

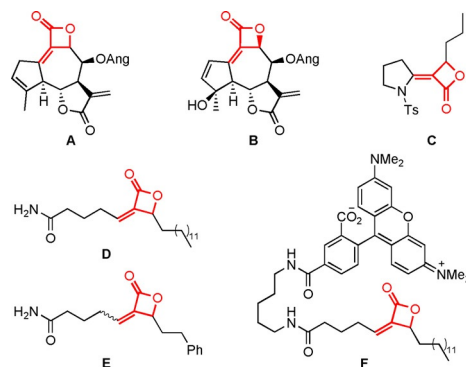
## Carbonylation

Ligand-Controlled Palladium-Catalyzed Carbonylation of Alkynols: Highly Selective Synthesis of  $\alpha$ -Methylene- $\beta$ -LactonesYao Ge<sup>+</sup>, Fei Ye<sup>+</sup>, Jiawang Liu, Ji Yang, Anke Spannenberg, Haijun Jiao, Ralf Jackstell, and Matthias Beller\*

**Abstract:** The first general and regioselective Pd-catalyzed cyclocarbonylation to give  $\alpha$ -methylene- $\beta$ -lactones is reported. Key to the success for this process is the use of a specific sterically demanding phosphine ligand based on *N*-arylated imidazole (**LII**) in the presence of Pd(MeCN)<sub>2</sub>Cl<sub>2</sub> as pre-catalyst. A variety of easily available alkynols provide under additive-free conditions the corresponding  $\alpha$ -methylene- $\beta$ -lactones in moderate to good yields with excellent regio- and diastereoselectivity. The applicability of this novel methodology is showcased by the direct carbonylation of biologically active molecules including natural products.

## Introduction

$\alpha$ -Alkylidene- $\beta$ -lactones have emerged as important synthetic targets due to their occurrence in a variety of natural compounds and biologically active molecules (Scheme 1).<sup>[1]</sup> For example, lactones **A**<sup>[1a-c]</sup> and **B**<sup>[1d]</sup> were separated from *Grazilia* species and *Disynaphia multicrenulata*. Moreover, **C** exhibits promising inhibitory activities against certain fungal pathogens.<sup>[1e]</sup> In addition,  $\alpha$ -alkylidene- $\beta$ -lactones **D** and **E** were studied as potent and selective inhibitors for serine hydrolase ABHD16A.<sup>[1f-g]</sup> Following this work, **F** also served as a sensitive probe for detecting ABHD16A activity in mouse brain membrane lysates.<sup>[1g]</sup> Apart from these medicinal applications, specifically  $\alpha$ -methylene- $\beta$ -lactones attracted interest in material sciences; for example, well-defined copolymers with controllable molecular weight and narrow polydispersity were prepared by ring-opening poly-



**Scheme 1.** Natural compounds and biologically active molecules with  $\alpha$ -methylene- $\beta$ -lactone skeleton.

merization. Here, the vinylidene groups of the lactones could be further functionalized, producing well-defined blocks with designable segments.<sup>[2]</sup> In organic chemistry, the high degree of functional groups in a compact manner allows diverse synthetic utilizations and makes this class of compounds interesting building blocks.<sup>[3]</sup> More specifically, owing to their inherent strain in the four-membered ring, they readily undergo ring opening reactions with a wide range of nucleophiles by either acyl C–O or alkyl C–O bond cleavage.<sup>[3f,g]</sup> Besides the usual electrophilic sites of the carbonyl and oxetane carbon atoms contained in  $\beta$ -lactones, Michael-type additions of nucleophiles and radicals at the methylene carbon atom are feasible<sup>[3h]</sup> and offer attractive possibilities for preparative purposes. Notably, the carboxy-activated *exo*-methylene group serves as reactive dienophile, while the  $\alpha,\beta$ -unsaturated carbonyl moiety promises potential as heterodiene for [4+2]-cycloadditions.<sup>[3e]</sup> Moreover,  $\alpha$ -methylene- $\beta$ -lactones constitute convenient allene equivalents as demonstrated in the decarboxylation to allenes on thermolysis.<sup>[3b,e]</sup>

