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Rapid assembly of 3-azidomethylfurans from 2-(1-alkynyl)-2-alken-1-ones enabled by silver catalysis

Lei-Lei Qian [a, b, 1], Ruxia Yi [a, 1], Xiang-Ting Min [a, b], Yan-Cheng Hu [a], Boshun Wan [a, **], Qing-An Chen [a, *]

[a] Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian, 116023, China
[b] University of Chinese Academy of Sciences, Beijing, 100049, China

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ABSTRACT

A rapid access to useful 3-azidomethylfurans is developed via Ag(I)-catalyzed cascade annulation/azidation of 2-(1-alkynyl)-2-alken-1-ones. The salient features of the protocol include mild reaction conditions, high efficiency, broad substrate scope, and easy scale-up. The formed azide group on the products could easily undergo further elaborations such as click cycloaddition and reduction.

1. Introduction

The furan derivatives are not only core structures in many natural products, but also important building blocks in organic synthesis [1–11]. Among them, 3-azidomethylfurans, featuring a combination of azide group and furan skeleton, are of particular interests [12–14]. Because the azide group can easily undergo diverse transformations that rapidly elaborate other complex furan-based heterocycles. For example, they are key intermediates in the total synthesis of naturally occurring alkaloid stemocurtisine [15], and also serve as precursors to prepare some bioactive molecules such as α-furanoltriazole [16–18] and furan-based G-quadruplex ligands [19–21] (Scheme 1). The known methods towards the synthesis of 3-azidomethylfurans generally rely on the azidation of pre-synthesized functionalized furan substrates, for example, nucleophilic substitution of 3-halidemethyl furans and Lewis acid promoted ring-opening of 3-oxiranefurans (Scheme 2, a, b) [22–25]. However, such furan precursors also require additional multi-step synthesis. Therefore, developing an efficient catalytic protocol that features the construction of the furan ring and the introduction of azide group in one step, would be highly appealing yet remains rare [26–29].

In recent years, the annulation of 2-(1-alkynyl)-2-alkenyl-1-ones has emerged as a versatile paradigm for the rapid assembly of furan skeletons [30–43]. Nevertheless, one-step synthesis of 3-azidomethylfurans from 2-(1-alkynyl)-2-alkenyl-1-ones still remains underexploited. In this context, we envisaged that commercially available $TMSN_3$ possibly serves as a nucleophile to incorporate with the annulation of 2-(1-alkynyl)-2-alkenyl-1-ones, resulting in the formation of 3-azidomethylfurans (Scheme 2, c). Herein, we successfully realized this goal via silver catalysis.

2. Results and discussion

Our investigation commenced with optimization of the reaction conditions by using the easily prepared reactant (*E*)-3-benzylidene-5-phenylpent-4-yn-2-one (**1a**) as the model substrate. When $AgSbF_6$ (10 mol%) was employed as the catalyst, the reaction of **1a** with $TMSN_3$ (1.5 equiv) could take place in DCE at 80 °C, affording the desired product 3-(azidomethyl)-2-methyl-5-phenylfuran **2a** in 29% yield (Table 1, entry 1). The structure of **2a** was confirmed by ^1H and ^{13}C NMR and HRMS. The addition of H_2O and HOAc as the

* Corresponding author.
** Corresponding author.
E-mail addresses: bswan@dicp.ac.cn (B. Wan), qachen@dicp.ac.cn (Q.-A. Chen).
[1] These authors contributed equally to this work.

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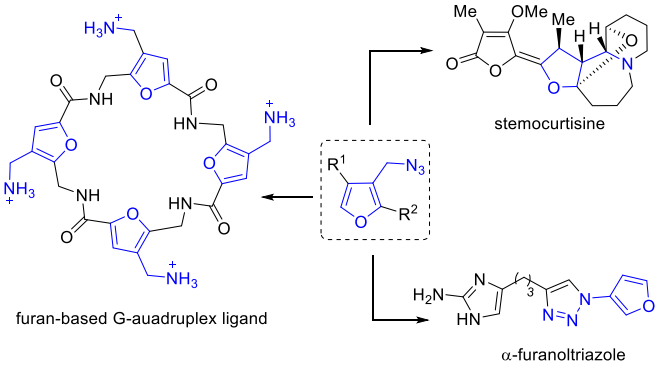
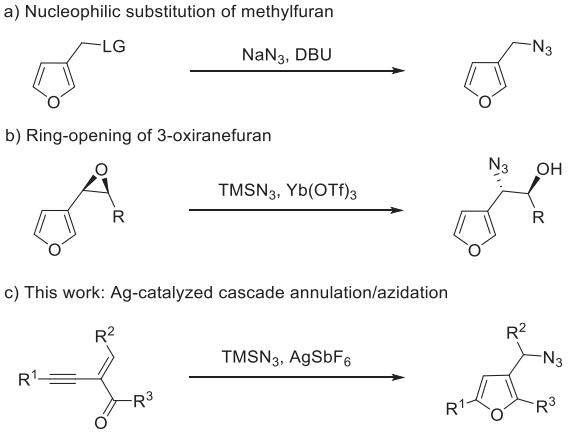


Scheme 1. Application of 3-azidomethylfuran.

