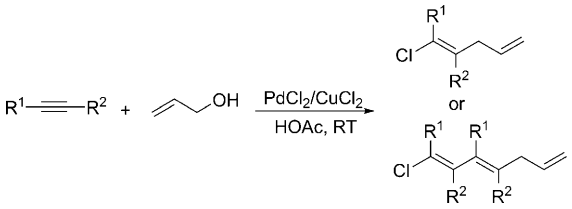
CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.201001318

Palladium(II)-Catalyzed Highly Regio- and Stereoselective Synthesis of 2-Chloro-1,3-diene Derivatives from Alkynols and Alkenes

Huanfeng Jiang,* Chunli Qiao, and Weibing Liu[a]

Over the past decade, transition-metal-catalyzed reactions have emerged as powerful and general methods for the synthesis of organic compounds.[1] C–C or C–heteroatom bond-formation processes, which are typically mediated by well-defined, air-stable palladium catalysis, are now ubiquitous in both academia and industry.[2] Recently, our group has developed an efficient C–C coupling reaction for diene synthesis by directly utilizing chloropalladation chemistry (Scheme 1).[3] On the basis of our work, we herein disclose a

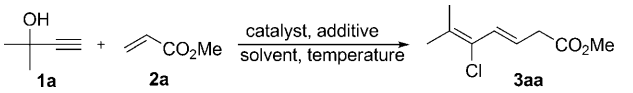


Scheme 1. Highly regio- and stereoselective intermolecular reaction to synthesize chloro-substituted dienes.

highly regio- and stereoselective synthetic method to construct (*E*)-2-chloro-1,3-dienes from alkynols and alkenes by using a $PdCl_2/CuCl_2$ catalyst system.[4] The 1,3-diene unit is an important synthon in organic synthesis[4] and many natural products that contain the 1,3-diene framework have showed potential biological activities, such as cell-cycle regulating properties and apoptotic, antifungal, and antiviral activities.[5]

Initial efforts were focused on the evaluation of palladium catalysts for the reaction of 2-methylbut-3-yn-2-ol (**1a**) with methyl acrylate (**2a**) to synthesize (*E*)-methyl 5-chloro-6-methylhepta-3,5-dienoate (**3aa**) (Table 1) by using copper(II) chloride dihydrate $CuCl_2 \cdot 2H_2O$ as the additive. As shown in Table 1, $Pd(OAc)_2$ and $PdCl_2$ were suitable catalysts for this reaction in dioxane (entries 1 and 3). Changing the additives, we found that copper(II) chloride dihydrate ($CuCl_2 \cdot 2H_2O$) led to preferable result (Table 1, entries 3–6). Among the various solvents examined, dioxane gave the best result (Table 1, entries 7–14). The optimal reaction temperature was 80 °C. Higher and lower reaction temperatures led the decrease in the yield. (Table 1, entries 12 and 13; cf. entry 3). However, there was a significant increase in the yield when prolonging the reaction time to 10 h and the desired product was obtained in 85% yield (Table 1, entry 14).

Table 1. Optimization of reaction conditions.[a]



Entry	Catalyst (5 mol%)	Additive (2.0 equiv)	Solvent	Yield[b] [%]
1	$Pd(OAc)_2$	$CuCl_2 \cdot 2H_2O$	1,4-dioxane	52
2	$[Pd_2(dba)_3]$[c]	$CuCl_2 \cdot 2H_2O$	1,4-dioxane	28
3	$PdCl_2$	$CuCl_2 \cdot 2H_2O$	1,4-dioxane	57
4	$PdCl_2$	$ZnCl_2$	1,4-dioxane	32
5	$PdCl_2$	CuCl	1,4-dioxane	0
6	$PdCl_2$	none	1,4-dioxane	0
7	$PdCl_2$	$CuCl_2 \cdot 2H_2O$	CH_3CN	trace
8	$PdCl_2$	$CuCl_2 \cdot 2H_2O$	toluene	trace
9	$PdCl_2$	$CuCl_2 \cdot 2H_2O$	DMSO	trace
10	$PdCl_2$	$CuCl_2 \cdot 2H_2O$	THF	50
11	$PdCl_2$	$CuCl_2 \cdot 2H_2O$	DCE	46
12[d]	$PdCl_2$	$CuCl_2 \cdot 2H_2O$	1,4-dioxane	43
13[e]	$PdCl_2$	$CuCl_2 \cdot 2H_2O$	1,4-dioxane	47
14[f]	$PdCl_2$	$CuCl_2 \cdot 2H_2O$	1,4-dioxane	85

