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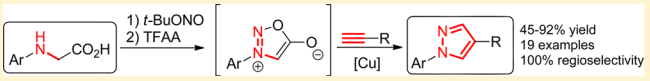
One-Pot Synthesis of 1,4-Disubstituted Pyrazoles from Arylglycines via Copper-Catalyzed Sydnone−Alkyne Cycloaddition Reaction

Simon Specklin, Elodie Decuypere, Lucie Plougastel, Soifia Aliani, and Frédéric Taran*

CEA, iBiTecS, Service de Chimie Bioorganique et de Marquage, Gif sur Yvette, F-91191, France

Supporting Information

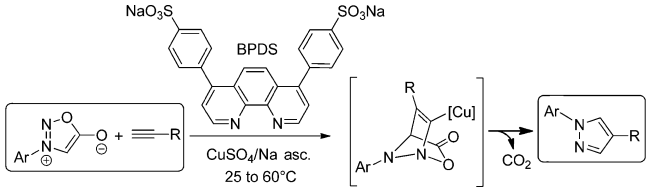
ABSTRACT: A robust method for constructing 1,4-pyrazoles from arylglycines was developed using the copper-catalyzed sydnone−alkyne cycloaddition reaction. The procedure offers a straightforward and general route to the pyrazole heterocycle through a three-step one-pot procedure.



Pyrazoles are small, "drug-like" heterocycles representing an important building block in medicinal chemistry.[1] Despite the numerous available methods,[2] there is still an ongoing search for simple and straightforward routes to polysubstituted pyrazoles.[3] Among them, the 1,3-dipolar cycloaddition reaction of sydnones with alkynes appeared as a marginal, but attractive, alternative approach to construct pyrazoles.[4] This reaction has been more particularly successfully exploited with alkyne boronates giving rise to a regiocontrolled formation of pyrazole boronic esters.[5] However, besides this nice example, this reaction is globally limited to electron-deficient alkynes, suffers from a lack of regioselectivity, and usually requires harsh conditions, especially elevated temperatures, therefore, reducing its attractiveness.

We recently described that Cu(I) salts complexed with phenanthroline-based ligands, such as the commercially available sulfonated bathophenanthroline (BPDS), are efficient catalysts for cycloaddition reactions involving *N*-aryl sydnones and terminal alkynes affording pure 1,4-pyrazoles under mild conditions and with a total regiocontrol (Scheme 1).[6] Reaction

Scheme 1. Cu-Catalyzed Sydnone−Alkyne Cycloaddition Reaction (CuSAC)



conditions are quite similar to those of the well-known Cu-catalyzed azide−alkyne cycloaddition reaction (CuAAC): a number of Cu(I) sources can be used directly in various organic solvents, but the reaction is better run in pure water or in *t*-BuOH/water mixtures using in situ reduction of Cu(II) salts by sodium ascorbate.

While this Cu-catalyzed sydnone−alkyne cycloaddition reaction (CuSAC) has shown many practical advantages (broad substrate tolerance, high regioselectivity, mild conditions,...), it requires a prior preparation of sydnone substrates. To improve the potential of this reaction, we propose in this contribution a one-pot protocol that allows the use of arylglycines as readily available substrates to form 1,4-pyrazoles in high yields.

Sydnones constitute a well-defined class of mesoionic compounds useful for heterocyclic chemistry and displaying several biological activities.[7] The original method of preparation[8] by cyclodehydration of an *N*-alkyl or aryl *N*-nitroso-α-amino acid is still the only general route to sydnones. Classical syntheses, therefore, involve two steps: (i) nitrosylation of amino acids, generally carried out by sodium nitrite in aqueous acidic conditions or using isoamyl nitrite,[9] and (ii) cyclization with acetic or trifluoroacetic anhydride.[10] To avoid manipulation of toxic nitrosamines, one-pot processes have been more recently developed but require dibromo-dimethylhydantoin[11] or *N*-dichloro-DABCO[12] as electrophilic additives.

Our first goal in this project was, therefore, to optimize a one-pot procedure yielding sydnone crudes that can be directly used in the CuSAC reaction without purification. We first investigated the cyclization step by testing a series of conditions listed in Table 1.

N-*p*-Tolyl-glycine, used as model substrate, was first nitrosylated by isopentyl nitrite to afford **2a** in quantitative isolated yield. This nitrosylation procedure was preferred to the classical one using sodium nitrite in order to avoid the need to remove water. 1,1′-Carbonyldiimidazole (CDI) was found to be the best reagent, allowing quantitative formation of sydnone **3a** from **2a**; dicyclohexyl carbodiimide (DCC) and trifluoroacetic anhydride (TFAA) were also found to be quite efficient (Table 1, entries 5−7). We then evaluated these three cyclization reagents for the one-pot formation of **3a** from **1a**. Direct addition of CDI, DCC, or TFAA to the crude nitrosylation reaction of **1a** with isopentyl nitrite led to the desired sydnone **3a** in only moderate yields (entries 1−3, Table 2). Hypothesizing that 3-methyl-butanol released from the nitrosylation step may react with the cyclization reagents, we tested *tert*-butyl

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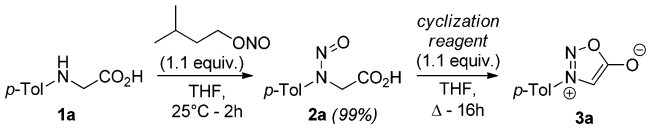
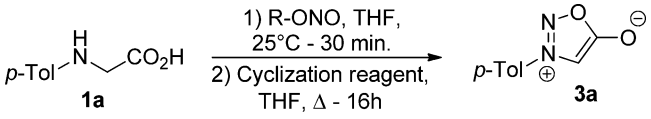
Table 1. Optimization of the Cyclization Step[a]



entry	cyclization reagent	3a (%)[b]
1	AcCl/Et_3N	0
2	$SOCl_2$/Et_3N	0
3	PyBOP/Et_3N	59
4	HBTU/Et_3N	76
5	DCC	92
6	TFAA	87
7	CDI	>99

[a]Reactions were performed on a 1 mmol scale at a concentration of 0.5 M. [b]Yields calculated by ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard.

Table 2. Optimization of the One-Pot Sydnone Formation[a]



entry	R	cyclization reagent	3a (%)[b]
1	$(CH_3)_2CH(CH_2)_2$–	DCC	49
2	$(CH_3)_2CH(CH_2)_2$–	TFAA	36
3	$(CH_3)_2CH(CH_2)_2$–	CDI	22
4	$(CH_3)_3C$–	DCC	71
5	$(CH_3)_3C$–	TFAA	84
6	$(CH_3)_3C$–	CDI	92

[a]Reactions were performed on a 1 mmol scale using 1.1 equiv. of nitrosylation and cyclization agents at a concentration of 0.5 M. [b]Yields calculated by ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard.

