JOC Article

Water-Triggered, Counter-Anion-Controlled, and Silver−Phosphines Complex-Catalyzed Stereoselective Cascade Alkynylation/Cyclization of Terminal Alkynes with Salicylaldehydes

Min Yu,[†,#] Rachid Skouta,[‡,#] Lei Zhou,[‡,§] Huan-feng Jiang,[§] Xiaoquan Yao,*[,†] and Chao-Jun Li*[,‡]

Department of Applied Chemistry, School of Material Science and Engineering, Nanjing University of Aeronautics and Astronautics, Nanjing 210016, P. R. China, Department of Chemistry, McGill University, Montreal, QC, Canada H3A 2K6, and College of Chemistry, South China University of Technology, Guangzhou 510640, P. R. China

yaoxq@nuaa.edu.cn; cj.li@mcgill.ca

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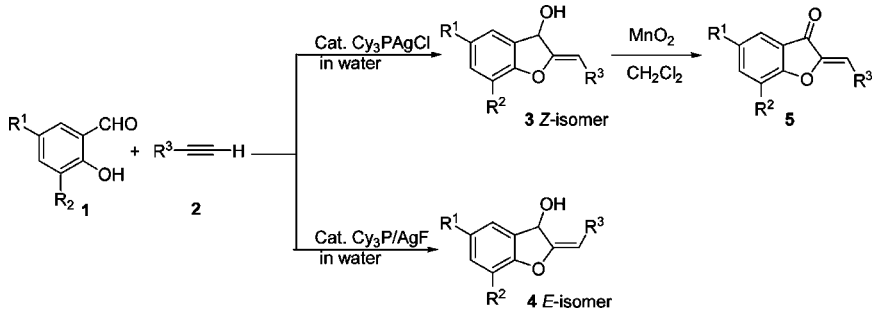

A highly efficient alkynylation-cyclization of terminal alkynes with salicylaldehydes leading to substituted 2,3-dihydrobenzofuran-3-ol derivatives was developed by using Cy_3P−silver complex as catalyst in water. Counter anions in the silver complex proved to be the key factor to *Z*/*E* stereoselectivity control. Aurones can also be obtained effectively from the cascade reaction followed by oxidation without further purification.

Introduction

Catalytic nucleophilic addition with the direct utilization of C−H bonds in water provides a highly atom-economical and environmentally friendly approach to form C−C bonds, which avoids the utilization of stoichiometric amounts of metal and halides when compared to classical methods.[1,2] As a Grignard-type reaction, the addition of terminal alkynes to aldehydes is of great interest because of the versatility of the corresponding propargylic alcohols.[3] Compared with the classical method using stoichiometric metal acetylides,[4] an alternative and more atom-economical approach involves the catalytic addition of terminal alkynes to aldehydes. Recently, various catalytic additions of alkynes to aldehydes were reported by Carreira,[5] Shibasaki,[6] and many others. During our earlier studies on the silver-catalyzed alkynylation of aldehydes in water,[7] we found that

[†] Nanjing University of Aeronautics and Astronautics.
[‡] McGill University.
[§] South China University of Technology.
[#] These authors contributed equally to this work.

(1) (a) For recent reviews on C-H activations, see: Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1698. Chatani, N.; Asaumi, T.; Yorimitsu, S.; Ikeda, T.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **2001**, *123*, 10935. Chen, H.; Schlecht, S.; Semple, T. C.; Hartwig, J. F. *Science* **2000**, *287*, 1995. Goldman, A. S. *Nature (London)* **1993**, *366*, 514. Crabtree, R. H. *J. Organomet. Chem.* **2004**, *689*, 4083. (f) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633. (b) For atom-economy, see: Trost, B. M. *Science* **1991**, *254*, 1471. Trost, B. M. *Angew. Chem., Int. Ed.* **1995**, *34*, 259. Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press, New York, 2000.

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(5) For a review on the zinc acetylide system, see: (a) Frantz, D. E.; Fässler, R.; Tomooka, C. S.; Carreira, E. M. *Acc. Chem. Res.* **2000**, *33*, 373. For a catalytic system, see: (b) Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687. (c) Fässler, R.; Tomooka, C. S.; Frantz, D. E.; Carreira, E. M. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5843. See also: (d) Jiang, B.; Chen, Z.; Tang, X. *Org. Lett.* **2002**, *4*, 3451. For stoichiometric additions to aldehyde, see: (f) Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806. (g) Boyall, D.; Frantz, D. Z.; Carreira, E. M. *Org. Lett.* **2002**, *4*, 2605.

