Palladium-Catalyzed Carbonylation of Unsaturated Carbon-Carbon Bonds

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Abstract

Palladium-Catalyzed Carbonylation of Unsaturated Carbon-Carbon Bonds

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This thesis is mainly concerned with the carbonylative functionalization of unsaturated organic substrates in the presence of homogeneous catalysts. More specifically, oxidative carbonylation of alkynes, alkoxycarbonylation of 1,3-dienes and platinum-catalyzed alkoxycarbonylation of olefins are presented. The resulting esters, maleimides and adipic acid diesters constitute important intermediates for both organic synthesis and chemical industry. Regarding methodology developments, firstly a catalytic oxidative carbonylation reaction with air as a green oxidant was developed. Additionally, we established a novel catalytic system that can smoothly convert butadiene to adipic acid diester, which has significant value as a nylon precursor. Furthermore, we reported the first efficient platinum-catalysed alkoxycarbonylations of sterically hindered olefins. In all above mentioned research, systematic optimization studies were performed, the scope and limitations of the respective protocol were investigated and presented.

Palladiumkatalysierte Carbonylierung von ungesättigten Kohlenstoff-Kohlenstoff-Bindungen

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Diese Arbeit befasst sich hauptsächlich mit der carbonylierenden Funktionalisierung ungesättigter organischer Substrate in Gegenwart homogener Katalysatoren. Insbesondere werden die oxidative Carbonylierung von Alkinen, die Alkoxycarbonylierung von 1,3-Dienen und die platinkatalysierte Alkoxycarbonylierung von Olefinen vorgestellt. Die resultierenden Ester, Maleimide und Adipinsäurediester sind wichtige Zwischenprodukte sowohl für die organische Synthese als auch für die chemische Industrie. In Bezug auf methodische Entwicklungen wurde zunächst eine katalytische oxidative Carbonylierungsreaktion mit Luft als Effektiver Oxidationsmittel entwickelt. Zusätzlich haben wir ein neuartiges katalytisches System etabliert, das Butadien problemlos in Adipinsäurediester umwandeln kann, das als Nylonvorläufer einen signifikanten Wert hat. Darüber hinaus berichteten wir über die ersten effizienten platinkatalysierten Alkoxycarbonylierungen von sterisch gehinderten Olefinen. In allen oben genannten Untersuchungen wurden systematische Optimierungsstudien durchgeführt, der Umfang und die Grenzen des jeweiligen Protokolls untersucht und vorgestellt.

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List of Abbreviations

acac	*Acetylacetone*
atm	*Atmosphere*
Ar	*Aryl*
BASF	*Badische Anilin- & Soda-Fabrik*
Bn	*Benzyl*
Bu	*Butyl*
^{t}Bu	*Tert-butyl*
Cy	*Cyclohexyl*
Cat.	*Catalyst*
cod	*Cycloocta-1,5-diene*
DEHP	*Bis(2-ethylhexyl) phthalate*
d	*Day*
dba	*trans, trans-Dibenzylideneacetone*
dppp	*1,3-Bis(diphenylphosphino)propane*
dppb	*1,4-Bis(diphenylphosphino)butane*
ee	*Enantiomeric excess*
etc.	*Et cetera*
et al.	*Et alii*
E	*Entgegen (describing the absolute stereochemistry of double bonds)*
EWG	*Electron-withdrawing group*
h	*Hour*
iso	Sum of branched products
LDA	*Lithiumdiisopropylamid*
L	*Ligand*
MeOH	*Methanol*
MSA	*Methanesulfonic acid*
n	*Amount of linear product*
N-	*Nitrogen substituted*

NMP	*N-Methylpyrrolidone*
NuH	*Nucleophile*
OAc	*Acetate*
OMe	*Methoxy*
Ph	*Phenyl*
PTSA	*para-Toluenesulfonic acid monohydrate*
Ph	*Phenyl*
PVC	*Polyvinylchloride*
S	*Solvent*
TM	*Transition metal*
TMS	*Trimethylsilyl*
THF	*Tetrahydrofuran*
TFA	*Trifluoroacetic acid*
TPPTS	*3,3',3''-Phosphanetriyltris(benzenesulfonic acid) trisodium salt*
TBS	*tert-Butyldimethylsilyl*
UCC	*Union Carbide Corporation*
X	*Leaving group, (pseudo)halide*
Xantphos	*4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene*
Z	*Zusammen (describing the absolute stereochemistry of double bonds)*

1.1. Background

Catalysis plays an vital role in both industry and academic research.[1] By using high-performance catalysts, reactions can take place in a way that spares resources, increasing the yield, avoiding by-products, and reducing the specific energy requirement. The contribution of catalysis to the society also reflected in the award of Nobel Prizes to the many chemists who have made significant contribution to the development of catalysis,[2-6] for example, Ostwald (1909), Haber (1918), Bosch and Bergius (1931), Ziegler and Natta (1963), Wilkinson and Fischer (1973), Sharpless, Noyori and Knowles (2001), Chauvin, Grubbs and Schrock (2005) and Heck, Negishi and Suzuki (2010). Their contribution range from high-pressure gas catalytic processes to novel catalysts design.

Catalysis adds value to our lives in many ways, ranging from increasing the worth of chemical products to reducing environmental emissions. Taking one well-known example of how catalysis plays a significant role in the synthesis of pharmaceuticals. In the early 1970s, Knowles developed a novel catalytic method at Monsanto by using a Rh-chiral phosphine catalyst.[7] This catalytic method allowed enantioselective hydrogenation of the enamide precursor to the medicine *l*-dopa (dopamine precursor), which is used to treat Parkinson's disease.[8-10] Later on, this novel catalytic method became widely used in organic synthesis as well as the production of other pharmaceuticals.

Catalysis also provides the basis for the creation of novel chemical structures, especially in the area of polymers. Well-known, Nylon was the first commercially successful synthetic thermoplastic polymer.[11-13] DuPont began its research project on this topic already in 1927. Thus, the first industrial production of nylon (nylon 6,6) started in 1935 by Wallace Hume Carothers.[14-17] Nowadays, nylon is one of the most useful synthetic products. It's a plastic that can be molded into daily necessities or fibers for making textiles. The successful production of nylon completely changed people's lifestyles since the late 1930s.

Widely accepted, catalysis is often divided into three branches: homogeneous, heterogeneous and bio-catalysis.[18-19] Among the many research topics in catalysis, carbonylation reactions are the most critical process in homogeneous catalysis, using carbon monoxide (CO) as a highly versatile C1 building block. Nowadays, more than 10 million metric tons of various carbonyl compounds (aldehydes, acids, and esters) are produced annually for numerous consumer products.[20-22] One obvious reason for the large scale applications of carbonylation reactions in the industry is that carbon monoxide is abundantly available either from fossil-based resources (coal, oil or gas) or from renewables (CO_2 or biowaste).