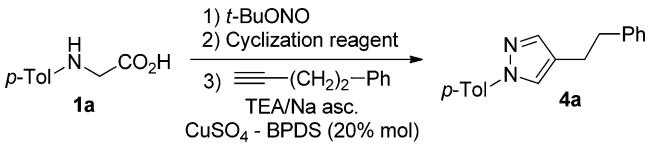
nitrite as a more hindered reactant and obtained **3a** in good yields (entries 4–6, Table 2).

We then evaluated the compatibility of this one-pot sydnone synthesis with the CuSAC reaction. The use of CDI was found to be prejudicial to the copper catalysis. The procedure involving TFAA was the most suitable for the CuSAC reaction, and yields were finally improved by avoiding the use of THF as solvent (Table 3). The nitrosylation and cyclization steps are thus better run under neat conditions allowing the use of the preferred *t*-BuOH/H_2O mixture for the CuSAC step.

The scope of this one-pot procedure was then investigated (Scheme 2). Various electron-rich or electron-poor *N*-aryl sydnones successfully participated in this transformation. Tolerance for variations in the acetylene component was particularly excellent and revealed the lack of functional group interference of the CuSAC reaction. In all cases, the 1,4-pyrazole was the only product formed; no trace of a 1,3-regioisomer was detected.

In conclusion, the one-pot process described here provides 1,4-disubstituted pyrazoles from readily available arylglycines in good yields and perfect regioselectivity. The procedure is experimentally simple and exhibits a broad scope; we, therefore, believe it should be a useful addition to other pyrazole synthetic routes.

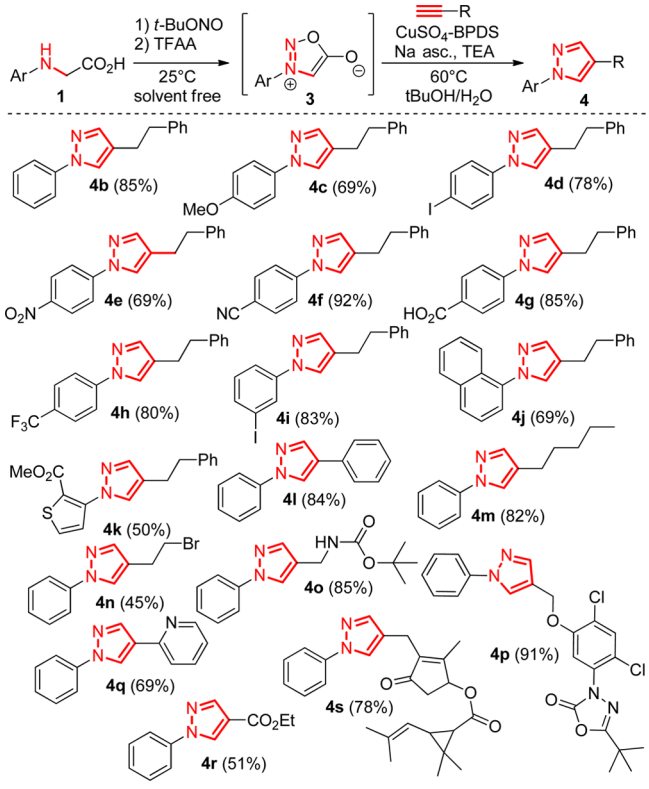
Table 3. Optimization of the One-Pot Pyrazole Formation from Arylglycine 1a[a]



	conditions		
entry	cyclization	CuSAC	4a (%)[b]
1	CDI, THF, 60 °C	THF/H_2O, 60 °C	6
2	DCC, THF, 60 °C	THF/H_2O, 60 °C	41
3	TFAA, THF, 25 °C	THF/H_2O, 60 °C	60
4[c]	DCC, neat, 60 °C	*t*-BuOH/H_2O, 60 °C	68
5[c]	TFAA neat, 25 °C	*t*-BuOH/H_2O, 60 °C	72

[a]Reactions were performed with 1 equiv. of **1a**, 1.1 equiv. of *t*-BuONO and cyclization reagent, 1 equiv. of TEA, 2 equiv. of Na asc., and 1 equiv. of alkyne in a (1:1) organo–aqueous solvent. [b]Isolated yields. [c]2.5 equiv. of cyclization reagent and TEA were used in these cases.

Scheme 2. Reaction Scope



EXPERIMENTAL SECTION

General Experimental Details. Solvents were dried by standard procedures prior to use. Purifications of reactions products were carried out by column chromatography using silica gel (40–63 μm). Analytical thin layer chromatographies were performed on silica gel 60-F plates. Visualization was accomplished with UV light and phosphomolybdic acid. Infrared spectra (IR) are reported as wavelength numbers (cm^{-1}). Infrared spectra for liquid products were obtained as a thin film on a NaCl disk, and spectra for solid products were collected by preparing a KBr pellet containing the title compound. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) were measured on a 400 MHz spectrometer. Chemical shifts are reported in parts per million (ppm, δ) downfield from residual solvent peaks, and coupling constants are reported as hertz (Hz). Splitting patterns are designated as singlet (s), broad singlet (br. s.), doublet (d), triplet

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(t),.... Splitting patterns that could not be interpreted or easily visualized are designated as multiplet (m). Electrospray mass spectra were obtained using an ESI/TOF mass spectrometer. Unless otherwise noted, all commercially available reagents and solvents were used without further purification. *N*-Phenyl-glycine **1b** was purchased from a commercial supplier.

2-((4-Methylphenyl)amino)acetic Acid (1a).[13] To a suspension of *p*-toluidine (16.1 g, 150 mmol) and sodium acetate (14.8 g, 180 mmol) in ethanol (50 mL) was added ethyl chloroacetate (22.1 g, 180 mmol). The mixture was refluxed for 7 h, left overnight at room temperature, and poured into crushed ice. The formed precipitate was filtrated and dried. To the intermediate ester in water (75 mL) was added sodium hydroxide (6.58 g, 165 mmol), and the mixture was refluxed for 30 min. After cooling, the reaction mixture was acidified to pH 2 by dropwise addition of a 4 M solution of HCl. The resulting precipitate was filtered, washed with water, and purified by recrystallization from a mixture ethanol/water 8/2 to afford 10.5 g (63.6 mmol, 42%) of glycine **1a** as a beige solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.87 (d, J = 8.4 Hz, 2H), 6.44 (d, J = 8.4 Hz, 2H), 3.72 (s, 2H), 2.12 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.2, 146.3, 129.7 (2C), 124.9, 112.6 (2C), 45.3, 20.5; IR (KBr, cm^{-1}) 2968, 2076, 2021, 1906, 1202, 1321, 1273, 1240, 1191, 1173, 1108, 1035, 1022, 1000, 981, 944, 903, 877, 864, 820; LCMS (ESI) m/z 166 [M + H]$^+$, 120 [M − CO_2 + H]$^+$; mp. 119−121 °C.

