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Article

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Selective Palladium-Catalyzed Carbonylation of Alkynes: An Atom-Economic Synthesis of 1,4-Dicarboxylic Acid Diesters

Jiawang Liu,[†] Kaiwu Dong,[†] Robert Franke,[‡,§] Helfried Neumann,[†] Ralf Jackstell,[†] and Matthias Beller*[,†]

[†]Leibniz-Institut für Katalyse e.V. an der Universität Rostock, Albert-Einstein-Str. 29a, Rostock, 18059, Germany

[‡]Lehrstuhl für Theoretische Chemie, Ruhr-Universität Bochum, 44780 Bochum, Germany

[§]Evonik Performance Materials GmbH, Paul-Baumann-Str. 1, 45772 Marl, Germany

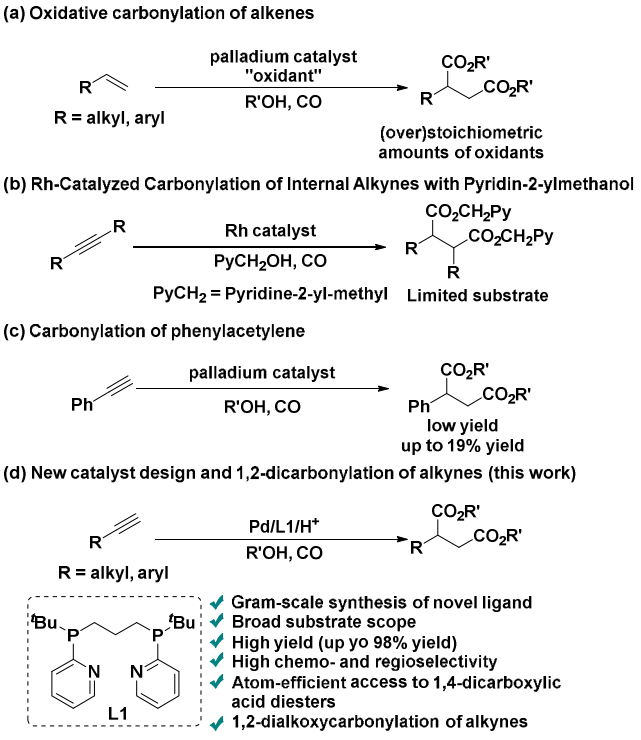
KEYWORDS: P ligand• palladium• 1,2-dialkoxycarbonylation• selectivity• alkynes.

ABSTRACT: A class of novel diphosphine ligands bearing pyridine substituents was designed and synthesized for the first time. The resulting palladium complexes of **L1** allow for chemo- and regioselective dialkoxycarbonylation of various aromatic and aliphatic alkynes affording a wide range of 1,4-dicarboxylic acid diesters in high yields and selectivities. Kinetic studies suggest the generation of 1,4-dicarboxylic acid diesters via cascade hydroesterification of the corresponding alkynes. Based on these investigations, the chemo- and regioselectivities of alkyne carbonylations can be controlled as shown by switching the ligand from **L1** to **L3** or **L9** to give α, β-unsaturated esters.

INTRODUCTION

1,4-Dicarboxylic acids represent an interesting structural motif for organic synthesis and biochemistry. In this respect, succinic acid diesters were used for the synthesis of inhibitors of renin, [1] and matrix metalloproteinase. [2] In addition, they are of general interest for polymers and material sciences. [3] However, compared to other (mono)carboxylic acids their full potential has not been exploited due to the more difficult synthesis.

In general, the oxidative alkoxycarbonylation of olefins constitutes a straightforward method for the synthesis of these compounds from readily available substrates (Scheme 1, a). [4] However, this methodology suffers from the low atom economy, the use of (over)stoichiometric amounts of oxidants and relatively high palladium catalyst loading. Alternatively, 1,4-dicarboxylic acid esters can be synthesized by dialkoxycarbonylation of alkynes. Despite the intrinsic advantage of this more atom-efficient route, dicarbonylations of alkynes have scarcely been explored. In this respect, Chatani and co-workers reported Rh-catalyzed chelation-assisted alkoxycarbonylation of internal alkynes (Scheme 1, b). However, this transformation needs the special alcohol pyridin-2-yl-methanol. [5] Palladium-catalyzed alkoxycarbonylations of terminal alkynes, reported by Alper, [6] Drent, [7] and others [8], afford mainly α-substituted propenoate esters. More recently, Cole-Hamilton and co-workers reported the alkoxycarbonylation of phenylacetylene with unusual linear regioselectivity, and the formation of α,ω-diesters from aliphatic terminal alkynes by utilizing 1,2-bis(di-tert.butyl-phosphinomethyl)benzene as the ligand.[9] In principle, both the branched and linear α,β-unsaturated esters can be potentially further transformed into dicarboxylates.[10] Nevertheless, to the best of our knowledge, no general catalytic process has been developed so far, although several catalysts have been tested for phenylacetylene and only low yield (up to 19% yield) was achieved from the activated alkyne (Scheme 1, c). [8e, 9, 11] Crucial for such domino process is the activity of the palladium catalyst both for the alkoxycarbonylation of the substrate alkyne and the in situ generated olefins, respectively. More specifically, a key challenge is the transformation of the sterically hindered internal olefin intermediate. Another problem is the control of regioselectivity in the two carbonylation steps. Consequently, there is a need for the development of more active catalysts for the 1,2-dialkoxycarbonylation of alkynes.



