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RESEARCH ARTICLE

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

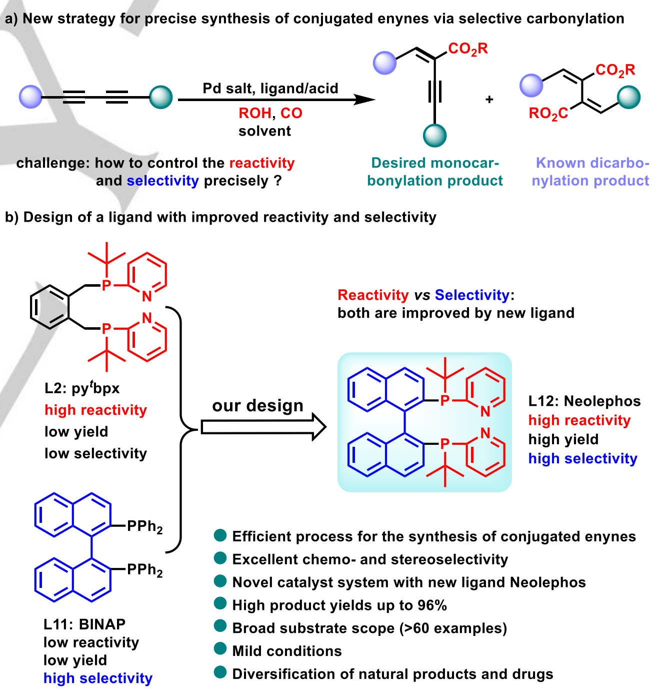
Jiawang Liu, Ji Yang, Carolin Schneider, Robert Franke, Ralf Jackstell and Matthias Beller*

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 (**L12**, 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, which showcase the possibilities of this novel methodology include an efficient one-pot synthesis of 4-aryl-4*H*-Pyrans as well as the rapid construction of various heterocyclic, bicyclic, 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 is also occurring 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, 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 development of 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 due to their key role in controlling the reactivity and selectivity of chemical transformations.[9] Applying transition metal complexes as catalysts, especially the electronic and steric nature of ligands are crucial, which often enables also 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 to known catalytic systems are essential for the development of useful synthetic methodologies.[11] As representative examples, we recently demonstrated the advantage of specific phosphine ligands with built-in-base function for palladium-catalyzed alkoxycarbonylations 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]



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

Based on these work, we started a program to investigate palladium-catalyzed carbonylation of 1,3-diynes,[14] which are easily available substrates from terminal alkynes via 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, which would afford synthetically useful 1,3-enynes. Notably, to the best of our knowledge no general catalytic monocarbonylation process of these substrates has been developed so far.[16] Obviously, a key

