JOC Article
pubs.acs.org/joc

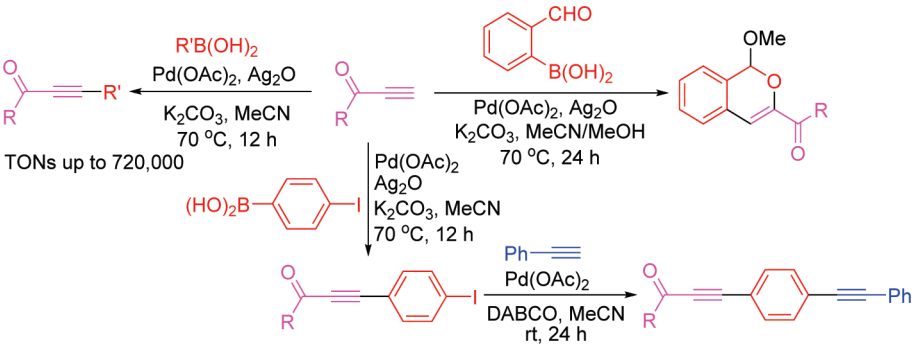
Palladium-Catalyzed Cross-Coupling of Electron-Poor Terminal Alkynes with Arylboronic Acids under Ligand-Free and Aerobic Conditions

Ming-Bo Zhou, Wen-Ting Wei, Ye-Xiang Xie, Yong Lei, and Jin-Heng Li*

Key Laboratory of Chemical Biology & Traditional Chinese Medicine Research (Ministry of Education), Hunan Normal University, Changsha 410081, China

jhli@hunnu.edu.cn

Received June 1, 2010



Palladium-catalyzed cross-coupling reaction of terminal alkynes with arylboronic acids has been described. In the presence of $Pd(OAc)_2$ and Ag_2O, a variety of terminal alkynes, including electron-poor terminal alkynes, smoothly underwent the reaction with numerous boronic acids to afford the corresponding internal alkynes in moderate to good yields. Moreover, this methodology was applied to the synthesis of 1*H*-isochromenes and diynes. It is noteworthy that the reaction proceeds under ligand-free and relative lower loading Pd conditions, and the maximal TONs (turnover numbers) of the reaction are up to 720,000.

Introduction

The alkyne skeleton is a prevalent motif found in many naturally occurring products[1] and materials.[2] Among the methods for constructing this skeleton, the Sonogashira cross-coupling reaction represents the most straightforward and efficient tool and has been widely explored since it was reported by Sonogashira, Cassar, and Heck independently.[3−5] Although many modified transformations have been reported for these purposes,[3−5] some limitations still remained: electron-poor alkynes usually give unsatisfactory results from the reaction with aryl halides. To overcome these limitations, Zou and co-workers reported a procedure for constructing internal alkynes through the cross-coupling of terminal alkynes with arylboronic acids using a palladium/silver system (eq 1, Scheme 1).[6] In the presence of $(dppf)PdCl_2$ and Ag_2O, terminal alkynes including an electron-poor alkyne (ethyl propiolate) underwent reaction with arylboronic acids at room temperature for 20−30 h, providing the corresponding

(1) For reviews, see: (a) Bohlmann, F.; Burkhart, F. T. Zero, C. *Naturally Occurring Acetylenes*; Academic: London, 1973. (b) Hunstman, V. D. *The Chemistry of the Carbon−Carbon Triple Bond*; Patai, S., Ed.; Wiley-Interscience: London, 1978; p 553. (c) Nicolaou, K. C.; Bulger, P. G.; Sarl-ah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442.

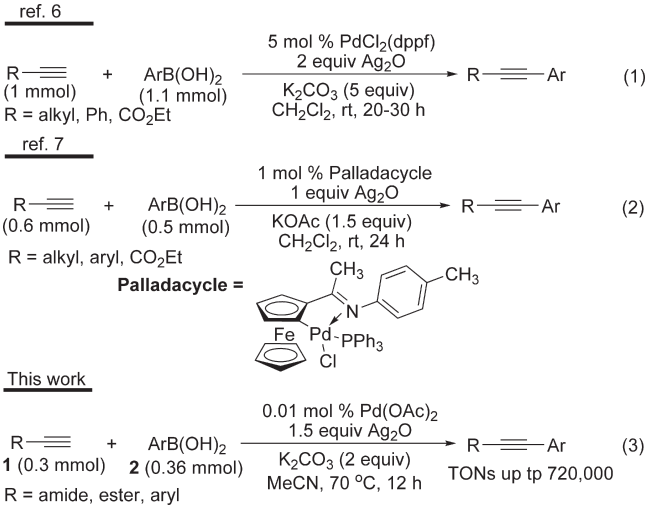
(2) For selected reviews and papers, see: (a) Bunz, U. H. F. *Chem. Rev.* **2000**, *100*, 1605. (b) Tour, J. M. *Acc. Chem. Res.* **2000**, *33*, 791. (c) Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 2632. (d) Martin, R. E.; Diederich, F. *Angew. Chem., Int. Ed.* **1999**, *38*, 1350.

(3) For selected reviews, see: (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467. (b) Sonogashira, K. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; p 203. (c) Moore, J. S. *Acc. Chem. Res.* **1997**, *30*, 402. (d) Sonogashira, K. *J. Organomet. Chem.* **2002**, *653*, 46. (e) Tykwinski, R. R. *Angew. Chem., Int. Ed.* **2003**, *42*, 1566. (f) Negishi, E.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979. (g) *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; Diederich, F., de Meijere, A., Eds.; Wiley-VCH: Weinheim, 2004. (h) *Transition Metals for Organic Synthesis; Building Block and Fine Chemicals*, 2nd ed.; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 2004. (i) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442. (j) Yin, L.; Liebscher, J. *Chem. Rev.* **2007**, *107*, 133. (k) Doucet, H.; Hierso, J.-C. *Angew. Chem., Int. Ed.* **2007**, *46*, 834. (l) Chinchilla, R.; Nájera, C. *Chem. Rev.* **2007**, *107*, 874.

(4) (a) Diek, H. A.; Heck, F. R. *J. Organomet. Chem.* **1975**, *93*, 259. (b) Cassar, L. *J. Organomet. Chem.* **1975**, *93*, 253. (c) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467. (d) Tang, B.-X.; Tang, D.-J.; Tang, S.; Yu, Q.-F.; Zhang, Y.-H.; Liang, Y.; Zhong, P.; Li, J.-H. *Org. Lett.* **2008**, *10*, 1063. (e) Jiang, T.-S.; Zhang, X.-G.; Li, J.-H. *Synthesis* **2009**, 3029. (f) Pinto, A.; Neuville, L.; Retailleau, P.; Zhu, J. *Org. Lett.* **2006**, *8*, 4927. (g) Pinto, A.; Neuville, L.; Zhu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 3291.

