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Hydroxyl Group-Assisted Palladium-Catalyzed Lactonization of Homoallylic Alcohols

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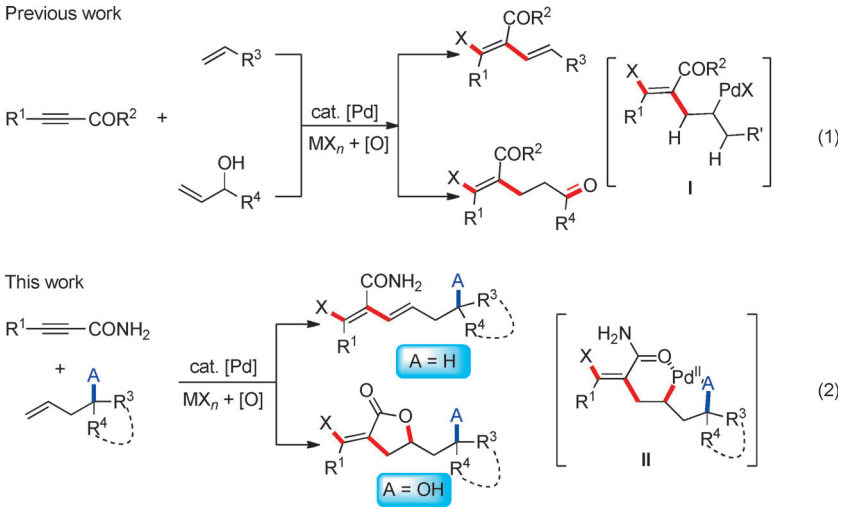
A convenient and highly efficient synthesis of α-methylene-γ-lactones through the palladium(II)-catalyzed lactonization of homoallylic alcohols with alkynamides has been reported. The hydroxyl group in the terminal olefins cooperates with the amide in alkynamides to promote the cyclization by suppressing the β-H elimination. This process provides a route to construct naturally occurring biologically multifunctional α-methylene-γ-lactones.

Introduction

The development of transition-metal-mediated transformations to construct carbon–carbon and carbon–hetero bonds in a convenient and concise manner continue to attract tremendous attention.[1] Of numerous examples, the nucleopalladation of carbon–carbon multiple bonds has been broadly used to synthesize various functional molecules.[2] And the nucleopalladation of alkynes, that is, Kaneda reaction,[3,4] provides an economical and supplementary approach to construct vinylpalladium intermediates, which are formed through the oxidative addition of vinyl–X (X = halide or trifluoromethanesulfonate) to Pd^0 or through the transmetalation of vinylmetallic reagents to the Pd^{II} center.[5] Classically, the alkenes used to capture the vinylpalladium intermediates are restricted to activated olefins, such as styrene or α,β-unsaturated carbonyls [Eq. (1)].[4b–d]



R^1 = Ar, Alkyl; R^2 = Alkoxyl, Alkyl, Ar; R^3 = electron-withdrawing group, Ar; R^4 = Ar, Alkyl

One of the main challenges in this type of reaction is the highly selective β-H elimination on the alkyl–Pd intermediate **I** if the alkenes without a significant electronic difference at the two olefinic sites are used as substrates.[6–8] Our group reported the oxidative cross-coupling reaction between alkynes and allylic alcohols to synthesize β-alkenyl ketones through selective β-H elimination.[4a] By means of the chelate effect, we envisioned that coordinating groups in appropriately remote sites could play the bidentate role to suppress the β-H elimination.[9] Because of our persistent attention on the Pd-catalyzed alkynes–alkenes cross-coupling reaction,[4,10] we herein report the hydroxyl group-assisted lactonization of homoallylic alcohols [Eq. (2)].[11,12]

The α-methylene-γ-lactone skeleton is an important moiety in natural products and demonstrates potential biological activities, such as andrographolide and some sesquiterpene lactones.[13] And it constitutes approximately 10% of the >30000 known natural products.[14e] Examples of hydroxyl group-containing biologically active α-methylene-γ-lactones, such as paeonilactone B, parthenolide, and hispitolide A (their functions include pain relief, anti-inflammatory, anticancer, and antiviral activities), are shown in Figure 1.[14] Thus, it is important

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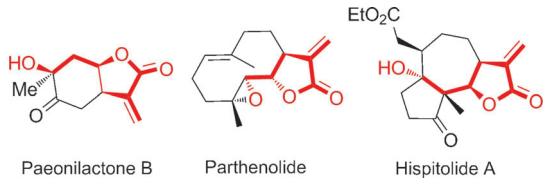


Figure 1. Examples for hydroxyl group-containing biologically active α-methylene-γ-lactones.

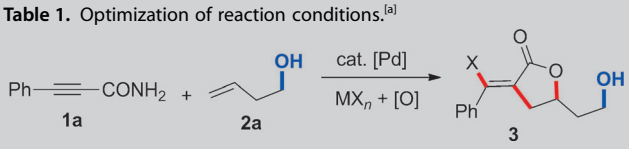
to design and synthesize multifunctional α-methylene-γ-lactones.