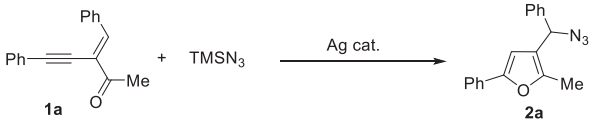


Scheme 2. Approaches for the synthesis of 3-(azidomethyl)furan.

additive led an significant improvement on yields (entries 2–3). However, no desired product was observed in the presence of stronger acid TfOH (entry 4). On the basis of this encouraging result, we then examined various reaction parameters such as solvents, silver catalysts, and temperatures. The yield of **2a** increased to 86% using toluene as the solvent (entry 8). AgOTf gave an inferior result, while other silver salts including $AgNTf_2$, AgOAc, and AgF were ineffective for this transformation (entries 11–14). Moreover, a nearly quantitative yield was obtained when lowering temperature to 40 °C (entries 15–17). A small decrease of the catalyst loading had minimal influence on the efficiency (entry 18). This reaction could also be carried out under air with a decreased yield (entry 19). Hence the optimized reaction conditions were determined as: **1a** (0.2 mmol), $TMSN_3$ (0.3 mmol), $AgSbF_6$ (0.01 mmol), HOAc (0.2 mmol), toluene (2.0 mL), at 40 °C under argon atmosphere.

With the optimal reaction conditions established, we directed our efforts to explore the substrate scope of the reaction. The results are summarized in Schemes 3 and 4. The substituents (R^1) on the alkyne terminus were first investigated. A broad range of aryl groups in R^1 were well compatible with the protocol, affording 3-(azidomethyl)furans **2b**–**2m** in 73–99% yields. The structure of **2d** was unambiguously assigned by a X-ray diffraction analysis. The electronic properties of the substituents on phenyl ring exerted no significant impact on the reaction outcome. In comparison, sterically hindered 2-Cl and 2-F substituted substrates could possibly impede the ring-closure step, thus leading to the corresponding products (**2b**, **2e**) in slightly decreased yields. The introduce of 1-Naphthyl in R^1 likely hampered the cyclization step, thus delivering the target product **2n** in a moderate yield. The alkyl

Table 1
Optimization of the reaction conditions.



Entry	Catalyst	Temperature (°C)	Solvent	Yield (%)[a]
1[b]	$AgSbF_6$	80	DCE	29
2[b,c]	$AgSbF_6$	80	DCE	48
3	$AgSbF_6$	80	DCE	54
4[b,d]	$AgSbF_6$	80	DCE	0
5	$AgSbF_6$	80	THF	35
6	$AgSbF_6$	80	DME	0
7	$AgSbF_6$	80	MeCN	42
8	$AgSbF_6$	80	toluene	86
9	$AgSbF_6$	80	MeOH	18
10	$AgSbF_6$	80	AcOH	55
11	AgOTf	80	toluene	68
12	$AgNTf_2$	80	toluene	0
13	AgOAc	80	toluene	0
14	AgF	80	toluene	0
15	$AgSbF_6$	60	toluene	93
16	$AgSbF_6$	40	toluene	99
17	$AgSbF_6$	25	toluene	90
18[e]	$AgSbF_6$	40	toluene	98[f]
19[g]	$AgSbF_6$	40	toluene	65

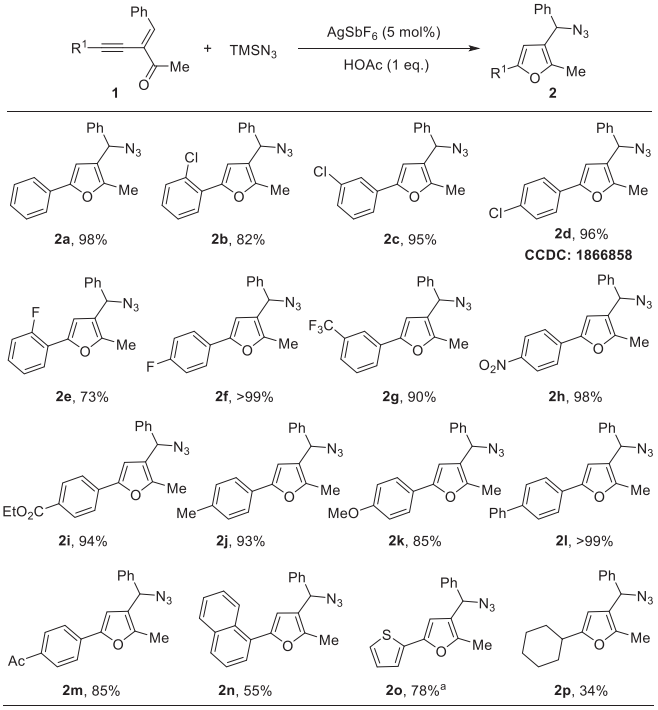
Reaction conditions: **1a** (0.20 mmol), $TMSN_3$ (0.30 mmol), catalyst (0.02 mmol), HOAc (0.20 mmol), solvent (2.0 mL), T °C, Ar, 10 h [a] Determined by ^1H NMR with 1,3,5-trimethoxybenzene as an internal standard. [b] No HOAc. [c] H_2O (2 eq.). [d] TfOH (1 eq.). [e] $AgSbF_6$ (0.01 mmol). [f] Isolated yield in 0.50 mmol scale. [g] air.

substituent, cyclohexyl for instance, was also amenable to the transformation, but gave a relatively low yield (**2p**). In the case of 2-thienyl derived substrate, the annulation failed under standard conditions, which was possibly ascribed to the strong coordination between the sulfur atom and the silver catalyst. However, using $Pd(OAc)_2$ as the catalyst, this expected reaction proceeded smoothly to deliver the product **2o** in 78% yield.

