

RSC Advances



This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. This *Accepted Manuscript* will be replaced by the edited, formatted and paginated article as soon as this is available.

You can find more information about *Accepted Manuscripts* in the [Information for Authors](#).

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard [Terms & Conditions](#) and the [Ethical guidelines](#) still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.

ARTICLE

One-pot synthesis of unsymmetrical diarylacetylenes via Sonogashira/Deacetonation/Sonogashira cross-coupling of two different aryl chlorides with 2-methyl-3-butyn-2-ol

Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

www.rsc.org/

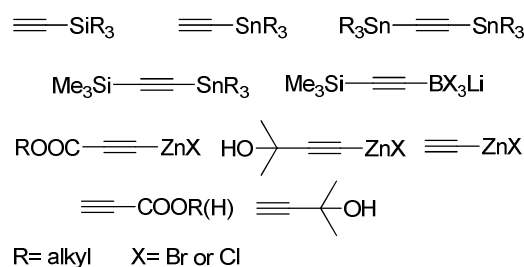
Kai Xu,^{a,b} Suyan Sun,^a Guodong Zhang,^a Fan Yan^{*a} and Yangjie Wu^{*a}

With the assistance of PdCl₂/X-Phos as the catalyst system, a green and efficient protocol for one-pot Sonogashira/Deacetonation/Sonogashira coupling reaction of two different aryl chlorides with 2-methyl-3-butyn-2-ol was developed, affording various unsymmetrical diarylacetylenes in mostly moderate to excellent yields. Note that the cheap and economically available aryl chlorides and 2-methyl-3-butyn-2-ol as the starting materials could be added to the catalyst system directly and simultaneously. Moreover, this tandem reaction could tolerate the substrates bearing one or even two *ortho*-sterically hindered groups and was also applicable to the synthesis of symmetrical diarylacetylenes. In addition, the competitive reaction was performed and a possible mechanism was also proposed.

Introduction

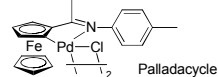
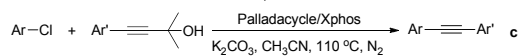
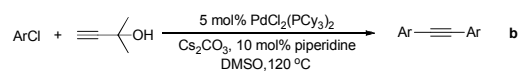
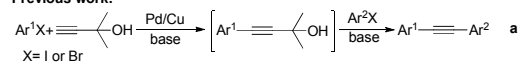
Sonogashira coupling has become one of the most powerful and reliable tools for the preparation of diarylacetylenes, which have their wide application as valuable building blocks in organic synthetic, pharmaceutical and materials sciences.¹ However, this coupling also suffered from an inevitable drawback and limitation: using terminal alkynes as the acetylene sources. Terminal alkynes bearing functional groups are usually expensive and not commercially available, which hampered its large scale industrial applications. Therefore, much work has been devoted to seeking for the easily available replacement to terminal alkynes, such as monoprotected acetylene derivatives bearing the hydroxyl, carboxyl, or other metal (Sn, Si, Zn, B) moieties (Scheme 1).²⁻⁵ Comparatively, 2-methyl-3-butyn-2-ol has a clear advantage over other acetylene sources due to its low cost.⁵ Promisingly, in the near future, the coupling reaction using 2-methyl-3-butyn-2-ol as the acetylene source may emerge as a widely applicable alternative to

Sonogashira reaction, namely as Sonogashira/Deacetonation/Sonogashira (SDS) cross-coupling (Scheme 2).

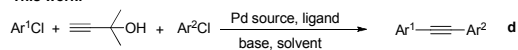


Scheme 1 The reported acetylene sources.

Previous work:



This work:



Scheme 2 Synthesis of Symmetrical or unsymmetrical diarylacetylenes by a tandem or one-pot SDS strategy.

^a The College of Chemistry and Molecular Engineering, Henan Key Laboratory of Chemical Biology and Organic Chemistry, Key Laboratory of Applied Chemistry of Henan Universities, Zhengzhou University, Zhengzhou 450052, People's Republic of China E-mail: yangf@zzu.edu.cn, wyj@zzu.edu.cn.

^b The College of Chemistry & Chemical Engineering, Shangqiu Normal University, Shangqiu 476000, People's Republic of China.

