Organic LETTERS

Letter

pubs.acs.org/OrgLett

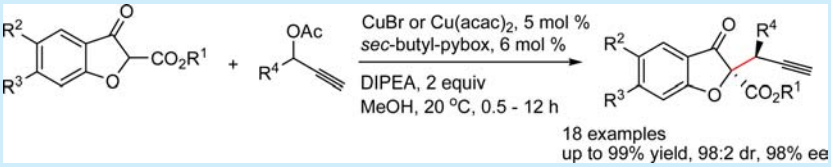
Diastereo- and Enantioselective Propargylation of Benzofuranones Catalyzed by Pybox-Copper Complex

Long Zhao,[†] Guanxin Huang,[†] Beibei Guo,[†] Lijun Xu,[‡] Jie Chen,[†] Weiguo Cao,[†] Gang Zhao,*[,‡] and Xiaoyu Wu*[,†]

[†]Department of Chemistry, College of Sciences, Shanghai University, 99 Shangda Road, Shanghai 200444, China

[‡]Key Laboratory of Synthetic Organic Chemistry of Natural Substances, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032, China

Supporting Information



ABSTRACT: Diastereo- and enantioselective preparation of 2,2-disubstituted benzofuran-3(2*H*)-one has been realized by a pybox-copper catalyzed reaction between 2-substituted benzofuran-3(2*H*)-one and propargyl acetate. The utility of this method was demonstrated by further transformation of the terminal alkyne into a methyl ketone without loss of enantiomeric purity.

2,2-Disubstituted benzofuran-3(2*H*)-ones and related frameworks characteristic of a quaternary stereogenic center at C2 are present in quite a number of natural products and bioactive molecules.[1] Despite intensive efforts devoted to the construction of this type of framework,[2,3] so far there are only a few reported asymmetric methods[3] which were achieved either through asymmetric Michael addition or by enantioselective halogenation (Figure 1).[3c−j]

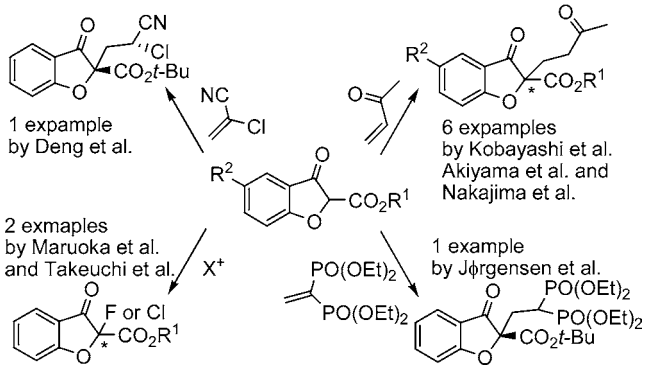


Figure 1. Previous examples of asymmetric nucleophilic addition of 2-substituted benzofuran-3(2*H*)-ones.

In 1994, Murahashi and co-workers reported the copper-catalyzed amination of propargyl phosphates and acetates under mild conditions.[4] A variety of methodologies have been successfully developed for direct propargylic substitution using propargylic alcohols or their derivatives since then.[5] Meanwhile, this process was rendered asymmetric via transition-metal catalysis by several research groups.[6−8] In our search for a new efficient method for diastereo- and enantioselective construction of 2-substituted benzofuran-3(2*H*)-ones, we envisioned that 2-substituted benzofuran-3(2*H*)-ones **1** would be suitable reaction partners for propargyl acetate **2**, providing access to 2,2-disubstituted benzofuran-3(2*H*)-ones **3**. Herein we wish to report a diastereo- and enantioselective propargylation of 2-substituted benzofuran-3(2*H*)-ones with propargylic acetate catalyzed by a pybox-copper complex.