Subsequently, the scope of alkene and ketone terminus were examined (Scheme 4). The annulation of **1v** bearing electron-withdrawing group on the phenyl ring of alkene terminus R^2 furnished 3-azidomethylfuran **2v** in 73% yield. A variety of aryl groups in ketone terminus R^3 were suitable with the process as well, giving the desired products in moderate to good yields (**2q**–**2u**, 54%–92%). Remarkably, subjecting a cyclic substrate **1w** to the standard conditions also led to the formation of product **2w** in 82% yield [44].

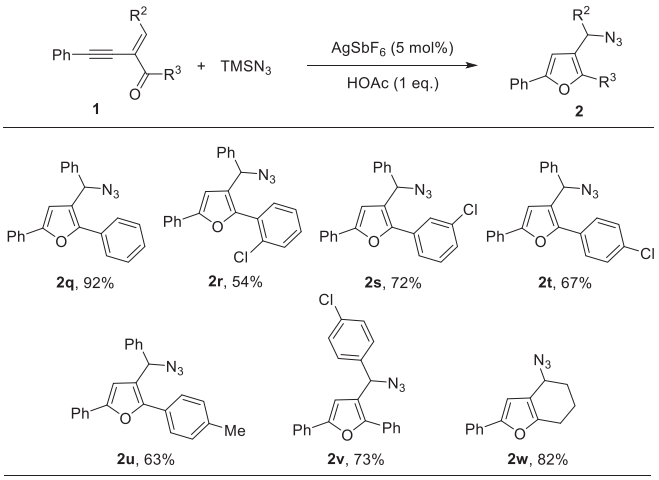
To illustrate the practicability of this approach, a gram-scale experiment was performed (Scheme 5). The annulation of 2-(1-alkynyl)-2-alken-1-one **1a** with $TMSN_3$ could be easily scaled up to 5.0 mmol without significant loss of the yield. Given the wide application of alkyl azides in organic synthesis, the synthetic elaborations of **2a** were further studied (Scheme 5). Cu-catalyzed click reaction of **2a** with phenylacetylene **3a** took place efficiently, affording triazole **4a** in 94% yield. The reduction of azide with $LiAlH_4$ formed the corresponding amine **5a** in a high yield.

On the basis of the previous reports [45,46], a plausible mechanism was proposed by using the reaction of (*E*)-3-benzylidene-5-phenylpent-4-yn-2-one (**1a**) as an example (Scheme 6). An initial coordination between the alkynyl moiety of **1a** and $AgSbF_6$ induces an intramolecular cyclization of the carbonyl group to afford carbocation **B**. Then nucleophilic addition of $TMSN_3$ to **B** gives intermediate **C**, followed by the protonation to furnish the product **2a** with the regeneration of silver catalyst.



Reaction conditions: **1** (0.50 mmol), $TMSN_3$ (0.75 mmol), $AgSbF_6$ (0.025 mmol), HOAc (0.50 mmol), toluene (5.0 mL), at 40 °C under argon atmosphere. Isolated yields are given. [a] $Pd(OAc)_2$ (0.05 mmol) were used.

Scheme 3. Substrate scope of the alkyne terminus.

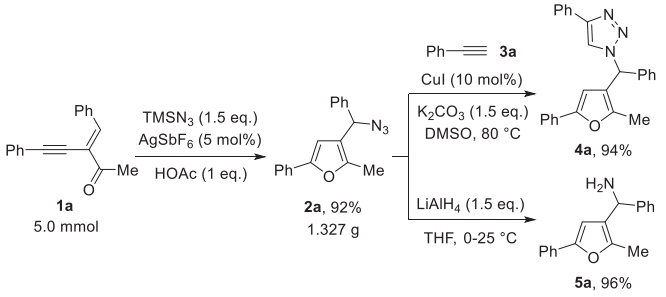


Reaction conditions: **1** (0.50 mmol), $TMSN_3$ (0.75 mmol), $AgSbF_6$ (0.025 mmol), HOAc (0.50 mmol), toluene (5.0 mL), at 40 °C under argon atmosphere. Isolated yields are given.

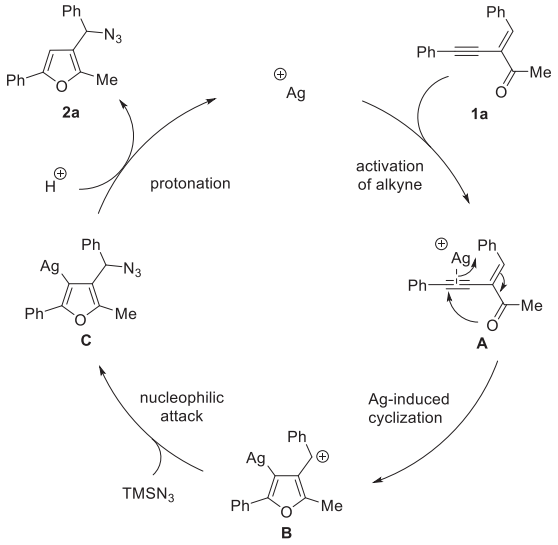
Scheme 4. Substrate scope of the alkene and ketone terminus.

