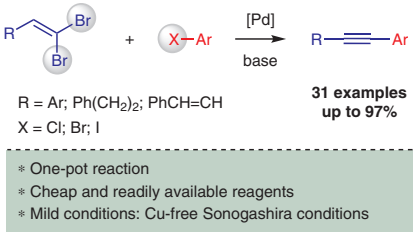
Synlett Y. Ji et al. Letter

Synthesis of Internal Alkynes through an Effective Tandem Elimination–Hydrodebromination–Cross-Coupling of *gem*-Dibromoalkenes with Halobenzenes

Yuan Ji[a]
Ning Zhong[a]
Zinan Kang[a]
Guobing Yan[*b]
Ming Zhao[*a]

[a] School of Chemical Engineering, China University of Mining and Technology, No. 1 Daxue Road, Xuzhou 221116, P. R. of China
[b] Department of Chemistry, Lishui University, Lishui 323000, P. R. of China
ming815zhao@aliyun.com
gbyan@lsu.edu.cn



Received: 17.06.2017
Accepted after revision: 24.08.2017
Published online: 14.09.2017
DOI: 10.1055/s-0036-1590907; Art ID: st-2017-w0486-l

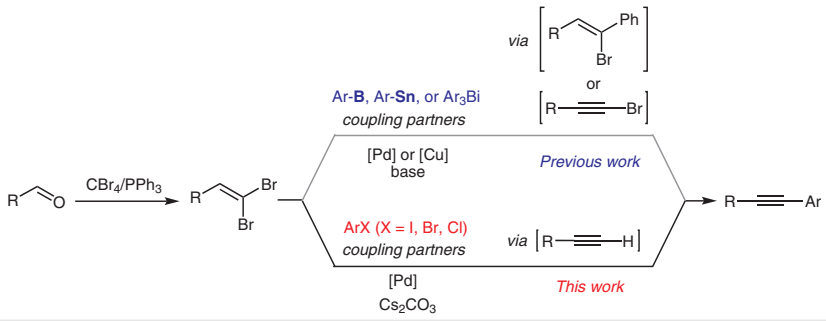
Abstract Carbon–carbon couplings are among the most important strategies for constructing functional molecules in organic synthetic chemistry, and cheap, diverse, and readily available coupling partners are crucial to these diverse reactions. In this contribution, we report the first palladium-catalyzed C–C cross-coupling reaction of two kinds of organic halide, a *gem*-dibromoalkene and a halobenzene, as the starting materials. Terminal alkynes were generated in situ through a tandem elimination–hydrodebromination process, and the internal alkyne final products were synthesized in one pot. The reaction proceeded under simple, facile, and classic copper-free Sonogashira coupling reaction conditions in good to excellent yields.

Key words alkynes, dibromoalkenes, halobenzenes, Sonogashira reaction, palladium catalysis, C–C coupling

Internal alkynes have been extensively applied as intermediates for the synthesis of bioactive compounds, natural products, pharmaceuticals, and functional materials.[1] Among other methods, the Sonogashira coupling reaction is considered to be a premium tool for the preparation of internal alkynes from aryl or alkenyl (pseudo)halides and terminal alkynes.[2] Thousands of papers have been published on this reaction since it was first reported by Sonogashira and co-workers.[3] However, for the synthesis of particular alkynes, the use of alternatives to terminal alkynes is essential.[4]

gem-Dibromoalkenes contain a pair of C–Br bonds that can serve as reactive sites for various types of cross-coupling reactions.[5] These compounds can be easily prepared from the corresponding aldehydes by treatment with CBr_4/PPh_3 (Scheme 1).[6,7] The construction of C–C,[5,8] C–N,[9] C–O,[4,9c,10] C–S,[11] or C–P[9c,12] bonds through activation of C–Br bonds to give valuable organic chemicals has been widely investigated. Notably, *gem*-dibromoalkenes or their equivalent bromoalkynes, formed in situ under basic conditions, have been used as alternatives to terminal alkynes for the synthesis of internal alkynes through C–C coupling reactions.[13] As efficient coupling partners, boronic acids[14] or borate esters (Ar-**B**),[15] arylstannanes (Ar-**Sn**),[16] and triarylbismuths (Ar_3**Bi**)[17] have been widely used in syntheses of internal alkynes with palladium or copper catalyst systems. The reactions probably proceed through two pathways: (i) palladium- or copper-catalyzed cross-coupling of Ar-**B**, Ar-**Sn**, or Ar_3**Bi** with one C–Br bond to give a trisubstituted alkene, which subsequently eliminates HBr to form internal alkyne; or (ii) the reverse tandem process of elimination followed by cross-coupling (Scheme 1; previous work). In addition, Yan et al. reported a synthesis of internal alkynes from *gem*-dibromoalkenes and iodobenzene promoted by $Ni/KF/Al_2O_3/CuI$; however, the need for microwave irradiation conditions and inapplicability of bromobenzene limited the range of applications of this reaction.[18]