DOI: 10.1021/jo101063p Published on Web 07/22/2010

SCHEME 1



internal alkynes in moderate to good yields. However, the reaction required high loading of (dppf)$PdCl_2$ (5 mol %) and phenylacetylene displayed less activity for the cross-coupling process. Subsequently, Wu and co-workers extended the scope to arylalkynes using the cyclopalladated ferrocenylimine and Ag_2O system (eq 2, Scheme 1).[7] Although both the aforementioned catalytic systems were efficient and provided an alternative route to internal alkynes, only an electron-poor alkyne was examined and highly expensive palladium−ligand catalytic systems were required.[8]

Generally, *N*,3-diarylpropiolamides can be prepared by the traditional Sonongashira method using electron-poor alkynes and aryl halides as the reaction partners; however, the yields are usually low to moderate based on the properties of both alkynes and aryl halides.[4] For example, treatment of *N*-methyl-*N*-phenylpropiolamide (**1a**) with iodobenzene, $PdCl_2(PPh_3)_2$ (5 mol %), and CuI (10 mol %) in Et_3N/THF afforded the desired product **3** in 62% yield at room temperature and 51% at 70 °C (Scheme 2).[4d−g] However, only a moderate yield was achieved for high active 1-(4-iodophenyl)ethanone under the same conditions. On the other hand, the Sonogashira cross-coupling reactions of ynones with aryl iodides cannot take place under the traditional Sonongashira conditions. To realize these reactions, some special reagents, such as diaryliodonium salts or in situ generated alkynylzinc derivatives, were required.[9] Thus, the development of a general and ligand-free method for extending the electron-poor alkyne scope is interesting. Here, we report a palladium-catalyzed cross-coupling of terminal alkynes, including electron-poor terminal alkynes, with boronic acids under ligand-free and relatively lower loading Pd conditions (eq 3, Scheme 1). It is noteworthy that the maximum TONs (turnover numbers) of the reaction are up to 720000.

Results and Discussion

The reaction between *N*-methyl-*N*-phenylpropiolamide (**1a**) and phenylboronic acid (**2a**) was chosen as a model reaction to screen the optimal reaction conditions, and the results are summarized in Table 1. To our delight, treatment of amide **1a** with **2a**, $Pd(OAc)_2$ (0.1 mol %), Ag_2O (1 equiv), and CH_3ONa (1 equiv) afforded the desired product **4** in 61% yield after 12 h (entry 1). Identical results were observed at a loading of 0.01 mol % of $Pd(OAc)_2$ (entry 2). Subsequently, both the amount of Ag_2O and the effect of bases were investigated (entries 3−12). We found that the reaction could not take place without Ag (entry 6), and 1.5 equiv of Ag_2O gave the best results in the presence of 2 equiv of K_2CO_3 base (entry 8). The other bases, including Na_2CO_3, Cs_2CO_3, and KOAc, affected the reaction slightly (entries 9−11). The results demonstrated that a moderate yield was still isolated using Ag_2O alone (entry 12). Two other solvents, *n*-PrCN and toluene, were tested, and they were less effective than MeCN (entries 13 and 14). Among the reaction temperatures examined, 70 °C provided the highest yield (entries 8 and 15−17). While 70 °C afforded the target product **4** in 88% yield (entry 15), both 100 and 50 °C decreased the yield slightly (entries 8 and 16). Gratifyingly, 72% yield of **4** was still achieved at room temperature after a prolonged time (48 h, entry 17). It is noteworthy that satisfactory yield can be obtained for 48 h even at 0.0001 mol % of $Pd(OAc)_2$ (TONs = 720000, entry 18), but no reaction is observed without Pd catalysis (entry 19). Either $PdCl_2$ or $PdCl_2$/dppf were suitable catalysts for the reaction, but they were inferior to $Pd(OAc)_2$ (entries 20 and 21). Finally, four other Ag salts were also evaluated, and they displayed less efficiency by comparison with Ag_2O (entries 22−25).[10] It is noteworthy that in the absence of K_2CO_3 a moderate yield can be isolated using 0.01 mol % of $Pd(OAc)_2$ and 3.5 equiv of Ag_2CO_3 (entry 25).

As shown in Table 2, the scope of the alkynes and boronic acids was explored under the optimal reaction conditions. Initially, a variety of boronic acids **2** were investigated by reaction with *N*-methyl-*N*-phenylpropiolamide (**1a**) (entries 1−12). The results demonstrated that several functional groups, including methyl, methoxy, fluoro, iodo, formyl, acetyl, nitro, and vinyl groups, on the aryl moiety of substrates **2** were perfectly tolerated. For example, methyl-substituted arylboronic acids **2b**−**d** smoothly underwent

(5) For selected papers, see: (a) Liang, B.; Dai, M.; Chen, J.; Yang, Z. *J. Org. Chem.* **2005**, *70*, 391. (b) Li, J.-H.; Liang, Y.; Xie, Y.-X. *J. Org. Chem.* **2005**, *70*, 4393. (c) Li, J.-H.; Hu, X.-C; Xie, Y.-X. *Tetrahedron* **2006**, *62*, 31. (d) Li, J.-H.; Li, J.-L.; Wang, D.-P.; Pi, S.-F.; Xie, Y.-X.; Zhang, M.-B.; Hu, X.-C. *J. Org. Chem.* **2007**, *72*, 2053. (e) Cheng, J.; Sun, Y.; Wang, F.; Guo, M.; Xu, J.-H.; Pan, Y.; Zhang, Z. *J. Org. Chem.* **2004**, *69*, 5428. (f) Zhang, W.; Wu, H.; Liu, Z.; Zhong, P.; Zhang, L.; Huang, X.; Cheng, J. *Chem. Commun.* **2006**, 4826. (g) Gelman, D.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2003**, *42*, 5993. (h) Mino, T.; Shirae, Y.; Saito, T.; Sakamoto, M.; Fujita, T. *J. Org. Chem.* **2006**, *71*, 9499. (i) Ma, D.; Liu, F. *Chem. Commun.* **2004**, 1934. (j) Thorand, S.; Krause, N. *J. Org. Chem.* **1998**, *63*, 8551. (k) Mori, A.; Kawashima, J.; Shimada, T.; Suguro, M.; Hirabayashi, K.; Nishihara, Y. *Org. Lett.* **2000**, *2*, 2935. (l) Castanet, A.; Colobert, F.; Schlama, T. *Org. Lett.* **2000**, *2*, 3559. (m) Consorti, C. S.; Flores, F. R.; Rominger, F.; Dupont, J. *Adv. Synth. Catal.* **2006**, *348*, 133. (n) Monnier, F.; Turtaut, F.; Duroure, L.; Taillefer, M. *Org. Lett.* **2008**, *10*, 3203.

(6) Zou, G.; Zhu, J.; Tang, J. *Tetrahedron Lett.* **2003**, *44*, 8709.

(7) Yang, F.; Wu, Y. *Eur. J. Org. Chem.* **2007**, 3476.

(8) For a paper on CuI-catalyzed cross-coupling of arylboronic acids with terminal alkynes, see: Pan, C.; Luo, F.; Wang, W.; Ye, Z.; Cheng, J. *Tetrahedron Lett.* **2009**, *50*, 5044.

(9) (a) Radhakrishnan, U.; Stang, P. J. *Org. Lett.* **2001**, *3*, 895. (b) Anastasia, L.; Negishi, E.-i. *Org. Lett.* **2001**, *3*, 3111. (c) Eckert, T.; Ipaktschi, J. *Synth. Commun.* **1998**, *28*, 327.

(10) For selected papers on Ag salt-promoted organic reactions, see: (a) Moreno-Mañas, M.; Pérez, M.; Pleixats, R. *J. Org. Chem.* **1996**, *61*, 2346. (b) Zou, G.; Reddy, Y. K.; Falck, J. R. *Tetrahedron Lett.* **2001**, *42*, 7213. (c) Satoh, T.; Ogino, S.; Miura, M.; Nomura, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 5063. (d) Nishihara, Y.; Onodera, H.; Osakada, K. *Chem. Commun.* **2004**, 192. (e) Letinois-Halbes, U.; Pale, P.; Berger, S. *J. Org. Chem.* **2005**, *70*, 9185.