Considering the value of  $\alpha$ -alkylidene- $\beta$ -lactones in organic synthesis, significant interest in their preparation exists.<sup>[4]</sup> Because of the dense functionalization, mainly special synthetic methods have been developed for this class of compounds including [2+2]-cycloaddition of ketenes,<sup>[3n,4a-c]</sup> lactonization of  $\beta$ -hydroxycarboxylic acids or derivatives,<sup>[3d,4d-g]</sup> elimination of selenoxide from  $\alpha$ -methyl-substituted lactones,<sup>[3b]</sup> and deoxygenation of  $\beta$ -peroxylactones.<sup>[3f,4g-h]</sup>

More recently, also rhodium- or palladium-catalyzed carbonylation of alkynols have been disclosed.<sup>[5]</sup> Thus,  $\alpha$ -(triorganosilyl)-methylene- $\beta$ -lactones (Scheme 2 a),<sup>[5a,b]</sup>

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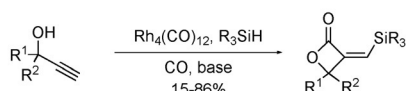
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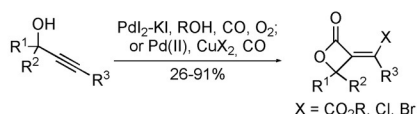
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a) Rh-catalyzed silylcarbocyclisation



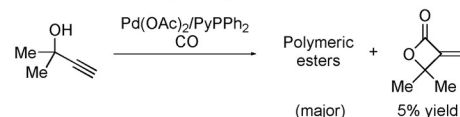
I. Matsuda *et al.*  
L. A. Aronica *et al.*

b) Oxidative carbonylation of alkynols



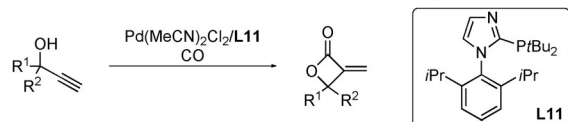
B. Gabriele *et al.*  
S. Ma *et al.*

c) Carbonylation of 1-methyl-2-butyne-1-ol



C. S. Consorti *et al.*

d) This work: general process for the synthesis of α-methylene-β-lactones



- Additive free conditions
- Novel catalyst system
- Broad substrate scope
- Excellent selectivity
- Late-stage functionalization
- Atom-efficient process to α-methylene-β-lactones

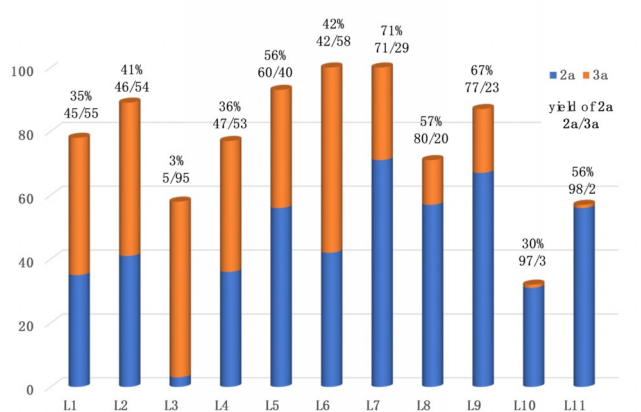
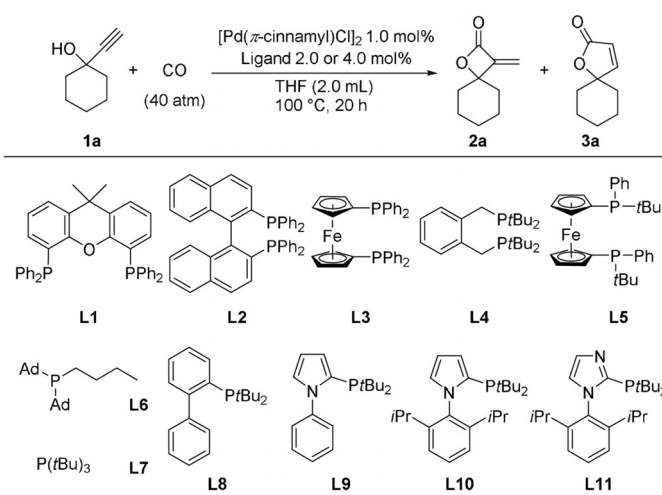
**Scheme 2.** Rhodium- or palladium-catalyzed cyclocarbonylation of alkynols.