(6) Takita, R.; Fukuta, Y.; Tsuji, R.; Ohshima, T.; Shibasaki, M. *Org. Lett.* **2005**, *7*, 1363.

(7) Yao, X.; Li, C.-J. *Org. Lett.* **2005**, *7*, 4395.

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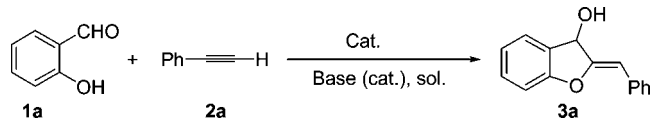
TABLE 1. Catalytic Alkynylation-Cyclization of Salicylaldehyde with Phenylacetylene[a]



1a **2a** **3a**

entry	catalyst	conditions	results[b]
1	Me_3PAuCl	water, *i*-Pr_2NEt 20 mol %, 100 °C	ND[c]
2	$Me_3PAuCl/AgOTf$ (1:1.1)[d]	water, *i*-Pr_2NEt 20 mol %, 100 °C	ND[c]
3	Ph_3PAuCl	water, *i*-Pr_2NEt 20 mol %, 100 °C	ND[c]
4	Ph_3PAgCl	water, *i*-Pr_2NEt 20 mol %, 100 °C	12%
5	Ph_3PAgBr	water, *i*-Pr_2NEt 20 mol %, 100 °C	trace
6	Ph_3PAgI	water, *i*-Pr_2NEt 20 mol %, 100 °C	trace
7	$Ph_3P/AgOTf$ (1.1:1)[d]	water, *i*-Pr_2NEt 20 mol %, 100 °C	trace
8	*n*-$Bu_3P/AgCl$ (1.2:1)[d]	water, *i*-Pr_2NEt 20 mol %, 100 °C	14%
9	Cy_3PAgCl	water, *i*-Pr_2NEt 20 mol %, 100 °C	22%
10	Cy_3PAgCl	water, Et_3N 20 mol %, 100 °C	10%
11	$Cy_3P/CuCl$ (1.2:1)[d]	water, *i*-Pr_2NEt 20 mol %, 100 °C	ND[c]
12	Cy_3PAgCl	MeCN, *i*-Pr_2NEt 20 mol %, 100 °C[e]	ND[c]
13	Cy_3PAgCl	water−toluene, *i*-Pr_2NEt 20 mol %, 100 °C[e]	trace
14	Cy_3PAgCl	water-EtOH, *i*-Pr_2NEt 20 mol %, 100 °C[f]	trace
15	Cy_3PAgCl	water-dioxane, *i*-Pr_2NEt 20 mol %, 100 °C[f]	trace
16	Cy_3PAgCl	water-DCE, *i*-Pr_2NEt 20 mol %, 100 °C[e]	20%
17	Cy_3PAgCl	water-CH_2Cl_2, *i*-Pr_2NEt 20 mol %, 100 °C[e]	31%
18	Cy_3PAgCl	water-CH_2Cl_2, *i*-Pr_2NEt 20 mol %, 60 °C[g]	67%
19	Cy_3PAgCl	water, phenylacetylene (4 equiv), *i*-Pr_2NEt 20 mol %, 100 °C	59%
20	Cy_3PAgCl	water, phenylacetylene (4 equiv), *i*-Pr_2NEt 20 mol %, 80 °C[h]	77%

[a] Conditions: salicylaldehyde (0.5 mmol), phenylacetylene (0.75 mmol, 1.5 equiv), catalyst (10 mol %), *i*-Pr_2NEt (20 mol %), water (1.5 mL), overnight. [b] Isolated yield. [c] Not detected. [d] Catalyst was prepared in situ at room temperature by mixing the two precursors in methylene chloride (0.5 mL) for 2 h, and then the solvent was removed under reduced pressure. [e] Water/organic solvent (v/v) = 3:1. [f] Water/organic solvent (v/v) = 2:1. [g] Reacted for 1 day. [h] Reacted for 8 h.

the metal acetylides of group IB such as Cu(I), Ag(I), and Au(I), which were believed to be reactive only to imines[8] and inert to carbonyl,[9] could be activated by a phosphine ligand and reacted with aldehydes. Following this approach, a cascade addition/cyclization of terminal alkynes with acetylenic aldehydes, catalyzed by a phosphine−gold(I) complex, led to 1-alkynyl-1*H*-isochromenes in water.[10] In both examples above, water (as well as the phosphine ligand) plays a key role to promote the reaction of metal acetylides and aldehydes.