Instead of using relatively expensive arylboronic acids, borate esters, organostannanes, or triarylbismuths to synthesize internal alkynes, we aimed to use aryl halides as cross-coupling partners with *gem*-dibromoalkenes (Scheme 1; this work). The merits of this procedure are the utilization of cheap, diverse, and readily available aryl halides, as well as the simple copper-free reaction conditions. The costs of introducing one mole of an aryl group from Ar-**B**, Ar-**Sn**, Ar_3**Bi**, PhI, or PhBr are shown in Figure 1. There is a huge price advantage in using halides as reactants. The key step of this reaction is the sequential elimination–dehalogenation of the dibromoalkene mediated by Cs_2CO_3. Moreover, the pot-economy synthesis with the terminal alkynes generated in situ might extent the scope of the substrates and enhance the efficiency of the transformations. To this end, a suitable base is needed which must be sufficiently powerful to induce the sequential elimination–dehalogenation reaction of the dibromoalkene, tolerate various func-

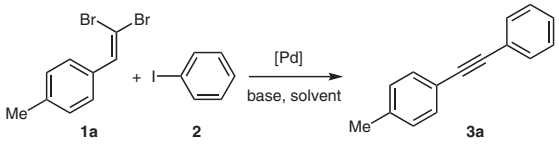


Scheme 1 Synthesis of internal alkynes from aldehydes by the Corey–Fuchs reaction and a subsequent one-pot reaction of the resulting *gem*-dibromoalkene with various reagents

tionalities, and be effective for the late-stage Sonogashira coupling. We surmised that Cs_2CO_3 might be a more suitable candidate than BuLi, *t*-BuOK, or tetrabutylammonium fluoride (TBAF).[19] Although 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was also suitable for the elimination–dehalogenation of dibromoalkenes, an alkyl substrate was not tolerated and the yields of the terminal alkynes were inferior to those obtained by using Cs_2CO_3.[19b,20]

As a preliminary experiment, we examined the elimination–dehalogenation reaction of *gem*-dibromoalkene **1a** with Cs_2CO_3 (See Supplementary Information; Scheme S1). Both the bromoalkyne and the terminal alkyne were isolated, although a low yield was obtained for the former. It has been suggested that water provides the protons for the hydrodebromination of the bromoalkyne, but there is still no clear evidence on this point.[19,20] Nevertheless, our experiments proved that Cs_2CO_3 is an efficient base in promoting the elimination–dehalogenation of **1a**, and might be a suitable base for the one-pot synthesis of internal alkynes. The optimization of the reaction conditions was carried out initially by using *gem*-dibromoalkene **1a** and iodobenzene (**2b**) as model substrates with Cs_2CO_3 as the base (Table 1). The reaction proceeded smoothly in the presence of 2 mol% of $Pd(OAc)_2$ and 5.0 equivalents of base, and the desired product **3a** was obtained in moderate yield (45%; Table 1,

Table 1 Optimization of the One-Pot Synthesis of Internal Alkynes from *gem*-Dibromoalkene **1a** and Iodobenzene (**2b**)[a]



Entry	Catalyst (mol%)	Base (equiv)	Temp[b] (°C)	Time[b] (h)	Yield[c] (%)
1	$Pd(OAc)_2$ (2)	$Cs(CO_3)_2$ (5)	20	1	45
2	$Pd(acac)_2$ (2)	$Cs(CO_3)_2$ (5)	60	25	0
3	Pd/C (5)	$Cs(CO_3)_2$ (5)	80	25	67
4	Pd/C (5)	$Cs(CO_3)_2$ (4)	80	25	64
5	**Pd/C (5)**	**$Cs(CO_3)_2$ (6)**	**80**	**25**	**80**
6	Pd/C (5)	$Cs(CO_3)_2$ (7)	80	25	76
7[d]	Pd/C (5)	$Cs(CO_3)_2$ (6)	80	25	50
8	Pd/C (3)	$Cs(CO_3)_2$ (6)	100	24	67
9[e]	–	$Cs(CO_3)_2$ (6)	90	4	0
10[e]	–	*t*-BuONa (7)	90	4	0
11	Pd/C (5) + CuI (20)	$Cs(CO_3)_2$ (6)	80	25	34[f]