α-(alkoxycarbonyl)-methylene-β-lactones (Scheme 2b),<sup>[5c-d]</sup> and (Z)-α-chloro/bromo-alkylidene-β-lactones (Scheme 2b)<sup>[5c-f]</sup> were obtained. Notably, the synthesis of parent α-methylene-β-lactones gained less success due to the highly reactive *exo*-methylene double bond. In fact, to the best of our knowledge, there is only one reported example for the carbonylation of 1-methyl-2-butyne-1-ol described, leading to 4,4-dimethyl-3-methyleneoxetan-2-one in 5% yield with probably polymeric esters as other products through a palladium-catalyzed process (Scheme 2c).<sup>[5g]</sup>

Despite these problems, we thought the cyclocarbonylation of propargylic alcohols in the presence of an improved catalyst would offer a most straightforward and atom-efficient access to these products. Thus, we became attracted by this challenge. Based on our interest in the development of carbonylation reactions,<sup>[6]</sup> herein, we report the first general and highly selective Pd-catalyzed carbonylation of propargylic alcohols to provide a family of new α-methylene-β-lactones (Scheme 2d).

## Results and Discussion

At the beginning of our studies, 1-ethynyl-1-cyclohexanol **1a** was chosen as model substrate. To identify a suitable catalyst system, a variety of ligands (in the case of diphosphine ligands 2 mol%, in the case of monophosphine ligands 4 mol%) were tested in the presence of [Pd(π-cinnamyl)Cl]<sub>2</sub> (Figure 1). Initially, the reactivity of bidentate phosphines **L1–L5** with different backbones and chelating units was evaluated. When **L1** (Xantphos), **L2** (BINAP), **L4** (d'bpX) and **L5** were applied, almost equal amounts of the desired β-lactone **2a** and butenolide **3a** were obtained. **L3** (DPPF)



**Figure 1.** Pd-catalyzed cyclocarbonylation of 1-ethynyl-1-cyclohexanol **1a**: Influence of phosphine ligands. Reaction conditions: **1a** (0.5 mmol), [Pd(π-cinnamyl)Cl]<sub>2</sub> (1.0 mol%), bidentate ligand (2.0 mol%) or monodentate ligand (4.0 mol%), and CO (40 bar) in tetrahydrofuran (THF) (2.0 mL) at 100 °C for 20 h. The ratio of **2a/3a** and the yield were determined by GC using mesitylene as the internal standard.

