

Synthetic Methods

Tailored Palladium Catalysts for Selective Synthesis of Conjugated Enynes by Monocarbonylation of 1,3-Diynes

Jiawang Liu⁺, Ji Yang⁺, Carolin Schneider, Robert Franke, Ralf Jackstell, and Matthias Beller*

Abstract: For the first time, the monoalkoxycarbonylation of easily available 1,3-diynes to give synthetically useful conjugated enynes has been realized. Key to success was the design and utilization of the new ligand 2,2'-bis(tert-butyl(pyridin-2-yl)phosphanyl)-1,1'-binaphthalene (Neolephos), which permits the palladium-catalyzed selective carbonylation under mild conditions, providing a general preparation of functionalized 1,3-enynes in good-to-high yields with excellent chemoselectivities. Synthetic applications that showcase the possibilities of this novel methodology include an efficient one-pot synthesis of 4-aryl-4H-pyrans as well as the rapid construction of various heterocyclic, bicyclic, and polycyclic compounds.

Introduction

1,3-Enynes have been recognized as versatile building blocks in organic synthesis, enabling further straightforward transformations for rapid construction of molecular complexity.^[1] Interestingly, this structural element also occurs in several natural products and pharmaceuticals.^[2] In addition, 1,3-enynes are of general importance for material sciences, specifically polymers.^[3] Traditional approaches to this class of compounds include olefination of propargyl aldehydes,^[4] dehydration of propargyl alcohols,^[5] and mainly metal-catalyzed cross-addition of alkynes.^[6] In addition, the transition-metal-catalyzed Sonogashira coupling reaction of alkynes with vinyl halides,^[7] and related cross-coupling reactions between terminal organometallic alkynes and alkenes,^[8] provide prevalent methodologies for their synthesis. Despite all these remarkable progresses, there is continuous interest in the development of a more efficient and general synthesis of

functionalized 1,3-enynes from readily available starting materials.

One of the main driving forces for the advancement of modern organic chemistry is the development of novel catalysts/ligands owing to their key role in controlling the reactivity and selectivity of chemical transformations.^[9] Applying transition-metal complexes as catalysts, especially considering the electronic and steric nature of the ligands is crucial, and often enables previously unknown transformations.^[10] Notably, for practical purposes often the activity of a given catalyst is the decisive factor for its application. Consequently, the design of new catalysts with both improved activity and selectivity compared with known catalytic systems is essential for the development of useful synthetic methodologies.^[11] As representative examples, we recently demonstrated the advantage of specific phosphine ligands with a built-in-base function for palladium-catalyzed alkoxy-carbonylation reactions of less-reactive olefins, including hindered *tri*- and *tetra*-substituted alkenes.^[12] Incorporation of *tert*-butyl and pyridine substituents on the phosphorous atom of several bidentate phosphine ligands dramatically improved the rate of the nucleophilic attack on the intermediate palladium acyl complex, which can be rate-limiting in these catalytic protocols.^[13]

Based on this work, we started a program to investigate the palladium-catalyzed carbonylation of 1,3-diynes,^[14] which are easily available from terminal alkynes via the Glaser coupling reaction and its variants.^[15] Indeed, utilization of the specific ligand 1,1'-ferrocenediyl-bis(*tert*-butyl(pyridin-2-yl)-phosphine) allowed for the carbonylation to give substituted conjugated dienes. Unfortunately, none of the explored catalyst systems allowed for a selective monocarbonylation that could afford synthetically useful 1,3-enynes. To the best of our knowledge no general catalytic monocarbonylation process of these substrates has been developed so far.^[16] Obviously, a key challenge for this transformation is to avoid the generation of double carbonylation products (Scheme 1, a). This challenge could be difficult owing to the similarity between diyne and enyne. Herein, we present a solution for this problem by careful control of the reaction conditions and design of the new ligand **L12**. A highly selective monocarbonylation of a variety of 1,3-diynes is possible, affording a precise synthesis of conjugated enynes (Scheme 1, b).

