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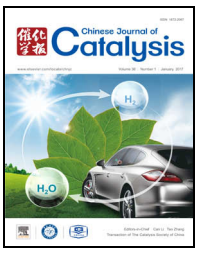

Article

Cu(I)-catalyzed cascade reaction of *N*-tosylhydrazones with 3-butyn-1-ol: A new synthesis of tetrahydrofurans

Mohammad Lokman Hossain [a], Kang Wang [a], Fei Ye [a], Yan Zhang [a], Jianbo Wang [a,b,*]

[a] *Beijing National Laboratory of Molecular Sciences (BNLMS) and Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, College of Chemistry and Molecular Engineering, Peking University, Beijing 100871, China*

[b] *State Key Laboratory of Organometallic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China*

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ABSTRACT

The Cu(I)-catalyzed cascade coupling/cyclization reaction of *N*-tosylhydrazones with 3-butyn-1-ol has been explored. This new strategy represents a simple platform for the synthesis of tetrahydrofurans in moderate to good yields.

1. Introduction

N-Tosylhydrazones are useful synthetic intermediates that have been employed in organic chemistry for almost 60 years. Compounds belonging to this particular class are air and moisture stable and can be readily prepared by the condensation of aldehydes or ketones with commercially available tosylhydrazine. In particular, *N*-tosylhydrazones have been proven to be useful substrates for the *in situ* generation of non-stabilized diazo compounds through the Bamford–Stevens reaction [1]. The diazo compounds generated in this way have been studied extensively in terms of their application to catalytic carbene transfer reactions [2]. More recently, *N*-tosylhydrazones have been established as versatile substrates in transition-metal-catalyzed cross-coupling reactions [3–7]. In this context, we previously reported the Cu(I)-catalyzed cross-coupling of terminal alkynes and *N*-tosylhydrazones as an efficient strategy for the formation of *tri*-substituted allenes (Scheme 1(A)) [8]. We subsequently modified and simplified this methodology, resulting in the development of several efficient methods for the construction of 1,3-disubstituted allenes [9] and *tetra*-substituted allenes [10] by the Cu-catalyzed cross-coupling reactions of terminal alkynes and *N*-tosylhydrazones. The work represents further extensions of our previous studies on Cu(I)-catalyzed allene synthesis from terminal alkynes and *N*-tosylhydrazones.

The Cu-carbene species involved in this type of reaction are formed from the *in situ*-generated diazo substrate, which undergoes a migratory insertion reaction, followed by a protonation or nucleophilic substitution step to give the allene product. Since allenes are reactive structures that can undergo a wide range of transformations [11–19], we envisaged that it could be

* Corresponding author. Tel: +86-10-62757248; Fax: +86-10-62751708; E-mail: wangjb@pku.edu.cn

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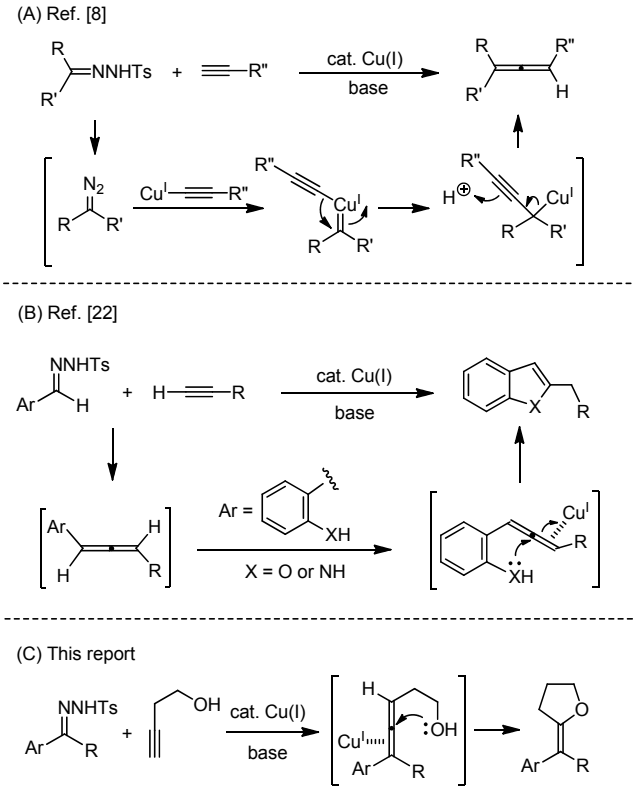


Scheme 1. Synthesis and tandem transformation of allenes through the Cu(I)-catalyzed cross-coupling of *N*-tosylhydrazones with terminal alkynes.

possible to intercept these intermediates in a cascade transformation sequence, thereby providing facile access to increasingly complex structures. In this context, we have shown that the allene intermediates generated by the Cu(I)-catalyzed coupling of *N*-tosylhydrazones with terminal alkynes undergo 6π-electron cycloaddition and isomerization reactions to afford phenanthrenes [20,21]. We have also demonstrated that the introduction of a suitable intramolecular nucleophile (i.e., an –OH or $–NH_2$ group) to the substrate allows for the initial allene product to undergo a cyclization to afford a benzofuran or indole (Scheme 1(B)) [22]. As part of our ongoing interest in the development of new reactions for organic synthesis, we report herein the Cu(I)-catalyzed cascade reaction of *N*-tosylhydrazones with 3-butyn-1-ol (Scheme 1(C)). Notably, this reaction provides facile access to tetrahydrofuran derivatives, which are an important compounds class with numerous applications across various areas of research [23–25].