proved to be not suitable at all, leading to **3a** in 55% with 3% yield for **2a**. No progress was achieved when monodentate ligand **L6** (BuPAD<sub>2</sub>) was used in this reaction. However, in the presence of **L7** (P<sup>*t*</sup>Bu<sub>3</sub>) a slightly improved regioselectivity (71/29) was obtained. Based on this result, we assumed that *tert*-butyl groups may have a positive influence on the desired branched selectivity. Thus, other monodentate ligands **L8–L11** were tried with different backbones bearing *tert*-butyl substituents on the phosphorus atom. Indeed, more-sterically hindered **L8** (JohnPhos) gave 80/20 selectivity and 57% yield of **2a**. When the *N*-phenyl-pyrrole-based ligand **L9** was applied, a similar selectivity (77/23) and a higher yield (67%) were observed. To further increase the steric bulk of the ligand, we introduced substituents on the *ortho* position of the phenyl group resulting in the new ligand **L10**, which was prepared in good yield in two reaction steps (see Supporting Information Scheme S1 for detail). With this ligand in hand, the regioselectivity could be improved to 97/3, albeit the reactivity was affected negatively (30% yield of **2a**). Finally, to our delight, the 1-(2,6-diisopropylphenyl)-1*H*-imidazole-

based phosphine **L11**,<sup>[7]</sup> gave an acceptable yield (56 %) and excellent 98/2 regioselectivity.

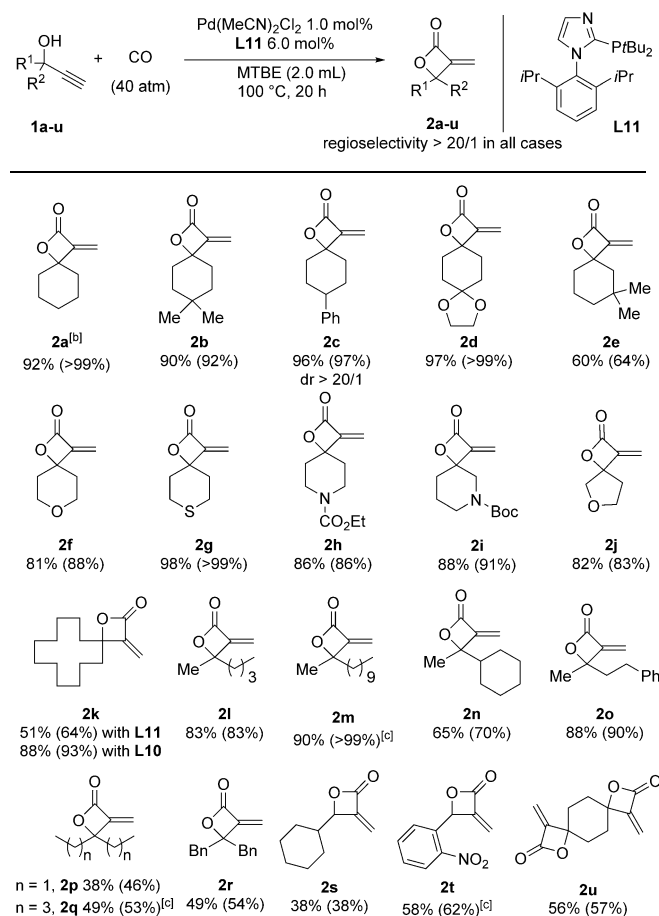
Next, we tried to improve the reactivity further in the presence of **L11** as the ligand of choice (see Supporting Information; Table S2–S6). Variation of critical parameters (solvent, pre-catalyst, temperature, pressure) revealed the following optimal conditions: 1 mol % Pd(MeCN)<sub>2</sub>Cl<sub>2</sub> as catalyst precursor, metal/ligand ratio of 1:6, methyl *tert*-butyl ether (MTBE) as solvent, 100 °C, 40 bar CO. Hence, the desired  $\beta$ -lactone **2a** was obtained in excellent yield (98 %) and regioselectivity (98/2).

