Tetrahedron Letters 54 (2013) 6485–6489

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

# Palladium-catalyzed cross-coupling of cyclopropylmethyl N-tosylhydrazones with aromatic bromides: an easy access to multisubstituted 1,3-butadienes

Qin Yang, Huining Chai, Tingting Liu, Zhengkun Yu *

*Dalian Institute of Chemical Physics, Chinese Academy of Sciences, 457 Zhongshan Road, Dalian, Liaoning 116023, China*

ARTICLE INFO

*Article history:*
Received 21 August 2013
Accepted 17 September 2013
Available online 25 September 2013

*Keywords:*
Palladium
Cyclopropylmethyl
*N*-Tosylhydrazones
Aromatic bromides
1,3-Butadienes

ABSTRACT

Direct synthesis of 1,1-disubstitued 1,3-butadienes has been efficiently realized from the cross-coupling of cyclopropylmethyl *N*-tosylhydrazones with aromatic bromides by means of $PdCl_2(MeCN)_2$ as catalyst. 1,1,4-Trisubstitued 1,3-butadiene derivatives were obtained in up to 70% yields through a one-pot procedure catalyzed by $Pd(OAc)_2$ in the presence of excessive amount of aromatic bromides. The present methodology provides an easy and efficient route to multisubstituted 1,3-butadienes.



Conjugate diene is a useful and fundamental structural motif in a wide range of biologically active molecules and organic materials.[1] Molecules bearing diene groups are usually versatile building blocks in numerous transformations such as Diels–Alder and cycloaddition reactions.[2] Much attention has been paid to the development of efficient synthetic protocols for the preparation of conjugate dienes.[3] The cross-coupling of two alkenyl species is the most direct procedure, including that mediated by palladium[4] and rhodium.[5] Transition metal-catalyzed hydrovinylation of alkynes is a commendable protocol to stereoselectively prepare 1,3-dienes.[6] Carbonyl alkenylation involving the Wittig reaction or its variants has been applied for this purpose.[7] Indirect transformations are also known for synthesizing 1,3-dienes.[8] $In(OTf)_3$-mediated aryl-substituted cyclopropyl carbonyl compounds were utilized to construct conjugate butadienes under sonication conditions.[8a] $Pd(PPh_3)_4$-catalyzed isomerization of methylenecyclopropanes formed 1,3-dienes in up to 98% yields.[8b] In the above mentioned literatures, the synthesis of conjugate dienes relies on the substrates containing an alkenyl group.

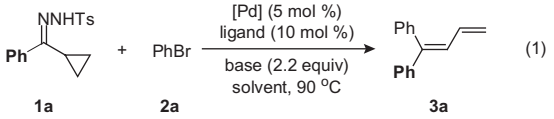
Recently, nonstabilized diazo precursors generated in situ from *N*-tosylhydrazones have been employed as the nucleophilic coupling partners for palladium-catalyzed cross-coupling to form a C=C bond.[9,10] In this aspect, electrophilic coupling partners, for example, aryl halides, aryl triflates, aryl nonaflates have been used in palladium-catalyzed cross-coupling reactions of *N*-tosylhydrazones.[11] Barluenga et al. found that *N*-tosylhydrazones derived from α,β-unsaturated ketones can react with aryl halides to afford conjugate dienes.[11e] Very recently, Wang and co-workers disclosed palladium(0)-catalyzed cross-coupling of cyclopropylmethyl *N*-tosylhydrazones with aryl iodides, in which few aryl bromides were employed as substrates, and they found that Pd(II) complexes could not act as the effective catalysts for the same cross-coupling reactions.[11b] To our delight, we surprisingly found that Pd(II) compounds such as $PdCl_2(MeCN)_2$, $PdCl_2$, and $Pd(OAc)_2$ could catalyze the cross-coupling of cyclopropylmethyl *N*-tosylhydrazones with aryl bromides under modified conditions. Herein, we report Pd(II)-catalyzed cross-coupling reactions of cyclopropylmethyl *N*-tosylhydrazones with aryl bromides to form 1,1-disubstitued 1,3-butadienes as well as 1,1,4-trisubstitued 1,3-butadienes in a one-pot fashion.