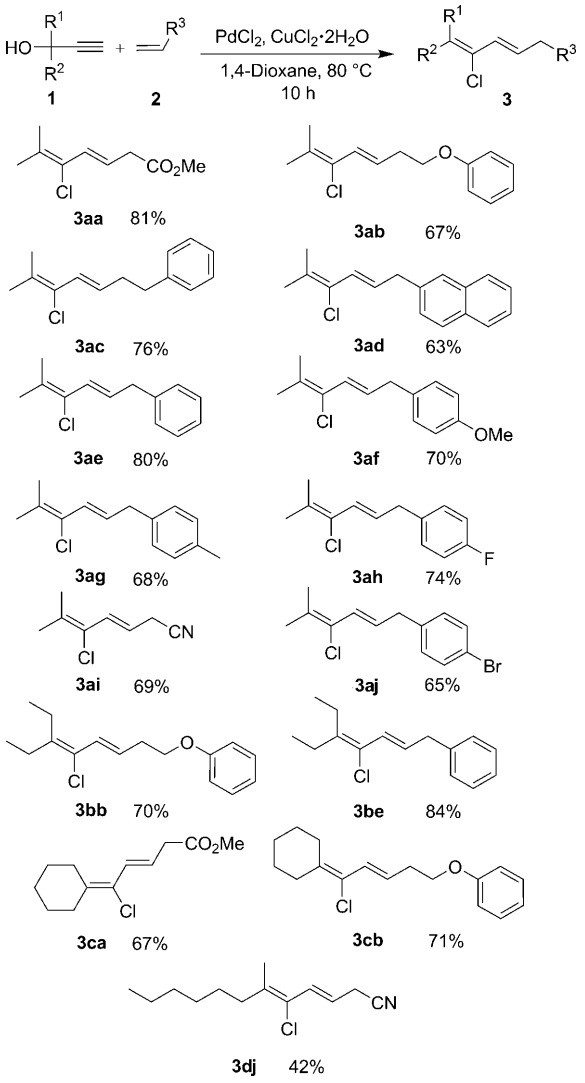
[a] Reaction conditions: **1a** (0.25 mmol) and **2a** (0.25 mmol) in solvent (2 mL) at 80 °C for 4 h. [b] GC yields. [c] dba = dibenzylideneacetone. [d] Reaction temperature: 60 °C. [e] 100 °C. [f] Reaction time: 10 h.

Under the optimized conditions, the reaction was applied to a range of substrates. A wide variety of *tert*-propargylic

[a] Prof. Dr. H. Jiang, C. Qiao, W. Liu
School of Chemistry and Chemical Engineering
South China University of Technology
Guangzhou 510640 (China)
Fax: (+86) 20-8711-2906
E-mail: jianghf@scut.edu.cn

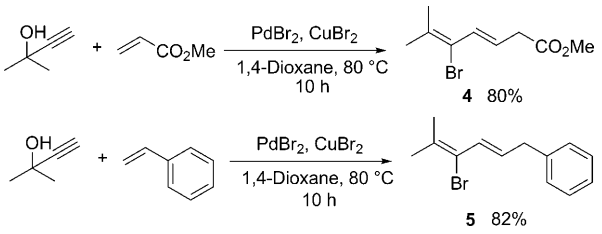
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201001318.

alcohols could successfully react with alkenes to afford the corresponding 2-chloro-1,3-diene derivatives (Scheme 2). As revealed in Scheme 2, alkenes with electron-withdrawing or



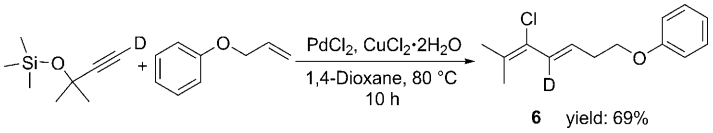
Scheme 2. Synthesis of 2-chloro-1,3-dienes from alkynols and alkenes.