Scheme 1. Selective synthesis of 1,4-dicarboxylic acid diesters via alkoxycarbonylation of alkenes or alkynes

The development of ligands plays a key role in enabling new transformations and controlling the selectivity in homogenous catalysis.

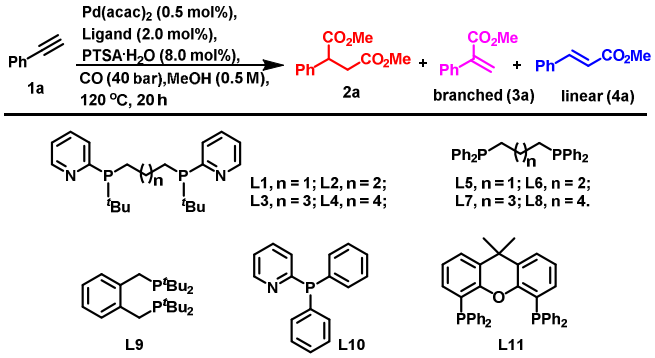
As an example, we recently reported the palladium-catalyzed alkoxycarbonylation of less-reactive olefins including highly hindered internal alkenes with high activities and good regioselectivities.[12] Here, the incorporation of *tert*-butyl and pyridine substituents on the phosphorous atom into the 1,2-bis((di-tert-butylphosphan-yl)methyl)benzene (btbpx) ligand dramatically improved the rate of the nucleophilic attack on the intermediate palladium acyl complex, which can be rate-limiting in these catalytic protocols.[13] 1,3-Bis-diphenylphosphinopropane (**L5**, dppp) and 1,4-bis-diphenylphosphinobutane (**L6**, dppb) are privileged ligands for a variety of catalytic applications, including several carbonylation reactions. Conceptually, we thought the introduction of both alkyl and pyridine substituents on the phosphorous similar to btbpx should lead to more active ligands, too. Surprisingly, to the best of our knowledge analogous ligands **L1**-**L4** have not been synthesized yet.

Based on our continuous interest in the development of novel carbonylation catalysts and their applications,[14] we herein present our recent investigation on the design and synthesis of ligands **L1**-**L4** (see supporting information for more details) and their superior applications in the dialkoxycarbonylation of alkynes affording 1,4-diesters in high yields (Scheme 1, d).

RESULTS AND DISCUSSION

To prove the possibility of catalytic 1,2-dialkoxycarbonylations, the reaction of phenylacetylene **1a** was performed under conditions typical for Pd-catalyzed olefin alkoxycarbonylation (0.5 mol% Pd catalyst, 8 mol% PTSA, 40 bar CO, 120 °C). Initially, $Pd(acac)_2$ was used as pre-catalyst in the presence of the novel unsymmetrical ligands **L1**-**L4** and related commercially available bidentate derivatives **L5**-**L8**. Furthermore, benchmark ligands such as btbpx **L9**, 2-diphenylphosphinopyridine **L10** and Xantphos **L11** were tested. As a proof of our concept, applying **L1** we obtained the desired product **2a** in high yield (88%) with good chemoselectivity (**2a**/**3a**/**4a** = 88/5/7, Table 1, entry 1). In the presence of **L2** with an extended methylene chain **2a** was also afforded, albeit with lower chemoselectivity and yield (38%)(Table 1, entry 2). Interestingly, using **L3** and **L4** with C5 and C6 backbones led to significantly less active catalysts, which are not able to further convert the branched product **3a**. Nevertheless, these ligands are attractive for the selective synthesis of such acrylates because of the good chemoselectivities (91-89%) observed (Table 1, entries 3 and 4). To demonstrate the importance of the phosphines bearing *tert*-butyl and pyridine substituents, we examined ligands **L5**-**L8**, which have the same backbones but diphenylphosphino end groups. Based on the fundamental work of Cole-Hamilton [9] and Drent, [7] state-of-the-art ligands 1,2-bis((di-tert-butylphosphan-yl)methyl)benzene **L9** and 2-diphenylphosphinopyridine **L10** were explored next. While the former ligand gave less than 5% of the 1,2-dicarbonylation product but afforded **4a** as the main product, the later ligand gave only traces of **2a** (Table 1, entry 9 and 10). Next to our new system, Xantphos **L11** gave the best performance to the desired product, albeit with moderate chemoselectivity (Table 1, entry 11). At this point it should be noted that the new ligand **L1** displayed the highest selectivity and activity allowing for the conversion of the initially formed monocarbonylation product. In the presence of this optimal ligand, the selectivity and yield of **2a** can be further improved to 95/2/3 and 94%, respectively, simply by lowering the temperature to 100 °C (Table 1, entry 12). Finally, **2a** was obtained in >99/0/<1 selectivity and 98% isolated yield using 1.0 mol% of catalyst (Table 1, entry 13).