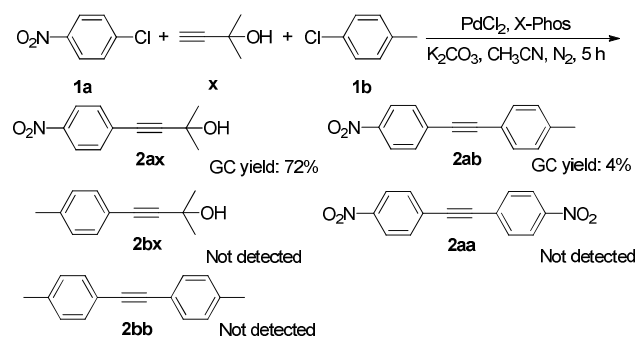
† Electronic Supplementary Information (ESI) available: See DOI: 10.1039/b000000x/.

The pioneering work of the tandem SDS cross-coupling

belonged to Kotschy and Novák, who realized the synthesis of substituted diarylacetylenes from aryl iodides or bromides using 2-methyl-3-butyn-2-ol as the acetylene source (Scheme 2a).^{5a} Notably, Hua and co-workers reported a one-pot SDS catalytic system for the preparation of symmetrical diarylacetylenes from the direct reaction of aryl chlorides with 2-methyl-3-butyn-2-ol, but the unsymmetrical diarylacetylenes were obtained in 20–32% yields from two different aryl chlorides with 2-methyl-3-butyn-2-ol (Scheme 2b).^{5b} Very recently, we also reported the first deacetonative coupling of aryl propargyl alcohols with aryl chlorides, but this catalyst system employed a complicated palladacycle as the catalyst. In addition, the aryl propargyl alcohols are not commercially available and need the preparation in advance (Scheme 2c).^{5c} Therefore, the successful direct synthesis of unsymmetrical diarylacetylenes just employing aryl chlorides and 2-methyl-3-butyn-2-ol as the coupling partners is still a challenge, and the reports remain rare.

Inspired by the above pioneering works, we envisioned that the one-pot synthesis of unsymmetrical diarylacetylenes could be accomplished *via* a simple and facile protocol by adding two different aryl chlorides and 2-methyl-3-butyn-2-ol to the reaction system directly and simultaneously (Scheme 2d). Once the new catalyst system was established, it would cut the cost significantly due to the more commercially available and inexpensive raw materials. The main challenges in this one-pot SDS coupling include activation of two C–Cl bonds, the deacetonation of 2-methyl-3-butyn-2-ol and the suppression of diverse kinds of side reactions.

Results and discussion

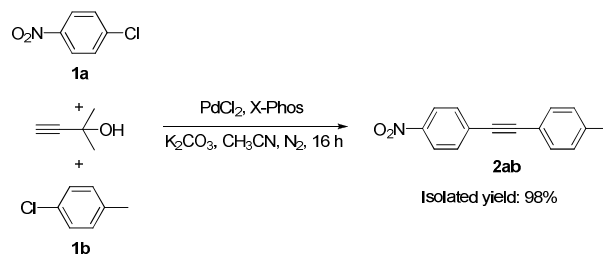


Scheme 3 The competitive reaction of two aryl chlorides with 2-methyl-3-butyn-2-ol: ^a Reagents and conditions: 4-nitrochlorobenzene (**1a**) (0.5 mmol), 2-methyl-3-butyn-2-ol (0.5 mmol), 4-chlorotoluene (**1b**) (0.5 mmol), PdCl₂ (4 mol%), X-Phos (4 mol%), and K₂CO₃ (0.5 mmol) in CH₃CN (2 mL) at 110 °C under a nitrogen atmosphere for 5 h. ^b GC yield based on the amount of 4-nitrochlorobenzene (**1a**).

Alkylphosphane ligands bearing a biphenyl skeleton, well-known as Buchwald's ligands, could be effective for the activation of C–Cl bond, and significant progress has been achieved by the groups of Buchwald, Fu, and others.⁶ With the aid of a Buchwald's ligand: 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (X-Phos), we initially performed a competitive reaction by performing the equivalent loading of 4-nitrochlorobenzene (**1a**), 4-chlorotoluene (**1b**), 2-methyl-3-butyn-2-ol, and the base in CH₃CN for 5 h (Scheme 3). Surprisingly, the product **2ax** was observed in GC 72% yield, accompanied by the generation of **2ab** in 4% GC yield. Other possible products such as **2bx**, **2aa**, and **2bb** were not detected at all. The results indicate that the reactivity of electron-poor 4-nitrochlorobenzene (**1a**) is far higher than that of 4-

chlorotoluene (**1b**), and we predicted that increasing the loading of the base and prolonging the reaction time would result in the continuous coupling of **2ax** with 4-chlorotoluene (**1b**) to afford the unsymmetrical diarylacetylene **2ab** as the main product.