2. Experimental

2.1. General

All of the reactions were performed under nitrogen in 10-mL microwave tubes. Dioxane was dried over Na metal before being used. Column chromatography was performed over 200–300 mesh silica gel (Qingdao, China). ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on Brucker ARX 400 spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) relative to the chemical shift of tetramethylsilane (TMS), which was used as an internal reference. Infrared (IR) spectra were recorded on Nicolet iS10 and the peaks reported in wavenumbers (cm^{-1}). HRMS analysis was conducted on Bruker APEX IV FTMS using a FT-ICR mass analyzer. The *N*-tosylhydrazones evaluated in the current study were prepared using a literature procedure [2]. Unless otherwise noted, materials obtained from commercial suppliers were used as supplied without further purification.

2.2. General procedure for the Cu(I)-catalyzed reaction of *N*-tosylhydrazones ***1a–g*** with 3-butyn-1-ol

3-Butyn-1-ol (**2**, 42 mg, 0.6 mmol) was added to a mixture of CuI (3.8 mg, 0.02 mmol), bathophenanthroline (6.64 mg, 0.02 mmol), tetrabutylammonium bromide (TBAB) (19.3 mg, 0.06 mmol), LiO^tBu (48 mg, 0.6 mmol) and *N*-tosylhydrazone (**1a**, 70 mg, 0.2 mmol) in 1,4-dioxane (1 mL) under nitrogen, and the resulting mixture was stirred at 110 °C for 4 h. Upon completion of the reaction, as determined by TLC, the reaction was cooled to room temperature and treated with TsOH (68.8 mg, 0.4 mmol), and the resulting mixture was stirred for 2 h at 80 °C. The reaction was then cooled to ambient temperature and evaporated to dryness to give a crude mixture, which was purified by column chromatography over silica gel to afford pure **3a** as a white solid (35 mg, 75%).

2-(Diphenylmethylene)tetrahydrofuran (**3a**). White solid (35 mg, 75%); mp = 101–103 °C; R_f = 0.55 (1:100, EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, J = 7.6 Hz, 2H), 7.31 (t, J = 7.4 Hz, 2H), 7.26–7.19 (m, 5H), 7.11 (t, J = 7.3 Hz, 1H), 4.26 (t, J = 6.7 Hz, 2H), 2.61 (t, J = 7.5 Hz, 2H), 2.01 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.2, 142.1, 139.9, 130.5, 128.9, 128.2, 127.7, 126.0, 125.3, 110.6, 71.3, 30.2, 24.9; IR (film): 3030, 2289, 1641, 1599, 1497, 1203, 1175, 1037, 910, 701, 656 cm^{-1}; EI-MS (m/z, relative intensity): 236 (M^+, 90), 217 (3), 207 (5), 180 (40), 165 (100), 152 (10), 115 (12), 83 (5); HRMS (EI) calcd. for $C_{17}H_{17}O$ $[M+H]^+$: 237.1271; found: 237.1274.

2-(Di-p-tolylmethylene)tetrahydrofuran (**3b**). Waxy liquid, (32 mg, 60%); R_f = 0.55 (1:100, EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, J = 8.1 Hz, 2H), 7.12–7.04 (m, 6H), 4.22 (t, J = 6.7 Hz, 2H), 2.60 (t, J = 7.5 Hz, 2H), 2.34 (s, 3H), 2.29 (s, 3H), 2.02–1.95 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 139.2, 137.3, 135.4, 134.7, 130.2, 128.9, 128.8, 128.4, 110.3, 71.1, 30.0, 24.9, 21.1, 21.0; IR (film): 2974, 2918, 1712, 1642, 1609, 1510, 1408, 1172, 1034, 819, 665 cm^{-1}; EI-MS (m/z, relative intensity): 264 (M^+, 100), 249 (3), 235 (5), 221 (8), 208 (40), 193 (60), 178 (38), 165 (10), 152 (5), 139 (3), 129 (8), 115 (5), 89 (5); HRMS (EI) calcd. for $C_{19}H_{21}O$ $[M+H]^+$: 265.1587; found: 265.1583.

2-(Di(thiophen-3-yl)methylene)tetrahydrofuran (**3c**). Light brown liquid (31 mg, 63%); R_f = 0.50 (1:100, EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (dd, J = 3.0, 4.9 Hz, 1H), 7.24 (dd, J = 1.2, 5.0 Hz, 1H), 7.20–7.17 (m, 2H), 7.08 (dd, J = 1.2, 2.9 Hz, 1H), 6.97 (dd, J = 1.1, 4.9 Hz, 1H), 4.32 (t, J = 6.8 Hz, 2H), 2.62 (t, J = 7.5 Hz, 2H), 2.02 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.2, 141.5, 140.1, 129.7, 128.4, 124.7, 123.7, 123.0, 120.6,

101.6, 71.7, 30.0, 24.7; IR (film): 2960, 2924, 1650, 1461, 1377, 1260, 1167, 1082, 1035, 795 cm^{-1}; EI-MS (*m*/*z*, relative intensity): 248 (M$^+$, 100), 237 (5), 219 (5), 207 (12), 192 (70), 177 (40), 147 (15), 134 (8), 89 (5); HRMS (EI) calcd. for $C_{13}H_{13}OS_2$ [M+H]$^+$: 249.0402; found: 249.0399.

