JOC The Journal of Organic Chemistry
Cite This: J. Org. Chem. 2018, 83, 4851−4858
Note
pubs.acs.org/joc

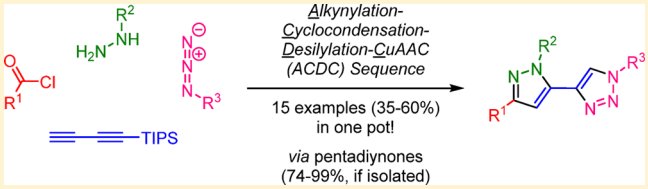
De Novo Ring-Forming Consecutive Four-Component Syntheses of 4-Pyrazolyl-1,2,3-triazoles from (Triisopropylsilyl)butadiyne as a C4 Building Block

Patrik Niesobski,[†] Fabian Klukas,[†] Henning Berens,[†] Gamall Makhloufi,[‡] Christoph Janiak,[‡] and Thomas J. J. Müller*[,†]

[†]Institut für Organische Chemie und Makromolekulare Chemie and [‡]Institut für Anorganische Chemie und Strukturchemie, Heinrich-Heine-Universität Düsseldorf, Universitätsstrasse 1, D-40225 Düsseldorf, Germany

Supporting Information

ABSTRACT: 4-Pyrazolyl-1,2,3-triazoles can be readily synthesized in a one-pot fashion and moderate yield by employing a consecutive four-component process consisting of a sequentially Pd−Cu-catalyzed alkynylation-cyclocondensation-desilylation-CuAAC process. Most distinctly, (triisopropylsilyl)butadiyne is employed as a four-carbon building block in this one-pot de novo formation of both heterocyclic moieties.



1,2,3-Triazoles and pyrazoles are not prevalent in nature, but both classes have received the utmost relevance as biologically active ingredients and as functional moieties in materials and coordination chemistry. Whereas 1,2,3-triazoles have primarily found application as resistant bioisosters of amide bonds against hydrolysis and enzymatic degradation[1] with a plethora of biological activities,[2] their practical use as a universal ligation unit and coordinating ligand in the field of material sciences and supramolecular assemblies has become increasingly important.[3] Pyrazoles, as 1,2-diazoles, have likewise gained enormous interest in medical research[4] with a broad spectrum of biological activity.[5] In addition, pyrazoles are well-known pluripotent ligands in coordination chemistry,[6] building blocks in heterocyclic synthesis,[7] and components in supramolecular structures.[8] Furthermore, they have been investigated as optical brighteners,[9] UV stabilizers[10] and emission solvatochromic polarity sensors[11] as well as constituents in photoinduced electron transfer systems[12] and agro chemicals.[13] Particularly interesting are conjugated pyrazolyl-1,2,3-triazole biheteroaryls and anellated analogues, such as pyrazole[3,4-*d*]-1,2,3-triazoles, which have been shown to possess antiproliferative features and light-induced DNA cleavage.[14] However, 4-pyrazolyl-1,2,3-triazoles are only scarcely found in the literature and all their syntheses have remained stepwise to date.[15]

Multicomponent syntheses of heterocycles initiated by transition metal catalysis[16] represent concise and highly practical approaches to functional heterocyclic scaffolds.[17] In recent years, we have developed consecutive multicomponent strategies based upon the catalytic generation of alkynones as versatile three-carbon building blocks in one-pot syntheses of heterocycles.[18] The Cu-catalyzed alkyne−azide cycloaddition (CuAAC) is not only a concise and direct access to 1,4-disubstituted 1,2,3-triazoles but even more so an excellent entry to multicomponent reactions.[19] Herein, we communicate consecutive four-component syntheses of 4-pyrazolyl-1,2,3-triazoles by Pd−Cu-catalyzed sequence[20] of Sonogashira alkynylation and CuACC in a one-pot fashion.

Our retrosynthetic analysis of 4-pyrazolyl-1,2,3-triazoles **1** commences with a CuAAC as the retrosynthetic cut for synthesizing 1,2,3-triazoles leading to azide **2** and pyrazolyl alkyne **3**, which can be directly traced back to silylated precursor **4** (Scheme 1). Pyrazole **4** can be regioselectively disconnected to hydrazine **6** and triisopropylsilyl [TIPS]-protected pentadiynone **5**, an ethynylogous alkynone. The Sonogashira disconnection of alkynones[21] furnishes a butadiyne **7** and an acid chloride **8**. Because silylated butadiynes are very useful building blocks in natural product synthesis[22] and materials science,[23] TIPS-protected butadiyne (**7**), which is considerably more stable than its TMS derivative,[24] is the obvious four-carbon building block as a starting material in this alkynylation-cyclocondensation-desilylation-CuAAC (ACDC) sequence analysis as a consecutive four-component process.

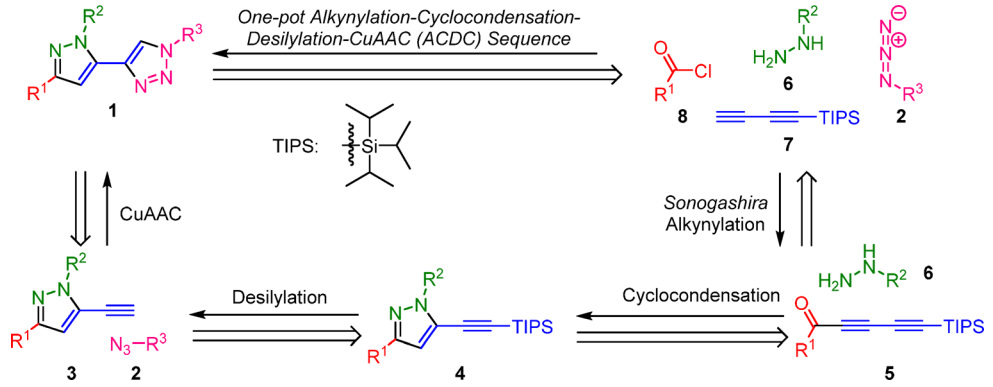
Interestingly, TIPS-protected butadiyne (**7**) was only employed once in a consecutive three-component reaction to give unsymmetrically substituted bis(1,2,3-triazoles) by 2-fold CuAAC.[25]

Noteworthily, the synthesis of pentadiynones **5** has only been achieved by gold-catalyzed 1,3-transposition of ynones[26] but never by the conceptionally simple Sonogashira alkynylation of acid chlorides **8**. Therefore, we set out to probe the catalytic alkynylation of (hetero)aroyl chlorides **8** with TIPS-butadiyne **7** under modified Sonogashira conditions (Scheme 2).[21] TIPS-protected pentadiynones **5** were obtained in good to

Received: February 14, 2018
Published: March 22, 2018

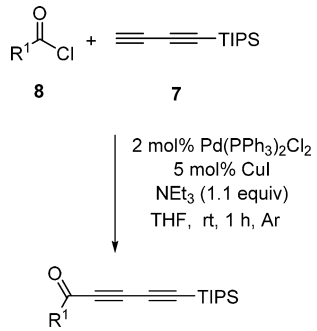
DOI: 10.1021/acs.joc.8b00430
J. Org. Chem. 2018, 83, 4851−4858

Scheme 1. Retrosynthetic Analysis of 4-Pyrazolyl-1,2,3-triazoles 1



excellent yields with a scope of the (hetero)aromatic substituents ranging from electron rich to electron poor.

Scheme 2. Sonogashira Synthesis of TIPS-Protected Pentadiynones 5 from (Hetero)aroyl Chlorides 8 and TIPS-Butadiyne 7



5a (R^1 = Ph, 99%)
5b (R^1 = *p*-Tol, 95%)
5c (R^1 = *p*-ClC_6H_4, 74%)
5d (R^1 = *p*-$MeOC_6H_4$, 82%)
5e (R^1 = 2-thienyl, 74%)

With this smooth formation of TIPS-protected pentadiynones in hand, we reasoned that the Michael reactivity of the alkynone moiety could readily participate in a heterocyclization with a hydrazine as a binucleophile,[27] whereas the terminal alkynyl portion, after desilylation, could undergo a concluding CuAAC, furnishing 4-pyrazolyl-1,2,3-triazoles **1** in a one-pot fashion. Thus, after a quick optimization study, 1,4-dioxane was identified as the solvent of choice for the ACDC sequence, and in contrast to previous findings,[27] no further addition of acetic acid in the microwave-assisted cyclocondensation step was necessary. Therefore, upon reacting TIPS-butadiyne **7** and (hetero)aroyl chlorides **8** under Sonogashira conditions, followed by subsequent cyclocondensation with hydrazines **6** in the same reaction vessel, and quick desilylation with TBAF, the reaction concluded by CuAAC with azides **2** without further addition of copper or palladium catalysts at room temperature to give the title compounds **1** in moderate to good yields (Scheme 3). The scope of this one-pot synthesis of 4-pyrazolyl-1,2,3-triazoles is rather broad and ranges from electron rich to electron poor (hetero)aromatic and even secondary and tertiary aliphatic substituents in the acid chlorides **8** as well as aliphatic- and aromatic-functionalized azides **2** as reactants with perfect control of the regioselectivity. However, it has to be mentioned that aromatic hydrazines, because of their lower nucleophilicity, cannot be employed as substrates in the pyrazole-forming step. Although the overall yield of 35−60% for the formation of the pyrazolyltriazoles **1** in this one-pot four-step process might be considered to be only moderate, one has to keep in mind that the average yield per bond forming and cleaving step accounts to 84−92% and is quite efficient.