Initially, the reaction of cyclopropylmethyl *N*-tosylhydrazone[11b] (**1a**) and bromobenzene (**2a**) was chosen to screen the reaction conditions (Table 1).[12] The target product **3a** was obtained in 69% yield by means of $Pd(PPh_3)_4$ as catalyst, Xphos as ligand, LiO*t*-Bu as base, and dioxane as solvent (Table 1, entry 1), while a better yield (75%) could be achieved in the case of using $Pd(OAc)_2$ as catalyst (Table 1, entry 2). This preliminary result encouraged us to perform the reaction in the presence of various Pd(II) sources. It was found that $PdCl_2$ and $Pd(PPh_3)_2Cl_2$ also effectively promoted the reaction (Table 1, entries 3 and 4). Surprisingly, $Pd(MeCN)_2Cl_2$ remarkably improved the reaction efficiency, affording **3a** in 81% isolated yield (Table 1, entry 5). Both base and ligand effects were obvious to affect the product yields (Table 1, entries 5–15), and among the screened bases, that is, LiO*t*Bu, $Cs_2CO_3$, $K_3PO_4$, KO*t*Bu,

* Corresponding author. Tel./fax: +86 411 8437 9227.
*E-mail address:* zkyu@dicp.ac.cn (Z. K. Yu).

0040-4039/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2013.09.072

**Table 1**
Palladium-catalyzed cross-coupling of *N*-tosylhydrazone (**1a**) with bromobenzene (**2a**) to synthesize 1,1-disubstituted butadiene (**3a**)[a]




**1a** **2a** **3a**

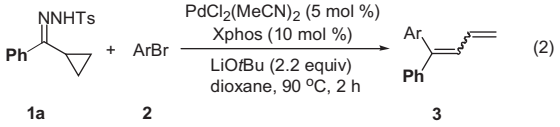
| Entry | [Pd] source | Ligand | Base | Solvent | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 | $Pd(PPh_3)_4$ | Xphos | LiO*t*Bu | Dioxane | 69 |
| 2 | $Pd(OAc)_2$ | Xphos | LiO*t*Bu | Dioxane | 75 |
| 3 | $PdCl_2$ | Xphos | LiO*t*Bu | Dioxane | 79 |
| 4 | $Pd(PPh_3)_2Cl_2$ | Xphos | LiO*t*Bu | Dioxane | 71 |
| 5 | $Pd(MeCN)_2Cl_2$ | Xphos | LiO*t*Bu | Dioxane | 89 (81)[c] |
| 6 | $Pd(MeCN)_2Cl_2$ | Xphos | $Cs_2CO_3$ | Dioxane | 22 |
| 7 | $Pd(MeCN)_2Cl_2$ | Xphos | $K_3PO_4$ | Dioxane | 43 |
| 8 | $Pd(MeCN)_2Cl_2$ | Xphos | KO*t*Bu | Dioxane | trace |
| 9 | $Pd(MeCN)_2Cl_2$ | Xphos | NaO*t*Bu | Dioxane | 45 |
| 10 | $Pd(MeCN)_2Cl_2$ | Xantphos | LiO*t*Bu | Dioxane | trace |
| 11 | $Pd(MeCN)_2Cl_2$ | $PCy_3$ | LiO*t*Bu | Dioxane | trace |
| 12 | $Pd(MeCN)_2Cl_2$ | $PPh_3$ | LiO*t*Bu | Dioxane | 54 |
| 13 | $Pd(MeCN)_2Cl_2$ | dppf | LiO*t*Bu | Dioxane | 41 |
| 14 | $Pd(MeCN)_2Cl_2$ | dppp | LiO*t*Bu | Dioxane | 53 |
| 15 | $Pd(MeCN)_2Cl_2$ | BINAP | LiO*t*Bu | Dioxane | 14 |
| 16 | $Pd(MeCN)_2Cl_2$ | Xphos | LiO*t*Bu | Toluene | 81 |
| 17 | $Pd(MeCN)_2Cl_2$ | Xphos | LiO*t*Bu | NMP | 79 |
| 18 | $Pd(MeCN)_2Cl_2$ | Xphos | LiO*t*Bu | DME | 84 |
| 19 | $Pd(MeCN)_2Cl_2$ | Xphos | LiO*t*Bu | DMF | 55 |
| 20[d] | $Pd(MeCN)_2Cl_2$ | Xphos | LiO*t*Bu | Dioxane | 90 (82)[c] |
| **21**[d,e] | **$Pd(MeCN)_2Cl_2$** | **Xphos** | **LiO*t*Bu** | **Dioxane** | **95 (93)**[c] |