According to the above viewpoints, we then performed the SDS coupling reaction by adding a larger loading of the base and prolonging the reaction time in favour of the deacetonation step. And a mixture of 4-nitrochlorobenzene (**1a**), 2-methyl-3-butyn-2-ol, 4-chlorotoluene (**1b**) and 4 equivalents K₂CO₃ was added in acetonitrile simultaneously under a nitrogen atmosphere for 16 h. To our surprise, the unsymmetrical diarylacetylene **2ab** as the only product could be assembled in an excellent yield of 98% without any other byproducts, which was in accordance with the hypotheses derived from the competitive reaction (Scheme 4).

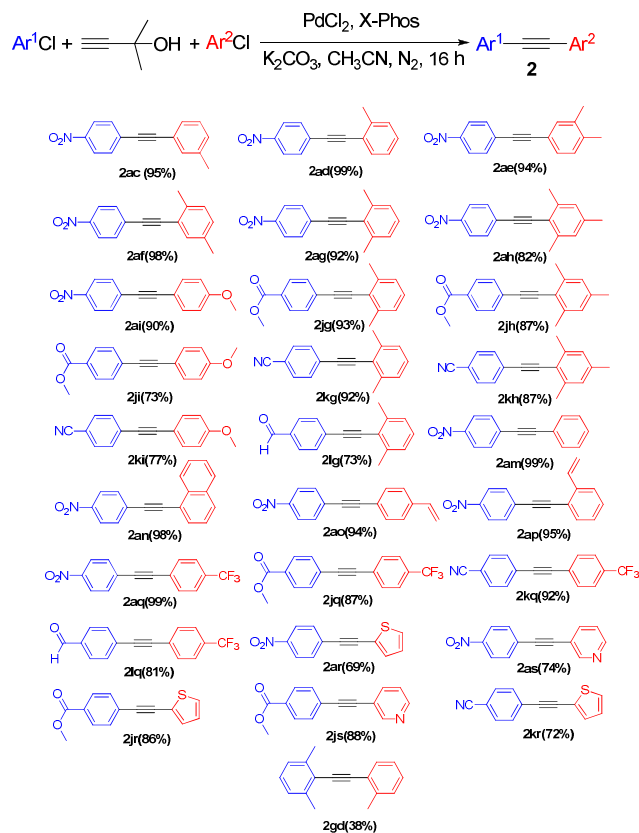


Scheme 4 The one-pot SDS coupling reaction of 4-nitrochlorobenzene, 4-chlorotoluene, and 2-methyl-3-butyn-2-ol: ^a Reagents and conditions: 4-nitrochlorobenzene (**1a**) (0.5 mmol), 2-methyl-3-butyn-2-ol (0.5 mmol), 4-chlorotoluene (**1b**) (0.5 mmol), PdCl₂ (4 mol%), X-Phos (4 mol%), and K₂CO₃ (2 mmol) in CH₃CN (2 mL) at 110 °C under a nitrogen atmosphere for 16 h. ^b Isolated yield based on the amount of 4-nitrochlorobenzene (**1a**).