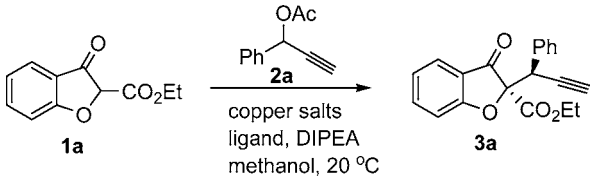
To gain some insight into the behavior of the propargylation reaction and obtain a racemic sample required for determination of the enantiomeric excess by HPLC, we first examined the reaction between ethyl 3-oxo-2,3-dihydrobenzofuran-2-carboxylate (**1a**) and 1-phenylprop-2-ynyl acetate (**2a**) promoted by a combination of CuI and an achiral ligand at 20 °C with methanol as the solvent and DIPEA as the base (Table 1, entries 1−2). As reported by Hu et al., similar conditions had proven effective for propargylation of cyclic 1,3-diketones when using chiral P,N,N-ligands.[8d] In our study, the desired products were obtained in high yields with rather moderate diastereoselectivities for both bidentate N,N-ligand bpy and tridentate N,N,N-ligand pybox (Figure 1). The latter was found to be more effective than the former with complete consumption of the starting material **2a** in less than 10 min.

The preliminary promising results with achiral ligands prompted us to develop an asymmetric version of this reaction. To our delight, a combination of CuI and ligand **A** (*sec*-Bu-pybox) derived from L-isoleucine led to a propargylation product in almost quantitative yield, with excellent enantioselectivity (94% ee) and high diastereoselectivity (92:8) (Table 1, entry 3). Various copper salts were screened and found to give

Received: September 3, 2014
Published: October 17, 2014

   dx.doi.org/10.1021/ol502615y | *Org. Lett.* 2014, 16, 5584−5587

Table 1. Screening of Reaction Conditions for the Propargylation between 1a and 2a[a]



entry	copper salts	ligand	time (h)	yield (%)[b]	ee (%)[c]	dr[c]
1	CuI	bpy	4	85	–	3:2
2	CuI	pybox	0.1	91	–	7:3
3	CuI	**A**	0.5	99	94	92:8
4	CuBr	**A**	0.5	94	98	98:2
5	CuCl	**A**	4	47	86	88:12
6	$Cu(OAc)_2$	**A**	4	92	96	96:4
7	$Cu(OTf)_2$	**A**	4	94	93	92:8
8	$Cu(acac)_2$	**A**	4	97	96	96:4
9	$Cu(CH_3CN)_4BF_4$	**A**	4	97	94	95:5
10	$Cu(acac)_2$	**B**	4	94	92	93:7
11	$Cu(acac)_2$	**C**	4	60	35	58:42
12	CuBr	**C**	0.5	68	30	50:50
13	$Cu(acac)_2$	**D**	4	48	27	54:46
14	CuBr	**D**	0.5	84	17	50:50
15	$Cu(acac)_2$	**E**	4	89	81	79:21
16[d]	$Cu(acac)_2$	**F**	4	–	–	–
17[d]	$Cu(acac)_2$	**G**	4	–	–	–
18[e]	CuBr	**A**	2	90	96	95:5

[a]General conditions: **1a** (0.4 mmol), **2a** (0.2 mmol), copper salt (5 mol %), ligand (6 mol %), and DIPEA (2 equiv) in methanol (4 mL) at 20 °C. [b]Yield referred to isolated **3a** and its diastereoisomer. [c]Enantiomeric excess and diastereoselectivity of **3a** were determined by chiral HPLC analysis. [d]No formation of desired product was observed. [e]Reaction performed at 0 °C.

similar results, as excellent ee's and high dr's were achieved (entries 3–9), except for CuCl with only a moderate yield (entry 5). Since CuBr and $Cu(acac)_2$ were slightly better than the others (entries 4, 8), they were chosen for further investigation of other reaction parameters.

Other tridentate ligands, **B**, **C**, and **D**, and bidentate ligands, **E**, **F**, and **G**, were also evaluated for the propargylation reaction (Figure 2). Ligand **B** (*i*-Pr-pybox) with less bulky groups as compared with ligand **A** provided the products in comparable yield and selectivity as ligand **A** (entry 10), while **C** (*t*-Bu-pybox) and **D** (indenyl-pybox) bearing more bulky groups led to low yields, low ee's, and poor dr's (entries 11–14). Furthermore, of the bidentate ligands screened, ligand **E** gave moderate results: 89% yield, 81% ee, and 79:21 dr (entry 15), while the other two, **F** and **G**, were ineffective (entries 16, 17). When the temperature was lowered to 0 °C, the performance of the reaction was almost identical to that at 20 °C, albeit a longer reaction time was required (entry 18). Further attempts to improve the performance of this reaction by changing the base or the solvent were unsuccessful (not shown; see Supporting Information (SI) for details), as no better results were obtained.