Table 1. Pd-catalyzed alkoxycarbonylation of phenylacetylene: Variation of ligands and reaction conditions[a]



entry	Ligand	Conv. (%)[b]	**2a**/**3a**/**4a**[b]	Yield (%) of **2a**[b]
1	**L1**	>99	88/5/7	88
2	**L2**	>99	40/26/30	38
3	**L3**	>99	0/91/9	0
4	**L4**	>99	0/89/11	0
5	**L5**	>99	41/6/53	29
6	**L6**	>99	6/41/53	<5
7	**L7**	76	0/77/23	0
8	**L8**	74	0/83/17	0
9	**L9**	>99	5/1/94	<5
10	**L10**	>99	1/98/1	trace
11	**L11**	>99	68/2/30	60
12[c]	**L1**	>99	95/2/3	94
13[d]	**L1**	**>99**	**>99/0/<1**	**99 (98[e])**
14[f]	**L3**	>99	0/95/5	0 (90[g])

[a] Unless otherwise noted, all reactions were performed in MeOH (2.0 mL) at 120 °C for 20 h in the presence of **1a** (1.0 mmol), $Pd(acac)_2$ (1.52 mg, 0.005 mmol), $PTSA{\cdot}H_2O$ (16 mg, 0.08 mmol), ligand (0.02 mmol, 0.04 mmol for **L10**) and CO (40 bar). [b] The conversion, the ratio of **2a**/**3a**/**4a** and the yield were determined by GC using isooctane as the internal standard. [c] 100 °C. [d] 1.0/4.0/16.0 mol% of Pd/ligand/$PTSA{\cdot}H_2O$ was used. [e] Isolated yield of **2a** by column chromatography. [f] 80 °C. [g] Isolated yield of the branched product **3a** by column chromatography.

In order to understand the different ligand behavior in more detail, we studied the progress of the alkoxycarbonylation of phenylacetylene **1a** in the presence of **L1**, **L3**, and **L9**. First, we performed the Pd-catalyzed alkoxycarbonylation of **1a** in the presence of **L1**. As shown in Figure 1 (a), there is an induction period (about one hour), which is in part a result of the initial heating of the autoclave from rt to 100°C. After that, the yield of desired product **2a** increased quickly and the starting material **1a** was fully converted after two hours. Over the course of the reaction, formation of **3a** and **4a** was observed only in small amounts (maximum 20% yield),

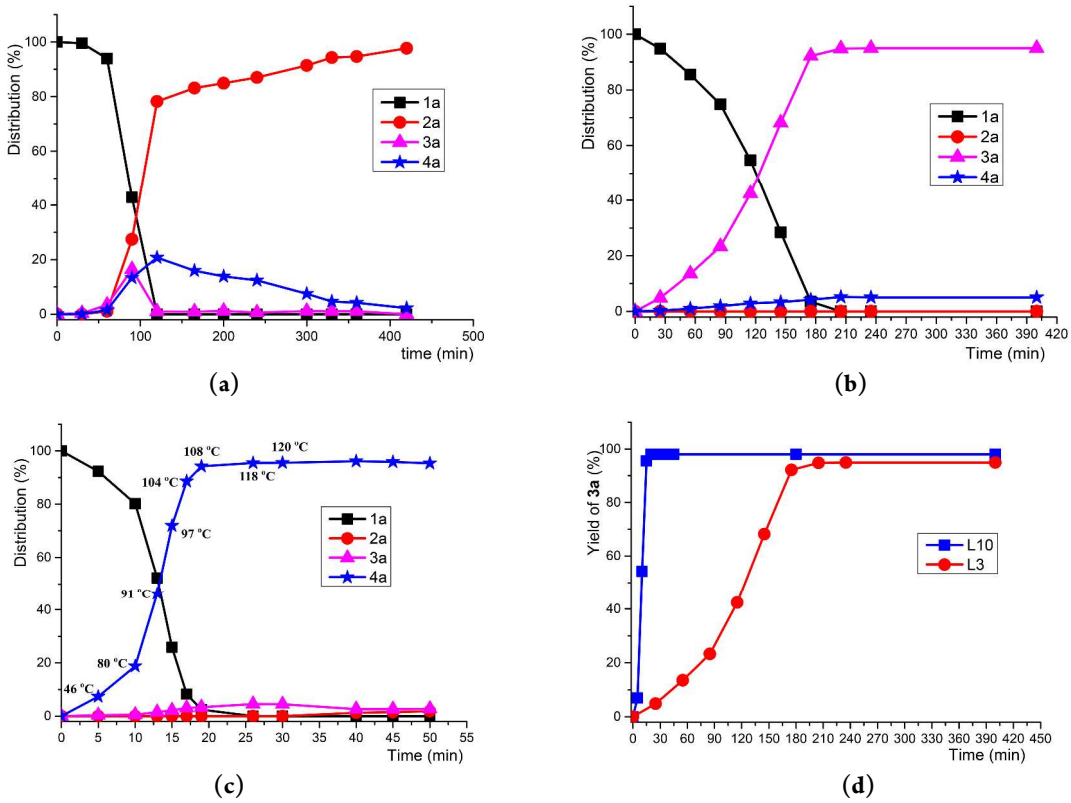
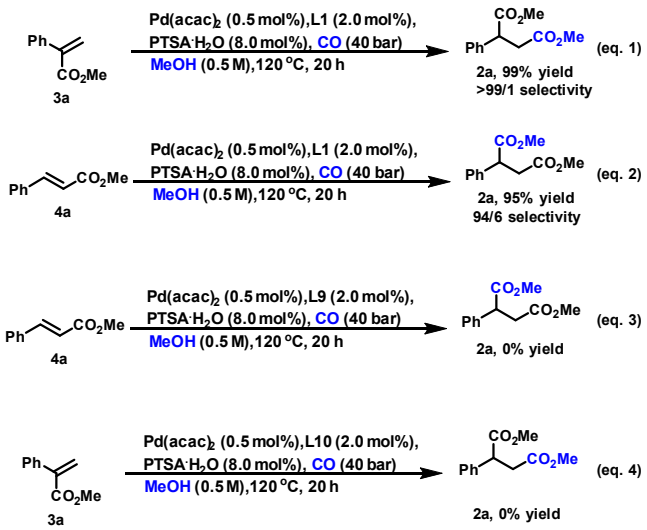