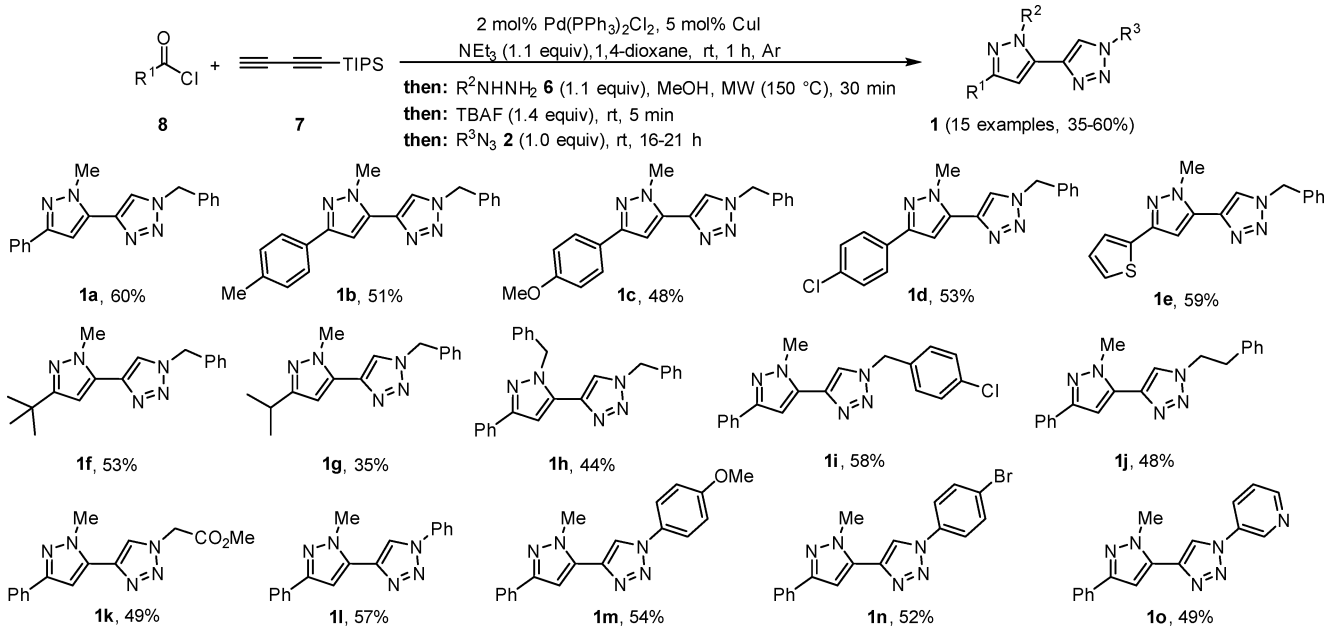
The handling with aliphatic azides **2** might be hazardous, but fortunately, they can often be generated in situ.[19] For three examples of this variation, i.e., the in situ formation of aliphatic azides from aliphatic bromides or chlorides **9** and cesium azide by nucleophilic substitution in the terminal CuAAC was illustrated (Scheme 4). It is worth mentioning that the addition of 10 mol % sodium ascorbate is important for the regeneration of the copper catalyst during the extended reaction time of 3 d. The yields of the title compounds in this extended consecutive five-component reaction ranges between 49 and 62%, thereby enhancing the average yield per bond forming and cleaving step to 90−94%. Besides this high bond-forming efficiency, it is also worth mentioning that all components are introduced in almost stoichiometric amounts. All of this renders this novel de novo coupling-doubly ring-forming process highly practical.

The structures of the pyrazolyl-triazoles **1** were unambiguously assigned by extensive spectroscopic characterization (^{1}H NMR, ^{13}C NMR, IR spectroscopy, mass spectrometry) and additionally by an X-ray structural analysis of compound **1a** (Figure 1).[28]

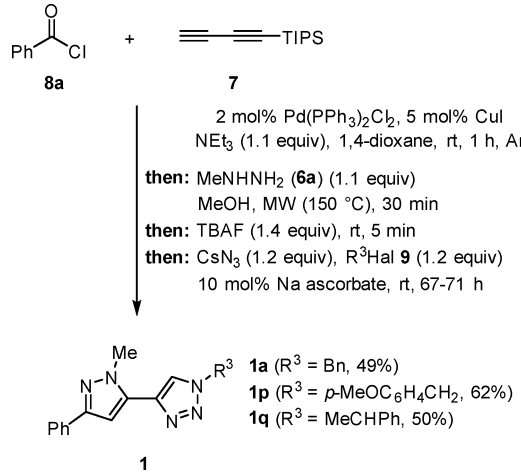
In conclusion, 4-pyrazolyl-1,2,3-triazoles can be readily synthesized by a consecutive four-component reaction employing an alkynylation-cyclocondensation-desilylation-CuAAC (ACDC) sequence in a one-pot fashion. Moreover, this synthesis represents a sequentially Pd−Cu-catalyzed de novo process for accessing biheteroaryls in a concise and diversity-oriented fashion where the catalyst sources are only introduced in the first step and operate without further addition and are intercepted by cyclocondensation and desilylation in the concluding triazole formation. An extension to a consecutive five-component process can be achieved by even performing the organic azide formation in situ in the concluding CuAAC step. Further studies to expand the methodological scope and the materials properties of these biheterocycles are currently underway.

DOI: 10.1021/acs.joc.8b00430
J. Org. Chem. 2018, 83, 4851−4858

Scheme 3. Consecutive Four-Component Synthesis of 4-Pyrazolyl-1,2,3-triazoles 1



Scheme 4. Consecutive Five-Component Synthesis of 4-Pyrazolyl-1,2,3-triazoles 1



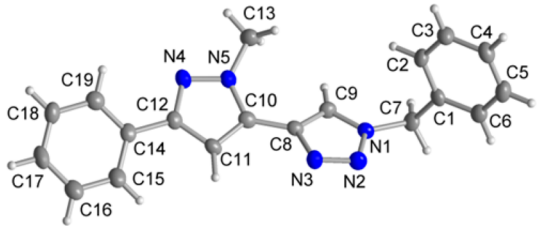


Figure 1. Molecular structure of compound **1a** (thermal ellipsoids shown at 50% probability). See the Supporting Information for further details on the crystal structure.

EXPERIMENTAL SECTION

General Information. All reactions involving palladium−copper catalysis were performed in degassed oxygen free solvents under an argon atmosphere using Schlenk and syringe techniques. Column chromatography: silica gel 60 mesh 230−400 (Macherey-Nagel, Düren). TLC: silica gel plates (60 F254 Merck, Darmstadt). Melting points (uncorrected values): Büchi Melting Point B-535. ^{1}H and ^{13}C NMR spectra in $CDCl_3$: Bruker Avance DRX 500. The assignments of quaternary C, CH, CH_2, and CH_3 nuclei have been made by using 135-DEPT spectra. IR: Bruker Vector 22 FT-IR and Shimadzu IR AFFINITY-1. MS: Bruker Ultraflex TOF (electron ionization or electron spray ionization). Elemental analyses were carried out in the microanalytical laboratories of the Institute of Pharmacy, Heinrich-Heine-Universität Düsseldorf. Aliphatic[29] (**2b−2d**) and aromatic[30] azides (**2f−2h**) were prepared according to a literature procedure, and the spectroscopic data were consistent with the literature.

Synthesis of TIPS-Butadiyne (7).[31] Bromine (5 mL, 97.6 mmol, 0.90 equiv) was slowly added via syringe to an aqueous KOH solution (15.6 g, 278 mmol, 2.57 equiv, 200 mL H_2O) at 0 °C (ice bath), and the stirring was maintained for 15 min. Then, 2-methylbut-3-yn-2-ol (10 mL, 108 mmol, 1.00 equiv) was added dropwise via syringe to the mixture and stirring was continued for 30 min. The ice bath was removed, and after 30 min at room temp the reaction mixture was extracted with ether (4 × 25 mL). The organic layers were combined and dried with anhydrous $MgSO_4$. The crude product was adsorbed on Celite and purified by flash purification system (*n*-hexane/ethyl acetate 10:1) to afford 4-bromo-2-methylbut-3-yn-2-ol as a colorless oil (13.4 g, 82.2 mmol, 80%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.52 (s, 6 H), 2.05 (s, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 31.3 (CH_3), 43.0 (C_{quat}), 66.4 (C_{quat}), 84.5 (C_{quat}). MS (EI) *m*/*z* (%): 164 ([^{81}Br − M]$^+$, 10), 162 ([^{79}Br − M]$^+$, 10), 149 (93), 147 (100), 83 (9), 69 (9), 43 (46).

CuCl (66.0 mg, 0.67 mmol, 2 mol %) was placed in a dry Schlenk tube under nitrogen (3 cycles of evacuation and flushing with nitrogen). Then, a solution of butylamine (27 mL) in water (63 mL) was added. The solution immediately turned blue but decolorized upon addition of a spatula tip full of hydroxylamine hydrochloride. After (triisopropylsilyl)acetylene (5.32 g, 29.2 mmol, 1.0 equiv) was added, the reaction was immediately cooled by an ice bath before 4-bromo-2-methylbut-3-yn-2-ol (7.20 g, 44.2 mmol, 1.5 equiv) was added. After stirring for 15 min at 0 °C, the ice bath was removed, and every few minutes a spatula tip full of hydroxylamine hydrochloride was added to the reaction mixture until no decolorization was observed (~40 min). The aqueous mixture was extracted with Et_2O (4 × 50 mL). The combined organic layers were washed with H_2O (100 mL), dried with anhydrous $MgSO_4$, filtered, and the solvent was removed under vacuo. The crude product was diluted in a small amount of *n*-hexane and filtered through a short pad of silica with *n*-hexane to afford, after removal of the solvent, 2-methyl-6-(triisopropylsilyl)hexa-3,5-diyn-2-ol as a yellow solid (7.09 g, 26.8 mmol,

DOI: 10.1021/acs.joc.8b00430
J. Org. Chem. 2018, 83, 4851−4858

92%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.08 (s, 21 H), 1.54 (s, 6 H), 2.17 (s, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 11.4 (CH), 18.7 (CH_3), 31.2 (CH_3), 65.6 (C_{quat}), 67.8 (C_{quat}), 80.9 (C_{quat}), 84.9 (C_{quat}), 89.0 (C_{quat}). MS (EI) m/z (%): 264 ([M]$^+$, 5) 221 (100), 193 (35), 179 (27), 165 (21), 151 (31), 139 (17), 135 (19), 125 (20), 109 (22), 85 (10), 75 (41).