With optimized reaction conditions established, a range of easily available and structurally diverse propargylic alcohols were examined (Table 1). It is worthy to note that all of the desired  $\alpha$ -methylene- $\beta$ -lactones were obtained in isolated yield with excellent regioselectivity and diastereoselectivity. Notably, the latter is likely to be controlled by the substrates. The alkynols with different substituents (dimethyl, phenyl,

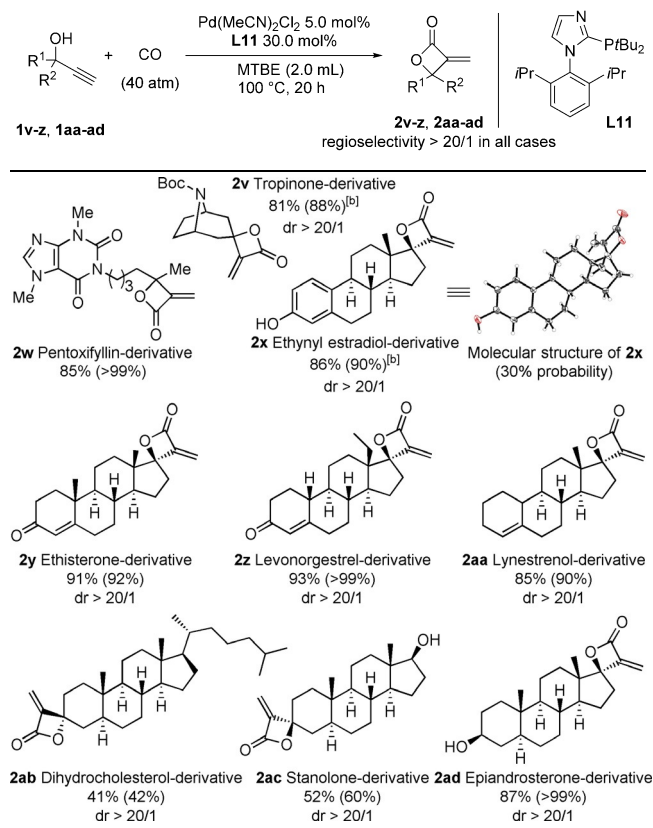
ketal) on the 3- or 4-position of cyclohexyl group were transformed into the corresponding products **2a–2e** in yields of 60–97 % and excellent selectivity. This protocol can be readily scaled-up to carbonylation of 1.0 gram of **1a**. This reaction proceeded smoothly, providing **2a** in 92 % yield. Substrates **1f–1i** containing heteroatoms (oxygen, sulfur, nitrogen) proved to be viable too and gave the corresponding  $\beta$ -lactones **2f–2i** in 81–98 % yields with >20/1 selectivity. Five-membered ring substrates such as **1j** can be also applied successfully in this carbonylation reaction (83 % yield of **2j**). In case of the carbonylation of the 1-ethynylcyclododecan-1-ol **1k**, the use of **L10** instead of **L11** led to a higher yield of **2k** (88 %). Noncyclic alkynols **1l–1r** bearing different alkyl and benzyl groups underwent lactonization smoothly and gave the desired products **2l–2r** in 38–90 % yields. By increasing the catalyst loading (5 mol % Pd(MeCN)<sub>2</sub>Cl<sub>2</sub>, 30 mol % **L11**), the corresponding products **2m** and **2q** were isolated in 90 % and 49 % yield, respectively, with >20/1 regioselectivity. When  $\alpha$ -monoalkyl-substituted propynyl alcohol **1s** was subjected to the optimized conditions, **2s** was obtained, albeit in a lower isolated yield. On the other hand, starting from  $\alpha$ -monoaryl-substituted alkynol **1t**, carbonylation proceeded at increased catalyst loading to give **2t** in 58 % yield. Interestingly, dicarbonylated product **2u** was obtained directly in 56 % isolated yield by carbonylation of dialkynol **1u**. It should be noted that the synthesis of such multiply  $\beta$ -lactone is not an easy task. In fact, to our knowledge no such transformation has been described yet.