Figure 1. (a) Compounds distribution of Pd-catalyzed alkoxycarbonylation of phenylacetylene **1a** in the presence of **L1**. Reaction condition: 1.0 mol% of Pd $(acac)_2$, 4.0 mol% of **L1**, 16.0 mol% PTSA·H_2O, 10 mol of phenylacetylene (1.1 mL), 20 mL of MeOH, 100 °C, CO (40 bar); (b) Compounds distribution of Pd-catalyzed alkoxycarbonylation of phenylacetylene **1a** in the presence of **L3**. Reaction condition: 0.5 mol% of Pd $(acac)_2$, 2.0 mol% of **L1**, 8.0 mol% PTSA·H_2O, 10 mol of phenylacetylene (1.1 mL), 20 mL of MeOH, 80 °C, CO (40 bar); (c) Compounds distribution of Pd-catalyzed alkoxycarbonylation of phenylacetylene **1a** in the presence of **L9**. Reaction condition: 0.5 mol% of Pd $(acac)_2$, 2.0 mol% of **L9**, 8.0 mol% PTSA·H_2O, 10 mol of phenylacetylene (1.1 mL), 20 mL of MeOH, 120 °C, CO (40 bar); (d) Comparison of **L3** and **L10** in the Pd-catalyzed alkoxycarbonylation of phenylacetylene **1a**. Reaction condition: 0.5 mol% of Pd $(acac)_2$, 2.0 mol% of **L3** or 4.0 mol% of **L10**, 8.0 mol% PTSA·H_2O, 10 mol of phenylacetylene (1.1 mL), 20 mL of MeOH, 80 °C, CO (40 bar).



Scheme 2. Control experiments

which is explained by their fast transformation into **2a**. In agreement with this observation, independent reactions using **3a** and **4a** under standard conditions gave **2a** in excellent yields and selectivities (99% and 96% yields, >99/1 and 94/6 selectivities, respectively (Scheme 2, eq. 1 and eq. 2). In more detail Figure 1 (a) also reveals that the alkoxycarbonylation of **4a** is slower than **3a** as shown by the increased reaction time. Hence, the carbonylation of **4a** should be the rate-limiting step in this dicarbonylation process.

Next, the same reaction of **1a** with the chain-extended ligand **L3** was investigated [Figure 1 (b)]. Interestingly, here **3a** was formed selectively without further carbonylation, due to the much lower activity of the Pd/**L3** catalyst system for alkoxycarbonylation of olefins.[15] On the other hand, **4a** can be obtained highly selective in the presence of **L9**, which does not react with internal alkenes [Figure 1 (c)]. Thus, excellent regioselectivity for the linear product was observed. It's worthy to note that this catalytic system (Pd/L9) is active even at low temperature. Indeed, after 5 minutes at a temperature of 46°C the yield of the linear product **4a** is already around 10%.

Finally, a comparison of **L3** and **L10**, which is also an excellent ligand for branched selectivity, was performed under the same reaction conditions. As shown in Figure 1 (d), although the activity is lower than **L10**, the reaction of **1a** in the presence of **L3** was accomplished within three hours in excellent yield and regioselectivity. To explain the superior behavior of **L1** compared to the previous state-of-the-art ligands, control experiments were conducted under the same reaction conditions using **3a** and **4a** in the presence of **L9** and **L10**, respectively. However, no desired product **2a** was observed (Scheme 2, eq. 3 and eq. 4).