Results and Discussion

The coupling reaction between 3-phenylpropiolamide (**1a**) and homoallylic alcohol (**2a**) was chosen as a model reaction for optimization studies (Table 1). We initially examined the feasibility of this model reaction with oxygen as the oxidant, which was previously established for the alkenes–alkynes coupling reaction.[4c–e,9a,d–e] The reaction of **1a** with 1.2 equiv. of **2a** performed in CH_3CN at room temperature in the presence of 5 mol% of $PdCl_2$ and 8 equiv. of LiCl gave the desired product **3a** in 34% yield with the increase in oxygen pressure to 8 atm (1 atm = 101.3 kPa; entries 1–3).[15] Thus, the screening of the solvent for this transformation revealed that acetonitrile was the most suitable solvent (entries 4 and 5). Further investigation revealed that $CuCl_2{\cdot}2H_2O$ significantly increases the yield of the desired product (entries 6–8). The use of 5 mol% of $Pd(OAc)_2$ slightly increases the yield of the product (entries 9 and 10). The blank experiment showed that no α-methylene-γ-lactone appeared in the absence of the Pd catalyst (entry 11). Inspired by the result of the transformation initiated by chloropalladation, we investigated similar transformations with bromonium ion and acetoxyl group as nucleophiles to initiate the trans-selective Kaneda reaction of **1a**.[4a,e] Unfortunately, those nucleophiles were not compatible with this transformation (entries 12–14).

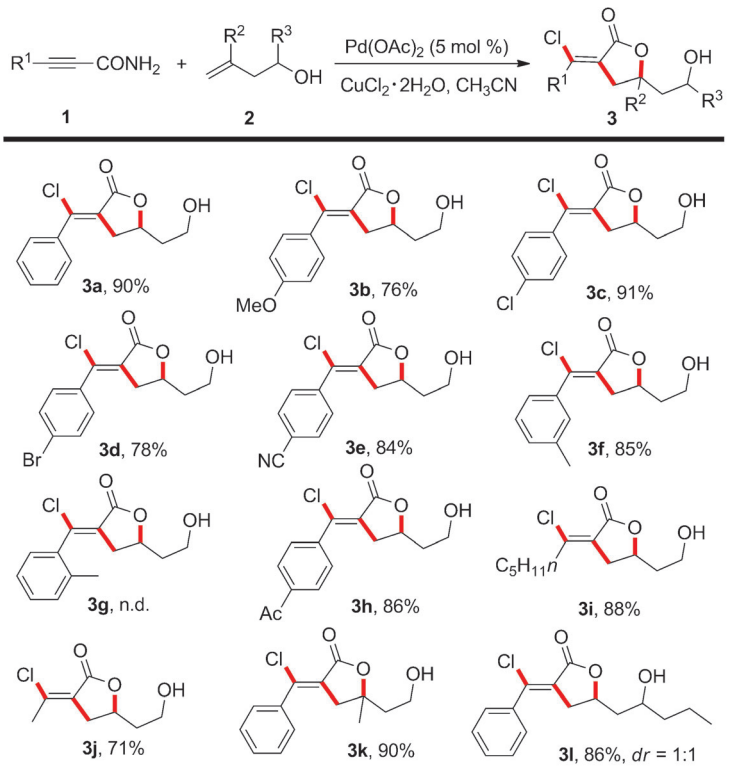
We began our study with the homoallylic alcohol with dual function as regulating group and substrate and tested the Pd-catalyzed lactonization. Notably, the alkenes without the hydroxyl group yielded only the β-H elimination product (see below for details), which indicated that the absence of the chelate effect disfavored the cycloaddition. As shown in Scheme 1, this reaction could be applied to various alkynamides. A series of *para*-substituted 3-phenylpropiolamides, with either electron-donating (**3b**) or electron-withdrawing groups (**3e** and **h**), could be converted to the corresponding α-methylene-γ-lactones in good to excellent yields. The electron-donating group decreased the activity of nucleopalladation by making the C–C triple bond more electron-rich. Halo substituents, such as Cl and Br, were well tolerated, which provided the possibility for fur-

Table 1. Optimization of reaction conditions.[a]



Entry	Pd catalyst	Additive/oxidant	Solvent	Yield[b] [%]
1	$PdCl_2$	LiCl/1 atm O_2	CH_3CN	<5
2	$PdCl_2$	LiCl/4 atm O_2	CH_3CN	12
3	$PdCl_2$	LiCl/8 atm O_2	CH_3CN	34
4	$PdCl_2$	LiCl/8 atm O_2	HOAc	–
5	$PdCl_2$	LiCl/8 atm O_2	1,4-dioxane	17
6[c]	$PdCl_2$	LiCl/$CuCl_2{\cdot}2H_2O$	CH_3CN	37
7[d]	$PdCl_2$	LiCl/$CuCl_2{\cdot}2H_2O$	CH_3CN	67
8[e]	$PdCl_2$	$CuCl_2{\cdot}2H_2O$	CH_3CN	83 (80)
9[e]	$Pd(OAc)_2$	$CuCl_2{\cdot}2H_2O$	CH_3CN	92 (90)
10[e]	$Pd(CH_3CN)_2Cl_2$	$CuCl_2{\cdot}2H_2O$	CH_3CN	88
11[e]	–	$CuCl_2{\cdot}2H_2O$	CH_3CN	n.d.
12[e]	$Pd(OAc)_2$	$CuBr_2$	CH_3CN	18
13[e]	$Pd(OAc)_2$	$Cu(OAc)_2$	CH_3CN	n.d.
14[e]	$Pd(OAc)_2$	$Cu(OAc)_2$	HOAc	n.d.

