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Cyclization

Gold-Catalyzed Cascade Reactions of Furan-ynes with External Nucleophiles Consisting of a 1,2-Rearrangement: Straightforward Synthesis of Multi-Substituted Benzo[*b*]furans

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Abstract: A gold-catalyzed cycloisomerization of silyl-protected 2-(1-alkynyl)-2-alken-1-(2-furanyl)-1-ols with various nucleophiles including water, alcohol, aniline, sulfonamide, and electron-rich arene has been developed. The method provides a highly efficient access to 5,7-disubstituted or 2,5,7-trisubstituted benzo[*b*]furans with a wide diversity of substituents under mild reaction conditions, which are not easily available by other methods. Remarkably, an interesting rearrangement of the alkyl group from C2 to the C3 position of the furan ring takes place during the cyclization process. The following gold-assisted allylic substitution enables an elaboration of benzo[*b*]furans on its side chain of the C5 position with a wide range of functional groups.

Introduction

The benzo[*b*]furans constitute an important class of heterocyclic compounds that widely occur as a core structural motif in biologically active natural products and pharmaceutical agents.[1] For example, obovaten is one of the characteristic member of the neolignan family, which is known as an active antitumor agent.[2] 2-Aminoethylbenzofurans such as "**a**" in Figure 1 represent a new class of non-imidazole H_3 antagonists,

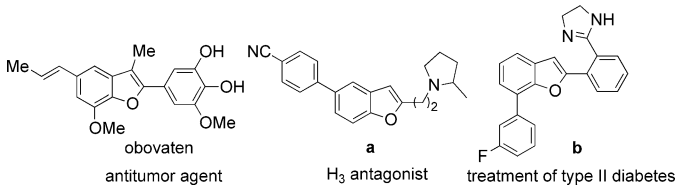

Figure 1. Biologically active benzo[*b*]furans.

which retain high potency at human and rat receptors with efficient CNS penetration.[3] The 2,7-disubstituted benzofuran **b** can be used for the treatment of type II diabetes (Figure 1).[4] Therefore, the development of general and efficient methodologies for the synthesis of benzo[*b*]furans, especially those that can operate under mild reaction conditions, is highly desired. Most of the synthetic approaches concentrated on the construction of the furan framework by using *ortho*-functionalized phenols,[5,6] such as palladium-catalyzed tandem reaction of *o*-halophenols with terminal alkynes,[6] whereas there are few reports based on the aromatic benzene ring formation.[7] The development of the new strategy through formation of the benzene ring of benzofurans would be quite useful because it may allow the introduction of the substituents on the phenyl ring in a highly regioselective manner. Recently, we carried out a series of gold-catalyzed[8] cascade reactions of furan-ynes through an *endo-dig*-type cyclization leading to a variety of functionalized products such as benzenes, phenanthrenes, and fulvenes.[9] The methodology has been applied to the synthesis of 1-naphthol derivatives from *tert*-butyldimethylsilyl (TBS)-protected (*o*-alkynyl)phenyl 2-furylcarbinols.[10] Inspired by these results and during our further study on gold-catalyzed formation of fulvenes[9c] (Scheme 1, [Eq. (1)]), we envisioned that the use of more readily available substrate of silyl-protected 2-(1-alkynyl)-2-alken-1-(2-furanyl)-1-ols **1** compared with the substrates shown in Scheme 1, Equation (1), might also undergo a similar type of cyclization to furnish siloxy-substituted fulvenes. However, to our surprise, the reaction proceeded efficiently to generate the benzo[*b*]furan **2** through construction of the benzene ring in the presence of external nucleophiles instead of fulvene (Scheme 1, [Eq. (2)]). Interestingly, a rearrangement of the C2 alkyl group on the furan ring was involved in these reactions. Recently, Hashmi et al. reported a 2,3-shift reaction of furans tethered with aryl- or heteroaryl-substituted alkynes leading to 2,7-disubstituted benzo[*b*]furans[7a] (Scheme 1, [Eq. (3)]). Our reaction presented here allows a facile synthesis of 5,7-disubstituted and 2,5,7-trisubstituted benzo[*b*]furans with a wider reaction scope. Moreover, the side