2-(Bis(4-fluorophenyl)methylene)tetrahydrofuran (**3d**). White solid (38 mg, 70%); mp = 87–89 °C; R_f = 0.38 (1:60, EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (dd, *J* = 5.7, 7.8 Hz, 2H), 7.13 (dd, *J* = 5.6, 7.6 Hz, 2H), 7.01 (t, *J* = 8.2 Hz, 2H), 6.93 (t, *J* = 8.3 Hz, 2H), 4.27 (t, *J* = 6.7 Hz, 2H), 2.57 (t, *J* = 7.5 Hz, 2H), 2.02 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2 (d, *J* = 75.3 Hz), 159.8 (d, *J* = 75.0 Hz), 155.2, 137.8 (d, *J* = 3.4 Hz), 135.8 (d, *J* = 3.2 Hz), 131.9 (d, *J* = 7.9 Hz), 130.3 (d, *J* = 7.5 Hz), 115.2 (d, *J* = 21.2 Hz), 114.5 (d, *J* = 21.1 Hz), 108.6, 71.5, 30.1, 24.9; IR (film): 2969, 2901, 1642, 1603, 1507, 1223, 1033, 836, 800, 652 cm^{-1}; EI-MS (*m*/*z*, relative intensity): 272 (M$^+$, 95), 243 (3), 216 (50), 201 (100), 183 (8), 133 (4), 120 (3), 101 (8); HRMS (EI) calcd. for $C_{17}H_{15}F_2O$ [M+H]$^+$: 273.1086; found: 273.1082.

2-(Bis(4-chlorophenyl)methylene)tetrahydrofuran (**3e**). White waxy solid (40 mg, 66%); R_f = 0.43 (1:100, EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.28 (m, 4H), 7.20 (d, *J* = 8.7 Hz, 2H), 7.10 (d, *J* = 8.5 Hz, 2H), 4.28 (t, *J* = 6.8 Hz, 2H), 2.58 (t, *J* = 7.5 Hz, 2H), 2.06–1.99 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 140.1, 138.0, 131.8, 130.1, 128.6, 127.9, 108.5, 71.6, 29.7, 24.8; IR (film): 2924, 1642, 1691, 1176, 1091, 1033, 907, 731 cm^{-1}; EI-MS (*m*/*z*, relative intensity): 304 (M$^+$, 100), 248 (50), 234 (15), 213 (25), 199 (60), 178 (40), 163 (28), 149 (5), 137 (5), 125 (10), 99 (8); HRMS (EI) calcd. for $C_{17}H_{15}Cl_2O$ [M+H]$^+$: 305.0495; found: 305.0490.

2-(Bis(4-(trifluoromethyl)phenyl)methylene)tetrahydrofuran (**3f**). Colorless liquid (46 mg, 62%); R_f = 0.45 (1:100, EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53–7.33 (m, 8H), 4.32 (t, *J* = 6.7 Hz, 2H), 2.61 (t, *J* = 7.5 Hz, 2H), 2.05 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 142.1, 140.3, 133.9, 132.0, 129.0, 128.2, 127.1 (q, *J* = 3.6 Hz), 125.6 (d, *J* = 3.8 Hz), 123.3 (d, *J* = 3.7 Hz), 122.1 (d, *J* = 3.7 Hz), 108.4, 72.0, 30.5, 24.7; IR (film): 2951, 1643, 1331, 1280, 1260, 1166, 1123, 1074 cm^{-1}; EI-MS (*m*/*z*, relative intensity): 372 (M$^+$, 100), 353 (10), 330 (5), 316 (8), 302 (10), 282 (5), 247 (6), 233 (60), 183 (8); HRMS (EI) calcd. for $C_{19}H_{15}F_6O$ [M+H]$^+$: 373.1022; found: 373.1017.

2-(Bis(4-methoxyphenyl)methylene)tetrahydrofuran (**3g**). Light yellow liquid (35 mg, 58%); R_f = 0.40 (1:30, EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.7 Hz, 2H), 6.83 (dd, *J* = 8.7, 23.0 Hz, 4H), 4.24 (t, *J* = 6.7 Hz, 2H), 3.81 (s, 3H), 3.77 (s, 3H), 2.59 (t, *J* = 7.5 Hz, 2H), 2.60–1.96 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 157.1, 144.5, 142.0, 136.5, 131.4, 130.2, 130.0, 129.3, 127.6, 124.6, 113.6, 113.2, 71.1, 55.2, 29.9, 25.0, 21.6, 21.4; IR (film): 2925, 2853, 1608, 1509, 1246, 1173, 1033, 653 cm^{-1}; EI-MS (*m*/*z*, relative intensity): 296 (M$^+$, 100), 281 (10), 267 (10), 253 (12), 240 (75), 225 (40), 207 (45), 165 (15), 113(20); HRMS (EI) calcd. for $C_{19}H_{21}O_3$ [M+H]$^+$ 297.1485; found: 297.1490.

2-(Di-m-tolylmethylene)tetrahydrofuran (**3h**). White oil (25.8 mg, 50%); R_f = 0.55 (1:100, EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23–7.16 (m, 2H), 7.18–7.12 (m, 2H), 7.04–6.99 (*m*, 3H), 6.94–6.93 (d, *J* = 6.9 Hz, 2H), 4.24 (t, *J* = 6.7 Hz, 2H), 2.61 (t, *J* = 7.5 Hz, 2H), 2.31 (s, 3H), 2.28 (s, 3H), 1.99 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 142.1, 140.0, 137.7, 129.7, 128.0, 127.6, 127.5, 126.7, 126.3, 110.7, 71.3, 30.2, 25.0, 21.6, 21.5; IR (film): 3030, 2970, 2316, 1642, 1599, 1484, 1246, 1164, 1040, 784, 704 cm^{-1}; EI-MS (*m*/*z*, relative intensity): 264 (M$^+$, 100), 231 (5), 221 (10), 208 (50), 193 (60), 178 (50), 165 (10), 152 (5), 129 (5), 115 (3); HRMS (EI) calcd. for $C_{19}H_{21}O$ [M+H]$^+$: 265.1587; found: 265.1585.