The importance of this novel methodology is showcased by the late-stage modification of biologically active and natural products,<sup>[8]</sup> which provides easy access to diverse  $\alpha$ -methylene- $\beta$ -lactones, highlighting the substrate scope of this protocol and its potential utility in organic synthesis (Table 2). Due to the poor solubility of some of the complex substrates, typically 5 mol % of palladium catalyst was applied. Under otherwise similar conditions, in all cases the reactions proceeded well with excellent regio- and diastereoselectivities. More specifically, tropinone-derived propargylic alcohol **1v** delivered the desired product **2v**, with good efficiency (81 % yield). Pentoxifyllin, a drug with anti-inflammatory properties, was transformed to the corresponding product **2w** smoothly (85 % yield). Recently, much attention has been paid to steroidal containing spiro-heterocycles for their characteristic physiological activities.<sup>[9]</sup> Thus, we investigated reactions of pharmaceutically relevant steroidal alkynols: ethynyl estradiol, ethisterone, levonorgestrel, and lynestrenol, which are used for contraception and gynecological disorders. All these compounds participated efficiently in this transformation to provide the carbonylative products **2x–2z**, **2aa** in high yields (85–93 %). Notably, the molecular structure of ethynyl estradiol derivative **2x** was unambiguously confirmed by X-ray structure analysis.<sup>[10]</sup> Similarly,  $\alpha$ -methylene- $\beta$ -lactones **2ab–2af** derived from other steroid hormones such as dihydrocholesterol, stanalone and epiandrosterone, were obtained in 41–87 % yields with excellent selectivity. Moreover, homopropargylic alcohols also proved to be suitable substrates and afforded the corresponding 5-membered products with excellent regioselectivity (see Supporting Information, Scheme S2).

**Table 1:** Pd-catalyzed cyclocarbonylation of alkynols: Substrate scope.<sup>[a]</sup>

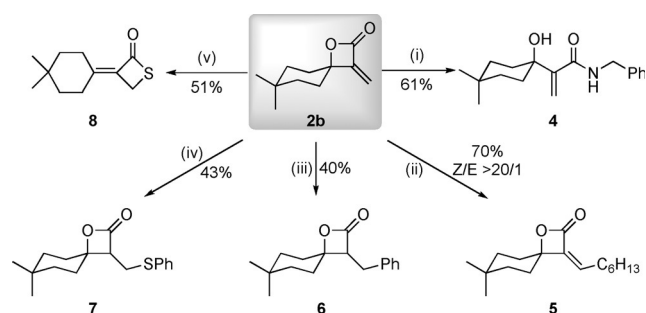


[a] Unless otherwise noted, all reactions were performed in MTBE (2.0 mL) at 100 °C for 20 h in the presence of **1** (0.5 mmol), Pd-(MeCN)<sub>2</sub>Cl<sub>2</sub> (1.3 mg, 0.005 mmol), **L11** (11.2 mg, 0.03 mmol), and CO (40 bar). Isolated yields were given before the parentheses. The NMR yields (values within the parentheses), regioselectivity of **2/3** and diastereoselectivity of **2** were determined by crude <sup>1</sup>H NMR analyses using dibromomethane as the internal standard. [b] **1a** (1 g, 8 mmol), Pd(MeCN)<sub>2</sub>Cl<sub>2</sub> (21 mg, 0.08 mmol), **L11** (178 mg, 0.48 mmol), MTBE (30 mL). [c] 0.1 mmol of **1** was used.

**Table 2:** Pd-catalyzed cyclocarbonylation of alkynols derived from biologically active and natural products.<sup>[a]</sup>