Results and Discussion

In general, for palladium-catalyzed alkoxy-carbonylations the choice of ligand is crucial for controlling the selectivity and activity of the overall transformation. Thus, we inves-

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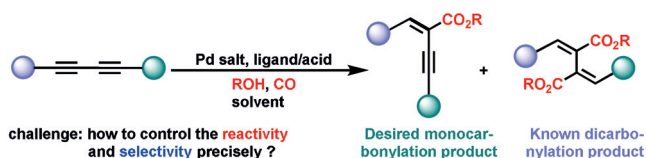
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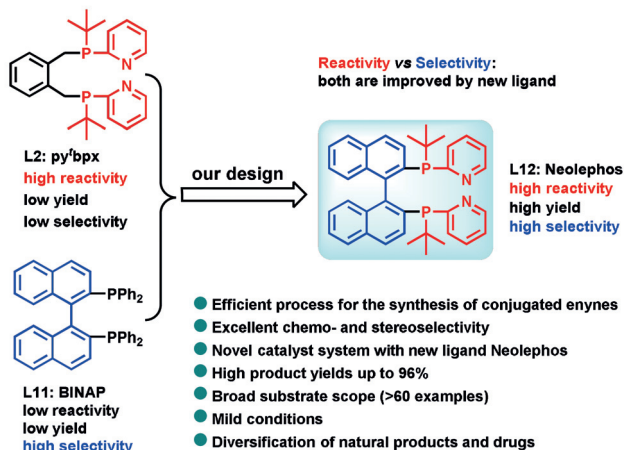
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a) New strategy for precise synthesis of conjugated enynes via selective carbonylation

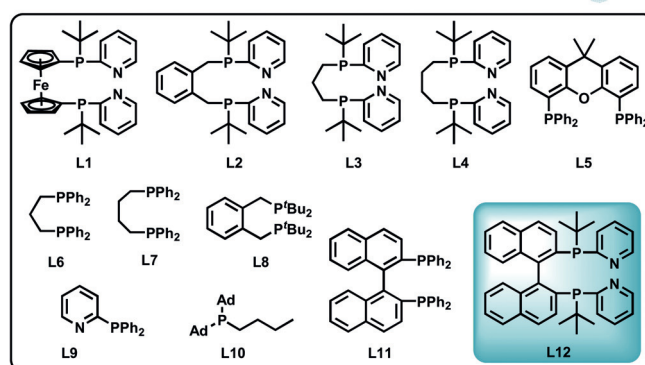
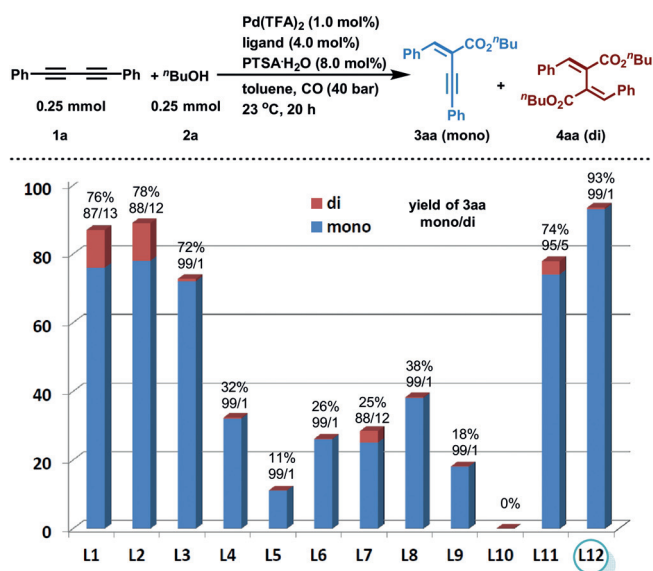


b) Design of a ligand with improved reactivity and selectivity



Scheme 1. Synthesis of conjugated 1,3-enynes: Strategy and ligand design.

igated the effect of different phosphine ligands in the benchmark reaction of commercially available 1,4-diphenylbuta-1,3-diyne **1a** and *n*-butanol **2a** [40 bar CO, toluene, 1.0 mol% Pd(TFA)₂, 4.0 mol% bidentate and 8.0 mol% monodentate phosphines, and PTSA·H₂O (*p*-toluenesulfonic acid monohydrate)], as shown in Scheme 2. To avoid multiple carbonylation reactions, only 1 equivalent of alcohol was used, and the reactions were generally run at room temperature. To our delight, the desired enyne **3aa** was obtained in 76% yield when **L1** was applied, demonstrating the general feasibility of a monocarbonylation process. In addition, the generation of the double carbonylation product **4aa** (**3aa**/**4aa** = 87/13) was observed. Unfortunately, the separation of both products was tedious. Thus, we were interested in more selective catalyst systems and tried other bidentate ligands **L2**–**L4** bearing *tert*-butyl and pyridyl substituents on the phosphorus atom. In the presence of **L2**, **3aa** was afforded in slightly higher yield; however, no improvement of the chemoselectivity was achieved. When using **L3** or **L4** with a different ligand backbone, the overall yield of carbonylation products was lower, although high selectivity for **3aa** was realized. Other state-of-the-art ligands that are commonly used in carbonylations, such as 4,5-bis(diphenylphosphino)-9,9-dimethyl-xanthene (Xantphos, **L5**),^[17] 1,3-bis(diphenylphosphino)propane (dppp, **L6**),^[18] 1,4-bis(diphenylphosphino)butane (dppb, **L7**),^[19] 1,2-bis((di-*tert*-butylphosphanyl)methyl)benzene (d'tbpX, **L8**),^[20] 2-diphenylphosphinopyridine (**L9**),^[21] and di(1-adamantyl)-*n*-butyl-phosphine (BuPAD₂, **L10**),^[22] did not give the desired product in more than 40% yield. Interestingly, when using racemic 2,2'-bis(diphenylphosphanyl)-1,1'-binaphthalene (**L11**, BINAP)^[10b,23] as a ligand, **3aa** was obtained in 74% yield and more surprisingly the chemoselectivity was also increased to 95/5. Comparing

