi$ $[M + H]^+$ 398.230; found 398.232.

Preparation of *N*-Benzyl-5-(benzyloxy)pent-1-yn-3-amine (31): To a suspension of benzylamine (1 equiv.) and molecular sieves (0.5 g/mmol, 4 Å, pellets) in THF (0.33 M) was added 3-benzyloxy-propionaldehyde (1 equiv.) in THF (1 M). After 2.5 h stirring at room temperature, the molecular sieves were separated by filtration and the filtrate was added to a vial containing $[Ir(COD)Cl]_2$ (5 mol-%). Ethynyltrimethylsilane (1.5 equiv.) was added in one portion, and the resulting light-yellow mixture was stirred at room temperature. After 22 h, conversion was measured by NMR spectroscopy. When unreacted imine remained, additional ethynyltrimethylsilane (1.5 equiv.) was added and the mixture was stirred for an additional 48 h. Upon complete consumption of the imine, K_2CO_3 (0.3 equiv.) in MeOH (0.02 M) was added. After 5 h, water (10 mL/mmol aldehyde) was added and the mixture was extracted with CH_2Cl_2 (4× 20 mL/mmol aldehyde). The organic layer was washed with brine (40 mL/mmol aldehyde), dried using a phase separator, and concentrated under reduced pressure. Purification by silica gel chromatography (EtOAc/petroleum ether) gave the product, yield 52% {>95% pure by NMR spectroscopic analysis and a single spot by TLC [R_f = 0.19 (EtOAc/petroleum ether, 1:10)]}; clear oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.21 (m, 10 H), 4.50 (s, 2 H), 4.04 (d, *J* = 12.9 Hz, 1 H), 3.80 (d, *J* = 12.9 Hz, 1 H), 3.77–3.58 (m, 3 H), 2.33 (d, *J* = 2.1 Hz, 1 H), 2.03–1.91 (m, 2 H), 1.55 (br. s, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 140.1, 138.5, 128.54, 128.52, 127.8, 127.7, 127.1, 85.1, 73.2, 71.9, 67.4, 51.5, 47.1, 35.9 ppm. IR ($CHCl_3$ film): $\tilde{\nu}$ = 3292 (m), 2864 (m), 1453 (m), 1100 (s) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{19}H_{22}NO$ $[M + H]^+$ 280.170; found 280.169.

Preparation of [2-(4-Chlorophenyl)-4-methyloxazol-5-yl]methanol (29): Silane **28** (44.8 mg, 0.100 mmol) was dissolved in $BF_3{\cdot}(AcOH)_2$ (1 mL, 36% BF_3 basis) and heated to 100 °C. After 1 h, the mixture was poured onto $NaHCO_3$ (aq. satd. 10 mL), extracted with CH_2Cl_2 (2× 10 mL), dried using a phase separator, and concentrated. The crude mixture was dissolved in THF (0.5 mL) and MeOH (0.5 mL), $NaHCO_3$ (8.40 mg, 0.100 mmol), KF (17.4 mg, 0.300 mmol), and H_2O_2 (35% in H_2O, 85.6 μL, 1.00 mmol) were added sequentially. The resulting mixture was heated to reflux. After 30 min, the reaction mixture was cooled to room temperature, poured onto water (10 mL), extracted with CH_2Cl_2 (2× 10 mL), dried using a phase separator, and concentrated under reduced pressure. Purification by silica gel chromatography (EtOAc/petroleum ether, 1:1) gave **29** (21.0 mg, 94%) as a white solid; m.p. 124.4–127.4 °C; >95% pure by NMR spectroscopic analysis and a single spot by TLC [R_f = 0.44 (EtOAc/petroleum ether, 1:1)]. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.03–7.88 (m, 2 H), 7.49–7.35 (m, 2 H), 4.69 (s, 2 H), 2.24 (s, 3 H), 1.93 (br. s, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.9, 145.8, 136.7, 135.5, 129.3, 127.8, 126.0, 54.5, 11.6 ppm. IR ($CHCl_3$ film): $\tilde{\nu}$ = 3215 (s, br), 1547 (w), 1483 (m), 1408 (m), 1092 (s) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{11}H_{11}ClNO_2$ $[M + H]^+$ 224.048; found 224.046.

Preparation of 2-(5-Methyl-2-phenyloxazol-4-yl)ethanol (33):[30] To a stirred solution of benzyl ether **32** (13.5 mg, 0.0460 mmol) in EtOH (3 mL) under a nitrogen atmosphere was added $Pd(OH)_2$ (1 spatula tip, 30% w/w on C). The atmosphere was changed to H_2 (purged three times using H_2 from a balloon). The reaction mixture was stirred for 30 min, after which TLC showed complete consumption of starting material, and the H_2 atmosphere was changed back to N_2 (purged three times). The reaction mixture was filtered through a short plug of Celite (washed with EtOAc), and concentrated under reduced pressure. The crude mixture was purified by silica gel chromatography (EtOAc/petroleum ether, 25–33%) and the product-containing fractions were pooled and concentrated under reduced pressure to leave the primary alcohol **33** (8.9 mg, 95%) as a pale-yellow solid; m.p. 66.0–67.7 °C; >95% pure by NMR spectroscopic analysis and a single spot by TLC [R_f = 0.32 (EtOAc/petroleum ether, 1:1)]. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.03–7.92 (m, 2 H), 7.50–7.36 (m, 3 H), 3.93 (dt, *J* = 5.8, 5.8 Hz, 2 H), 3.27 (t, *J* = 6.1 Hz, 1 H), 2.72 (t, *J* = 5.5 Hz, 2 H), 2.34 (s, 3 H) ppm.

Supporting Information (see footnote on the first page of this article): Experimental procedures and spectroscopic data for *N*-benzylpropargylamines. ^1H and ^{13}C NMR spectra for all new compounds. Full details of the computational work.

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