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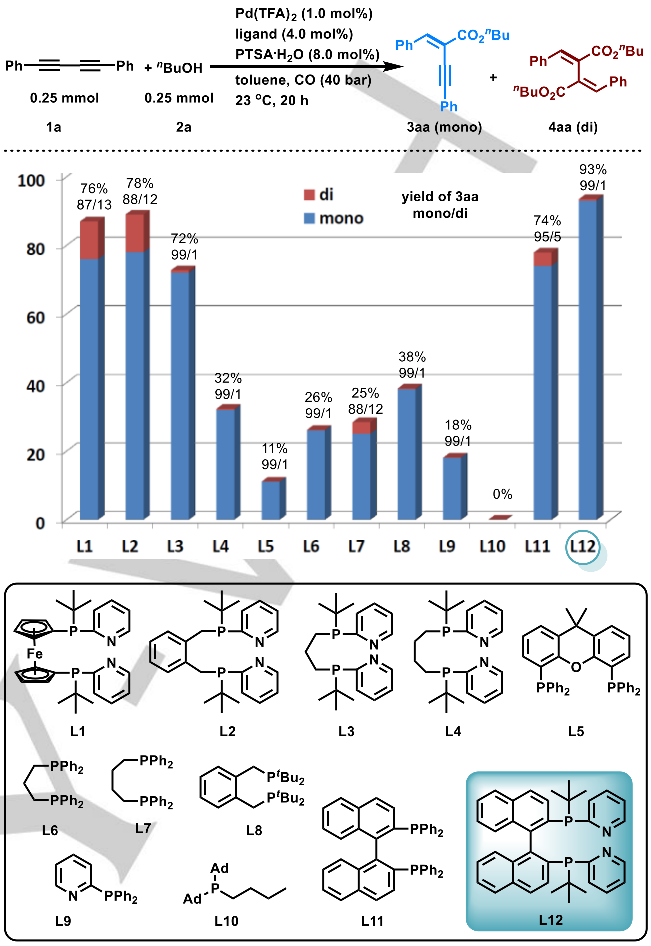
challenge for this transformation is to avoid the generation of double carbonylation products (Scheme 1, a), which could be difficult owing to the similarity between diyne and enyne. Herein, we present a solution for this problem by careful control of the reaction conditions and design of the new ligand **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 alkoxycarbonylations the choice of ligand is crucial for controlling the selectivity and activity of the overall transformation. Thus, we investigated 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·H_2O (*p*-toluenesulfonic acid monohydrate)). In order to avoid multiple carbonylation reactions, only 1 equiv. 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 applying **L1** 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. Using **L3** or **L4** with different ligand backbone, the overall yield of carbonylation products was lower, although high selectivity for **3aa** was realized. Other state-of-the-art ligands which 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*-butylphosphan-yl)methyl)benzene (d^{t}bpx, **L8**),[20] 2-diphenylphosphinopyridine (**L9**)[21] and di(1-adamantyl)-*n*-butyl-phosphine (BuPAd$_2$, **L10**)[22] did not gave the desired product in more than 40% yield. Interestingly, using racemic 2,2'-bis(diphenylphosphanyl)-1,1'-binaphthalene (**L11**, BINAP)[10b, 23] as ligand, **3aa** was obtained in 74% yield and more surprisingly the chemoselectivity was also increased to 95/5. Comparing **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 has never been synthesized, yet. Gratifyingly, 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 since the different stereoisomers have no significant influence in this transformation (for more details, see *SI*).



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·H_2O (4.0 mg, 8.0 mol%) in toluene (1.0 mL). Yields and chemoselectivity were determined by GC and GC-MS analysis.

In order 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 weak acid (Table 1, entries 1 and 2). Even trifluoroacetic acid gave only trace amounts of **3aa**, while pyridine-2-sulfonic acid afforded the desired product in 12 % yield (Table 1, entries 3, 4). Interestingly, using camphorsulfonic acid (CSA), the preferred product **3aa** could be 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% (4h) and 97% (20 h) yield, respectively (Table 1, entries 12 and 13). Notably, smooth transformations with excellent yields and selectivities were also observed in the presence of excess amount of 1-butanol or at higher temperature (Table 1, entries 14 and 15), which demonstrated the preferred selectivity for monocarbonylation.

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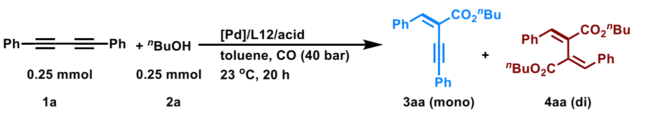
Table 1. Pd-catalyzed monocarbonylation of 1,4-diphenylbuta-1,3-diyne: Investigation of reaction conditions [a]



entry	[Pd]	acid	**3aa/4aa**	yield of **3aa**
1	$Pd(TFA)_2$	No acid	-/-	0
2	$Pd(TFA)_2$	HOAc	-/-	0
3	$Pd(TFA)_2$	TFA	-/-	<5
4	$Pd(TFA)_2$	$2\text{-}PySO_3H$	99/1	12
5	$Pd(TFA)_2$	HOTf	99/1	45
6	$Pd(TFA)_2$	$PTSA{\cdot}H_2O$	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 mol ^nBuOH was used. [d] 40 °C. [e] Isolated yield.