[a] Reaction conditions: **1a**, 0.5 mmol; **2a**, 0.5 mmol; [Pd], 0.025 mmol; ligand, 0.05 mmol; base, 1.1 mmol; solvent, 2 mL; 0.1 MPa $N_2$, 1 h.
[b] GC yield by using mesitylene as the internal standard.
[c] Yield of the isolated product in parentheses.
[d] 2 h.
[e] Compound **1a,** 0.6 mmol.

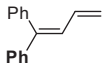
and NaO*t*Bu, LiO*t*Bu behaved as the most effective base and KO*t*Bu did not work (Table 1, entries 5–9). Ligands Xantphos and $PCy_3$ failed to facilitate the reaction, $PPh_3$, dppf, dppb, and BINAP did not efficiently acted as compared to Xphos ligand (Table 1, entries 5 and 10–15). Solvents also affected the formation of **3a** (Table 1, entries 5 and 16–19). Extending the reaction time slightly increased the product yield (Table 1, entry 20), and increasing the amount of *N*-tosylhydrazone **1a** led to the desired product in 93% isolated yield (Table 1, entry 21). Thus, the reaction conditions were optimized to those for entry 21 in Table 1.

To establish the generality of the protocol, the substrate scope for aromatic bromides (**2**) was explored (Table 2). Electron-donating groups such as methyl and methoxy, and electron-withdrawing substituents F, Cl, MeCO, and $NO_2$ were tolerant in the aryl bromide substrates, and the products of type **3** were obtained in 83–98% yields. Only in the case of using 4-methoxyphenyl bromide, the target product **3h** was collected in a lower yield (51%). It should be noted that (*Z*)/(*E*)-isomers of the products were obtained from the reactions, and their molar ratios were close to 1:1 when a 4- or 3-substituent was present in the aryl bromide substrates. However, a 2-methyl substituent remarkably altered the stereoselectivity of product **3d** (*Z*/*E* = 92:8). The increased steric hindrance from naphthyl resulted in *Z*/*E* = 92:8 in product **3j**, revealing the (*Z*)-isomer as the major product. As expected, when 1-bromo-4-chlorobenzene was used as the substrate, the aryl bromide functionality was preferentially transformed to product **3g** and the chloro moiety was tolerated. However, by means of Wang's catalytic system, the aryl chloro functionality could be coupled with the *N*-tosylhydrazone at the same time,[11b] suggesting that the present catalytic system can demonstrate a better substituent tolerance. A heteroaryl also has impact on the stereochemistry of the product, that is, **3k**. The aryl dibromide, that is, 1,4-$C_6H_4Br_2$,

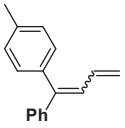
**Table 2**
Synthesis of 1,1-disubstituted butadienes (**3**) from the reactions of *N*-tosylhydrazones (**1a**) with ArBr (**2**)[a,b]