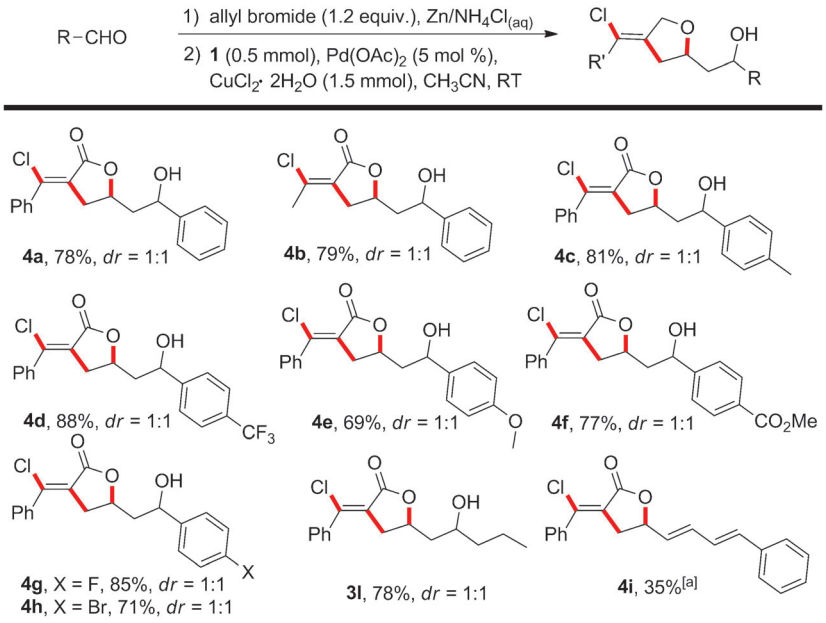
[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), Pd catalyst (5 mol%), additive (4 mmol) in the solvent (0.5 mL) at RT for 12 h; [b] Yield was determined from GC analysis with dodecane as the internal standard and the number in parentheses was isolated yield. [c] LiCl (4 mmol) and $CuCl_2{\cdot}2H_2O$ (0.5 mmol); [d] LiCl (4 mmol) and $CuCl_2{\cdot}2H_2O$ (1 mmol); [e] Cu salt (1.5 mmol).



Scheme 1. Substrate scope of alkynamides for the Pd-catalyzed lactonization of homoallylic alcohols. The reactions were performed at RT and by using homoallylic alcohol (0.6 mmol), alkynamide (0.5 mmol), $Pd(OAc)_2$ (5 mol%), $CuCl_2{\cdot}2H_2O$ (1.5 mmol), and acetonitrile (0.5 mL) for 12 h. *dr* = Diastereomeric ratio.

ther functionalization (**3c** and **d**). In contrast to the *para*- and *meta*-substituted alkynamides, the *ortho*-substituted material could not be converted to the products (**3f** and **g**). With use of but-2-ynamide and oct-2-ynamide in this transformation, the corresponding products could be obtained in good yields (**3i** and **j**). 3-Methylbut-3-en-1-ol and hept-1-en-4-ol were both suitable for this transformation (**3k** and **l**).

Homoallylic alcohols are versatile synthetic intermediates, as exemplified by their application toward natural product synthesis.[16] Various derivatives can be obtained with stoichiometric metals (e.g., Mn, Mg, Zn, Sn, In, and Cr) under Barbier-type conditions.[17] Thus, we used aldehyde (0.7 mmol), 2 equiv. of Zn, and 1.2 equiv. of allyl bromide in 3 mL of the THF/NH_4Cl solvent (1:3 v/v) at room temperature for 12 h to afford homoallylic alcohols. Upon the completion of the reaction, crude products, extracted with ethyl ether, were subjected to the Pd-catalyzed lactonization of homoallylic alcohols with alkynamides without further purification (Scheme 2). First, a series of homoallylic secondary alcohols were examined in the reaction system. The functional group compatibility of homoallylic alcohols was excellent, which provided the possibility for further functionalization. For example, methoxyl, halogen, and ester groups were tolerated in this transformation (**4e–h**). Both electron-donating and electron-withdrawing group substituted 1-phenylbut-3-en-1-ols could be transformed to the devised α-methylene-γ-lactones in good yields (**4c** and **d**). The aliphatic aldehyde was also applicable to this system (**3l**). With use of cinnamic aldehyde as the substrate (**4i**), the dehydrated product was obtained instead of the desired product.



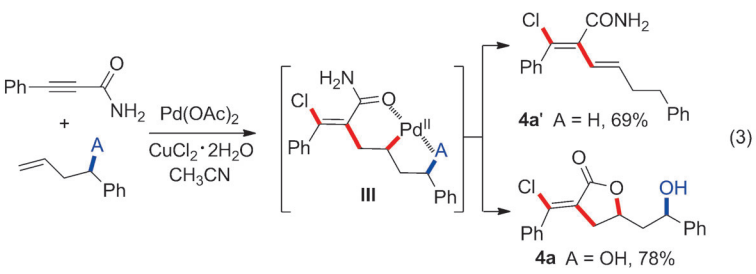
Scheme 2. Substrate scope of the lactonization of homoallylic alcohols with alkynamides. The reactions were performed at RT by using aldehyde (0.7 mmol), allyl bromide (1.2 equiv.), Zn (2 equiv.), and THF/NH_4Cl (1:3 v/v, 3 mL) for 12 h. The crude products were extracted with ethyl ether. The terminal alkynamide (0.5 mmol), $Pd(OAc)_2$ (5 mol%), $CuCl_2{\cdot}2H_2O$ (1.5 mmol, and acetonitrile (0.5 mL) were added overnight at RT. [a] Cinnamic aldehyde was used as the substrate.