An impressive example to show the applicability of carbonylation reactions is the manufacture of acetic acid. The methanol carbonylation based route (Monsanto or Cativa process) has such an economic advantage over the other routes that currently more than 85% of acetic acid

manufacturing is based upon this route.[23-26] The cost of producing acetic acid via this process is approximately only half of the original two steps' Wacker route.

Due to its enormous value, a lot of funding and energy has been invested into carbonylation processes. As a concise summary, in the introduction chapter we mainly focus on some landmark and recent advances in carbonylation research catalyzed by transition metals (especially precious metal palladium). For other types of carbonylation reactions, readers are referred to related literature.[27-56]

1.2. Representative catalysts and ligands

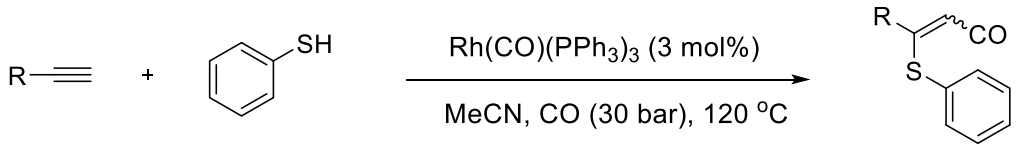
1.2.1. Representative metals

1.2.1.1. Palladium

For various carbonylation reactions, palladium complexes display often high activity and versatility among the different catalytically active metals. Consequently, palladium-based catalysts received considerable concern in recent research and they have been used to produce several industrial products on large scale.[57-60] Because of their wide application and excellent performance, we will mainly focus on discussing this topic in chapter 1.3.

1.2.1.2. Rhodium

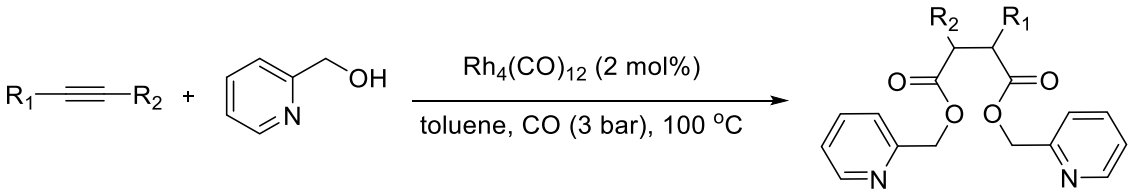
Compared with palladium catalysts, rhodium-based systems are a more powerful tool for carbonylations involving activation of C-H bonds under mild and sometimes phosphine-free conditions.[61-63] In this regard, some representative examples are shown below. At the same time, rhodium is the most active metal catalyst being used in hydroformylation reactions by far. Here, it is usually applied in concentrations of only 1-100 ppm in the reaction. In contrast, cobalt-based hydroformylation catalysts need to maintain a catalyst concentration in the range of 1-10 g/kg to get satisfactory activity. For rhodium catalyzed hydroformylations, the original discovery occurred in 1965. At that time, Wilkinson and co-workers discovered the utility of triphenylphosphane as ligand, which laid the basis for the following progress of an industrial procedure in the 1970s.[64-66] For terminal olefins, the hydroformylation will be highly regioselective If this ligand is applied surplus to rhodium. For example, take propylene as a substrate, the industrially less interesting branched byproduct is suppressed to less than 10% among all the products formed. Because of this selectivity control, Wilkinson's catalytic system has become a standard and is still being widely used for hydroformylations.



Scheme 1. Ogawa's work: The first rhodium-catalyzed thioformylation reaction.

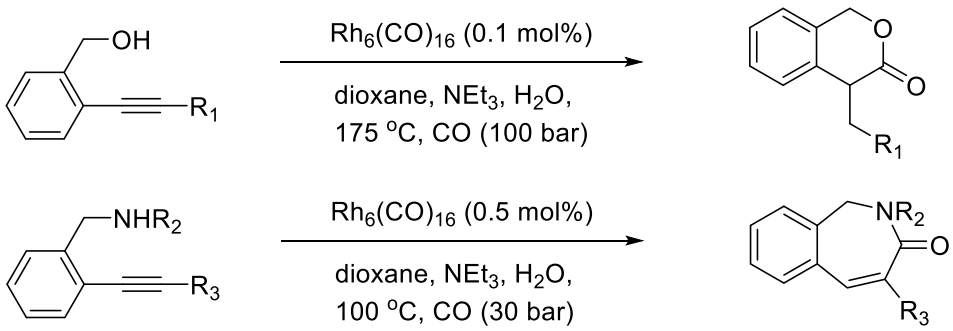
In 1995, the first highly regioselective rhodium-catalyzed thioformylation was reported by Ogawa and Sonoda, by reaction of alkynes with aromatic thiols and carbon monoxide (Scheme 1).[67] This reaction was completed in a highly selective way and reflected a good compatibility with functional groups by using rhodium(I) complexes.[68]

Following this work, Chatani and co-workers established the alkoxycarbonylation of internal alkynes with 2-pyridinylmethanol in the presence of a suitable rhodium catalyst (Scheme 2).[69] This reaction is quite peculiar and represents the first example for simultaneous double carbonylation of alkynes yielding dicarboxylate esters. Based on control trials, the reaction was found to proceed through the ketene intermediate rather than through two consecutive alkoxycarbonylation steps.



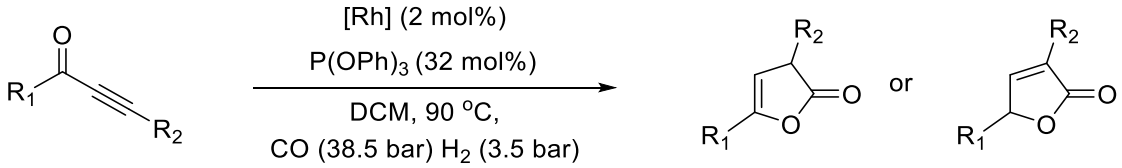
Scheme 2. Chatani's work: Rhodium-catalyzed dialkoxycarbonylation reaction of alkynes.

In 1998, Takahashi reported a novel synthesis of 3-isochromanones catalyzed by rhodium catalyst.[70-71] Starting from 2-alkynylbenzyl alcohols, isochromanones were synthesised in 50-80% yields under water-gas shift conditions (Scheme 3). Analogously, when used 2-alkynylbenzylamines as starting chemicals, a variety of benzazepinones could be formed, but showing a decreased selectivity for the aimed product even with increased catalyst usage.