2-((4-Methoxyphenyl)amino)acetic Acid (1c).[13] To a suspension of *p*-anisidine (18.5 g, 150 mmol) and sodium acetate (14.8 g, 180 mmol) in ethanol (50 mL) was added ethyl chloroacetate (22.1 g, 180 mmol). The mixture was refluxed for 7 h, left overnight at room temperature, and poured into crushed ice. The formed precipitate was filtrated and dried. To the intermediate ester in water (75 mL) was added sodium hydroxide (6.58 g, 165 mmol), and the mixture was refluxed for 30 min. After cooling, the reaction mixture was acidified to pH 2 by dropwise addition of a 4 M solution of HCl. The resulting precipitate was filtered, washed with water, and purified by recrystallization from a mixture ethanol/water 8/2 to afford 15.4 g (85.1 mmol, 57%) of glycine **1c** as a beige solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.71 (m, 2H), 6.51 (m, 2H), 3.73 (s, 2H), 3.63 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.3, 151.4, 142.8, 114.9 (2C), 113.5 (2C), 55.7, 45.8; IR (KBr, cm^{-1}) 2957, 1561, 1394, 1314, 1259, 1234, 1194, 1181, 1169, 1104, 1032, 1005, 989, 885, 869, 835, 8917, 803; LCMS (ESI) m/z 182 [M + H]$^+$, 136 [M − CO_2 + H]$^+$; mp. 151−153 °C.

2-((4-Iodophenyl)amino)acetic Acid (1d). To a solution of *p*-iodoaniline (3.29 g, 45.0 mmol) in MeOH (170 mL) at 0 °C were added NaOAc (2.46 g, 30.0 mmol), glacial acetic acid (3.43 *mL*, 60.0 mmol), glyoxylic acid monohydrate (2.07 g, 22.5 mmol), and $NaBH_3CN$ (0.942 g, 15.0 mmol). The solution was warmed slowly to rt over 2 h. The mixture was filtered through a plug of Celite and washed with a solution of 1% acetic acid in EtOAc. Brine was added, and the aqueous layer was extracted twice with EtOAc. The organic layers were combined, dried over $MgSO_4$, and concentrated. The crude product was purified by recrystallization from a mixture of ethanol/water 8/2 to afford 2.121 g (7.66 mmol, 51%) of glycine **1d** as a beige solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.55 (br. s, 1H), 7.32 (d, J = 8.6 Hz, 2H), 6.12 (br. s, 1H), 6.39 (d, J = 8.6 Hz, 2H), 3.77 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.3, 148.0, 137.0, 114.8, 76.7, 44.4; IR (KBr, cm^{-1}) 3417, 2883, 1873, 1715, 1589, 1505, 1435, 1392, 1349, 1316, 1292, 1270, 1234, 1181, 1145, 1113, 1059, 993, 914, 810; LCMS (ESI) m/z 278 [M + H]$^+$; HRMS(ESI) m/z calcd for $C_8H_9NO_2I$ (M + H$^+$): 277.9678; found: 277.9673; mp. 119−121 °C.

2-((4-Nitrophenyl)amino)acetic Acid (1e). To a suspension of 4-nitroaniline (13.8 g, 100 mmol) in water (100 mL) was added chloroacetic acid (18.9 g, 200 mmol). The mixture was refluxed overnight, and the resulting precipitate was filtered and successively washed with water and with a mixture of hexane/diethyl ether. The solid was dissolved in an aqueous solution of 6 M NaOH, and the resulting solution was washed with EtOAc. The organic layer was extracted with a solution of 6 M NaOH, and the combined aqueous extracts were acidified at 0 °C to pH 2 with a HCl solution. The resulting precipitate was filtered, washed with water, and dried to afford 11.9 g (60.7 mmol, 61%) of glycine **1e** as a yellow solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.80 (br. s, 1H), 8.00 (d, J = 9.2 Hz, 2H), 7.44 (t, J = 6.1 Hz, 1H), 6.66 (d, J = 9.2 Hz, 2H), 3.98 (d, J = 6.1 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.5, 154.3, 136.4, 126.1 (2C), 111.3 (2C), 44.1; IR (KBr, cm^{-1}) 3364, 3099, 1737, 1601, 1532, 1495, 1466, 1438, 1407, 1362, 1291, 1180, 1143, 1111, 993, 916, 843; LCMS (ESI) m/z 197 [M + H]$^+$; HRMS(ESI) m/z calcd for $C_8H_7N_2O_4$ (M − H$^-$): 195.0406; found: 195.0406; mp. 224−226 °C.

2-((4-Cyanophenyl)amino)acetic Acid (1f).[14] To a suspension of 4-aminobenzonitrile (1.77 g, 15 mmol) in water (40 mL) was added chloroacetic acid (2.84 g, 30 mmol). The mixture was refluxed overnight, and the resulting precipitate was filtered. The solid was dissolved in an aqueous solution of 6 M NaOH, and the resulting solution was washed with EtOAc. The organic layer was extracted with a solution of 6 M NaOH, and the combined aqueous extracts were acidified at 0 °C to pH 2 with a HCl solution. The resulting precipitate was filtered, washed with water, and dried to afford 1.25 g (7.11 mmol, 47%) of glycine **1f** as a beige solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.7 (br s, 1H), 7.46 (d, J = 8.9 Hz, 2H), 6.89 (t, J = 5.5 Hz, 1H), 6.64 (d, J = 8.9 Hz, 2H), 3.90 (d, J = 5.5 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.8, 151.9, 133.3 (2C), 120.5, 112.2 (2C), 96.4, 43.9; IR (KBr, cm^{-1}) 3379, 3028, 2217, 1730, 1600, 1530, 1442, 1408, 1341, 1261, 1201, 1167, 1142, 956, 911, 849, 825, 731, 640; LCMS (ESI) m/z 177 [M + H]$^+$; mp. 240−243 °C.

4-((Carboxymethyl)amino)benzoic Acid (1g). To a solution of sodium chloroacetate (2.33 g, 20.0 mmol) in water (20 mL) was added 4-aminobenzoic acid (2.74 g, 20.0 mmol). The resulting mixture was stirred at reflux for 10 h. After cooling to room temperature, the precipitate was filtered, washed with water, and purified by recrystallization from ethanol to afford 2.50 g (12.8 mmol, 64%) of glycine **1g** as a white solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.67 (d, J = 8.7 Hz, 2H), 6.66 (br. s., 1H), 6.57 (d, J = 8.7 Hz, 2H), 3.87 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.1, 167.5, 152.1, 131.0, 117.6 (2C), 111.2 (2C), 44.1; IR (KBr, cm^{-1}) 3427, 2544, 1703, 1598, 1527, 1410, 1334, 1319, 1280, 1246, 1188, 1152, 1126, 979, 953, 931, 839, 771, 691, 625; LCMS (ESI) m/z 196 [M + H]$^+$; HRMS(ESI) m/z calcd for $C_9H_8NO_4$ (M − H$^-$): 194.0453; found: 194.0449; mp. 258−261 °C.