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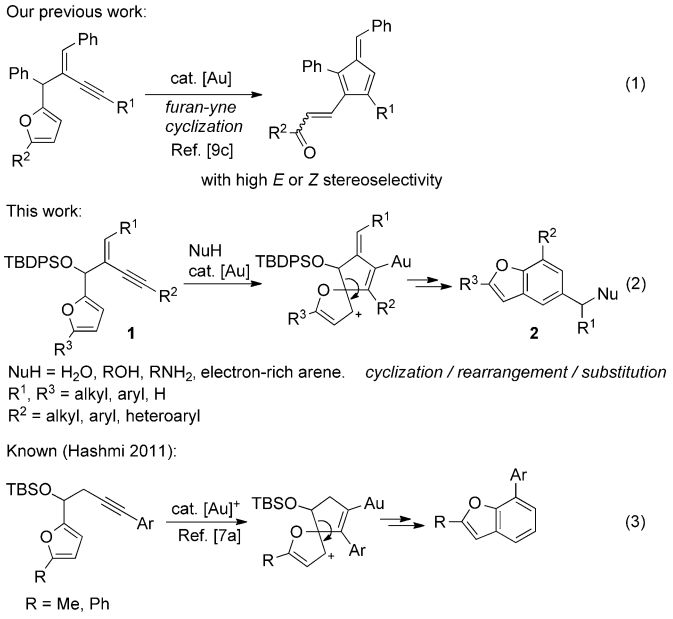


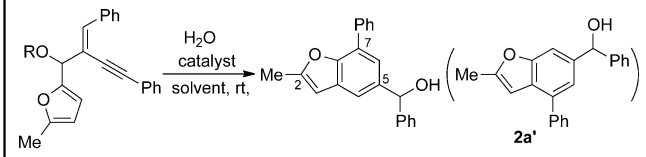
Scheme 1. Gold-catalyzed transformation of furan-ynes.

chain of the C5 substituent of the benzofuran products can be further elaborated by using a variety of functional groups.

Results and Discussion

The requisite substrates are easily synthesized by the addition of a (2-furanyl)lithium reagent to an enynyl aldehyde followed by protection with silyl chloride or through Sonogashira coupling of the corresponding aryl or vinyl halides with terminal alkynes.[11] Our studies began with the investigation of the possible cyclization of *tert*-butyldiphenylsilyl (TBDPS)-protected 2-furylcarbinol **1a**. In light of the superior catalytic activity of JohnPhos(MeCN)AuSbF$_6$ (catalyst **A**) bearing a biarylphosphine ligand in various gold-catalyzed reactions,[12] catalyst **A** (5 mol%) was first employed as the catalyst. The reaction proceeded at room temperature in THF to give benzo[*b*]furan **2a** in 38% yield after 14 h (Table 1, entry 1). The presence of an OH group indicated that **2a** might be formed by the reaction of **1a** with a small amount of water contained in the reaction system. In the presence of 4 Å molecular sieves (MS), no reaction occurred at room temperature or at 80 °C, because most of **1a** was recovered (Table 1, entries 2 and 3). As expected, addition of H_2O (2.0 equiv) to the reaction mixture led to a drastic improvement in which 89% of **2a** could be obtained within 3 h (Table 1, entry 4). Increasing the amount of H_2O to 5.0 equiv resulted in a shorter reaction time and higher product yield (93%, Table 1, entry 5). When the TBS-protected substrate **1a′** was employed, the yield of **2a** decreased to 75%, possibly due to the lower stability of **1a′** compared with **1a** in acidic medium (Table 1, entry 6). Changing the solvent to 1,2-dichloroethane (DCE) or toluene resulted in lower yields of **2a** (35–58%, Table 1, entries 7 and 8). Thus, THF was proved to be the best solvent, possibly due to the fact that it can stabilize the cationic intermediate formed during the reaction process.

