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Stereoselective Synthesis of Highly Substituted Conjugated Dienes via Pd-Catalyzed Carbonylation of 1,3-Diynes

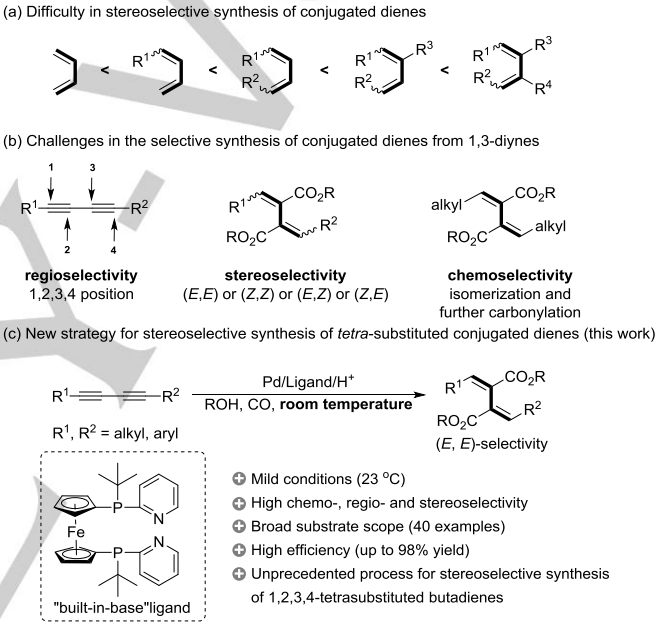
Jiawang Liu, Ji Yang, Wolfgang Baumann, Ralf Jackstell, and Matthias Beller*

Abstract: The stereoselective synthesis of conjugated dienes was realized for the first time via Pd-catalyzed alkoxycarbonylation of easily available 1,3-diynes. Key to success is the utilization of the specific ligand 1,1'-ferrocenediyl-bis(*tert*-butyl(pyridin-2-yl)phosphine) (**L1**), which allows this novel transformation to proceed at room temperature. A range of 1,2,3,4-tetra-substituted conjugated dienes are obtained in this straightforward access in high yields and selectivities. The synthetic utility of the protocol is showcased in the concise synthesis of several important intermediates for construction of natural products *rac*-Cagayanin, *rac*-Galbulin, *rac*-Agastinol and Cannabisin G.

Conjugated dienes incorporate an interesting structural moiety presenting unique reactivity, which also is used in natural products and several biologically active pharmaceuticals.[1] In fact, conjugated dienes cannot be regarded as two isolated olefins since they have higher HOMO and lower LUMO energetic orbitals which determine their transformations.[2] Hence, they served as versatile building blocks and found many applications in organic synthesis[3] and materials science.[4]

Traditional approaches to conjugated dienes mainly include olefination of unsaturated carbonyl compounds [5] and elimination reactions from allylic or dihalogenated compounds.[6] In addition, recently developed transition-metal-catalyzed coupling reactions of alkenyl metals or alkynes with alkenyl (pseudo)halides afford a straightforward methodology for their synthesis.[7] However, the pre-preparation of alkenyl nucleophiles and/or electrophiles requires additional steps in these processes. Despite the effectiveness of the current methods, so far the rapid construction of 1,2,3,4-tetrasubstituted conjugated dienes continues to be scarce.[8] Compared to simpler di- or tri-substituted 1,3-dienes, their tetra-substituted counter parts contain substituents at all four positions, creating more difficulties to control the stereoselectivity (Scheme 1, a). More specifically, every carbon-carbon double bond should be constructed stereoselectively and with substituents incorporated in a regioselective manner. Thus, the development of new methodologies, particularly for the stereoselective synthesis of multi-substituted conjugated dienes remains difficult.