[a] Reaction conditions: (i) **1a** (0.68 mmol), base, DMSO (2.0 mL), 115 °C, 15 h; then (ii) catalyst, **2** (0.4 mmol).
[b] The temperature and time are for the second step.
[c] Isolated yield.
[d] DMF (2.0 mL) was added in the second step.
[e] All the starting materials were added in once.
[f] The 1,3-diyne homocoupling product from the intermediate alkyne was obtained as the main byproduct.

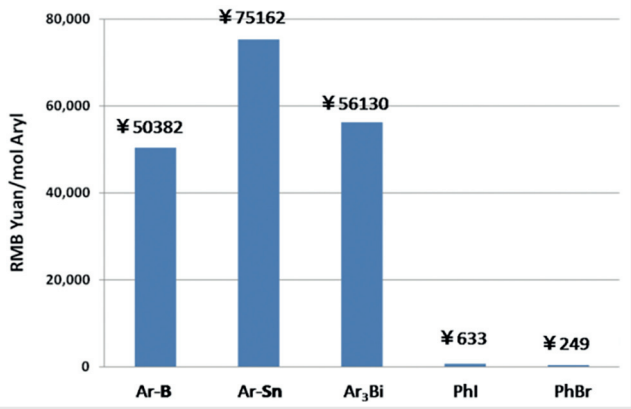
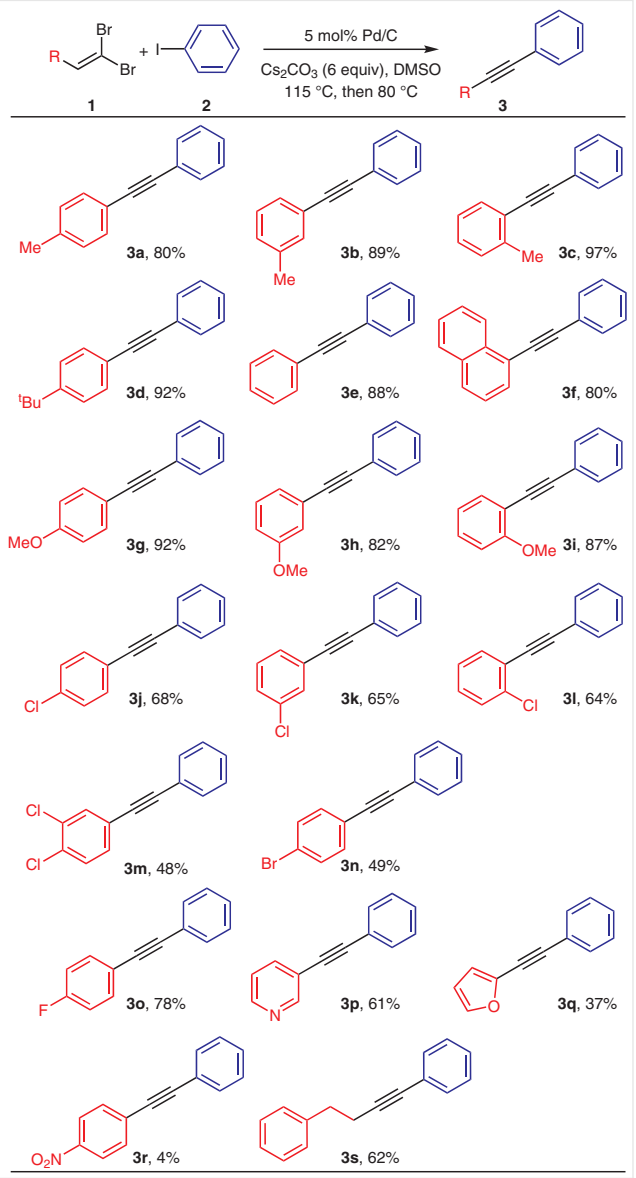


Figure 1 Sale prices of various reagents for synthesis of internal alkynes from a *gem*-dibromoalkene. Ar-**B** = $PhB(OH)_2$ (>97%), Ar-**Sn** = $PhSnMe_3$ (98%), and Ar_3**Bi** = $(2\text{-}MeOC_6H_4)_3Bi$, as supplied by Sigma-Aldrich LLC.