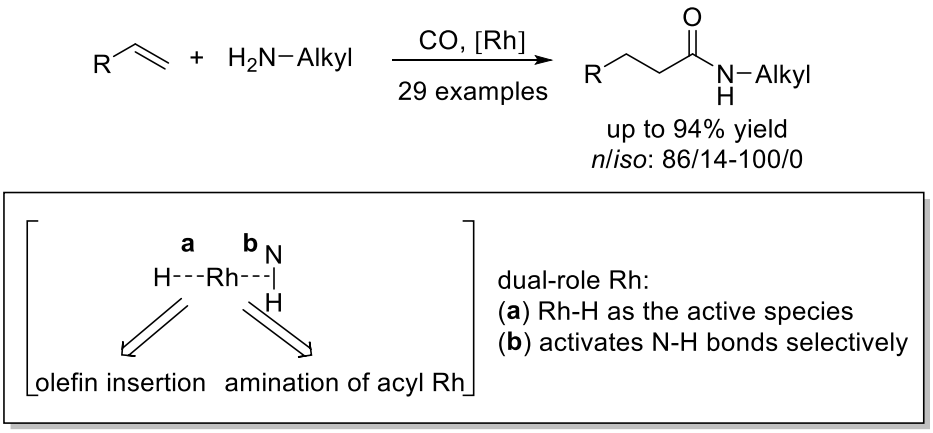
Scheme 3. Takahashi's work: Carbonylative synthesis of 3-isochromanones.

In 2000, Alper and Van den Hoven reported a zwitterionic rhodium catalyst supported by triphenyl phosphite. This complex smoothly catalyzed cyclohydrocarbonylation of alkynones to give furanones in a regioselective manner in 61-93 % yields (Scheme 4). [72]



Scheme 4. Alper's work: Rhodium-cyclohydrocarbonylation of alkynones.

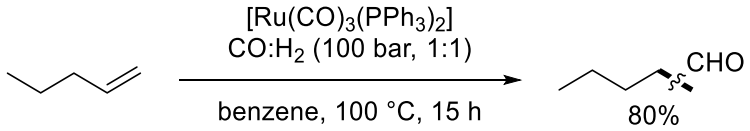
In 2015, our group developed a general and efficient aminocarbonylation process, this procedure transformed olefins and aliphatic amines to amides by using rhodium cartalyst.[73] With commercially available rhodium pre-catalysts, various olefins and aliphatic amines were transformed into the desired N-alkyl amides in medium to high yields with excellent regioselectivities. Notably, the hydroamidation of olefins with aliphatic amines has priority even in the presence of excessive aryl amines or alcohols. Mechanistic studies discovered the [Rh(I)−H] complexes as active species and the aminolysis of the rhodium-acyl complexes as the rate-limiting step.



Scheme 5. Our group's work: Rhodium-catalyzed aminocarbonylation of olefins.

1.2.1.3. Ruthenium

Similar to the work on rhodium catalysts, the first well-defined ruthenium-catalyzed hydroformylation was reported in 1965 by Wilkinson and co-workers.[74] More specifically, they showed that $Ru(CO)_3(PPh_3)_2$ was capable to convert 1-pentene to C6 aldehydes under high pressure of syngas at 100 °C (Scheme 6). The reaction reflected good reactivity with a yield of aldehydes in the range of 80-85%.



Scheme 6. First example of a ruthenium-catalyzed hydroformylation reaction.

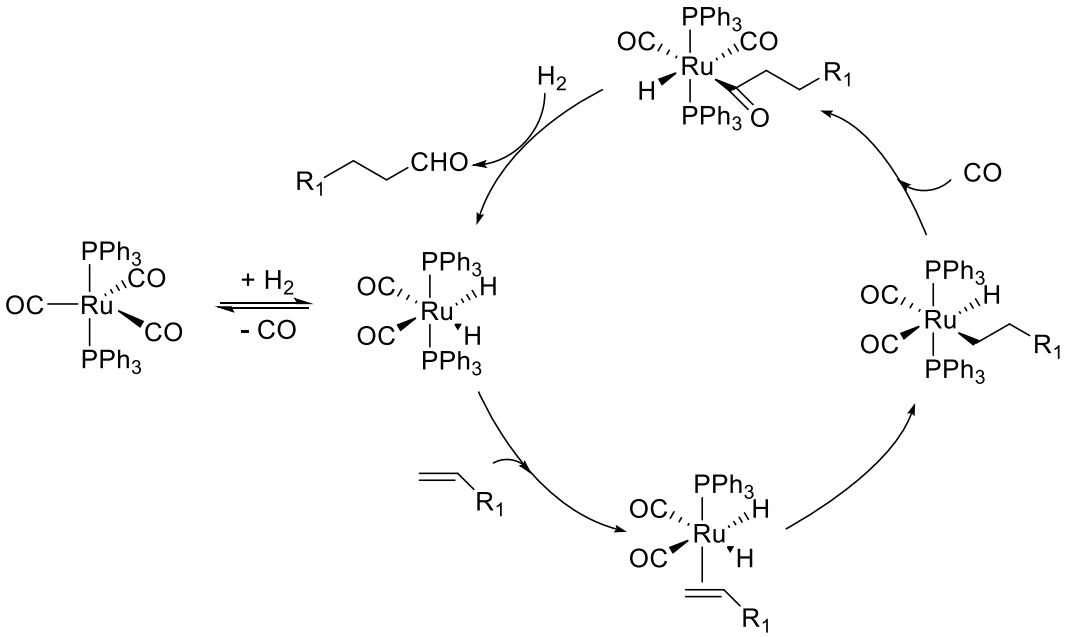
Later on, Millidge reported the synthesis of C4 aldehydes and alcohols at 80 bar pressure and 250 °C, employing a ruthenium catalyst supported on zeolite in xylene. The aldehyde products were obtained in 74% yield with *n/iso ratio* of 2.3. Furthermore in 1973, Schulz and Bellstedt reported a comprehensive study on the ruthenium-catalyzed hydroformylation of propylene.[75] The ruthenium carbonyl complex was prepared *in-situ* from ruthenium oxide hydrate or ruthenium trichloride. The influences of different reaction parameters were investigated. The authors concluded that only gradual differences exist in the catalytic behaviour of ruthenium carbonyl complexes for the propylene hydroformylation as compared to cobalt and rhodium catalysts. Besides, the stability of the ruthenium carbonyl complexes allowed the reaction to be performed at a comparatively lower pressure (< 100 bar). Then, Wilkinson and co-workers used ten different ruthenium-complexes to compare their catalytic effects.[76] It turned out that the ratio of linear to branched aldehydes was essentially constant (Table 1). Isolation of the same ruthenium complex $Ru(CO)_3(PPh_3)_2$ from each reaction indicated that the active species in the hydroformylation reaction should be this complex. Meanwhile, comparison of the mononuclear ruthenium catalysts with the cluster trirutheniumdodecacarbonyl proved the latter to be less active under identical conditions.