The TIPS-protected diynol (1.75 g, 6.04 mmol, 1 equiv), potassium carbonate (1.01 g, 7.34 mmol), and 18-crown-6 (0.52 g, 1.98 mmol) were added to toluene (15 mL) and heated at 100 °C for 40 min. After cooling to room temp, the solvent was removed in vacuo. The crude product was diluted in a small amount of *n*-hexane and filtered through a pad of silica with *n*-hexane to afford, after removal of the solvent, (buta-1,3-diyn-1-yl)tris(propan-2-yl)silane (**7**) as a slightly red oil (1.16 g, 26.8 mmol, 85%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.09 (s, 21 H), 2.07 (s, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 11.3 (CH), 18.7 (CH_3), 65.6 (C_{quat}), 68.8 (C_{quat}), 82.2 (C_{quat}), 89.2 (C_{quat}). MS (GC-MS) m/z (%): 206 ([M]$^+$, 6), 163 (100), 135 (81), 120 (35), 107 (96), 93 (90), 83 (13), 77 (19), 53 (12).

General Procedure (GP1) for the Synthesis of Compounds 5a–e. Bis(triphenylphosphane)palladium(II) dichloride (7.00 mg, 10.0 μmol, 2.00 mol %), CuI (3.80 mg, 25.0 μmol, 4.00 mol %), and acyl chloride **8** (0.500 mmol, 1.00 equiv, if solid) were placed in a flame-dried Schlenk tube under argon, and the vial was evacuated and flushed with argon three times. Then, THF (1 mL) and (buta-1,3-diyn-1-yl)tris(propan-2-yl)silane (**7**) (124 mg, 0.600 mmol, 1.20 equiv) were added along with acyl chloride (if liquid). The solution was degassed with argon for 5 min before triethylamine (53.1 mg, 0.525 mmol, 1.05 equiv) was added. The reaction mixture was stirred at room temp for 1 h. The crude product was adsorbed on Celite, and the purification was performed using a flash purification system (*n*-hexane/THF).

*1-Phenyl-5-(triisopropylsilyl)penta-2,4-diyn-1-one (**5a**).* According to GP1, 153 mg (0.493 mmol, 99%) of **5a** was obtained as a brown oil after purification by flash chromatography (*n*-hexane/THF 40:1). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 1.10–1.16 (m, 21 H), 7.50 (t, ^3J = 7.8 Hz, 2 H), 7.63 (t, ^3J = 7.4 Hz, 1 H), 8.14 (d, ^3J = 7.1 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 151 MHz): δ 11.3 (CH), 18.6 (CH_3), 71.9 (C_{quat}), 77.8 (C_{quat}), 87.8 (C_{quat}), 95.5 (C_{quat}), 128.8 (CH), 129.8 (CH), 134.7 (CH), 136.6 (C_{quat}), 177.1 (C_{quat}). MS (GC-MS) m/z (%): 267 ([M − C_3H_7]$^+$, 100), 239 (34), 225 (15), 211 (42), 197 (36), 183 (15), 179 (13), 169 (17), 165 (25), 139 (13), 129 (10), 105 (25), 92 (10), 77 (29). IR (ATR): $\tilde{\nu}$ 3269, 3065, 2943, 2891, 2866, 2727, 2621, 2286, 2199, 2095, 1773, 1726, 1692, 1643, 1597, 1582, 1462, 1450, 1422, 1385, 1368, 881, 843, 791, 775 cm^{-1}. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{20}H_{27}OSi$ 311.1826; found 311.1828.

*1-(p-Tolyl)-5-(triisopropylsilyl)penta-2,4-diyn-1-one (**5b**).* According to GP1, 154 mg (0.475 mmol, 95%) of **5b** was obtained as a brown oil after purification by flash chromatography (*n*-hexane/THF 40:1). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 1.10–1.15 (m, 21 H), 2.44 (s, 3 H), 7.29 (d, ^3J = 8.0 Hz, 2 H), 8.02 (d, ^3J = 8.1 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 151 MHz): δ 11.3 (CH), 18.6 (CH_3), 22.0 (CH_3), 72.0 (C_{quat}), 88.0 (C_{quat}), 95.1 (C_{quat}), 129.6 (CH), 129.9 (CH), 134.3 (C_{quat}), 145.9 (C_{quat}), 176.7 (C_{quat}). MS (GC-MS) m/z (%): 281 ([M − C_3H_7]$^+$, 100), 253 (33), 239 (15), 225 (37), 211 (32), 197 (12), 183 (16), 179 (19), 119 (21), 91 (24), 75 (17). IR (ATR): $\tilde{\nu}$ 3034, 2943, 2891, 2866, 2727, 2409, 2282, 2199, 2095, 1639, 1604, 1573, 1508, 1460, 1408, 1385, 1368, 881, 831, 814, 795, 737 cm^{-1}. Anal. Calcd for $C_{21}H_{28}OSi$ (324.19): C 77.72, H 8.70. Found: C 77.51, H 8.64.

*1-(4-Chlorophenyl)-5-(triisopropylsilyl)penta-2,4-diyn-1-one (**5c**).* According to GP1, 128 mg (0.371 mmol, 74%) of **5c** was obtained as a brown oil after purification by flash chromatography (*n*-hexane/THF 100:1). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 1.09–1.14 (m, 21 H), 7.48 (d, ^3J = 8.5 Hz, 2 H), 8.07 (d, ^3J = 8.5 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 151 MHz): δ 11.3 (CH), 18.6 (CH_3), 71.5 (C_{quat}), 78.3 (C_{quat}), 87.7 (C_{quat}), 96.2 (C_{quat}), 129.2 (CH), 131.1 (CH), 135.0 (C_{quat}), 141.4 (C_{quat}), 175.8 (C_{quat}). MS (GC-MS) m/z (%): 344 ([M]$^+$, 1), 309 (13), 303 (39), 302 (28), 301 (100), 275 (15), 273 (36), 259 (14), 247 (21), 246 (11), 245 (53), 233 (18); 231 (45), 217 (16), 203 (16), 199 (16), 163 (15), 139 (28), 122 (13), 111 (18), 108 (13) 103 (10), 77 (10), 75 (42). IR (ATR): $\tilde{\nu}$ 2943, 2891, 2866, 2199, 2095, 1643, 1585, 1570, 1485, 1460, 1400, 1368, 881, 842, 743 cm^{-1}. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{20}H_{26}ClOSi$ 345.1436; found 345.1436.

*1-(4-Methoxyphenyl)-5-(triisopropylsilyl)penta-2,4-diyn-1-one (**5d**).* According to GP1, 140 mg (0.413 mmol, 82%) of **5d** was obtained as a brown oil after purification by flash chromatography (*n*-hexane/THF 10:1). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 1.08–1.14 (m, 21 H), 3.89 (s, 3 H), 6.96 (d, ^3J = 7.6 Hz, 2 H), 8.10 (d, ^3J = 8.9 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 11.3 (CH), 18.7 (CH_3), 55.8 (CH_3), 72.0 (C_{quat}), 77.1 (C_{quat}), 88.0 (C_{quat}), 94.7 (C_{quat}), 114.1 (CH), 130.1 (C_{quat}), 132.3 (CH), 165.0 (C_{quat}), 175.6 (C_{quat}). MS (GC-MS) m/z (%): 340 ([M]$^+$, 5), 297 (100), 269 (34), 255 (18), 241 (39), 227 (34), 213 (11), 199 (17), 195 (24), 135 (30), 120 (14), 107 (12), 77 (14), 75 (15). IR (ATR): $\tilde{\nu}$ 3007, 2943, 2891, 2866, 2398, 2197, 2093, 1636, 1593, 1574, 1508, 1460, 1443, 1422, 1385, 1368, 881, 843, 810, 799, 783, 754 cm^{-1}. Anal. Calcd for $C_{21}H_{28}O_2Si$ (340.19): C 74.07, H 8.29. Found: C 74.14, H 8.59.

*1-(Thiophen-2-yl)-5-(triisopropylsilyl)penta-2,4-diyn-1-one (**5e**).* According to GP1, 118 mg (0.372 mmol, 74%) of **5e** was obtained as a brown oil after purification by flash chromatography (*n*-hexane/THF 40:1). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 1.11–1.13 (m, 21 H), 7.17 (t, ^3J = 4.4 Hz, 1 H), 7.74 (d, ^3J = 4.9 Hz, 1 H), 7.97 (d, ^3J = 3.8 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 11.3 (CH), 18.6 (CH_3), 71.2 (C_{quat}), 76.3 (C_{quat}), 87.7 (C_{quat}), 95.4 (C_{quat}), 128.6 (CH), 135.9 (CH), 136.1 (CH), 144.7 (C_{quat}), 168.8 (C_{quat}). MS (GC-MS) m/z (%): 316 ([M]$^+$, 5), 275 (12), 274 (30), 273 (100), 245 (36), 231 (14), 218 (10), 217 (54), 203 (47), 189 (20), 175 (26), 171 (19), 135 (11), 127 (11), 111 (28), 108 (11), 94 (14), 75 (20). IR (ATR): $\tilde{\nu}$ 3103, 2943, 2889, 2864, 2276, 2199, 2093, 1622, 1514, 1460, 1408, 1385, 1354, 878, 839, 783 cm^{-1}. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{18}H_{25}OSSi$ 317.1390; found 317.1392.

General Procedure (GP2) for the Synthesis of Compounds 1a–o. Bis(triphenylphosphine)palladium(II) dichloride (7.0 mg, 10 μmol, 2.0 mol %) and CuI (4.8 mg, 25 μmol, 5.0 mol %) were placed in a flame-dried 10 mL microwave tube under argon, and the vial was evacuated and flushed with argon three times (for experimental details see Table S1). 1,4-Dioxane (1 mL) and (buta-1,3-diyn-1-yl)tris(propan-2-yl)silane (**7**) (124 mg, 0.60 mmol, 1.20 equiv) were added along with acyl chloride **8** (0.50 mmol, 1.00 equiv). The solution was degassed with argon for 5 min before triethylamine (73 μL, 0.53 mmol, 1.05 equiv) was added. The reaction mixture was stirred at room temp to complete conversion (1–3 h, monitored by TLC). Then, hydrazine **6** (0.55 mmol, 1.10 equiv) and methanol (0.5 mL) were added, and the reaction mixture was heated under microwave irradiation to 150 °C for 30 min. After cooling to room temp, a solution of tetrabutylammonium fluoride in 1,4-dioxane (1 M, 700 μL, 0.70 mmol, 1.40 equiv) was added, and the reaction mixture was stirred at room temp for 5 min before azide **2** (0.50 mmol, 1.00 equiv) was added. The reaction mixture was stirred at room temp overnight (16–21 h). The crude product was adsorbed on Celite, and the purification was performed using a flash purification system (*n*-hexane/acetone).