(*Z*)-2,3-Dihydrobenzofuran-3-ol derives (**3**) are key intermediates for the syntheses of aurones (**5**), which have exhibited a wide range of biological activities and have been used as antifungal agents, tyrosinase inhibitors, antioxidants, etc.[11] Among the reported methods for synthesizing aurones,[12] the gold(I)-catalyzed cyclization of 2-(1-hydroxy-3-arylprop-2-ynyl)phenols followed by oxidation of the cyclized product **3** with MnO_2 reported very recently by Pale and co-workers provides a highly efficient route to these compounds.[13] However, following this method, the starting materials had to be prepared by using the stoichiometric nucleophilic addition between salicylaldehydes and lithium acetylides, of which 2 equiv were required: 1 equiv to quench the proton from the phenol group and the other to react with the aldehyde.

On the basis of the silver(I)- and gold(I)-catalyzed aldehyde-alkynylation reaction that we reported earlier,[14] herein, we describe a novel highly efficient and stereoselective approach to construct the dihydrobenzofuran structure directly from salicylaldehydes and terminal alkynes by a catalyzed cascade addition/cyclization reaction, in which a catalytic amount of silver(I) catalyst is used together with a catalytic amount of a tertiary amine in water. The counter anions in the catalyst behave as a switch to control the *Z/E* selectivity of the reaction. Furthermore, after extracting from water with an organic solvent, the organic phase can then be oxidized directly without any further purification to give aurones.

Results/Discussions

In our previous studies on the alkynylation of acetylenic aldehydes,[10] Me_3PAuCl provided the best catalytic activity. However, in the prototype reaction between salicylaldehyde and phenylacetylene of our current studies, neither alkynylation product nor further cyclization product was observed after overnight reaction with Me_3PAuCl as a catalyst at 100 °C (entry

(8) For an account on the addition of terminal alkynes to imines, see: (a) Wei, C.; Li, Z.; Li, C.-J. *Synlett* **2004**, 1472. See also: (b) Wei, C.; Mague, J. T.; Li, C.-J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5749. (c) Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* **2002**, *124*, 5683. (d) Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* **2003**, *125*, 9584. (e) Wei, C.; Li, Z.; Li, C.-J. *Org. Lett.* **2003**, *5*, 4473. (f) Li, Z.; Wei, C.; Chen, L.; Varma, R. S.; Li, C.-J. *Tetrahedron Lett.* **2004**, *45*, 2443. (g) Li, C.-J.; Wei, C. *Chem. Commun* **2002**, 268. (h) Li, C.-J. *Acc. Chem. Res.* **2002**, *35*, 533. (i) Li, C.-J.; Wei, C. *Green Chem.* **2002**, *4*, 39. (j) Zani, L.; Bolm, C. *Chem. Commun.* **2006**, 4263.

(9) It was widely accepted that metal acetylides generated from Group IB metals could not participate in the nucleophilic C=O addition; see refs 5c and 6.

(10) Yao, X.; Li, C.-J. *Org. Lett.* **2006**, *8*, 1953.

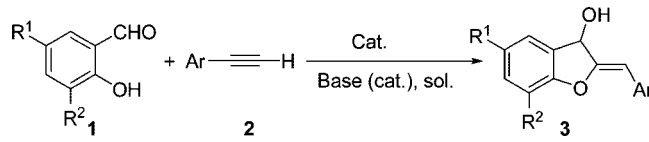
(11) For a review, see: Boumendjel, A. *Curr. Med. Chem.* **2003**, *10*, 2621.

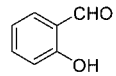
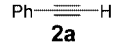
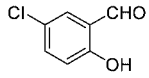
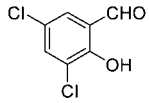
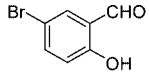
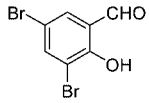
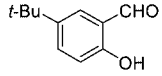
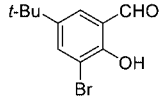
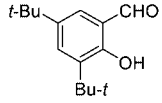
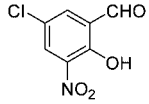
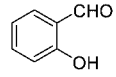
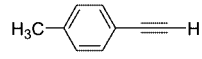
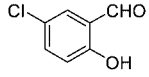
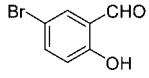
(12) For selected examples, see: (a) Imafuku, K.; Honda, M.; McOmie, J. F. W. *Synthesis* **1987**, 199. (b) Thakkar, K.; Cushman, M. *J. Org. Chem.* **1995**, *60*, 6499. (c) Garcia, H.; Iborra, S.; Primo, J.; Miranda, M. A. *J. Org. Chem.* **1986**, *51*, 4432. (d) An, Z.-W.; Catellani, M.; Chiusoli, G. P. *J. Organomet. Chem.* **1990**, *397*, 371. (e) Jong, T.-T.; Leu, S.-J. *J. Chem. Soc., Perkin Trans. 1* **1990**, 423.