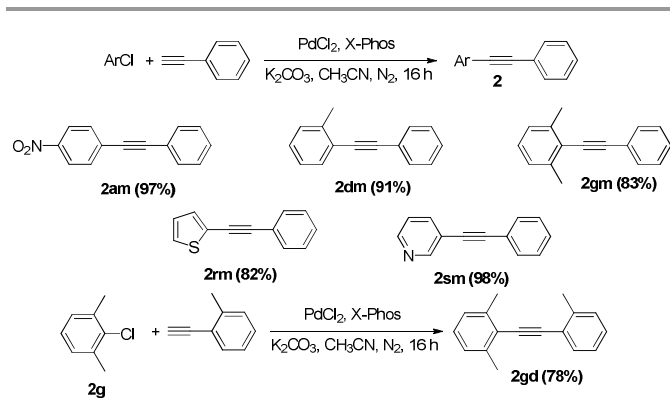
According to the above viewpoints, the scope of the aryl chlorides was then investigated under the optimized reaction conditions (Scheme 5). Generally, the catalyst system afforded the desired unsymmetrical diarylacetylenes with unexpected high yields mostly ranging from 69% to 99%, and few byproducts such as symmetrical diarylacetylenes or diyne compounds derived from the dimerization of alkynes were detected, which is different from the results from Hua's report (Scheme 5).^{5b} In detail, one aryl chloride is a higher reactive electron-poor substrate and the other is an inactive electron-rich or electron-neutral aryl chloride, which would conform to our designed reaction model, and the unsymmetrical diarylacetylenes were afforded in good to excellent yields (Scheme 5, **2ac–2ap**). In the case of the two electron-poor aryl chlorides selected, large difference of their reactivity in our system would be necessary (Scheme 5, **2aq–2kr**). However, the reaction of the two electron-rich aryl chlorides only generated the desired product in a yield of 38%, which may be attributed to their similar reactivity in this SDS reaction (Scheme 5, **2gd**). Notably, the reaction scope could be extended to the aryl chloride bearing two *ortho*-sterically hindered groups such as 2-chloro-*m*-xylene (**1g**) and 2-chloromesitylene (**1h**) (Scheme 5, **2ag**, **2ah**, **2jg**, **2jh**, **2kg**, **2kh**, and **2lg**). Moreover, the reaction could tolerate various functional groups (e.g., CH₃O, methoxycarbonyl, NO₂, CN, CHO, and vinyl) and heterocyclic chlorides (**1r** and **1s**) (Scheme 5, **2ac–2kr**). Especially, during the reaction process of the aryl chloride bearing a vinyl group, the classical Heck coupling products were not detected at all (Scheme 5, **2ao** and **2ap**).

As expected, the catalytic system could be applicable to the Sonogashira cross-coupling of phenylacetylene with aryl chlorides. In detail, whether the aryl chloride was electron-poor

or electron-rich, the desired products could be obtained in good to excellent yields (Scheme 6). The reaction could also tolerate heterocyclic chlorides (**2rm** and **2sm**). Also, the cross-coupling of the ortho sterically hindered aryl chloride could give the product in a good yield (**2gm** and **2gd**). In particular, this protocol provides the **2gd** with a significantly higher yield of 78% attributed to the reduction of competitive reaction compared to the method applied in Scheme 5.

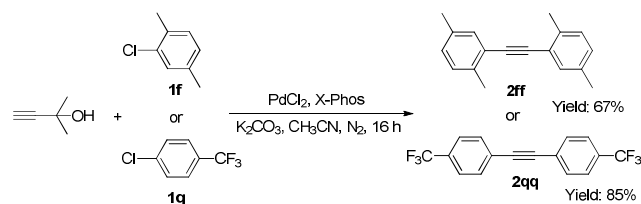


Scheme 5 The substrate scope of the one-pot SDS reaction: ^a Reagents and conditions: Ar¹Cl (0.5 mmol), 2-methyl-3-butyn-2-ol (0.6 mmol), Ar²Cl (0.6 mmol), PdCl₂ (4 mol%), X-Phos (4 mol%), and K₂CO₃ (2 mmol) in CH₃CN (2 mL) at 110 °C under a nitrogen atmosphere for 16 h. ^b Isolated yield based on the amount of Ar¹Cl.



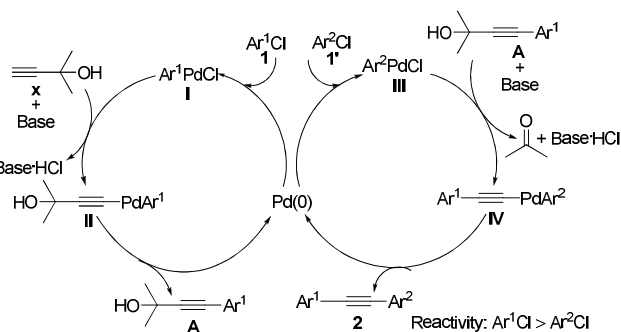
Scheme 6 The Sonogashira cross-coupling of aryl chloride with phenylacetylene: ^a Reagents and conditions: ArCl (0.5 mmol), terminal alkyne (0.6 mmol), PdCl₂ (2 mol%), X-Phos (4 mol%), and K₂CO₃ (0.75 mmol) in CH₃CN (2 mL) at 110 °C under a nitrogen atmosphere for 16 h. ^b Isolated yield based on the amount of ArCl.