2-(Bis(3-methoxyphenyl)methylene)tetrahydrofuran (**3i**). White oil (34.8 mg, 59%); R_f = 0.40 (1:40, EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (t, *J* = 7.9 Hz, 2H), 7.16 (t, *J* = 7.9 Hz, 2H), 7.05–7.04 (*m*, 1H), 6.95(d, *J* = 7.9 Hz, 1H), 6.75–6.79 (m, 3H), 6.88 (dd, *J* = 2.0, 7.9 Hz, 1H), 4.27 (t, *J* = 6.7 Hz, 2H), 3.77 (s, 3H), 3.74 (m, 3H), 2.61 (t, *J* = 7.5 Hz, 2H), 2.00 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 159.2, 155.7, 143.4, 141.2, 129.2, 128.6, 123.1, 116.1, 114.9, 111.6, 110.6, 110.3, 71.5, 55.2, 55.1, 30.4, 24.8; IR (film): 2920, 2845, 1643, 1600, 1490, 1283, 1222, 1032, 876, 779 cm^{-1}; EI-MS (*m*/*z*, relative intensity): 296 (M$^+$, 100), 281 (3), 253 (3), 240 (30), 225 (20), 209 (20), 195 (10), 181 (5), 165 (5), 152 (5), 139 (5); HRMS (EI) calcd. for $C_{19}H_{21}O_3$ [M+H]$^+$: 297.1485; found: 297.1484.

2-(Bis(3-fluorophenyl)methylene)tetrahydrofuran (**3j**). White oil (34.3 mg, 63%); R_f= 0.50 (1:100, EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.26 (m, 1H), 7.20–7.15 (m, 2H), 7.08–7.06 (*m*, 1H), 6.97–6.88 (m, 3H), 6.84-6.79 (m, 1H), 4.30 (t, *J* = 6.8 Hz, 2H), 2.60 (t, *J* = 7.5 Hz, 2H), 2.03 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9 (d, J_F = 245.9 Hz), 161.7 (d, J_F = 243.4 Hz), 155.8, 142.7 (d, J_F = 7.8 Hz), 140.5 (d, J_F = 8.2 Hz), 128.7 (d, J_F = 8.6 Hz), 127.9 (d, J_F = 8.6 Hz), 125.2 (d, J_F = 2.7 Hz), 123.3 (d, J_F = 2.7 Hz), 116.3 (d, J_F = 20.6 Hz), 114.5 (d, J_F = 22.5 Hz), 112.3 (d, J_F = 20.9 Hz), 111.1 (d, J_F = 21.4 Hz), 107.8, 70.8, 29.5, 23.7; IR (film): 2978, 2344, 1640, 1609, 1580, 1486, 1439, 1183, 1165, 1039, 780, 744 cm^{-1}; EI-MS (*m*/*z*, relative intensity): 272 (M$^+$, 100), 253 (3), 230 (10), 216 (30), 201 (80), 183 (10), 170 (3), 133 (5), 115 (5), 101 (8); HRMS (EI) calcd. for $C_{17}H_{15}F_2O$ [M+H]$^+$: 273.1085; found: 273.1085.

2-(Bis(2-fluorophenyl)methylene)tetrahydrofuran (**3k**). White oil (30.7 mg, 56%); R_f = 0.50 (1:100, EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.28 (m, 1H), 7.20–7.16 (m, 3H), 7.14–6.97 (*m*, 4H), 4.21 (t, *J* = 6.7 Hz, 2H), 2.62 (t, *J* = 7.5 Hz, 2H), 2.05 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4 (d, J_F = 246.1 Hz), 160.1 (d, J_F = 247.4 Hz), 157.8, 132.3 (d, J_F = 3.5 Hz), 132.0 (d, J_F = 3.9 Hz), 128.5 (d, J_F = 15.6 Hz), 128.1 (d, J_F = 8.2 Hz), 127.9 (d, J_F = 8.3 Hz), 127.3 (d, J_F = 15.4 Hz), 123.8 (d, J_F = 3.4 Hz), 123.6 (d, J_F = 3.3 Hz), 115.7 (d, J_F = 23.0 Hz), 115.6 (d, J_F = 22.5 Hz), 97.9, 71.9, 28.9, 24.9; IR (film): 3058, 2848, 1662, 1645, 1576, 1490, 1225, 1179, 991, 758 cm^{-1}; EI-MS (*m*/*z*, relative intensity): 272 (M$^+$, 100), 253 (1), 243 (3), 240 (20), 216 (40), 201 (90), 183 (20), 170 (2), 133 (5), 101 (5); HRMS (EI) calcd. for $C_{19}H_{15}F_2O$ [M+H]$^+$: 273.1085; found: 273.1083.

*2.3. General procedure for the Cu(I)-catalyzed reaction of N-tosylhydrazones **4a–c** with 3-butyn-1-ol*

3-Butyn-1-ol (**2**, 42 mg, 0.6 mmol) was added to a mixture of CuI (3.8 mg, 0.02 mmol), bathophenanthroline (6.64 mg, 0.02 mmol), TBAB (19.3 mg, 0.06 mmol), LiO^{t}Bu (48 mg, 0. 6 mmol) and *N*-tosylhydrazone (**4a**, 85.3 mg, 0.2 mmol) in 1,4-dioxane (1 mL) under nitrogen, and the resulting mixture was stirred at 110 °C for 4 h. Upon completion of the reaction, as determined by TLC analysis, the mixture was cooled to room temperature and treated with TsOH (68.8 mg, 0.4 mmol), and the resulting mixture was stirred at 80 °C for 2 h. The mixture was then cooled to ambient temperature and evaporated under vacuum to give a crude residue, which was purified by column chromatography over silica gel to afford pure **5a** as white solid (42 mg, 67%).