3. Conclusion

In summary, we have developed a rapid access to 3-azidomethylfurans via Ag(I)-catalyzed cascade annulation/azidation of 2-(1-alkynyl)-2-alken-1-ones. This methodology features high efficiency, broad substrate scope, and mild reaction conditions, and its practicability is also highlighted by a gram-scale experiment. The facile synthetic elaborations of azide group, such as click cycloaddition and reduction reaction, would enable our work to find potential applications in the construction of other complex furan-based heterocycles.



Scheme 5. Gram-scale experiment and further derivatization.



Scheme 6. Proposed reaction mechanism.

4. Experimental section

4.1. General

Commercially available reagents were used without further purification. Solvents were treated prior to use according to the standard methods. All reactions were carried out under an atmosphere of argon using standard Schlenk techniques or in an argon-filled glove-box unless otherwise noted. Column chromatography was carried out on silica gel (300−400 mesh) using a forced flow of eluent at 0.3−0.5 bar pressure. For TLC, silica gel GF254 was used and visualized by fluorescence quenching under UV light. NMR Spectra were recorded on a Bruker 400 MHz NMR spectrometer in the solvents indicated. The chemical shifts for ^1H NMR were recorded in ppm downfield using the central peak of $CDCl_3$ (7.26 ppm) as the internal standard. The chemical shifts for ^{13}C NMR were recorded in ppm downfield using the central peak of $CDCl_3$ (77.16 ppm) as the internal standard. Coupling constants (J) are reported in Hz and refer to apparent peak multiplications.

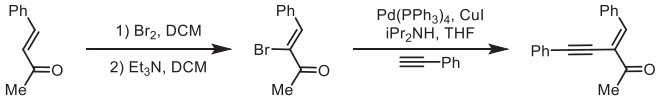
Although we have experienced no hazards during the course of this work, but all reactions with azides should be conducted behind a blast shield in a fume hood with care. Personal protective equipment must be worn, including a lab coat, safety glasses, and

gloves with adequate chemical resistance. Keep the hood clear of any unnecessary chemicals and equipment.

Organic azides are potentially explosive substances that can decompose with introduction of external energy (heat, light, pressure, etc). When affording new organic azides, we should keep in mind that the number of nitrogen atoms less than one third of the sum of number of carbon atoms and oxygen atoms ($N_C + N_O$)/$N_N \geq 3$.

The products 3-azidomethylfurans are very stable and can be stored at room temperature in air. Commercially available trimethylsilyl azide ($TMSN_3$) must be sealed and stored in refrigerator. Use of $TMSN_3$ should be performed in a fume hood since it is a flammable liquid with toxic properties with route of inhalation. Organic azide waste should be placed in a separate, explicitly-labeled container designated solely for azide waste.

4.2. General procedure for synthesis of 2-(1-alkynyl)-2-alken-1-ones (**1a**-**1w**) [47]



2-(1-Alkynyl)-2-alken-1-ones was prepared by a slightly modified procedure. Bromine (1.92 g, 12.0 mmol, 1.2 equiv.) was added dropwise to a solution of chalcone (10.0 mmol, 1.0 equiv.) in DCM (10 mL) at 0 °C. The mixture was stirred for 1 h at the same temperature before quenching by the addition of a saturated $Na_2S_2O_3$ solution (20 mL). The aqueous phase was separated and extracted with DCM (20 mL × 3). The organic phases were combined and washed with brine. After drying with $MgSO_4$, the solvent was removed under vacuum. The residue was dissolved in DCM (10 mL), then Et_3N (1.69 mL, 12.0 mmol, 1.2 equiv.) was added, and the mixture was heated at reflux for 1.5 h. After cooling to room temperature, the solvent was removed under vacuum and water (20 mL) was added. The aqueous phase was extracted with DCM (20 mL × 3). The organic phases were combined and washed with brine. After drying with $MgSO_4$, the solvent was removed under vacuum, and the crude product was purified by flash chromatography to give the 2-Br-2-alken-1-one. $Pd(Ph_3P)_4$ (577.8 mg, 0.50 mmol, 0.05 equiv.) and CuI (190.5 mg, 1.0 mmol, 0.1 equiv.) were added to a solution of 2-Br-2-alken-1-one (10.0 mmol, 1.0 equiv.) in THF (4.0 mL) and $^{i}Pr_2NH$ (4.20 mL, 30.0 mmol, 3.0 equiv.) under Ar at room temperature. Phenylacetylene (1.10 mL, 10.0 mmol, 1.2 equiv.) was added by syringe. The mixture was stirred for 2 h until TLC indicated completion of the reaction. The mixture was diluted with EtOAc (20 mL), washed with 1N HCl and brine, and dried with $MgSO_4$. After removing the solvent under vacuum, the crude product was purified by flash chromatography to give 2-(1-alkynyl)-2-alken-1-one as a yellow solid.

4.3. General procedure for synthesis of 3-azidomethylfurans (**2a**-**2w**)

Under an argon atmosphere, $TMSN_3$ (1.5 eq.) and HOAc (1.0 eq.) were added to a mixture of 2-(1-alkynyl)-2-alken-1-ones **1** (0.50 mmol) and $AgSbF_6$ (5 mol%) in a 15 mL Schlenk tube in toluene (5.0 mL). The mixture was stirred at 40 °C until the substrate **1** was consumed. The solvent was evaporated and the crude product was directly purified by flash column chromatography on silica gel (eluent: petroleum ether/ethyl acetate) to give the desired product **2**.