*1-Benzyl-4-(1-methyl-3-phenyl-1H-pyrazol-5-yl)-1H-1,2,3-triazole (**1a**).* According to GP2, 95 mg (60%) of **1a** was obtained as a colorless solid after purification by flash chromatography (*n*-hexane/acetone 4:1). Mp 158–159 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.24 (s, 3 H), 5.61 (s, 2 H), 6.70 (s, 1 H), 7.30–7.43 (m, 8 H), 7.66 (s, 1 H), 7.80 (d, ^3J = 7.0 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 39.1 (CH_3), 54.6 (CH_2), 102.8 (CH), 121.8 (CH), 125.7 (CH), 128.0 (CH), 128.4 (CH), 128.8 (CH), 129.2 (CH), 129.5 (CH), 133.0 (C_{quat}), 134.3 (C_{quat}), 134.6 (C_{quat}), 139.3 (C_{quat}), 150.5 (C_{quat}). MS (EI) m/z (%): 315 ([M]$^+$, 100), 287 (50), 259 (27), 196 (32), 183 (42), 156 (9), 115 (6), 91 (51), 66 (11). IR (ATR): $\tilde{\nu}$ 3132, 3061, 3038, 2963, 2945, 1562, 1485, 1472, 1447, 1431, 1418, 839, 799, 766, 743 cm^{-1}. Anal. Calcd for $C_{19}H_{17}N_5$ (315.15): C 72.36, H 5.43, N 22.21. Found: C 72.09, H 5.28, N 21.92.

*1-Benzyl-4-(1-methyl-3-(p-tolyl)-1H-pyrazol-5-yl)-1H-1,2,3-triazole (**1b**).* According to GP2, 84 mg (51%) of **1b** was obtained as a colorless solid after purification by flash chromatography (*n*-hexane/acetone 4:1). Mp 115–117 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 2.36

DOI: 10.1021/acs.joc.8b00430
J. Org. Chem. 2018, 83, 4851–4858

(s, 3 H), 4.19 (s, 3 H), 5.59 (s, 2 H), 6.66 (s, 1 H), 7.19 (d, ^3J = 7.6 Hz, 2 H), 7.33 (d, ^3J = 7.0 Hz, 2 H), 7.41 (d, ^3J = 7.0 Hz, 3 H), 7.64 (s, 1 H), 7.67 (d, ^3J = 7.4 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 21.2 (CH_3), 38.9 (CH_3), 54.3 (CH_2), 102.4 (CH), 121.5 (CH), 125.4 (CH), 128.2 (CH), 129.0 (CH), 129.3 (CH), 129.3 (CH), 130.3 (C_{quat}), 134.2 (C_{quat}), 134.2 (C_{quat}), 137.4 (C_{quat}), 139.3 (C_{quat}). MS (EI) m/z (%): 329 ([M]$^+$, 100), 300 (42), 273 (22), 210 (23), 183 (36), 149 (20), 91 (34). IR (ATR): $\tilde{\nu}$ 3152, 3109, 3088, 3049, 3026, 2941, 2920, 2860, 1699, 1603, 1493, 1473, 1445, 1425, 1398, 1364, 841, 820, 777 cm^{-1}. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{20}H_{20}N_5$ 330.1713; found 330.1718.

*1-Benzyl-4-(3-(4-methoxyphenyl)-1-methyl-1H-pyrazol-5-yl)-1H-1,2,3-triazole (**1c**).* According to GP2, 82 mg (48%) of **1c** was obtained as a colorless solid after purification by flash chromatography (*n*-hexane/acetone 2:1). Mp 94−96 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 3.82 (s, 3 H), 4.19 (s, 3 H), 5.59 (s, 2 H), 6.62 (s, 1 H), 6.92 (d, ^3J = 8.6 Hz, 2 H), 7.33 (d, ^3J = 6.8 Hz, 2 H), 7.37−7.42 (m, 2 H), 7.64 (s, 1 H), 7.71 (d, ^3J = 8.6 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 38.9 (CH_3), 54.5 (CH_2), 55.4 (CH_3), 102.2 (CH), 114.1 (CH), 121.7 (CH), 126.1 (C_{quat}), 126.8 (CH), 128.3 (CH), 129.1 (CH), 129.4 (CH), 134.4 (C_{quat}), 139.4 (C_{quat}), 150.5 (C_{quat}), 159.4 (C_{quat}). MS (EI) m/z (%): 345 ([M]$^+$, 100), 316 (21), 289 (19), 226 (18), 183 (37), 91 (38). IR (ATR): $\tilde{\nu}$ 3140, 3119, 3061, 2997, 2963, 2941, 2833, 1680, 1672, 1611, 1537, 1522, 1485, 1452, 1433, 1400, 1360, 883, 829, 795, 773 cm^{-1}. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{20}H_{19}N_5O$ 346.1662; found 346.1669.

*1-Benzyl-4-(3-(4-chlorophenyl)-1-methyl-1H-pyrazol-5-yl)-1H-1,2,3-triazole (**1d**).* According to GP2, 93 mg (53%) of **1d** was obtained as a colorless solid after purification by flash chromatography (*n*-hexane/acetone 3:1). Mp 159−161 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 4.20 (s, 3 H), 5.60 (s, 2 H), 6.66 (s, 1 H), 7.31−7.36 (m, 4 H), 7.38−7.43 (m, 3 H), 7.64 (s, 1 H), 7.71 (d, ^3J = 8.5 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 39.1 (CH_3), 54.5 (CH_2), 102.7 (CH), 121.7 (CH), 126.8 (CH), 128.3 (CH), 128.9 (CH), 129.2 (CH), 129.4 (CH), 131.8 (C_{quat}), 133.5 (C_{quat}), 134.3 (C_{quat}), 134.7 (C_{quat}), 139.2 (C_{quat}), 149.5 (C_{quat}). MS (EI) m/z (%): 349 ([M]$^+$, 100), 320 (53), 293 (25), 230 (36), 183 (58), 156 (12), 139 (13), 91 (66), 66 (14), 58 (11), 43 (47). IR (ATR): $\tilde{\nu}$ 3130, 3090, 3032, 2984, 2943, 2918, 2886, 2847, 1474, 1445, 1429, 1395, 1366, 833, 826, 791, 777, 750 cm^{-1}. Anal. Calcd for $C_{19}H_{16}N_5Cl$ (349.1): C 65.24, H 4.61, N 20.02. Found: C 65.11, H 4.76, N 19.75.

*1-Benzyl-4-(1-methyl-3-(thiophen-2-yl)-1H-pyrazol-5-yl)-1H-1,2,3-triazole (**1e**).* According to GP2, 95 mg (59%) of **1e** was obtained as a colorless solid after purification by flash chromatography (*n*-hexane/acetone 2:1). Mp 108−110 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 4.18 (s, 3 H), 5.59 (s, 2 H), 6.59 (s, 1 H), 7.03 (dd, ^3J = 5.0 Hz, 3.6 Hz, 1 H), 7.23 (d, ^3J = 5.1 Hz, 1 H), 7.29 (d, ^3J = 3.5 Hz, 1 H), 7.33 (d, ^3J = 7.1 Hz, 2 H), 7.41 (t, ^3J = 7.4 Hz, 3 H), 7.64 (s, 1 H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 39.0 (CH_3), 54.5 (CH_2), 102.6 (CH), 121.8 (CH), 123.6 (CH), 124.5 (CH), 127.6 (CH), 128.3 (CH), 129.2 (CH), 129.4 (CH), 134.3 (C_{quat}), 134.5 (C_{quat}), 136.5 (C_{quat}), 139.1 (C_{quat}), 145.9 (C_{quat}). MS (EI) m/z (%): 321 ([M]$^+$, 100), 292 (25), 265 (13), 202 (20), 183 (28), 91 (33). IR (ATR): $\tilde{\nu}$ 3136, 2943, 1601, 1587, 1555, 1501, 1456, 1429, 1418, 1396, 1373, 1360, 847, 827, 795, 777, 733 cm^{-1}. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{17}H_{16}N_5S$ 322.1121; found 322.1127.

*1-Benzyl-4-(3-(tert-butyl)-1-methyl-1H-pyrazol-5-yl)-1H-1,2,3-triazole (**1f**).* According to GP2, 82 mg (53%) of **1f** was obtained as a colorless solid after purification by flash chromatography (*n*-hexane/acetone 4:1). Mp 103−105 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.30 (s, 9 H), 4.10 (s, 3 H), 5.57 (s, 2 H), 6.26 (s, 1 H), 7.28−7.40 (m, 5 H), 7.58 (s, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 30.7 (CH_3), 32.1 (C_{quat}), 38.6 (CH), 54.4 (CH_2), 102.1 (CH), 121.4 (CH), 128.3 (CH), 129.1 (CH), 129.4 (CH), 133.2 (C_{quat}), 134.4 (C_{quat}), 139.8 (C_{quat}), 161.2 (C_{quat}). MS (EI) m/z (%): 295 ([M]$^+$, 61), 267 (10), 252 (63), 225 (28), 210 (100), 183 (17), 176 (30), 160 (14), 91 (71), 65 (12). IR (ATR): $\tilde{\nu}$ 3125, 3036, 2963, 2901, 2860, 1506, 1456, 1427, 1360 826, 800, 723 cm^{-1}. Anal. Calcd for $C_{17}H_{21}N_5$ (295.18): C 69.12, H 7.17, N 23.71. Found: C 69.37, H 7.14, N 23.85.