entry 1). No product was obtained when palladium acetylacetonate [$Pd(acac)_2$] was used, even at an elevated temperature (entry 2). It is interesting that we found Pd nanoparticles supported on activated carbon (Pd/C) to be the most efficient catalyst, and the isolated yield of **3a** reached 67% with 5 mol% of Pd/C at 80 °C (entry 3). It was not advantageous to use a decreased amount of base (entry 4). The best results were obtained when 6.0 equivalents of Cs_2CO_3 were added, and the product **3a** was obtained in 80% isolated yield (entry 5). Larger amount of base depressed the yield slightly (entry 6). The addition of DMF, another solvent commonly used in Sonogashira couplings, resulted in poor performance (entry 7). A decreased yield was obtained when less than 3 mol% of the Pd/C catalyst was used (entry 8). Under Pd-free conditions, no **3a** was formed (entries 9 and 10), although *t*-BuONa has been reported to mediate several types of C–C bond-formation reactions in the absence of a transition metal.[21] The addition of CuI decreased the yield significantly to 34%, due to the homocoupling reaction of the terminal alkyne generated in situ (entry 11).

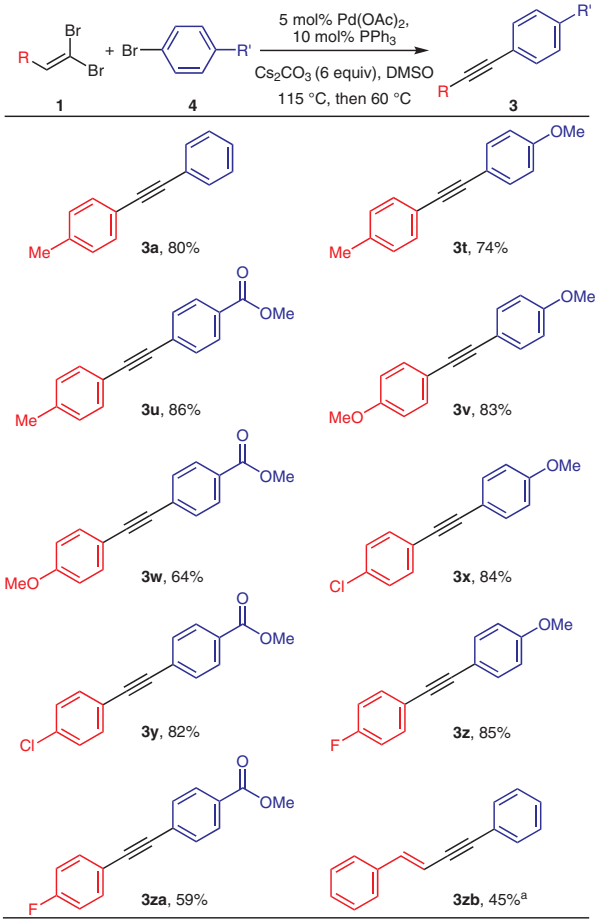
With the optimized conditions in hand, we investigated various *gem*-dibromoalkenes as coupling partners for iodobenzene, as summarized in Scheme 2.[22] Both electron-rich and nonfunctionalized aryl-substituted dibromoalkenes were converted into the corresponding internal alkynes in good to excellent yields of 80–97% (**3a–i**). The reaction tolerated halo substituents, which can be used for further functionalization (**3j–o**). Note that steric congestion did not depress the yields in this reaction, as substrates with an *ortho*-substituent on the aromatic ring also worked effectively to give the corresponding products in high yields (**3c**, **3i**, and **3l**). Further investigations showed that *gem*-dibromoalkenes with hetaryl (2-pyridyl or 2-furyl) substituents were also good substrates for this transformation, and gave the corresponding alkynes **3p** and **3q** in 61 and 37% yield,



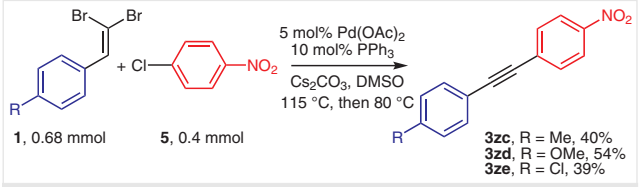
Scheme 2 Synthesis of internal alkynes from *gem*-dibromoalkenes and iodobenzene. *Reaction conditions for the one-pot, two-step procedure*: (i) **1** (0.68 mmol), Cs_2CO_3 (2.4 mmol), DMSO (2 mL), 115 °C, 15 h; (ii) PhI (0.4 mmol), Pd/C (5 mol%), 80 °C, 25 h. Isolated yields are reported in all the cases.

respectively. A nitro-substituted substrate was unfortunately a poor reactant and gave product **3r** in only 4% yield. Finally, an alkyl substrate was compatible with this reaction, and the corresponding product **3s** was isolated in 62% yield.