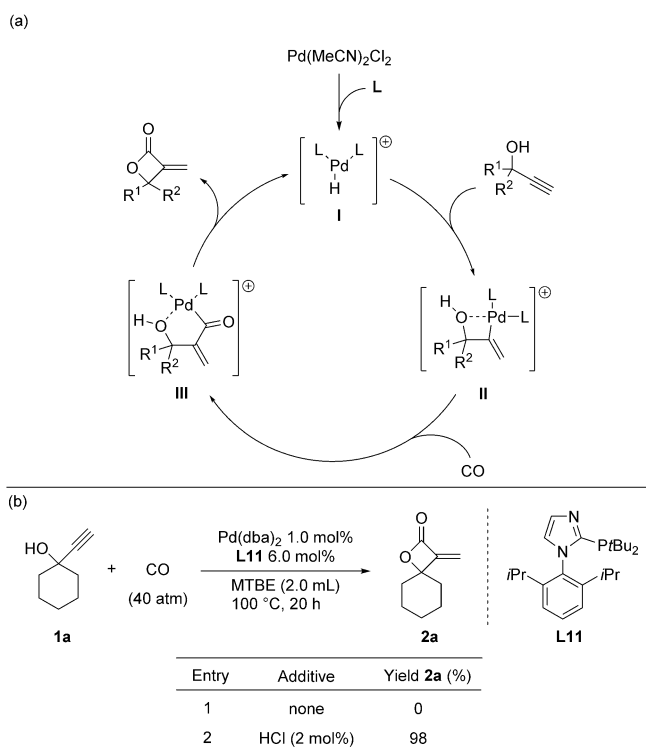
[a] Unless otherwise noted, all reactions were performed in MTBE (2.0 mL) at 100 °C for 20 h in the presence of **1** (0.1 mmol), Pd-(MeCN)<sub>2</sub>Cl<sub>2</sub> (1.3 mg, 0.005 mmol), L11 (11.2 mg, 0.03 mmol), and CO (40 bar). Isolated yields were given before the parentheses. The NMR yields (values within the parentheses), regioselectivity of **2/3** and diastereoselectivity of **2** were determined by crude <sup>1</sup>H NMR analyses using dibromomethane as the internal standard. [b] 0.5 mmol of **1** was used.

It should be noted that more than 80% of the here described  $\alpha$ -methylene- $\beta$ -lactones are prepared for the first time. This clearly demonstrates the synthetic value of this novel methodology. We assumed that our new products can be conveniently used as interesting basic building blocks.<sup>[3]</sup> Thus, to showcase their utility, selected follow-up transformations were conducted by using **2b** as the starting material (Scheme 3). To illustrate the possibility to prepare functionalized acrylic acid derivatives,  $\alpha$ -methylene- $\beta$ -lactone **2b** readily underwent ring opening with benzylamine in the presence of Pd(OAc)<sub>2</sub>, affording  $\beta$ -hydroxy amide **4** in 61% yield. Furthermore,  $\alpha$ -methylene- $\beta$ -lactones provide an easy and efficient entry into  $\alpha$ -alkylidene- $\beta$ -lactones applying cross metathesis in the presence of Grubbs II catalyst. Indeed, a good yield of **5** was obtained with high Z-selectivity (stereochemistry determined by NOESY study, see Supporting Information for detail). Particularly, this route allows for the efficient preparation of focused libraries of  $\beta$ -lactones, which have found use as biological research probes and therapeutic agents.<sup>[11]</sup> Addition of carbon- or hetero-nucleophiles gives access to  $\alpha$ -alkylated  $\beta$ -lactones. Exemplarily, the

**Scheme 3.** Further synthetic transformations of **2b**. Reagents and conditions: (i) Pd(OAc)<sub>2</sub>, PPh<sub>3</sub>, BnNH<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, rt for 16 h. (ii) Grubbs' 2nd generation, 1-octene, CH<sub>2</sub>Cl<sub>2</sub>, reflux for 10 h. (iii) [Rh(cod)Cl]<sub>2</sub>, KOH/ H<sub>2</sub>O, PhB(OH)<sub>2</sub>, dioxane, 60 °C for 1 h. (iv) PhSH, Et<sub>3</sub>N, MeOH, rt, 24 h. (v) Lawesson's Reagent, PhCH<sub>3</sub>, reflux for 6 h.