(E)-2-([1,1'-Biphenyl]-4-yl(phenyl)methylene)tetrahydrofuran (**5a**). White solid (42 mg, 67%); mp = 141–142 °C; R_f = 0.45 (1:200, EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 7.6 Hz, 2H), 7.55 (d, J = 8.3 Hz, 2H), 7.45–7.41 (m, 4H), 7.27–7.25 (m, 4H), 7.13 (t, J = 7.3 Hz, 1H), 4.27 (t, J = 6.7 Hz, 2H), 2.70 (t, J = 7.5 Hz, 2H), 2.04 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 141.9, 141.2, 139.1, 137.8, 130.6, 129.2, 128.6, 128.3, 126.9, 126.4, 126.1, 110.2, 71.5, 30.3, 24.8; IR (film): 3051, 2927, 1631, 1596, 1489, 1442, 1260, 1171, 1033, 765, 692 cm^{-1}; EI-MS (m/z, relative intensity): 312 (M$^+$, 100), 256 (40), 241 (38), 165 (20), 121 (25); HRMS (EI) calcd. for $C_{23}H_{21}O$ [M+H]$^+$ 313.1587; found: 313.1588.

(E)-2-((3,4-Dimethylphenyl)(phenyl)methylene)tetrahydrofuran (**5b**). White solid (38 mg, 72%); mp = 90–91 °C; R_f = 0.46 (1:200, EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, J = 7.6 Hz, 2H), 7.24 (dd, J = 6.3, 9.0 Hz, 2H), 7.12–7.07 (m, 2H), 6.96-6.93 (m, 2H), 4.25 (t, J = 6.7 Hz, 2H), 2.62 (t, J = 7.5 Hz, 2H), 2.26 (s, 3H), 2.22 (s, 3H), 2.03-1.96 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 140.2, 139.5, 136.2, 134.2, 131.6, 129.4, 128.9, 127.9, 127.7, 125.1, 110.4, 110.2, 71.3, 30.2, 24.9, 19.8, 19.4; IR (film): 3018, 2920, 1641, 1503, 1443, 1171, 1039, 819, 701, cm^{-1}; EI-MS (m/z, relative intensity): 264 (M$^+$, 100), 249 (6), 221 (10), 207 (60), 193 (45), 178 (40), 165 (12), 96 (20); HRMS (EI) calcd. for $C_{19}H_{21}O$ [M+H]$^+$ 265.1587; found: 265.1589.

(E)-2-((4-Chlorophenyl)(phenyl)methylene)tetrahydrofuran (**5c**). White solid (37 mg, 68%); mp = 107–108 °C; R_f = 0.43 (1:100, EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 7.4 Hz, 2H), 7.29–7.23 (m, 4H), 7.12 (d, J = 8.4 Hz, 3H), 4.26 (t, J = 6.7 Hz, 2H), 2.60 (t, J = 7.5 Hz, 2H), 2.02 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 139.6, 138.6, 130.8, 127.9, 127.4, 126.8, 124.5, 108.6, 70.4, 29.2, 23.9; IR (film): 2960, 2887, 1642, 1596, 1490, 1259, 1089, 1031, 1015, 920, 767 cm^{-1}; EI-MS (m/z, relative intensity): 270 (M$^+$, 100), 214 (35), 200 (15), 179 (50), 165 (80), 139 (5), 115 (5), 82 (6); HRMS (EI) calcd. for $C_{17}H_{16}ClO$ [M+H]$^+$ 271.0884; found: 271.0886.

*2.4. General procedure for the Cu(I)-catalyzed reaction of N-tosylhydrazones **7a–c** and 3-butyn-1-ol*

3-Butyn-1-ol (**2**, 63 mg, 0.9 mmol) was added to a mixture of CuI (5.7 mg, 0.03 mmol), bathophenanthroline (9.96 mg, 0.03 mmol), TBAB (28.98 mg, 0.09 mmol), Li^{t}OBu (72 mg, 0.9 mmol) and *N*-tosylhydrazone (**7a**, 68.4 mg, 0.3 mmol) in 1,4-dioxane (1 mL) under nitrogen, and the resulting mixture was stirred at 110 °C for 4 h. Upon completion of the reaction, as determined by TLC analysis, the mixture was cooled to room temperature and treated with TsOH (103.2 mg, 0.6 mmol) before being heated at 70 °C for 2 h. The mixture was then cooled to room temperature and evaporated under vacuum to give a crude mixture, which was purified by column chromatography over silica gel to afford pure **8a** as a colorless liquid (43 mg, 63%).

(E)-2-(4-(Trifluoromethyl)benzylidene)tetrahydrofuran (**8a**). Colorless liquid (43 mg, 63%); R_f = 0.42 (1:50, EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J = 8.1 Hz, 2H), 7.24 (d, J = 10.0 Hz, 2H), 5.93 (s, 1H), 4.16 (t, J = 6.8 Hz, 2H), 2.84 (t, J = 7.4 Hz, 2H), 2.17-2.10 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 141.6, 129.8, 125.2 (q, J = 3.8 Hz, *CF*$_3$), 98.3, 69.8, 28.7, 25.1; IR (film) 2931, 1653, 1371, 1180, 1123, 1084 cm^{-1}; EI-MS (m/z, relative intensity): 228 (M$^+$, 95), 209 (20), 186 (100), 158 (85), 138 (18), 89 (15); HRMS (EI) calcd. for $C_{12}H_{12}F_3O$ [M+H]$^+$ 229.0835; found: 229.0837.

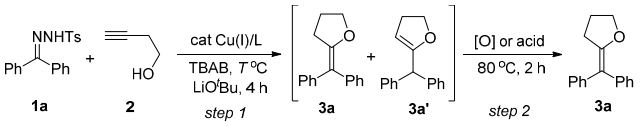
(E)-4-((Dihydrofuran-2(3H)-ylidene)methyl)benzonitrile (**8b**). Colorless liquid (39 mg, 70%); R_f = 0.35 (1:30, EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 5.90 (s, 1H), 4.18 (t, J = 6.9 Hz, 2H), 2.85 (dt, J = 1.9, 7.6 Hz, 2H), 2.15 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 142.9, 132.1, 126.9, 119.5, 107.1, 98.6, 70.0, 29.0, 25.1; IR (film): 2924, 2854, 2219, 1708, 1661, 1602, 1392, 1173, 1028, 984, 845, 734 cm^{-1}; EI-MS (m/z, relative intensity): 185 (M$^+$, 90), 177 (2), 143 (100), 129 (15), 115 (75), 102 (5), 88 (10); HRMS (EI) calcd. for $C_{12}H_{12}NO$ [M+H]$^+$ 186.0913; found: 186.0916.