Encouraged by these results, we attempted to use bromobenzenes as more-challenging but cheaper coupling partners to prepare other diarylalkynes and conjugated enynes. After a brief optimization, we found that $Pd(OAc)_2/PPh_3$ was an effective catalytic system, giving **3a** in 80% yield; the results for this and other products are



Scheme 3 Synthesis of internal alkynes from *gem*-dibromoalkenes and bromobenzene. *Reaction conditions for the one-pot, two-step procedure*: (i) **1** (0.68 mmol), Cs_2CO_3 (2.4 mmol), DMSO (2 mL), 115 °C, 15 h; (ii) PhBr (0.4 mmol), $Pd(OAc)_2$ (5 mol%), PPh_3 (10 mol%), 60 °C, 25 h. Isolated yields are reported in all the cases.[a]The reaction was carried out by using 3 mol% of $Pd(OAc)_2$.



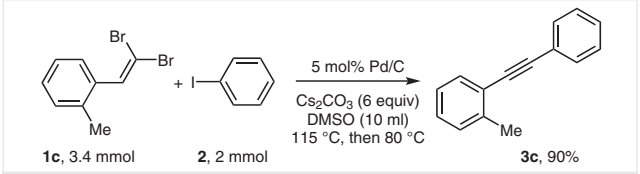
Scheme 4 Synthesis of diaryl alkynes from *gem*-dibromoalkenes and 1-chloro-4-nitrobenzene

shown in Scheme 3.[23] Diaryl alkynes with electron-donating groups on the two benzene rings were obtained with high yields (**3t** and **3v**). An electron-withdrawing ester group also fitted this reaction well, giving products **3u**, **3w**, **3y**, and **3za** in yields of 86, 64, 82, and 59%, respectively. Three other halides **3x–z** (59–85%) were synthesized efficiently, and enyne **3zb** was also prepared in moderate yield, which demonstrating the general applicability of this transformation.

Generally, aryl chlorides are considered less reactive in transition-metal-catalyzed coupling reactions. Interestingly, aryl chlorides bearing nitro groups reacted smoothly under the standard conditions for the reaction of bromobenzenes, albeit with moderate yields (39–54%; Scheme 4).[23] It is well known that the nitro group can be transformed into various other functional groups.

The possibility of Cu residues being present in the $Pd(OAc)_2$ was examined by inductively coupled plasma mass spectrometry, and the results showed that only 0.02 mol% of Cu was present in one mole of $Pd(OAc)_2$, which meant that 0.001 mol% of Cu had been introduced into the cross-coupling reaction together with 5 mol% of $Pd(OAc)_2$. Furthermore, we performed additional studies on the cross-coupling of **1a** with bromobenzene, in which 0.1 mol% CuI was introduced as a co-catalyst (Scheme S2). No obvious enhancement on the yield of **3a** was observed. We therefore suggest that the reaction probably proceeds with a Cu-free catalytic system.

Next, we sought to evaluate the scalability of the reaction. The synthesis of **3c** was carried out under optimized conditions, and the product was obtained in excellent yield (90%, Scheme 5). This result demonstrated the robustness of the protocol to scaling up.



Scheme 5 Scale-up of the synthesis of internal alkyne **3c** from *gem*-dibromoalkene **1c** and iodobenzene

In summary, we have developed a one-pot, two-step cascade synthesis of internal alkynes by using two types of organic halide: a *gem*-dibromoalkene and a halobenzene. The reaction proceeded smoothly under copper-free Sonogashira coupling conditions, and tolerated various functional groups, such as ester, bromo, chloro, fluoro, nitro, methoxy, or alkyl. In addition, *gem*-dibromoalkenes with alkyl, vinyl, or hetaryl (2-pyridyl or 2-furyl) substituents worked well and afforded the corresponding internal alkynes and enynes in good to excellent yields. The huge cost advantage of this method compared with previous methods makes it practicable to synthesize internal alkynes on a large scale for commercial use. This synthetic strategy might permit other chemical transformations to be performed with *gem*-dibromoalkenes as alternatives reactants to terminal alkynes.