In addition, synthesis of symmetrical diarylacetylenes could also be achieved *via* this type of one-pot SDS coupling strategy, which was presented as Scheme 7. The reaction employed one aryl chloride and 2-methyl-3-butyn-2-ol under the above optimized reaction conditions apart from the adjustment of the substrates ratio. Two representative substrates: 2-chloro-*p*-xylene (**1f**) and 4-chlorobenzotrifluoride (**1q**) could be tolerated well to give the corresponding products in the yields of 67% and 85%, respectively.



Scheme 7 Synthesis of symmetrical diarylacetylenes *via* one-pot SDS coupling: ^a 2-methyl-3-butyn-2-ol (0.5 mmol), ArCl (1.2 mmol), PdCl₂ (4 mol%), X-phos (4 mol%), K₂CO₃ (2 mmol), in CH₃CN (2 mL) at 110 °C under a nitrogen atmosphere for 16 h. ^b Isolated yield based on the amount of 2-methyl-3-butyn-2-ol.

On the basis of the reported works and our own results, a proposed mechanism for this type one-pot SDS coupling was outlined in Scheme 8. The first step was the oxidative addition of the more reactive aryl chloride (**1**) to Pd(0) species to give the Pd(II) intermediate **I**. Then, in the presence of the base the reaction took place between intermediate **I** and 2-methyl-3-butyn-2-ol to form the Pd(II) intermediate **II**. The reductive elimination of the intermediate **II** generated the Sonogashira product of aryl propargyl alcohol **A** and the active Pd(0) species. On the other hand, the oxidative addition of the less reactive aryl chloride (**1'**) to Pd(0) species afforded the Pd(II) intermediate **III**. The reaction of arylpropargyl alcohol **A** with the intermediate **III** in the presence of the base occurred to form the Pd(II) intermediate **IV** and release a molecular acetone. Finally, the reductive elimination of the intermediate **IV** took place to afford the unsymmetrical diarylacetylene (**2**) and regenerate the active Pd(0) species.



Scheme 8 A proposed mechanism of palladium-catalyzed one-pot SDS coupling reaction.

Conclusions

In conclusion, we developed a general and efficient palladium-catalyzed one-pot SDS coupling reaction of two different aryl chlorides with 2-methyl-3-butyn-2-ol, affording various unsymmetrical diarylacetylenes in mostly moderate to excellent yields. Notably, the economical and readily available aryl chlorides and 2-methyl-3-butyn-2-ol as the raw materials could be added to the catalyst system simultaneously, thus providing

the possibility of this simple and green catalyst system in industrial application. Interestingly, when the aryl chloride possessed a vinyl group, the SDS reaction could selectively occur and classical Heck coupling products were not detected at all. Moreover, this SDS reaction could tolerate the substrates bearing one or even two *ortho*-sterically hindered groups. In addition, the reaction system was also applicable to the synthesis of symmetrical diarylacetylenes and the classical Sonogashira cross-coupling using phenylacetylene as the substrate. Further synthetic applications of these methodologies are currently underway in our laboratory.

Experimental

Representative procedure for the one-pot synthesis of unsymmetrical diarylalkynes via the SDS cross-coupling. 4-nitrochlorobenzene (78.7 mg, 0.5 mmol), 2-methyl-3-buten-2-ol (59 μ L, 0.6 mmol), 4-chlorotoluene (71 μ L, 0.6 mmol), PdCl₂ (3.6 mg, 4 mol%), X-Phos (9.5 mg, 4 mol%) and K₂CO₃ (276 mg, 2 mmol) were dissolved in CH₃CN (2 mL) in a 10 mL vial under a nitrogen atmosphere. After the reaction was heated at 110 °C for 16 h, the mixture was filtered through a pad of Celite and washed with ethyl acetate. The mixture was added into H₂O (25 mL) and extracted with ethyl acetate (10 mL) three times. The combined organic layer was dried over anhydrous Na₂SO₄ and filtered. After removal of the solvent *in vacuo*, the residue was purified by flash chromatography on silica gel (ethyl acetate/hexane=1:5) to give the pure product **2ab** (116.3 mg, 98%).

Acknowledgements

We are grateful to the Natural Science Foundation of China (Nos. 21172200, 21102134) for financial support.