With the optimized reaction conditions in hand (Table 1, entries 4 and 8), we set out to explore the scope of the reaction with regard to diversely substituted propargyl acetates (Table 2). We first examined aryl-substituted substrates **2b–h** (entries 1–10). To our pleasure, phenyl-substituted acetates with either

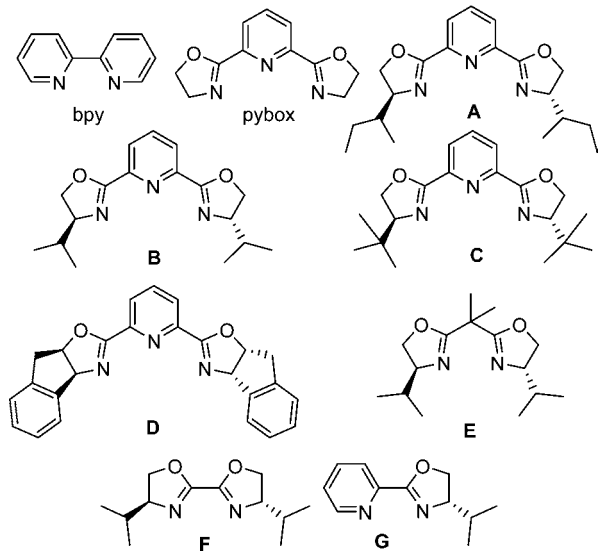
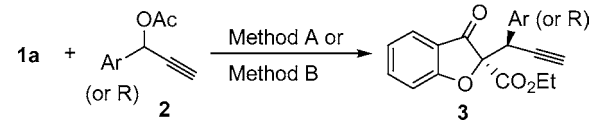


Figure 2. Achiral and chiral ligands used in this study.

Table 2. Expanding the Substrate Scope of Propargyl Acetates[a]



entry	Ar (or R)	2	method[a]	3	yield (%)[b]	ee (%)[c]	dr[c]
1	4-CH_3-C_6H_4	**2b**	A	**3b**	91	94	91:9
2	4-CH_3O-C_6H_4	**2c**	A	**3c**	91	93	90:10
3	4-Cl-C_6H_4	**2d**	A	**3d**	90	92	91:9
4	4-CF_3-C_6H_4	**2e**	A	**3e**	79	88	91:9
5	4-CF_3-C_6H_4	**2e**	B	**3e**	70	94	97:3
6	3,5-$(CF_3)_2$-C_6H_3	**2f**	A	**3f**	78	83	90:10
7	3,5-$(CF_3)_2$-C_6H_3	**2f**	B	**3f**	72	86	92:8
8	4-Br-C_6H_4	**2g**	A	**3g**	90	86	95:5
9	*α*-naphthyl	**2h**	A	**3h**	90	78	86:14
10	*α*-naphthyl	**2h**	B	**3h**	93	78	89:11
11	*n*-butyl	**2i**	A	**3i**	45	88	92:8
12	–[d]	**2j**	A	**3j**	40	13	–

[a]General conditions: **1a** (0.4 mmol), **2** (0.2 mmol), CuBr (5 mol %, *method A*) or $Cu(acac)_2$ (5 mol %, *method B*), ligand **A** (6 mol %), and base (2 equiv) in methanol (4 mL) at 20 °C. [b]Yield referred to isolated **3** and its diastereoisomer. [c]Enantiomeric excess and diastereoselectivity of **3** were determined by chiral HPLC analysis. [d]2-Methylbut-3-yn-2-yl acetate (**2j**) was employed.