2-((4-Trifluoromethylphenyl)amino)acetic Acid (1h). To a solution of *p*-trifluoromethylaniline (322 mg, 2.00 mmol) in MeOH (25.0 mL) at 0 °C were added NaOAc (328 mg, 4.00 mmol), glacial acetic acid (0.460 *mL*, 8.00 mmol), glyoxylic acid monohydrate (276 mg, 3.00 mmol), and $NaCNBH_3$ (126 mg, 2.00 mmol). The solution was warmed slowly to rt over 2 h. The mixture was filtered through a plug of Celite and washed with a solution of 1% acetic acid in EtOAc. Brine was added, and the aqueous layer was extracted twice with EtOAc. The organic layers were combined, dried over $MgSO_4$, and concentrated under *vacuum*. The crude product was purified by recrystallization from a mixture of ethanol/water 8/2 to afford 130 mg (0.59 mmol, 30%) of glycine **1h** as a beige solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.38 (d, J = 8.5 Hz, 2H), 6.72−6.57 (m, 3H), 3.87 (s, 2H), 3.59−3.14 (br. s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.1, 151.3, 126.2 (2C), 125.3 (q, J = 267 Hz), 115.8 (q, J = 32 Hz), 111.6 (2C), 44.1; IR (KBr, cm^{-1}) 3421, 2899, 1901, 1731, 1616, 1585, 1538, 1491, 1441, 1412, 1319, 1281, 1242, 1188, 1164, 1151, 1110, 1062, 1005, 926, 825; LCMS (ESI) m/z 220 [M + H]$^+$; HRMS(ESI) m/z calcd for $C_9H_7NO_2F_3$ (M − H$^-$): 218.0429; found: 218.0427; mp. 141−143 °C.

2-((3-Iodophenyl)amino)acetic Acid (1i). To a solution of *m*-iodoaniline (2.28 g, 10.4 mmol) in MeOH (120 mL) at 0 °C were added NaOAc (1.71 g, 20.8 mmol), glacial acetic acid (2.38 *mL*, 41.6 mmol), glyoxylic acid monohydrate (1.44 g, 15.6 mmol), and $NaCNBH_3$ (654 mg, 10.4 mmol). The solution was warmed slowly to rt over 2 h. The mixture was filtered through a plug of Celite and washed with a solution of 1% acetic acid in EtOAc. Brine was added, and the aqueous layer was extracted twice with EtOAc. The organic layers were combined, dried over $MgSO_4$, and concentrated under *vacuum*. The crude product was purified by recrystallization from a mixture of ethanol/water 8/2 to afford 2.39 g (8.6 mmol, 83%) of

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glycine **1i** as a beige solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.91−6.81 (m, 3H), 6.55 (dt, J = 7.1 Hz, J = 2.4 Hz, 1H), 3.75 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 210.0, 187.6, 168.5, 162.2, 158.0, 149.2, 133.1, 82.0; IR (KBr, cm^{-1}) 3384, 2865, 1915, 1802, 1725, 1588, 1570, 1512, 1494, 1477, 1435, 1386, 1343, 1320, 1304, 1263, 1234, 1173, 1146, 1086, 1063, 1005, 983, 961, 912, 870, 859, 845; LCMS (ESI) m/z 278 [M + H]$^+$; HRMS(ESI) m/z calcd for $C_8H_9NO_2I$ (M + H$^+$): 277.9678; found: 277.9684; mp. 125−127 °C.

2-(Naphthalen-1-ylamino)acetic Acid (1j).[15] To a solution of 1-naphthalenamine (286 mg, 2.00 mmol) in MeOH (25 mL) at 0 °C were added NaOAc (328 mg, 4.00 mmol), glacial acetic acid (0.46 *mL*, 8.00 mmol), glyoxylic acid monohydrate (276 mg, 3.00 mmol), and $NaBH_3CN$ (126 mg, 2.00 mmol). The solution was warmed slowly to rt over 2 h. The mixture was filtered through a plug of Celite and washed with a solution of 1% acetic acid in EtOAc. Brine was added, and the aqueous layer was extracted twice with EtOAc. The organic layers were combined, dried over $MgSO_4$, and concentrated. The crude product was purified by recrystallization from a mixture of ethanol/water 8/2 to afford 155 mg (0.77 mmol, 39%) of glycine **1j** as a beige solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11 (dd, J = 7.3 Hz, J = 2.0 Hz, 1H), 7.77 (dd, J = 9.3 Hz, J = 2.2 Hz, 1H), 7.44 (m, 2H), 7.27 (t, J = 8.0 Hz, 1H), 7.14 (d, J = 8.0 Hz, 1H), 6.35 (d, J = 7.3 Hz, 1H), 3.98 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.6, 143.6, 134.0, 128.0, 126.6, 125.7, 124.2, 122.9, 121.4, 116.0, 103.0, 44.9; IR (KBr, cm^{-1}) 3402, 2572, 1723, 1622, 1583, 1520, 1481, 1463, 1452, 1434, 1417, 1404, 1372, 1340, 1286, 1259, 1212, 1171, 1141, 1092, 1039, 1016, 995, 975, 915, 880,867, 850; LCMS (ESI) m/z 202 [M + H]$^+$; mp. 201−203 °C.

2-((2-(Methoxycarbonyl)thiophen-3-yl)amino)acetic Acid (1k). To a solution of methyl 3-amino-2-thiophenecarboxylate (472 mg, 3 mmol) in MeOH (34 mL) at 0 °C were added sodium acetate (492 mg, 6 mmol), glacial acetic acid (686 μL, 12 mmol), glyoxylic acid monohydrate (414 mg, 4.5 mmol), and sodium cyanoborohydride (189 mg, 3 mmol). The solution was warmed slowly to room temperature overnight, and the mixture was then filtered through a plug of silica gel and washed with 1% glacial acetic acid in ethyl acetate. The solution was washed with brine, dried over magnesium sulfate, and concentrated. The crude product was purified by recrystallyzation in ethyl acetate and heptane to afford 348 mg (1.6 mmol, 54%) of glycine **1k** as a white powder; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.66 (d, J = 5.1 Hz, 1H), 7.07 (t, J = 5.5 Hz, 1H), 6.73 (d, J = 5.1 Hz, 1H), 4.00 (d, J = 5.5 Hz, 2H), 3.70 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.9, 164.1, 155.3, 133.1, 177.4, 97.4, 50.9, 46.4; IR (KBr, cm^{-1}) 3370, 3099, 2950, 1718, 1663, 1569, 1453, 1439, 1425, 1389, 1293, 1256, 1234, 1162, 1105, 1085, 908, 881, 840, 775, 735, 678, 655, 626; LCMS (ESI) m/z 216 [M + H]$^+$; HRMS(ESI) m/z calcd for $C_8H_{10}NO_4S$ (M + H$^+$): 216.0331; found: 216.0331; mp. 162−165 °C.