SCHEME 2. Controlled Experiments: The Traditional Sonongashira Reaction of *N*-Methyl-*N*-phenylpropiolamide with Aryl Iodides

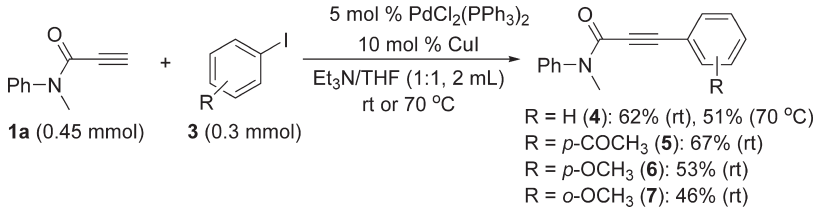
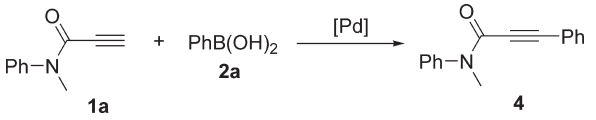


TABLE 1. Screening Optimal Conditions[a]



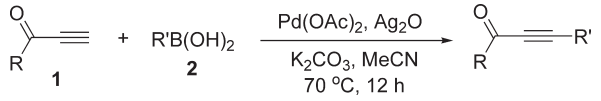
entry	[Pd] (mol %)	[Ag] (mol %)	base (equiv)	solvent	*T* (°C)	yield (%)
1	$Pd(OAc)_2$ (0.1)	Ag_2O (1)	CH_3ONa (1)	MeCN	100	61
2	$Pd(OAc)_2$ (0.01)	Ag_2O (1)	CH_3ONa (1)	MeCN	100	60
3	$Pd(OAc)_2$ (0.01)	Ag_2O (2)	CH_3ONa (1)	MeCN	100	75
4	$Pd(OAc)_2$ (0.01)	Ag_2O (1.5)	CH_3ONa (1)	MeCN	100	75
5[b]	$Pd(OAc)_2$ (0.01)	Ag_2O (0.5)	CH_3ONa (1)	MeCN	100	40
6	$Pd(OAc)_2$ (0.01)		CH_3ONa (1)	MeCN	100	trace
7	$Pd(OAc)_2$ (0.01)	Ag_2O (1.5)	CH_3ONa (2)	MeCN	100	63
8	$Pd(OAc)_2$ (0.01)	Ag_2O (1.5)	K_2CO_3 (2)	MeCN	100	85
9	$Pd(OAc)_2$ (0.01)	Ag_2O (1.5)	Na_2CO_3 (2)	MeCN	100	53
10	$Pd(OAc)_2$ (0.01)	Ag_2O (1.5)	Cs_2CO_3 (2)	MeCN	100	65
11	$Pd(OAc)_2$ (0.01)	Ag_2O (1.5)	KOAc (2)	MeCN	100	72
12	$Pd(OAc)_2$ (0.01)	Ag_2O (1.5)		MeCN	100	63
13	$Pd(OAc)_2$ (0.01)	Ag_2O (1.5)	K_2CO_3 (2)	*n*-PrCN	100	61
14	$Pd(OAc)_2$ (0.01)	Ag_2O (1.5)	K_2CO_3 (2)	toluene	100	72
15	$Pd(OAc)_2$ (0.01)	Ag_2O (1.5)	K_2CO_3 (2)	MeCN	70	88
16	$Pd(OAc)_2$ (0.01)	Ag_2O (1.5)	K_2CO_3 (2)	MeCN	50	84
17[c]	$Pd(OAc)_2$ (0.01)	Ag_2O (1.5)	K_2CO_3 (2)	MeCN	rt	72
18[c]	$Pd(OAc)_2$ (0.0001)	Ag_2O (1.5)	K_2CO_3 (2)	MeCN	70	72
19		Ag_2O (1.5)	K_2CO_3 (2)	MeCN	70	0
20	$PdCl_2$ (0.01)	Ag_2O (1.5)	K_2CO_3 (2)	MeCN	70	80
21[d]	$PdCl_2$ (0.01)	Ag_2O (1.5)	K_2CO_3 (2)	MeCN	70	76
22	$Pd(OAc)_2$ (0.01)	$AgNO_3$ (1.5)	K_2CO_3 (2)	MeCN	70	66
23	$Pd(OAc)_2$ (0.01)	AgOAc (1.5)	K_2CO_3 (2)	MeCN	70	71
24	$Pd(OAc)_2$ (0.01)	$AgBF_4$ (1.5)	K_2CO_3 (2)	MeCN	70	67
25	$Pd(OAc)_2$ (0.01)	Ag_2CO_3 (3.5)		MeCN	70	67

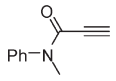
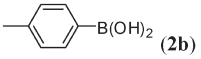
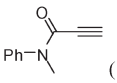
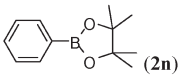
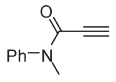
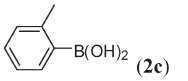
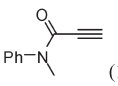
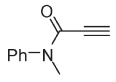
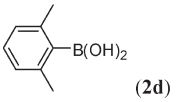
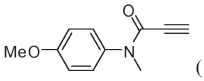
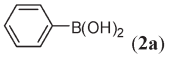
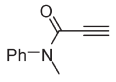
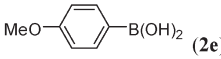
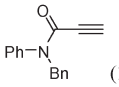
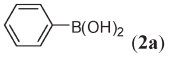
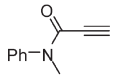
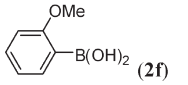
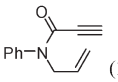
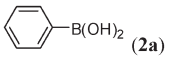
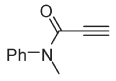
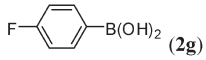
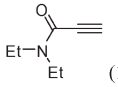
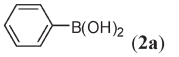
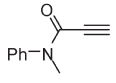
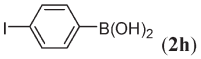
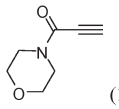
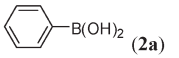
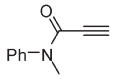
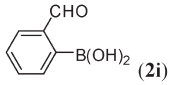
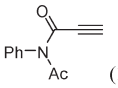
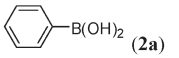
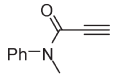
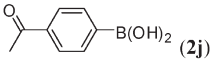
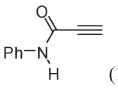
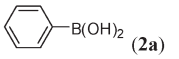
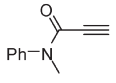
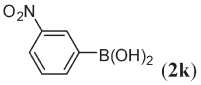
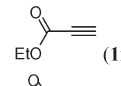
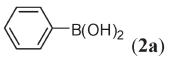
[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.36 mmol), base, and solvent (2 mL) at 100 °C for 12 h. [b]For 16 h. [c]For 48 h. [d]dppf (0.02 mol %) was added.