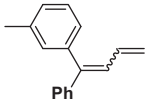

**1a** **2** **3**



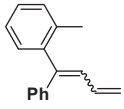

**3a**, 93%



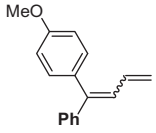

**3b**, 98%
(*Z*/*E* = 50:50)



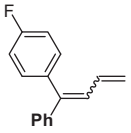

**3c**, 98%
(*Z*/*E* = 50:50)



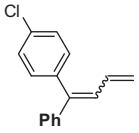

**3d**, 97%
(*Z*/*E* = 92:8)



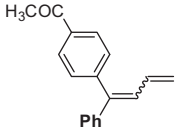

**3e**, 93%
(*Z*/*E* = 60:40)



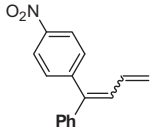

**3f**, 89%
(*Z*/*E* = 52:48)



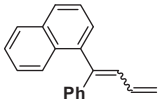

**3g**, 83%
(*Z*/*E* = 50:50)



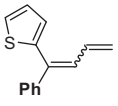

**3h**, 51%
(*Z*/*E* = 52:48)



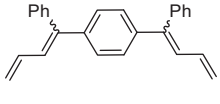

**3i**, 95%
(*Z*/*E* = 53:47)




**3j**, 73%
(*Z*/*E* = 92:8)



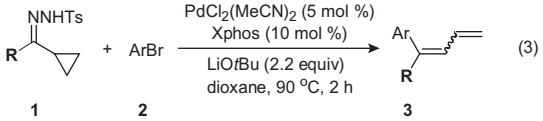

**3k**, 88%
(*Z*/*E* = 77:23)

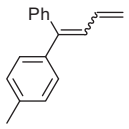



**3l**, 78[c]%

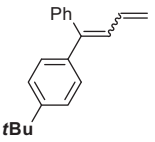
[a] Reaction conditions: **1a**, 0.6 mmol; **2**, 0.5 mmol; $PdCl_2(MeCN)_2$, 0.025 mmol; Xphos, 0.05 mmol; LiO*t*Bu, 1.1 mmol; dioxane, 2 mL; 0.1 MPa $N_2$, 90 °C, 2 h.
[b] Isolated yields based on **2**. The *Z*/*E* ratios of **3** were determined by $^1H$ NMR analysis.
[c] 0.25 mmol 1,4-$C_6H_4Br_2$ was used. The *Z*/*E* ratio of **3l** could not be determined by $^1H$ NMR analysis.

**Table 3**
Synthesis of 1,1-disubstituted butadienes (**3**) from the reactions of *N*-tosylhydrazones (**1**) with ArBr (**2**)[a,b]

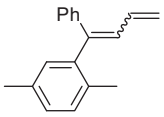


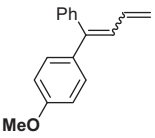

**3b**, 90%
(*Z*/*E* = 50:50)



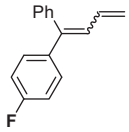

**3m**, 94%
(*Z*/*E* = 50:50)



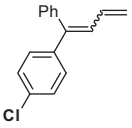

**3n**, 86%
(*Z*/*E* = 96:4)



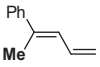

**3e**, 95%
(*Z*/*E* = 57:43)



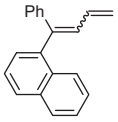

**3f**, 92%
(*Z*/*E* = 53:47)



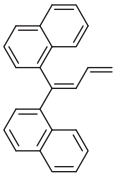

**3g**, 97%
(*Z*/*E* = 50:50)



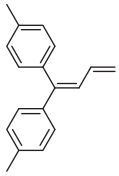

**3o**, 44%[c]



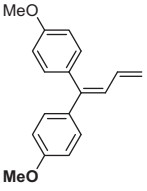

**3j**, 38%
(*Z*/*E* = 92:8)



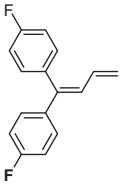
**3p**, 54%



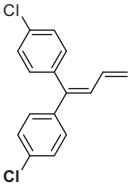
**3q**, 92%




**3r**, 88%




**3s**, 95%




**3t**, 87%

[a] Reaction conditions: **1**, 0.6 mmol; **2**, 0.5 mmol; $PdCl_2(MeCN)_2$, 0.025 mmol; Xphos, 0.05 mmol; LiO*t*Bu, 1.1 mmol; dioxane, 2 mL; 0.1 MPa $N_2$, 90 °C, 2 h.
[b] Isolated yields. The *Z*/*E* ratios of **3** were determined by $^1H$ NMR analysis.
[c] 20 h.

reacted with **1a** to form the corresponding bis(1,3-butadiene) **3l** in 78% yield, featuring a skipped tetraene.