Table 1. Hydroformylation of 1-hexene with ruthenium complexes.

Complex	Conversion [%]	Aldehyde selectivity [%]	Linear to branch ratio
$Ru(CO)_3(PPh_3)_2$	83	100	2.4
$Ru(H)_2(CO)_2(PPh_3)_2$	86	99	2.4
$Ru(H)_2(CO)(PPh_3)_2$	87	97	2.4
$RuH(NO)(PPh_3)_3$	85	100	2.0
$Ru(H)_2(PPh_3)_4$	81	87	2.1
$Ru(H)_4(PPh_3)_3$	80	81	2.4
$Ru(CO_2CH_3)_2(PPh_3)_2$	85	100	2.0
$Ru(CO_2CF_3)_2(PPh_3)_2$	79	100	2.0
$Ru(CO_2CMe_3)_2(PPh_3)_2$	88	100	2.9
$Ru_3(CO)_{12}$	24	-	-

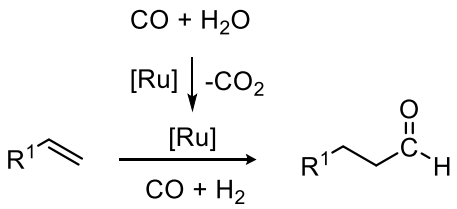
Based on the mechanism of the rhodium-catalyzed hydroformylation reaction, Wilkinson proposed a similar catalytic pathway for ruthenium complexes. Firstly, one carbonyl ligand dissociates from the metal center and hydrogen oxidatively adds to the metal center, which appears to be the rate determining step of the reaction. Subsequently, dissociation of the

phosphine ligand forms a vacant coordination site, allowing coordination of the olefin. Almost synchronously, insertion of CO into the metal-alkyl bond leads to the formation of corresponding active acyl species. Eventually, transfer of a second hydrogen atom and subsequent reductive elimination consequences in the formation of the desired product and regeneration of the active complex (Scheme 7).



Scheme 7. Proposed catalytic cycle of ruthenium-catalyzed hydroformylation.

Pettit's and co-workers used carbon monoxide and H_2O instead of syngas.[77] Under such conditions, H_2 is produced in-situ by water-gas shift reaction and can be used for the following hydroformylation. Approximately 43% of the corresponding aldehyde was produced with good regioselectivity at 100 °C (Scheme 8).



Scheme 8. Ruthenium-catalyzed hydroformylation reaction under water-gas shift conditions.

In 1999, Gao and Tsai synthesized the air-stable and water-soluble ruthenium cluster $Ru_3(CO)_9(TPPMS)_3$ (Figure 1).[78] The stability of this complex was shown by IR, X-ray and some other tests. Later, they used this complex in the hydroformylation of propylene in water at 120 °C. Compared to the commonly used catalyst $[NEt_4][Ru_3H(CO)_{11}]$ an improved TOF =

61 was achieved. It is presumed that similar to catalytic hydrogenation reactions a dihydrido ruthenium(II) complex constitutes the active species in these hydroformylation reactions.

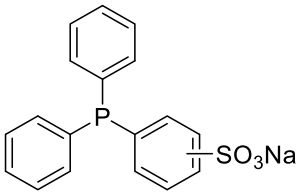
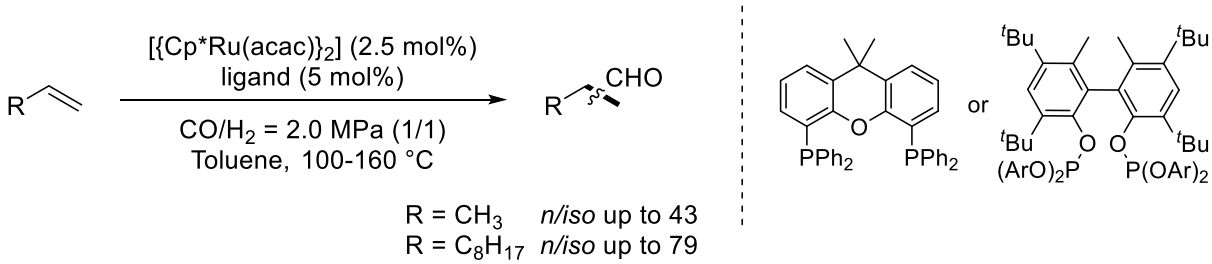


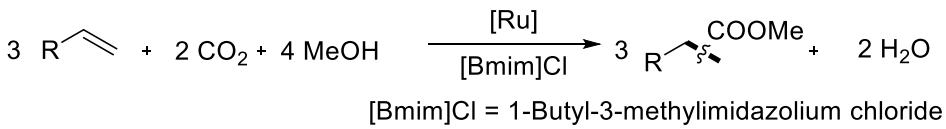
Figure 1. Water-soluble monosulfonated triphenylphosphine ligand.

In 2012, Nozaki and Takahashi reported an innovative ruthenium system[79] including the bidentate phosphine ligand Xantphos or phosphite ligands to ensure regioselectivity. Though the activity remained to be improved, a high regioselectivity was obtained as described in Scheme 9.



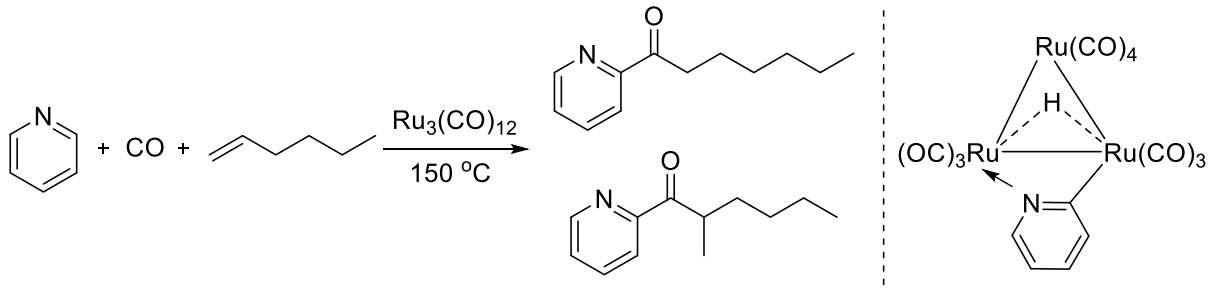
Scheme 9. Ruthenium catalysts with bidentate phosphorous ligands.