Scheme 2. Pd-catalyzed carbonylation of 1,4-diphenylbuta-1,3-diyne: Investigation of ligands. Unless otherwise noted, all reactions were performed under 40 atm CO at room temperature for 20 h in the presence of **1a** (0.25 mmol), **2a** (0.25 mmol), Pd(TFA)₂ (0.0025 mmol, 0.83 mg), ligand (4.0 mol% for **L1**–**L8**, **L11**, **L12** and 8.0 mol% for **L9**, **L10**), PTSA·H₂O (4.0 mg, 8.0 mol%) in toluene (1.0 mL). Yields and chemoselectivity were determined by GC and GC-MS analysis.

L6 with **L3** and **L7** with **L4**, as well as **L8** with **L2**, demonstrates the superior behavior of the *tert*-butyl-2-pyridylphosphino group in the respective ligands. Consequently, we prepared the analogous ligand **L12**, which to the best of our knowledge had never been synthesized before. Gratifyingly, by applying **L12** the desired monocarbonylation product **3aa** was obtained in 93% yield with 99/1 chemoselectivity. It should be noted that **L12** consists of a mixture of stereoisomers, which could be used directly in this reaction because the different stereoisomers have no significant influence in this transformation (for more details, see the Supporting Information).

To improve the benchmark reaction further, we evaluated the influence of critical reaction parameters in the presence of **L12**. As shown in Table 1, no reaction occurred without acid or with weak acid (Table 1, entries 1 and 2). Even trifluoroacetic acid gave only trace amounts of **3aa**, whereas pyridine-2-sulfonic acid afforded the desired product in 12% yield (Table 1, entries 3 and 4). Interestingly, by using camphorsulfonic acid (CSA), the preferred product **3aa** could be

Table 1: Pd-catalyzed monocarbonylation of 1,4-diphenylbuta-1,3-diyne: Investigation of reaction conditions.^[a]

Entry	[Pd]	Acid	3 aa/4 aa	Yield of 3 aa [%]
1	Pd(TFA) ₂	no acid	–	0
2	Pd(TFA) ₂	HOAc	–	0
3	Pd(TFA) ₂	TFA	–	< 5
4	Pd(TFA) ₂	2-PySO ₃ H	99/1	12
5	Pd(TFA) ₂	HOTf	99/1	45
6	Pd(TFA) ₂	PTSA·H ₂ O	99/1	93
7	Pd(TFA) ₂	(+)-CSA	99/1	96
8 ^[b]	Pd(TFA) ₂	(+)-CSA	99/1	68
9 ^[b]	Pd(acac) ₂	(+)-CSA	99/1	77
10 ^[b]	PdCl ₂	(+)-CSA	–	0
11 ^[b]	Pd ₂ (dba) ₃	(+)-CSA	99/1	25
12 ^[b]	Pd(OAc) ₂	(+)-CSA	99/1	88
13	Pd(OAc) ₂	(+)-CSA	99/1	97 (94) ^[e]
14 ^[c]	Pd(OAc) ₂	(+)-CSA	99/1	97
15 ^[d]	Pd(OAc) ₂	(+)-CSA	99/1	97

[a] Unless otherwise noted, all reactions were performed under 40 atm CO at room temperature for 20 h in the presence of **1a** (0.25 mmol), **2a** (0.25 mmol), [Pd] (1.0 mol% in terms of palladium atom), **L12** (4.0 mol%), acid (8.0 mol%) in toluene (1.0 mL). The yield and chemoselectivity (**3aa/4aa**) were determined by GC analysis. [b] The reaction time was 4 h. [c] 0.5 mmol *n*BuOH was used. [d] 40 °C. [e] Yield of isolate product.

achieved in 96% yield with excellent chemoselectivity (Table 1, entry 6). It should be noted that using CSA as the co-catalyst also improved the solubility of catalysts. Besides, the palladium precursor had a significant influence on the productivity and palladium acetate was found to be the most active metal salt giving **3aa** in 88% (4 h) and 97% (20 h) yield (Table 1, entries 12 and 13). Notably, smooth transformations with excellent yields and selectivities were also observed in the presence of an excess amount of 1-butanol or at higher temperature (Table 1, entries 14 and 15), which demonstrated the preferred selectivity for monocarbonylation.