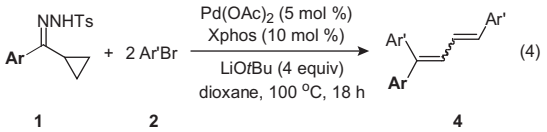
Next, the scope of substrates *N*-tosylhydrazones (**1**) was investigated (Table 3). A relatively broad range of *N*-tosylhydrazone derivatives smoothly underwent the cross-coupling to produce the target products **3** in 87–97% yields. The substituent effect from those electron-donating or -withdrawing groups on the aryl moieties of *N*-tosylhydrazones (**1**) did not exhibit obvious impact on their reactivity. However, the alkyl *N*-tosylhydrazone only showed a moderate reactivity, yielding the target product (*E*)-**3o** in 44% yield over a period of 20 h. 2-Methyl substituent remarkably increased the stereoselectivity of product **3n** (*Z*/*E* = 96:4). The bulky naphthyl *N*-tosylhydrazone did not exhibit a high reactivity either, producing **3j** and **3p** in 38% and 54% yields, respectively. When both the two substrates bear the same aryl moieties, the resultant products, that is, **3a** and **3p**–**t**, only exhibit one configuration. It is noteworthy that products of type **3** can be efficiently prepared through both the procedures described in equations 2 and 3 by altering the aryl functionalities in **1** and **2**.

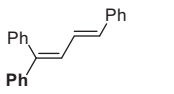
Heck-type reaction is usually applied for the preparation of substituted alkenes in the presence of a base under palladium catalysis. We envisioned that **3** generated in situ could further react with aryl bromides under suitable conditions, affording the corresponding trisubstituted 1,3-diene derivatives. We tested the reaction of **1a** with PhBr (**2a**) by increasing the loadings of PhBr and LiO*t*Bu each to at least two equivalents under the stated conditions as shown in Tables 2 and 3. To our delight, the desired product, that is, **4a**, was formed in 55% yield at 100 °C within 18 h. After screening the palladium catalysts, we found that the reaction underwent more efficiently by using of $Pd(OAc)_2$ as catalyst. LiO*t*Bu base facilitated the transformation of **3a** to **4a**, whereas other bases did not work very well for this step reaction. Ligands and solvents also affected the formation of the intermediate species **3a**. Eventually, the conditions for the cross-coupling of **1a** with **2a** to form **4a** were optimized to 5 mol % $Pd(OAc)_2$ as catalyst, 10 mol % Xphos as ligand, and LiO*t*Bu (4 equiv) as base, dioxane as solvent, 100 °C for 18 h, and the reaction was carried out in a 10-mL sealed tube to yield **4a** in 64% yield.[13]

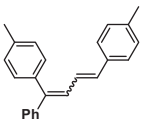
Under the optimized reaction conditions, diverse reactions of *N*-tosylhydrazones (**1**) with aryl bromides (**2**) were investigated (Table 4). Both the electron-donating and -withdrawing substituents such as methyl, methoxy, chloro, and fluoro were tolerant. The steric hindrance from 2-methyl or naphthyl is evident, leading to **4c** and **4e** in relatively poor yields (32% and 26%). It seems that such a steric effect lessened the reaction efficiency for both the cross-coupling of **1** with **2** and the subsequent Heck reaction of intermediate **3** with **2** in the reaction sequence. In other cases, the trisubstituted 1,3-diene products were obtained in moderate to good yields (33–70%). 1,1,4-Trisubstitued 1,3-dienes are usually synthesized from the reactions of alkenyl halides, alkenes, or 1,3-dienes with aryl halides.[3] To the best of our knowledge, a one-pot process has not been established in this area.

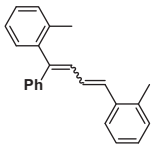
A plausible mechanism for the formation of 1,3-diene (**3**) is proposed as depicted in Scheme 1. Palladium(II) complex **A** is generated from the oxidative addition of aryl bromide (**2**) to the in-situ formed Pd(0) species. The diazo compound **A'** generated in situ from the decomposition of *N*-tosylhydrazone (**1**) reacts with **A** to produce palladium-carbene species **B**. A migratory insertion of

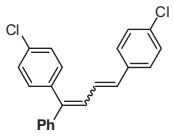
**Table 4**
One-pot synthesis of 1,1,4-trisubstituted 1,3-butadienes (**4**)[a,b]