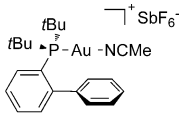
Table 1. Optimization studies for the formation of benzo[*b*]furan **2a**.



1a, R = TBDPS, **1a'**, R = TBS **2a** not observed

Entry	Substrate	Catalyst [5 mol%]	Solvent	H_2O [equiv]	*t* [h]	Yield of **2a**[a] [%]
1	**1a**	**A**	THF	–	14	38
2[b]	**1a**	**A**	THF	–	5	–[c]
3[b,d]	**1a**	**A**	THF	–	9	–[e]
4	**1a**	**A**	THF	2	3	89
5	**1a**	**A**	THF	5	1.5	93
6	**1a′**	**A**	THF	5	6.5	75
7	**1a**	**A**	DCE	5	9	35
8	**1a**	**A**	toluene	5	6	58
9	**1a**	[Au(PPh$_3$)][SbF$_6$]	THF	5	40	72
10	**1a**	[Au(PPh$_3$)][NTf$_2$]	THF	5	9	56
11	**1a**	[Au(IPr)][SbF$_6$]	THF	5	22	72
12	**1a**	[Au(PPh$_3$)(OTf)]	THF	5	16	24
13	**1a**	[AuCl$_3$]	THF	5	15	12
14	**1a**	[Au(PPh$_3$)Cl]	THF	5	5	–[f]
15	**1a**	[AgSbF$_6$]	THF	5	3.5	NR[g]

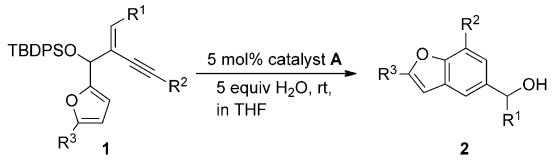
[a] Yields of the isolated products. [b] In the presence of 4 Å MS. [c] A yield of 96% of **1a** was recovered. [d] $T = 80$ °C, in a sealed tube. [e] A yield of 97% of **1a** was recovered. [f] A yield of 98% of **1a** was recovered. [g] NR = No reaction.

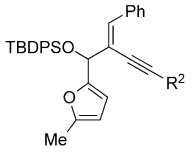
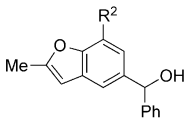
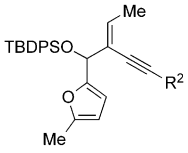
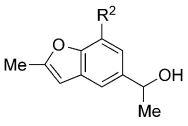
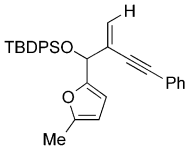
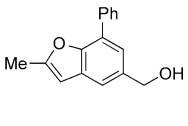
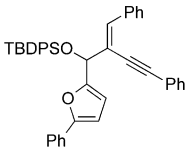
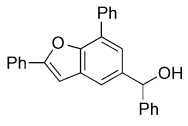
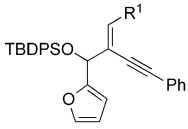
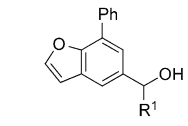