4.3.1. 3-(Azido(phenyl)methyl)-2-methyl-5-phenylfuran (**2a**)

Yellow solid; 141.5 mg; 98% yield; mp 66–67 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 8.0 Hz, 2H), 7.40–7.32 (m, 7H), 7.26–7.22 (m, 1H), 6.49 (s, 1H), 5.66 (s, 1H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.3, 149.1, 139.3, 130.6, 128.8, 128.7, 128.1, 127.4, 127.0, 123.6, 120.4, 105.3, 60.9, 12.3; HRMS (Q-TOF, ESI) calcd for $C_{18}H_{16}NO^+$ $[M - N_2 + H]^+$ 262.1226, found 262.1235.

4.3.2. 3-(Azido(phenyl)methyl)-5-(2-chlorophenyl)-2-methylfuran (**2b**)

Yellow solid; 133.3 mg; 82% yield; mp 72–73 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, J = 8.0, 1.6 Hz, 1H), 7.32–7.30 (m, 5H), 7.25–7.16 (m, 2H), 7.09–7.05 (m, 1H), 6.93 (s, 1H), 5.58 (s, 1H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 149.2, 148.5, 139.1, 130.8, 129.9, 128.93, 128.87, 128.2, 128.0, 127.5, 127.0, 126.9, 120.5, 111.5, 61.0, 12.3; HRMS (Q-TOF, ESI) calcd for $C_{18}H_{15}ClNO^+$ $[M - N_2 + H]^+$ 296.0837, found 296.0839.

4.3.3. 3-(Azido(phenyl)methyl)-5-(3-chlorophenyl)-2-methylfuran (**2c**)

Yellow solid; 153.7 mg; 95% yield; mp 34–35 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57–7.56 (m, 1H), 7.44–7.42 (m, 1H), 7.39–7.30 (m, 5H), 7.24–7.22 (m, 1H), 7.17–7.15 (m, 1H), 6.47 (s, 1H), 5.62 (s, 1H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.9, 149.8, 139.1, 134.8, 132.3, 130.0, 128.9, 128.2, 127.2, 127.0, 123.6, 121.6, 120.7, 106.5, 60.8, 12.3; HRMS (Q-TOF, ESI) calcd for $C_{18}H_{15}ClNO^+$ $[M - N_2 + H]^+$ 296.0837, found 296.0846.

4.3.4. 3-(Azido(phenyl)methyl)-5-(4-chlorophenyl)-2-methylfuran (**2d**)

Yellow solid; 155.3 mg; 96% yield; mp 82–83 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52–7.50 (m, 2H), 7.38–7.35 (m, 4H), 7.33–7.31 (m, 3H), 6.45 (s, 1H), 5.63 (s, 1H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.3, 149.5, 139.1, 132.9, 129.1, 128.93, 128.87, 128.2, 126.9, 124.8, 120.7, 105.8, 60.8, 12.3; HRMS (Q-TOF, ESI) calcd for $C_{18}H_{15}ClNO^+$ $[M - N_2 + H]^+$ 296.0837, found 296.0839.

4.3.5. 3-(Azido(phenyl)methyl)-5-(2-fluorophenyl)-2-methylfuran (**2e**)

Yellow solid; 111.8 mg; 73% yield; mp 55–56 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79–7.75 (m, 1H), 7.38–7.36 (m, 4H), 7.32–7.29 (m, 1H), 7.19–7.13 (m, 2H), 7.09–7.04 (m, 1H), 6.69 (d, J = 3.5 Hz, 1H), 5.65 (s, 1H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5 (d, J = 250.5 Hz), 149.1, 146.4 (d, J = 2.9 Hz), 139.1, 128.9, 128.3, 128.22, 128.15, 127.0, 125.7 (d, J = 3.2 Hz), 124.3 (d, J = 3.4 Hz), 120.7, 118.9 (d, J = 12.0 Hz), 116.0 (d, J = 21.4 Hz), 110.6 (d, J = 11.7 Hz), 60.9, 12.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ −113.91; HRMS (Q-TOF, ESI) calcd for $C_{18}H_{15}FNO^+$ $[M - N_2 + H]^+$ 280.1132, found 280.1138.

4.3.6. 3-(Azido(phenyl)methyl)-5-(4-fluorophenyl)-2-methylfuran (**2f**)

Yellow solid; 156.2 mg; >99% yield; mp 58–59 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59–7.55 (m, 2H), 7.40–7.38 (m, 4H), 7.35–7.31

(m, 1H), 7.07–7.02 (m, 2H), 6.41 (s, 1H), 5.65 (s, 1H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2 (d, J = 246.8 Hz), 151.5, 149.1, 139.2, 128.9, 128.2, 127.0 (d, J = 3.3 Hz), 126.9, 125.3 (d, J = 8.0 Hz), 120.5, 115.8 (d, J = 21.9 Hz), 105.0 (d, J = 1.5 Hz), 60.8, 12.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ −114.38; HRMS (Q-TOF, ESI) calcd for $C_{18}H_{15}FNO^+$ $[M - N_2 + H]^+$ 280.1132, found 280.1146.