*1-Benzyl-4-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-1H-1,2,3-triazole (**1g**).* According to GP2, but on 1 mmol scale, 101 mg (35%) of **1g** was obtained as a colorless solid after purification by flash chromatography (*n*-hexane/acetone 4:1). Mp 108−109 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.24 (d, ^3J = 7.6 Hz, 6 H), 2.96 (sep, ^3J = 6.9 Hz, 1 H), 4.09 (s, 3 H), 5.57 (s, 2 H), 6.21 (s, 1 H), 7.28−7.41 (m, 5 H), 7.58 (s, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 23.1 (CH_3), 27.8 (CH), 38.5 (CH_3), 54.4 (CH_2), 102.3 (CH), 121.5 (CH), 128.3 (CH), 129.1 (CH), 129.4 (CH), 133.4 (C_{quat}), 134.4 (C_{quat}), 139.7 (C_{quat}), 158.5 (C_{quat}). MS (GC-MS) m/z (%): 281 ([M]$^+$, 25), 253 (19), 238 (23), 210 (40), 183 (20), 162 (28), 105 (17), 91 (100), 77 (30), 65 (22), 51 (33). IR (ATR): $\tilde{\nu}$ 3123, 3067, 3032, 2960, 2928, 2868, 1605, 1514, 1496, 1456, 1433, 1383, 1362, 881, 792, 743 cm^{-1}. Anal. Calcd for $C_{16}H_{19}N_5$ (281.16): C 68.30, H 6.81, N 24.89. Found: C 68.41, H 6.93, N 24.75.

*1-Benzyl-4-(1-benzyl-3-phenyl-1H-pyrazol-5-yl)-1H-1,2,3-triazole (**1h**).* According to GP2, 94 mg (44%) of **1h** was obtained as a colorless solid after purification by flash chromatography (*n*-hexane/acetone 3:1). Mp 133−134 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.52 (s, 2 H), 5.81 (s, 2 H), 6.77 (s, 1 H), 7.16−7.42 (m, 13 H), 7.44 (s, 1 H), 7.84 (d, ^3J = 7.0 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 54.4 (CH_2), 54.5 (CH_2), 103.4 (CH), 121.9 (CH), 125.8 (CH), 127.3 (CH), 127.5 (CH), 128.0 (CH), 128.3 (CH), 128.6 (CH), 128.8 (CH), 129.1 (CH), 129.4 (CH), 133.1 (C_{quat}), 134.3 (C_{quat}), 134.5 (C_{quat}), 137.5 (C_{quat}), 138.9 (C_{quat}), 151.0 (C_{quat}). MS (EI) m/z (%): 391 ([M]$^+$, 75), 314 (16), 272 (100), 259 (10), 245 (29), 169 (18), 142 (13), 115 (13), 91 (76), 65 (11). IR (ATR): $\tilde{\nu}$ 3127, 3109, 3086, 3030, 2934, 1605, 1495, 1454, 1423, 1362 845, 822, 797, 766, 729 cm^{-1}. Anal. Calcd for $C_{25}H_{21}N_5$ (391.18): C 76.70, H 5.41, N 17.89. Found: C 76.70, H 5.44, N 17.62.

*1-(4-Chlorobenzyl)-4-(1-methyl-3-phenyl-1H-pyrazol-5-yl)-1H-1,2,3-triazole (**1i**).* According to GP2, 104 mg (58%) of **1i** was obtained as a colorless solid after purification by flash chromatography (*n*-hexane/acetone 3:1). Mp 136−137 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.21 (s, 3 H), 5.56 (s, 2 H), 6.70 (s, 1 H), 7.25−7.42 (m, 7 H), 7.65 (s, 1 H), 7.79 (d, ^3J = 7.0 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 39.1 (CH_3), 53.7 (CH_2), 102.8 (CH), 121.6 (CH), 125.6 (CH), 127.9 (CH), 128.8 (CH), 129.6 (CH), 132.8 (C_{quat}), 133.2 (C_{quat}), 134.3 (C_{quat}), 134.3 (C_{quat}), 135.3 (C_{quat}), 150.6 (C_{quat}). MS (EI) m/z (%): 349 ([M]$^+$, 100), 321 (57), 293 (33), 286 (11), 258 (14), 217 (53), 196 (50), 183 (67), 169 (12), 154 (10), 125 (64), 89 (25), 77 (13), 66 (17). IR (ATR): $\tilde{\nu}$ 3156, 3105, 3034, 2990, 2970, 2945, 2924, 2884, 1599, 1493, 1456, 1410 812, 791, 764, 740 cm^{-1}. Anal. Calcd for $C_{19}H_{16}ClN_5$ (349.11): C 65.24, H 4.61, N 20.02. Found: C 64.98, H 4.56, N 20.12.

*4-(1-Methyl-3-phenyl-1H-pyrazol-5-yl)-1-phenethyl-1H-1,2,3-triazole (**1j**).* According to GP2, 82 mg (48%) of **1j** was obtained as a colorless solid after purification by flash chromatography (*n*-hexane/acetone 3:1). Mp 135−136 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 3.27 (t, ^3J = 7.1 Hz, 2 H), 4.15 (s, 3 H), 4.67 (t, ^3J = 7.1 Hz, 2 H), 6.67 (s, 1 H), 7.12 (d, ^3J = 7.0 Hz, 2 H), 7.27−7.43 (m, 6 H), 7.80 (d, ^3J = 7.1 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 36.8 (CH_2), 38.9 (CH_3), 52.0 (CH_2), 102.7 (CH), 122.2 (CH), 125.6 (CH), 127.4 (CH), 127.8 (CH), 128.7 (CH), 128.8 (CH), 129.0 (CH), 133.2 (C_{quat}), 134.6 (C_{quat}), 136.9 (C_{quat}), 138.5 (C_{quat}), 150.6 (C_{quat}). MS (EI) m/z (%): 329 ([M]$^+$, 100), 300 (16), 273 (24), 210 (45), 182 (24), 171 (9), 139 (15), 105 (26), 91 (14), 79 (20), 77 (21). IR (ATR): $\tilde{\nu}$ 3105, 3076, 3030, 2945, 2841, 1950, 1614, 1603, 1493, 1449, 1431, 1362 854, 810, 770, 746 cm^{-1}. Anal. Calcd for $C_{20}H_{19}N_5$ (329.16): C 72.92, H 5.81, N 21.26. Found: C 72.95, H 5.81, N 21.23.

*Methyl 2-(4-(1-Methyl-3-phenyl-1H-pyrazol-5-yl)-1H-1,2,3-triazol-1-yl)acetate (**1k**).* According to GP2, 103 mg (49%) of **1k** was obtained as a colorless solid after purification by flash chromatography (*n*-hexane/acetone 3:1). Mp 151−152 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.85 (s, 3 H), 4.23 (s, 3 H), 5.25 (s, 2 H), 6.78 (s, 1 H), 7.31 (t, ^3J = 7.3 Hz, 1 H), 7.41 (t, ^3J = 7.4 Hz, 1 H), 7.82 (d, ^3J = 7.1 Hz, 2 H), 7.91 (s, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 39.0 (CH_3), 50.9 (CH_2), 53.4 (CH_3), 103.0 (CH), 123.2 (CH), 125.7 (CH), 127.9 (CH), 128.8 (CH), 133.2 (C_{quat}), 134.3 (C_{quat}), 139.5 (C_{quat}), 150.7 (C_{quat}), 166.6 (C_{quat}). MS (EI) m/z (%): 297 ([M]$^+$, 100), 240 (35),

DOI: 10.1021/acs.joc.8b00430
J. Org. Chem. 2018, 83, 4851−4858

226 (33), 210 (18), 196 (69), 184 (67), 171 (21), 153 (10), 139 (21), 126 (10), 77 (13). IR (ATR): $\tilde{\nu}$ 3140, 3076, 2949, 2853, 1763, 1601, 1477, 1436, 1406, 1364, 831, 793, 772, 741 cm^{-1}. Anal. Calcd for $C_{15}H_{15}N_5O_2$ (297.12): C 60.60, H 5.09, N 23.56. Found: C 60.79, H 5.05, N 23.73.

*4-(1-Methyl-3-phenyl-1H-pyrazol-5-yl)-1-phenyl-1H-1,2,3-triazole (**1l**).* According to GP2, 86 mg (57%) of **1l** was obtained as a colorless solid after purification by flash chromatography (*n*-hexane/acetone 3:1). Mp 115−116 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.33 (s, 3 H), 6.86 (s, 1 H), 7.34 (t, ^3J = 7.3 Hz, 1 H), 7.44 (t, ^3J = 7.4 Hz, 2 H), 7.51 (t, ^3J = 7.3 Hz, 1 H), 7.59 (t, ^3J = 7.5 Hz, 2 H), 7.81 (d, ^3J = 7.1 Hz, 2 H), 7.86 (d, ^3J = 7.1 Hz, 2 H), 8.22 (s, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 39.1 (CH_3), 103.0 (CH), 120.1 (CH), 120.8 (CH), 125.8 (CH), 128.2 (CH), 129.4 (CH), 130.1 (CH), 132.5 (C_{quat}), 134.5 (C_{quat}), 136.8 (C_{quat}), 139.4 (C_{quat}), 150.5 (C_{quat}). MS (EI) *m*/*z* (%): 301 ([M]$^+$, 29), 273 (100), 230 (71), 202 (13), 196 (10), 169 (17), 142 (16), 127 (16), 77 (23), 51 (11). IR (ATR): $\tilde{\nu}$ 3111, 3063, 2941, 2860, 1892, 1599, 1495, 1450, 1439, 1368, 808, 758, 738 cm^{-1}. Anal. Calcd for $C_{18}H_{15}N_5$ (301.13): C 71.74, H 5.02, N 23.24. Found: C 71.69, H 5.00, N 23.25.