the reaction with substrate **1a**, $Pd(OAc)_2$ (0.01 mol %), and Ag_2O (1.5 equiv), and the yields were affected by the steric hindrance in the order **2b** (90%) > **2c** (86%) > **2d** (75%) (entries 1−3). Interestingly, only boronic acid group in substrate **2h** could react with alkyne **2a**, and the active iodo group was inert under the optimal conditions: this provides an attractive route to introduction of new functional groups in this skeleton (entry 7). We were pleased that substrates **2i** and **2l**, with an active formylaryl or vinylaryl group, were tolerated well (entries 8 and 11). Notably, (*E*)-prop-1-enylboronic acid (**2m**) was suitable for the reaction under the optimal conditions (90%, entry 12). Interestingly, two other boronic electrophiles, phenylboronic acid pinacol ester (**2n**) and $PhBF_3K$ (**2o**), were also compatible under the standard conditions (entries 13 and 14). Subsequently, a number of electron-poor alkynes, either amide or ester, were examined in the presence of phenylboronic acid (**2a**), $Pd(OAc)_2$ (0.01 mol %), and Ag_2O (1.5 equiv) (entries 15−22). We found that *N*,*N*-disubstituted amides **1b**−**f** were successfully reacted with phenylboronic acid (**2a**) in moderate to good yields (entries 15−19), but *N*-acetyl-*N*-phenylamide **1g** has no activity under the same conditions (entry 20). Unfortunately, monosubstituted amide **1h** was also inert for the reaction (entry 21). Ester **1i** was tested, and 71% yield was obtained by reacting with phenylboronic acid (**2a**), $Pd(OAc)_2$, and Ag_2O (entry 22). However, propiolic acid (**1j**) has no activity for the reaction under the same conditions (entry 23). It is noteworthy that ynone (**1k**) can smoothly undergo the reaction with boronic acid (**2k**), $Pd(OAc)_2$, and Ag_2O in 54% yield (entry 24).[9]

As shown in Scheme 3, a number of aromatic and aliphatic alkynes were initially investigated under standard conditions. In the presence of $Pd(OAc)_2$ (0.01 mol %), Ag_2O (1.5 equiv), K_2CO_3 (2 equiv), and MeCN (2 mL), phenylacetylene (**1j**) was a suitable substrate for the reaction with phenylboronic acid (**2a**), providing the desired product **27** in 74%. However, the reaction of ethynyltrimethylsilane with *p*-tolylboronic acid (**2b**) was unsuccessful (**28**). To our delight, aliphatic alkynes, bearing a *tert*-butyl, *n*-pentyl, or cyclopropyl group, were consistent with the standard conditions (**29**−**31**). Although the yields were not satisfactory from the reactions of amides **1** with 2-formylphenylboronic

TABLE 2. The Sonogashira Cross-coupling Reactions of Electron-Poor Terminal Alkynes (1) with Boronic Acids (2) in the Presence of $Pd(OAc)_2$ and Ag_2O[a]



entry	alkyne **1**	boronic acid **2**	yield (%)	entry	alkyne **1**	boronic acid **2**	yield (%)
1	 (**1a**)	 (**2b**)	90 (**8**)	13	 (**1a**)	 (**2n**)	70 (**4**)
2	 (**1a**)	 (**2c**)	86 (**9**)	14	 (**1a**)	$PhBF_3K$ (**2o**)	85 (**4**)
3	 (**1a**)	 (**2d**)	75 (**10**)	15	 (**1b**)	 (**2a**)	88 (**17**)
4	 (**1a**)	 (**2e**)	84 (**6**)	16	 (**1c**)	 (**2a**)	93 (**18**)
5	 (**1a**)	 (**2f**)	81 (**7**)	17	 (**1d**)	 (**2a**)	74 (**19**)
6	 (**1a**)	 (**2g**)	85 (**11**)	18	 (**1e**)	 (**2a**)	75 (**20**)
7	 (**1a**)	 (**2h**)	82 (**12**)	19	 (**1f**)	 (**2a**)	90 (**21**)
8	 (**1a**)	 (**2i**)	52 (**13**)	20	 (**1g**)	 (**2a**)	trace (**22**)
9	 (**1a**)	 (**2j**)	92 (**5**)	21	 (**1h**)	 (**2a**)	trace (**23**)
10	 (**1a**)	 (**2k**)	98 (**14**)	22	 (**1i**)	 (**2a**)	71 (**24**)
11	(**1a**)	(**2l**)	72 (**15**)	23	(**1j**)	(**2b**)	trace (**25**)
12	(**1a**)	(**2m**)	90 (**16**)	24[b]	(**1k**)	(**2k**)	54 (**26**)

[a]Reaction conditions: **1** (0.3 mmol), **2** (0.36 mmol), $Pd(OAc)_2$ (0.01 mol %), Ag_2O (1.5 equiv), K_2CO_3 (2 equiv), and MeCN (2 mL) at 70 °C for 12 h. [b]$Pd(OAc)_2$ (3 mol %).

acid (**2i**) in the presence of MeOH, two interesting tandem 1*H*-isochromene products **32** and **33** were obtained in one pot.[11]

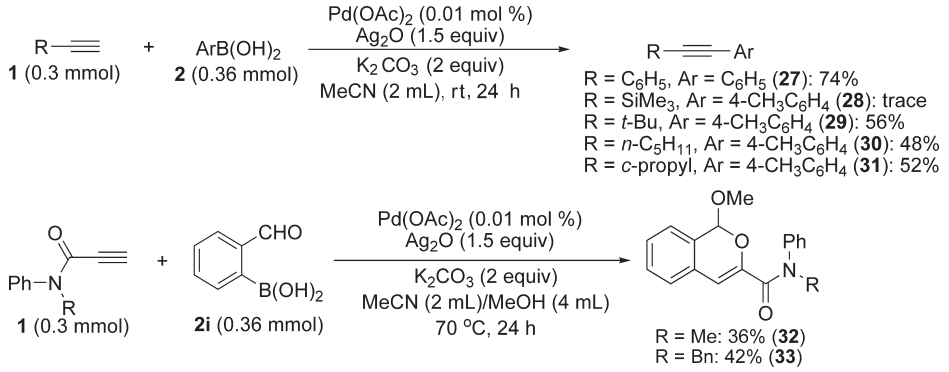
The above results showed that the iodo group was inert under the optimal conditions (entry 7 in Table 2). Thus, this novel methodology was applied to the one-pot synthesis of diynes through a dual Sonogashira cross-coupling process (Scheme 4). Treatment of 4-iodophenylboronic acid (**2h**) with amides (**1a** and **1f**) or ester (**1i**), $Pd(OAc)_2$ (0.01 mol %), and Ag_2O (1.5 equiv) first afforded the corresponding iodo-containing products in good yields. Subsequently, the reactions of iodo-containing products with phenylacetylene were carried out using our previously reported $Pd(OAc)_2$/DABCO catalytic system,[5b,12] providing the target diynes in excellent yields.