To understand the behavior of **L12** in controlling the chemoselectivity, we studied the kinetic process of the alkoxy carbonylation of 1,4-diphenylbuta-1,3-diyne **1a** with *n*-butanol (1.0 equiv). As shown in Figure 1(a), the yield of desired product **3aa** increased gradually and the starting material **1a** was fully converted after 12 hours. Over the course of the reaction, the double carbonylation product was not detected at all. To get more insight into the activity and selectivity of ligand **L12**, the reaction was also performed at room temperature with a large excess of methanol (solvent). As depicted in Figure 1(b), the monocarbonylation product **3ab** was generated in high chemoselectivity over 25 hours, and only after that time the second carbonylation occurred at very low rate. Even after 3 days, the double carbonylation product was observed only in 10% distribution, showing the pronounced rate differences between the first and second carbonylation step.

On the basis of these results and our previous work on the mechanism of alkoxy carbonylation using ligands **L1–L4**^[12–14],

as well as the mechanistic studies by Cole-Hamilton, Drent, and Sparkes,^[24] we propose the following catalytic cycle for ligand **L12** [Figure 1(c)]. Initially, the stable Pd^{II} salt is reduced in situ to Pd⁰ in the presence of an excess amount of phosphine ligands,^[25] followed by a protonation process to afford the active complex **A**. It is likely that this palladium hydride species is in equilibrium with the N-protonated pyridinium complex.^[13] Subsequently, π -coordination of one carbon–carbon triple bond to the metal center occurs, followed by the insertion of the alkyne into the palladium hydride bond, affording the alkenyl–Pd intermediate **B**. After CO insertion, the complex **C** is formed and N-assisted methanolysis of intermediate **C** via transition state **D** provides the desired monocarbonylation product **3ab** and regenerates the active palladium hydride species, to finish cycle I. On the other hand, the carbon–carbon triple bond of **3ab** might coordinate to the active palladium hydride species again and insertion of the triple bond will give intermediate **E**, which undergoes another CO insertion process to afford acyl palladium species **F**. Finally, N-assisted methanolysis affords the undesired product **4ab** and again regenerates palladium hydride species **A** to complete cycle II.

Following our original goal to develop a general protocol for the synthesis of functionalized 1,3-enynes, we started to explore the substrate scope. With the optimized reaction conditions in hand (for details see the Supporting Information), we studied the monoalkoxy carbonylation of 30 different 1,3-diyne by using Pd(OAc)₂/**L12**/(+)-CSA (1.0/4.0/8.0 mol%) as the catalyst. As shown in Table 2, a variety of substrates, including symmetric aromatic and aliphatic, and more importantly also non-symmetric substrates, bearing a range of functional groups, are transformed into the corresponding conjugated enynes in good-to-excellent yields (53–95%). Notably, in all these cases high chemoselectivities (mono/di = 99/1) and exclusive generation of the *E*-stereoisomers was observed. Aromatic 1,3-diyne **1a–i** with either electron-donating (OMe, Me, *t*Bu) or electron-withdrawing (F, CF₃) substituents on the phenyl ring provided the corresponding products **3aa–3ai** in high yields (83–95%) and excellent selectivity under very mild conditions (room temperature). Substituents in the *ortho*-position of the phenyl ring have a significant influence on both reactivity and selectivity of this reaction. As an example, the 1,4-di-*o*-tolylbuta-1,3-diyne **1k** gave **3ka** in 83% yield at 70 °C with 86/14 regioselectivity. Pleasingly, the thiofuran-substituted substrate was well tolerated by the catalyst; thus, **3la** was obtained in 93% yield. Next, we investigated the reactivity of aliphatic 1,3-diyne. Gratifyingly, the palladium-catalyzed monoalkoxy carbonylation of various substrates proceeded selectively, affording the corresponding carbonylative products in good yields and selectivities. It should be noted that no other side product was observed in all these cases, although the desired products may undergo isomerization processes. The simple 1,3-diyne **1m–1o** and the cyclohexyl- and cyclopropyl-substituted 1,3-diyne **1p** and **1q**, also gave the preferred products in 55–90% yield and high selectivity under mild conditions.