In 2013, our group showed the application of abundantly available CO_2 as C1 building block for the alkoxycarbonylation reaction of olefins (Scheme 10). In the presence of a ruthenium carbonyl catalyst system including an ionic liquid industrially important olefins were converted into higher-value carbonyl compounds.[80] Compared to previous systems, this catalytic system showed improved activity and produced carbon monoxide from carbon dioxide. As an advantage, the use of sensitive and expensive reducing agents is avoided compared to other known systems, for example, Grignard reagents, diethylzinc or triethylaluminum.



Scheme 10. Ruthenium-catalyzed alkoxycarbonylation of alkenes with carbon dioxide.

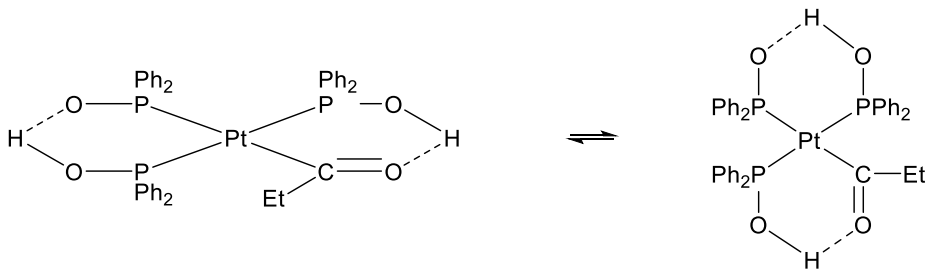
In 1992, Moore and Grimmer reported the first ruthenium-catalyzed carbonylative C-H activation reaction. They discovered that in the presence of catalytic amounts of simple $Ru_3(CO)_{12}$, pyridine and other β-nitrogen-containing aromatic compounds reacted with olefins and CO in an ortho-acylation reaction (Scheme 11).[81] The suggested mechanism involves the formation of coordinatively unsaturated metal centers of the trinuclear cluster, then coordination by pyridine, subsequent ortho-metalation to give the key intermediate, which finally yields the acylated product.



Scheme 11. Grimmer's work: Ruthenium-catalyzed carbonylative C-H activation reaction.

1.2.1.4. Platinum

Platinum-catalyzed carbonylation reactions mainly focussed on hydroformylation reactions. For example, as early in 1986, Frijns reported that platinum complexes with a general formula $Pt(H)(Ph_2PO)(Ph_2POH)(PPh_3)$ catalyzed the hydroformylation of 1-heptene/2-heptene,[82] yielding the linear product with high selectivity (90%). The intermediate complexes (Scheme 13) were successfully isolated and identified.



Scheme 13. Frijns' work: The intermediate complexes for platinum-catalyzed hydroformylation.

In 1990, Venanzi reported a platinum(0) complex promoted by CH_3SO_3H to become an active catalyst for hydroformylation of styrene with a yield of 67% and 88% linear selectivity (Figure 2).[83]

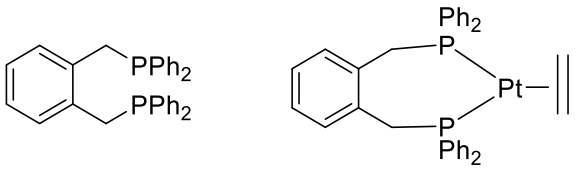


Figure 2. Venanzi's work: Platinum-complex for hydroformylation of styrene.

Due to the relatively low activity of platinum catalysts compared to palladium ones, they have not yet applied to alkoxycarbonylation reactions. More specifically, the catalytic performance of platinum complexes (rate) is typically four orders of magnitude lower than palladium.[84] Thus, only scarce reports are known, mainly focusing on the mechanistic aspects of such reactions.[85-90] However, in recent years the price of Pd is highly dynamic and has increased significantly, due to the large demand for this metal in industrial & environmental catalysis. Thus, the current price of bulk platinum is about half of that of palladium (Figure 3). This situation stimulated us to to think about the possibility of using Pt instead of Pd in carbonylation reactions.

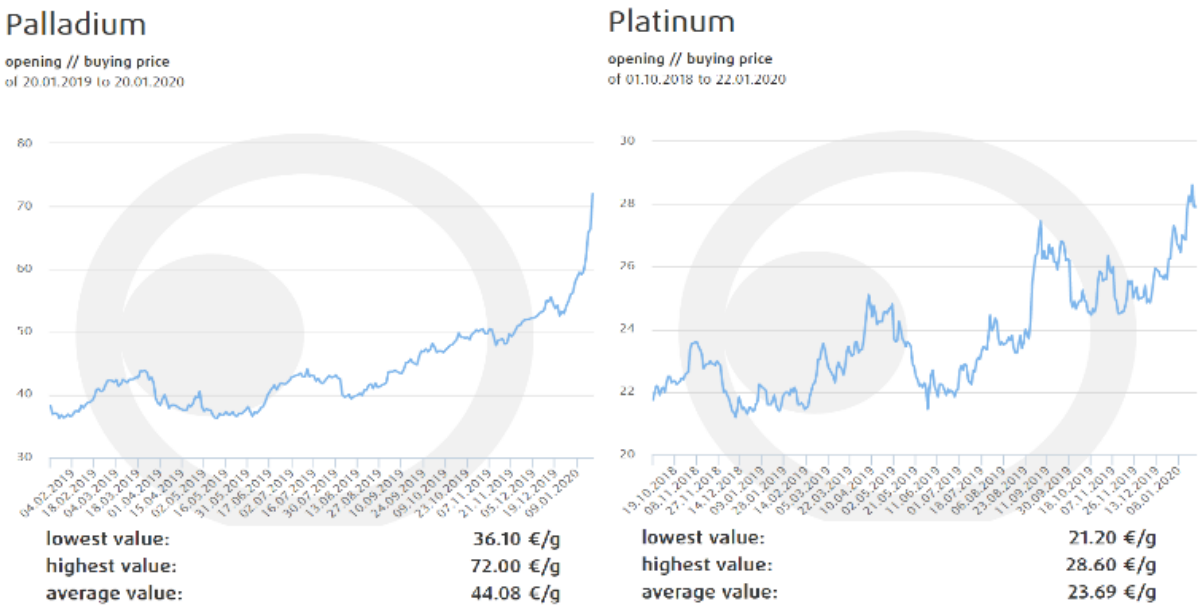
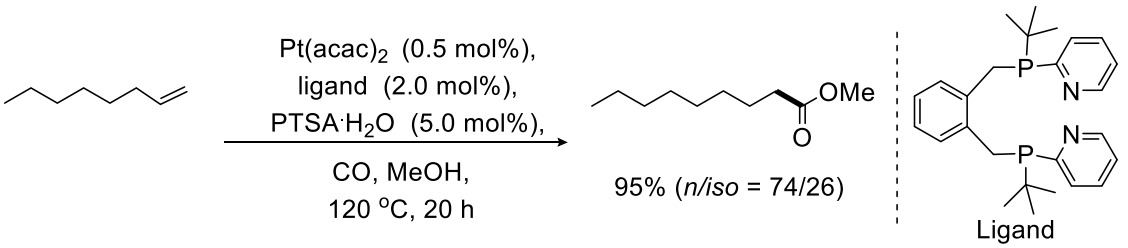