Rh-catalyzed conjugate addition of phenylboronic acid to **2b** provided **6** in 40% yield and the treatment of **2b** with thiophenol and triethylamine provided  $\alpha$ -(thiomethyl)- $\beta$ -lactone **7** via a nucleophilic conjugate addition. Finally, four-membered thiolactones can be made in a facile manner by employing Lawesson's reagent. The synthesis of  $\alpha$ -methylene- $\beta$ -S-thiolactone **8** illustrated the diverse possibilities for the construction of novel sulfur heterocycles.

Regarding the mechanism of this novel carbonylation reaction, in principle two main pathways are possible (Scheme 4a): 1) Initially, the active palladium hydride species **I** could be generated in situ by the combination of palladium precursor with phosphine ligands,<sup>[12]</sup> in which an excess of phosphine ligand (L11) is needed to reduce the initial Pd<sup>II</sup>

**Scheme 4.** a) Proposed mechanism. b) Control experiments.



precursor. After coordination of the alkyne to this complex followed by migratory insertion into the Pd–H bond, the corresponding alkenyl-Pd complex **II** should be obtained, which is transformed into the corresponding acyl complex **III** via CO coordination and insertion. Finally, intramolecular nucleophilic attack of hydroxyl on the acyl carbonyl leads to the formation of the desired lactone and regeneration of the  $[Pd-H]^+$  species. Alternatively, the  $Pd^{II}$  precursor is reduced in situ to a  $Pd^0$  species (probably by an excess amount of phosphine ligands). The  $Pd^0$  species undergoes insertion into the oxygen-hydrogen bond of alkynol affording the corresponding alkoxypalladium complex. Then, insertion of CO into palladium-oxygen bond would give the Pd acyl species. Intramolecular addition of the palladium hydride to the triple bond would form metallacycle complex, which leads to the formation of the desired lactone and regenerates the catalyst (see Supporting Information, Scheme S4). In order to differentiate between these two possibilities, control experiments were performed. As shown in Scheme 4b (entry 1), the carbonylation of propargylic alcohol **1a** was also carried out with a  $Pd^0$  pre-catalyst. However, in the presence of  $Pd(dba)_2$  under the standard reaction conditions, no conversion was observed. In contrast, using  $Pd(dba)_2$  in the presence of 2 mol% of hydrochloric acid gave the desired product **2a** in 98% yield (Scheme 4b, entry 2). These experiments provided clear evidence for a mechanism involving catalytically active palladium hydride species. Although the detailed reaction mechanism of the cyclocarbonylation of propargylic alcohols remains to be further elucidated, based on our previous studies on alkoxycarbonylations<sup>[6b,13]</sup> as well as mechanistic studies by Cole-Hamilton, Drent and Sparkes,<sup>[14]</sup> it is most likely that this reaction goes through the Pd hydride mechanism shown in Scheme 4a.<sup>[15]</sup>

## Conclusion

In summary, we developed the first catalyst system for a general and selective cyclocarbonylation of alkynols to produce synthetically useful  $\alpha$ -methylene- $\beta$ -lactones. By applying a distinctive ligand, a wide range of propargylic alcohols was efficiently transformed into the corresponding  $\alpha$ -methylene- $\beta$ -lactones in good yields (up to 98%) with high regio- and diastereoselectivity ( $>20/1$ ). The applicability of this methodology is specifically highlighted by the functionalization of biologically active and natural molecules. Combining this novel procedure with established functionalizations allows for an efficient preparation of privileged  $\beta$ -lactone scaffolds. This efficient procedure features the following advantages: high atom economy, additive free reaction conditions, availability of substrates and obtained excellent selectivities. It complements the current methodologies for carbonylations in organic synthesis as shown by the synthesis of 30 products; the vast majority of them are new.

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## Conflict of interest

The authors declare no conflict of interest.

**Keywords:** alkynol · carbonylation · catalysis · palladium · phosphine ·  $\alpha$ -methylene- $\beta$ -lactone

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