Furthermore, substrates bearing substituents such as chloride, cyano, ester, and trimethylsilyl also smoothly under-

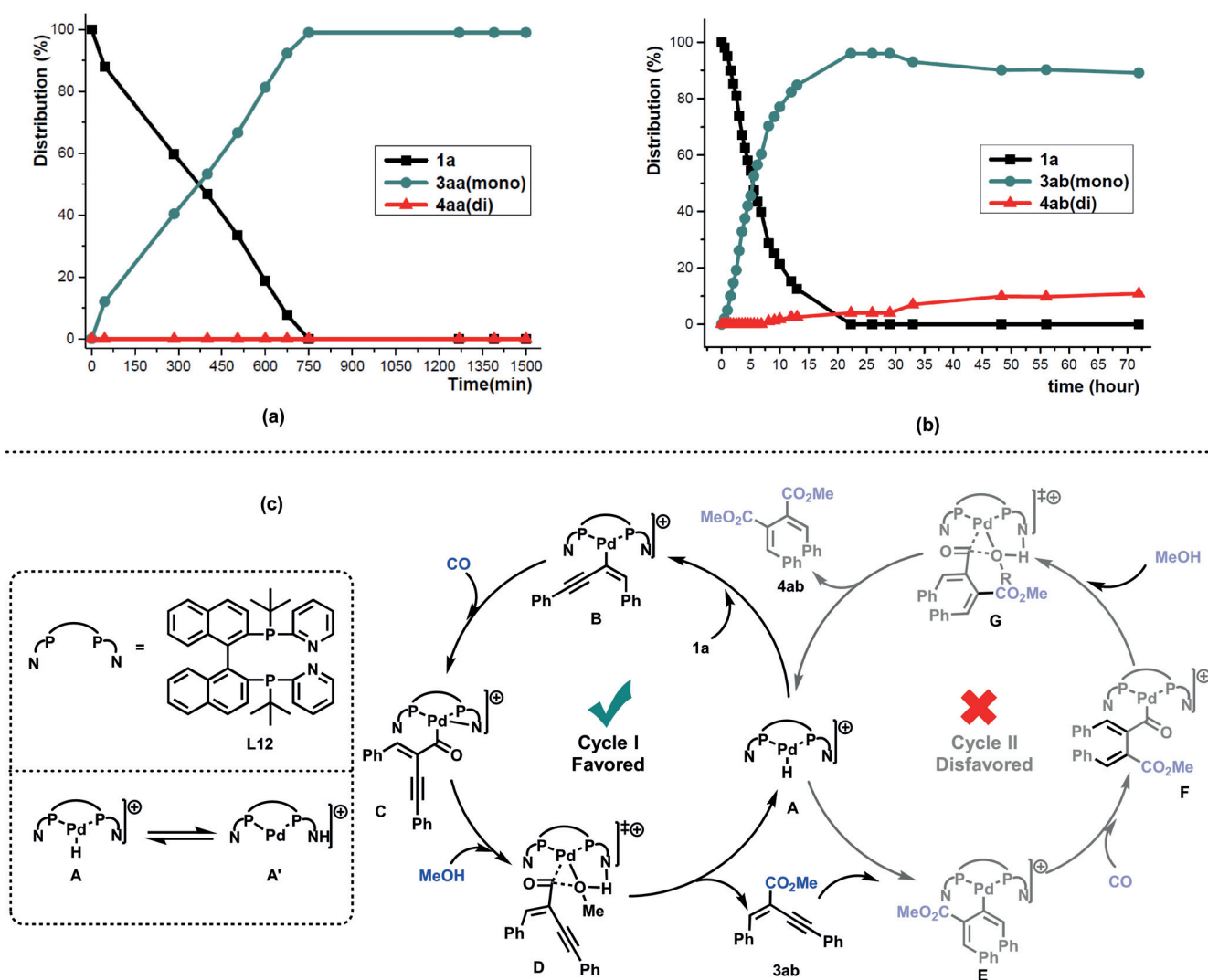
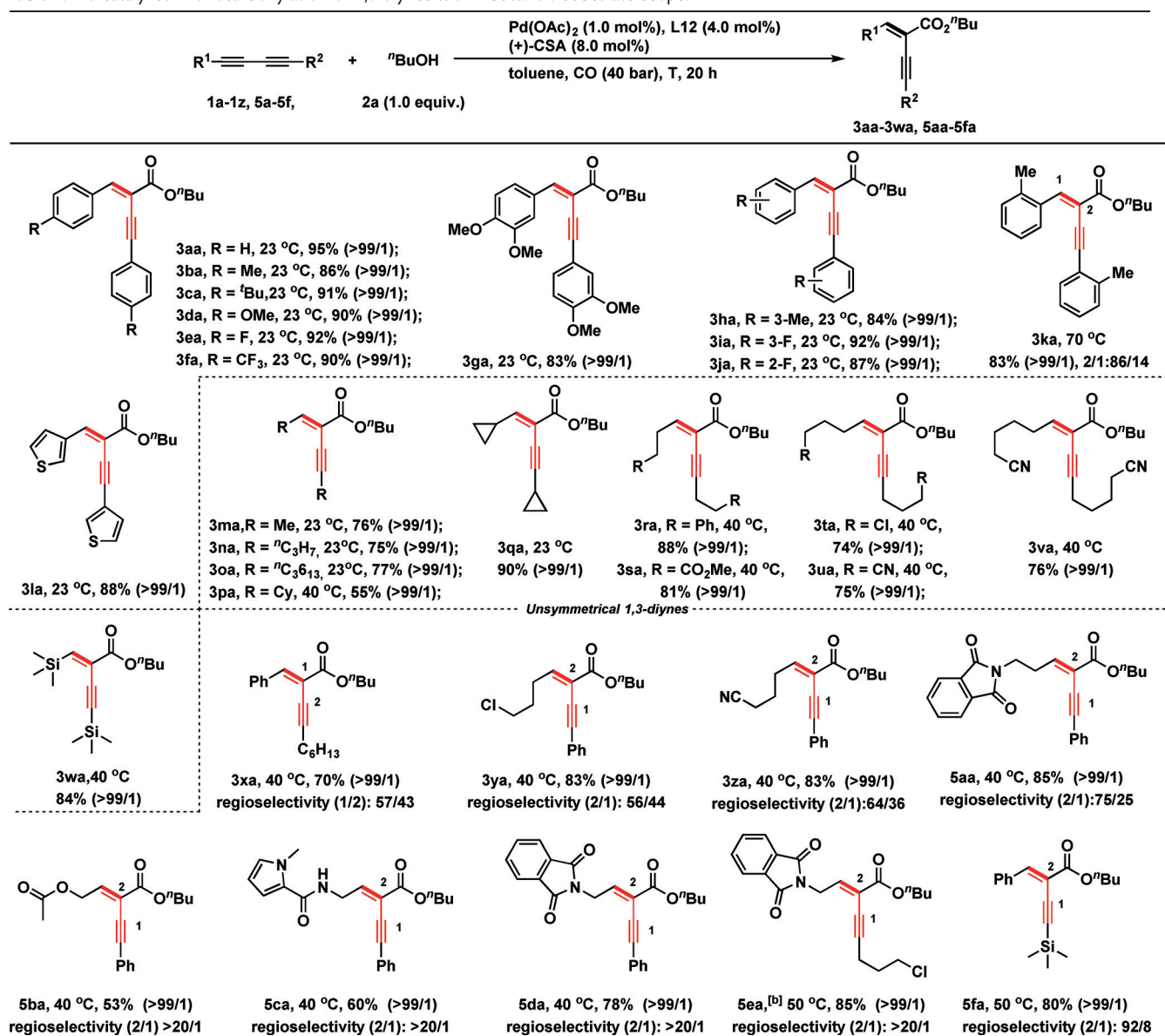