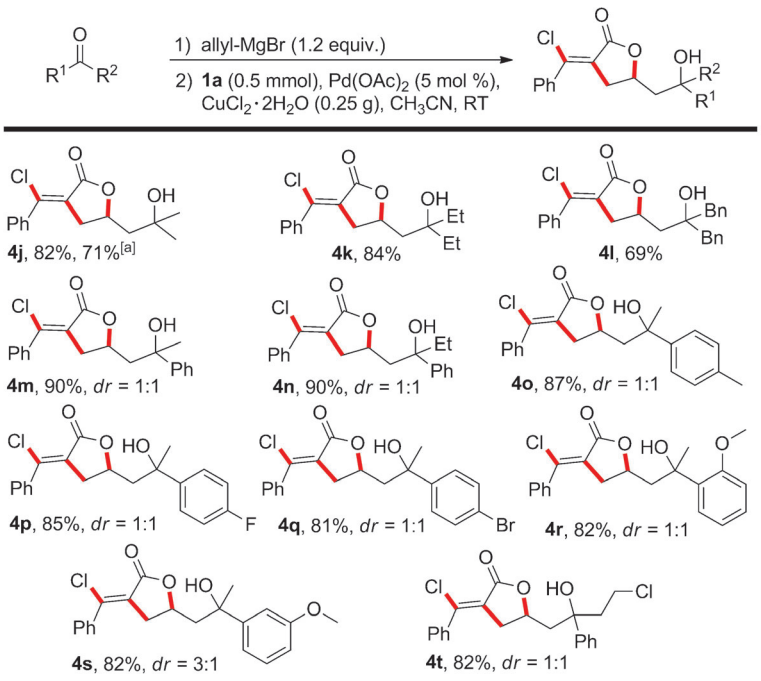
Subsequently, the scope of the reaction was expanded to a range of homoallylic tertiary alcohols. Similarly, homoallylic tertiary alcohols were easily synthesized through the combination of allyl–MgBr and ketone at 0 °C and directly subjected to the next step of the reaction after extraction with ethyl ether (Scheme 3). Aliphatic ketones could be converted to the desired products in high yields (Scheme 3, **4j** and **k**). With the extension of the reaction scale to 3 mmol scale, the isolated yield of **4j** was 71%. Dibenzylketone was also a suitable substrate (**4l**). A series of benzophenones could be converted to the corresponding α-methylene-γ-lactones in good to excellent yields (**4m–s**). β-Chloro ketone also underwent the transformation in good yield (**4t**). Notably, the alkyl halide and aryl halide were both tolerant in this reaction (**4q** and **t**).

The transformations using cyclic ketones as substrates afforded the corresponding α-methylene-γ-lactone products, even though in various yields (Scheme 4). In contrast to cyclobutanone and cyclooctanone, the yields of the corresponding products were much higher than those of cyclohexanone and cycloheptanone used as substrates. It could be due to the ring tension. Furthermore, dihydro-2*H*-pyran-4(3*H*)-one and 1,4-dioxaspiro[4.5]decan-8-one led to the formation of the desired products **4y** and **z** only in moderate yields. Finally, the isolated yield for the reaction of 2-adamantanone was 74%. The structure of **4bc** was confirmed by X-ray crystallographic analysis (see the Supporting Information for details).

To further confirm that the chelate effect of the hydroxyl group towards the Pd^{II} center was crucial for the Pd-catalyzed lactonization of olefins, a comparative experiment was performed [Eq. (3)].[18]

As expected, but-3-enylbenzene (A = H), without a coordinating group, was transformed to the β-H elimination product **4a'**

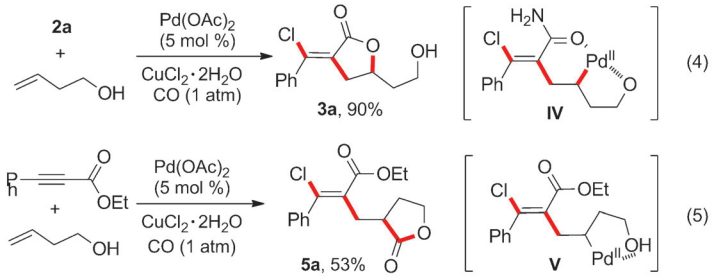




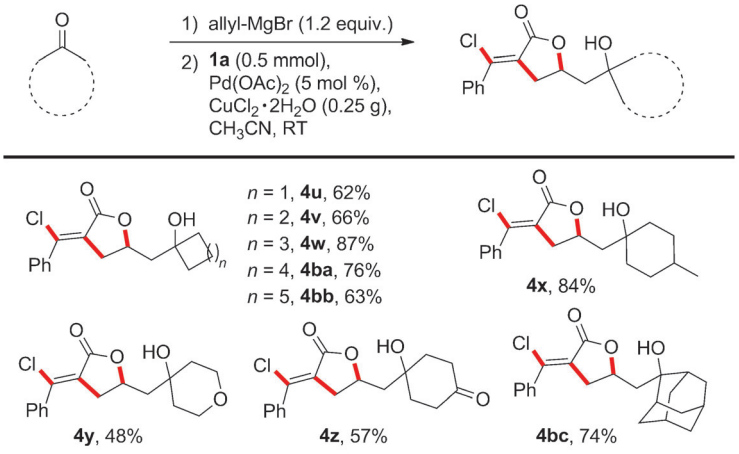
Scheme 3. Scope of tertiary homoallylic alcohols for Pd-catalyzed lactonization reactions. Reaction conditions: $T=0\,^{\circ}C$, ketone (0.7 mmol), allyl–MgBr (1.2 equiv.), and THF (2 mL), $t=3$ h. The crude products were extracted with ethyl ether. Alkynamide (0.5 mmol), $Pd(OAc)_2$ (5 mol%), $CuCl_2{\cdot}2H_2O$ (0.25 g), and acetonitrile (0.5 mL) were added overnight at RT. [a] Ketone (5 mmol) and alkynamide (3 mmol) were used.

