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Water-Triggered and Gold(I)-Catalyzed Cascade Addition/Cyclization of Terminal Alkynes with *ortho*-Alkynylaryl Aldehyde

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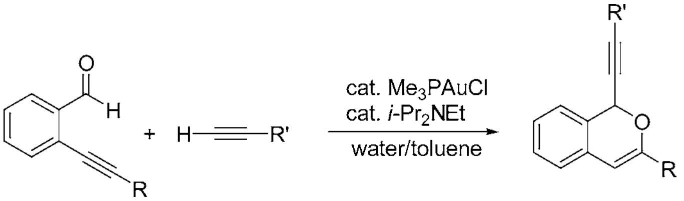
ABSTRACT



A highly efficient alkynylation–cyclization of terminal alkynes with *ortho*-alkynylaryl aldehydes leading to 1-alkynyl-1*H*-isochromenes was developed by using a gold–phosphine complex as catalyst in water. The reaction was dually promoted by an electron-donating phosphine ligand and water and was chelation-controlled.

Metal-mediated Grignard-type reactions represent some of the most common methodologies in C−C bond formations. Methods based on the catalytic reaction of C−H bonds provide a highly atom-economic alternative, which avoids the utilization of stoichiometric amounts of metal and halides when compared to classical methods.[1] Furthermore, the development of catalytic [Grignard-type] C−H bond reactions in aqueous media can potentially simplify protection and deprotection of functional groups incompatible to classical reactions.[2]

Isochromenes are common structural units in natural products and exhibit interesting biological activities such as antibiotic properties.[3] Among the methods to construct such structures, the nucleophilic addition to alkynylaryl aldehydes followed by an alcohol−alkyne cyclization is the most useful.[4] To the best of our knowledge, terminal alkynes have not been reported as nucleophiles in such reactions to generate isochromene derivatives.[5] During our earlier studies on the silver-catalyzed alkynylation of aldehydes,[6] we realized that the metal acetylides of group IB such as Cu(I), Ag(I), and Au(I), which were believed to only be reactive to imines[7] and inert to carbonyl,[8] might be activated by a phosphine ligand and water. Herein, we report a cascade

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(1) (a) For a recent review, see: Dyker, G. *Angew. Chem. Int. Ed.* **1999**, *38*, 1698. (b) Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695.

(2) For representative reviews, see: (a) Li, C.-J. *Chem. Rev.* **1993**, *93*, 2023. (b) Lindstrom, U. M. *Chem. Rev.* **2002**, *102*, 2751. (c) Li, C.-J. *Chem. Rev.* **2005**, *105*, 3095. For the Grignard-type reaction in water, see: (d) Li, C.-J. *Green Chem.* **2002**, *4*, 1. (e) Li, C.-J. *Tetrahedron* **1996**, *52*, 5643.

(3) (a) Biber, B.; Muske, J.; Ritzan, M.; Graft, U. *J. Antibiot.* **1998**, *51*, 381. (b) Maruse, N.; Goto, M. *J. Antibiot.* **1998**, *51*, 545. (c) Wang, W.; Breining, T.; Li, T.; Milbum, R.; Attardo, G. *Tetrahedron Lett.* **1998**, *39*, 2459 and the references therein.

(4) For representative examples, see: (a) Asao, N.; Nogami, T.; Takahashi, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 764. (b) Patil, N. T.; Yamamoto, Y. *J. Org. Chem.* **2004**, *69*, 5139. (c) Nakamura, H.; Ohtaka, M.; Yamamoto, Y. *Tetrahedron Lett.* **2002**, *43*, 7631. (d) Asao, N.; Chan, C. S.; Takahashi, K.; Yamamoto, Y. *Tetrahedron* **2005**, *61*, 11322. (e) Patil, N. T.; Pahadi, N. K.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 10096. (f) Wei, L.-L.; Wei, L.-M.; Pan, W.-B.; Wu, M.-J. *Synlett* **2004**, 1497. Some examples for the electrophilic cyclization: (g) Barluenga, J.; Vazquez-Villa, H.; Ballesteros, A.; Gonzalez, J. M. *J. Am. Chem. Soc.* **2003**, *125*, 9028. (h) Yue, D.; Ca, N. D.; Larock, R. C. *Org. Lett.* **2004**, *6*, 1581.

(5) In the reaction using acetylenic imines as substrates to prepare dihydroisoquinolines, one example with terminal alkynes was reported. Asao, N.; Yudha S. S.; Nogami, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 5526.

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

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addition/cyclization of terminal alkynes with acetylenic aldehydes catalyzed by a phosphine–gold(I) complex,[9] leading to 1-alkynyl-1H-isochromenes in water (eq 1, Figure 1). Furthermore, to the best of our knowledge, it is also the first example of a gold-catalyzed alkynylation of aldehydes.