Figure 1. (a) Compounds distribution of Pd-catalyzed alkoxy-carbonylation of **1a** in the presence of **L12** (reaction conditions: 1.0 mol% of Pd(OAc)₂, 4.0 mol% of **L12**, 8.0 mol% (+)-CSA, 5 mol of **1a**, 5.0 mmol of 1-butanol, 20 mL of toluene, 23 °C). (b) Compounds distribution of Pd-catalyzed methoxy-carbonylation of **1a** in the presence of **L12** (reaction conditions: 1.0 mol% of Pd(TFA)₂, 4.0 mol% of **L12**, 8.0 mol% PTSA·H₂O, 2.5 mol of **1a**, 25 mL of MeOH, 23 °C). (c) Plausible catalytic cycle for the generation of **3ab** and **4ab**.

went monocarbonylation and gave the desired products **3sa–3wa** in 74–84% yields. Next, the scope of non-symmetric 1,3-diyne, which are more challenging substrates from the viewpoint of regioselectivity, was examined. As shown in Table 2, reaction of the non-functionalized 1-phenyl-4-hexyl-1,3-butadiyne **1x** gave selectively the monocarbonylative product, albeit as a mixture of two regioisomers with 57/43 selectivity. Although in this case the carbonylation proceeded slightly further at the phenyl-substituted alkyne group, interestingly, **1y**, **1z**, and **5a** bearing chloride, cyano, and amide end groups led to regioisomers **3ya** (44/56), **3za** (36/64), and **5aa** (25/75), respectively, as the main products. Nevertheless, depending on the substrate the regioselectivity for the monocarbonylation can also be very high, allowing the synthesis of interesting functionalized building blocks. More specifically, propargyl ester/amide-derived 1,3-diyne **5b**, **5c**, **5d**, and **5e**, which are often sensitive to palladium catalysis, worked particularly well, affording the corresponding prod-

ucts with excellent regioselectivities (>20/1). Moreover, carbonylation of unsymmetrical 1,3-diyne **5f** preferentially occurred at the phenyl-substituted triple bond, affording product **5fa** regioselectively (92/8) in 80% yield.