General Procedure for the Synthesis of Pyrazoles from Arylglycines. To the neat stirred glycine (0.2 mmol) was added *t*-butylnitrite (90 wt %, 29 μL, 0.22 mmol), and the mixture was vigorously stirred for 30 min. Trifluoroacetic anhydride (70 μL, 0.5 mmol) was then added, and the mixture was further stirred for 30 min. To the reaction mixture were then successively added *t*-BuOH (1 mL), Et_3N (167 μL), a solution of bathophenanthrolinedisulfonic acid disodium salt hydrate (24 mg, 40 μmol) in water (0.5 mL), a solution of copper(II) sulfate pentahydrate (10 mg, 40 μmol) in water (0.5 mL), alkyne (0.2 mmol), and sodium ascorbate (79 mg, 0.4 mmol). The mixture was stirred at 60 °C for 16 h, and a 0.05 M solution of HEDTA was added. The mixture was extracted with CH_2Cl_2, and the combined organic phases were dried over $MgSO_4$ and concentrated. The residue was then purified by flash chromatography, yielding the corresponding pyrazoles.

*4-Phenethyl-1-(p-tolyl)-1H-pyrazole (**4a**).* According to the general procedure, reaction of glycine **1a** with 4-phenyl-1-butyne, followed by flash chromatography (SiO_2, heptane/EtOAc 90:10), afforded pyrazole **4a** (37.9 mg, 0.14 mmol, 72%) as a yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.54−7.48 (m, 3H), 7.34−7.28 (m, 2H), 7.25−7.19 (m, 5H), 2.90 (m, 4H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.7, 140.7, 138.1, 136.0, 130.0 (2C), 128.6 (2C), 128.5 (2C), 126.2, 125.0, 122.9, 118.9 (2C), 37.3, 26.3, 21.0; IR (NaCl, cm^{-1}) 3085, 3061, 3027, 2923, 2859, 1720, 1613, 1568, 1519, 1496, 1454, 1426, 1398, 1333, 1317, 1250, 1219, 1178, 1155, 1118, 1108, 1075, 1040, 1018, 955, 855, 814, 750, 719, 698; LCMS (ESI) m/z 263 [M + H]$^+$; HRMS(ESI) m/z calcd for $C_{18}H_{19}N_2$ (M + H$^+$): 263.1548; found: 263.1539; mp. 41−43 °C.

*4-Phenethyl-1-phenyl-1H-pyrazole (**4b**).*[6] According to the general procedure, reaction of glycine **1b** with 4-phenyl-1-butyne, followed by flash chromatography (SiO_2, heptane/EtOAc 90:10), afforded pyrazole **4b** (42.0 mg, 0.17 mmol, 85%) as a beige solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67−7.60 (m, 3H), 7.54 (s, 1H), 7.43 (m, 2H), 7.34−7.27 (m, 2H), 7.25−7.19 (m, 3H), 2.91 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.6, 141.0, 140.3, 129.5 (2C), 128.6 (2C), 128.5 (2C), 126.2, 125.1, 123.1, 118.9 (2C), 37.2, 26.3; IR (NaCl, cm^{-1}) 3083, 3026, 2922, 2852, 1597, 1568, 1495, 1463, 1453, 1408, 1257, 1212, 1177, 1160, 1074, 1045, 1027, 1006, 955, 902, 842, 828, 751, 718, 696, 650; LCMS (ESI) m/z 263 [M + H]$^+$; mp. 47−49 °C.

*1-(p-Methoxyphenyl)-4-phenethyl-1H-pyrazole (**4c**).* According to the general procedure, reaction of glycine **1c** with 4-phenyl-1-butyne, followed by flash chromatography (SiO_2, heptane/EtOAc 95:5), afforded pyrazole **4c** (38.2 mg, 0.14 mmol, 69%) as a beige solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57−7.49 (m, 4H), 7.35−7.28 (m, 2H), 7.25−7.19 (m, 3H), 6.95 (m, 2H), 3.84 (s, 3H), 2.89 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 141.7, 140.4, 134.2, 128.6 (2C), 128.5 (2C), 126.2, 125.2, 122.7, 120.5 (2C), 114.5 (2C), 55.7, 37.3, 26.3; IR (NaCl, cm^{-1}) 2914, 2854, 1597, 1561, 1513, 1494, 1453, 1445, 1392, 1317, 1302, 1244, 1189, 1172, 1151, 1106, 1041, 1023, 952, 923, 906, 859, 849, 810, 831, 798, 768, 745, 710, 654, 636, 624, 609; LCMS (ESI) m/z 279 [M + H]$^+$; HRMS(ESI) m/z calcd for $C_{18}H_{19}N_2O$ (M + H$^+$): 279.1497; found: 279.1494; mp. 47−49 °C.

*1-(p-Iodophenyl)-4-phenethyl-1H-pyrazole (**4d**).* According to the general procedure, reaction of glycine **1d** with 4-phenyl-1-butyne, followed by flash chromatography (SiO_2, heptane/EtOAc 95:5), afforded pyrazole **4d** (58.6 mg, 0.16 mmol, 78%) as a yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (m, 2H), 7.58 (s, 1H), 7.53 (s, 1H), 7.40 (m, 2H), 7.34−7.28 (m, 2H), 7.25−7.18 (m, 3H), 2.89 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4, 140.0, 138.4 (2C), 128.6 (2C), 128.5 (2C), 126.2, 124.8, 123.5, 120.5 (2C), 90.0, 37.1, 26.2; IR (NaCl, cm^{-1}) 3110, 3096, 3023, 3000, 2939, 2916, 2854, 1949, 1898, 1585, 1493, 1450, 1421, 1396, 1309, 1219, 1188, 1112, 1095, 1061, 1074, 1010, 985, 952, 909, 854, 829, 816, 804, 753, 729, 702; LCMS (ESI) m/z 375 [M + H]$^+$; HRMS(ESI) m/z calcd for $C_{17}H_{16}N_2I$ (M + H$^+$): 375.0358; found: 375.0344; mp. 79−81 °C.

*1-(p-Nitrophenyl)-4-phenethyl-1H-pyrazole (**4e**).* According to the general procedure, reaction of glycine **1e** with 4-phenyl-1-butyne, followed by flash chromatography (SiO_2, heptane/EtOAc 95:5 to 85:15), afforded pyrazole **4e** (40.2 mg, 0.14 mmol, 69%) as a yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (m, 2H), 7.79 (m, 2H), 7.69 (s, 1H), 7.58 (s, 1H), 7.35−7.28 (m, 2H), 7.26−7.18 (m, 3H), 2.91 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.2, 144.5, 143.1, 141.2, 128.62 (2C), 128.60 (2C), 126.4, 125.5 (2C), 125.1, 124.9, 118.2 (2C), 36.9, 26.1; IR (NaCl, cm^{-1}) 3125, 3093, 3028, 2934, 2856, 2364, 1611, 1600, 1514, 1452, 1395, 1341, 1308, 1223, 1155, 1113, 1075, 1035, 1013, 947, 910, 866, 847, 825, 795, 748, 739, 708, 698, 684; LCMS (ESI) m/z 294 [M + H]$^+$; HRMS(ESI) m/z calcd for $C_{17}H_{16}N_3O_2$ (M + H$^+$): 294.1243; found: 294.1232; mp. 130−133 °C.