(E)-2-(2-Chloro-4-(trifluoromethyl)benzylidene)tetrahydrofuran (**8c**). Colorless liquid (46 mg, 58%); R_f = 0.40 (1:40, EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 1.4 Hz, 1H), 7.44 (d, J = 8.3 Hz, 1H), 7.28 (dd, J = 1.8, 8.4 Hz, 1H), 6.13 (s, 1H), 4.20 (t, J = 6.8 Hz, 2H), 2.79 (dt, J = 1.9, 7.5 Hz, 2H), 2.13 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 136.8, 129.8, 124.5 (q, J = 3.9 Hz), 122.3 (dd, J = 3.8, 7.6 Hz), 95.1, 70.2, 28.4, 25.1; IR (film): 2923, 2854, 1660, 1605, 1417, 1328, 1168, 1129, 1083 cm^{-1}; EI-MS (m/z, relative intensity): 262 (M$^+$, 80), 243 (20), 220 (100), 192 (60), 157 (40), 138 (18), 87 (13); HRMS (EI) calcd. for $C_{12}H_{11}ClF_3O$ [M+H]$^+$ 263.0448; found: 263.0445.

3. Results and discussion

The symmetrical *N*-tosylhydrazone **1a**, which was derived from benzophenone and 3-butyn-1-ol (**2**), was selected as a model substrate for this reaction with copper(I) iodide as the catalyst. Under similar reaction conditions to those previously reported by our group for the Cu(I)-catalyzed cross-coupling of *N*-tosylhydrazones with alkynes [9,10,21,22], the reaction afforded an isomeric mixture of the tetrahydrofuran product **3a** and dihydrofuran **3a'** (Table 1, entry 1). The structures of **3a** and **3a'** were established based on their NMR and MS data. The structure of **3a** was further confirmed by X-ray crystallography (Fig. 1) [26]. In this experiment, we also observed a very small amount of the corresponding allene, the structure of which was confirmed by ^{1}H and ^{13}C NMR spectroscopy. A series of screen-

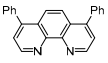
Table 1
Optimization of the reaction conditions.



Entry	Cu(I)/L (10 mol%)	Solvent	[O] or acid	*T*/ °C	Yield [a]
1	CuI	Dioxane	—	90	**3a**+**3a'**, 45%
2	CuI/phen	Dioxane	—	90	**3a**+**3a'**, 57%
3	CuI/phen	Toluene	—	90	**3a**+**3a'**, 30%
4	CuI/phen	DCE	—	90	**3a**+**3a'**, 25%
5	$Cu(MeCN)_4PF_6$/phen	Dioxane	—	90	**3a**+**3a'**, 38%
6	$Cu(OAc)_2$/phen	Dioxane	—	90	**3a**+**3a'**, 10%
7	$Cu(OEt)_2$/phen	Dioxane	—	90	**3a**+**3a'**, 8%
8	CuCl/phen	Dioxane	—	90	**3a**+**3a'**, 35%
9	CuI/phen	Dioxane	—	110	**3a**+**3a'**, 64%
10	CuI/phen	Dioxane	BQ	110	Decomposed
11	CuI/phen	Dioxane	DDQ	110	Decomposed
12	CuI/phen	Dioxane	TsOH	90	**3a**, 59%
13	CuI/phen	Dioxane	TsOH	110	**3a**, 68%
14	CuI/phen	Dioxane	TFA	110	**3a**, 66%
15	CuI/bathophen	Dioxane	TsOH	110	**3a**, 75%

Reaction conditions: For step 1, **1a** (0.2 mmol), **2** (3.0 equiv.), Cu(I) (10 mol%), phen or bathophen (10 mol%), TBAB (30 mol%) and base (3.0 equiv.) in dioxane (1 mL) at 90–110 °C for 4 h. For step 2, [O] or TsOH (2.0 equiv) at 70–80 °C for 2 h.

[a] Isolated yield after column chromatography.

Phen:  , Bathophen: 

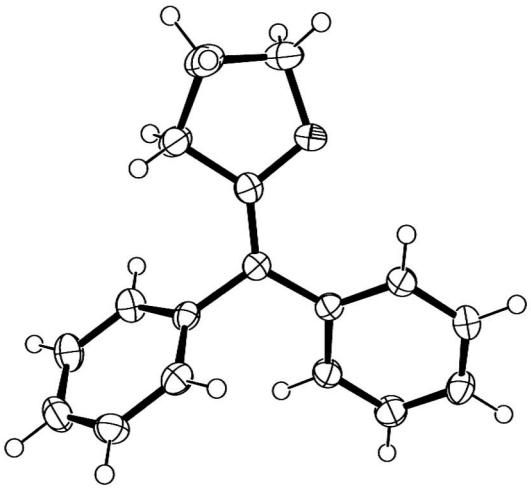
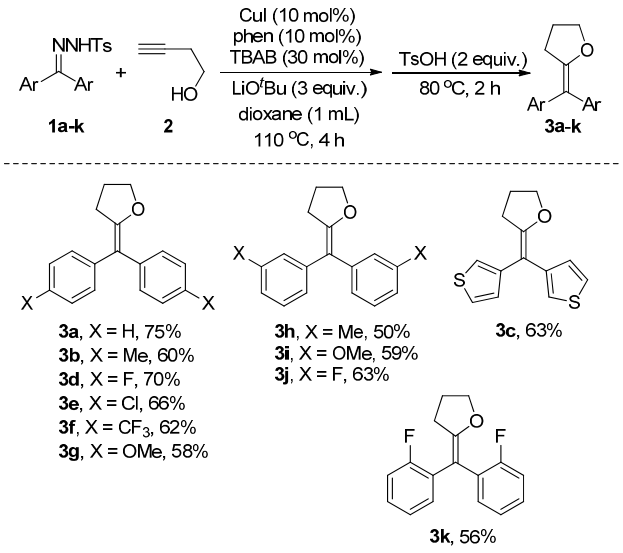


Fig. 1. X-ray structure of **3a**. Thermal ellipsoids shown at 30% probability.