To understand the behavior of **L12** in controlling the chemoselectivity, we studied the kinetic process of the alkoxycarbonylation of 1,4-diphenylbuta-1,3-diyne **1a** with *n*-butanol (1.0 equiv.). As shown in Figure 2 (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. In order to get more insight into the activity and selectivity of ligand **L12**, the reaction was also performed at room temperature using a large excess of methanol (solvent). As depicted in Figure 2 (b), again 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 alkoxycarbonylation using ligands **L1**-**L4**[12-14] as well as the mechanistic studies by Cole-Hamilton, Drent and Sparkes[24], here we propose the following catalytic cycle for ligand **L12** [Figure 2 (c)]. Initially, the stable Pd(II) salt is *in situ* reduced to Pd(0) in the presence of excess amount of phosphine ligands[25] followed by protonation process to afford the active complex **A**. Probably, 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 close the 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 optimized reaction conditions in hand (for details see Supporting Information), we studied the monoalkoxycarbonylation of 30 different 1,3-diynes 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 ones 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-diynes **1a**–**i** with either electron-donating (OMe, Me, ^tBu) or electron-withdrawing (F, CF_3) substituents on the phenyl ring provided the corresponding products **3aa**–**3ai** in high yields (83-95%) and excellent selectivity at 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-diynes. Gratifyingly, the palladium-catalyzed monoalkoxycarbonylation of various given 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. Besides, the simple 1,3-diynes **1m**-**1o**, the cyclohexyl- and cyclopropyl-substituted 1,3-diynes **1p** and **1q**, also gave the preferred products in 55-90% yield and high selectivity under mild conditions.

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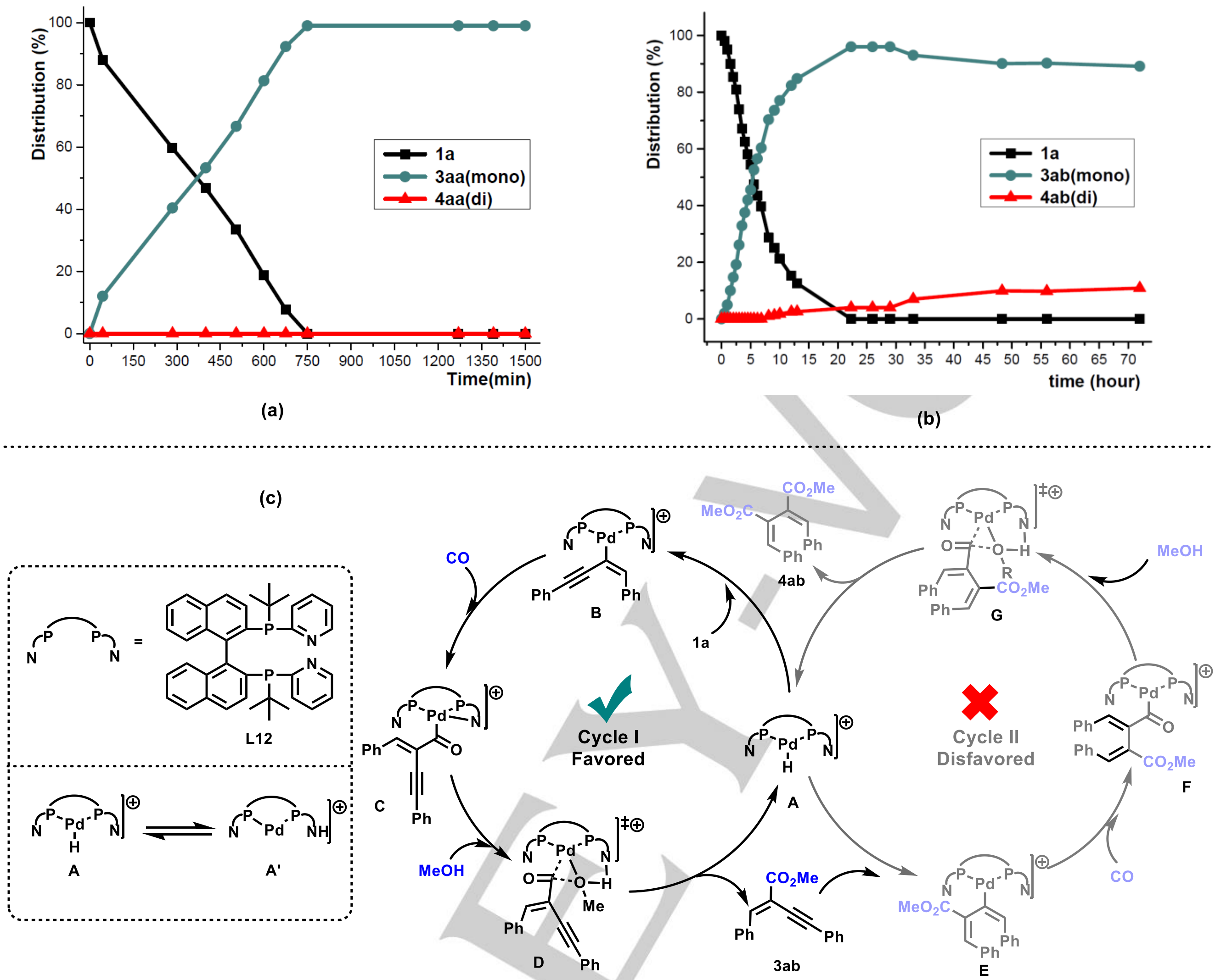