catalyst **A**

The frequently used gold(I) complexes such as [Au(PPh$_3$)][SbF$_6$], [Au(PPh$_3$)][NTf$_2$], or [Au(IPr)][SbF$_6$] (IPr = 2,6-bis(diisopropylphenyl)imidazol-2-ylidene; NTf$_2$ = bis(trifluoromethanesulfonyl)imidate) could also catalyze this cycloisomerization reaction to afford moderate to good yields of **2a** (Table 1, entries 9–11), however, the use of less electrophilic [Au(PPh$_3$)][OTf] (OTf = trifluoromethanesulfonate) only led to 24% yield of **2a** (Table 1, entry 12). Control experiments with [AuCl(PPh$_3$)] or [AgSbF$_6$] could not afford the desired benzofuran **2a** (Table 1, entries 14 and 15). The use of non-protected 2-furylcarbinol such as (*E*)-2-benzylidene-1-(5-methylfuran-2-yl)-4-phenylbut-3-yn-1-ol only afforded a complicated mixture under gold-catalyzed conditions shown in Table 1, entry 5. To our surprise, X-ray crystal analysis of analogous products **2i** and **3i**[13] (see below) indicated that the structure of **2a** is a 2,5,7-trisubstituted benzofuran, but not a 2,4,6-trisubstituted benzofuran **2a′** formed by direct hydroarylation of the furan ring through its C3 position followed by subsequent allylic substitution. The results indicated that a rearrangement of the alkyl group from C2 to the C3 position of the furan ring occurred during the cyclization process. The substituent "castling" process[14] to form a 2,7-disubstituted benzofuran was also observed by Hashmi et al. as shown in Scheme 1, Equation (3).[7a]

Next, we investigated the substrate scope under the reaction conditions shown in entry 5, Table 1, and the results are



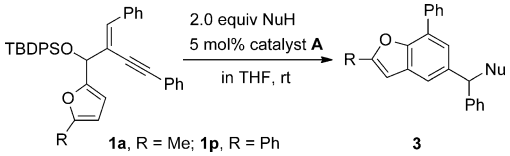
Substrate	Product[a]	Substrate	Product[a]
			
1b, R^2 = *p*-$OMeC_6H_4$	**2b**, 1 h, 78%	**1m**, R^2 = Ph	**2m**, 1 h, 83%
		1n, R^2 = *n*Bu	**2n**, 1 h, 77%
1c, R^2 = *o*-$OMeC_6H_4$	**2c**, 1 h, 88%		
1d, R^2 = *m*-$OMeC_6H_4$	**2d**, 1 h, 67%		
1e, R^2 = 3,4,5-tri$OMeC_6H_2$	**2e**, 0.5 h, 99%	**1o**	**2o**, 2 h, 80%
1f, R^2 = *p*-ClC_6H_4	**2f**, 5 h, 86%		
1g, R^2 = *p*-$CF_3C_6H_4$	**2g**, 24 h, 71%		
1h, R^2 = *p*-$NO_2C_6H_4$	**2h**, 20 h, 60%[b]	**1p**	**2p**, 2.5 h, 74%
1i, R^2 = 2-thienyl	**2i**, 1 h, 84%		
1j, R^2 = *n*Bu	**2j**, 2 h, 84%		
1k, R^2 = cyclopropyl	**2k**, 10 min, 86%	**1q**, R^1 = Me	**2q**, 2 h, 50%
		1r, R^1 = Ph	**2r**, 16 h, 91%
1l, R^2 = CH_2OBn	**2l**, 3 h, 66%[b]	**1s**, R^1 = H	–[c]

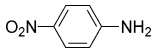
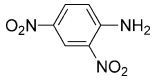
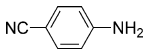
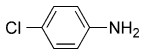
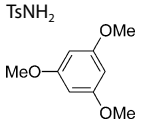
Scheme 2. Synthesis of benzo[*b*]furans by the gold-catalyzed cascade reaction of furan-ynes **1**. [a] Yields of the isolated products. [b] 10 mol% of catalyst **A** was used. [c] Complex mixture.