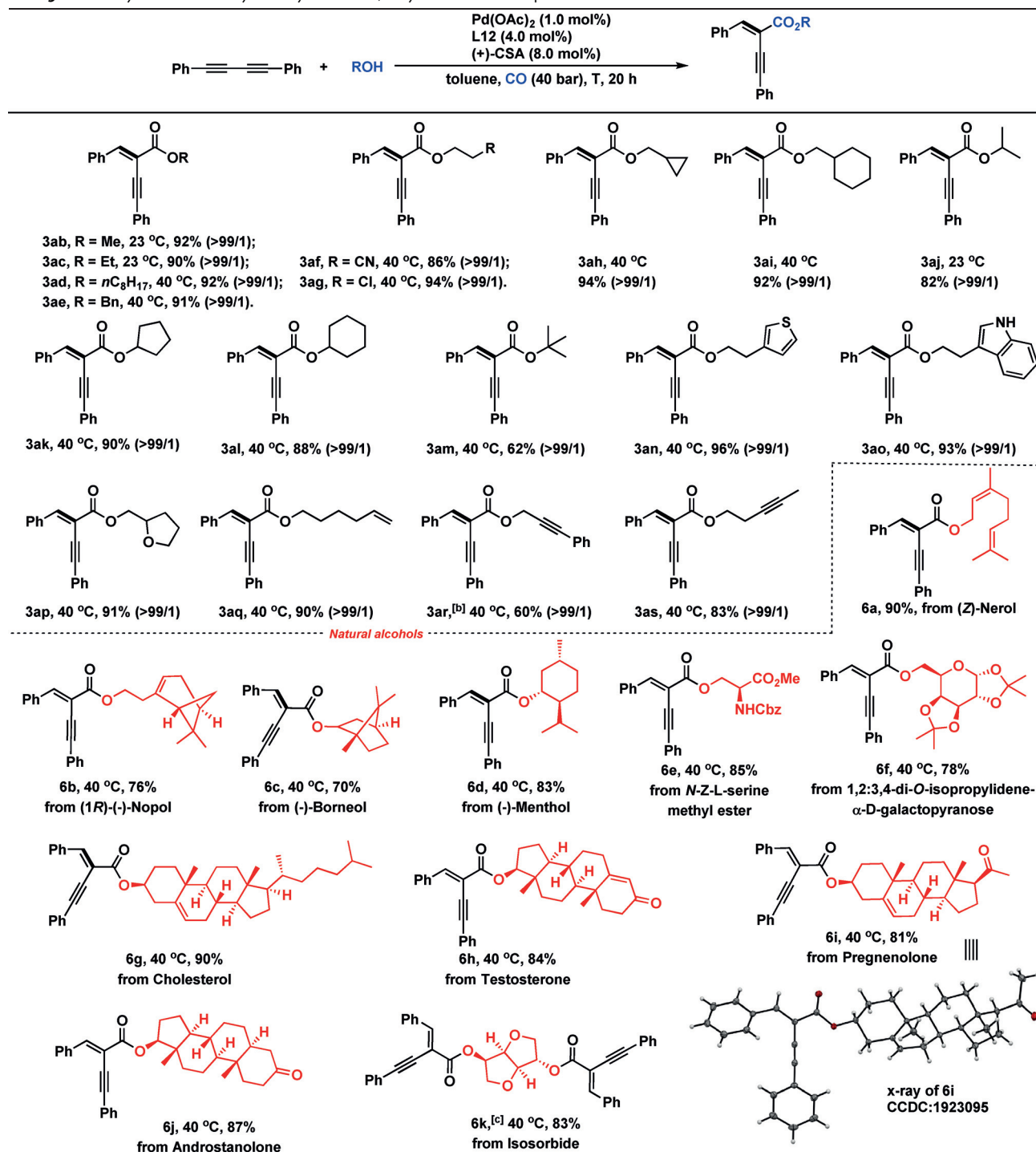
Next, we examined the general scope of this mono-alkoxy-carbonylation process with respect to the reactivity of alcohols. Thus, a variety of simple primary aliphatic alcohols, including some functionalized derivatives (**2f** and **2g**), were tested under the optimal reaction conditions. As shown in Table 3, the corresponding esters (**3ab–3ah**) were generated in high yields (86–94%) with chemoselectivities of >99/1. Moreover, less reactive secondary alcohols underwent this reaction smoothly in very good yields and selectivities (**3aj–3al**, 82–90% yields, >99/1 chemoselectivities). Surprisingly, even *tert*-butanol as an example of a tertiary alcohol was suitable for this transformation to give **3am**. Furthermore, alcohols **2n–2p** containing heterocyclic rings proved to be viable substrates and gave the corresponding products **3an–**