(13) Harkat, H.; Blanc, A.; Weibel, J.-M.; Pale, P. *J. Org. Chem.* **2008**, *73*, 1620.

(14) For recent reviews on silver-catalyzed reactions, see: (a) Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3199. (b) Weibel, J.-M.; Blanc, A.; Pale, P. *Chem. Rev.* **2008**, *108*, 3149. (c) Halbes-Letinois, U.; Weibel, J.-M.; Pale, P. *Chem. Soc. Rev.* **2007**, *36*, 759. (d) Li, Z.; He, C. *Eur. J. Org. Chem.* **2006**, 4313–4322.

TABLE 2. Catalytic Alkynylation-Cyclization of Salicylaldehydes with Arylacetylenes[a]

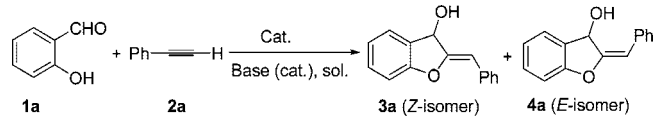


entry	salicylaldehydes		acetylene	conditions	products	yield[b] (%)
1		**1a**	 **2a**	80 °C, 8 h	**3a**	77[c]
2		**1b**	**2a**	70 °C, 8 h	**3b**	79
3		**1c**	**2a**	60 °C, 7 h	**3c**	57
4		**1d**	**2a**	70 °C, 8 h	**3d**	83
5		**1e**	**2a**	65 °C, 7 h	**3e**	60
6		**1f**	**2a**	100 °C, 12 h	**3f**	58 (65% conv[d])
7		**1g**	**2a**	80 °C, 8 h	**3g**	73
8		**1h**	**2a**	150 °C, 7 h	**3h**	48 (52% conv[d])
9		**1i**	**2a**	65 °C, 5 h	**3i**	49
10		**1a**	 **2b**	80 °C, 8 h	**3j**	68
11		**1b**	**2b**	70 °C, 6 h	**3k**	64
12[e]		**1b**	**2b**	65 °C, 24 h	**3k**	81
13		**1d**	**2b**	70 °C, 8 h	**3l**	63

[a] Conditions: salicylaldehyde (0.25 mmol), phenylacetylene (1 mmol, 4 equiv), Cy_3PAgCl (10 mol %), *i*-Pr_2NEt (20 mol %), water (1.5 mL). [b] Isolated yield. [c] 0.5 mmol of salicylaldehyde and 2 mmol of phenylacetylene were used. [d] Calculated based on the recovered starting material. [e] Reaction was carried out in water/CH_2Cl_2, with 2 equiv of alkyne.

1, Table 1). No reaction was observed with changing either the counteranions or the ligands (entries 2 and 3, Table 1). When Ph_3PAgCl was used, the desired product was obtained in only 12% yield with a low conversion of the starting material (entry 4, Table 1). Changing the counter ions did not show any improvement for the reaction (entries 5−7, Table 1). *n*-Bu_3PAgCl gave results similar to those with Ph_3PAgCl (entry 8 vs entry 4, Table 1). Cy_3P and Cl^- provided the best combination of ligand and counter anion, and a 22% yield was observed (entry 9, Table 1). It is worth noting that introduction of some organic solvents decreased the reactivities, with the exceptions of DCE and methylene chloride. The desired product **3a** was isolated in 67% yield with a mixture of CH_2Cl_2/water as solvent at 60 °C for 1 day (entries 12−18, Table 1).[15] The use of 4 equiv of phenylacetylene for 8 h at 80 °C gave the desired product in 77% yield (entry 20, Table 1). A higher

TABLE 3. Reaction of Salicylaldehyde with Phenylacetylene using AgF/PCy_3 as Catalyst[a]

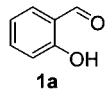
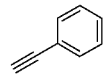
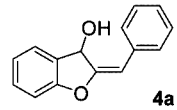
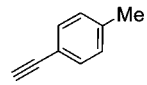
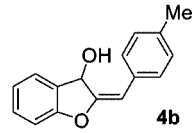
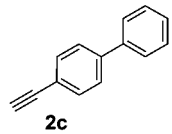
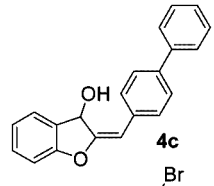
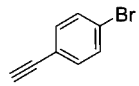
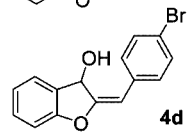
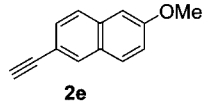
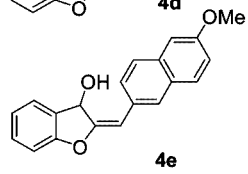
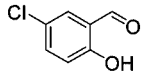
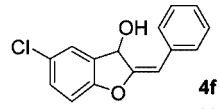
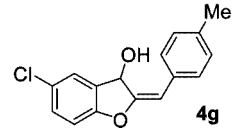