As one of the most important processes in homogeneous catalysis, palladium-catalyzed carbonylation of alkynes/alkenes have been extensively investigated and applied in academia and industry for several decades.[9] Based on our continuous interest in carbonylations, recently we become attracted to investigate the selective carbonylation of 1,3-diynes, which are readily available from terminal alkynes by Glaser and related coupling reactions.[10] To the best of our knowledge, such transformations have never been reported before, but afford an easy possibility for the selective synthesis of multiple substituted conjugated dienes.[11]



Scheme 1. Selective Synthesis of 1,2,3,4-tetra-Substituted Conjugated Dienes: Challenges and New Method

Obviously, control of selectivity is a key challenge of our envisioned synthesis: a) Carbonylation of the substrate (1,3-diynes) having two triple bonds containing four active positions may result in different regioisomers (Scheme 1b, left). b) Furthermore, four different stereoisomers of the desired *tetra*-substituted conjugated dienes can be formed (Scheme 1b, middle). c) Finally, the initially formed alkyl-substituted α,β-unsaturated ester intermediates might undergo further cascade isomerization and carbonylation processes (Scheme 1b, right)[12].

Recently, we developed novel bidentate ligands with integral basic sites by incorporation of pyridine substituents on the phosphorous atom.[13] Here, the nitrogen atom acts as a proton shuttle to speed up the rate-determining esterification step in alkoxycarbonylation reactions.[14] Based on that work, we had the idea that these ligands might be able to accelerate double carbonylation reactions of diynes, thus leading to the generation of the desired 1,2,3,4-tetrasubstituted conjugated dienes selectively. Following this idea, herein we present the first example of selective palladium-catalyzed alkoxycarbonylation of 1,3-diynes at room temperature (Scheme 1, c).

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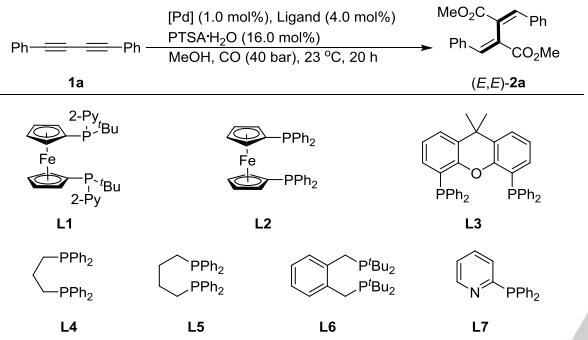
At the beginning of our studies, we investigated the effect of ligands bearing *tert*-butyl and pyridine substituents on the phosphorous atom for the methoxycarbonylation of 1,4-diphenylbuta-1,3-diyne **1a** under typical alkoxycarbonylation conditions (1.0 mol% Pd catalyst, 16.0 mol% PTSA·H_2O, 40 bar CO, 120 ºC). Comparing 1,2-bis((*tert*-butyl(pyridin-2-yl)phosphanyl)methyl)benzene, 1,3-bis(*tert*-butyl(pyridin-2-yl)-phosphanyl)propane, 1,4-bis(*tert*-butyl(pyridin-2-yl)-phosphanyl)-butane and 1,1'-ferrocenediyl-bis(*tert*-butyl-(pyridin-2-yl)-phosphine) (**L1**) showed the best performance for the latter ligand and the desired product **2a** was obtained in 92% yield with 97/3 selectivity (Table *S1*). Isolation and NMR analysis revealed the major side product to be the regioisomer dimethyl (*E*)-4-((*E*)-benzylidene)-2-phenylpent-2-enedioate (see SI).

Table 1. Pd-catalyzed stereoselective carbonylation of 1,4-diphenylbuta-1,3-diyne[a].