Figure 2. (a) Compounds distribution of Pd-catalyzed alkoxycarbonylation of **1a** in the presence of **L12** (reaction conditions: 1.0 mol% of Pd $(OAc)_2$, 4.0 mol% of **L12**, 8.0 mol% (+)-CSA, 5 mol of 1a, 5.0 mmol of 1-butanol, 20 mL of toluene, 23 °C). (b) Compounds distribution of Pd-catalyzed methoxycarbonylation of 1a in the presence of **L12** (Reaction condition: 1.0 mol% of Pd $(TFA)_2$, 4.0 mol% of L12, 8.0 mol% PTSA·H_2O, 2.5 mol of 1a, 25 mL of MeOH, 23 °C). (c) Plausible catalytic cycle for the generation of **3ab** and **4ab**.

Furthermore, substrates bearing substituents such as chloride, cyano, ester and trimethylsilyl also smoothly underwent monocarbonylation and gave the desired products **3sa**–**3wa** in 74-84% yields. Then, the scope of non-symmetric 1,3-diynes, 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. While in this case the carbonylation proceeded slightly more 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) as the main products. Nevertheless, depending on the substrate the regioselectivity for the monocarbonylation can be also very high allowing the synthesis of interesting functionalized building blocks. More specifically, propargyl ester/amide-derived 1,3-diynes **5b**, **5c**, **5d** and **5e** which are often sensitive to palladium catalysis, worked particularly well, affording the corresponding products with excellent regioselectivies (>20/1). Moreover, carbonylation of unsymmetrical 1,3-diyne **5f** preferentially occurred at the phenyl-substituted triple bond, affording regioselectively (92/8) product **5fa** in 80% yield.

Next, we examined the general scope of this monoalkoxy-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