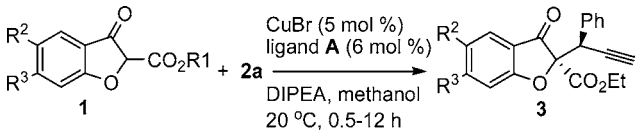
electron-donating or -withdrawing substituents all performed well to deliver the propargylated products in good to excellent yields and ee's with high dr's. For substrate **2e**, with one trifluoromethyl group, and substrate **2f**, with two trifluoromethyl groups, the ee's and dr's were slightly improved at the expense of the yields, when the reaction was promoted by $Cu(acac)_2$ instead of CuBr (entries 4–7). *α*-Naphthyl-propargyl acetate **2h** was also fit for this reaction (entries 9–10), as a 90% yield, 78% ee, and dr of 86:14 were achieved when CuBr was employed. It failed to give a higher ee with $Cu(acac)_2$, though a slightly better yield and dr were attained (entry 10). Two alkyl-substituted propargyl acetates were also

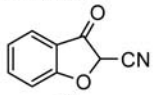
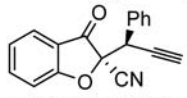
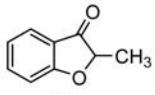
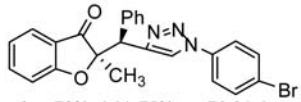
dx.doi.org/10.1021/ol502615y | *Org. Lett.* 2014, 16, 5584–5587

examined for this reaction (entries 11−12). *n*-Butyl-substituted **2i** reacted sluggishly and delivered the desired product in moderate yield, while the ee and dr were comparable to those of aryl substrates. Use of substrate **2j** derived from commercially available 2-methylbut-3-yn-2-ol resulted in a poor yield and ee.

We next investigated the substrate scope of this reaction concerning differently substituted benzofuranones (Table 3).

Table 3. Expanding the Substrate Scope of Benzofuranones[a]



entry	R^1, R^2, R^3, **1**	**3**	yield (%)[b]	ee (%)[c]	dr[c]
1	Me, H, H, **1b**	**3ab**	91	94	91:9
2	Et, Br, H, **1c**	**3ac**	91	93	90:10
3	Et, H, MeO, **1d**	**3ad**	90	92	91:9
4	Et, Me, H, **1e**	**3ae**	79	88	91:9
5	 **1f**	 **3af** 75% yield, 60% ee, 77:23 dr			
6[d]	 **1g**	 **3ag** 72% yield, 75% ee, 79:21 dr			

[a]General conditions: **1a** (0.4 mmol), **2** (0.2 mmol), CuBr (5 mol %), ligand **A** (6 mol %), and base (2 equiv) in methanol (4 mL) at 20 °C for 0.5 to 12 h. [b]Yield referred to isolated **3** and its diastereoisomer. [c]Enantiomeric excess and diastereoselectivity of **3** were determined by chiral HPLC analysis. [d]The propargylated product was treated with 1-azido-4-bromobenzene in the presence of CuI and sodium ascorbate.

Substrate **1b**, a methyl ester, worked well to give the desired product in almost quantitative yield with excellent ee and high dr (entry 1). Substrates with either an electron-poor or -rich benzoid portion were all well suited to our current system (entries 2−4). Notably, the size of the substituent on C2 of benzofuranone had a significant influence on the outcome of this reaction, since **1f** with a cyano group and **1g** with a methyl group furnished the corresponding propargylated products with only modest ee's and dr's (entries 5−6). In the case of **1g**, determination of the ee and dr value of the product was facilitated by its derivative obtained from cyclization with 1-azido-4-bromobenzene.[9] The relative stereochemistry of **3a** and absolute stereochemistry of **3ag** were determined by single-crystal X-ray diffraction analysis (see SI for details).[10]

Based on the propargylation mechanisms proposed previously by Murahashi et al.,[4] Nishibayashi et al.,[6] Maarseveen et al., and Hu et al.,[7,8] we proposed a plausible mechanism for the reaction between **1a** and **2a** as depicted in Figure 3. First, chelation of propargyl acetate to the chiral copper complex formed a π complex (**I**).[11] Next, deprotonation of the acetylenic hydrogen with DIPEA delivered a Cu-acetylide complex (**II**), which would be readily transformed into a Cu-alkenylidene complex (**III**) upon loss of an acetate group. Notably, the involvement of the Cu-alkenylidene complex as a key intermediate has recently been verified by Nishibayashi et al.[7e] Finally, the addition of **1a** to the copper complex from the less hindered α-side, via the chiral induction model shown in Figure 1, afforded **3a** with excellent ee and dr.