*1-(4-Methoxyphenyl)-4-(1-methyl-3-phenyl-1H-pyrazol-5-yl)-1H-1,2,3-triazole (**1m**).* According to GP2, 101 mg (54%) of **1m** was obtained as a colorless solid after purification by flash chromatography (*n*-hexane/acetone 3:1). Mp 158−159 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.88 (s, 3 H), 4.27 (s, 3 H), 6.81 (s, 1 H), 7.05 (d, ^3J = 9.0 Hz, 2 H), 7.31 (t, ^3J = 7.3 Hz, 1 H), 7.41 (t, ^3J = 7.4 Hz, 2 H), 7.68 (d, ^3J = 9.1 Hz, 2 H), 7.83 (d, ^3J = 7.0 Hz, 2 H), 8.10 (s, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 39.1 (CH_3), 55.8 (CH_3), 102.9 (CH), 115.0 (CH), 120.1 (CH), 122.4 (CH), 125.7 (CH), 127.9 (CH), 128.8 (CH), 130.1 (C_{quat}), 133.2 (C_{quat}), 134.3 (C_{quat}), 139.4 (C_{quat}), 150.7 (C_{quat}), 160.3 (C_{quat}). MS (EI) *m*/*z* (%): 331 ([M]$^+$, 8), 303 (100), 288 (26), 260 (20), 217 (11), 169 (12), 127 (19), 77 (11). IR (ATR): $\tilde{\nu}$ 3123, 3080, 3061, 2976, 2938, 2901, 2841, 1609, 1516, 1447, 1418, 1358, 821, 800, 768, 741 cm^{-1}. Anal. Calcd for $C_{19}H_{17}N_5O$ (331.14): C 68.87, H 5.17, N 21.13. Found: C 68.82, H 5.12, N 21.12.

*1-(4-Bromophenyl)-4-(1-methyl-3-phenyl-1H-pyrazol-5-yl)-1H-1,2,3-triazole (**1n**).* According to GP2, 110 mg (52%) of **1n** was obtained as a colorless solid after purification by flash chromatography (*n*-hexane/acetone 3:1). Mp 144−145 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.27 (s, 3 H), 6.82 (s, 1H), 7.32 (t, ^3J = 7.3 Hz, 1 H), 7.42 (t, ^3J = 7.4 Hz, 2 H), 7.68−7.72 (m, 4 H), 7.83 (d, ^3J = 7.1 Hz, 2 H), 8.16 (s, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 39.2 (CH_3), 103.1 (CH), 119.7 (CH), 122.1 (CH), 123.1 (CH), 125.7 (CH), 128.0 (CH), 128.8 (CH), 133.1 (C_{quat}), 133.2 (C_{quat}), 133.9 (C_{quat}), 135.7 (C_{quat}), 139.9 (C_{quat}), 150.8 (C_{quat}). MS (EI) *m*/*z* (%): 381 ([^{81}Br − M]$^+$, 7), 379 ([^{79}Br − M]$^+$, 7), 353 (9), 351 (9), 332 (18), 272 (100), 229 (10), 169 (13), 127 (13), 77 (8). IR (ATR): $\tilde{\nu}$ 2961, 2934, 2862, 1603, 1510, 1456, 1427, 1366, 827, 816, 800, 779, 756, 725 cm^{-1}. Anal. Calcd for $C_{18}H_{14}BrN_5$ (379.04): C 56.86, H 3.71, N 18.42. Found: C 56.91, H 3.85, N 18.40.

*3-(4-(1-Methyl-3-phenyl-1H-pyrazol-5-yl)-1H-1,2,3-triazol-1-yl)-pyridine (**1o**).* According to GP2, 110 mg (52%) of **1o** was obtained as a colorless solid after purification by flash chromatography (*n*-hexane/acetone 2:1). Mp 140−142 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 4.27 (s, 3 H), 6.83 (s, 1 H), 7.31 (t, ^3J = 7.4 Hz, 1 H), 7.40 (t, ^3J = 7.7 Hz, 2 H), 7.62 (s_{br}, 1 H), 7.82 (d, ^3J = 7.1 Hz, 2 H), 8.20 (d, ^3J = 8.2 Hz, 1 H), 8.23 (s, 1 H), 8.45−9.95 (m_{br}, 2 H). ^{13}C NMR ($CDCl_3$, 151 MHz): δ 38.2 (CH_3), 103.2 (CH), 119.7 (CH), 125.6 (CH), 128.0 (CH), 128.2 (C_{quat}), 128.8 (CH), 133.1 (C_{quat}), 133.7 (C_{quat}), 140.1 (C_{quat}), 150.8 (C_{quat}). MS (EI) *m*/*z* (%): 302 ([M]$^+$, 35), 273 (100), 246 (13), 231 (14), 196 (11), 171 (13), 144 (56), 127 (12), 78 (10), 77 (11), 51 (10). IR (ATR): $\tilde{\nu}$ 3156, 3098, 3057, 3038, 2997, 2943, 1585, 1483, 1437, 1391, 1364, 862, 84), 806, 772, 741 cm^{-1}. Anal. Calcd for $C_{17}H_{14}N_6$ (302.13): C 67.54, H 4.67, N 27.80. Found: C 67.42, H 4.60, N 27.51.

General Procedure (GP3) for the Synthesis of Compounds 1a, 1p, and 1q. Bis(triphenylphosphine)palladium(II) dichloride (7.0 mg, 10 μmol, 2.0 mol %) and CuI (4.8 mg, 25 μmol, 5.0 mol %) were placed in a flame-dried 10 mL microwave tube under argon, and the vial was evacuated and flushed with argon three times. 1,4-Dioxane (1 mL), (buta-1,3-diyn-1-yl)tris(propan-2-yl)silane (**7**) (124 mg, 0.60 mmol, 1.20 equiv), and benzoyl chloride (**8a**) (70 mg, 0.50 mmol, 1.00 equiv) were added successively. The solution was degassed with argon for 5 min before triethylamine (73 μL, 0.53 mmol, 1.05 equiv) was added. The reaction mixture was stirred at room temp to complete conversion (1 h, monitored by TLC). Then, methylhydrazine (**6a**) (25 mg, 0.54 mmol, 1.1 equiv) and methanol (0.5 mL) were added before the mixture was heated under microwave irradiation to 150 °C for 30 min. After cooling to room temp, a solution of tetrabutylammonium fluoride in 1,4-dioxane (1 M, 0.70 mmol, 1.40 equiv) was added; the reaction mixture was stirred at room temp for 5 min before halide **9** (0.60 mmol, 1.20 equiv), cesium azide (105 mg, 0.60 mmol, 1.20 equiv), and sodium ascorbate (9.90 mg, 0.05 mmol, 10 mol %) were successively added to the reaction mixture, and stirring at room temp to complete conversion (67−71 h) was continued. The crude product was adsorbed on Celite, and the purification was performed using a flash purification system (*n*-hexane/acetone).

*1-Benzyl-4-(1-methyl-3-phenyl-1H-pyrazol-5-yl)-1H-1,2,3-triazole (**1a**).* According to GP3, 75 mg (49%) of **1a** was obtained with 102 mg of benzyl bromide (**9a**, 0.60 mmol, 1.2 equiv) as a colorless solid after purification by flash chromatography (*n*-hexane/acetone 4:1). Mp 158−159 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.21 (s, 3 H), 5.59 (s, 2 H), 6.70 (s, 1 H), 7.28−7.42 (m, 8 H), 7.65 (s, 1 H), 7.79 (d, ^3J = 7.1 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 39.0 (CH_3), 54.5 (CH_2), 102.7 (CH), 121.7 (CH), 125.6 (CH), 127.8 (CH), 128.3 (CH), 128.7 (CH), 129.2 (CH), 129.4 (CH), 133.2 (C_{quat}), 134.3 (C_{quat}), 134.5 (C_{quat}), 139.4 (C_{quat}), 150.6 (C_{quat}). MS (EI) *m*/*z* (%): 315 ([M]$^+$, 100), 287 (51), 259 (29), 196 (29), 183 (50), 156 (12), 91 (52), 66 (12).

*1-(4-Methoxybenzyl)-4-(1-methyl-3-phenyl-1H-pyrazol-5-yl)-1H-1,2,3-triazole (**1p**).* According to GP3, 105 mg (62%) of **1p** was obtained with 97.0 mg of 4-methoxybenzyl chloride (**9b**, 0.62 mmol, 1.2 equiv) as a yellow oil after purification by flash chromatography (*n*-hexane/acetone 3:1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.81 (s, 3 H), 4.20 (s, 3 H), 5.51 (s, 2 H), 6.68 (s, 1 H), 6.93 (d, ^3J = 8.7 Hz, 2 H), 7.26−7.31 (m, 3 H), 7.35−7.41 (m, 2 H), 7.62 (s, 1 H), 7.76−7.80 (m, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 39.0 (CH_3), 54.0 (CH_2), 55.5 (CH_3), 102.7 (CH), 114.7 (CH), 121.5 (CH), 125.6 (CH), 126.2 (C_{quat}), 127.8 (CH), 128.7 (CH), 129.9 (CH), 133.3 (C_{quat}), 134.5 (C_{quat}), 139.2 (C_{quat}), 150.6 (C_{quat}), 160.2 (C_{quat}). MS (EI) *m*/*z* (%): 345 ([M]$^+$, 90), 317 (28), 302 (16), 289 (20), 213 (19), 196 (26), 121 (100), 105 (20), 91 (12), 77 (24). IR (ATR): $\tilde{\nu}$ 3127, 3065, 3038, 2999, 2940, 2911, 2864, 2835, 1611, 1585, 1512, 1493, 1456, 1433, 1362847, 824, 800, 766, 735 cm^{-1}. HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{20}H_{20}N_5O$ 346.1666; found 346.1662.