References

- (a) K. Sonogashira, Y. Tohda and N. Hagihara, *Tetrahedron Lett.*, 1975, **16**, 4467–4470; (b) K. Sonogashira, *J. Organomet. Chem.*, 2002, **653**, 46–49; (c) R. R. Tykwinski, *Angew. Chem., Int. Ed.*, 2003, **42**, 1566–1568; (d) K. C. Nicolaou, P. G. Bulger and D. Sarlah, *Angew. Chem., Int. Ed.*, 2005, **44**, 4442–4489; (e) R. Chinchilla and C. Nájera, *Chem. Rev.*, 2007, **107**, 874–922; (f) H. Doucet and J.-C. Hierso, *Angew. Chem., Int. Ed.*, 2007, **46**, 834–871; (g) H. Plenio, *Angew. Chem., Int. Ed.*, 2008, **47**, 6954–6956; (h) R. Chinchilla and C. Nájera, *Chem. Soc. Rev.*, 2011, **40**, 5084–5121.
- For the representative review on the acetylene source, see: E. Negishi and L. Anastasia, *Chem. Rev.*, 2003, **103**, 1979–2017.
- For examples using the ethynyltrimethylsilane as the acetylene source, see: (a) M. R. Buchmeiser and K. Wurst, *J. Am. Chem. Soc.*, 1999, **121**, 11101–11107; (b) M. J. Wu, L. M. Wei, C. F. Lin, S. P. Leou and L. L. Wei, *Tetrahedron*, 2001, **57**, 7839–7844; (c) G. W. Kabalka, L. Wang and R. M. Pagni, *Tetrahedron*, 2001, **57**, 8017–8028; (d) M. J. Mio, L. C. Kopel, J. B. Braun, T. L. Gadzikwa, K. L. Hull, R. G. Brisbois, C. J. Markworth and P. A. Grieco, *Org. Lett.*, 2002, **4**, 3199–3202; (e) C. Y. Yi and R. M. Hua, *J. Org. Chem.*, 2006, **71**, 2535–2537; (f) W. J. Sommer and M. Weck, *Adv. Synth. Catal.*, 2006, **348**, 2101–2113; (g) H. Huang, H. Liu, H. Jiang and K. X. Chen, *J. Org. Chem.*, 2008, **73**, 6037–6040; (h) Q. Z. Tang, D. X. Xia, X. Q. Jin, Q. Zhang, X. Q. Sun and C. Y. Wang, *J. Am. Chem. Soc.*, 2013, **135**, 4628–4631.
- For examples using the propiolic acid as the acetylene source, see: (a) J. Moon, M. Jeong, H. Nam, J. Ju, J. H. Moon, H. M. Jung and S. Lee, *Org. Lett.*, 2008, **10**, 945–948; (b) K. Park, G. Bae, J. Moon, J. Choe, K. H. Song and S. Lee, *J. Org. Chem.*, 2010, **75**, 6244–6251; (c) K. Park, G. Bae, A. Park, Y. Kim, J. Choe, K. H. Song and S. Lee, *Tetrahedron Lett.*, 2011, **52**, 576–580; (d) J. Park, E. Park, A. Kim, S.-A. Park, Y. Lee, K.-W. Chi, Y. H. Jung and I. S. Kim, *J. Org. Chem.*, 2011, **76**, 2214–2219; (e) S. Tartaglia, O. D. Lucchi and L. J. Gooben, *Eur. J. Org. Chem.*, 2012, **2012**, 1431–1438; (f) W. Kim, K. Park, A. Park, J. Choe and S. Lee, *Org. Lett.*, 2013, **15**, 1654–1657.
- For examples using 2-methyl-3-buten-2-ol as the acetylene source, see: (a) Z. Novák, P. Nemes and A. Kotschy, *Org. Lett.*, 2004, **6**, 4917–4920; (b) C. Y. Yi, R. M. Hua, H. X. Zeng and Q. F. Huang, *Adv. Synth. Catal.*, 2007, **349**, 1738–1742; (c) H. Hu, F. Yang and Y.-J. Wu, *J. Org. Chem.*, 2013, **78**, 10506–10511.
- For examples using Buchwald's ligands in Sonogashira reaction, see: (a) T. Hundertmark, A. F. Littke, S. L. Buchwald and G. C. Fu, *Org. Lett.*, 2000, **2**, 1729–1731; (b) B. H. Lipshutz, D. W. Chung and B. Rich, *Org. Lett.*, 2008, **10**, 3793–3796; (c) W. W. Zhang, X. G. Zhang and J. H. Li, *J. Org. Chem.*, 2010, **75**, 5259–5264; (d) B. D. Carné-Carvalet, A. Archambeau, C. Meyer, J. Cossy, B. Folléas, J.-L. Brayer and J.-P. Demoute, *Org. Lett.*, 2011, **13**, 956–959.