Figure 3. Recent prices for palladium and platinum.

In the framework of this thesis, we developed a general platinum-catalyzed alkoxy-carbonylation conversion for olefins (Scheme 14). By using specific ligands, the activity of the metal center is improved, and the catalyst system becomes comparable in activity with the palladium catalyst. At the same time, this Pt catalytic system showed excellent reactivity for bulk olefin feedstocks and good compatibility for various functional groups, which provides new inspiration for platinum-catalyzed alkoxycarbonylations.



Scheme 14. A general platinum-catalyzed alkoxycarbonylation of olefins

1.2.2. General type of ligands

Among all the reaction parameters, the ligand with its different electronic and steric properties is an important factor and has a dramatic impact on the reactivity of the catalyst. Thus, for decades countless new ligands have been designed and prepared to improve reaction outcomes. In this part, we provide some concise and representative introduction about phosphine ligands.

1.2.2.1. Monophosphine ligands

Early studies of organometallic catalysts focused on the use simple monophosphine ligands, such as triphenylphosphine and trialkylphosphines.[91-92] Selected specific structures of monophosphines are listed below (Figure 4).[93-98] Among those monodentate phosphines ligands, **L2** and **L11** are of most significance for the synthesis of MMA and branched carbonylative products. These two types of reactions will be introduced in detail in chapter 3.

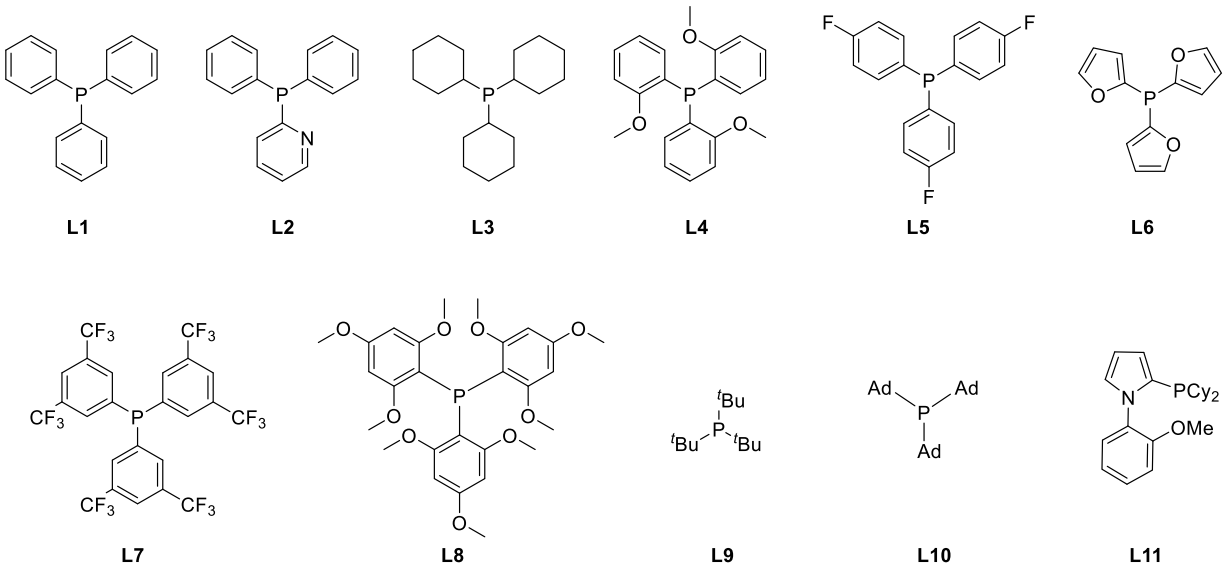


Figure 4. Commonly used monophosphine ligands for carbonylations.

1.2.2.2. Monodentate P-O ligands

Monodentate P-O ligand is another widely used ligand. Advantageous, organophosphites are less sensitive towards oxidation than phosphines, makes them more suitable for industrial production. Because of the P-O bonds, they are weak σ-donors but strong π-acceptors, this feature facilitates the dissociation of CO from the metal center.99-109 Therefore, such ligands are more suitable for hydroformylation reactions. In relative experiments of Rh-catalyzed hydroformylation, phosphites ligand contributes a substantial increase in the reaction rate compared to phosphine ligand.[110-112] Further research shows the selectivity of linear product can be enhanced by incorporation of sterically demanding substituents in the organic backbone. Bulky alkyl groups in the *ortho*- of the P-O bond facilitate this obligation and also donate to an improved activity and stability. These properties were invesgated carefully by van Leeuwen's group employing the phosphite ligand **L13** bearing a *tert*-butyl group in the *ortho*-position of the aromatic ring.[113-115]

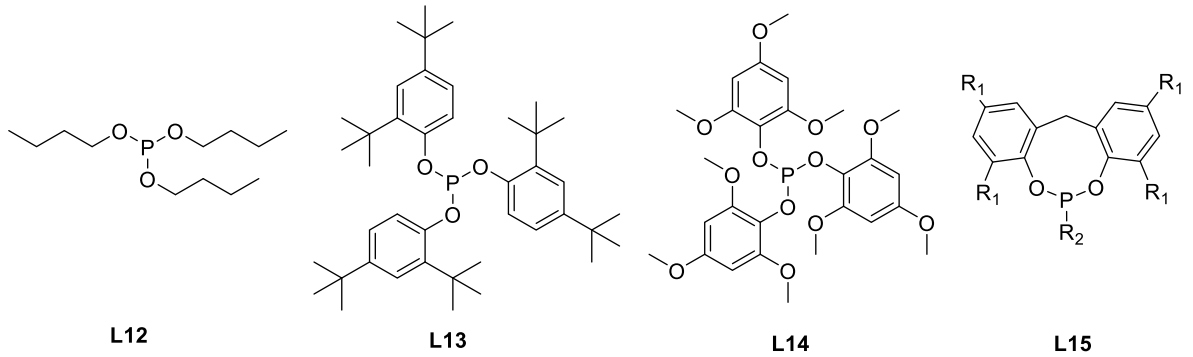


Figure 5. Commonly used monodentate P-O ligands for carbonylation.