*4-(1-Methyl-3-phenyl-1H-pyrazol-5-yl)-1-(1-phenylethyl)-1H-1,2,3-triazole (**1q**).* According to GP3, 81 mg (50%) of **1q** was obtained with 112 mg of 4-methoxybenzyl chloride (**9c**, 0.61 mmol, 1.2 equiv) as a colorless solid after purification by flash chromatography (*n*-hexane/acetone 3:1). Mp 100−101 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.06 (d, ^3J = 7.0 Hz, 3 H), 4.23 (s, 3 H), 5.88 (q, ^3J = 7.1 Hz, 1 H), 6.69 (s, 1 H), 7.29−7.44 (m, 8 H), 7.63 (s, 1 H), 7.79 (d, ^3J = 7.2 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.5 (CH_3), 39.1 (CH_3), 60.7 (CH), 102.7 (CH), 120.8 (CH), 125.6 (CH), 126.7 (CH), 127.8 (CH), 128.8 (CH), 129.0 (CH), 129.3 (CH), 133.2 (C_{quat}), 134.6 (C_{quat}), 139.0 (C_{quat}), 139.6 (C_{quat}), 150.6 (C_{quat}). MS (EI) *m*/*z* (%): 329 ([M]$^+$, 100), 301 (25), 286 (51), 259 (12), 196 (62), 183 (34), 170 (11), 105 (43), 103 (16), 79 (16), 77 (21), 66 (15). IR (ATR): $\tilde{\nu}$ 3144, 3125, 3034, 2980, 2935, 2879, 1497, 1472, 1441, 1383, 831, 808, 772, 746 cm^{-1}. Anal. Calcd for $C_{20}H_{19}N_5$ (329.16): C 72.92, H 5.81, N 21.26. Found: C 72.80, H 5.89, N 21.11.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.8b00430.

NMR spectra of compounds of **1**, **5** and **7** (PDF)

Crystallographic data of compound **1a** (CIF)

DOI: 10.1021/acs.joc.8b00430
J. Org. Chem. 2018, 83, 4851−4858

AUTHOR INFORMATION

Corresponding Author

*E-mail: ThomasJJ.Mueller@hhu.de.

ORCID

Christoph Janiak: 0000-0002-6288-9605

Thomas J. J. Müller: 0000-0001-9809-724X

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We cordially thank Fonds der Chemischen Industrie for the financial support.

DEDICATION

Dedicated to Prof. Dr. Dr. h.c. Helmut Ritter on the occasion of his 70th birthday.

REFERENCES

(1) For example reviews and synthesis and relevance of 1,2,3-triazoles, see: (a) Kolb, H. C.; Sharpless, K. B. The growing impact of click chemistry on drug discovery. *Drug Discovery Today* **2003**, *8*, 1128−1137. (b) Horne, W. S.; Stout, C. D.; Ghadiri, M. R. A Heterocyclic Peptide Nanotube. *J. Am. Chem. Soc.* **2003**, *125*, 9372−9376. (c) Horne, W. S.; Yadav, M. K.; Stout, C. D.; Ghadiri, M. R. Heterocyclic Peptide Backbone Modifications in an α-Helical Coiled Coil. *J. Am. Chem. Soc.* **2004**, *126*, 15366−15367. (d) Tron, G. C.; Pirali, T.; Billington, R. A.; Canonico, P. L.; Sorba, G.; Genazzani, A. A. Click chemistry reactions in medicinal chemistry: Applications of the 1,3-dipolar cycloaddition between azides and alkynes. *Med. Res. Rev.* **2008**, *28*, 278−308. (e) Liang, L.; Astruc, D. The copper(I)-catalyzed alkyne-azide cycloaddition (CuAAC) "click" reaction and its applications. An overview. *Coord. Chem. Rev.* **2011**, *255*, 2933−2945. (f) Kappe, C. O.; Van der Eycken, E. Click chemistry under non-classical reaction conditions. *Chem. Soc. Rev.* **2010**, *39*, 1280−1290. (g) Meldal, M.; Tornøe, C. W. Cu-Catalyzed Azide−Alkyne Cycloaddition. *Chem. Rev.* **2008**, *108*, 2952−3015. (h) Hein, J. E.; Fokin, V. V. Copper-catalyzed azide−alkyne cycloaddition (CuAAC) and beyond: new reactivity of copper(I) acetylides. *Chem. Soc. Rev.* **2010**, *39*, 1302−1315. (i) Chen, Z.; Liu, Z.; Cao, G.; Li, H.; Ren, H. Recent Advances in Multicomponent Synthesis of 1,4,5-Trisubstituted 1,2,3-Triazoles. *Adv. Synth. Catal.* **2017**, *359*, 202−224.

(2) For example reviews, see: (a) Agalave, S. G.; Maujan, S. R.; Pore, V. S. Click Chemistry: 1,2,3-Triazoles as Pharmacophores. *Chem. - Asian J.* **2011**, *6*, 2696−2718. (b) Kacprzak, K.; Skiera, I.; Piasecka, M.; Paryzek, Z. Alkaloids and Isoprenoids Modification by Copper(I)-Catalyzed Huisgen 1,3-Dipolar Cycloaddition (Click Chemistry): Toward New Functions and Molecular Architectures. *Chem. Rev.* **2016**, *116*, 5689−5743. (c) Dheer, D.; Singh, V.; Shankar, R. Medicinal attributes of 1,2,3-triazoles: Current developments. *Bioorg. Chem.* **2017**, *71*, 30−54.

(3) For example reviews, see: (a) Sokolova, N. V.; Nenajdenko, V. G. Recent advances in the Cu(I)-catalyzed azide−alkyne cycloaddition: focus on functionally substituted azides and alkynes. *RSC Adv.* **2013**, *3*, 16212−16242. (b) Ziarani, G. M.; Hassanzadeh, Z.; Gholamzadeh, P.; Asadi, S.; Badiei, A. Advances in click chemistry for silica-based material construction. *RSC Adv.* **2016**, *6*, 21979−22006. (c) Tiwari, V. K.; Mishra, B. B.; Mishra, K. B.; Mishra, N.; Singh, A. S.; Chen, X. Cu-Catalyzed Click Reaction in Carbohydrate Chemistry. *Chem. Rev.* **2016**, *116*, 3086−3240.

(4) For example reviews, see: (a) Khan, M. F.; Alam, M. M.; Verma, G.; Akhtar, W.; Akhter, M.; Shaquiquzzaman, M. The therapeutic voyage of pyrazole and its analogs: A review. *Eur. J. Med. Chem.* **2016**, *120*, 170−201. (b) Xu, Z.; Gao, C.; Ren, Q.-C.; Song, X.-F.; Feng, L.-S.; Lv, Z.-S. Recent advances of pyrazole-containing derivatives as anti-tubercular agents. *Eur. J. Med. Chem.* **2017**, *139*, 429−440.

(5) For example reviews, see: (a) Küçükgüzel, Ş. G.; Şenkardeş, S. Recent advances in bioactive pyrazoles. *Eur. J. Med. Chem.* **2015**, *97*, 786−815. (b) Faria, J. V.; Vegi, P. F.; Miguita, A. G. C.; dos Santos, M. S.; Boechat, N.; Bernardino, A. M. R. Recently reported biological activities of pyrazole compounds. *Bioorg. Med. Chem.* **2017**, *25*, 5891−5903.

(6) For example reviews, see: (a) Mukherjee, R. Coordination chemistry with pyrazole-based chelating ligands: molecular structural aspects. *Coord. Chem. Rev.* **2000**, *203*, 151−218. (b) Ward, M. D.; McCleverty, J. A.; Jeffery, J. C. Coordination and supramolecular chemistry of multinucleating ligands containing two or more pyrazolyl-pyridine 'arms'. *Coord. Chem. Rev.* **2001**, *222*, 251−272. (c) Trofimenko, S. Coordination chemistry of pyrazole-derived ligands. *Chem. Rev.* **1972**, *72*, 497−509. (d) Doidge, E. D.; Roebuck, J. W.; Healy, M. R.; Tasker, P. A. Phenolic pyrazoles: Versatile polynucleating ligands. *Coord. Chem. Rev.* **2015**, *288*, 98−117.

(7) For example reviews, see: (a) Kumar, V.; Kaur, K.; Gupta, G. K.; Sharma, A. K. Pyrazole containing natural products: Synthetic preview and biological significance. *Eur. J. Med. Chem.* **2013**, *69*, 735−753. (b) Schmidt, A.; Dreger, A. Recent Advances in the Chemistry of Pyrazoles. Properties, Biological Activities, and Syntheses. *Curr. Org. Chem.* **2011**, *15*, 1423−1463.

(8) For representative examples, see: (a) Gemming, S.; Schreiber, M.; Thiel, W.; Heine, T.; Seifert, G.; Avelino de Abreu, H.; Anderson Duarte, H. Tunable discotic building blocks for liquid crystalline displays. *J. Lumin.* **2004**, *108*, 143−147. (b) Sachse, A.; Penkova, L.; Noël, G.; Dechert, S.; Varzatskii, O. A.; Fritsky, I. O.; Meyer, F. Efficient Syntheses of Some Versatile 3,5-Bifunctional Pyrazole Building Blocks. *Synthesis* **2008**, *2008*, 800−806. (c) Maeda, H.; Ito, Y.; Kusunose, Y.; Nakanishi, T. Dipyrrolylpyrazoles: anion receptors in protonated form and efficient building blocks for organized structures. *Chem. Commun.* **2007**, 1136−1138.

(9) Dorlars, A.; Schellhammer, C.-W.; Schroeder, J. Heterocycles as Structural Units in New Optical Brighteners. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 665−679.

(10) Catalan, J.; Fabero, F.; Claramunt, R. M.; Santa Maria, M. D.; Foces-Foces, M. d. l. C.; Hernandez Cano, F.; Martinez-Ripoll, M.; Elguero, J.; Sastre, R. New ultraviolet stabilizers: 3- and 5-(2′-hydroxyphenyl)pyrazoles. *J. Am. Chem. Soc.* **1992**, *114*, 5039−5048.

(11) Götzinger, A. C.; Theßeling, F. A.; Hoppe, C.; Müller, T. J. J. One-Pot Coupling−Coupling−Cyclocondensation Synthesis of Fluorescent Pyrazoles. *J. Org. Chem.* **2016**, *81*, 10328−10338.