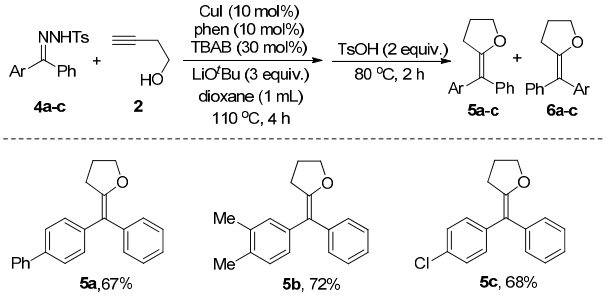
ing experiments were performed to determine the optimum solvent for this transformation, and the results revealed that the polar aprotic solvent dioxane gave the best results (Table 1, entries 3 and 4). We also tested various bases, including K_2CO_3, Cs_2CO_3, NaOH, KOH, NaH, LiO^{t}Bu and $NaOCH_3$, as well as several phase transfer catalysts (PTCs), including tetrabutylammonium bromide (TBAB), tetrabutylammonium chloride (TBAC) and tetrabutylammonium iodide (TBAI). The results of these experiments revealed that the use of a combination of LiO^{t}Bu and TBAB gave the highest yield of the desired product.

Following on from these preliminary results, we proceeded to screen several other important parameters with the aim of further improving the yield and the chemoselectivity of this reaction. We initially evaluated a series of different Cu catalysts using phenanthroline as a ligand (Table 1, entries 5–9). The results revealed that the use of the CuI catalyst in combination with phenanthroline resulted in improved performance (Table 1, entries 2 and 9). However, the nature of the catalyst did not appear to have an adverse impact on the ratio of **3a** and **3a'**. We therefore decided to convert the isomeric mixture generated from the Cu(I)-catalyzed coupling reaction into a single product using either an oxidation or an acid-promoted rearrangement. However, in the presence of an oxidant such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), 1,4-benzoquinone (BQ) or $PhI(OAc)_2$, the isomeric mixture decomposed to form a complex mixture (Table 1, entries 10 and 11). Pleasingly, the treatment of the completed Cu(I)-catalyzed reaction mixture with 2 equiv. of TsOH or trifluoroacetic acid (TFA) for 2 h at 80 °C afforded **3a** as a single product in moderate yield (Table 1, entries 12–14). Based on these results, we screened several other reaction parameters, including the reaction temperature, reaction time and molar ratio of the substrates. Finally, we concluded that the optimum conditions for this transformation were as follows: 1:3 (mol/mol) ratio of *N*-tosylhydrazone **1a** and 3-butyn-1-ol (**2**), 10 mol% CuI, 10 mol% bathophenanthroline, 30 mol% TBAB and 3.0 equiv. of LiO^{t}Bu at 110 °C (Table 1, entry 15).

With the optimum reaction conditions in hand, we proceeded to investigate the scope and generality of this reaction by screening a variety of *N*-tosylhydrazones (**1a–k**), which were derived from the corresponding symmetrical diarylmethanones, with 3-butyn-1-ol (**2**). As shown in Scheme 2,



Scheme 2. Evaluation of the substrate scope of *N*-tosylhydrazones derived from symmetrical diarylmethanones. Reaction conditions: *N*-tosylhydrazone **1a–k** (0.2 mmol), 3-butyn-1-ol (**2**, 3.0 equiv.), CuI (10 mol%), bathophenanthroline (L) (10 mol%), TBAB (30 mol%) and LiO^{t}Bu (3.0 equiv.) in dioxane (1 mL) at 110 °C for 4 h. TsOH (2.0 equiv. was then added, and the resulting mixture was heated at 80 °C for 2 h. Isolated yield by column chromatography.

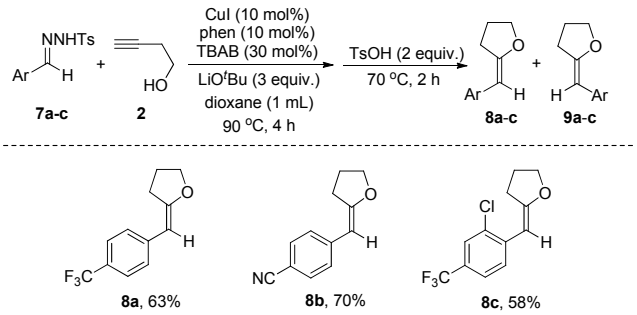


Scheme 3. Reactions of *N*-tosylhydrazones derived from unsymmetrical diarylmethanone. The reactions were conducted under the same conditions as those described above in Scheme 2. The yields refer to the isomeric mixtures prior to being purified by column chromatography.