1.2.2.3. Bidentate ligands

Ligands can not only stabilize the respective metal center, but also fundamentally change the selectivity and activity of the catalyst system.[116] In carbonylation reactions, most commonly used ligands are bidentate phosphine ligands.

As an example, the diphosphine ligand dppe (1,2-bis-(diphenylphosphino)etane)is already known since 1959 several derivatives have been prepared.[117-118] In general, the properties of this and other bidentate ligands and the performance of its complexes in catalysis, can be varied by changing the ligand backbone.[119] In carbonylation reactions one of the most prominent bisphosphine ligands are Xantphos derivatives.[120] Xantphos is derived from the heterocycle xanthene. It has a particularly wide bite angle (108°).[121-122] Such ligands have been widely used in the hydroformylation and alkoxycarbonylation of olefins. Due to the importance of r bisphosphine ligands intensive efforts focused on their synthesis and numerous new structures were reported. In the following chapter 1.3, we will highlight specific reactions and describe the different ligands and their applications.

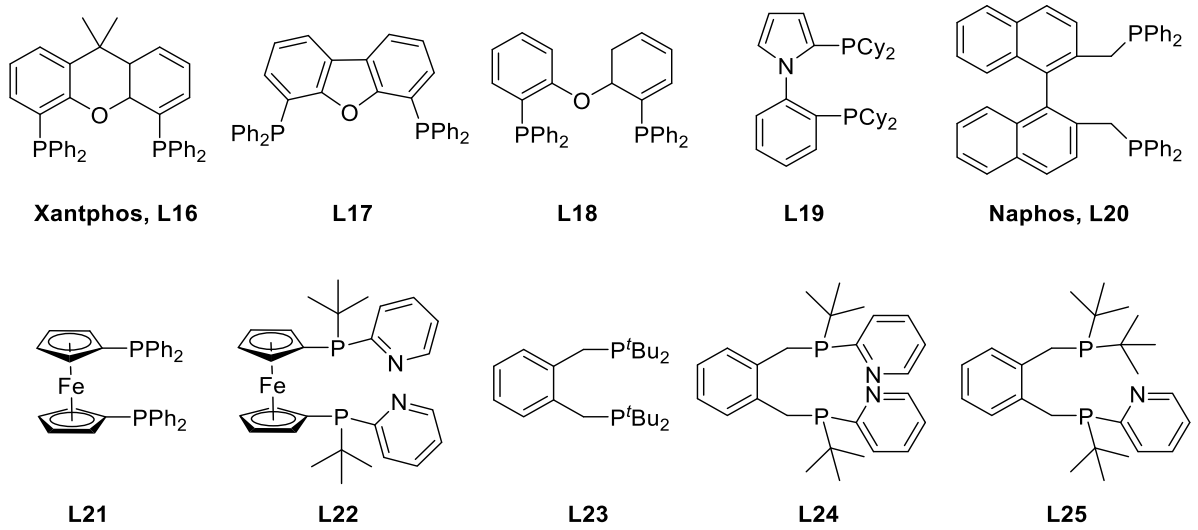


Figure 6. Commonly used bidentate P-ligands for carbonylations.

1.3. Palladium-catalyzed carbonylation

Carbon monoxide (CO), a colorless, odorless gas, was described already by the Greek and Romans.[123-129] It is widespread in nature, for example, found in atmospheric research, the photochemical reactions in the troposphere could produce about 5×10^{12} kg per year.[130] For industrial chemistry, CO is used as one of the commonest bulk chemicals, especially as C1 sources for carbonylation chemistry or in the form of the mixture of CO and H_2, which is known as synthesis gas, used for Fischer–Tropsch synthesis and hydroformylation.[131-132]

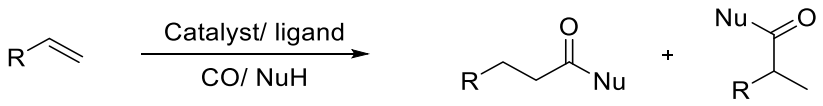
Carbonyl compounds represent a significant class of synthetic intermediates in organic chemistry with growing industrial implications.[133-136] Among numerous methods available for their synthesis, metal-catalyzed carbonylation constitutes one of the most prominent methods, due to its efficiency, atom-economy and excellent selectivity. Carbonylation reactions have been known since the early work of Reppe in the 1930s who used cobalt or nickel under severe and harsh conditions.[137] Progress in catalysis allowed to optimize the strict conditions and design novel catalysts so that a variety of high value products can be obtained. In this regard early work using palladium catalysts by Chiusoli, Pino, and Knifton is notable.[138] Today more efficient and sophisticated complexes are practical precursors to catalyze a variety of carbonylation reactions *vide infra*.

1.3.1. Palladium-catalyzed carbonylation of alkenes

Olefins are one of the most important feedstock for organic synthesis due to their abundance and availability. Lower olefins are mainly derived from cracking processes. In terms of quantity, ethylene and propene are among the most important basic organic chemicals. Higher olefins

can be produced by the oligomerization of ethylene using different catalytic systems, such as Ziegler process,[139-140] Shell higher olefin process (SHOP).[141-143]