*4.3.7. 3-(Azido(phenyl)methyl)-2-methyl-5-(3-(trifluoromethyl) phenyl)furan (**2g**)*

Yellow solid; 160.2 mg; 90% yield; mp 37–38 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.77–7.75 (m, 1H), 7.49–7.46 (m, 2H), 7.43–7.33 (m, 5H), 6.58 (s, 1H), 5.67 (s, 1H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.82, 150.01, 139.05, 131.28, 131.25 (q, J = 32.43 Hz), 129.24, 128.92, 128.25, 126.94, 126.56, 124.17 (d, J = 272.4 Hz), 123.74 (q, J = 3.9 Hz), 120.87, 120.29 (q, J = 3.9 Hz), 106.70, 60.76, 12.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.83; HRMS (Q-TOF, ESI) calcd for $C_{19}H_{15}F_3NO^+$ $[M - N_2 + H]^+$ 330.1100, found 330.1113.

*4.3.8. 3-(Azido(phenyl)methyl)-2-methyl-5-(4-nitrophenyl)furan (**2h**)*

Yellow solid; 164.2 mg; 98% yield; mp 110–111 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22–8.19 (m, 2H), 7.72–7.69 (m, 2H), 7.43–7.33 (m, 5H), 6.71 (s, 1H), 5.67 (s, 1H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.6, 150.0, 146.4, 138.8, 136.2, 129.0, 128.4, 126.9, 124.4, 123.7, 121.7, 109.5, 60.7, 12.5; HRMS (Q-TOF, ESI) calcd for $C_{18}H_{15}N_2O_3^+$ $[M - N_2 + H]^+$ 307.1077, found 307.1088.

*4.3.9. Ethyl 4-(4-(azido(phenyl)methyl)-5-methylfuran-2-yl) benzoate (**2i**)*

Colorless oil; 170.0 mg; 94% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02–8.00 (m, 2H), 7.65–7.63 (m, 2H), 7.39–7.32 (m, 5H), 6.61 (s, 1H), 5.68 (s, 1H), 4.37 (q, J = 7.1 Hz, 2H), 2.39 (s, 3H), 1.39 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 151.3, 150.3, 139.0, 134.4, 130.1, 128.9, 128.9, 128.2, 126.9, 123.1, 121.1, 107.6, 61.1, 60.8, 14.5, 12.4; HRMS (Q-TOF, ESI) calcd for $C_{21}H_{20}NO_3^+$ $[M - N_2 + H]^+$ 334.1438, found 334.1440.

*4.3.10. 3-(Azido(phenyl)methyl)-2-methyl-5-(p-tolyl)furan (**2j**)*

Yellow solid; 141.5 mg; 93% yield; mp 94–95 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52–7.50 (m, 2H), 7.40–7.39 (m, 4H), 7.35–7.32 (m, 1H), 7.18–7.16 (m, 2H), 6.44 (s, 1H), 5.66 (s, 1H), 2.39 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5, 148.7, 139.3, 137.2, 129.4, 128.8, 128.1, 128.0, 127.0, 123.5, 120.3, 104.5, 60.9, 21.4, 12.3; HRMS (Q-TOF, ESI) calcd for $C_{19}H_{18}NO^+$ $[M - N_2 + H]^+$ 276.1383, found 276.1392.

*4.3.11. 3-(Azido(phenyl)methyl)-5-(4-methoxyphenyl)-2-methylfuran (**2k**)*

Yellow solid; 128.7 mg; 81% yield; mp 38–39 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.41 (m, 2H), 7.27–7.26 (m, 4H), 7.22–7.20 (m, 1H), 6.79–6.76 (m, 2H), 6.24 (s, 1H), 5.52 (s, 1H), 3.69 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 152.3, 148.3, 139.3, 128.8, 128.0, 126.9, 125.0, 123.7, 120.2, 114.1, 103.6, 60.9, 55.3, 12.2; HRMS (Q-TOF, ESI) calcd for $C_{19}H_{18}NO_2^+$ $[M - N_2 + H]^+$ 292.1332, found 292.1339.

*4.3.12. 5-([1,1′-Biphenyl]-4-yl)-3-(azido(phenyl)methyl)-2-methylfuran (**2l**)*

Yellow solid; 182.4 mg; >99% yield; mp 83–84 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59–7.57 (m, 2H), 7.53–7.49 (m, 4H), 7.36–7.33 (m, 2H), 7.30–7.29 (m, 4H), 7.27–7.23 (m, 2H), 6.43 (s, 1H), 5.56 (s, 1H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 149.3, 140.7, 140.0, 139.2, 129.6, 128.92, 128.85, 128.1, 127.5, 127.4, 127.0, 124.0, 120.6, 105.5, 60.9, 12.3; HRMS (Q-TOF, ESI) calcd for $C_{24}H_{20}NO^+$ $[M - N_2 + H]^+$ 338.1539, found 338.1541.