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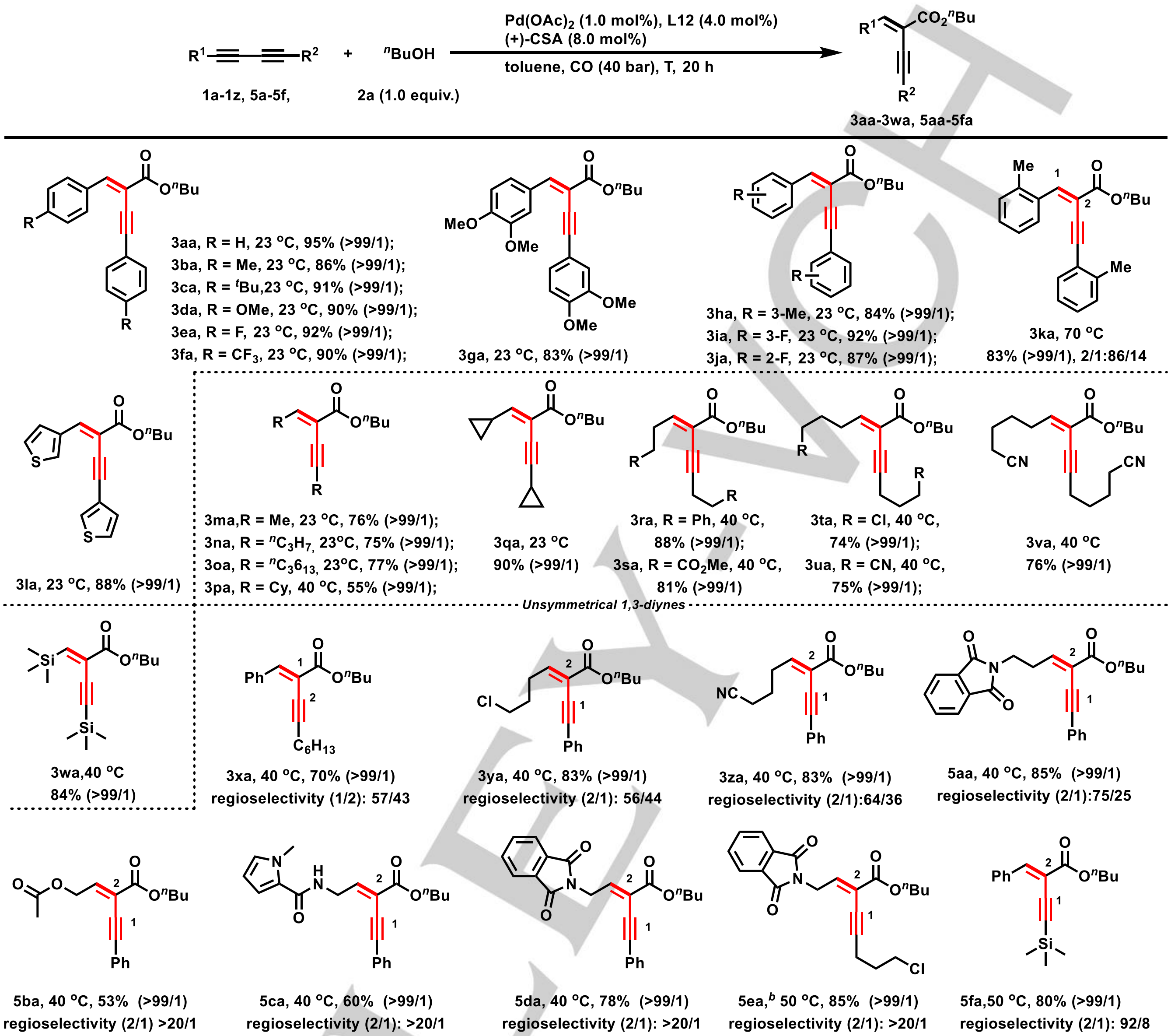
Table 2. Pd-catalyzed monocarbonylation of 1,3-diynes with *n*-butanol: Substrate scope [a]



[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 were isolated yields for all products by column chromatography. The chemoselectivity in brackets (mono/di) were determined by GC analysis. The regioselectivity of **3xa**-**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.

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**-**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, the constituent of cosmetic fragrances such as (*Z*)-Nerol and (*R*)-