1a **2a** **3a** (*Z*-isomer) **4a** (*E*-isomer)

entry	catalyst (mol %)	conditions	yield of **3a**:**4a**, %[b]
1	AgF/PCy_3 (10/10)	water, *i*-Pr_2NEt 20 mol %, 100 °C, 1 d	30 only **4a**
2	AgF/PCy_3 (5/5)	water, *i*-Pr_2NEt 10 mol %, 90 °C, 2 d	**56 only 4a**
3	AgF/PCy_3 (2.5/2.5)	water, *i*-Pr_2NEt 5 mol %, 90 °C, 2 d	49 only **4a**
4	AgF (5)	water, *i*-Pr_2NEt 10 mol %, 90 °C, 2 d	no reaction
5	AgF/PCy_3 (5/5)	water/toluene, *i*-Pr_2NEt 10 mol %, 90 °C, 2 d	24 (**3a**:**4a** = 2:1)
6	AgF/PCy_3 (5/5)	water/EtOH, *i*-Pr_2NEt 10 mol %, 90 °C, 2 d	54 (**3a**:**4a** = 1.2:1)
7	AgF/PCy_3 (5/5)	water/*t*-BuOH, *i*-Pr_2NEt 10 mol %, 90 °C, 2 d	55 (**3a**:**4a** = 2:1)
8	AgF/PCy_3 (5/5)	water/*n*-BuOH, *i*-Pr_2NEt 10 mol %, 90 °C, 2 d	74 (**3a**:**4a** = 7.2:1)
9	AgF/PCy_3 (5/5)	water/*i*-PrOH, *i*-Pr_2NEt 10 mol %, 90 °C, 2 d	80 (**3a**:**4a** = 3.7:1)
10	AgF/PCy_3 (5/5)	water/THF, *i*-Pr_2NEt 10 mol %, 90 °C, 2 d	82 (**3a**:**4a** = 5.3:1)

[a] Reaction conditions: salicylaldehyde (1 mmol), phenylacetylene (2 mmol), AgF (5 mol %), Cy_3P (5 mol %), water (5 mL). If organic cosolvent was used: water/org sol = 4.5/0.5 (mL/mL). [b] NMR yield with CH_3NO_2 as internal standard.

TABLE 4. Silver-Catalyzed Annulation of Aldehydes with Alkynes[a]

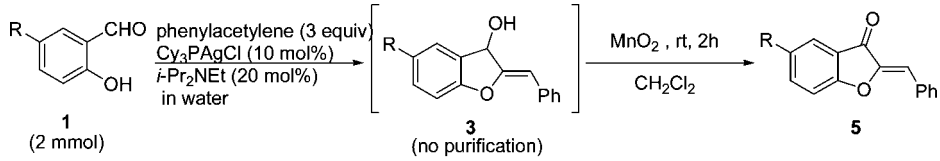
entry	aldehyde	alkyne	product	yield(%)[b]
1	 **1a**	 **2a**	 **4a**	56
2	**1a**	 **2b**	 **4b**	59
3	**1a**	 **2c**	 **4c**	55
4	**1a**	 **2d**	 **4d**	49
5	**1a**	 **2e**	 **4e**	57[c]
6	 **1b**	**2a**	 **4f**	77
7	**1b**	**2b**	 **4g**	79

[a] Conditions: all reactions were carried out at 90−95 °C for 48 h in a sealed tube under nitrogen, with aldehyde (1 equiv), alkyne (2 equiv), AgF (5 mol %), PCy_3 (6 mol %), *i*-Pr_2NEt (10 mol %) and 5 mL of deoxygenated water. [b] Isolated yields. [c] 10 mol % of the catalyst was used.

reaction temperature was not beneficial (entry 19, Table 1). Interestingly, only *Z*-isomer was observed in all these reactions.

Subsequently, various salicylaldehydes were reacted with terminal alkynes under the optimized conditions (Table 2). Moderate to good yields of the *Z*-isomers were obtained selectively. Salicylaldehydes with halides on 5-position proved to be beneficial to the reaction, and an 83% yield was obtained with 5-bromo-salicylaldehyde (entries 2 and 4, Table 2).