*4.3.13. 1-(4-(4-(Azido(phenyl)methyl)-5-methylfuran-2-yl)phenyl) ethan-1-one (**2m**)*

Yellow solid; 140.7 mg; 85% yield; mp 64–65 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93–7.91 (m, 2H), 7.65–7.63 (m, 2H), 7.38–7.29 (m, 5H), 6.62 (s, 1H), 5.64 (s, 1H), 2.56 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.3, 151.1, 150.5, 138.9, 135.4, 134.5, 128.9, 128.8, 128.2, 126.9, 123.2, 121.1, 107.9, 60.7, 26.6, 12.3; HRMS (Q-TOF, ESI) calcd for $C_{20}H_{18}NO_2^+$ $[M - N_2 + H]^+$ 304.1332, found 304.1342.

*4.3.14. 3-(Azido(phenyl)methyl)-2-methyl-5-(naphthalen-1-yl) furan (**2n**)*

Yellow oil; 93.3 mg; 55% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28–8.26 (m, 1H), 7.73–7.71 (m, 1H), 7.67–7.65 (m, 1H), 7.59–7.57 (m, 1H), 7.41–7.24 (m, 8H), 7.21–7.16 (m, 1H), 6.47 (s, 1H), 5.57 (s, 1H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.7, 149.4, 139.3, 134.0, 130.2, 128.8, 128.6, 128.6, 128.2, 128.1, 127.0, 126.7, 126.0, 125.9, 125.5, 125.4, 120.2, 109.6, 61.0, 12.3; HRMS (Q-TOF, ESI) calcd for $C_{22}H_{18}NO^+$ $[M - N_2 + H]^+$ 312.1383, found 312.1390.

*4.3.15. 3-(Azido(phenyl)methyl)-2-methyl-5-(thiophen-2-yl)furan (**2o**)*

Under an argon atmosphere, $TMSN_3$ (1.5 eq.) and HOAc (1.0 eq.) were added to a mixture of 2-(1-alkynyl)-2-alken-1-one **1o** (0.50 mmol) and $Pd(OAc)_2$ (10 mol%) in a 15 mL Schlenk tube in toluene (5.0 mL). The mixture was stirred at 40 °C until the substrate **1o** was consumed. Then the solvent was evaporated and the crude product was directly purified by flash column chromatography on silica gel (eluent: petroleum ether/ethyl acetate) to give the desired product **2o**. Yellow solid; 114.5 mg; 78% yield; mp 64–65 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.34 (m, 4H), 7.33–7.29 (m, 1H), 7.18–7.17 (m, 2H), 7.00–6.98 (m, 1H), 6.32 (s, 1H), 5.61 (s, 1H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.7, 147.9, 139.1, 133.6, 128.9, 128.2, 127.7, 127.0, 124.1, 122.5, 120.4, 105.3, 60.8, 12.2; HRMS (Q-TOF, ESI) calcd for $C_{16}H_{14}NOS^+$ $[M - N_2 + H]^+$ 268.0791, found 268.0790.

*4.3.16. 3-(Azido(phenyl)methyl)-5-cyclohexyl-2-methylfuran (**2p**)*

Colorless oil; 50.0 mg; 34% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.26 (m, 5H), 5.76 (s, 1H), 5.55 (s, 1H), 2.53–2.48 (m, 1H), 2.25 (s, 3H), 1.96–1.95 (m, 2H), 1.76–1.65 (m, 3H), 1.31–1.20 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 147.1, 139.6, 128.7, 127.9, 127.0, 118.2, 102.9, 61.1, 37.3, 31.6, 31.5, 26.2, 26.0, 12.0; HRMS (Q-TOF, ESI) calcd for $C_{18}H_{22}NO^+$ $[M - N_2 + H]^+$ 268.1696, found 268.1697.

*4.3.17. 3-(Azido(phenyl)methyl)-2,5-diphenylfuran (**2q**)*

Yellow solid; 162.0 mg; 92% yield; mp 83–84 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64–7.62 (m, 2H), 7.58–7.56 (m, 2H), 7.38–7.25 (m, 10H), 7.21–7.17 (m, 1H), 6.64 (s, 1H), 5.84 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3, 150.3, 138.9, 130.3, 129.0, 128.9, 128.437, 128.3, 127.9, 127.3, 126.7, 124.0, 121.6, 107.0, 60.7; HRMS (Q-TOF, ESI) calcd for $C_{23}H_{18}NO^+$ $[M - N_2 + H]^+$ 324.1383, found 324.1391.

*4.3.18. 3-(Azido(phenyl)methyl)-2-(2-chlorophenyl)-5-phenylfuran (**2r**)*

Yellow solid; 105.0 mg; 54% yield; mp 78–79 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70–7.68 (m, 2H), 7.53–7.51 (m, 1H), 7.46–7.43 (m, 1H), 7.38–7.26 (m, 10H), 6.69 (s, 1H), 5.65 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 148.3, 139.0, 134.6, 132.5, 130.8, 130.4, 130.3, 129.2, 128.8, 128.8, 128.1, 128.0, 127.1, 126.9, 124.1, 124.0, 105.5, 60.4; HRMS (Q-TOF, ESI) calcd for $C_{23}H_{17}ClNO^+$ $[M - N_2 + H]^+$ 358.0993, found 358.0996.