-donating groups are suitable for this protocol; the electronic properties of the substituents on the alkenes has no significant influence on the reaction (**3aa**–**3aj**). For example, the coupling reaction of **1a** with acrylonitrile (**2j**) or 1-(allyloxy)benzene (**2b**) as well as 1-ethynylcyclohexanol (**1c**) with methyl acrylate (**2a**) or 1-(allyloxy)benzene (**2b**) all led to the corresponding 2-chloro-1,3-dienes in reasonable yield (**3aj, 3ab, 3ca**, and **3cb**). This transformation proceeded smoothly with high regio- and stereoselectivity and afforded the desired product in moderate to excellent yields for those alkynols substituted with the same groups ($R^1 = R^2$). For example, the reaction of **1a**, 3-ethylpent-1-yn-3-ol (**1b**), and 1-ethynylcyclohexanol (**1c**) with **2b** led to the corresponding product in 67, 70, and 71% isolated yields, respectively. When R^1 and R^2 were different, the reaction led to inferior results. The transformation of 3-methylnon-1-yn-3-ol (**1d**) with **2j** was a typical example and only gave (3*E*, 5*Z*)-5-chloro-6-methyldodeca-3,5-dienenitrile (**3dj**) in 42% isolated yield. Interestingly, this strategy can also be applied to synthesize other halosubstituted 1,3-dienes. For example, the reaction can proceed smoothly and give the corresponding product in good isolated yield when using $PdBr_2$ and $CuBr_2$ as the catalyst system (Scheme 3).



Scheme 3.

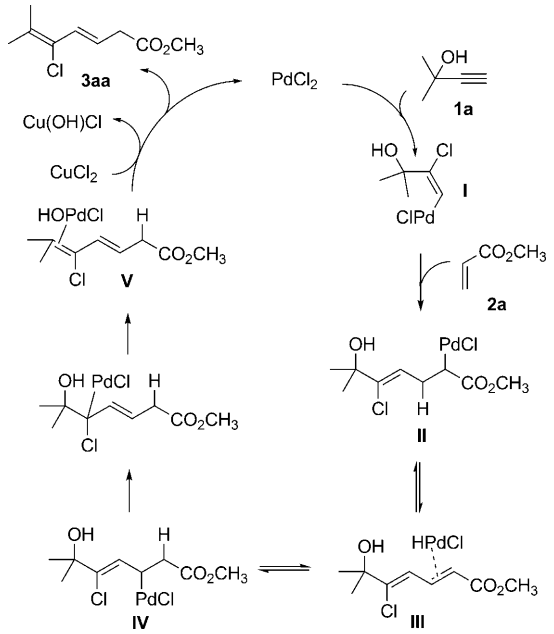
To probe the credibility of our proposed mechanism and shed more light on the formation of 2-chloro-1,3-diene derivatives, several experiments were carried out. First, we tested the acidity of the reaction solution after the reactions were completed. The results indicated that the reaction solution was slightly acidic and the pH value was among in the range 5–6. Next, deuterium-labeled 3-methyl-3-[(trimethylsilyl)oxy]-1-butyne was used as a modified substrate to distinguish the hydrogen position of the terminal alkyne. As depicted in Scheme 4, deuterium product **6** was obtained exclusively in 69% isolated yield and the deuterium atom (96% examined by ^{1}H NMR spectroscopy) was still present.



Scheme 4.