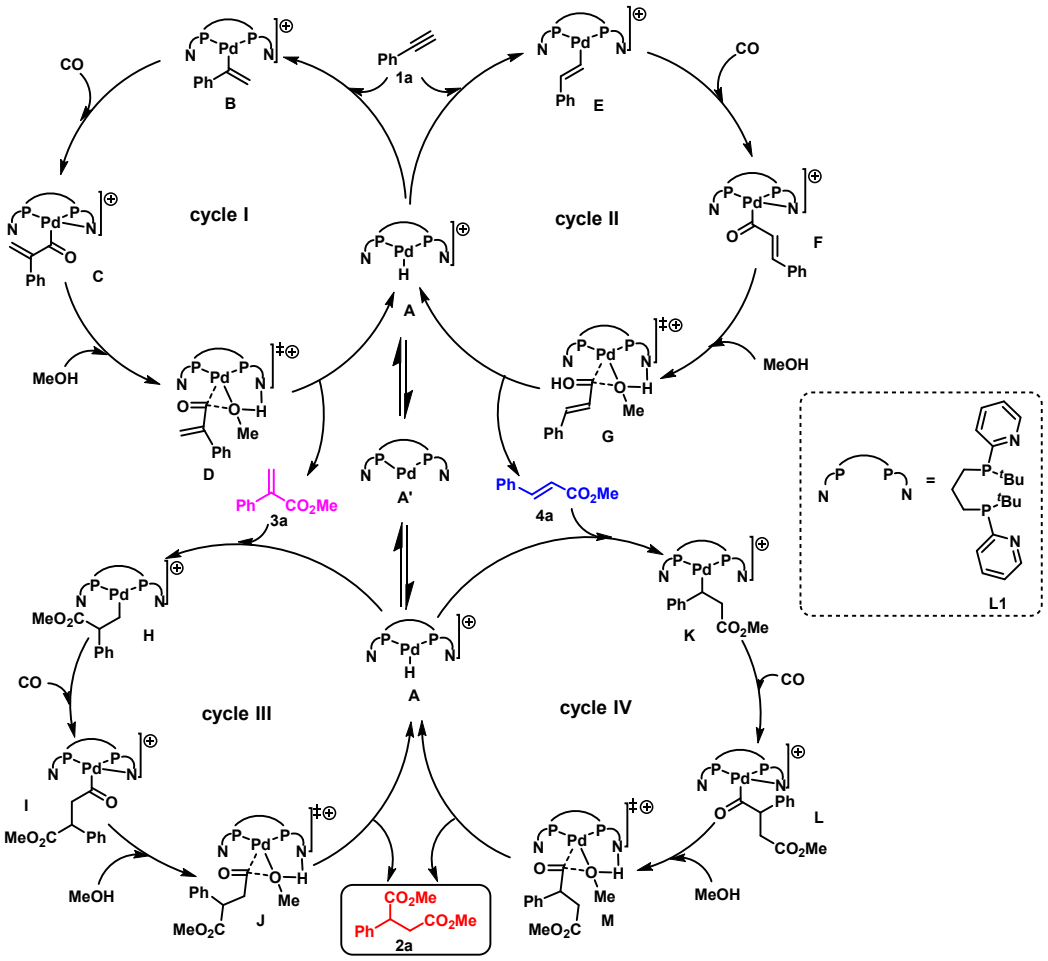
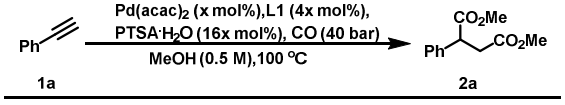


Figure 2. Proposed catalytic cycle for Pd-catalyzed 1,2-dicarbonylation of alkynes in the presence of L1

On the basis of all these results, we propose the following catalytic cycle for the novel palladium-catalyzed 1,2-dicarbonylation of alkynes in the presence of **L1** (Figure 2). Initially, the stable Pd(II) catalyst precursor is in situ reduced to Pd(0) species **A'** in the presence of excess amount of phosphine ligands.[16] The next step is the protonation of the complex **A'** to afford the active palladium hydride species **A**. Probably, the proton binds in equilibrium to the N atom of the pyridine ring on the phosphine ligand and directly to the palladium center. [15] Subsequently, π-coordination of the carbon-carbon triple bond to the metal center, followed by the insertion of the alkyne into the palladium hydride bond, affords alkenyl-Pd intermediate **B** and **E**. These regioisomers undergo CO insertion to give the acyl palladium species **C** and **F**, respectively. *N*-Assisted methanolysis of intermediates **C** and **F** via transition state **D** and **G** provides the branched and linear α,β-unsaturated esters **3a** and **4a** individually and regenerates the active palladium hydride species, to finish cycles **I** and **II**. In the presence of **L1**, **3a** coordinates to palladium hydride species again and selective insertion of the terminal double bond will give the intermediate **H**, which undergoes another CO insertion process to afford acyl palladium species **I**. Finally, *N*-assisted methanolysis of intermediate **I** affords the desired 1,4-dicarbonylic acid diester **2a** and again regenerates palladium hydride species **A** to close the cycle **III**.

On the other hand, the internal olefin **4a**, which is the least reactive olefin, also coordinates to **A**, followed by the selective insertion into the palladium hydride bond, affording palladium intermediate **K**. After CO insertion, the palladium complex **L** is formed and again *N*-assisted methanolysis leads to **2a** and regenerates the active hydride complex **A** to end cycle **IV**.