Funding Information

This work was supported by Fundamental Research Funds for the Central Universities (No. 2015XKMS048), the Natural Science Foundation of Jiangsu Province (No. BK20160254), the National Natural Science Foundation of China (No. 21572094), and A Project Funded by the Priority Academic Program Development of Jiangsu Higher Education Institutions.

Acknowledgment

This work was supported by Fundamental Research Funds for the Central Universities (No. 2015XKMS048), the Natural Science Foundation of Jiangsu Province (No. BK20160254), the National Natural Science Foundation of China (No. 21572094), and A Project Funded by the Priority Academic Program Development of Jiangsu Higher Education Institutions

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1590907.

References and Notes

(1) (a) Chinchilla, R.; Nájera, C. *Chem. Rev.* **2014**, *114*, 1783. (b) Boyarskiy, V. P.; Ryabukhin, D. S.; Bokach, N. A.; Vasilyev, A. V. *Chem. Rev.* **2016**, *116*, 5894.

(2) (a) Doucet, H.; Hierso, J. C. *Angew. Chem. Int. Ed. Engl.* **2007**, *46*, 834. (b) Chinchilla, R.; Nájera, C. *Chem. Soc. Rev.* **2011**, *40*, 5084.

(3) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467. (b) Cassar, L. *J. Organomet. Chem.* **1975**, *93*, 253. (c) Dieck, H. A.; Heck, F. R. *J. Organomet. Chem.* **1975**, *93*, 241.

(4) Liu, J.; Zhang, X.; Shi, L.; Liu, M.; Yue, Y.; Li, F.; Zhuo, K. *Chem. Commun.* **2014**, *50*, 9887.

(5) (a) Legrand, F.; Jouvin, K.; Evano, G. *Isr. J. Chem.* **2010**, *50*, 588. (b) Chelucci, G. *Chem. Rev.* **2012**, *112*, 1344.

(6) (a) Desai, N. B.; McKelvie, N.; Ramirez, F. *J. Am. Chem. Soc.* **1962**, *84*, 1745. (b) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *13*, 3769.

(7) **1-(2,2-Dibromovinyl)-4-methylbenzene (1a); Typical Procedure**

CBr_4 (3.316 g, 10 mmol) was added to a solution of Ph_3P (5.246 g, 20 mmol) in CH_2Cl_2 (15 mL) at 0 °C, and the mixture was stirred for 10 min. 4-Tolualdehyde (0.601 g, 5 mmol) was added, and the mixture was stirred at r.t. for 1 h. After removal of solvent, hexane (30 mL) was added and the mixture was filtered through Celite. The filtrate was concentrated under reduced pressure, and the product was purified by flash column chromatography to give a yellow oil; yield: 1.325 g (96%).

(8) (a) Aziz, J.; Baladi, T.; Piguel, S. *J. Org. Chem.* **2016**, *81*, 4122. (b) Berciano, B. P.; Lebrequier, S.; Besselièvre, F.; Piguel, S. *Org. Lett.* **2010**, *12*, 4038. (c) Shi, W.; Lei, A. W. *Tetrahedron Lett.* **2014**, *55*, 2763. (d) Ye, S.; Yang, X.; Wu, J. *Chem. Commun.* **2010**, *46*, 2950. (e) Riveiros, R.; Saya, L.; Sestelo, J. P.; Sarandeses, L. A. *Eur. J. Org. Chem.* **2008**, *2008*, 1959.

(9) (a) Coste, A.; Karthikeyan, G.; Couty, F.; Evano, G. *Angew. Chem. Int. Ed. Engl.* **2009**, *48*, 4381. (b) Coste, A.; Couty, F.; Evano, G. *Org. Lett.* **2009**, *11*, 4454. (c) Jouvin, K.; Coste, A.; Bayle, A.; Legrand, F.; Karthikeyan, G.; Tadiparthi, K.; Evano, G. *Organometallics* **2012**, *31*, 7933. (d) Das, B.; Salvanna, N.; Reddy, G. C.; Balasubramanyam, P. *Tetrahedron Lett.* **2011**, *52*, 6497. (e) Huh, D. H.; Ryu, H.; Kim, Y. G. *Tetrahedron* **2004**, *60*, 9857. (f) Fayol, A.; Fang, Y.-Q.; Lautens, M. *Org. Lett.* **2006**, *8*, 4203. (g) Beltrán-Rodil, S.; Edwards, M.; Pugh, D.; Reid, M.; Taylor, R. J. K. *Synlett* **2009**, *2010*, 602.