*p-(4-Phenethyl-1H-pyrazol-1-yl)benzonitrile (**4f**).* According to the general procedure, reaction of glycine **1f** with 4-phenyl-1-butyne, followed by flash chromatography (SiO_2, heptane/EtOAc 95:5 to 90:10), afforded pyrazole **4f** (50.5 mg, 0.18 mmol, 92%) as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (m, 4H), 7.65 (s, 1H, 7.65 (s, 1H), 7.34−7.28 (m, 2H), 7.26−7.17 (m, 3H), 2.90 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.9, 142.5, 141.0, 133.6 (2C), 128.5 (2C), 128.4 (2C), 126.2, 124.7, 124.4, 118.5, 118.4, 109.0, 36.8, 26.0; IR (NaCl, cm^{-1}) 3120, 3083, 3063, 3030, 2935, 2227, 1719, 1608, 1518, 1497, 1454, 1430, 1377, 1320, 1226, 1181, 1158, 1111, 1079, 1021, 948, 872, 860, 827, 771, 727, 711, 695, 655; LCMS (ESI) m/z 274 [M + H]$^+$; HRMS(ESI) m/z calcd for $C_{18}H_{16}N_3$ (M + H$^+$): 274.1344; found: 274.1338; mp. 92−95 °C.

*p-(4-Phenethyl-1H-pyrazol-1-yl)benzoic Acid (**4g**).*[6] According to the general procedure using a larger amount of trifluoroacetic

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anhydride (111 μL, 0.80 mmol) and Et_3N (279 μL, 2.00 mmol), reaction of glycine **1g** with 4-phenyl-1-butyne, followed by flash chromatography (SiO_2, heptane/EtOAc 8:2 to 6:4 with 1% AcOH), afforded pyrazole **4g** (49.5 mg, 0.17 mmol, 85%) as a yellow solid; ^{1}H NMR (400 MHz, acetone-d_6) δ 8.23 (s, 1H), 8.12 (m, 2H), 7.93 (m, 2H), 7.59 (s, 1H), 7.31−7.23 (m, 4H), 7.21−7.15 (m, 1H), 2.92 (m, 4H); ^{13}C NMR (100 MHz, acetone-d_6) δ 167.0, 144.4, 142.7, 142.5, 132.0 (2C), 129.3 (2C), 129.1 (2C), 128.3, 126.8, 126.2, 125.0, 118.3 (2C), 37.5, 26.8; IR (NaCl, cm^{-1}) 2927, 2546, 1673, 1605, 1567, 1519, 1496, 1425, 1391, 1315, 1288, 1206, 1178, 1132, 1116, 1132, 1076, 1028, 948, 855, 838, 810, 800, 769, 742, 721, 692, 650; LCMS (ESI) m/z 293 [M + H]$^+$; mp. 187−190 °C.

*4-Phenethyl-1-(p-(trifluoromethyl)phenyl)-1H-pyrazole (**4h**).* According to the general procedure, reaction of glycine **1h** with 4-phenyl-1-butyne, followed by flash chromatography (SiO_2, heptane/EtOAc 95:5 to 90:10), afforded pyrazole **4h** (50.5 mg, 0.16 mmol, 80%) as a yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 8.8 Hz, 2H), 7.69 (d, J = 8.8 Hz, 2H), 7.66 (s, 1H), 7.56 (s, 1H)7.35−7.27 (m, 2H), 7.26−7.18 (m, 3H), 2.91 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.7, 142.1, 141.4, 128.7 (2C), 128.6 (2C), 127.9 (q, J_{C-F} = 33.0 Hz), 126.8 (q, J_{C-F} = 3.8 Hz, 2C), 126.3, 125.5, 124.1 (q, J_{C-F} = 271.4 Hz), 124.0, 118.4 (2C), 37.1, 26.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.2 (s, 3F); IR (NaCl, cm^{-1}) 2927, 1615, 1573, 1522, 1496, 1453, 1433, 1395, 1374, 1319, 1219, 1155, 1118, 1106, 1067, 1031, 1015, 948, 865, 842, 827, 807, 779, 756, 723, 700, 650; LCMS (ESI) m/z 317 [M + H]$^+$; HRMS(ESI) m/z calcd for $C_{18}H_{16}N_2F_3$ (M + H$^+$): 317.1266; found: 317.1254; mp. 92−94 °C.

*1-(m-Iodophenyl)-4-phenethyl-1H-pyrazole (**4i**).* According to the general procedure, reaction of glycine **1i** with 4-phenyl-1-butyne, followed by flash chromatography (SiO_2, heptane/EtOAc 95:5), afforded pyrazole **4i** (62.2 mg, 0.17 mmol, 83%) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (t, J = 1.9 Hz, 1H), 7.61−7.55 (m, 3H), 7.51 (s, 1H), 7.34−7.28 (m, 2H), 7.25−7.18 (m, 3H), 7.17 (t, J = 8.1 Hz, 1H), 2.89 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.6, 141.4, 141.2, 135.0, 130.9, 128.6 (2C), 128.5 (2C), 127.7, 126.3, 124.9, 123.6, 117.8, 94.5, 37.1, 26.2; IR (NaCl, cm^{-1}) 3085, 3062, 3026, 2924, 2858, 1588, 1567, 1485, 1453, 1429, 1395, 1334, 1297, 1215, 1169, 1075, 1064, 1039, 1019, 993, 956, 907, 859, 778, 736, 700, 679; LCMS (ESI) m/z 375 [M + H]$^+$; HRMS(ESI) m/z calcd for $C_{17}H_{16}N_2I$ (M + H$^+$): 375.0358; found: 375.0344.