It should be noted, that this novel dialkoxycarbonylation process can be performed with high catalyst turnover numbers (TON = 1600) without any further optimization, simply by increasing the substrate amount (Scheme 3).

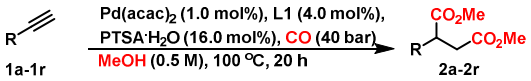


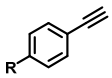
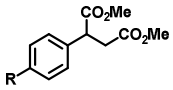
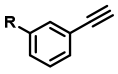
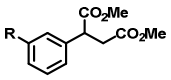
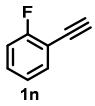
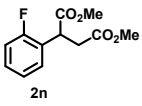
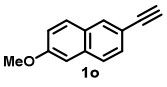
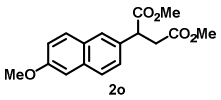
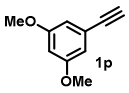
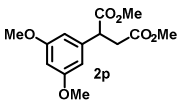
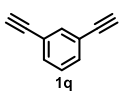
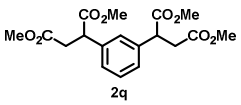
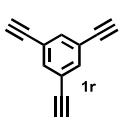
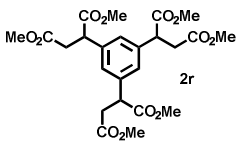
10 mmol 1a, 1.0 mol% [Pd]	2.1 g, 95% yield 99/1 selectivity
20 mmol 1a, 0.05 mol% [Pd]	80% yield TON = 1600

Scheme 3. Gram-scale synthesis of 2a.

With the optimized reaction conditions established (for details see Supporting Information), we explored the substrate scope of our catalytic protocols. First, we studied the novel dialkoxycarbonylation of different terminal alkynes using $Pd(acac)_2$/**L1**/PTSA (1.0/4.0/16.0 mol%) as the catalyst. As shown in Table 2 and

Table 2. Pd-catalyzed dialkoxycarbonylation of aromatic alkynes: Substrate scope [a]

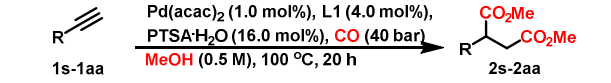


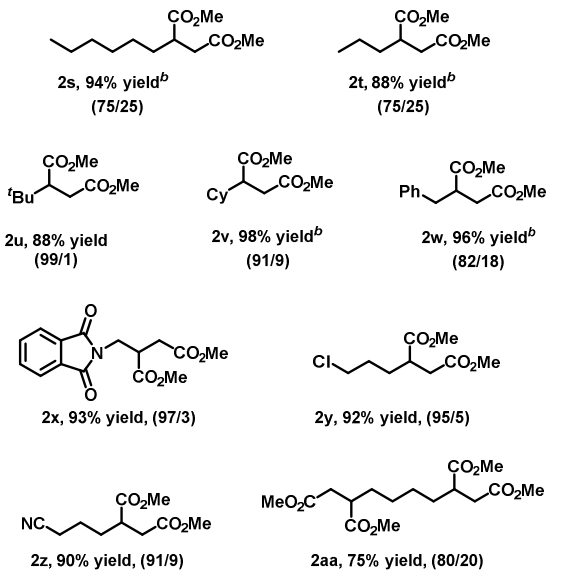
Entry	Alkynes	Products	Yield (%) (Sel.)
			
1	**1a**, R = H	**2a**, R = H	98 (99/1)
2	**1b**, R = Me	**2b**, R = Me	94 (99/1)
3	**1c**, R = F	**2c**, R = F	97 (99/1)
4	**1d**, R = OMe	**2d**, R = OMe	95 (99/1)
5	**1e**, R = CN	**2e**, R = CN	85 (99/1)
6	**1f**, R = Cl	**2f**, R = Cl	87 (99/1)
7	**1g**, R = Br	**2g**, R = Br	86 (99/1)
8	**1h**, R = CF_3	**2h**, R = CF_3	92 (99/1)
9	**1i**, R = CO_2Me	**2i**, R = CO_2Me	89 (99/1)
10	**1j**, R = ^{t}Bu	**2j**, R = ^{t}Bu	95 (99/1)
			
11	**1k**, R = Me	**2k**, R = Me	95 (99/1)
12	**1l**, R = Cl	**2l**, R = Cl	90 (99/1)
13	**1m**, R = F	**2m**, R = F	92 (99/1)
14			84 (98/2)
15			88 (99/1)
16			94 (99/1)
17[b]			86 (99/1)
18[b]			63 (99/1)

[a] Unless otherwise noted, all reactions were performed in MeOH (2.0 mL) at 100 °C for 20 h in the presence of **1** (1.0 mmol), $Pd(acac)_2$ (3.04 mg. 0.01 mmol), $PTSA{\cdot}H_2O$ (32 mg, 0.16 mmol), **L1** (15.5 mg, 0.04 mmol) and CO (40 bar). The yields were isolated yields for all products by column chromatography and the selectivity was determined by GC analysis using isooctane as the internal standard. [b] 0.5 mmol alkyne was used.