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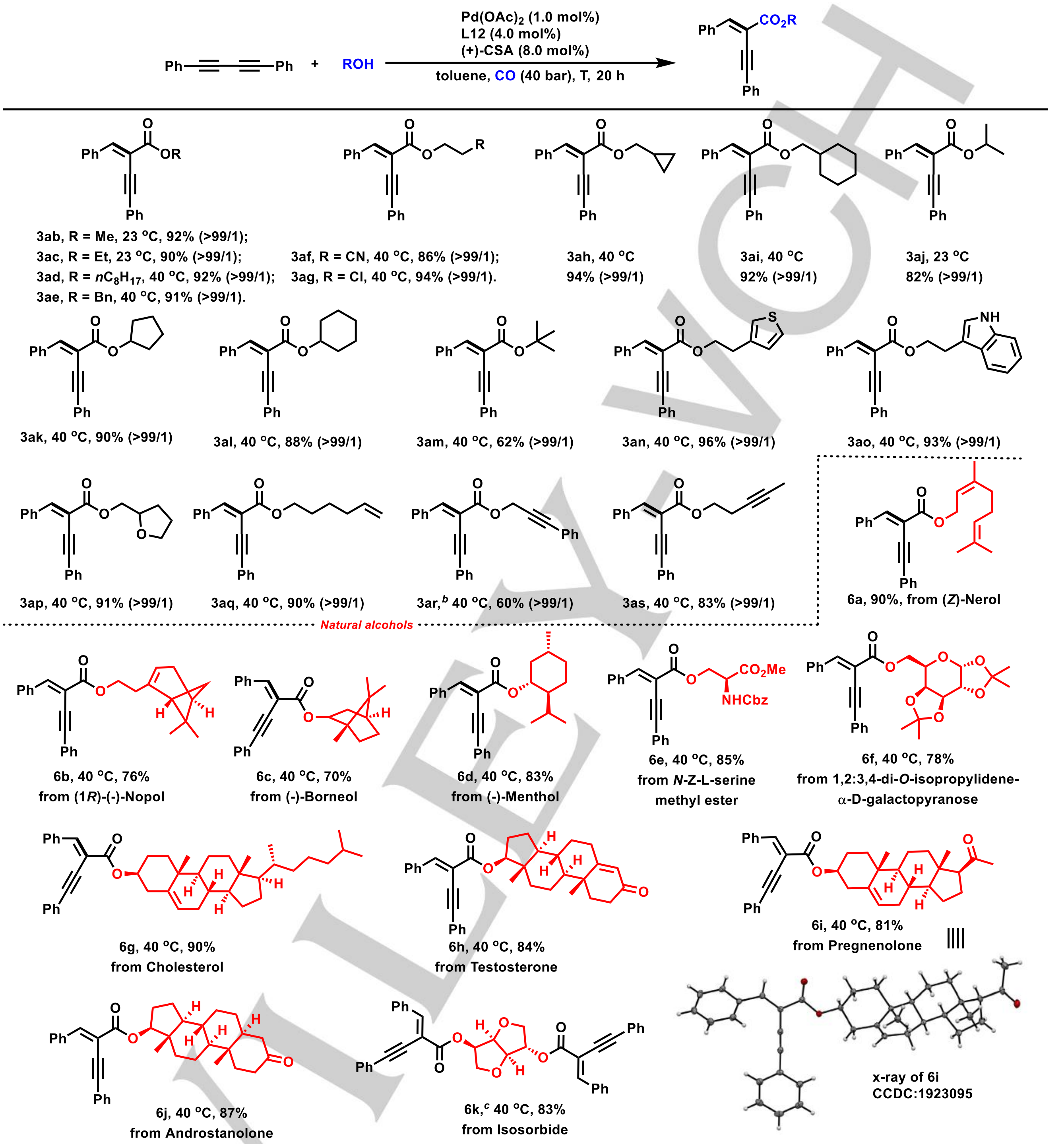
Table 3. Pd-catalyzed monoalkoxycarbonylation of 1,3-diynes: Alcohol scope[a]



[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 were isolated yields for all products 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.

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 which is also the component of many essential oils and natural insect repellent, and (-)-Menthol, which is widely used in many aspects for its medicinal value, furnished the carbonylative

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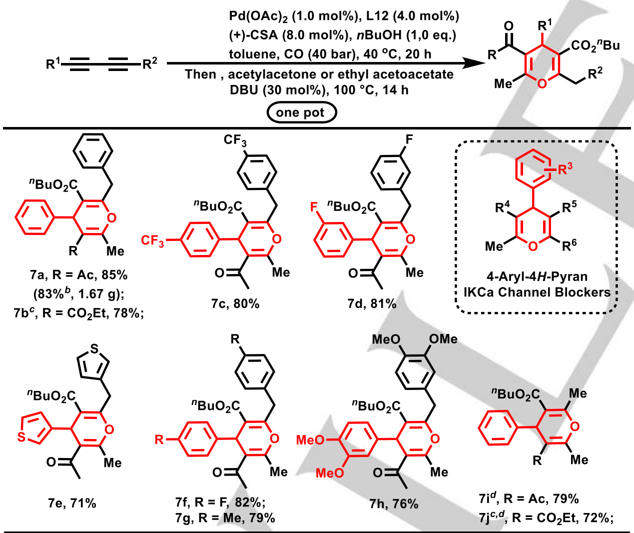
products **6c** and **6d** in 70-83% yield. Applying *L*-serine and α-*D*-galactopyranose derivatives as other representative examples of biologically relevant molecules afforded the desired products **6e** and **6f** in 78-85% yield. Furthermore, cholesterol, which is an essential structural component of all animal cells that 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, and the structure of **6i** was confirmed further by the X-ray diffraction. Finally, Isosorbide, a diol which is used to treat brain edema and glaucoma, was also compatible in this protocol, producing **6k** in 83% yield.