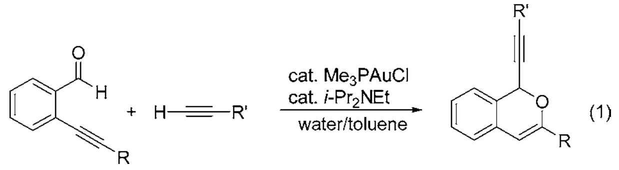
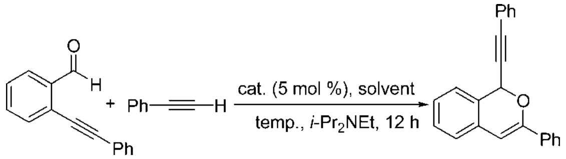


Figure 1. Water-triggered and gold(I)-catalyzed cascade addition/cyclization of terminal alkynes with *ortho*-alkynylaryl aldehyde.

Table 1. Catalytic Alkynylation/Cyclization of 2-(Phenylethynyl) Benzaldehyde with Phenylacetylene[a]



entry	catalysts	conditions	yield (%)[b]
1	Cy_3PAgCl	water, 80 °C	0
2	$Cy_3PAgCl/AgOTf$	water, 80 °C	trace
3[c]	Ph_3PAuCl	water, 80 °C	11
4[c]	Me_3PAuCl	water, 80 °C	44
5	Me_3PAuCl	water/toluene (5:1), 70 °C	75
6	Me_3PAuCl	water/toluene (10:1), 70 °C	56
7	Me_3PAuCl	water/toluene (1:1), 70 °C	87
8	Me_3PAuCl	water/toluene (1:5), 70 °C	72
9	Me_3PAuCl	toluene, 70 °C	no conv.
10	Me_3PAuCl	water/*t*-BuOH (5:1), 70 °C	33
11	Me_3PAuCl	water/dioxane (5:1), 70 °C	75
12	$Me_3PAuCl/AgOTf$	water/toluene (1:1), 70 °C	no conv.
13	$Me_3PAuCl/AgSbF_6$	water/toluene (1:1), 70 °C	no conv.
14	$Me_3PAuCl/AgBF_4$	water/toluene (1:1), 70 °C	no conv.
15	AuCl	water/toluene (1:1), 70 °C	0
16	Et_3PAuCl	water/toluene (1:1), 70 °C	no conv.
17	$AuCl/Bu_3P$	water/toluene (1:1), 70 °C	no conv.
18	$AuCl/PCy_3$	water/toluene (1:1), 70 °C	no conv.

[a] Aldehyde (0.125 mmol), phenylacetylene (0.25 mmol), i-Pr_2NEt (20 mol %), H_2O (0.5 mL). [b] Yields were determined by ^1H NMR with 0.1 mmol of nitromethane as an internal standard (no conv.= no conversion). [c] 0.25 mmol scale, 1 mL of H_2O.

In our previous silver-catalyzed alkynylation of aldehydes,[6] Cy_3PAgCl (containing an electron-donating phosphine ligand) proved to be the most active catalyst. However, with Cy_3PAgCl as a catalyst in the present study, only a small amount of the alkynylation product was observed after overnight reaction at 80 °C, and no further cyclization occurred (entry 1, Table 1). When Ph_3PAuCl was used as the catalyst, a trace amount of isochromene **3a** was obtained together with benzannulation[10] and alkynylation as the side reactions (entry 3, Table 1). After screening several phosphine–gold complexes, Me_3PAuCl showed the best catalytic activity for the reaction. With the addition of toluene as a cosolvent, the reaction becomes smooth and easy to stir (entries 4 and 7).[11] Up to 87% of **3a** was achieved in a 1:1 mixture of toluene and water at 70 °C in 12 h, in the presence of 5 mol % of Me_3PAuCl and 20 mol % of i-Pr_2NEt. Other electron-donating phosphine ligands were also tested (entries 16–18); surprisingly, no desired product was observed. In the absence of a phosphine ligand, only a small amount of benzannulation product was formed (entry 15). On the other hand, it is worthy to note that noncoordinating counteranions such as ^-OTf, SbF_6^-, and BF_4^- inhibit the reaction and result in the polymerization of phenylacetylene. Furthermore, water plays a key role in this reaction and no reaction was observed in the absence of water (entry 9).