(10) (a) Li, P.; Alper, H. *J. Org. Chem.* **1986**, *51*, 4354. (b) Shen, W.; Kunzer, A. *Org. Lett.* **2002**, *4*, 1315. (c) Ye, W.; Mo, J.; Zhao, T.; Xu, B. *Chem. Commun.* **2009**, 3246. (d) Jouvin, K.; Bayle, A.; Legrand, F.; Evano, G. *Org. Lett.* **2012**, *14*, 1652.

(11) (a) Murahashi, S. I.; Yamamura, M.; Yanagisawa, K. I.; Nobuaki, M.; Kondo, K. *J. Org. Chem.* **1979**, *44*, 2408. (b) Cristau, H. J.; Chabaud, B.; Labaudiniere, R.; Christol, H. *J. Org. Chem.* **1986**, *51*, 875. (c) Jin, H.; Yang, Y. W.; Kuang, C. X.; Yang, Q. *Synlett* **2011**, *2011*, 2886. (d) Ni, Z.; Wang, S.; Mao, H.; Pan, Y. *Tetrahedron Lett.* **2012**, *53*, 3907.

(12) (a) Lera, M.; Hayes, C. J. *Org. Lett.* **2000**, *2*, 3873. (b) Wang, Y.; Gan, J.; Liu, L.; Yuan, H.; Gao, Y.; Liu, Y.; Zhao, Y. *J. Org. Chem.* **2014**, *79*, 3678. (c) Liu, L.; Wang, Y.; Zeng, Z.; Xu, P.; Gao, Y.; Yin, Y.; Zhao, Y. *Adv. Synth. Catal.* **2013**, *355*, 659. (d) Evano, G.; Tadiparthi, K.; Couty, F. *Chem. Commun.* **2011**, *47*, 179.

(13) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173.

(14) (a) Rahimi, A.; Schmidt, A. *Synthesis* **2010**, *2010*, 2621. (b) Liu, J.; Dai, F.; Yang, Z.; Wang, S.; Xie, K.; Wang, A.; Chen, X.; Tan, Z. *Tetrahedron Lett.* **2012**, *53*, 5678. (c) Yan, H.; Lu, L.; Sun, P.; Zhu, Y.; Yang, H.; Liu, D.; Rong, G.; Mao, J. *RSC Adv.* **2013**, *3*, 377.

(15) (a) Chelucci, G.; Capitta, F.; Baldino, S.; Pinna, G. A. *Tetrahedron Lett.* **2007**, *48*, 6514. (b) Chelucci, G.; Capitta, F.; Baldino, S. *Tetrahedron* **2008**, *64*, 10250.

(16) Shen, W.; Wang, L. *J. Org. Chem.* **1999**, *64*, 8873.

(17) (a) Rao, M. L. N.; Jadhav, D. N.; Dasgupta, P. *Org. Lett.* **2010**, *12*, 2048. (b) Rao, M. L. N.; Dasgupta, P.; Murty, V. N. *RSC Adv.* **2015**, *5*, 24834.

(18) Yan, J. C.; Wang, Z. Y.; Wang, L. *J. Chem. Res.* **2004**, 71; DOI: 10.3184/030823404323000864.

(19) (a) Habrant, D.; Rauhala, V.; Koskinen, A. M. P. *Chem. Soc. Rev.* **2010**, *39*, 2007. (b) Zhao, M.; Kuang, C.; Yang, Q.; Cheng, X. *Tetrahedron Lett.* **2011**, *52*, 992. (c) Liu, S.; Chen, X.; Hu, Y.; Yuan, L.; Chen, S.; Wu, P.; Wang, W.; Zhang, S.; Zhang, W. *Adv. Synth. Catal.* **2015**, *357*, 553.

(20) Morri, A. K.; Thummala, Y.; Doddi, V. R. *Org. Lett.* **2015**, *17*, 4640.

(21) (a) Shirakawa, E.; Itoh, K.-i.; Higashino, T.; Hayashi, T. *J. Am. Chem. Soc.* **2010**, *132*, 15537. (b) Sun, C.-L.; Shi, Z.-J. *Chem. Rev.* **2014**, *114*, 9219.

(22) **Cross-Coupling of *gem*-Dibromoalkenes with Iodobenzene; General Procedure**

A mixture of the appropriate *gem*-dibromoalkene **1** (0.68 mmol), Cs_2CO_3 (2.4 mmol), and DMSO (2 mL) was stirred at 115 °C for 15 h. When **1** was completely consumed, PhI (0.4 mmol) and Pd/C (5 mol%) were added and the mixture was deaerated with N_2 and stirred at 80 °C for 25 h. The mixture was then cooled to r.t., diluted with EtOAc (30 mL), and washed with H_2O (3 × 10 mL). The organic phases were combined, dried ($MgSO_4$), and concentrated, and the residue was purified by column chromatography (silica gel, hexane).