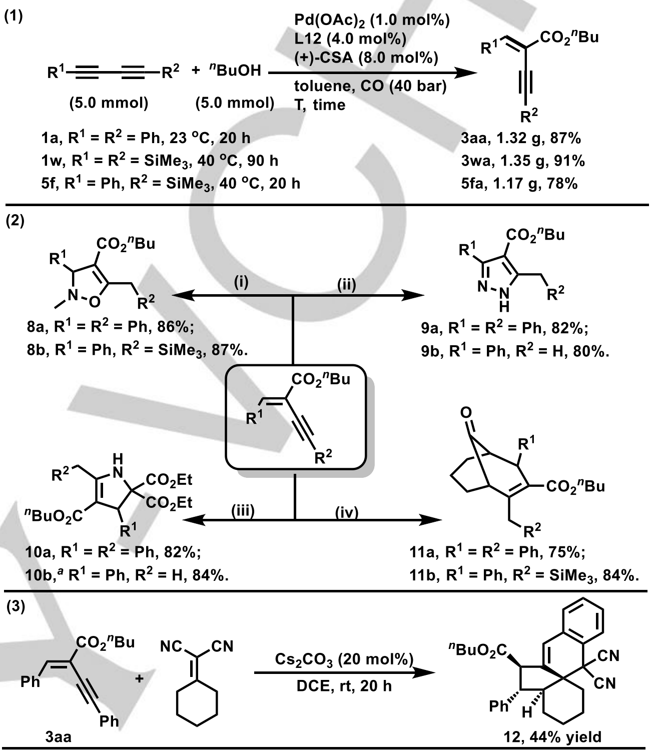
To demonstrate exemplarily the usefulness of the resulting products as intermediates in organic synthesis, we performed the effective synthesis of several 4-phenyl-4*H*-pyrans **7a**-**7j** in 71-85% yield directly from different (non)symmetrical1,3-diynes (Table 4). This novel one-pot process includes our carbonylation reaction combined with a base-catalyzed [3+2] cycloaddition. It should be noted that 4-aryl-4*H*-pyrans, especially the products **7i** and **7j**, have been identified as potent and specific IKCa channel blockers[26a] and 4*H*-pyran scaffolds found many applications in biologically and pharmacologically active molecules. [26]

Table 4. Direct synthesis of substituted 4-phenyl-4*H*-pyrans[a]



[a] Reaction conditions: step1: 1,3-diynes (0.25 mmol), *n*-butanol (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), toluene (1.0 mL), 40 °C, 20 h and step 2: acetylacetone (0.3 mmol), DBU (30 mol%), DMF (1.0 mL) were added and heated to 100 °C for 14 h. The yields were isolated yields for all products by column chromatography. [b] The isolated yield of **7a** using 5 mmol scale of 1,3-diyne. [c] Ethyl acetoacetate (0.3 mmol) was used instead of acetylacetone. [d] The 1,3-diyne **5f** was used and the trimethylsilyl group was removed under these conditions.

Advantageously, the presented methodology can be easily scaled up as shown by the gram-scale synthesis of **3aa**, **3wa** and **5fa** using 5.0 mmol of 1,4-diphenylbuta-1,3-diyne **1a**, 1,4-bis(trimethylsilyl)buta-1,3-diyne **1w** and trimethyl(phenylbuta-1,3-diyn-1-yl)silane **5f** under standard reaction conditions, affording **3aa**, **3wa** and **5fa** in 87%, 91%, and 78% yield, respectively [Scheme 3, (1)].



Scheme 3. Gram-scale synthesis of **3aa**, **3wa**, and **5fa** and their further synthetic transformations. Reagents and conditions: (i) MeNHOH·HCl , trimethylamine, DCE, 0 °C for 10 h, then rt for 10 h. (ii) $NH_2NH_2{\cdot}H_2O$, K_2CO_3, DMA, 40 C, air, 24 h. (iii) Diethyl aminomalonate hydrochloride, DBU, DMF, 40 °C, 12 h. (iv) Cyclohexanone, pyrrolidine, $InCl_3$, 4Å molecular sieves, DCE, 80 °C, 20 h. [a] rt, 20 h.