Table 3, a variety of terminal alkynes, including aromatic and aliphatic ones bearing a range of functional groups, are transformed into the corresponding 1,4-dicarboxylic acid diesters in good to excellent yields (63-98%) with decent to high chemoselectivities (75/25->99/1). For example, aromatic alkynes **1a–j** with either electron-donating (OMe, Me, ^{t}Bu) or electron-withdrawing (F, Cl, Br, CF_3, CN, CO_2Me) substituents on the phenyl ring provided the corresponding products **2a–j** in high yields (85-98%) and excellent chemoselectivities (99/1). Related alkynes **1k–p** with substituents in the *m*- or *o*-position of the phenyl ring similarly afforded the desired products **2k–p** in very good yields and selectivities. Alkynes bearing bromo and chloro substituents **1f**, **1g**, which are often sensitive to palladium catalysis, also worked well, without adverse effect on the reaction. Interestingly, tetra- and even hexa-carbonylated products **2q** and **2r**, are obtained directly in 86% and 63% isolated yields by carbonylation of di- and tri-alkynes **1q** and **1r**, respectively. It should be noted that the synthesis of such multiple carboxylated products is in general not an easy task, although the resulting products are of interest for polyesters, etc.. Moreover, aliphatic alkynes gave the corresponding α,β-diesters selectively (75/25-99/1) in 75-98%. In this respect, our catalyst is complementary to the work of Cole-Hamilton and co-workers, [9] which described the synthesis of α,ω-diesters from such alkynes via cascade methoxycarbonylation-isomerization-methoxycarbonylation.

Table 3. Pd-catalyzed dialkoxycarbonylation of aliphatic alkynes: Substrate scope [a]





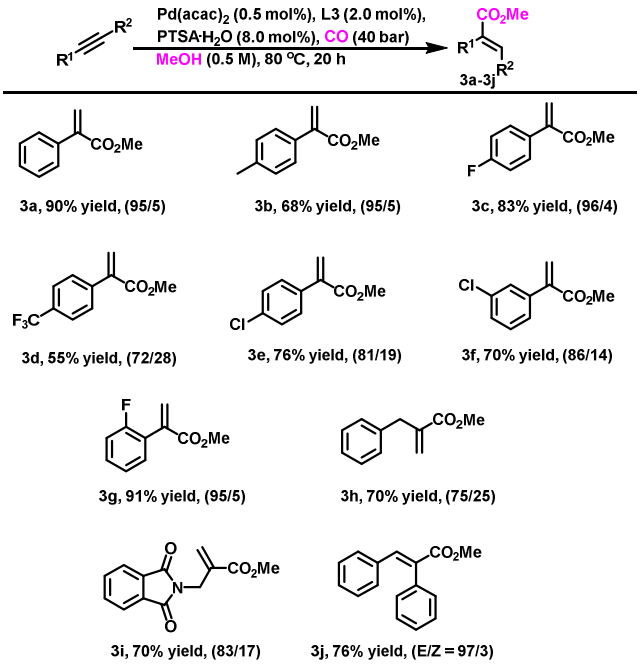
[a] Unless otherwise noted, all reactions were performed in MeOH (2.0 mL) at 100 °C for 20 h in the presence of **1** (1.0 mmol), $Pd(acac)_2$ (3.04 mg. 0.01 mmol), $PTSA{\cdot}H_2O$ (32 mg, 0.16 mmol), **L1** (15.5 mg, 0.04 mmol) and CO (40 bar). The yields were isolated yields for all products by column chromatography and the ratio of **2**/isomers was determined by GC analysis using isooctane as

the internal standard. [b] Isolated combined yield of **2** and isomers by column chromatography.

Reactions of 1-octynes **1s** and 1-pentynes **1t** proceeded smoothly to give **2s** and **2t** in 94% and 88% combined yields, respectively. On the other hand, the reaction of *tert*-butyl acetylene **1u** without α-hydrogen, gave the desired product **2u** in 88% yield with very good selectivity (99/1). Cyclohexyl acetylene also gave the α,β-diester **2v** in 98% yield with 91/9 (product/isomers) selectivity. Other substrates bearing functional groups, for example phthalimido, chloro and cyano, underwent dimethoxycarbonylation smoothly and gave the desired products **2x**-**z** in 90-93% yield with good selectivities (91/9-97/3). Interestingly, the tetracarbonylated single isomer **2aa** could be obtained in 75% isolated yield via directly alkoxycarbonylation of octa-1,7-diyne.

In the course of the development of this novel dialkoxycarbonylation of alkynes it was discovered that the new ligand **L3** allows for a regio- and chemoselective monocarbonylation of alkynes *vide supra*. In order to understand whether this is a general behavior or only specific for the model substrate, we studied the carbonylation reaction of several substrates in the presence of this ligand (Table 4). To our delight, a variety of aromatic and aliphatic alkynes reacted well under the optimized conditions to yield α,β-unsaturated esters **3a**-**3j** in 55-91% yield and regioselectivities up to 96/4. Functional groups on the phenyl ring of the substrate have a significant but irregular effect on the regioselectivity of **3a**-**3g**. Notably, products **3h** and **3i** bearing the terminal double bond which might isomerize to the more stable internal double bond were obtained both in 70% yield via direct alkoxycarbonylation from the corresponding alkynes. To the best of our knowledge, these substrates have not alkoxycarbonylated yet. Finally, the reaction of the less reactive tolane was performed and gratifyingly product **3j** was obtained in good yield (76%) with high selectivity (E/Z = 97/3).