summarized in Scheme 2. The reaction proved to be quite general with respect to substitution of R^1–R^3, since aryl, alkyl, and hydrogen groups were all suitable for R^1 and R^3, and aryl, heteroaryl, and alkyl groups were suitable for R^2 substituents, providing a broad diversity of the products. Gold catalyst **A** showed high catalytic performance in this system, since most of the reactions could be completed within several hours at room temperature, and the desired benzo[*b*]furans were obtained in moderate to high yields. The substituent effects on the alkyne terminus (R^2) were examined first. The reactions tolerated both electron-rich (*p*-MeO, *o*-MeO, *m*-MeO, 3,4,5-tri(MeO)) and electron-poor (*p*-Cl, *p*-CF_3, *p*-NO_2) aryl substituents, furnishing the corresponding benzofuran derivatives **2b**–**2h** in 60–99% yields. Usually, electron-rich alkynes made the reaction faster than the electron-poor ones. Interestingly, a sterically encumbered *o*-MeO-substituted substrate **1c** was smoothly converted into the corresponding **2c** in a high yield of 88%, possibly due to the weak interaction of the MeO group with gold catalyst, which facilitates the formation of a gold-alkyne complex. The 3,4,5-tri(MeO)-substituted **1e** afforded **2e** in quantitative yield. The strong electron-withdrawing $-NO_2$ functionality was also compatible for this reaction, however, only 60% of **2h** was obtained after stirring at room temperature for 20 h using 10 mol% of catalyst **A**. The thienyl group was well-tolerated, leading to **2i** in 84% yield. In particular, a range of alkyl-substituted alkynes such as *n*-butyl, cyclopropyl, or benzyloxymethyl-substituted alkynes were efficiently transformed into benzofurans **2j**–**2l** in 66–86% yields. The alkyl-substituted furan-ynes were not mentioned in Hashmi's work[7a] described in Scheme 1. Our reactions enlarged the reaction scope significantly for this chemistry. Next, the substituents on the alkene terminus (R^1) were examined. Methyl-substituted substrates, either with an aryl or alkyl group on its alkyne terminus, underwent the cyclization smoothly to provide **2m** and **2n** in 83 and 77% yields, respectively. The alkene substituent could also be a hydrogen, and the corresponding **2o** was obtained in 80% yield with a $-CH_2OH$ functionality. The substituent effects on the furanyl moiety (R^3) were also investigated. The 5-phenyl-substituted furan **1p** with a phenyl group on the alkene moiety was also suitable under the reaction conditions, furnishing multi-substituted benzofuran **2p** in 74% yield. We also studied the reactivity of unsubstituted furan substrates **1q**–**1s**. It was found that the nature of the substituents on the alkene terminus had a marked influence on the cyclization process. Substrates **1q** and **1r** with alkyl or aryl groups on the alkene moiety reacted with water without problem to give **2q** and **2r** in 50 and 91% yields, respectively. However, substrate **1s** with a terminal alkene moiety did not deliver the desired benzofuran, but instead, a complicated reaction mixture was observed.

We proceeded to examine the reactions with a range of nucleophiles using **1a** or **1p** as the furan-yne component, and the results are summarized in Table 2. It was found that a variety of alcohols could be used as effective nucleophiles for this reaction. For example, treatment of **1a** with methanol or ethanol afforded the corresponding cycloisomerization products **3a** and **3b** in 70 and 80% yields, respectively (Table 2, entries 1 and 2).[15] Benzyl alcohol or allyl alcohol were also well-suited, leading to **3c** and **3d** in 79 and 62% yields, respectively (Table 2, entries 3 and 4). Anilines were also successfully em-

Table 2. Gold-catalyzed cyclization of furan-ynes **1** with various nucleophiles.