As mentioned in the introduction *vide supra*, 1,3-enynes are important synthons in organic in organic chemistry. With this particular carbonylation methodology available, we are able to provide a diverse array of new building blocks. Indeed, except for two compounds (**3ab** and **3ac**) all the other prepared products were synthesized here for the first time, also demonstrating the novelty of our approach. To showcase the usefulness of these now easily accessible building blocks, various follow up transformations were conducted using **3aa** or **5fa** as starting material (Scheme 3). For example, *tri*-substituted 2,3-dihydroisoxazoles **8a** and **8b** were obtained in 86-87% yield in the presence of *N*-methyl hydroxylamine hydrochloride and TEA [(triethyl)-amine].[27] The similar reaction was performed using hydrazine and K_2CO_3, affording pyrazole compound **9a** in 82%.[28] Interestingly, when using **5fa** under the same conditions, the trimethylsilyl group was removed and product **9b** was afforded in 80% yield. Treatment of **3aa** with diethyl aminomalonate hydrochloride and DBU provided the 2,3-dihydro-1*H*-pyrroles **10a** via a formal [3+2] cycloaddition.[29] Similarly, **10b** was produced in

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84% yield from **5fa** under slightly modified conditions and again the trimethylsilyl group was removed. Moreover, the bicyclo[3.3.1]alkenones **11a** and **11b**, which are present in numerous bioactive natural products were also achieved by In-catalyzed intermolecular α, α'-annulation of enamine with **3aa** and **5fa**.[30] Finally, the facile synthesis of angularly fused polycycles **12**[31] illustrated the diverse possibilities of the prepared conjugated enynes for the construction of complex molecules.

Conclusion

In summary, we have developed the first general monoalkoxycarbonylation of 1,3-diynes with aliphatic alcohols to produce a variety of synthetically useful conjugated 1,3-enynes with excellent chemoselectivities. Key to success is the design of a tailored palladium catalyst based on the new ligand Neolephos, allowing efficient monocarbonylation. Notably, most of the synthesized products are new, because the preparation of this scaffold was previously not an easy task. The synthetic utility of our protocol was showcased further in the rapid construction of various heterocyclic, bicyclic, polycyclic compounds from alkynes in only three steps (alkyne → 1,3-diyne → 1,3-enyne → heterocycles). We believe this procedure as well as the new ligand design will complement the available toolbox of carbonylation reactions.

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Keywords: P ligand• palladium• monocarbonylation• conjugated enynes• selectivity

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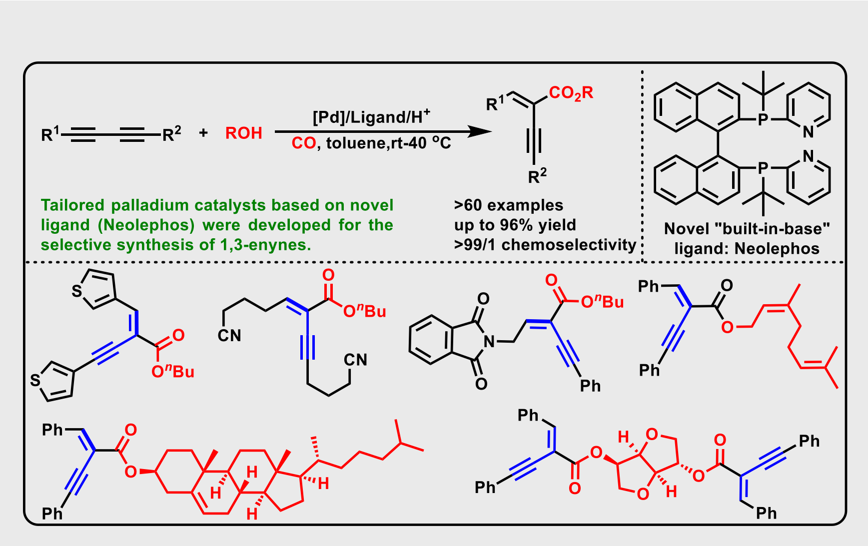

*Jiawang Liu, Ji Yang, Carolin Schneider, Robert Franke, Ralf Jackstell and Matthias Beller**

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

Precise synthesis enabled by novel catalyst: The new "built-in-base" ligand Neolephos was designed and applied in Pd-catalyzed monocarbonylation of 1,3-diynes, allowing for precise synthesis of conjugated enynes in good to high yield with excellent chemo- and stereoselectivity. The presented methodology can be used for simple diversification of natural products and pharmaceuticals, including steroids, diols, amino acids, and carbohydrates.

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