SCHEME 1. Cascade Addition/Cyclization and Oxidation to Aurones



Overall yield from **1** to **5**: **5a** R = H, 75.1%

5d R = Br, 72.6%

However, the yields decreased somewhat with the introduction of a second halide on 3-position (entries 2 and 4 vs entries 3 and 5, respectively), which might be partly due to the easier decomposition of the corresponding products under the current reaction conditions. On the other hand, the presence of *tert*-butyl groups seem to slow down the reaction; a much higher reaction temperature and a lower conversion were observed (entries 6 and 8, Table 2). The yield also decreased slightly when tolylacetylene was used instead of phenylacetylene. However, using a mixture of CH_2Cl_2/water as solvent increased the yield of product **3k** to 81% (entry 12, Table 2). It should be noted that all these reactions showed excellent stereoselectivities for the *Z*-isomers under these conditions.

Surprisingly, when a Cy_3PAgF catalyst, generated in situ from AgF and Cy_3P, was used instead of Cy_3PAgCl, the *E*-isomer **4a**[16] was observed stereoselectively in moderate yield under the same conditions (entry 1, Table 3). With 5 mol % Cy_3PAgF catalyst at 90 °C, **4a** was obtained stereoselectively in 56% yield (entry 2, Table 3). Introducing some organic cosolvents, although increasing the yields, switched the selectivity from the *E*-isomer to predominantly the *Z*-isomers (entries 5−10, Table 3). With 10% THF in water as solvent, up to 82% combined yield of **3a** and **4a** was achieved with **3a** as the major product (entry 10, Table 3).

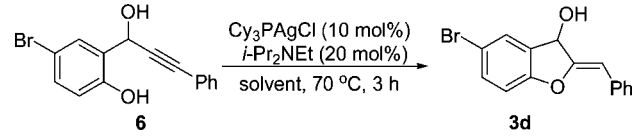
Subsequently, a variety of salicylaldehydes and arylacetylenes were examined under the same reaction conditions. The *E*-isomers **4a**−**g** were obtained stereoselectively in all cases by using AgF/PCy_3 as catalyst and *i*-Pr_2NEt as base in water at 90 °C. In this reaction, some substituted arylalkynes gave similar results (entries 1−5, Table 4), whereas the substituent on salicylaldehyde showed stronger influence on the reactivity. The reaction of 5-chloro-salicylaldehyde with phenylacetylene and 4-methylphenylacetylene gave the desired products in 77% and 79% yields, respectively (Table 4, entries 6 and 7).

The crude product **3a** or **3d**, from the cascade reaction on an enlarged scale, was extracted by CH_2Cl_2 from water and then was oxidized by MnO_2 directly without further purification. The final aurone products **5a** and **5d** were isolated in good yields (Scheme 1).

To further understand the mechanism of the reaction, propargylic alcohol **6** was prepared via the addition of lithium phenylacetylide to salicylaldehyde.[13] The propargylic alcohol obtained was investigated in several solvents using Cy_3PAgCl as catalyst under the present conditions (Table 5). The phenylacetylene/water system gave the highest yields compared to those of other organic solvents (entry 1, Table 5). It is worth noting that the catalytic cyclization can also proceed with a moderate yield in acetonitrile (entry 2, Table 5).

Thus, a tentative mechanism for the silver(I)-catalyzed cascade alkynylation/cyclization of salicylaldehydes is described in Scheme 2. Reaction of terminal alkynes with Cy_3AgCl in the presence of a weak base generates the silver(I) acetylide

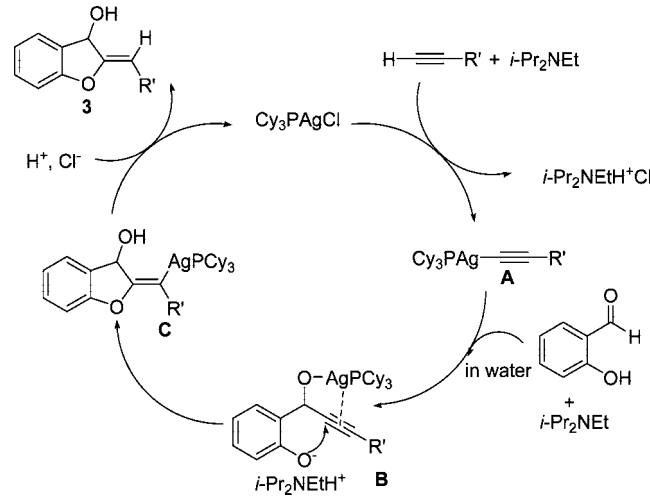
TABLE 5. Silver(I)-Catalyzed Cyclization of 6[a]



entry	solvent	yield of **3d** (%)[b]
1[c]	phenylacetylene/water	71
2	MeCN	22 (36% conv)
3	toluene	7.4 (12% conv)

[a] Conditions: all reactions were carried out at 70 °C for 3 h in a sealed tube under nitrogen, with **6** (0.25 mmol), Cy_3PAgCl (10 mol %), *i*-Pr_2NEt (20 mol %), and 1.5 mL of corresponding solvent. [b] Isolated yields. [c] 1 mmol of phenylacetylene was used.