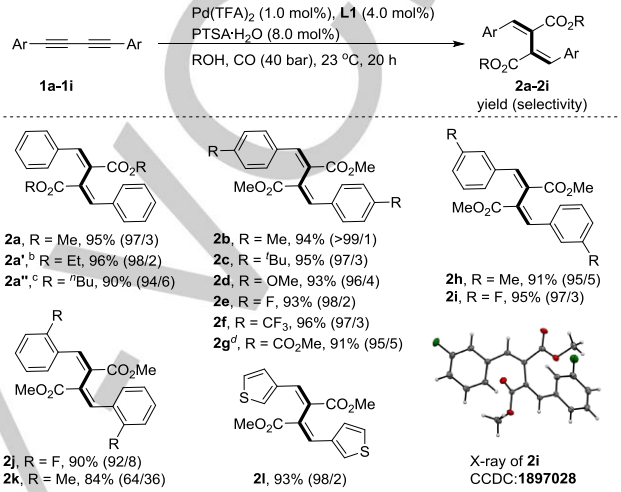


entry	ligand	[Pd]	Selectivity[b]	yield of **2a**[c]
1	**L1**	$Pd(acac)_2$	97/3	96
2	**L2**	$Pd(acac)_2$	37/63	10
3	**L3**	$Pd(acac)_2$	-/-	0
4	**L4**	$Pd(acac)_2$	-/-	0
5	**L5**	$Pd(acac)_2$	-/-	0
16	**L6**	$Pd(acac)_2$	24/76	5
7	**L7**	$Pd(acac)_2$	-/-	trace
8[d]	**L1**	$Pd(acac)_2$	97/3	96
9[e]	**L1**	$Pd(acac)_2$	97/3	74
10[e]	**L1**	$PdCl_2$	-/-	0
11[e]	**L1**	$Pd_2(dba)_3$	95/5	30
12[e]	**L1**	$Pd(OAc)_2$	97/3	56
13[e]	**L1**	**$Pd(TFA)_2$**	**97/3**	**96 (95)**[f]

[a] Reaction conditions: **1a** (0.25 mmol), [Pd] (1.0 mol%), **L** (4.0 mol%) PTSA·H_2O (16.0 mol%), CO (40 atm), MeOH (1.0 mL), 20 h, 23 °C. [b] The selectivity describes the ratio of (*E*,*E*)-**2a** compared to other double carbonylation products determined by GC and GC-MS (for more details, see SI). [c] The yield was determined by GC analysis using isooctane as the internal standard. [d] PTSA·H_2O (8.0 mol%). [e] PTSA·H_2O (8.0 mol%), 4 h. [f] Isolated yield.

Notably, the reaction proceeded smoothly already at room temperature (23 ºC) in the presence of **L1** affording **2a** in 96% (see supporting information for more details). Testing commercially available ligands **L2**-**L7** which are commonly used in various carbonylation reactions,[15] gave only poor results and in all cases the desired product **2a** was observed in <10% yield and with poor selectivity. On the other hand, the combination of $Pd(TFA)_2$/**L1** led to **2a** in excellent yield and selectivity in short time (4h) using lower concentration of PTSA·H_2O (Table 1, entry 13).

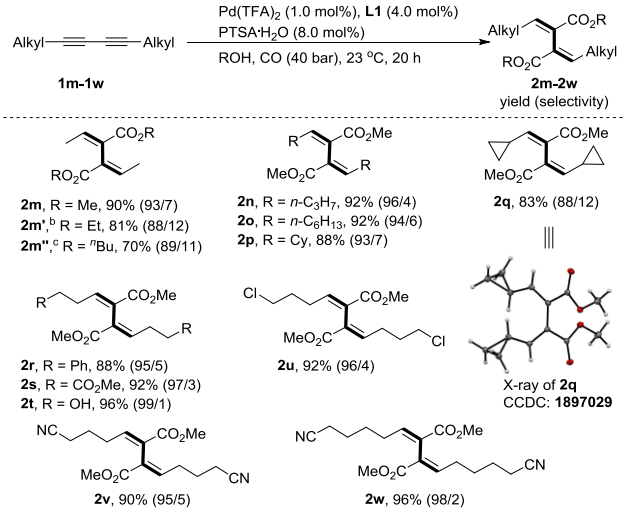
Table 2. Carbonylation of 1,4-diarylbuta-1,3-diynes: Substrate scope[a]



[a] Reaction conditions: substrates (0.25 mmol), $Pd(TFA)_2$ (1.0 mol%), **L1** (4.0 mol%) PTSA·H_2O (8.0 mol%), CO (40 atm),23 °C, methanol (1.0 mL), 20 h. Isolated yield. The selectivity in brackets was determined by GC analysis. [b] EtOH was used. [c] ^{n}BuOH was used. [d] 2/8/16 mol% Pd/**L1**/ PTSA·H_2O were used.