A possible mechanism as outlined in Scheme 5 was proposed.[6−8,10] Initially, the reaction between Pd(II) and alkynylsilver or alkyne with the aid of base affords intermediate **A**. Transmetalation of intermediate **A** with arylboronic acid **2** subsequently takes place leading to intermediate **B**. Finally, reductive elimination of intermediate **B** gives the desired product and Pd(0) species. Pd(0) species can

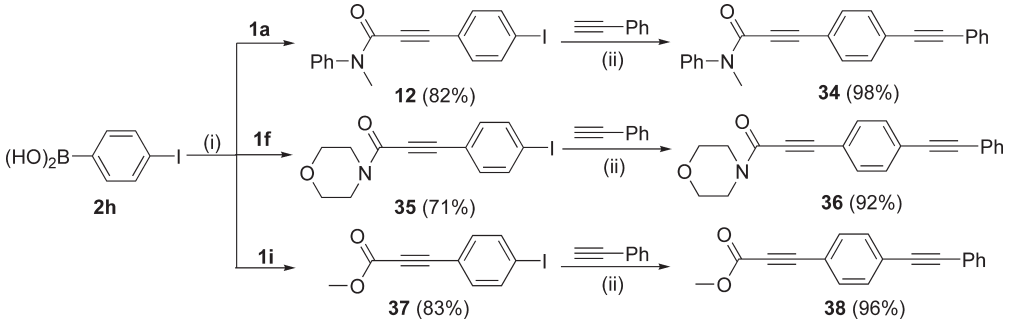
(11) Chandra, A.; Singh, B.; Khanna, R. S.; Singh, R. M. *J. Org. Chem.* **2009**, *74*, 5664.

(12) (a) Li, J.-H.; Zhang, X.-D.; Xie, Y.-X. *Synthesis* **2005**, 804. (b) Luque, R.; Macquarrie, D. J. *Org, Biomol. Chem.* **2009**, *7*, 1627.

SCHEME 3. Reactions of Other Substrates

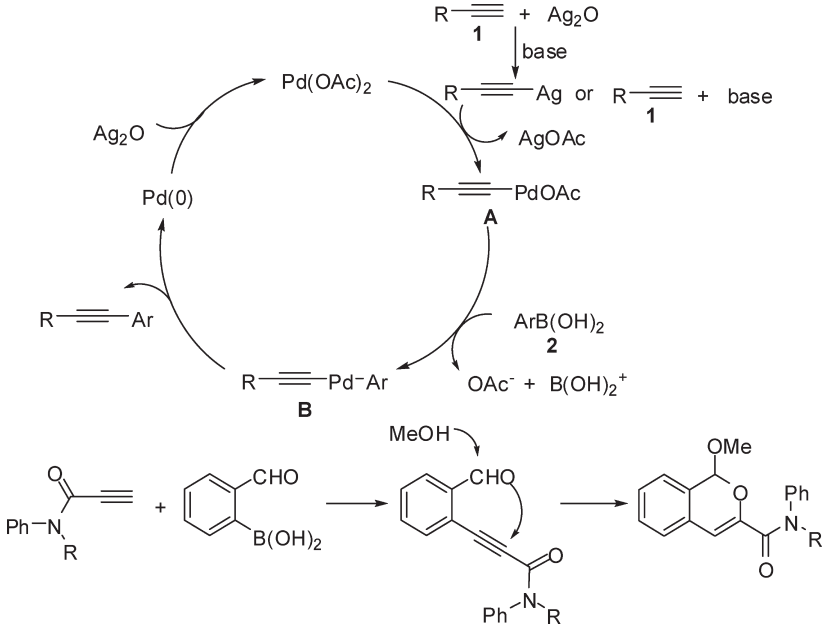


SCHEME 4. Synthesis of Diynes[a]



[a]Reaction conditions: (i) **1** (0.3 mmol), **2h** (0.36 mmol), $Pd(OAc)_2$ (0.01 mol %), Ag_2O (1.5 equiv), K_2CO_3 (2 equiv) and MeCN (2 mL) at 70 °C for 12 h; (ii) Phenylacetylene (1.5 equiv), $Pd(OAc)_2$ (0.001 mol %), DABCO (3 equiv), and MeCN (2 mL) at room temperature for 24 h.

SCHEME 5. Possible Mechanism



be readily oxidized by Ag_2O to the active Pd(II) species. Therefore, we deduce at least four roles that Ag_2O plays in the reaction, including the following: (1) base, (2) the reaction partner for the generation of the active alkynylsilver in situ, (3) promoter for the activation of the alkynylpalladium complex **A** facilitating the transmetalation of aryl group from arylboronic acid, and (4) oxidant to regenerate the active Pd(II) species.

For the synthesis of 1*H*-isochromenes, a possible step was described according to the reported mechanism:[11] the corresponding 2-ethynylbenzaldehydes were first generated from the reaction of amides **1** with 2-formylphenylboronic acid (**2i**),

and then nucleophilic addition of MeOH to 2-ethynylbenzaldehydes readily took place leading to the target products.

In summary, we have developed a palladium-catalyzed cross-coupling protocol for selectively preparing internal alkynes. In the presence of $Pd(OAc)_2$ and Ag_2O, a variety of terminal alkynes, particularly electron-poor terminal alkynes, smoothly underwent the reaction with numerous boronic acids to afford the corresponding internal alkynes in moderate to good yields. In comparison with the previously reported results, several features were established: (1) this reaction is general; (2) this reaction is carried out under a relative lower loading Pd conditions: the maximal TONs of the reaction are up to 720,000; and (3) the reaction was applied to the synthesis of 1*H*-isochromenes and diynes.

Experimental Section

Typical Experimental Procedure for the $Pd(OAc)_2$-Catalyzed Cross-Coupling Reaction. Alkyne **1** (0.3 mmol), boronic acid **2** (0.36 mmol), $Pd(OAc)_2$ (0.01 mol %), Ag_2O (1.5 equiv), K_2CO_3 (2 equiv), and MeCN (2 mL) were added to a Schlenk tube in turn. Then the solution was stirred at 70 °C for the indicated time (12 h) until complete consumption of starting material as monitored by TLC and GC−MS analysis. After the reaction was finished, the mixture was filtered, extracted with ethyl acetate, and evaporated in vacuum. The residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate) to afford the desired product.

***N*-Methyl-*N*,3-diphenylpropiolamide (4):**[4] white solid; mp 65.2−66.3 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (t, J = 7.5 Hz, 2H), 7.40−7.38 (m, 1H), 7.36 (d, J = 7.5 Hz, 2H), 7.34−7.30 (m, 1H), 7.27−7.22 (m, 2H), 7.13 (d, J = 8.0 Hz, 2H), 3.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.3, 143.2, 132.4, 129.9, 129.1, 128.2, 127.9, 127.3, 120.3, 90.8, 82.5, 36.3; IR (KBr, cm^{-1}) 2207, 1634; LRMS (EI, 70 eV) m/z 235 (M^+, 34), 129 (100).

3-(4-Acetylphenyl)-*N*-methyl-*N*-phenylpropiolamide (5):[4] pale yellow solid; mp 92.2−93.9 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, J = 8.5 Hz, 2H), 7.47 (t, J = 7.5 Hz, 2H), 7.41 (t, J = 7.5 Hz, 1H), 7.37 (d, J = 8.0 Hz, 2H), 7.22 (d, J = 8.5 Hz, 2H), 3.40 (s, 3H), 2.56 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.0, 153.8, 143.0, 137.4, 132.4, 129.2, 128.3, 128.1, 127.3, 125.0, 89.3, 84.8, 36.3, 26.6; IR (KBr, cm^{-1}) 2222, 1681, 1626, 1594; LRMS (EI, 70 eV) m/z 277 (M^+, 56), 171 (100), 128 (32).