SCHEME 2. Proposed Mechanism for the Silver(I)-Catalyzed Cascade Alkynylation/Cyclization of Salicylaldehyde



species **A**. The acetylide then reacts with aldehyde to give intermediate **B**, in the presence of water, followed by a silver(I)-promoted *trans*-attack of phenol to the triple bond to give the vinylsilver intermediate **C**. Coordination of the alcohol and the triple bond to Ag(I) provides a stereochemistry control for the *trans*-attack (generating the *Z*-isomer). The carbon−silver bond is then protonated to give the final product **3** with regeneration of the catalyst. However, the model above could not provide a reasonable explanation for the *E*-isomer selectivity with the AgF/Cy_3P catalytic system. The investigation of the exact mechanism is ongoing.

In conclusion, a highly efficient alkynylation-cyclization of terminal alkynes with salicylaldehydes leading to (*Z*)-2-benzylidene-2,3-dihydrobenzofuran-3-ol was developed by using Cy_3PAgCl complex as catalyst in water. The *E*-isomers can also

be obtained stereoselectively with AgF/Cy_3P as the in situ catalyst. Furthermore, the crude product of the cascade reaction can be oxidized to aurone effectively without any purification. The detailed mechanism and the scope of the reaction are currently under further investigations.

Experimental Section

Typical Procedure 1 (Entry 1, Table 2). Cy_3PAgCl (21.2 mg, 0.05 mmol, 10 mol %) was mixed with 1.5 mL of distilled water, 53 μL of salicylaldehyde (0.5 mmol), 0.22 mL of phenylacetylene (**2a**) (2 mmol, 4 equiv), and 17 μL of *i*-Pr_2NEt (0.01 mmol, 20 mol %) in a sealed tube under nitrogen atmosphere. The mixture was stirred at room temperature overnight and then was heated to 80 °C (bath temperature) for 8 h. The reaction was stopped and extracted with ether (3 × 5 mL). The extraction was dried with Na_2SO_4 and concentrated under a reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent = hexanes/EtOAc 20−30:1). Compound **3a** was obtained in 77% of yield. **3a**:[13] CA registry no. [1008105-79-0]. IR (KBr): ν_{max} 3414, 1683, 1612, 1601, 1479, 1290, 1236, 1088, 1022, 908 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.74 (d, J = 7.9 Hz, 2H), 7.50 (d, J = 7.2 Hz, 1H), 7.42−7.34(m, 3H), 7.28−7.24 (m, 1H), 7.12−7.09 (m, 2H), 6.02 (s, 1H), 5.76 (d, J = 12 Hz, 1H), 2.32(d, J = 12 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 157.8, 157.0, 134.5, 130.6, 128.7, 128.5, 126.9, 126.8, 125.7, 122.9, 110.7, 106.0, 72.5; GC/MS *m*/*z* (%) 224 (M^+), 223 (100), 207, 178, 147, 131, 120, 103, 89, 77.

Typical Procedure 2 (Entry 12, Table 2). Cy_3PAgCl (21.2 mg, 0.05 mmol), aldehydes (0.5 mmol), alkynes (1 mmol), and *i*-Pr_2NEt (17 μL, 0.10 mmol) in a mixture of deoxygenated water and CH_2Cl_2 (3:1, 2 mL) were heated in a sealed tube at 60 °C for 24 h under nitrogen. The reaction was stopped and extracted with ether (3 × 5 mL). The extracted organic layer was dried with Na_2SO_4 and concentrated under a reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent = hexanes/EtOAc 15−20:1). Compound **3k** was obtained in 81% of yield by this procedure. **3k**: IR (KBr) ν_{max} 3356, 2920, 2855, 2358, 1689, 1610, 1511, 1473, 1237, 1182, 1135, 1099, 1020, 905 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.59 (d, J = 8.0 Hz, 2H), 7.47 (s, 1H), 7.31 (dd, J = 2.4, 8.4 Hz, 2H), 7.20 (d, J = 7.9 Hz, 1H), 7.02 (d, J = 8.6 Hz, 1H), 6.00 (s, 1H), 5.74 (d, J = 9.0 Hz, 1H), 2.38(s, 3H), 2.33 (d, J = 9.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 156.3, 155.9, 137.0, 131.3, 130.6, 129.2, 128.7, 128.6, 127.7, 125.8, 111.7, 106.6, 72.3, 21.3; GC/MS *m*/*z* (%) 272 (M^+), 255, 237, 205, 192, 181, 165, 118 (100), 105, 91; HRMS calcd for $C_{16}H_{13}ClO_2$ 272.0604, found 272.0602.