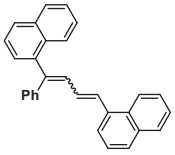


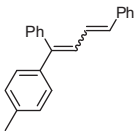


**4a**, 64%

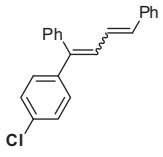

**4b**, 57%
(*Z*,*E*/*E*,*E* = 51:49)

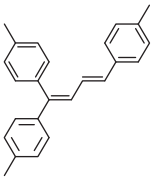

**4c**, 32%
(*Z*,*E*/*E*,*E* = 90:10)

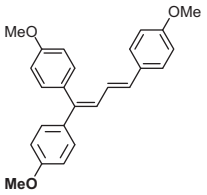

**4d**, 53%[c]

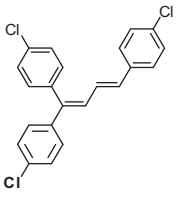

**4e**, 26%
(*Z*,*E*/*E*,*E* = 84:16)

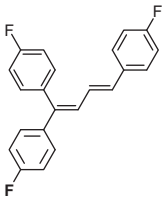

**4f**, 68%
(*Z*,*E*/*E*,*E* = 53:47)


**4g**, 61%[c]

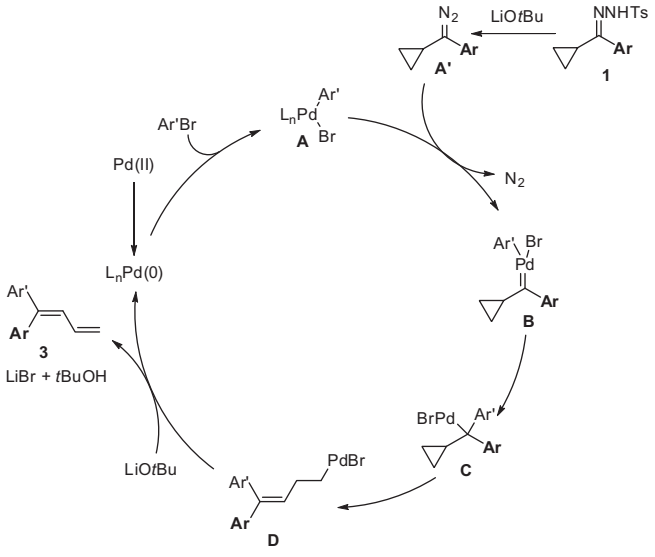

**4h**, 70%


**4i**, 67%


**4j**, 33%


**4k**, 62%

[a] Reaction conditions: compound **1**, 0.5 mmol; **2**, 1.5 mmol; $Pd(OAc)_2$, 0.025 mmol; Xphos, 0.05 mmol; LiO*t*Bu, 2.0 mmol; dioxane, 2 mL; 0.1 MPa $N_2$, 18 h. The reactions were performed in a 10-mL sealed tube.
[b] Isolated yields. The *Z*,*E*/*E*,*E* ratios of **4** were determined by $^1H$ NMR analysis.
[c] The *Z*,*E*/*E*,*E* ratios were not successfully determined by $^1H$ NMR analysis.




**Scheme 1.** Proposed mechanism.

the aryl moiety originated from **2** occurs to afford alkyl palladium(II) species **C**.[11b] β-Carbon–Pd elimination proceeds to form intermediate **D** which subsequently undergoes β-hydride elimination to form the target product **3**.[8b]

In summary, we have disclosed an efficient protocol to synthesize 1,3-butadienes from the direct cross-coupling of cyclopropylmethyl *N*-tosylhydrazones with aryl bromides. 1,1-Disubstituted 1,3-butadienes can be obtained in up to 98% yields by using $PdCl_2(MeCN)_2$ as catalyst. By altering the conditions and using $Pd(OAc)_2$ as catalyst 1,1,4-trisubstituted 1,3-butadienes were also prepared in moderate yields. The present methodology provides a direct route to multisubstituted conjugate butadienes.

## Acknowledgment

We are grateful to the National Natural Science Foundation of China (21272232) for support of this research.

## Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.09.072.