Subsequently, various acetylenic aldehydes were reacted with terminal alkynes under the standard reaction conditions (Table 2). With (2-phenylethynyl)aldehyde, both electron-rich and electron-poor arylacetylenes provide good yields of the desired products (entries 1–3). An alkenylalkyne was slightly less effective (entry 4), and the use of an aliphatic alkyne resulted in a low yield of the corresponding product (entry 5). On the other hand, n-butyl-substituted acetylenic aryl aldehyde **1b** provided the best yields (entries 6–10). However, a bulky R^1 decreased the reactivity (entries 11–13), possibly because of the increased steric effect. It is noteworthy to mention that the electron-donating terminal alkynes are slightly more reactive than the electron-deficient ones (e.g., entry 12 vs entries 11 and 13).

To understand the mechanism of the reaction, we examined the reaction between terminal alkynes and simple aldehydes (eq 2, Figure 2). Surprisingly, no catalytic activity was observed in the reaction of phenylacetylene with benzaldehydes under the standard conditions. This result

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(7) For an account of the reaction, 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. M.; 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**, 39.

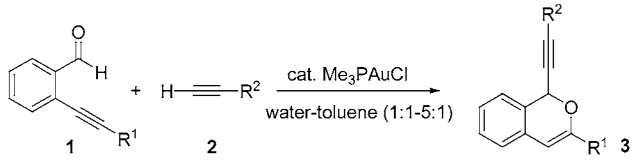
(8) It was widely accepted that metal acetylides generated from Group IB metals could not participate in the nucleophilic C=O addition. See: (a) Fässler, R.; Tomooka, C. S.; Frantz, D. E.; Carreira, E. M. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5843. (b) Takita, R.; Fukuta, Y.; Tsuji, R.; Ohshima, T.; Shibasaki, M. *Org. Lett.* **2005**, *7*, 1363.

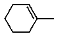
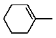
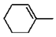
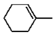
(9) For recent examples of R_3PAuCl-catalyzed reactions, see: (a) Johansson, M. J.; Gorin, D. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 18002. (b) Gorin, D. J.; Davis, N. R.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 11260. (c) Markham, J. P.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 9708. (d) Shi, X.; Gorin, D. J.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 5802. (e) Yang, C.-G.; He, C. *J. Am. Chem. Soc.* **2005**, *127*, 6966. (f) Zhang, J.; Yang, C.-G.; He, C. *J. Am. Chem. Soc.* **2006**, *128*, 1798. (g) Brouwer, C.; He, C. *Angew. Chem., Int. Ed.* **2006**, *45*, early view. (h) Han, X.; Widenhoefer, R. A. *Angew. Chem., Int. Ed.* **2006**, *45*, early view. For representative reviews on gold-catalyzed reactions, see: (i) Hashmi, A. S. K. *Gold Bull.* **2003**, *36*, 3. (j) Hashmi, A. S. K. *Gold Bull.* **2004**, *37*, 51. (k) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2005**, *44*, 6990. (l) Ma, S.; Gu, Z. *Angew. Chem., Int. Ed.* **2006**, *45*, 200.

(10) (a) Asao, N.; Nogami, T.; Lee, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 10921. (b) Asao, N.; Sato, K.; Menggenbateer; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 3682.

(11) For reactions at small scales, the substrates tend to stick on the surface of the stir bar or on the side of the tube, which results in lower conversions. Adding toluene as a cosolvent avoids such a problem.

Table 2. Trimethylphosphinegold(I) Chloride Cascade Catalyzed Alkynylation/Cyclization[a]



entry	R^1	R^2	conditions	product	yield (%)[b]
1	Ph (**1a**)	Ph (**2a**)	70 °C/1 d	**3a**	81
2	Ph	*p*-CH_3-C_6H_4- (**2b**)	70 °C/1 d	**3b**	78
3	Ph	*p*-Br-C_6H_4- (**2c**)	70 °C/1 d	**3c**	74
4	Ph	 (**2d**)	70 °C/1 d	**3d**	61(68% conv.)[c]
5[d]	Ph	n-C_6H_{13}- (**2e**)	90 °C/1 d	**3e**	16 (27% conv.)[c]
6	*n*-Bu (**1b**)	Ph	60 °C, 1 d	**3f**	86
7	*n*-Bu	*p*-CH_3-C_6H_4-	60 °C/1 d	**3g**	89
8	*n*-Bu	*p*-Br-C_6H_4-	60 °C/1 d	**3h**	85
9	*n*-Bu		60 °C/1 d	**3i**	78
10	*n*-Bu	*p*-CH_3O-C_6H_4- (**2f**)	60 °C/1 d	**3j**	83
11	*t*-Bu (**1c**)	Ph	90 °C/1 d	**3k**	43 (52% conv.)[c]
12	*t*-Bu	*p*-Br-C_6H_4-	90 °C/1 d	**3l**	18 (21% conv.)[c]
13	*t*-Bu	*p*-CH_3O-C_6H_4-	90 °C/1 d	**3m**	44 (48% conv.)[c]
14	 (**1d**)	Ph	70 °C/1 d	**3n**	49 (59% conv.)[c]
15		*p*-CH_3-C_6H_4-	70 °C/1 d	**3o**	65 (80% conv.)[c]