On the basis of these preliminary results, a mechanistic proposal for this transformation, exemplified by the formation of **3aa**, is depicted in Scheme 5. Vinylpalladium intermediate **I** is initially formed by *trans*-chloropalladation of the alkyne in the presence of excess halide ions,[6] followed by the insertion of methyl acrylate to generate an alkylpalladium species **II**.[7] Further palladium β-hydride elimination of intermediate **II** afforded the intermediate **III**, which underwent re-addition of the palladium hydride to the double bond with the opposite regiochemistry and produced another alkylpalladium species **IV**.[8] Subsequent allylic rearrangement of intermediate **IV** would generate alkylpalladium compound **V**.[9] Finally, β-hydroxyelimination[10] produced the observed 1,3-diene product **3aa** and $PdCl_2$ were regenerated in the presence of $CuCl_2$ for the next cycle.

In conclusion, we have described a facile and efficient method for the synthesis of 2-chloro-1,3-diene derivatives by



Scheme 5. A mechanistic rationale for the transformation.

a Pd-catalyzed intermolecular reaction from alkynols and alkenes. The high regio- and stereoselectivity and tolerance for a range of functional groups as well as the mild reaction conditions and good to excellent yields make the present protocol very attractive. It is a good alternative for the synthesis of halosubstituted-1,3-diene derivatives. The scope (including the asymmetrically substituted propargylic alcohols, the symmetrically and the asymmetrically polysubstituted alkenes), mechanism, and applications of this strategy are under investigation in our group, and the results will be reported in due course.

Experimental Section

Full experimental details and characterization data are given in the Supporting Information.

General method: All of the reactions were carried out at 80 °C in a Schlenk tube equipped with magnetic stirrer bar for 10 h. All solvents and reagents were used as received. ^{1}H NMR spectra were recorded in $CDCl_3$ at 400 or 600 MHz and ^{13}C NMR spectra were recorded in $CDCl_3$ at 100 or150 MHz. GC-MS was performed by using electron ionization (EI). TLC was performed by using commercially prepared 100–400 mesh silica gel plates (GF_{254}), and visualization was effected at 254 nm. All the other chemicals were purchased from Aldrich Chemicals.

Typical procedure for the reaction of 1a and 2a (Table 1, 3aa): A mixture of $PdCl_2$ (8.85 mg, 0.05 mmol), $CuCl_2{\cdot}2H_2O$ (336 mg, 2.0 mmol), 1,4-dioxane (2 mL), **1a** (84 mg, 1.0 mmol), and **2a** (86 mg, 1 mmol) were added successively in Schlenk tube. After stirring for 10 h at 80 °C, the solution was directly subjected to isolation by PTLC (GF_{254}) eluted with a 50:1 *n*-hexane/ethyl acetate mixture, which gave **3aa** as a pale yellow oil (152.2 mg, 81 %).

Acknowledgements

The authors are grateful to the National Natural Science Foundation of China (nos. 20625205, 20772034 and 20932002) and Doctoral Fund of Ministry of Education of China (20090172110014) for financial support.

Keywords: alkenes · homogeneous catalysis · palladium · regioselectivity · stereoselectivity

[1] a) H. Doucet, J.-C. Hierso, *Angew. Chem.* **2007**, *119*, 850–888; *Angew. Chem. Int. Ed.* **2007**, *46*, 834–871; b) J. B. Johnson, T. Rovis, *Angew. Chem.* **2008**, *120*, 852–884; *Angew. Chem. Int. Ed.* **2008**, *47*, 840–871; c) *Metal-Catalyzed Cross Coupling Reactions*, 2nd ed. (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, **2004**.

[2] a) K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem.* **2005**, *117*, 4516–4563; *Angew. Chem. Int. Ed.* **2005**, *44*, 4442–4489; b) J. F. Hartwig, *Acc. Chem. Res.* **2008**, *41*, 1534–1544; c) G. C. Fu, *Acc. Chem. Res.* **2008**, *41*, 1555–1564.