*1-(Naphthalen-1-yl)-4-phenethyl-1H-pyrazole (**4j**).* According to the general procedure, reaction of glycine **1j** with 4-phenyl-1-butyne, followed by flash chromatography (SiO_2, heptane/EtOAc 95:5 to 90:10), afforded pyrazole **4j** (41.0 mg, 0.14 mmol, 69%) as a brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (td, J = 7.3 Hz and J = 2.3 Hz, 2H), 7.78 (d, J = 7.3 Hz, 1H), 7.67 (s, 1H), 7.57−7.48 (m, 4H), 7.46 (s, 1H), 7.36−7.29 (m, 2H), 7.27−7.20 (m, 3H), 2.97 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.7, 140.7, 137.6, 134.4, 130.1, 129.1, 128.75, 128.72 (2C), 128.5 (2C), 128.2, 127.2, 126.7, 126.2, 125.2, 123.4, 123.1, 121.9, 37.4, 26.3; IR (NaCl, cm^{-1}) 3084, 3056, 3026, 2924, 2858, 1597, 1577, 1511, 1496, 1469, 1453, 1423, 1399, 1329, 1261, 1217, 1179, 1160, 1114, 1075, 1019, 860, 799, 772, 750, 717, 698; LCMS (ESI) m/z 299 [M + H]$^+$; HRMS(ESI) m/z calcd for $C_{21}H_{19}N_2$ (M + H$^+$): 299.1548; found: 299.1534.

*3-(4-Phenethyl-1H-pyrazol-1-yl)thiophene-2-carboxylic Acid (**4k**).* According to the general procedure, reaction of glycine **1k** with 4-phenyl-1-butyne, followed by flash chromatography (SiO_2, heptane/EtOAc 80:20 to 60:40), afforded pyrazole **4k** (31.0 mg, 0.10 mmol, 50%) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.50 (s, 1H), 7.50 (d, J = 5.4 Hz, 1H), 7.45 (d, J = 5.4 Hz, 1H), 7.33−7.27 (m, 2H), 7.25−7.18 (m, 3H), 3.85 (s, 3H), 2.90 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 143.1, 141.7, 141.3, 130.7, 130.5, 128.6 (2C), 128.5 (2C), 126.7, 126.2, 122.2, 118.0, 52.4, 37.2, 26.3; IR (NaCl, cm^{-1}) 3088, 3062, 3026, 2949, 2858, 1715, 1574, 1545, 1496, 1455, 1438, 1421, 1398, 1264, 1235, 1210, 1110, 1085, 1071, 975, 955, 874, 774, 698; LCMS (ESI) m/z 313 [M + H]$^+$; HRMS(ESI) m/z calcd for $C_{17}H_{17}N_2O_2S$ (M + H$^+$): 313.1011; found: 313.1000.

*1,4-Diphenyl-1H-pyrazole (**4l**).*[6] According to the general procedure, reaction of *N*-phenylglycine **1b** with phenylacetylene, followed by flash chromatography (SiO_2, heptane/EtOAc 90:10), afforded pyrazole **4l** (37.0 mg, 0.17 mmol, 84%) as a yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 8.02 (s, 1H), 7.75 (d, J = 7.9 Hz, 2H), 7.57 (d, J = 7.3 Hz, 2H), 7.48 (t, J = 7.9 Hz, 2H), 7.41 (t, J = 7.3 Hz, 2H), 7.30 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.2, 139.0, 132.2, 129.7 (2C), 129.2 (2C), 127.1, 126.8, 125.9 (2C), 125.2, 123.5, 119.3 (2C); IR (KBr, cm^{-1}) 3038, 1595, 1504, 1464, 1400, 1389, 1362, 1324, 1295, 1257, 1238, 1190, 1171, 1143, 1095, 1086, 1074, 1033, 1014, 954, 902, 863, 845, 801; LCMS (ESI) m/z 221 [M + H]$^+$; mp. 93−95 °C.

*4-Pentyl-1-phenyl-1H-pyrazole (**4m**).*[16] According to the general procedure, reaction of *N*-phenylglycine **1b** with 1-heptyne, followed by flash chromatography (SiO_2, heptane/EtOAc 95:5), afforded pyrazole **4m** (34.8 mg, 0.16 mmol, 82%) as a bright yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.68−7.66 (m, 2H), 7.55 (s, 1H), 7.45−7.41 (m, 2H), 7.26−7.23 (m, 1H), 2.53 (t, J = 7.6 Hz, 2H), 1.66−1.58 (m, 2H), 1.38−1.34 (m, 4H), 0.93−0.90 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.9, 140.2, 129.3 (2C), 125.9, 124.6, 124.0, 118.7 (2C), 31.4, 30.4, 24.1, 22.4, 14.0 ; IR (KBr, cm^{-1}) 2955, 2856, 2926, 1600, 1571, 1503, 1463, 1395, 1328, 1251, 1211, 1176, 1072, 1012, 1042, 952, 901, 854, 788, 752, 688, 652; LCMS (ESI) m/z 215 [M + H]$^+$.

*4-(2-Bromoethyl)-1-phenyl-1H-pyrazole (**4n**).* According to the general procedure using less Et_3N (125 μL, 0.90 mmol), reaction of *N*-phenylglycine **1b** with 4-bromo-1-butyne, followed by flash chromatography (SiO_2, heptane/EtOAc 90:10 to 95:5), afforded pyrazole **4n** (22.8 mg, 0.09 mmol, 45%) as a yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.67 (m, 2H), 7.62 (s, 1H), 7.45 (m, 2H), 7.28 (m, 1H), 3.56 (t, J = 7.2 Hz, 2H), 3.13 (t, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.9, 140.2, 129.6 (2C), 126.5, 125.6, 120.6, 119.1 (2C), 33.0, 28.3; IR (KBr, cm^{-1}) 2922, 2964, 1724, 1598, 1570, 1503, 1464, 1446, 1432, 1398, 1370, 1331, 1266, 1220, 1206, 1181, 1155, 1108, 1073, 1042, 1031, 1012, 952, 905, 855, 799, 750688, 651, 622; LCMS (ESI) m/z 251 [M(^{79}Br) + H]$^+$, 253 [M(^{81}Br) + H]$^+$; HRMS(ESI) m/z calcd for $C_{11}H_{12}N_2Br$ (M[^{79}Br] + H$^+$): 251.0184; found: 251.0172; mp. 42−44 °C.

*tert-Butyl N-((1-Phenyl-1H-pyrazol-4-yl)methyl)carbamate (**4o**).* According to the general procedure, reaction of *N*-phenylglycine **1b** with *N*-Boc-propargylamine, followed by flash chromatography (SiO_2, heptane/EtOAc 85:15), afforded pyrazole **4o** (46.6 mg, 0.17 mmol, 85%) as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.67−7.62 (m, 3H), 7.43 (m, 2H), 7.27 (m, 1H), 4.85 (br s, 1H), 4.24 (d, J = 5.8 Hz, 2H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 140.6, 140.1, 129.5 (2C), 126.6, 125.8, 121.4, 119.1 (2C), 79.7, 35.2, 28.5 (3C); IR (KBr, cm^{-1}) 3322, 2978, 1682, 1599, 1504, 1398, 1364, 1346, 1246, 1158, 1073, 1039, 1023, 949, 901, 870, 810, 782, 752, 707, 673, 650, 618; LCMS (ESI) m/z 274 [M + H]$^+$; HRMS(ESI) m/z calcd for $C_{15}H_{20}N_3O_2$ (M + H$^+$): 274.1556; found: 274.1544; mp. 78−81 °C.