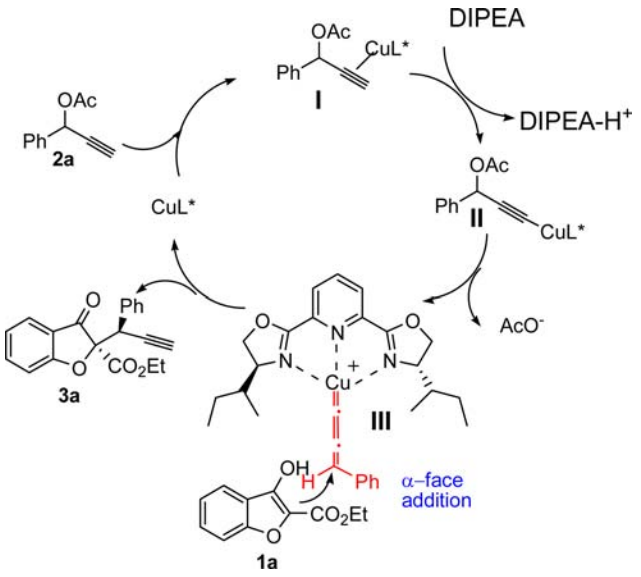
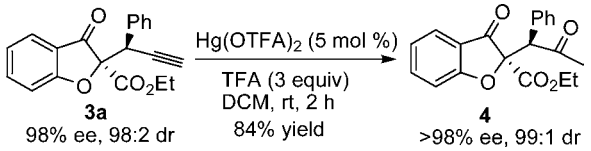


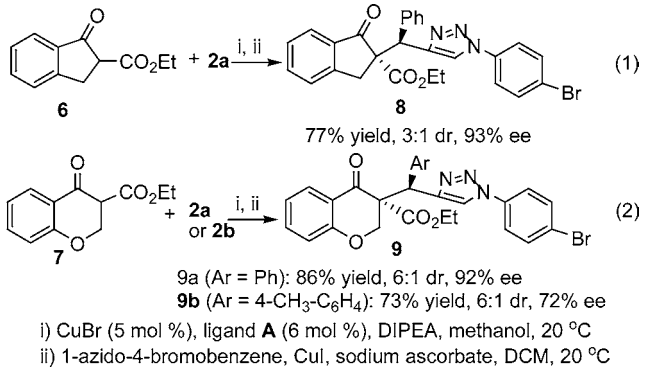
Figure 3. Proposed catalytic cycle and chiral induction model for propargylation of benzofuranone **1a**.

To explore the synthetic potential of the current methodology, the reaction between **1a** and **2a** was carried out on a larger scale (2 mmol) (2 mol % of CuBr and 2.4 mol % ligand **A**) and the reaction proceeded smoothly to provide the propargylated product in a similar manner to those on a 0.2 mmol scale. Furthermore, the terminal alkyne was transformed into a methyl ketone by treating it with $Hg(OTFA)_2$ (5 mol %) and TFA (3 equiv) in DCM at rt for 2 h (Scheme 1).[12] Notably, no loss of enantiomeric purity was observed during this transformation.

Scheme 1. Oxidation of the Terminal Alkyne into a Methyl Ketone



Besides benzofuranones, indanone substrate **6** and benzopyranone **7** were also tested in the current research. To our delight, both substrates worked well with good yields, good to excellent ee's, and moderate dr's achieved [eqs 1−2].[9]



dx.doi.org/10.1021/ol502615y | Org. Lett. 2014, 16, 5584−5587

In summary, we have developed a diastereo- and enantioselective propargylation reaction of 2-substituted benzofuran-3(2*H*)-ones catalyzed by a copper-pybox complex. A series of 2,2-disubstituted benzofuran-3(2*H*)-ones bearing two vicinal chiral centers and one terminal alkyne function were obtained in good to excellent yields and ee's in most cases. The utility of this method was demonstrated by a relatively large scale synthesis of **3a** and further transformation of **3a** into ketone **4** without loss of enantiomeric purity. Furthermore, this methodology was found to be also applicable to indanone- and benzopyranone-based substrates.