3-(4-Methoxyphenyl)-*N*-methyl-*N*-phenylpropiolamide (6):[4] pale yellow solid; mp 93.6−94.9 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (t, J = 7.5 Hz, 2H), 7.40−7.35 (m, 3H), 7.07 (d, J = 9.0 Hz, 2H), 6.75 (d, J = 8.5 Hz, 2H), 3.77 (s, 3H), 3.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.8, 154.6, 143.3, 134.2, 129.0, 127.8, 127.4 113.9, 112.2, 91.4, 81.9, 55.2, 36.2; IR (KBr, cm^{-1}) 2210, 1636, 1593; LRMS (EI, 70 eV) m/z 265 (M^+, 33), 159 (100).

3-(2-Methoxyphenyl)-*N*-methyl-*N*-phenylpropiolamide (7):[4] pale yellow solid; mp 86.3−87.8 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45−7.35 (m, 5H), 7.29 (d, J = 8.5 Hz, 1H), 7.10 (d, J = 7.5 Hz, 1H), 6.82−6.75 (m, 2H), 3.69 (s, 3H), 3.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.0, 154.4, 143.2, 134.4, 131.5, 129.0, 127.5, 127.3, 120.2, 110.6, 109.7, 87.7, 86.4, 55.4, 36.4; IR (KBr, cm^{-1}) 2210, 1638, 1581; LRMS (EI, 70 eV) m/z 265 (M^+, 9), 159 (72), 147 (52), 131 (44), 115 (100).

***N*-Methyl-*N*-phenyl-3-*p*-tolylpropiolamide (8):**[4] pale yellow solid;mp 84.0−85.3 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (t, J = 7.5 Hz, 2H), 7.40−7.35 (m, 3H), 7.03 (s, 4H), 3.39 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.4, 143.2, 140.4, 132.3, 129.0, 129.0, 127.8, 127.3, 117.2, 91.2, 82.1, 36.3, 21.5; IR (KBr, cm^{-1}): 2231, 1634, 1589; LRMS (EI, 70 eV) m/z 249 (M^+, 38), 143 (100), 40 (48).

***N*-Methyl-*N*-phenyl-3-*o*-tolylpropiolamide (9):**[4] colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (t, J = 7.0 Hz 2H), 7.36 (t, J = 8.0 Hz 3H), 7.24−7.20 (m, 2H), 7.06 (t, J = 7.5 Hz, 2H), 3.38 (s, 3H), 1.92 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.4, 143.3, 141.1 133.1, 129.8, 129.4, 129.3,128.0, 127.5, 125.5, 120.3, 89.8, 86.3, 36.5, 19.9; IR (KBr, cm^{-1}) 2218, 1638, 1581; LRMS (EI, 70 eV) m/z 249 (M^+, 43), 143 (100), 115 (68).

3-(2,6-Dimethylphenyl)-*N*-methyl-*N*-phenylpropiolamide (10):[4] white solid; mp 95.4−96.7 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (t, J = 8.0 Hz, 2H), 7.34 (d, J = 7.5 Hz, 3H), 7.09 (t, J = 7.5 Hz, 1H), 6.92 (d, J = 7.5 Hz, 2H), 3.38 (s, 3H), 2.06 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.5, 143.4, 141.9, 129.4, 129.3, 128.0, 127.6, 126.6, 120.4, 90.7, 88.7, 36.6, 20.5; IR (KBr, cm^{-1}) 2204, 1634, 1593; LRMS (EI, 70 eV) m/z 263 (M^+, 22), 157 (100), 128 (40).

3-(4-Fluorophenyl)-*N*-methyl-*N*-phenylpropiolamide (11):[4] white solid; mp 50.3−51.6 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (t, J = 7.5 Hz, 2H), 7.41−7.35 (m, 3H), 7.13−7.10 (m, 2H), 6.93 (t, J = 8.5 Hz, 2H), 3.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.3, 162.3, 154.1, 143.1, 134.5, 134.5, 129.1, 128.0, 127.4, 115.8, 115.6, 89.7, 82.3, 36.3; IR (KBr, cm^{-1}): 2231, 1638, 1597; LRMS (EI, 70 eV) m/z 253 (M^+, 49), 147 (100).

3-(4-Iodophenyl)-*N*-methyl-*N*-phenylpropiolamide (12):[4] white solid, 54.1−55.6 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, J = 8.5 Hz, 2H), 7.45 (t, J = 7.5 Hz, 2H), 7.40−7.34 (m, 3H), 6.83 (d, J = 7.5 Hz, 2H), 3.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.0, 143.1, 137.6, 133.6, 129.1, 128.0, 127.4, 119.8, 96.5, 89.7, 83.7, 36.3; IR (KBr, cm^{-1}) 2218, 1646, 1593; LRMS (EI, 70 eV) m/z 361 (M^+, 64), 255 (100), 128 (46).

3-(2-Formylphenyl)-*N*-methyl-*N*-phenylpropiolamide (13): yellow solid; mp 63.2−64.5 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.36 (s, 1H), 7.82 (d, J = 7.0 Hz, 1H), 7.54−7.45 (m, 6H), 7.37−7.35 (m, 2H), 3.41 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.5, 153.6, 142.7, 136.8, 134.2, 133.6, 130.3, 129.5, 128.5, 127.4, 126.9, 123.6, 88.4, 85.9, 36.5; IR (KBr, cm^{-1}): 2214, 1699, 1634, 1593; LRMS (EI, 70 eV) m/z 263 (M^+, 10), 234 (100), 101 (67); HRMS (EI) for $C_{17}H_{13}NO_2$ (M^+) calcd 263.0946, found 263.0943.

***N*-Methyl-3-(3-nitrophenyl)-*N*-phenylpropiolamide (14):** yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18−8.16 (m, 1H), 7.90 (s, 1H), 7.51−7.44 (m, 5H), 7.39−7.37 (m, 2H), 3.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.5, 147.9, 142.8, 137.8, 129.6, 129.4, 128.4, 127.4, 127.2, 124.5, 122.2, 87.7, 84.3, 36.4; IR (KBr, cm^{-1}) 2210, 1638, 1585; LRMS (EI, 70 eV) m/z 280 (M^+, 99), 174 (83), 128 (100); HRMS (EI) for $C_{16}H_{12}N_2O_3$ (M^+) calcd 280.0848, found 280.0846.

***N*-Methyl-*N*-phenyl-3-(4-vinylphenyl)propiolamide (15):** colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47−7.35 (m, 5H), 7.30−7.26 (m, 2H), 7.09 (d, J = 8.0 Hz, 2H), 6.66−6.60 (m, 1H), 5.74 (d, J = 17.5 Hz, 1H), 5.30 (d, J = 11.0 Hz, 1H), 3.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.3, 143.2, 139.0, 135.8, 132.6, 129.1, 127.9, 127.2, 126.0, 119.4, 115.8, 90.8, 83.1, 36.3; IR (KBr, cm^{-1}) 2216, 1642, 1493; LRMS (EI, 70 eV) m/z 261 (M^+, 4), 253 (49), 147 (100); HRMS (EI) for $C_{18}H_{15}NO$ (M^+) calcd 261.1154, found 261.1151.

(***E*)-*N*-Methyl-*N*-phenylhex-4-en-2-ynamide (16):** colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (t, J = 7.5 Hz, 2H), 7.34 (t, J = 7.5 Hz, 1H), 7.28 (d, J = 8.0 Hz, 2H), 6.05−5.98 (m, 1H), 5.36−5.30 (m, 1H), 3.34 (s, 3H), 1.72 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.4, 145.2, 143.1, 129.0, 127.6, 127.1, 108.9, 90.2, 81.0, 36.3, 18.9; IR (KBr, cm^{-1}): 2202, 1626, 1593, 1495; LRMS (EI, 70 eV) m/z 199 (M^+, 16), 198 (29), 184 (70), 93(100); HRMS (EI) for $C_{13}H_{13}NO$ (M^+) calcd 199.0997, found 199.0995.