With the optimized reaction conditions in hands, we proceeded to explore the reactivity of other symmetric 1,4-diarylbuta-1,3-diynes. As depicted in Table 2, various aromatic 1,3-diynes **1b-1l** bearing diverse substituents and heterocycles, are transformed into the corresponding conjugated carbonylation products in high yields with good to excellent selectivities.

Table 3. Carbonylation of 1,4-dialkylbuta-1,3-diynes: Substrate scope[a]



[a] Reaction conditions: substrates (0.25 mmol), $Pd(TFA)_2$ (1.0 mol%), **L1** (4.0 mol%) PTSA·H_2O (8.0 mol%), CO (40 atm), 23 °C, methanol (1.0 mL), 20 h. Isolated yield. The selectivity in brackets was determined by GC analysis. [b] EtOH was used [c] ^{n}BuOH was used.

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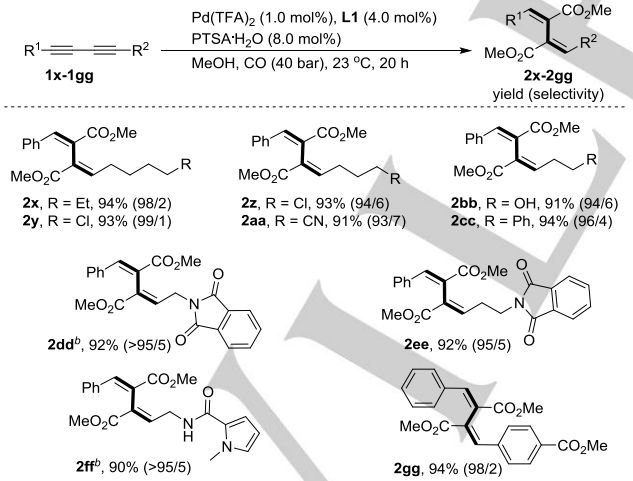
More specifically, the reactions of **1a** can be extended to ethanol and butanol, affording **2a'** and **2a''** in 96 and 90% yield, respectively. 1,3-Diynes **1b**-**i** with either electron-donating (Me, ^{t}Bu, OMe) or electron-withdrawing (F, CF_3, CO_2Me) groups on the phenyl ring provided the corresponding products **2b–i** similarly in 91-96%. Substituents in the ortho-position of the phenyl ring have a significant influence on the selectivity of this reaction. For example, **2j** was afforded in 90% yield and 92/8 selectivity because of the small volume of the fluorine atom, while 1,4-di-*o*-tolylbuta-1,3-diyne **1k** gave **2k** in 84% yield with 64/36 selectivity. Moreover, heterocycle-substituted 1,3-diyne based on thiophene proved to be viable substrate and gave **2l** in 93% yield.