*4.3.19. 3-(Azido(phenyl)methyl)-2-(3-chlorophenyl)-5-phenylfuran (**2s**)*

Yellow solid; 138.7 mg; 72% yield; mp 88–89 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75–7.73 (m, 2H), 7.68 (s, 1H), 7.52–7.50 (m, 1H), 7.47–7.32 (m, 10H), 6.77 (s, 1H), 5.90 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 148.5, 138.6, 135.0, 131.9, 130.2, 130.0, 129.1, 128.9, 128.5, 128.23, 128.21, 127.3, 126.5, 124.5, 124.2, 122.8, 107.3, 60.7; HRMS (Q-TOF, ESI) calcd for $C_{23}H_{17}ClNO^+$ $[M - N_2 + H]^+$ 358.0993, found 358.0991.

*4.3.20. 3-(Azido(phenyl)methyl)-2-(4-chlorophenyl)-5-phenylfuran (**2t**)*

Yellow solid; 130.2 mg; 67% yield; mp 91–92 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74–7.72 (m, 2H), 7.61–7.57 (m, 2H), 7.44–7.36 (m, 9H),7.33–7.30 (m, 1H), 6.74 (s, 1H), 5.88 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.5, 149.0, 138.6, 134.2, 130.1, 129.2, 129.1, 128.9, 128.7, 128.5, 128.1, 127.8, 127.3, 124.1, 122.1, 107.2, 60.7; HRMS (Q-TOF, ESI) calcd for $C_{23}H_{17}ClNO^+$ $[M - N_2 + H]^+$ 358.0993, found 358.0997.

*4.3.21. 3-(Azido(phenyl)methyl)-5-phenyl-2-(p-tolyl)furan (**2u**)*

Yellow solid; 115.2 mg; 63% yield; mp 62–63 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60–7.58 (m, 2H), 7.45–7.43 (m, 2H), 7.33–7.20 (m, 7H), 7.15–7.13 (m, 3H), 6.59 (s, 1H), 5.80 (s, 1H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0, 150.6, 139.1, 138.4, 130.4, 1297, 128.9, 128.8, 128.3, 127.8, 127.5, 127.3, 126.7, 124.0, 121.0, 106.9, 60.7, 21.4; HRMS (Q-TOF, ESI) calcd for $C_{24}H_{20}NO^+$ $[M - N_2 + H]^+$ 338.1539, found 338.1539.

*4.3.22. 3-(Azido(4-chlorophenyl)methyl)-2,5-diphenylfuran (**2v**)*

Yellow solid; 140.0 mg; 73% yield; mp 59–60 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72–7.70 (m, 2H), 7.64–7.62 (m, 2H), 7.47–7.43 (m, 2H), 7.41–7.36 (m, 7H), 7.30–7.26 (m, 1H), 6.66 (s, 1H), 5.59 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.5, 150.5, 137.5, 134.2, 130.2, 130.1, 129.1, 129.0, 128.9, 128.7, 128.5, 128.1, 126.7, 124.1, 121.1, 106.7, 60.0; HRMS (Q-TOF, ESI) calcd for $C_{23}H_{17}ClNO^+$ $[M - N_2 + H]^+$ 358.0993, found 358.0997.

*4.3.23. 4-Azido-2-phenyl-4,5,6,7-tetrahydrobenzofuran (**2w**)*

Yellow oil; 98.0 mg; 82% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64–7.62 (m, 2H), 7.38–7.34 (m, 2H), 7.25–7.23 (m, 1H), 6.64 (s, 1H), 4.46 (t, J = 3.7 Hz, 1H), 2.78–2.71 (m, 1H), 2.67–2.60 (m, 1H), 2.04–1.86 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0, 152.9, 130.9, 128.8, 127.4, 123.6, 117.9, 104.5, 55.0, 29.6, 23.0, 19.6; HRMS (Q-TOF, ESI) calcd for $C_{14}H_{14}NO^+$ $[M - N_2 + H]^+$ 212.1070, found 212.1078.

*4.4. 1-((2-Methyl-5-phenylfuran-3-yl)(phenyl)methyl)-4-phenyl-1H-1,2,3-triazole (**4a**)*

Yellow solid; 110.0 mg; 94% yield; mp 175–176 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 7.4 Hz, 2H), 7.77 (s, 1H), 7.59 (d, J = 7.4 Hz, 2H), 7.41–7.29 (m, 8H), 7.24–7.21 (m, 1H), 7.17–7.15 (d, J = 6.0 Hz, 2H), 7.00 (s, 1H), 6.44 (s, 1H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.6, 150.1, 138.4, 130.6, 130.3, 129.1, 128.9, 128.8, 128.6, 128.3, 127.6, 127.1, 125.9, 123.6, 119.3, 105.7, 60.6, 12.2; HRMS (Q-TOF, ESI) calcd for $C_{26}H_{22}N_3O^+$ $[M + H]^+$ 392.1757, found 392.1758.

*4.5. (2-methyl-5-phenylfuran-3-yl)(phenyl)methanamine (**5a**)*

Yellow oil; 76.0 mg; 96% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J = 7.4 Hz, 2H), 7.40 (d, J = 7.4 Hz, 2H), 7.34–7.29 (m, 4H), 7.24–7.16 (m, 2H), 6.58 (s, 1H), 5.09 (s, 1H), 2.31 (s, 3H), 2.26 (br, 2H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.7, 147.2, 145.0, 131.0, 128.6, 128.6, 127.1, 126.9, 126.6, 125.7, 123.4, 105.1, 51.6, 12.2; HRMS (Q-TOF, ESI) calcd for $C_{14}H_{14}NO^+$ $[M + H]^+$ 264.1383, found 264.1394.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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