***N*-(4-Methoxyphenyl)-*N*-methyl-3-phenylpropiolamide (17):**[4] yellow solid; mp 78.4−79.7 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34−7.31 (m, 1H), 7.28−7.23 (m, 4H), 7.18 (d, J = 8.0 Hz, 2H), 6.95 (d, J = 7.5 Hz, 2H), 3.85 (s, 3H), 3.35 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.0, 154.5, 136.0, 132.3, 130.1, 128.5, 128.2, 120.4, 114.2, 90.8, 82.5, 55.5, 36.5; IR (KBr, cm^{-1}) 2218, 1638, 1507; LRMS (EI, 70 eV) m/z 265 (M^+, 34), 159 (100).

***N*-Benzyl-*N*,3-diphenylpropiolamide (18):**[4] pale yellow solid; mp 84.2−85.7 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36−7.15 (m, 13H), 7.09 (d, J = 8.0 Hz, 2H), 5.00 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.4, 141.6, 136.6, 132.4, 129.9, 128.9, 128.7, 128.6, 128.4, 128.2, 128.1, 127.5, 120.3, 91.4, 82.5, 52.2; IR (KBr, cm^{-1}) 2216, 1634, 1589; LRMS (EI, 70 eV) m/z 311 (M^+, 39), 129 (100), 91 (44).

***N*-Allyl-*N*,3-diphenylpropiolamide (19):** white solid; mp 66.3−67.6 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43−7.39 (m, 3H), 7.33 (t, J = 7.5 Hz, 3H), 7.22 (t, J = 7.5 Hz, 2H), 7.11 (d, J = 8.0 Hz, 2H), 5.92−5.87 (m, 1H), 5.19−5.15 (m, 2H), 4.42 (d, J = 6.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.0, 141.8, 132.4, 132.3, 129.9, 129.0, 128.4, 120.4, 118.3, 91.0, 82.6, 51.3; IR (KBr, cm^{-1}) 2221, 1628; LRMS (EI, 70 eV) m/z 261 (M^+, 14), 232 (19), 129 (100); HRMS (EI) for $C_{18}H_{15}NO$ (M^+) calcd 261.1154, found 261.1150.

***N*,*N*-Diethyl-3-phenylpropiolamide (20):**[13] colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, J = 7.5 Hz, 2H), 7.41 (t, J = 7.5 Hz, 1H), 7.36 (t, J = 7.5 Hz, 2H), 3.69−3.65 (m, 2H), 3.50−3.46 (m, 2H), 1.28 (t, J = 7.5 Hz, 2H), 1.18 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 153.9, 132.2, 129.8, 128.4, 120.7, 88.9, 81.8, 43.5, 39.2, 14.3, 12.8; IR (KBr, cm^{-1}): 2213, 1636; LRMS (EI, 70 eV) m/z 201 (M^+, 31), 129 (100).

1-Morpholino-3-phenylprop-2-yn-1-one (21):[14] colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, J = 7.5 Hz, 2H), 7.43 (m, 1H), 7.37 (t, J = 7.5 Hz, 2H), 3.85 (t, J = 5.0 Hz 2H), 3.76 (t, J = 5.0 Hz, 2H), 3.71 (s, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.1, 132.3, 130.1, 128.5, 120.1, 91.2, 80.6, 66.8, 66.4, 47.2, 41.9; IR (KBr, cm^{-1}) 2218, 1626; LRMS (EI, 70 eV) m/z 215 (M^+, 29), 129 (100).

Ethyl 3-phenylpropiolate (24):[14] yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, J = 7.5 Hz, 2H), 7.47−7.43 (m, 1H), 7.38 (t, J = 7.5 Hz, 2H), 4.32−4.28 (m, 2H), 1.36 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.1, 133.0, 130.6, 128.5, 120.0, 86.0, 80.7, 62.1, 14.1; IR (KBr, cm^{-1}) 2210, 1709; LRMS (EI, 70 eV) m/z 174 (M^+, 15), 129 (100), 102 (87).

3-(3-Nitrophenyl)-1-phenylprop-2-yn-1-one (26):[15] white solid; mp 142.0−143.6 °C (uncorrected); ^{1}H NMR (500 MHz) δ 8.53 (s, 1H), 8.34 (d, J = 8.0 Hz, 1H), 8.22 (d, J = 7.5 Hz, 2H), 8.00 (s, d, J = 7.5 Hz, 1H), 7.70−7.64 (m, 2H), 7.56 (t, J = 7.5 Hz, 2H); ^{13}C NMR (125 MHz) δ 177.4, 148.2, 138.4, 136.4, 134.6, 129.9, 129.6, 128.8, 127.6, 125.2, 122.0, 89.0, 88.0; IR (KBr, cm^{-1}) 2208, 1634; LRMS (EI, 70 eV) m/z 251 (M^+, 73), 223 (100), 176 (53), 177 (31), 128 (45), 77 (49).

1,2-Diphenylethyne (27):[4] white solid; mp 59.4−60.3 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54−7.52 (m, 4H), 7.37−7.32 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 131.6, 128.3, 128.2, 123.3, 89.4; IR (KBr, cm^{-1}) 2216; LRMS (EI, 70 eV) m/z 178 (M^+, 100).

1-(3,3-Dimethylbut-1-ynyl)-4-methylbenzene (28):[16] colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (d, J = 9.0 Hz, 2H), 7.00 (d, J = 7.0 Hz, 2H), 2.25 (s, 3H), 1.24 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.3, 131.4, 128.8, 121.0, 97.7, 79.0, 31.1, 27.9, 21.4; LRMS (EI, 70 eV) m/z 172 (M^+, 40),157 (100), 142 (44).

1-(Hept-1-ynyl)-4-methylbenzene (30):[7] colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, J = 8.0 Hz, 2H), 7.07 (d, J = 8.0 Hz, 2H), 2.38 (t, J = 7.5 Hz, 2H), 2.31 (s, 3H), 1.60 (t, J = 7.5 Hz, 2H), 1.44−1.41 (m, 4H), 0.92 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.3, 131.4, 128.9, 121.0, 89.6, 80.5, 31.1, 28.5, 22.2, 21.3, 19.4, 14.0; LRMS (EI, 70 eV) m/z 186 (M^+, 33),157 (33), 142 (38), 131(69), 129 (100).

1-(Cyclopropylethynyl)-4-methylbenzene (31):[17] colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (d, J = 8.0 Hz, 2H), 6.97 (d, J = 8.0 Hz, 2H), 2.23 (s, 3H), 1.37−1.32 (m, 1H), 0.76−0.74 (m, 2H), 0.71−0.70 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.3, 131.4, 128.9, 120.8, 92.5, 75.8, 21.3, 8.5, 0.1; LRMS (EI, 70 eV) m/z 130 (M^+, 100), 115 (65), 74 (53).