and a trace of the lactonization product could be detected. As mentioned above, with use of the homoallylic alcohol as the substrate, the corresponding α-methylene-γ-lactone **4a** could be isolated in 78% yield. And it clearly demonstrated that the chelate effect of the hydroxyl group could completely suppress the β-H elimination.

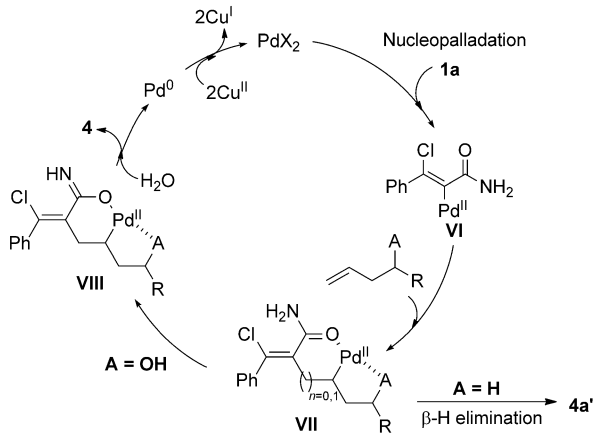
On the basis of our previous studies on the halopalladation of alkynoates,[4] we believed that alkynamides also play a key role in those difunctionalization reactions. Thus, we used **2a** and ethyl 3-phenylpropiolate and reacted each of them with the homoallylic alcohol under 1 atm CO under the standard reaction conditions [Eqs. (4) and (5)]. The α-methylene-γ-lactone **3a** was obtained without a decrease in the yield [Eq. (4)]. CO-insertion product **5a** was isolated in 53% yield in the reaction of 3-phenylpropiolate and homoallylic alcohol under 1 atm CO.[19] The amide in the alkynamide accelerated the formation of the $C(sp^3)$–O bond.[20] And the $C(sp^3)$–O bond formation was faster than the insertion of CO to the alkyl–Pd^{II} intermediate **IV** [Eq. (5)].



On the basis of the above results, a possible mechanism for the hydroxyl group-assisted Pd-catalyzed lactonization of homoallylic alcohols with alkynamides is proposed (Scheme 5). This reaction was initiated by the halopalladation of alkynamides, which afforded vinylpalladium intermediate **VI**. Subsequently, intermediate **VI** was captured by the alkene via migratory insertion to produce intermediate **VII**. If the alkene did not contain a coordinating group (but-3-enylbenzene, A = H), intermediate **VII** would undergo β-H elimination. The amide of the alkynamide cooperated with the hydroxyl group in the olefin to chelate Pd. The coordinative saturation of the metal center represents an established strategy to suppress β-H elimination.[9,21] With the coordinating groups in the homoallylic site, the five- to six-membered ring palladacycle intermediate **VII** transformed to intermediate **VIII** by isomerization, followed by $C(sp^3)$–O bond formation to give five-membered ring based lactones. Finally, the Pd^{II} active species was regenerated through the oxidation of Cu^{2+}.



Scheme 4. Scope of tertiary homoallylic alcohols for Pd-catalyzed lactonization reactions. See the caption of Scheme 3 for the reaction conditions.



Scheme 5. Possible reaction mechanism.

Conclusions

We have reported a mild and efficient Pd^{II}-catalyzed lactonization of homoallylic alcohols with alkynamides assisted by the synergistic effects of the two coupling partners. The hydroxyl group in olefins plays dual roles not only as a helping hand to stabilize the metal center through the chelate effect but also as a key fragment in organic molecules. This new strategy is applied to construct a bioactive α-methylene-γ-lactone skeleton that contains multifunctionalized groups that is further converted synthetically. We believe that this new and convenient strategy represents a significant step forward for the remote group-assisted difunctionalization of alkenes in Pd chemistry.

Experimental Section

General

All reactions were performed in 10 mL tubes. TLC was performed with commercially prepared 100–400 mesh silica gel plates (GF254), and visualization was effected at 254 nm. All reagents were purchased as reagent grade and used without further purification. The ^1H NMR spectra were recorded at 400 MHz with TMS as an internal standard, and the ^{13}C NMR spectra were recorded at 100 MHz with $CDCl_3$ by using a BRUKER DRX-400 spectrometer . The chemical shifts were referenced to signals at 7.24 and 77.0 ppm, respectively. The IR spectra were obtained either as KBr pellets or as liquid films between two KBr pellets by using a Bruker Vector 22 spectrometer.

Typical method for the synthesis of α-methylene-γ-lactone

First, a mixture of the alkynamide (0.5 mmol), homoallylic alcohol (0.6 mmol), $Pd(OAc)_2$ (5 mol%), $CuCl_2{\cdot}2H_2O$ (0.25 g), and CH_3CN (0.5 mL) was added to a dried Schlenk tube, and the solution was stirred at RT for the desired reaction time. Then, the mixture was stirred at RT for 12 h. Upon the completion of the reaction, the reaction mixture was washed with saturated aqueous NaCl solution (2×10 mL) and then extracted with EtOAc (2×10 mL). Finally, the organic layers were combined, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was separated by using column chromatography to obtain the pure products **3a–l** and **4a–bc**.