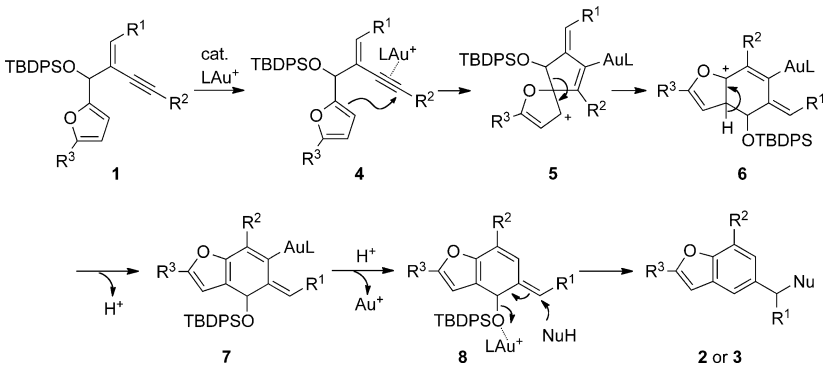


Entry	Enyne	NuH	*t* [h]	Product	Yield [%][a]
1	**1a**	MeOH	1	**3a**	70
2	**1a**	EtOH	1	**3b**	80
3	**1a**		1	**3c**	79
4	**1a**		1	**3d**	62
5	**1a**		1	**3e**	96
6	**1a**		1	**3f**	78
7	**1a**		2	**3g**	81[b]
8	**1a**		14	**3h**	75[c]
9	**1p**	$TsNH_2$	2	**3i**	47[d]
10	**1a**		3	**3j**	62[e]

[a] Yields of the isolated product. [b] $T = 50\,^{\circ}C$, in THF. [c] $T = 80\,^{\circ}C$, in toluene. [d] 3.0 equiv of $TsNH_2$ was used, 50 °C, in toluene. [e] 10 mol% catalyst **A** was used, 60 °C, in toluene.

ployed as nucleophiles for this cyclization;[16] for example, anilines bearing strong electron-withdrawing 4-NO_2 or 2,4-diNO_2-substituent afforded the corresponding benzofurans **3e** and **3f** in 96 and 78% yields, respectively, within 1 h (Table 2, entries 5 and 6). The use of *p*-CN-substituted aniline afforded **3g** in 81% yield at 50 °C (Table 2, entry 7). A weak electron-withdrawing *p*-Cl-substituted aniline underwent the reaction only at higher reaction temperature (80 °C) to give **3h** in 75% yield (Table 2, entry 8). This might be due to the coordination of amine to the metal center, which decreased the activity of the catalyst. When $TsNH_2$ was employed as a nucleophile, a moderate yield of **3i** (47%) could be obtained (Table 2, entry 9). Electron-rich arenes such as 1,3,5-trimethoxybenzene also reacted with **1a** in the presence of 10 mol% catalyst **A** to afford **3j** in 62% yield (Table 2, entry 10). So far, no positive results were obtained by using 1,3-dicarbonyl compounds such as pentane-2,4-dione or 1,3-diphenylpropane-1,3-dione.

A proposed reaction mechanism[17] for this gold-catalyzed cycloisomerization of furan-ynes in the presence of external nucleophiles is depicted in Scheme 3. The reaction starts with the activation of the alkyne moiety in **1** through coordination with the gold catalyst. This is followed by attack of the C2 position of furan ring to the triple bond in a manner of 5-*endo-dig* cyclization to give a spirocyclic intermediate **5**. Then, a Wagner–Meerwein rearrangement[7a,18] of the alkyl group followed by elimination of a proton gives intermediate **7**. Protodeauration of **7** delivers intermediate **8**. Allylic substitution of **8** with external nucleophile, possibly assisted by gold catalyst,[19] affords the benzo[*b*]furans **2** or **3**.



Scheme 3. Proposed reaction mechanism

Conclusion

We have developed a gold-catalyzed cycloisomerization of furan-ynes bearing a silyloxy group at the α-position of the furan rings with various nucleophiles, which provides a highly efficient route for the synthesis of multi-substituted benzo[*b*]-furans. The reactions tolerate a wide variety of functional groups both on the furanyne substrates and the nucleophiles, making this approach highly attractive. The method is useful to pharmaceutical chemists for drug discovery and development. Mechanistically, it is suggested that the formation of a spirocyclic cationic intermediate followed by 1,2-rearrangement and gold-catalyzed allylic substitution is involved in the reaction process. It is anticipated that the use of other heterocycles such as thiophene, pyrrole, indole, and so on, instead of the furan moiety might also be suited for this chemistry. Further extensions toward this subject are in progress.

Experimental Section

General procedure for the synthesis of benzo[*b*]furans 2 and 3

The nucleophile (for the amount, see Scheme 2 and Table 2) and catalyst **A** (11.6 mg, 0.015 mmol) were added to a solution of furan-yne **1** (0.3 mmol) in THF (6 mL). The resulting mixture was stirred at room temperature or indicated temperature until the reaction was complete as monitored by thin-layer chromatography. The solvent was evaporated under the reduced pressure and the residue was purified by column chromatography on silica gel to afford the product **2** or **3**.