3-(4-Iodophenyl)-1-morpholinoprop-2-yn-1-one (35): white solid; mp 154.6−155.8 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73−7.72 (m, 2H), 7.26−7.24 (m, 2H), 3.83−3.81 (m, 2H), 3.76−3.74 (m, 2H), 3.70 (s, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.9, 137.8, 133.6, 119.6, 96.8, 90.2, 81.8, 66.8, 66.4, 47.3, 42.0; IR (KBr, cm^{-1}) 2210, 1625; LRMS (EI, 70 eV) m/z 341 (M^+, 73), 254 (100), 128 (80); HRMS (EI) for $C_{13}H_{12}INO_2$ (M^+) calcd 340.9913, found 340.9910.

Ethyl 3-(4-iodophenyl)propiolate (37):[15] colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, J = 7.0 Hz, 2H), 7.29 (d, J = 7.0 Hz, 2H), 4.32−4.28 (m, 3H), 1.35 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 153.8, 137.9, 134.1, 119.1, 97.4, 84.9, 81.8, 62.2, 14.0; IR (KBr, cm^{-1}) 2210, 1712; LRMS (EI, 70 eV) m/z 300 (M^+, 28), 255 (45), 228 (100).

Typical Experimental Procedure for the Synthesis of 1*H*-Isochromenes. Alkyne **1** (0.3 mmol), boronic acid **2** (0.36 mmol), $Pd(OAc)_2$ (0.01 mol %), Ag_2O (1.5 equiv), K_2CO_3 (2 equiv), MeCN (2 mL), and MeOH (4 mL) were added to a Schlenk tube in turn. Then the solution was stirred at 70 °C for the indicated time (24 h) until complete consumption of starting material as monitored by TLC and GC−MS analysis. After the reaction was finished, the mixture was filtered, extracted with ethyl acetate, and evaporated in vacuum. The residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate) to afford the desired product.

1-Methoxy-*N*-methyl-*N*-phenyl-1*H*-isochromene-3-carboxamide (32): yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45−7.39 (m, 4H), 7.35−7.31 (m, 2H), 7.28 (d, J = 7.5 Hz, 1H), 7.17 (d, J = 7.5 Hz, 1H), 6.51 (s, 1H), 5.37 (s, 1H), 3.60 (s, 3H), 3.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.3, 161.4, 144.6, 138.6, 134.3, 130.7, 129.9, 129.4, 127.3, 127.1, 123.1, 120.7, 108.6, 89.1, 55.9, 36.9; IR (KBr, cm^{-1}) 1663; LRMS (EI, 70 eV) m/z 295 (M^+, 3), 263 (66), 189 (100), 145 (89); HRMS (EI) for $C_{18}H_{17}NO_3$ (M^+) calcd. 295.1208, found 295.1204.

***N*-Benzyl-1-methoxy-*N*-phenyl-1*H*-isochromene-3-carboxamide (33).** yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44−7.42 (m, 2H), 7.34−7.21 (m, 9H), 7.12 (t, J = 8.5 Hz, 3H), 6.53 (s, 1H), 5.34 (s, 1H), 5.15 (d, J = 7.5 Hz, 1H), 4.89 (d, J = 7.5 Hz, 1H), 3.61 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.1, 161.9, 143.1, 138.7, 138.1, 134.3, 130.8, 129.9, 129.2, 128.7, 128.3, 128.3, 127.3, 127.0, 123.1, 120.7, 108.7, 88.9, 55.9, 52.5; IR (KBr, cm^{-1}) 1665; LRMS (EI, 70 eV) m/z 371 (M^+, 4), 339 (59), 189 (100), 145 (76); HRMS (EI) for $C_{24}H_{21}NO_3$ (M^+) calcd 371.1521, found 371.1518.

Typical Experimental Procedure for the $Pd(OAc)_2$-Catalyzed Sonogashira Cross-Coupling Reaction of Aryl Iodides:[5b] Iodophenylproiolamides **12**, **35**, or **37** (0.3 mmol), phenylacetylene **1j** (0.45 mmol), $Pd(OAc)_2$ (0.001 mol %), DABCO (3 equiv), and MeCN (2 mL) were added to a Schlenk tube in turn. Then the solution was stirred at room temperature for the indicated time (24 h) until complete consumption of starting material as monitored by TLC and GC−MS analysis. After the reaction

(13) Kamijo, S.; Kanazawa, C.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 9260.

(14) Kramer, S.; Dooleweerdt, K.; Lindhardt, A. T.; Rottländer, M.; Skrydstrup, T. *Org. Lett.* **2009**, *11*, 4208.

(15) Savechenkov, P. Y.; Rudenko, A. P.; Vasilév, A. V.; Fukin, G. K. *Russ. J. Org. Chem.* **2005**, *41*, 1316.

(16) Vogel, P.; Dubbaka, S.-R. *Adv. Synth. Catal.* **2004**, *346*, 1793.

(17) Ye, S.-Y.; Yu, Z.-X. *Org. Lett.* **2004**, *12*, 804.

was finished, the mixture was filtered, extracted with ethyl acetate, and evaporated in vacuum. The residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate) to afford the desired product.

***N*-Methyl-*N*-phenyl-3-(4-(phenylethynyl)phenyl)propiolamide (34):** white solid; mp 102.4.5−103.6 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55−7.44 (m, 4H), 7.41−7.34 (m, 8H), 7.11 (d, J = 7.5 Hz, 2H), 3.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.1, 143.1, 132.3, 131.6, 131.4, 129.2, 128.7, 128.4, 128.0, 127.4, 125.0, 122.7, 120.0, 92.1, 90.3, 88.6, 84.0, 36.4; IR (KBr, cm^{-1}) 2214, 1621; LRMS (EI, 70 eV) m/z 335 (M^+, 46), 229 (100), 200 (21); HRMS (EI) for $C_{24}H_{17}NO$ (M^+) calcd 335.1310, found 335.1312.

1-Morpholino-3-(4-(phenylethynyl)phenyl)prop-2-yn-1-one (36): white solid; mp 146.8−147.5 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54−7.52 (m, 6H), 7.36 (t, J = 3.5 Hz, 3H), 3.84 (t, J = 5.0 Hz, 2H), 3.76 (t, J = 5.0 Hz, 2H), 3.71(s, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 153.0, 132.3, 131.7, 131.6, 128.7, 128.4, 125.3, 122.6, 119.8, 92.4, 90.7, 88.5, 82.1, 66.9, 66.5, 47.3, 42.0; IR (KBr, cm^{-1}): 2197, 1617; LRMS (EI, 70 eV) m/z 315 (M^+, 61), 229 (100), 200 (30); HRMS (EI) for $C_{21}H_{17}NO_2$ (M^+) calcd 315.1259, found 315.1257.

Ethyl 3-(4-(phenylethynyl)phenyl)propiolate (38): white solid; mp 99.5−100.6 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.56−7.50 (m, 6H), 7.36 (t, J = 3.5 Hz, 2H), 4.32−4.28 (m, 2H), 1.36 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.9, 132.8, 131.6, 131.6, 128.7, 128.4, 125.7, 122.6, 119.1, 92.5, 88.5, 85.4, 82.0, 62.1, 14.0; IR (KBr, cm^{-1}) 2206, 1703; LRMS (EI, 70 eV) m/z 274 (M^+, 47), 229 (31), 202 (100); HRMS (EI) for $C_{19}H_{14}O_2$ (M^+) calcd 274.0994, found 274.0991.

Acknowledgment. We thank the Scientific Research Fund of Hunan Provincial Education Department (No. 08A037) and the National Natural Science Foundation of China (No. 20872112) for financial support.

Supporting Information Available: Copies of spectra. This material is available free of charge via the Internet at http://pubs.acs.org.