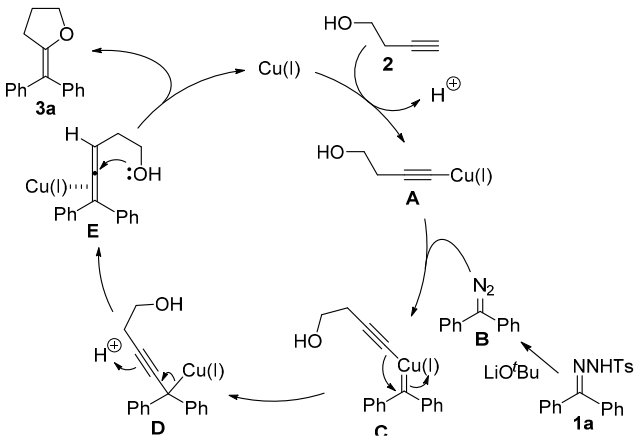
these reactions afforded the corresponding 2-(diarylmethylene)tetrahydrofurans **3a–k** in moderate to good yields. Notably, *N*-tosylhydrazones bearing an electron-rich or electron-deficient substituent on the *para, meta* or *ortho* positions of their aromatic rings were found to be good substrates for this transformation. The *N*-tosylhydrazone derived from di-3-thienyl ketone (**1c**) also reacted smoothly to give the corresponding product **3c** in 63% yield.

Encouraged by the successful tandem cyclization of the symmetrical *N*-tosylhydrazones with 3-alkynol, we proceeded to extend this strategy to a series of unsymmetrical *N*-tosylhydrazones, which were derived from the corresponding unsymmetrical ketones. As shown in Scheme 3, *N*-tosylhydrazones **4a–c** reacted with 3-alkynol (**2**) to give the corresponding 2-(diarylmethylene)tetrahydrofurans **5a–c** with good stereoselectivity. The outcome of the reaction was found to be largely unaffected by the structure of the unsymmetrical *N*-tosylhydrazone substrate or the nature of the substituents on the aromatic ring. All of these reactions gave the *E* isomer as the major product, with only trace amounts of the corresponding *Z* isomers **6a–c** being detected by crude ^{1}H NMR and GC-MS analysis. Pleasingly, the minor *Z* isomers were separated or isomerized to the corresponding *E* isomers during column chromatographic purification over silica gel.

Finally, we investigated the reaction of several unsymmetrical *N*-tosylhydrazones **7a–c,** which were derived from the corresponding aromatic aldehydes, with 3-alkynol (**2**) under the optimized reaction conditions. As demonstrated in Scheme 4, the substituent at the para position of the aromatic ring of the *N*-tosylhydrazones had no discernible impact on the reaction. The presence of an electron-withdrawing group was therefore tolerated under these conditions, affording the corresponding 2-(diarylmethylene)tetrahydrofurans in moderate yields. Similarly, the *E* isomers **8a–c** were determined to be the major products, with only small amounts of the corresponding *Z* isomers **9a–c** being detected by ^{1}H NMR and GC-MS analysis of the crude products in each case. Once again, the minor isomers were readily separated or isomerized to the corresponding *E* isomer by column chromatography over silica gel.



Scheme 4. Reaction of *N*-tosylhydrazones derived from aromatic aldehydes. The reactions were conducted under the same conditions as those described above in Scheme 2. The yields refer to the isomeric mixtures prior to their purification by column chromatography.



Scheme 5. Proposed reaction mechanism of Cu(I)-catalyzed cascade reaction of *N*-tosylhydrazones with 3-butyn-1-ol.

Based on the results described above we proposed a plausible mechanism to account for this Cu(I)-catalyzed tandem cyclization, which is shown in Scheme 5. The initial reaction of 3-butyn-1-ol with the Cu(I) catalyst would give the Cu(I) acetylide **A**, which would react with the *in situ* generated diazo intermediate **B** to generate the Cu(I)-carbene species **C**. The alkynyl migratory insertion of Cu(I)-carbene **C** to the carbenic carbon would give intermediate **D**, which would be protonated to give allene. Finally, allene **E** would undergo a cyclization reaction via an intramolecular nucleophilic addition reaction to afford the final product **3a**, with the concomitant regeneration of the Cu(I) catalyst.

4. Conclusions

We have investigated a Cu(I)-catalyzed tandem cyclization reaction of *N*-tosylhydrazones with 3-butyn-1-ol. This reaction represents a straightforward approach for the synthesis of 2-(diarylmethylene)tetrahydrofurans and proceeds via the formation of a carbene intermediate, followed by sequential cyclization and isomerization steps. These results further demonstrate the generality of this approach for the formation of allenes via the Cu(I)-catalyzed reaction of *N*-tosylhydrazones with terminal alkynes [27].

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Graphical Abstract

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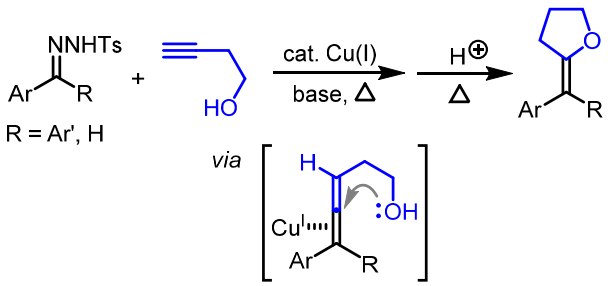
Cu(I)-catalyzed cascade reaction of *N*-tosylhydrazones with 3-butyn-1-ol: A new synthesis of tetrahydrofurans

Mohammad Lokman Hossain, Kang Wang, Fei Ye, Yan Zhang, Jianbo Wang*
Peking University; State Key Laboratory of Organometallic Chemistry, Chinese Academy of Sciences

A simple and efficient method has been developed for the synthesis of tetrahydrofurans. This method is based on the Cu(I)-catalyzed cascade coupling/cyclization reaction of *N*-tosylhydrazones with 3-butyn-1-ol, and involves a Cu(I) carbene migratory insertion as one of its key steps.



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