[a] Conditions: 0.125 mmol of aldehyde, 0.25 mmol of alkynes, 5 mol % of Me_3PAuCl, and 20 mol % of *i*-Pr_2NEt in 0.5 mL of water and 0.5 mL of toluene. [b] Isolated yield. [c] The conversion was calculated from the ^1H NMR of the crude reaction mixture with 0.1 mmol of nitromethane as an internal standard. [d] 0.1 mL of toluene was used with 0.5 mL of H_2O.

suggests that the *o*-alkynyl in substrate **1** might function as a chelating-activating group.[12]

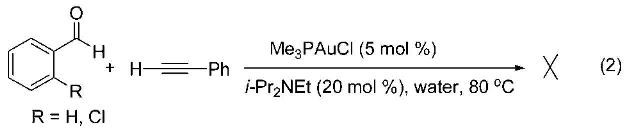
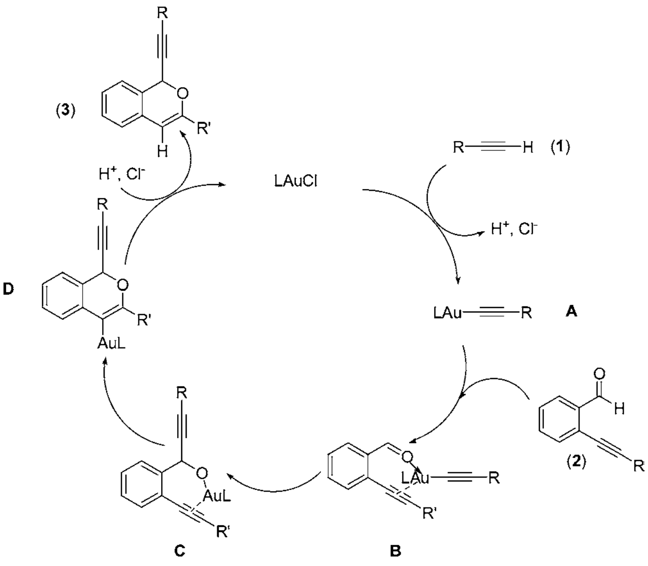


Figure 2. Catalytic alkynylation of benzaldehydes with phenylacetylene in water.

Thus, a tentative mechanism for the water-triggered gold(I)-catalyzed cascade addition/cyclization is proposed in Scheme 1. Reaction of terminal alkynes with Me_3AuCl in the presence of a weak base generates the gold(I) acetylide species **A**, which then forms the chelating intermediate **B** and activates the carbonyl group. The acetylide then reacts with the aldehyde to give intermediate **C** followed by the attack to the triple bond to give the vinylgold intermediate **D**; the carbon−gold bond is then quenched to give the final product **3** by protonolysis and regenerates the catalyst.[13,14]

Scheme 1. Tentative Mechanism for the Gold(I)-Catalyzed Cascade Alkynylation/Cyclization



In conclusion, a highly efficient alkynylation−cyclization of terminal alkynes with *ortho*-alkynylaryl aldehydes leading to 1-alkynyl-1*H*-isochromenes was developed by using a gold−phosphine complex as catalyst in water. The reaction was dually promoted by an electron-donating phosphine ligand and water and was chelation-controlled. The detailed mechanism and the scope of this reaction are currently under investigation.

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Supporting Information Available: Representative experimental procedures and characterization of all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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[12] Asao, N.; Asano, T.; Ohishi, T.; Yamamoto, Y. *J. Am. Chem. Soc.* **2000**, *122*, 4817.

[13] Another possible mechanism might involve the formation of a benzopyrylium cation (especially in the benzannulation of *o*-alkynyl(oxo)-benzenes with alkynes). See refs 4e and 10; for other recent related examples, see: (a) Buzas, A.; Gagosz, F. *Org. Lett.* **2006**, *8*, 515. (b) Kusama, H.; Miyashita, Y.; Takaya, J.; Iwasawa, N. *Org. Lett.* **2006**, *8*, 289. However, in all these cases, high-valent metals and/or noncoordinating anions are required.

[14] The chelating model also provides an explanation for the fact that the reaction is sensitive to the size of the phosphine ligand: the smaller ligand Me_3P gives the best results.