■ ASSOCIATED CONTENT

Supporting Information

General experimental conditions, NMR spectra, and HPLC analysis of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: zhaog@mail.sioc.ac.cn.
*E-mail: wuxy@shu.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We acknowledge research support from the National Natural Science Foundation of China (No. 21272150 and No. 21072125). Dr. Hanwei Hu at Genchemistry is also gratefully acknowledged for helpful discussions.

■ REFERENCES

(1) (a) Oxford, A. E.; Raistrick, H.; Simonart, P. *Biochem. J.* **1939**, *33*, 240−248. (b) Davies, R. R. *Antifungal Chemotherapy*; Wiley & Sons: New York, 1980; p 149. (c) Proksch, P.; Edrada, R.; Ebel, R.; Bohnenstengel, F. I.; Nugroho, B. W. *Curr. Org. Chem.* **2001**, *5*, 923−938 and references therein.

(2) (a) Davey, A. E.; Schaeffer, M. J.; Taylor, R. J. K. *J. Chem. Soc., Chem. Commun.* **1991**, 1137−1139. (b) Davey, A. E.; Schaeffer, M. J.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2657−2666. (c) Dobler, M. R.; Bruce, I.; Cederbaum, F.; Cooke, N. G.; Diorazio, L. J.; Hall, R. G.; Irving, E. *Tetrahedron Lett.* **2001**, *42*, 8281−8284. (d) Diedrichs, N.; Ragot, J. P.; Thede, K. *Eur. J. Org. Chem.* **2005**, 1731−1735. (e) Li, H. S.; Fu, B.; Wang, M. A.; Li, N.; Liu, W. J.; Xie, Z. Q.; Ma, Y. Q.; Qin, Z. H. *Eur. J. Org. Chem.* **2008**, 1753−1758. (f) Thuaud, F.; Bernard, Y.; Turkeri, G.; Dirr, R.; Aubert, G.; Cresteil, T.; Baguet, A.; Tomasetto, G.; Svitkin, Y.; Sonenberg, N.; Nebigil, C. G.; Désaubry, L. *J. Med. Chem.* **2009**, *52*, 5176−5187. (g) Ribeiro, N.; Thuaud, F.; Bernard, Y.; Gaiddon, C.; Cresteil, T.; Hild, A.; Hirsch, E. C.; Nebigil, C. G.; Désaubry, L. *J. Med. Chem.* **2012**, *55*, 10064−10073.

(3) (a) For a review, see: Li, Y.; Li, X.; Cheng, J. P. *Adv. Synth. Catal.* **2014**, *356*, 1172−1198. (b) Pirrung, M. C.; Brown, W. L.; Rege, S.; Laughton, P. *J. Am. Chem. Soc.* **1991**, *113*, 8561−8562. (c) Shibata, N.; Suzuki, E.; Takeuchi, Y. *J. Am. Chem. Soc.* **2000**, *122*, 10728−10729. (d) Nakajima, M.; Yamamoto, S.; Yamaguchi, Y.; Nakamura, S.; Hashimoto, S. *Tetrahedron* **2003**, *59*, 7307−7313. (e) Wang, Y.; Liu, X. F.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 3928−3930. (f) Ogawa, C.; Kizu, K.; Shimizu, H.; Takeuchi, M.; Kobayashi, S. *Chem.—Asian. J.* **2006**, *1*, 121−124. (g) Capuzzi, M.; Perdicchia, D.; Jørgensen, K. A. *Chem.—Eur. J.* **2008**, *14*, 128−135. (h) Akiyama, T.; Katoh, T.; Mori, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 4226−4228. (i) Wang, X. S.; Lan, Q.; Shirakawa, S.; Maruoka, K. *Chem. Commun.* **2010**, *46*, 321−323. (j) Dong, N.; Li, X.; Wang, F.; Cheng, J. P. *Org. Lett.* **2013**, *15*, 4896−4899.

(4) Imada, Y.; Yuasa, M.; Nakamura, I.; Murahashi, S.-I. *J. Org. Chem.* **1994**, *59*, 2282−2284.