Table 2: Pd-catalyzed monocarbonylation of 1,3-diyne with *n*-butanol: Substrate scope.^[a]

[a] Unless otherwise noted, all reactions were performed under 40 atm CO for 20 h in the presence of **1** (0.25 mmol), **2a** (0.25 mmol), Pd(OAc)₂ (1.0 mol%, 0.56 mg), L12 (4.0 mol%, 5.84 mg), (+)-CSA (8.0 mol%, 4.6 mg) in toluene (1.0 mL) at specified temperature. The yields are those of product isolated by column chromatography. The chemoselectivity in brackets (mono/di) were determined by GC analysis. The regioselectivity of **3aa–3za** and **5aa–5fa** were determined by ¹H NMR analysis of the crude products. [b] 2/8/16 mol% of Pd/L12/(+)-CSA was used.

3ap in 91–96% yields with >99/1 selectivities. To our surprise, this transformation could also be performed in the presence of alkene (**2q**) or isolated alkynes (**2r** and **2s**) giving the highly functionalized carbonylative products **3aq–3as** in 60–90% yields; thus, demonstrating interesting chemoselectivity. Notably, diverse alcohols can be used in this transformation, also highlighting the substrate scope of this protocol and its potential utility in organic synthesis (Table 3). More specifically, constituents of cosmetic fragrances, such as (*Z*)-Nerol and (*R*)-Nopol, bearing carbon–carbon double bonds, gave the corresponding products **6a** and **6b** in 90 and 76% yield, respectively. Moreover, (–)-Borneol, a traditional Chinese medicine that is also the component of many

essential oils and natural insect repellent, and (–)-Menthol, which is widely used for its medicinal value, furnished the carbonylative products **6c** and **6d** in 70–83% yield. Applying L-serine and α-D-galactopyranose derivatives as other representative examples of biologically relevant molecules afforded the desired products **6e** and **6f** in 78–85% yield. Furthermore, cholesterol, which is an essential structural component of all animal cells and is required to maintain the structural integrity of membranes, was identified to be a good substrate in this transformation. Similarly, steroid hormones such as Testosterone, Pregnenolone, and Androstanolone participated in this transformation efficiently to provide the modified bio-active compounds **6h–6j** in high yields. The

Table 3: Pd-catalyzed monoalkoxycarbonylation of 1,3-diyne: Alcohol scope.^[a]

[a] Unless otherwise noted, all reactions were performed under 40 atm CO for 20 h in the presence of **1a** (0.25 mmol), alcohols (0.375 mmol), Pd(OAc)₂ (1.0 mol%, 0.56 mg), **L12** (4.0 mol%, 5.84 mg), (+)-CSA (8.0 mol%, 4.6 mg) in toluene (1.0 mL) at specified temperature. The yields are those of product isolated by column chromatography. The chemoselectivity in brackets (mono/di) were determined by GC analysis. [b] 2/8/16 mol% of Pd(OAc)₂/**L12**/(+)-CSA were used. [c] Reaction conditions: alcohol (0.2 mmol), **1a** (0.5 mmol), Pd(OAc)₂ (1.12 mg), **L12** (11.68 mg), (+)-CSA (9.2 mg) in toluene (1.0 mL), 40 °C, 20 h.

structure of **6i** was confirmed further by X-ray diffraction. Finally, Isosorbide, a diol that is used to treat brain edema and glaucoma, was also compatible in this protocol, producing **6k** in 83% yield.

To demonstrate the usefulness of the resulting products as intermediates in organic synthesis, we performed the effective synthesis of several 4-phenyl-4*H*-pyrans **7a–7j** in 71–85% yield directly from different (non)symmetrical 1,3-diyne

bicyclic, and polycyclic compounds from alkynes in only three steps (alkyne \rightarrow 1,3-diyne \rightarrow 1,3-enyne \rightarrow heterocycles). We believe this procedure, as well as the new ligand design, will complement the available toolbox of carbonylation reactions.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: conjugated enynes · monocarbonylation · P ligands · palladium · selectivity

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