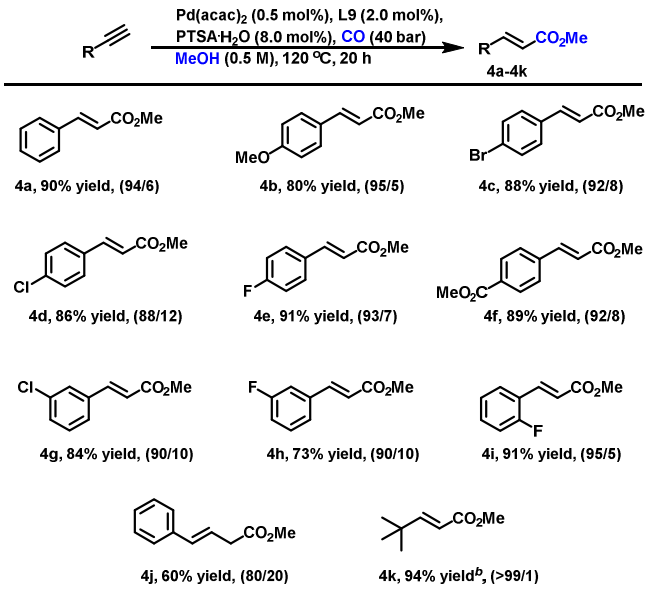
Table 4. Branched selective Pd-catalyzed alkoxycarbonylation of alkynes: Substrate scope [a]



[a] All reactions were performed in MeOH (2.0 mL) at 80 °C for 20 h in the presence of **1** (1.0 mmol), $Pd(acac)_2$ (1.52 mg, 0.005 mmol), $PTSA{\cdot}H_2O$ (16 mg, 0.08 mmol), **L3** (8.3 mg, 0.02 mmol) and CO (40 bar). The yields were isolated yields for all products by column chromatography, and the ratio of **b**/**l** was determined by GC analysis using isooctane as the internal standard.

Finally using ligand **L9** instead of **L1** and **L3**, the alkoxycarbonylation of the same substrates leads preferentially to the corresponding linear products. Hence, by simply switching the ligand three different carbonylation products can be obtained under otherwise similar reaction conditions. The scope of this linear alkoxycarbonylation was also explored and the results are summarized in Table 5. Here, linear products (**4a**-**4k**) were observed in 60-91% yields and 80/20->99/1 selectivities. Especially for aromatic alkynes bearing different functional groups, the regioselectivity was high.

Table 5. Linear selective Pd-catalyzed alkoxycarbonylation of alkynes: Substrate scope [a]



[a] Unless otherwise noted, all reactions were performed in MeOH (2.0 mL) at 120 °C for 20 h, in the presence of **1** (1.0 mmol), $Pd(acac)_2$ (1.52 mg. 0.005 mmol), $PTSA{\cdot}H_2O$ (16 mg, 0.08 mmol), **L9** (8.0 mg, 0.02 mmol) and CO (40 bar), the yields were isolated yields for all products by column chromatography and the ratio of **l**/**b** was determined by GC analysis using isooctane as the internal standard. [b] GC yield using isooctane as the internal standard.

In conclusion, we developed the first palladium-catalyzed 1,2-dicarbonylation of terminal alkynes. This methodology allows for the synthesis of a wide range of 1,4-dicarboxylic acid diesters. Key to success for this transformation is the utilization of the new ligand **L1** bearing a *tert*-butylpyridine phosphorous unit designed by us. Furthermore, by simple changing the ligand from **L1** to **L3** or **L9**, the chemo- and regioselectivities of alkyne carbonylations can be controlled to give α,β-unsaturated esters.

ASSOCIATED CONTENT

Supporting Information

Additional experimental results and procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org

AUTHOR INFORMATION

Corresponding Author

Matthias.Beller@catalysis.de

Author Contributions

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript. /

Notes

The authors declare no competing financial interest.

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ABBREVIATIONS

PTSA·H_2O, *p*-toluenesulfonic acid monohydrate; Py, Pyridine.

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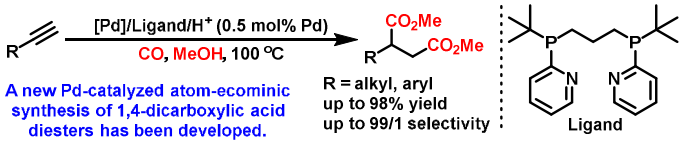

A new Pd-catalyzed atom-ecominic synthesis of 1,4-dicarboxylic acid diesters has been developed.

R = alkyl, aryl
up to 98% yield
up to 99/1 selectivity