(5) For reviews, see: (a) Ljungdahl, N.; Kann, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 642−644. (b) Ding, C.-H.; Hou, X.-L. *Chem. Rev.* **2011**, *111*, 1914−1937. (c) Detz, R. J.; Hiemstra, H.; van Maarseveen, J. H. *Eur. J. Org. Chem.* **2009**, 6263−6276. (d) Debleds, O.; Gayon, E.; Vrancken, E.; Campagne, J.-M. *Beilstein J. Org. Chem.* **2011**, *7*, 866−877. (e) Nishibayashi, Y. *Synthesis* **2012**, *44*, 489−503.

(6) (a) Inada, Y.; Nishibayashi, Y.; Uemura, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 7715−7717. (b) Matsuzawa, H.; Kanao, K.; Miyake, Y.; Nishibayashi, Y. *Org. Lett.* **2007**, *9*, 5561−5564. (c) Matsuzawa, H.; Miyake, Y.; Nishibayashi, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 6488−6491. (d) Fukamizu, K.; Miyake, Y.; Nishibayashi, Y. *J. Am. Chem. Soc.* **2008**, *130*, 10498−10499. (e) Ikeda, M.; Miyake, Y.; Nishibayashi, Y. *Angew. Chem., Int. Ed.* **2010**, *49*, 7289−7293. (f) Ikeda, M.; Miyake, Y.; Nishibayashi, Y. *Chem.—Eur. J.* **2012**, *18*, 3321−3328.

(7) (a) Detz, R. J.; Delville, M. M. E.; Hiemstra, H.; van Maarseveen, J. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 3777−3780. (b) Detz, R. J.; Abiri, Z.; le Griel, R.; Hiemstra, H.; van Maarseveen, J. H. *Chem.—Eur. J.* **2011**, *17*, 5921−5930. (c) Hattori, G.; Matsuzawa, H.; Miyake, Y.; Nishibayashi, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 3781−3783. (d) Shibata, M.; Nakajima, K.; Nishibayashi, Y. *Chem. Commun.* **2014**, *50*, 7874−7877. (e) Hattori, G.; Sakata, K.; Matsuzawa, H.; Tanabe, Y.; Miyake, Y.; Nishibayashi, Y. *J. Am. Chem. Soc.* **2010**, *132*, 10592.

(8) (a) Fang, P.; Hou, X. L. *Org. Lett.* **2009**, *11*, 4612−4615. (b) Zhang, C.; Hu, X. H.; Wang, Y. H.; Zheng, Z.; Xu, J.; Hu, X. P. *J. Am. Chem. Soc.* **2012**, *134*, 9585−9588. (c) Zhu, F. L.; Zou, Y.; Zhang, D. Y.; Wang, Y. H.; Hu, X. H.; Chen, S.; Xu, J.; Hu, X. P. *Angew. Chem., Int. Ed.* **2014**, *53*, 1410−1414. (d) Han, F. Z.; Zhu, F. L.; Wang, Y. H.; Zou, Y.; Hu, X. H.; Chen, S.; Hu, X. P. *Org. Lett.* **2014**, *16*, 588−591. (e) Zhu, F. L.; Wang, Y. H.; Zhang, D. Y.; Hu, X. H.; Chen, S.; Hou, C. J.; Xu, J.; Hu, X. P. *Adv. Synth. Catal.* DOI: 10.1002/adsc.201400218. (f) Zhu, F. L.; Wang, Y. H.; Zhang, D. Y.; Xu, J.; Hu, X. P. *Angew. Chem., Int. Ed.* **2014**, *53*, 10223−10227.

(9) In these cases, the propargylated products were of the same polarity as the starting materials on TLC; therefore they were subjected to cyclization with 1-azido-4-bromobenzene to facilitate purification and characterization.

(10) CCDC-1014538 (for **3a**) and CCDC-1022280 (for **3ag**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(11) Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V. V.; Noodleman, L.; Sharpless, K. B.; Fokin, V. V. *J. Am. Chem. Soc.* **2005**, *127*, 210−216.

(12) (a) Cao, T.; Linton, E. C.; Deitch, J.; Berritt, S.; Kozlowski, M. C. *J. Org. Chem.* **2012**, *77*, 11034−11055. (b) Imagawa, H.; Takahiro Kurisaki, T.; Nishizawa, M. *Org. Lett.* **2004**, *6*, 3679−3681.