## References and notes

1. (a) Erb, W.; Zhu, J. P. *Nat. Prod. Rep.* **2013**, *30*, 161; (b) Biermann, U.; Bornscheuer, U.; Meier, M. A. R.; Metzger, J. O.; Schäfer, H. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 3854; (c) Trisuwan, K.; Rukachaisirikul, V.; Sukpondma, Y.; Preedanon, S.; Phongpaichit, S.; Rungjindamai, N.; Sakayaroj, J. *J. Nat. Prod.* **2008**, *71*, 1323.
2. (a) Dzhemilev, U. M.; Tolstikov, G. A.; Khusnutdinov, R. I. *Russ. J. Org. Chem.* **2009**, *45*, 957; (b) Welker, M. E. *Tetrahedron* **2008**, *64*, 11529; For selected examples, see: (c) Patel, R. M.; Argade, N. P. *Org. Lett.* **2013**, *15*, 14; (d) Bouillon, J.-P.; Mykhaylychenko, S.; Melissen, S.; Martinez, A.; Harakat, D.; Shermolovich, Y. G. *Tetrahedron* **2012**, *68*, 8663.
3. (a) Shang, X. J.; Liu, Z. Q. *Chem. Soc. Rev.* **2013**, *42*, 3253; Wang, G. W.; Mohan, S.; Negishi, E.-i. *Proc. Natl. Acad. Sci.* **2011**, *108*, 11344.
4. (a) Delcamp, J. H.; Gormisky, P. E.; White, M. C. *J. Am. Chem. Soc.* **2013**, *135*, 8460; (b) Zheng, C. W.; Wang, D.; Stahl, S. S. *J. Am. Chem. Soc.* **2012**, *134*, 16496; (c) Zhang, Y. X.; Cui, Z. L.; Li, Z. J.; Liu, Z.-Q. *Org. Lett.* **1838**, *2012*, 14; (d) Yamashita, M.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2010**, *12*, 592; (e) Yu, H. F.; Jin, W. W.; Sun, C. L.; Chen, J. P.; Du, W. M.; He, S. B.; Yu, Z. K. *Angew. Chem., Int. Ed.* **2010**, *49*, 5792.
5. Besset, T.; Kuhl, N.; Patureau, F. W.; Glorius, F. *Chem.-Eur. J.* **2011**, *17*, 7167.
6. (a) Saito, N.; Saito, K.; Shiro, M.; Sato, Y. *Org. Lett.* **2011**, *13*, 2718; (b) Shibata, Y.; Hirano, M.; Tanaka, K. *Org. Lett.* **2008**, *10*, 2829; (c) Nakao, Y.; Yada, A.; Ebata, S.; Hiyama, T. *J. Am. Chem. Soc.* **2007**, *129*, 2428.
7. (a) Cui, H.; Li, Y.; Zhang, S. L. *Org. Biomol. Chem.* **2012**, *10*, 2862; (b) Dong, D.-J.; Li, H.-H.; Tian, S.-K. *J. Am. Chem. Soc.* **2010**, *132*, 5018; (c) Zhou, R.; Wang, C. Z.; Song, H. B.; He, Z. J. *Org. Lett.* **2010**, *12*, 976.
8. (a) Ranu, B. C.; Banerjee, S. *Eur. J. Org. Chem.* **2006**, 3012; (b) Shi, M.; Wang, B.-Y.; Huang, J.-W. *J. Org. Chem.* **2005**, *70*, 5606.
9. (a) Xiao, Q.; Zhang, Y.; Wang, J. B. *Acc. Chem. Res.* **2013**, *46*, 236; (b) Shao, Z. H.; Zhang, H. B. *Chem. Soc. Rev.* **2012**, *41*, 560; (c) Barluenga, J.; Valdés, C. *Angew. Chem., Int. Ed.* **2011**, *50*, 7486.
10. (a) Chen, H. J.; Huang, L.; Fu, W.; Liu, X. H.; Jiang, H. F. *Chem.-Eur. J.* **2012**, *18*, 10497; (b) Barluenga, J.; Quiñones, N.; Cabal, M.-P.; Aznar, F.; Valdés, C. *Angew. Chem., Int. Ed.* **2011**, *50*, 2350; (c) Zhou, L.; Ye, F.; Ma, J. C.; Zhang, Y.; Wang, J. B. *Angew. Chem., Int. Ed.* **2011**, *50*, 3510; (d) Chen, Z.-S.; Duan, X.-H.; Wu, L.-Y.; Ali, S.; Ji, K.-G.; Zhou, P.-X.; Liu, X.-Y.; Liang, Y.-M. *Chem.-Eur. J.* **2011**, *17*, 6918; (e) Brachet, E.; Hamze, A.; Peyrat, J.-F.; Brion, J.-D.; Alami, M. *Org. Lett.* **2010**, *12*, 4042; (f) Barluenga, J.; Tomás-Gamasa, M.; Aznar, F.; Valdés, C. *Chem.-Eur. J.* **2010**, *16*, 12801; (g) Zhao, X.; Jing, J.; Lu, K.; Zhang, Y.; Wang, J. B. *Chem. Commun.* **2010**, 1724; (h) Xiao, Q.; Ma, J.; Yang, Y.; Zhang, Y.; Wang, J. B. *Org. Lett.* **2009**, *11*, 4732; (i) Barluenga, J.; Escribano, M.; Moriel, P.; Aznar, F.; Valdés, C. *Chem.-Eur. J.* **2009**, *15*, 13291; (j) Barluenga, J.; Tomás-Gamasa, M.; Moriel, P.; Aznar, F.; Valdés, C. *Chem.-Eur. J.* **2008**, *14*, 4792.
11. (a) Florentino, L.; Aznar, F.; Valdés, C. *Org. Lett.* **2012**, *14*, 2323; (b) Zhou, L.; Ye, F.; Zhang, Y.; Wang, J. B. *Org. Lett.* **2012**, *14*, 922; (c) Barluenga, J.; Florentino, L.; Aznar, F.; Valdés, C. *Org. Lett.* **2011**, *13*, 510; (d) Barluenga, J.; Escribano, M.; Aznar, F.; Valdés, C. *Angew. Chem., Int. Ed.* **2010**, *49*, 6856; (e) Barluenga, J.; Tomás-Gamasa, M.; Aznar, F.; Valdés, C. *Adv. Synth. Catal.* **2010**, *352*, 3235; (f) Tréguier, B.; Hamze, A.; Provot, O.; Brion, J.-D.; Alami, M. *Tetrahedron Lett.* **2009**, *50*, 6549; (g) Barluenga, J.; Moriel, P.; Valdés, C.; Aznar, F. *Angew. Chem., Int. Ed.* **2007**, *46*, 5587.