Acknowledgements

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Keywords: alkenes · C–O bond formation · lactonization · palladium · elimination

[1] a) G. Zeni, R. C. Larock, *Chem. Rev.* **2006**, *106*, 4644; b) G. Zeni, R. C. Larock, *Chem. Rev.* **2004**, *104*, 2285; c) N. P. Patil, Y. Yamamoto, *Chem. Rev.* **2008**, *108*, 3395; d) E. Negishi, C. Coperet, S. Ma, S. Y. Liou, F. Liu, *Chem. Rev.* **1996**, *96*, 365.

[2] a) R. I. McDonald, G. Liu, S. S. Stahl, *Chem. Rev.* **2011**, *111*, 2981; b) A. Minatti, K. Muñiz, *Chem. Soc. Rev.* **2007**, *36*, 1142; c) J. A. Keith, P. M. Henry, *Angew. Chem.* **2009**, *121*, 9200; *Angew. Chem. Int. Ed.* **2009**, *48*, 9038; d) P. Zhao, D. Chen, G. Song, K. Han, X. Li, *J. Org. Chem.* **2012**, *77*, 1579.

[3] a) K. Kaneda, T. Uchiyama, Y. Fujiwara, T. Imanaka, S. Teranishi, *J. Org. Chem.* **1979**, *44*, 55; b) L. Zhao, X. Lu, *Angew. Chem.* **2002**, *114*, 4519; *Angew. Chem. Int. Ed.* **2002**, *41*, 4343; c) G. Zhu, X. Lu, *Organometallics* **1995**, *14*, 4899; d) G. Yin, G. Liu, *Angew. Chem.* **2008**, *120*, 5522; *Angew. Chem. Int. Ed.* **2008**, *47*, 5442; e) Y. Li, K. J. Jardine, R. Tan, D. Song, V. Dong, *Angew. Chem.* **2009**, *121*, 9870; *Angew. Chem. Int. Ed.* **2009**, *48*, 9690; f) Q. Zhang, X. Lu, *J. Am. Chem. Soc.* **2000**, *122*, 7604; g) Q. Zhang, X. Lu, X. Han, *J. Org. Chem.* **2001**, *66*, 7676; h) W. Wu, A. Kong, X. Lu, *J. Org. Chem.* **2006**, *71*, 3854; i) L. L. Welbes, T. W. Lyons, K. A. Cychosz, M. S. Sanford, *J. Am. Chem. Soc.* **2007**, *129*, 5836; j) X. Tong, M. Beller, M. K. Tse, *J. Am. Chem. Soc.* **2007**, *129*, 4906; k) C. Feng, T.-P. Lop, *J. Am. Chem. Soc.* **2010**, *132*, 17710.

[4] a) Y. Wen, L. Huang, H. Jiang, H. Chen, *J. Org. Chem.* **2012**, *77*, 2029; b) L. Huang, Q. Wang, X. Liu, H. Jiang, *Angew. Chem.* **2012**, *124*, 5794; *Angew. Chem. Int. Ed.* **2012**, *51*, 5696; c) P. Zhou, L. Huang, H. Jiang, A. Wang, X. Li, *J. Org. Chem.* **2010**, *75*, 8279; d) P. Zhou, M. Zheng, H. Jiang, X. Li, C. Qi, *J. Org. Chem.* **2011**, *76*, 4759; e) P. Zhou, H. Jiang, L. Huang, *Chem. Commun.* **2011**, *47*, 1003; f) J. Huang, L. Zhou, H. Jiang, *Angew. Chem.* **2006**, *118*, 1979; *Angew. Chem. Int. Ed.* **2006**, *45*, 1945; g) H. Jiang, C. Qiao, W. Liu, *Chem. Eur. J.* **2010**, *16*, 10968; h) H. Jiang, X. Liu, L. Zhou, *Chem. Eur. J.* **2008**, *14*, 11305.

[5] Selected examples for obtaining vinyl–PdX intermediates: a) C. Zheng, D. Wang, S. S. Stahl, *J. Am. Chem. Soc.* **2012**, *134*, 16496; b) P. Pinho, A. J. Minnaard, B. L. Feringa, *Org. Lett.* **2003**, *5*, 259.

[6] a) E. W. Werner, T.-S. Mei, A. J. Burckle, M. S. Sigman, *Science* **2012**, *338*, 1455; b) G. D. Daves, A. Hallberg, *Chem. Rev.* **1989**, *89*, 1433; c) W. Cabri, I. Candiani, A. Bedeschi, R. Santi, *J. Org. Chem.* **1990**, *55*, 3654; d) K. S. A. Vallin, M. Larhed, A. Hallberg, *J. Org. Chem.* **2001**, *66*, 4340; e) J. Ruan, J. Xiao, *Acc. Chem. Res.* **2011**, *44*, 614; f) R. Matsubara, A. C. Gutierrez, T. F. Jamison, *J. Am. Chem. Soc.* **2011**, *133*, 19020; g) D. Pan, A. Chen, Y. Su, W. Zhou, S. Li, W. Jia, J. Xiao, Q. Liu, L. Zhang, N. Jiao, *Angew. Chem.* **2008**, *120*, 4807; *Angew. Chem. Int. Ed.* **2008**, *47*, 4729; h) J. Ruan, J. A. Iggo, N. G. Berry, J. Xiao, *J. Am. Chem. Soc.* **2010**, *132*, 16689.