[3] J. M. Huang, L. Zhou, H. F. Jiang, *Angew. Chem.* **2006**, *118*, 1979–1983; *Angew. Chem. Int. Ed.* **2006**, *45*, 1945–1949.

[4] For the reports of 1,3-dienes, see: a) S. Fustero, P. Bello, B. Fernandez, C. Del Pozo, G. B. Hammond, *J. Org. Chem.* **2009**, *74*, 7690–7696; b) J. McNulty, P. Das, *Tetrahedron Lett.* **2009**, *50*, 5737–5740; c) S. Laclef, C. J. Exner, M. Turks, V. Videtta, P. Vogel, *J. Org. Chem.* **2009**, *74*, 8882–8885; d) L. J. Perez, H. L. Shimp, G. C. Micalizio, *J. Org. Chem.* **2009**, *74*, 7211–7219; e) X. Huang, T. de Haro, C. Nevado, *Chem. Eur. J.* **2009**, *15*, 5904–5908; f) H.-J. Zhang, Z. Song, C. Wang, C. Bruneau, Z. Xi, *Tetrahedron Lett.* **2008**, *49*, 624–627; g) M. Ogasawara, H. Murakami, T. Furukawa, T. Takahashi, N. Shibata, *Chem. Commun.* **2009**, 7366–7368.

[5] a) D. Amans, V. Bellosta, J. Cossy, *Chem. Eur. J.* **2009**, *15*, 3457–3473; b) G. Ramamoorthy, C. M. Acevedo, E. Alvira, M. A. Lipton, *Tetrahedron: Asymmetry* **2008**, *19*, 2546–2554; c) A. M. Boldi, *Curr. Opin. Chem. Biol.* **2004**, *8*, 281–286; d) Y. Liao, Y.-H. Hu, J. Wu, Q. Zhu, M. Donovan, R. Fathi, Z. Yang, *Curr Med. Chem.* **2003**, *10*, 2285–2316; e) M. Kalesse, M. Christmann, *Synthesis* **2002**, 981–1003.

[6] *Trans*-chloropalladation of alkyne occurred predominantly in the presence of excess halide ion, see: a) Q. Zhang, W. Xu, X. Lu, *J. Org. Chem.* **2005**, *70*, 1505–1507; b) J.-E. Bäckvall, Y. I. M. Nilsson, R. G. P. Gatti, *Organometallics* **1995**, *14*, 4242–4246.

[7] Z. Wang, X. Lu, A. Lei, Z. Zhang, *J. Org. Chem.* **1998**, *63*, 3806–3807.

[8] a) Q. Huang, R. C. Larock, *Org. Lett.* **2002**, *4*, 2505–2508; b) Q. Huang, R. C. Larock, *J. Org. Chem.* **2003**, *68*, 7342–7349.

[9] a) B. M. Trost, P. J. Metzner, *J. Am. Chem. Soc.* **1980**, *102*, 3572–3577; b) R. C. Larock, K. Takagi, *J. Org. Chem.* **1984**, *49*, 2701–2705; c) Z.-H. Ren, Z.-H. Guan, Y.-M. Liang, *J. Org. Chem.* **2009**, *74*, 3145–3147; d) H.-P. Bi, L.-N. Guo, F.-R. Gou, X.-H. Duan, X.-Y. Liu, Y.-M. Liang, *J. Org. Chem.* **2008**, *73*, 4713–4716; e) X.-H. Duan, L.-N. Guo, H.-P. Bi, X.-Y. Liu, Y.-M. Liang, *Org. Lett.* **2006**, *8*, 5777–5780; f) H.-P. Bi, X.-Y. Liu, F.-R. Gou, L.-N. Guo, X.-H. Duan, Y.-M. Liang, *Org. Lett.* **2007**, *9*, 3527–3529.

[10] U. Hacksell, G. D. Daves, Jr., *Organometallics* **1983**, *2*, 772–775.

Received: May 15, 2010
Published online: August 16, 2010