12. *A general procedure for the direct synthesis of 1,1-disubstituted-1,3-butadienes (**3**) from the cross-coupling reactions of N-tosylhydrazones (**1**) with aryl bromides (**2**)—synthesis of **3a***: under nitrogen atmosphere, cyclopropylmethyl *N*-tosylhydrazone (**1a**, 189 mg, 0.6 mmol), $PdCl_2(MeCN)_2$ (6.5 mg, 0.025 mmol), 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (Xphos) (23.8 mg, 0.05 mmol), lithium *t*-butoxide (88 mg, 1.1 mmol), and dioxane (2 mL) were successively added to a 10-mL Schlenck flask with stirring. After the mixture was stirred for one minute, phenyl bromide (**2a**, 78.5 mg, 0.5 mmol) was added. The resultant mixture was stirred at 90 °C for 2 h. After cooled to ambient temperature, the reaction mixture was filtered through a short pad of celite and rinsed with 20 mL $CH_2Cl_2$. The combined filtrate was concentrated under reduced pressure and the resulting residue was purified by flash column chromatography on silica gel (eluent: petroleum ether (60–90 °C)) to afford product **3a** (96 mg, 93%) as a colorless oil.

13. *A general procedure for the direct synthesis of 1,1,3-trisubstituted-1,3-butadienes (**4**)—synthesis of **4a***: under nitrogen atmosphere, cyclopropylmethyl *N*-tosylhydrazone (**1a**, 157 mg, 0.5 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), Xphos (23.8 mg, 0.05 mmol), lithium *t*-butoxide (160 mg, 2 mmol), and dioxane (2 mL) were successively added to a 10-mL sealed tube with stirring. After the resultant mixture was stirred for one minute, phenyl bromide (**2a**, 236 mg, 1.5 mmol) was added. The reaction mixture was stirred at 100 °C for 18 h. After cooled to ambient temperature, the resultant mixture was filtered through a short pad of celite and rinsed with 20 mL $CH_2Cl_2$. The combined filtrate was concentrated under reduced pressure and the resulting residue was purified by flash column chromatography on silica gel (eluent: petroleum ether (60–90 °C)) to afford product **4a** (90 mg, 64%) as a colorless oil.