[7] a) Y. Su, N. Jiao, *Org. Lett.* **2009**, *11*, 2980; b) P. Hu, J. Kan, W. Su, M. Hong, *Org. Lett.* **2009**, *11*, 2341; c) C. Zhu, J. R. Falck, *Org. Lett.* **2011**, *13*, 1214; d) C. Zhu, J. R. Falck, *Angew. Chem.* **2011**, *123*, 6756; *Angew. Chem. Int. Ed.* **2011**, *50*, 6626; e) M. Chen, J. Wang, Z. Chai, C. You, A. Lei, *Adv. Synth. Catal.* **2012**, *354*, 341; f) A. S. Tsai, M. Brasse, R. G. Bergman, J. A. Ellman, *Org. Lett.* **2011**, *13*, 540.

[8] a) E. W. Werner, M. S. Sigman, *J. Am. Chem. Soc.* **2010**, *132*, 13981; b) E. W. Werner, M. S. Sigman, *J. Am. Chem. Soc.* **2011**, *133*, 9692; c) J. H.

Delcamp, M. C. White, *J. Am. Chem. Soc.* **2006**, *128*, 15076; d) J. H. Delcamp, A. P. Brucks, C. M. White, *J. Am. Chem. Soc.* **2008**, *130*, 11270.

[9] a) S. Rakshit, C. Grohmann, T. Besset, F. Glorius, *J. Am. Chem. Soc.* **2011**, *133*, 2350; b) H. Wang, F. Glorius, *Angew. Chem.* **2012**, *124*, 7430; *Angew. Chem. Int. Ed.* **2012**, *51*, 7318; c) N. Guimond, S. I. Gorelsky, K. Fagnou, *J. Am. Chem. Soc.* **2011**, *133*, 6449; d) B. J. Burke, L. E. Overman, *J. Am. Chem. Soc.* **2004**, *126*, 16820; e) E. M. Beccalli, E. Borsini, S. Brenna, S. Galli, M. Rigamonti, G. Broggini, *Chem. Eur. J.* **2010**, *16*, 1670.

[10] a) W. Wu, H. Jiang, *Acc. Chem. Res.* **2012**, *45*, 1736; b) Y. Li, X. Liu, H. Jiang, *Angew. Chem.* **2011**, *123*, 6465; *Angew. Chem. Int. Ed.* **2011**, *50*, 6341; c) Y. Wen, L. Huang, H. Jiang, *J. Org. Chem.* **2012**, *77*, 5418; d) Y. Shen, H. Jiang, Z. Chen, *J. Org. Chem.* **2010**, *75*, 1321; e) W. Wu, H. Jiang, Y. Gao, H. Huang, W. Zeng, D. Cao, *Chem. Commun.* **2012**, *48*, 10340.

[11] Examples for the Pd-catalyzed oxidative difunctionalization of alkenes: a) A. Wang, H. Jiang, H. Chen, *J. Am. Chem. Soc.* **2009**, *131*, 3846; b) M. K. Zhu, J. F. Zhao, T. P. Lop, *J. Am. Chem. Soc.* **2010**, *132*, 6284; c) A. Iglesias, E. G. Perez, K. Muniz, *Angew. Chem.* **2010**, *122*, 8286; *Angew. Chem. Int. Ed.* **2010**, *49*, 8109; d) G. L. J. Bar, G. C. Lloyd-jones, K. I. Booker-Milburn, *J. Am. Chem. Soc.* **2005**, *127*, 7308; e) D. Kalyani, A. D. Satterfield, M. S. Sanford, *J. Am. Chem. Soc.* **2010**, *132*, 8419; f) B. Zhao, H. Du, S. Cui, Y. Shi, *J. Am. Chem. Soc.* **2010**, *132*, 3523; g) G. Broggini, V. Barbera, E. M. Beccalli, U. Chiacchio, A. Fasana, S. Galli, S. Gazzola, *Adv. Synth. Catal.* **2013**, *355*, 1640; h) P. Chávez, J. Kirsch, J. Streuff, K. Muñiz, *J. Org. Chem.* **2012**, *77*, 1922; i) G. Yin, T. Wu, G. Liu, *Chem. Eur. J.* **2012**, *18*, 451; j) Y. Liu, R. Song, C. Wu, L. Gong, M. Hu, Z. Wang, Y. Xie, J. Li, *Adv. Synth. Catal.* **2012**, *354*, 347; k) C. Martínez, K. Muñiz, *Angew. Chem.* **2012**, *124*, 7138; *Angew. Chem. Int. Ed.* **2012**, *51*, 7031.

[12] Examples for the Wolfe-type difunctionalization of alkenes: a) N. R. Babij, J. P. Wolfe, *Angew. Chem.* **2013**, *125*, 9417; *Angew. Chem. Int. Ed.* **2013**, *52*, 9247; b) B. A. Hopkins, J. P. Wolfe, *Angew. Chem.* **2012**, *124*, 10024; *Angew. Chem. Int. Ed.* **2012**, *51*, 9886; c) N. R. Babij, J. P. Wolfe, *Angew. Chem.* **2012**, *124*, 4204; *Angew. Chem. Int. Ed.* **2012**, *51*, 4128; d) A. F. Ward, Y. Xu, J. P. Wolfe, *Chem. Commun.* **2012**, *48*, 609; e) J. P. Wolfe, M. A. Rossi, *J. Am. Chem. Soc.* **2004**, *126*, 1620; f) R. Lira, J. P. Wolfe, *J. Am. Chem. Soc.* **2004**, *126*, 13906.