(2-Methyl-7-phenylbenzofuran-5-yl)(phenyl)methanol (2a): Scale = 0.3 mmol. Column chromatography on silica gel (petroleum ether:

ethyl acetate = 10:1) afforded the title product isolated in 93% yield (87.7 mg) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$, Me_4Si): δ = 7.79 (d, J = 7.6 Hz, 2H), 7.42 (t, J = 7.6 Hz, 2H), 7.36–7.31 (m, 5H), 7.28–7.25 (m, 2H), 7.21–7.18 (m, 1H), 6.30 (s, 1H), 5.83 (s, 1H), 2.72 (br s, 1H), 2.39 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.13, 151.30, 144.06, 138.80, 136.45, 129.99, 128.53, 128.44, 128.31, 127.49, 127.27, 126.38, 124.47, 121.58, 117.32, 102.90, 76.25, 14.12 ppm; IR (neat): $\tilde{\nu}$ = 3571, 3398, 3059, 2919, 1953, 1607, 1494, 1450, 1406, 1337, 1264, 1206, 1077, 1033, 940, 877, 818, 770, 734, 696 cm^{-1}; HRMS (EI): *m/z* calcd for $C_{22}H_{18}O_2$: 314.1307; found: 314.1305.

5-(Methoxy(phenyl)methyl)-2-methyl-7-phenylbenzofuran (3a): Scale = 0.2 mmol. Column chromatography on silica gel (petroleum ether/ethyl acetate = 100:1) afforded the title product isolated in 70% (46.2 mg) yield as a light-yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$, Me_4Si): δ = 7.83 (d, J = 7.6 Hz, 2H), 7.48–7.20 (m, 10H), 6.36 (s, 1H), 5.36 (s, 1H), 3.41 (s, 3H), 2.43 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.11, 151.39, 142.48, 136.87, 136.60, 130.02, 128.59, 128.47, 128.34, 127.51, 127.30, 126.79, 124.53, 121.93, 117.76, 102.90, 85.58, 57.00, 14.18 ppm; IR (neat): 3089, 3057, 3030, 2923, 2820, 2049, 1949, 1881, 1732, 1607, 1494, 1451, 1405, 1338, 1244, 1204, 1114, 1091, 1074, 1030, 940, 877, 821, 769, 718, 695 cm^{-1}; HRMS (EI): *m/z* calcd for $C_{23}H_{20}O_2$: 328.1463; found: 328.1459.

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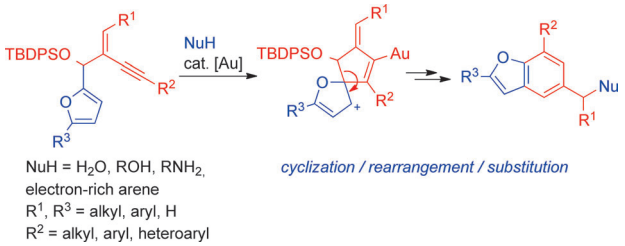

Substituent "castling": A gold-catalyzed cyclization of silyl-protected 2-(1-alkynyl)-2-alken-1-(2-furanyl)-1-ols with various nucleophiles has been developed, providing a highly efficient access to 5,7-disubstituted or 2,5,7-trisubstituted benzo[*b*]furans under mild reaction conditions with a wide diversity of substituents (see scheme; TBDPS=*tert*-butyldiphenylsilyl). A mechanistic proposal for these transformations involving a 1,2-rearrangement and allylic substitution is presented.

Cyclization

*N. Sun, X. Xie, Y. Liu**

■■ – ■■

Gold-Catalyzed Cascade Reactions of Furan-ynes with External Nucleophiles Consisting of a 1,2-Rearrangement: Straightforward Synthesis of Multi-Substituted Benzo[*b*]furans