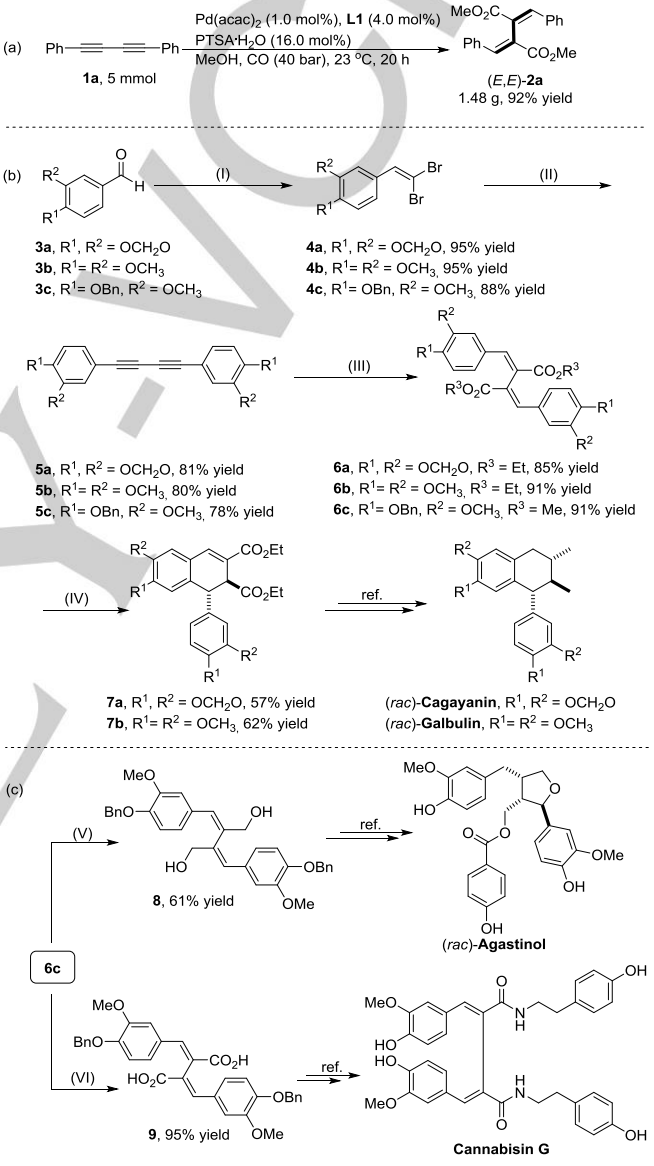
Next, we evaluated the reactivity of aliphatic 1,3-diynes. From the viewpoint of selectivity these substrates are more demanding as the resulting α,β-unsaturated esters product may undergo additional isomerization reactions. Nevertheless, Pd-catalyzed alkoxycarbonylations proceeded selectively to afford various conjugated dienes in high yields. As an example, the reaction of aliphatic substrate **2m** is performed in ethanol and butanol, affording the corresponding products **2m'** and **2m''** in 81% and 70% yield, respectively. Besides, linear long chain substrates **1n** and **1o**, cyclohexyl- and cyclopropyl-substituted 1,3-diynes **1p** and **1q**, also gave the desired products in high yields and selectivities without any other isomerized by-products. Furthermore, substrates bearing functional groups, for example, ester, hydroxyl, chloro, and cyano underwent carbonylation smoothly and gave the desired products **2s−w** in 88-96% yield with selectivities of 95/5-99/1. It should be noted that the synthesis of such multiple substituted aliphatic conjugated dienes is not an easy task. When using 1,4-di-*tert*-butyl-1,3-butadiyne only low conversion to the monocarbonylated product was observed due to steric hindrance of the substrate.

Table 4. Carbonylation of non-symmetric 1,4-disubstituted 1,3-diynes: Substrate scope[a]



[a] Reaction conditions: substrates (0.25 mmol), $Pd(TFA)_2$ (1.0 mol%), **L1** (4.0 mol%), PTSA·H_2O (8.0 mol%), CO (40 atm), 23 °C, methanol (1.0 mL), 20 h. Isolated yield. The selectivity in brackets was determined by GC analysis. [b] 2/8/16 mol% Pd/**L1**/ PTSA·H_2O were used.

With respect to organic synthesis, the double carbonylation of non-symmetric 1,3-diynes is exciting as it allows for rapid generation of molecular complexity. Gratifyingly, this novel procedure is compatible with various types of 1,3-diynes, consistently affording the corresponding products in high yields and selectivities. Reactions of **1x**-**1ee**, bearing diverse substituents proceeded easily to give the corresponding dienes in 91-94% yield with 93/7-99/1 selectivities. Moreover, **2ff** is obtained in 90% yield which demonstrated that *N*-heterocycles are well-tolerated by our catalyst. Finally, product **2gg** with two different aromatic substituents was also achieved more efficiently compared to a previous report.[16] It is worth mentioning that the presented methodology can be easily scaled up. Hence, the practical gram-scale synthesis of **2a** was performed and the desired product was obtained in 92% yield (Scheme 2, a).