Typical Procedure 3 (Entry 1, Table 4). AgF (3.2 mg, 0.025 mmol) and PCy_3 (8.4 mg, 0.03 mmol), aldehydes **1a** (0.5 mmol), alkynes **2a** (1 mmol), and *i*-Pr_2NEt (8.4 μL, 0.05 mmol) in 5 mL of deoxygenated water were heated in a sealed tube at 90−95 °C for 2 d under nitrogen. The reaction mixture was cooled to room temperature and extracted with EtOAc. The combined organic phase was dried with Na_2SO_4 and concentrated under a reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent = hexanes/EtOAc 20−30:1). Compound **4a** was obtained in 56% of yield. **4a**: IR (neat, NaCl) ν_{max} 3332, 2977, 2920, 1600, 1493, 1452, 1378, 1321, 1298, 1253, 1170, 1126, 1079, 1041, 945, 885, 843, 802, 775, 742, 698, 537 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.54−7.36(m, 7H), 7.28−7.22(m, 2H), 6.53(s, 1H), 5.94(b, 1H), 2.77(b, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ 158.7, 155.3, 140.5, 128.9, 128.6, 128.3, 127.1, 124.6, 123.1, 121.4, 111.6, 104.3, 70.9; GC/MS *m*/*z* (%) 224 (M^+), 207 (100), 195, 178, 165, 147, 119, 105, 91, 77, 63, 51; HRMS calcd for $C_{15}H_{12}O_2$ 224.0837, found 224.0834.

Typical Procedure 4 (Scheme 1). Following the procedure described in Typical Procedure 1, salicylaldehyde (**1a**) (2 mmol) reacted with phenylacetylene (**2a**) (6 mmol) in 3 mL of distilled water, in the presence of Cy_3PAgCl (10 mol %) and *i*-Pr_2NEt (20 mol %). When the reaction was stopped and cooled to room temperature, 3 mL of CH_2Cl_2 was added and stirred for several minutes. The aqueous layer was then removed by pipet and extracted with CH_2Cl_2 again (3 mL × 2). The combined organic solution was cooled in an ice bath, and then MnO_2[17] (10 mmol) was added. The mixture was stirred at room temperature for 2 h and filtered through Celite. The organic phase was concentrated under a reduced pressure, and the residue was purified by flash column chromatography on silica gel (eluent = hexanes/EtOAc 30−40:1). Compound **5a** was obtained in 75.1% of yield. **5a**:[13] CA registry no. [37542-14-6]. IR (KBr): ν_{max} 3058, 3020, 1713, 1660, 1599, 1477, 1302, 1128 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.95 (d, J = 7.3 Hz, 2H), 7.83 (d, J = 7.6 Hz, 1H), 7.67(t, J = 8.4 Hz, 1H), 7.51−7.41 (m, 3H), 7.36 (d, J = 8.3 Hz, 1H), 7.25 (t, J = 7.5 Hz, 1H), 6.93 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 184.8, 166.2, 146.9, 136.9, 132.3, 131.6, 129.9, 128.9, 124.7, 123.5, 121.7, 113.1, 113.0; GC/MS *m*/*z* (%) 222 (M^+), 221, 205, 165, 120, 92, 76, 58, 43 (100).

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Supporting Information Available: Full characterization data, ^1H and ^{13}C NMR spectra of additional compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) For the heterogeneous reaction on small scales, the substrates tend to stick on the surface of the stirring bar or the side of the tube, which results in lower conversions. The introduction of a lower-boiling solvent such as DCE and methylene chloride together with a higher reaction temperature may be helpful to keep the substrates in the reaction mixture and increase the yield.

(16) The *E*-**4a** stereochemistry was defined by 1D NOE, irradiating the peaks at 6.53 and 5.94 ppm. For the *E*-isomer, no NOE effect with each other was observed. Please see the spectra for *Z*-**3a** and *E*-**4a** in Supporting Information.

(17) Fresh MnO_2 was prepared from $MnSO_4$ and $KMnO_4$.