[13] a) L. Chen, H. Zhu, R. Wang, K. Zhou, Y. Jing, F. J. Qiu, *Nat. Prod.* **2008**, *71*, 825; b) C. Mang, S. Jakupovic, S. Schunk, H. Ambrosi, O. Schwarz, J. Jakupovic, *J. Comb. Chem.* **2006**, *8*, 268; c) A. J. Reynolds, A. J. Scott, C. I. Turner, M. S. Sherburn, *J. Am. Chem. Soc.* **2003**, *125*, 12108.

[14] a) R. R. A. Kitson, A. Millemaggi, R. J. Taylor, *Angew. Chem.* **2009**, *121*, 9590; *Angew. Chem. Int. Ed.* **2009**, *48*, 9426; b) M. G. Edwards, M. N. Kenworthy, R. R. A. Kitson, M. S. Scott, A. C. Whitwood, R. J. Taylor, *Angew. Chem.* **2008**, *120*, 1961; *Angew. Chem. Int. Ed.* **2008**, *47*, 1935; c) M. G. Edwards, M. N. Kenworthy, R. R. A. Kitson, A. Perry, M. S. Scott, A. C. Whitwood, R. J. Taylor, *Eur. J. Org. Chem.* **2008**, 4769; d) A. Albrecht, L. Albrecht, T. Janecki, *Eur. J. Org. Chem.* **2011**, 2747; e) T. P. Montgomery, A. Hassan, B. Y. Park, M. J. Krische, *J. Am. Chem. Soc.* **2012**, *134*, 11100; f) H. M. R. Hoffmann, J. Rabe, *Angew. Chem.* **1985**, *97*, 96; *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 94.

[15] a) A. Wang, H. Jiang, *J. Am. Chem. Soc.* **2008**, *130*, 5030; b) A. Wang, H. Jiang, X. Li, *J. Org. Chem.* **2011**, *76*, 6958; c) A. Wang, H. Jiang, *J. Org. Chem.* **2010**, *75*, 2321.

[16] a) K. C. Nicolaou, D. W. Kim, R. Baati, *Angew. Chem.* **2002**, *114*, 3853; *Angew. Chem. Int. Ed.* **2002**, *41*, 3701; b) K. P. Hornberger, C. L. Hamblet, J. L. Leighton, *J. Am. Chem. Soc.* **2000**, *122*, 12894; c) F. X. Felpin, J. L. Lebreton, *J. Org. Chem.* **2002**, *67*, 9192.

[17] a) L. Zhao, D. L. Burnell, *Tetrahedron Lett.* **2006**, *47*, 3291; b) J. J. Miller, M. S. Sigman, *J. Am. Chem. Soc.* **2007**, *129*, 2752; c) J. H. Dam, P. Fristrup, R. Madsen, *J. Org. Chem.* **2008**, *73*, 3228.

[18] The lactonization of olefins in Ref.[4a] is restricted to the activated olefins, such as styrene or α,β-unsaturated carbonyls. The Pd–alkyl species may be stabilized through the formation of π-benzyl or oxa-π-allyl species intermediates; a) J. E. Baeckvall, J. E. Nystroem, R. E. Nordberg, *J. Am. Chem. Soc.* **1985**, *107*, 3676; b) C. Liu, S. Tang, L. Zheng, D. Liu, H. Zhang, A. Lei, *Angew. Chem.* **2012**, *124*, 5760; *Angew. Chem. Int. Ed.* **2012**, *51*, 5662; c) L. Liao, R. Jana, K. B. Urkalan, M. S. Sigman, *J. Am. Chem. Soc.* **2011**, *133*, 5784; d) Q. Peng, H. Han, X. Zhang, Y.-D. Wu, *J. Org. Chem.* **2012**, *77*, 7487.

[19] a) Y. Tamaru, *J. Org. Chem.* **1991**, *56*, 1099; b) M. F. Semmelhack, N. Zhang, *J. Org. Chem.* **1989**, *54*, 4485; c) M. M. Cormick, R. Monahan, III., J. Soria, D. Goldsmith, D. Liotta, *J. Org. Chem.* **1989**, *54*, 4487.

[20] Examples for amide-assisted bond formation: a) M. H. Larraufie, G. Maestri, A. Beaume, E. Derat, C. Ollivier, L. Fensterbank, C. Courillon, E. Lacôte, M. Catellani, M. Malacria, *Angew. Chem.* **2011**, *123*, 12461; *Angew. Chem. Int. Ed.* **2011**, *50*, 12253; b) Y. Kita, Y. Nishii, T. Higuchi, K. Mashima, *Angew. Chem.* **2012**, *124*, 5821; *Angew. Chem. Int. Ed.* **2012**, *51*, 5723; c) Y. J. Park, J. W. Park, C. H. Jun, *Acc. Chem. Res.* **2008**, *41*, 222; d) O. Daugulis, H. Q. Do, D. Shabashov, *Acc. Chem. Res.* **2009**, *42*, 1074.

[21] J. Hartwig, *Organotransition Metal Chemistry-From Bonding to Catalysis*, University Science Books, Sausolito, CA, **2010**.

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