(12) (a) Yen, Y.-P.; Huang, T.-M.; Tseng, Y.-P.; Lin, H.-Y.; Lai, C.-C. Photoinduced Electron Transfer Reactions of 3,3-Dialkylated 4,5-Diphenyl-3H-Pyrazoles: A New Route to the Formation of the Solvent Adducts. *J. Chin. Chem. Soc.* **2004**, *51*, 393−398. (b) Karatsu, T.; Shiochi, N.; Aono, T.; Miyagawa, N.; Kitamura, A. Photoinduced Electron Transfer Reactions of 3H-Pyrazole Derivatives. Formation of Solvent Adduct by Specific Sensitizer. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 1227−1231.

(13) For example reviews, see: (a) Fustero, S.; Sánchez-Roselló, M.; Barrio, P.; Simón-Fuentes, A. From 2000 to Mid-2010: A Fruitful Decade for the Synthesis of Pyrazoles. *Chem. Rev.* **2011**, *111*, 6984−7034. (b) Giornal, F.; Pazenok, S.; Rodefeld, L.; Lui, N.; Vors, J.-P.; Leroux, F. R. Synthesis of diversely fluorinated pyrazoles as novel active agrochemical ingredients. *J. Fluorine Chem.* **2013**, *152*, 2−11.

(14) Manfredini, S.; Beatrice Vicentini, C.; Manfrini, M.; Bianchi, N.; Rutigliano, C.; Mischiati, C.; Gambari, R. Pyrazolo-triazoles as light activable dna cleaving agents. *Bioorg. Med. Chem.* **2000**, *8*, 2343−2346.

(15) (a) Dorokhov, V. A.; Komkov, A. V. Addition of acetylacetone and ethyl acetoacetate to carbodiimides promoted by nickel acetylacetonate. *Russ. Chem. Bull.* **2004**, *53*, 676−680. (b) Stevens, E. P.; Roque, D. R.; Neill, J. L.; Antoon, J. W. Synthesis of 1,2,3-Triazoles by Cycloadditions of Azides with Enol Ethers. *Synthesis* **2005**, *2005*, 2497−2502. (c) Smith, C. D.; Tchabanenko, K.; Adlington, R. M.; Baldwin, J. E. Synthesis of linked heterocycles via use of bis-acetylenic compounds. *Tetrahedron Lett.* **2006**, *47*, 3209−3212. (d) Ferreira, J. P. A.; Silva, V. L. M.; Elguero, J.; Silva, A. M. S.

DOI: 10.1021/acs.joc.8b00430
J. Org. Chem. 2018, 83, 4851−4858

Synthesis of new pyrazole-1,2,3-triazole dyads. *Tetrahedron Lett.* **2013**, *54*, 5391−5394.
(16) D'Souza, D. M.; Müller, T. J. J. Multi-component syntheses of heterocycles by transition-metal catalysis. *Chem. Soc. Rev.* **2007**, *36*, 1095−1108.
(17) For recent reviews, see: (a) Levi, L.; Müller, T. J. J. Multicomponent syntheses of functional chromophores. *Chem. Soc. Rev.* **2016**, *45*, 2825−2846. (b) Levi, L.; Müller, T. J. J. Multicomponent Syntheses of Fluorophores Initiated by Metal Catalysis. *Eur. J. Org. Chem.* **2016**, *47*, 2907−2918.
(18) For example reviews, see: (a) Willy, B.; Müller, T. J. J. Multicomponent Heterocycle Syntheses via Catalytic Generation of Alkynones. *Curr. Org. Chem.* **2009**, *13*, 1777−1790. (b) Gers-Panther, C. F.; Müller, T. J. J. Multicomponent Syntheses of Heterocycles Initiated by Catalytic Generation of Ynones and Ynediones. *Adv. Heterocycl. Chem.* **2016**, *120*, 67−98.
(19) Hassan, S.; Müller, T. J. J. Multicomponent Syntheses based upon Copper-Catalyzed Alkyne-Azide Cycloaddition. *Adv. Synth. Catal.* **2015**, *357*, 617−666.
(20) For instructive reviews on sequentially catalyzed processes, see: (a) Fogg, D. E.; dos Santos, E. N. Tandem catalysis: a taxonomy and illustrative review. *Coord. Chem. Rev.* **2004**, *248*, 2365−2379. (b) Wasilke, J.-C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. Concurrent Tandem Catalysis. *Chem. Rev.* **2005**, *105*, 1001−1020. (c) Ajamian, A.; Gleason, J. L. Two Birds with One Metallic Stone: Single-Pot Catalysis of Fundamentally Different Transformations. *Angew. Chem., Int. Ed.* **2004**, *43*, 3754−3760. (d) Lessing, T.; Müller, T. J. J. Sequentially Palladium-Catalyzed Processes in One-Pot Syntheses of Heterocycles. *Appl. Sci.* **2015**, *5*, 1803−1836.
(21) (a) Karpov, A. S.; Müller, T. J. J. New Entry to a Three-Component Pyrimidine Synthesis by TMS−Ynones via Sonogashira Coupling. *Org. Lett.* **2003**, *5*, 3451−3454. (b) D'Souza, D. M.; Müller, T. J. J. Catalytic alkynone generation by Sonogashira reaction and its application in three-component pyrimidine synthesis. *Nat. Protoc.* **2008**, *3*, 1660−1665.
(22) For representative examples, see: (a) Trost, B. M.; Quintard, A. Asymmetric Catalytic Alkynylation of Acetaldehyde: Application to the Synthesis of (+)-Tetrahydropyrenophorol. *Angew. Chem., Int. Ed.* **2012**, *51*, 6704−6708. (b) Ungeheuer, F.; Fürstner, A. Concise Total Synthesis of Ivorenolide B. *Chem. - Eur. J.* **2015**, *21*, 11387−11392. (c) Wang, L.; Shou, P. P.; Wei, S. P.; Zhang, C.; Li, S. X.; Liu, P. X.; Du, X.; Wang, Q. Total Synthesis of Chiral Falcarindiol Analogues Using BINOL-Promoted Alkyne Addition to Aldehydes. *Molecules* **2016**, *21*, 112. (d) Trost, B. M.; Chan, V. S.; Yamamoto, D. Enantioselective ProPhenol-Catalyzed Addition of 1,3-Diynes to Aldehydes to Generate Synthetically Versatile Building Blocks and Diyne Natural Products. *J. Am. Chem. Soc.* **2010**, *132*, 5186−5192.
(23) For recent representative examples, see: (a) Farha, O. K.; Wilmer, C. E.; Eryazici, I.; Hauser, B. G.; Parilla, P. A.; O'Neill, K.; Sarjeant, A. A.; Nguyen, S. T.; Snurr, R. Q.; Hupp, J. T. Designing Higher Surface Area Metal−Organic Frameworks: Are Triple Bonds Better Than Phenyls? *J. Am. Chem. Soc.* **2012**, *134*, 9860−9863. (b) Gulcur, M.; Moreno-Garcia, P.; Zhao, X.; Baghernejad, M.; Batsanov, A. S.; Hong, W.; Bryce, M. R.; Wandlowski, T. The Synthesis of Functionalised Diaryltetraynes and Their Transport Properties in Single-Molecule Junctions. *Chem. - Eur. J.* **2014**, *20*, 4653−4660. (c) Pigulski, B.; Arendt, A.; Tomilin, D. N.; Sobenina, L. N.; Trofimov, B. A.; Szafert, S. Transition-Metal Free Mechanochemical Approach to Polyyne Substituted Pyrroles. *J. Org. Chem.* **2016**, *81*, 9188−9198. (d) Desroches, M.; Courtemanche, M. A.; Rioux, G.; Morin, J. F. Synthesis and Properties of Rhomboidal Macrocyclic Subunits of Graphdiyne-Like Nanoribbons. *J. Org. Chem.* **2015**, *80*, 10634−10642.
(24) Valverde, I. E.; Delmas, A. F.; Aucagne, V. Click à la carte: robust semi-orthogonal alkyne protecting groups for multiple successive azide/alkyne cycloadditions. *Tetrahedron* **2009**, *65*, 7597−7602.
(25) Doak, B. C.; Scanlon, M. J.; Simpson, J. S. Synthesis of Unsymmetrical 1,1′-Disubstituted Bis(1,2,3-triazole)s Using Monosilylbutadiynes. *Org. Lett.* **2011**, *13*, 537−539.
(26) Kazem Shiroodi, R.; Soltani, M.; Gevorgyan, V. Gold-Catalyzed 1,3-Transposition of Ynones. *J. Am. Chem. Soc.* **2014**, *136*, 9882−9885.
(27) (a) Willy, B.; Müller, T. J. J. Regioselective Three-Component Synthesis of Highly Fluorescent 1,3,5-Trisubstituted Pyrazoles. *Eur. J. Org. Chem.* **2008**, *2008*, 4157−4168. (b) Willy, B.; Müller, T. J. J. Rapid One-Pot, Four-Step Synthesis of Highly Fluorescent 1,3,4,5-Tetrasubstituted Pyrazoles. *Org. Lett.* **2011**, *13*, 2082−2085.
(28) Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 1570646 (**1a**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: + 44−1223/336−033; e-mail: deposit@ccdc.cam.ac.uk).
(29) Maury, J.; Feray, L.; Bertrand, M. P.; Kapat, A.; Renaud, P. Unexpected conversion of alkyl azides to alkyl iodides and of aryl azides to *N*-*tert*-butyl anilines. *Tetrahedron* **2012**, *68*, 9606−9611.
(30) Smith, P. A. S.; Brown, B. B. The Reaction of Aryl Azides with Hydrogen Halides. *J. Am. Chem. Soc.* **1951**, *73*, 2438−2441.
(31) Turlington, M.; Du, Y.; Ostrum, S. G.; Santosh, V.; Wren, K.; Lin, T.; Sabat, M.; Pu, L. From Highly Enantioselective Catalytic Reaction of 1,3-Diynes with Aldehydes to Facile Asymmetric Synthesis of Polycyclic Compounds. *J. Am. Chem. Soc.* **2011**, *133*, 11780−11794.

DOI: 10.1021/acs.joc.8b00430
J. Org. Chem. 2018, 83, 4851−4858