*5-tert-Butyl-3-(2,4-dichloro-5-((1-phenyl-1H-pyrazol-4-yl)-methoxy)phenyl)-2,3-dihydro-1,3,4-oxadiazol-2-one (**4p**).* According to the general procedure using less Et_3N (125 μL, 0.90 mmol), reaction of *N*-phenylglycine **1b** with oxadiargyl, followed by flash chromatography (SiO_2, heptane/EtOAc 90:10 to 60:40), afforded pyrazole **4p** (83.4 mg, 0.18 mmol, 78%) as a beige solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.79 (s, 1H), 7.70 (m, 2H), 7.54 (s, 1H), 7.46 (m, 2H), 7.30 (m, 1H), 7.18 (s, 1H), 5.13 (s, 2H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 153.3, 152.3, 140.9, 140.0, 131.7, 131.5, 129.6 (2C), 126.9 (2C), 125.5, 123.7, 119.4 (2C), 117.9, 113.6, 63.3, 33.1, 27.2 (3C); IR (KBr, cm^{-1}) 2973, 1768, 1618, 1600, 1568, 1504, 1489, 1429, 1407, 1395, 1356, 1339, 1324, 1283, 1248, 1225, 1142, 1125, 1092, 1125, 1092, 1037, 974, 954, 906, 875, 863, 832, 796, 755, 712, 688, 658, 666; LCMS (ESI) m/z 459 [M + H]$^+$; HRMS(ESI) m/z calcd for $C_{22}H_{21}N_4O_3Cl_2$ (M + H$^+$): 459.0991; found: 459.0980; mp. 148−151 °C.

*2-(1-Phenyl-1H-pyrazol-4-yl)pyridine (**4q**).*[6] According to the general procedure, reaction of *N*-phenylglycine **1b** with 2-ethynylpyridine, followed by flash chromatography (SiO_2, heptane/EtOAc 70:30), afforded pyrazole **4q** (30.7 mg, 0.14 mmol, 69%) as a white powder; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60−8.58 (m, 1H), 8.52 (s, 1H), 8.18 (s, 1H), 7.77−7.75 (m, 2H), 7.70 (td, J = 7.7 Hz, 1.9 Hz,

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1H), 7.55 (br. d, J = 7.9 Hz, 1H), 7.49−7.44 (m, 2H), 7.31 (m, 1H), 7.15 (ddd, J = 7.5 Hz, 4.9 Hz, 1.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.3, 149.5, 139.8, 139.1, 136.8, 129.4, 126.8, 125.3, 125.0, 121.5, 119.8, 119.1; IR (KBr, cm^{-1}) 3052, 1700, 1652, 1594, 1557, 1505, 1411, 1260, 1192, 1152, 1034, 962, 870, 778, 756, 717, 690; LCMS (ESI) m/z 222 [M + H]$^+$; mp. 86−88 °C.

*Ethyl 1-Phenyl-1H-pyrazole-4-carboxylate (**4r**).*[6] According to the general procedure, reaction of *N*-phenylglycine **1b** with ethyl propiolate, followed by flash chromatography (SiO_2, heptane/EtOAc 95:5), afforded pyrazole **4r** (22.1 mg, 0.10 mmol, 51%) as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1H), 8.09 (s, 1H), 7.71−7.68 (m, 2H), 7.49−7.45 (m, 2H), 7.37−7.32 (m, 1H), 4.34 (q, J = 7.1 Hz, 2H), 1.37 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8, 142.1, 139.3, 129.9, 129.5, 127.5, 119.5, 116.9, 60.4, 14.3 ; IR (KBr, cm^{-1}) 2925, 2213, 1707, 1630, 1597, 1559, 1497, 1412, 1247, 1148, 1025, 996, 951, 908, 887, 853, 825, 768, 755, 686, 654; LCMS (ESI) m/z 217 [M + H]$^+$; mp. 88−91 °C.

*2-Methyl-4-oxo-3-((1-phenyl-1H-pyrazol-4-yl)methyl)cyclopent-2-en-1-yl 2,2-Dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropane-1-carboxylate (**4s**).* According to the general procedure using less Et_3N (125 μL, 0.90 mmol), reaction of *N*-phenylglycine **1b** with prallethrin, followed by flash chromatography (SiO_2, heptane/EtOAc 90:10 to 60:40), afforded pyrazole **4s** (65 mg, 0.16 mmol, 78%) in a diastereomeric mixture (dr: 47/53) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) *minor diastereomer* δ 7.76 (s, 1H), 7.63 (m, 2H), 7.52 (s, 1H), 7.42 (m, 2H), 7.25 (m, 1H), 5.77 (br d, J = 6.3 Hz, 1H), 4.90 (m, 1H), 3.46 (s, 2H), 2.90 (dd, J = 10.5 Hz and J = 6.2 Hz, 1H), 2.32 (dd, J = 18.7 Hz and J = 2.1 Hz, 1H), 2.11−2.06 (m, 1H), 2.07 (s, 3H), 1.73−1.69 (m, 6H), 1.40 (d, J = 5.3 Hz, 1H), 1.29 (s, 3H), 1.15 (s, 3H); *major diastereomer* δ 7.76 (s, 1H), 7.63 (m, 2H), 7.52 (s, 1H), 7.42 (m, 2H), 7.25 (m, 1H), 5.68 (br d, J = 6.2 Hz, 1H), 4.90 (m, 1H), 3.46 (s, 2H), 2.90 (dd, J = 10.5 Hz and J = 6.3 Hz, 1H), 2.32 (dd, J = 18.7 Hz and J = 2.0 Hz, 1H), 2.11−2.06 (m, 1H), 2.10 (s, 3H), 1.73−1.69 (m, 6H), 1.41 (d, J = 5.2 Hz, 1H), 1.26 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.04/203.99, 172.4, 165.4/165.3, 142.64/142.58, 140.9, 140.2, 136.10/136.07, 129.5 (2C), 126.4, 125.7, 120.90/120.82, 119.8, 119.0 (2C), 73.1/72.7, 42.2/41.8, 34.72/34.68, 33.4/33.2, 29.3, 25.7, 22.3/22.2, 20.7/20.5, 18.6, 18.1, 14.3/14.2 ; IR (KBr, cm^{-1}) 2923, 1709, 1655, 1599, 1504, 1413, 1396, 1379, 1339, 1281, 1234, 1192, 1149, 1113, 1075, 1040, 1011, 993, 952, 903, 855, 754, 689, 652; LCMS (ESI) m/z 419 [M + H]$^+$; HRMS(ESI) m/z calcd for $C_{26}H_{31}N_2O_3$ (M + H$^+$): 419.2335; found: 419.2344.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR for all products and ^{19}F NMR for compound **4h**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: frederic.taran@cea.fr.

Notes

The authors declare no competing financial interest

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