Scheme 2. Gram-scale synthesis of **2a** and synthetic applications of **6a**-**6c**. I) CBr_4, PPh_3, CH_2Cl_2, rt, 0.5 h. II) CuI, DBU, DMSO, rt, 12 h. III) $Pd(TFA)_2$, **L1**, PTSA·H_2O, MeOH or EtOH, CO, rt, 20 h; IV) HOTf, rt (21 h) or 45 °C (3 h), CH_2Cl_2. V) aq. NaOH, THF/H_2O, 100 °C, 2h. VI) $LiAlH_4$, $AlCl_3$, THF, rt, 1 h.

Finally, we showed the usefulness of this protocol in the synthesis of key intermediates for pharmaceutically interesting bio-active compounds. Hence, **6a**-**6c** were synthesized via Pd-catalyzed selective carbonylation of 1,3-diynes **5a**-**5c** in 85-91% yield. In the presence of triflic acid, **6a** and **6b** were transformed into **7a** and **7b** in 57% and 62% yield, respectively. The latter compounds are the key intermediates for the synthesis of the

naturally occurring lignans (*rac*)-Cagayanin and (*rac*)-Galbulin (Scheme 2, b).[16] Furthermore, the product **6c** was reduced to *trans*-(*E*)-dimethyl 2,3-bis(4-benzyloxy-3-methoxybenzylidene)-1,4-butanediol **8** in 61% yield, which has been applied in the synthesis of potential *anti*-apoptotic agent (*rac*)-Agastinol.[17] (*E*,*E*)-2,3-Bis(4-benzyloxy-3-methoxybenzy-lidene)succinic acid **9** was achieved in 95% yield from **6c**, and the product **9** can be directly used for the synthesis of Cannabisin G,[18] which showed cytotoxic activity against human prostate cancer LNCaP cells (Scheme 2, c)[19].

In summary, we have developed the first selective double carbonylation reactions of 1,3-diynes, which complements currently known methods. This catalytic protocol permits the synthesis of a wide range of synthetically useful 1,2,3,4-tetra-substituted conjugated dienes in high yields and selectivities. Key to success is the utilization of the specific "built-in-base" ligand **L1**, which allows these novel transformations to proceed under mild conditions (room temperature). The synthesis of **6a**-**6c** exemplarily shows the synthetic utility of this methodology, which provides valuable building blocks for modern organic synthesis in a straightforward manner.[20]

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Keywords: 1,3-dienes • carbonylation • stereoselectivity • palladium • P ligands

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[20] As suggested by a referee of this work, we performed also few experiments using two alcohols with distinct reactivity to proof whether this methodology offers a viable route to mixed ester compounds. Indeed, the reaction using MeOH (1.0 equiv.) and iso-PrOH or CyOH (1.0 equiv.) as nucleophiles led to 25% and 18%, respectively, of the mixed ester compounds. In the future, the selectivity of the process should be improved.

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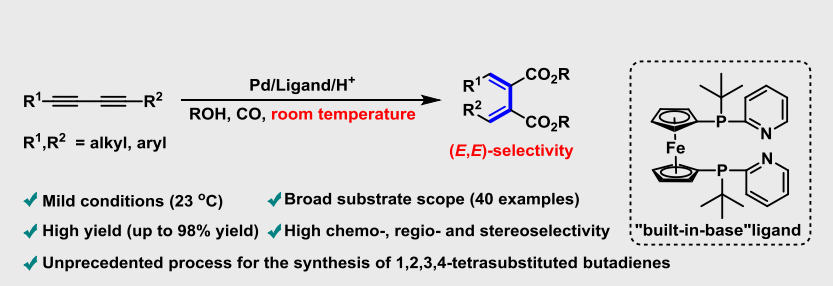

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Stereoselective Synthesis of Highly Substituted Conjugated Dienes via Pd-Catalyzed Carbonylation of 1,3-Diynes

Increasing molecular **CO**mplexity. Carbonylations of 1,3-diynes provides a general approach to a variety of synthetically useful conjugated dienes in high yields and chemo-, regio-, and stereoselectivities.