1,2-Dichloro-4-(phenylethynyl)benzene (3m)

White solid; yield: 47.4 mg (48%). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.60 (t, *J* = 5.6 Hz, 1 H), 7.54–7.48 (m, 2 H), 7.43–7.27 (m, 5 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 133.1, 132.5, 132.5, 131.6, 130.6, 130.3, 128.7, 128.3, 123.2, 122.4, 91.2, 86.9. HRMS (EI): *m/z* $[M]^+$ calcd for $C_{14}H_8Cl_2$: 246.0003; found: 246.0012.

(23) **Palladium-Catalyzed Cross-Coupling of *gem*-Dibromoalkenes 1 with Bromobenzene or 1-Chloro-4-nitrobenzene; General Procedure**

A mixture of the appropriate *gem*-dibromoalkene **1** (0.68 mmol), Cs_2CO_3 (2.4 mmol), and DMSO (2 mL) was stirred at 115 °C for 15 h. When the alkene **1** was completely consumed, bromobenzene (**4**) or 1-chloro-4-nitrobenzene (**5**) (0.4 mmol), $Pd(OAc)_2$ (5 mol%), and PPh_3 (10 mol%) were added and the mixture was deaerated with N_2 gas and stirred at 60 °C or 80 °C for 25 h. When the reaction was complete, the product was isolated and purified as described above.

1-Chloro-4-[(4-methoxyphenyl)ethynyl]benzene (3x)

Brown solid; yield: 81.5 mg (84%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50–7.36 (m, 4 H), 7.32–7.25 (m, 2 H), 6.92–6.77 (m, 2 H), 3.83–3.69 (m, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.0, 133.2, 132.8, 131.8, 128.8, 128.5, 122.3, 114.2, 90.5, 87.2, 55.5. HRMS (EI): *m/z* $[M]^+$ calcd for $C_{15}H_{11}ClO$: 242.0498; found: 242.0506.

Methyl 4-[(4-Chlorophenyl)ethynyl]benzoate (3y)

Brown solid; yield: 88.1 mg (82%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10–7.96 (m, 2 H), 7.61–7.50 (m, 2 H), 7.44 (t, *J* = 13.1 Hz, 2 H), 7.36–7.27 (m, 2 H), 3.98–3.83 (m, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.6, 134.9, 133.0, 131.6, 129.8, 129.7, 128.9, 127.7, 121.3, 91.2, 89.6, 52.3. HRMS (EI): *m/z* $[M]^+$ calcd for $C_{16}H_{11}ClO_2$ $[M]^+$ 270.0448; found: 270.0459.

1-Fluoro-4-[(4-methoxyphenyl)ethynyl]benzene (3z)

Brown solid; yield: 76.8 mg (85%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53–7.35 (m, 4 H), 7.06–6.95 (m, 2 H), 6.85 (d, *J* = 8.5 Hz, 2 H), 3.81 (d, *J* = 14.4 Hz, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 162.3 (J_{CF} = 249.2 Hz), 159.7, 133.3 (J_{CF} = 7.6 Hz), 133.0, 119.7 (J_{CF} = 3.0 Hz), 115.7, 115.4 (J_{CF} = 22.7 Hz), 114.1, 89.1, 87.0, 55.3.HRMS (EI): *m/z* $[M]^+$ calcd for $C_{15}H_{11}FO$: 226.0794; found: 226.0800.

Methyl 4-[(4-Fluorophenyl)ethynyl]benzoate (3za)

Brown solid; yield: 60.0 mg (59%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 8.2 Hz, 2 H), 7.64–7.41 (m, 4 H), 7.05 (t, *J* = 8.6 Hz, 2 H), 3.90 (d, *J* = 12.0 Hz, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.5, 162.8 (J_{CF} = 250.7 Hz), 133.7 (J_{CF} = 9.01 Hz), 131.5, 129.6, 128.4, 127.8, 118.8 (J_{CF} = 3.0 Hz), 115.8 (J_{CF} = 22.7 Hz), 91.3, 88.4, 52.2. HRMS (EI): *m/z* $[M]^+$ calcd for $C_{16}H_{11}FO_2$: 254.0743; found: 254.0750.