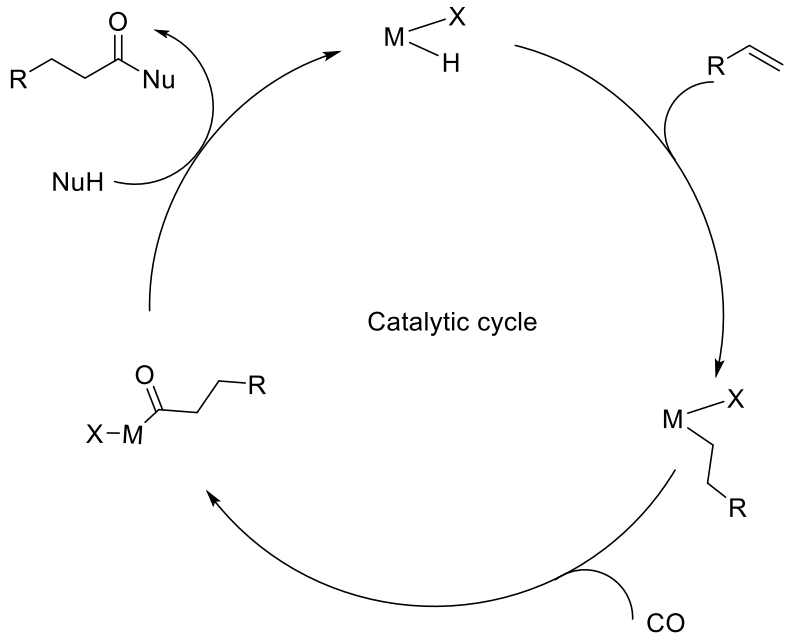
Alkene carbonylation reactions are nowadays the most important application of homogeneous catalysis in chemical industry regarding the production scale.[144] The investigation of alkene carbonylations was established since the pioneering work by Walter Reppe in BASF,[137, 144] who designed and invented high pressure reactors for handling flammable gaseous reactants. His innovative work in carbonylation reactions was done in 1930s by using cobalt/nickel catalysts under drastic conditions. Therefore, reactions involving the addition of carbon monoxide and acidic hydrogen donor to the organic substrate are also called "Reppe Chemistry". The high pressure is mainly used to stabilize the catalytic species $[CoH(CO)_4]$ or $[Ni(H)(X)(CO)_2]$. In 1938, the hydroformylation reaction (also called "oxo-synthesis") was discovered by Otto Roelen during the investigation of Fischer-Tropsch reaction in the presence of cobalt-based catalysts.[145-146] In 1967, von Kutepow and co-workers patented the hydroxycarbonylation of a terminal alkene using phosphine-containing palladium complexes for BASF.[147] In late 1990s, palladium-based systems consisting of $Pd(OAc)_2/PPh_3$ and Brønsted acid were discovered and described in a series of patents on the alkoxycarbonylation of ethylene to generate propionates. In recent years, the research on developing palladium based catalyst systems for carbonylation of alkene has received considerable attentions (Scheme 15).



Scheme 15. Carbonylation of olefins.

In general, the nucleophiles can be a variety of acidic hydrogen donors, such as alcohols (alkoxycarbonylation), H_2O (hydroxycarbonylation), as well as amines (aminocarbonylation).

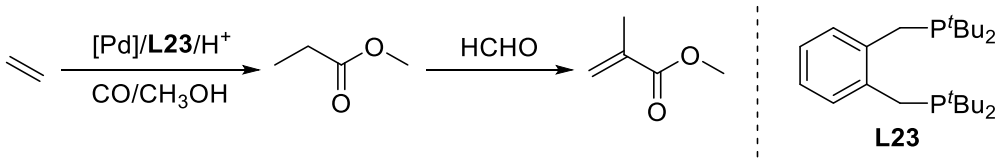
For the mechanism of those reactions, despite some differences in catalysts, substrates, and nucleophiles, the general accepted reaction mechanism can be summarized as a catalytic cycle (Scheme 16).[21, 148] It is proposed that the pre-catalyst react with acid additives to form the metal-hydride species, then the reaction starts with the corresponding metal-hydride species. Subsequent coordination and addition to the olefin, followed by insertion of carbon monoxide leads to the acyl metal complex. When the nucleophile promotions nucleophilic attack to the acylmetal species lead to the end of the catalytic cycle accompanied by the regeneration of the active metal-hydride catalyst.



Scheme 16. General reaction mechanism for carbonylation of alkenes.

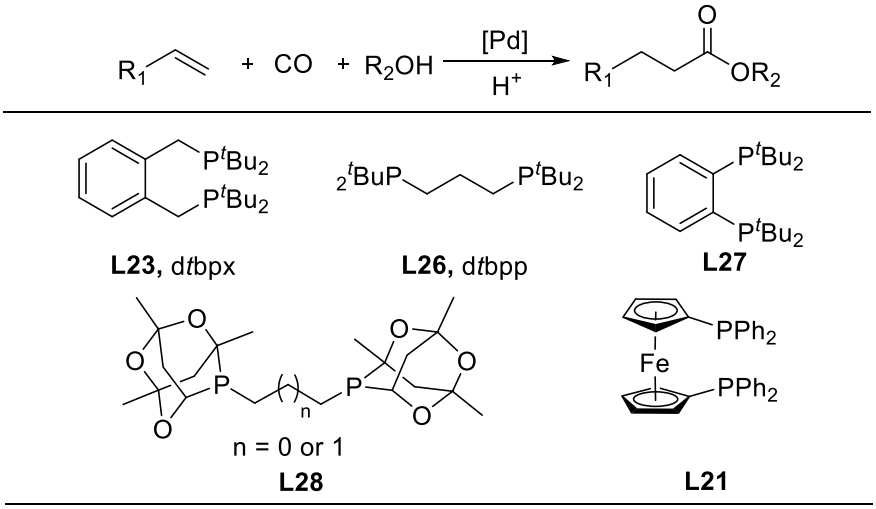
1.3.1.1. Palladium-catalyzed alkoxycarbonylation of alkenes

On the topic of "alkoxycarbonylation of alkenes", initial reports can be traced back to the research of Reppe, using [Ni(CO)$_4$] as catalyst under drastic conditions.[137, 144] Since then, transition-metal-catalyzed alkoxycarbonylation reactions have been dramatically improved. An important example of industrial application is the production of propionate from ethylene (Scheme 17) by a palladium/d*t*bpx/acid (Lucite process) catalyst system.[149] Further aldol-condensation with formaldehyde produces methyl methacrylate (MMA), which is the monomer for the production of poly(methyl methacrylate) (PMMA).[150-153]



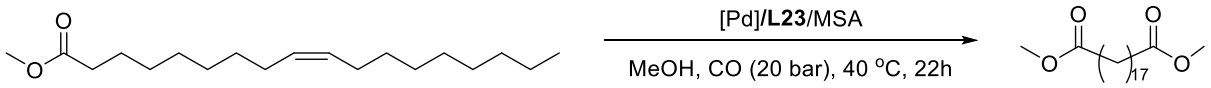
Scheme 17. Lucite alpha process.

Generally, the use of palladium precursors in combination with bulky chelating ligands such as d^{t}bpx, d^{t}bpp, bis(phosphaadamantyl)diphosphines, 1,1′-bis(diphenylphosphino)-metallocenes resulted in improved regioselectivity towards linear esters (Scheme 18). [154-158]



Scheme 18. Ligands for alkoxycarbonylation of internal olefins to linear esters.

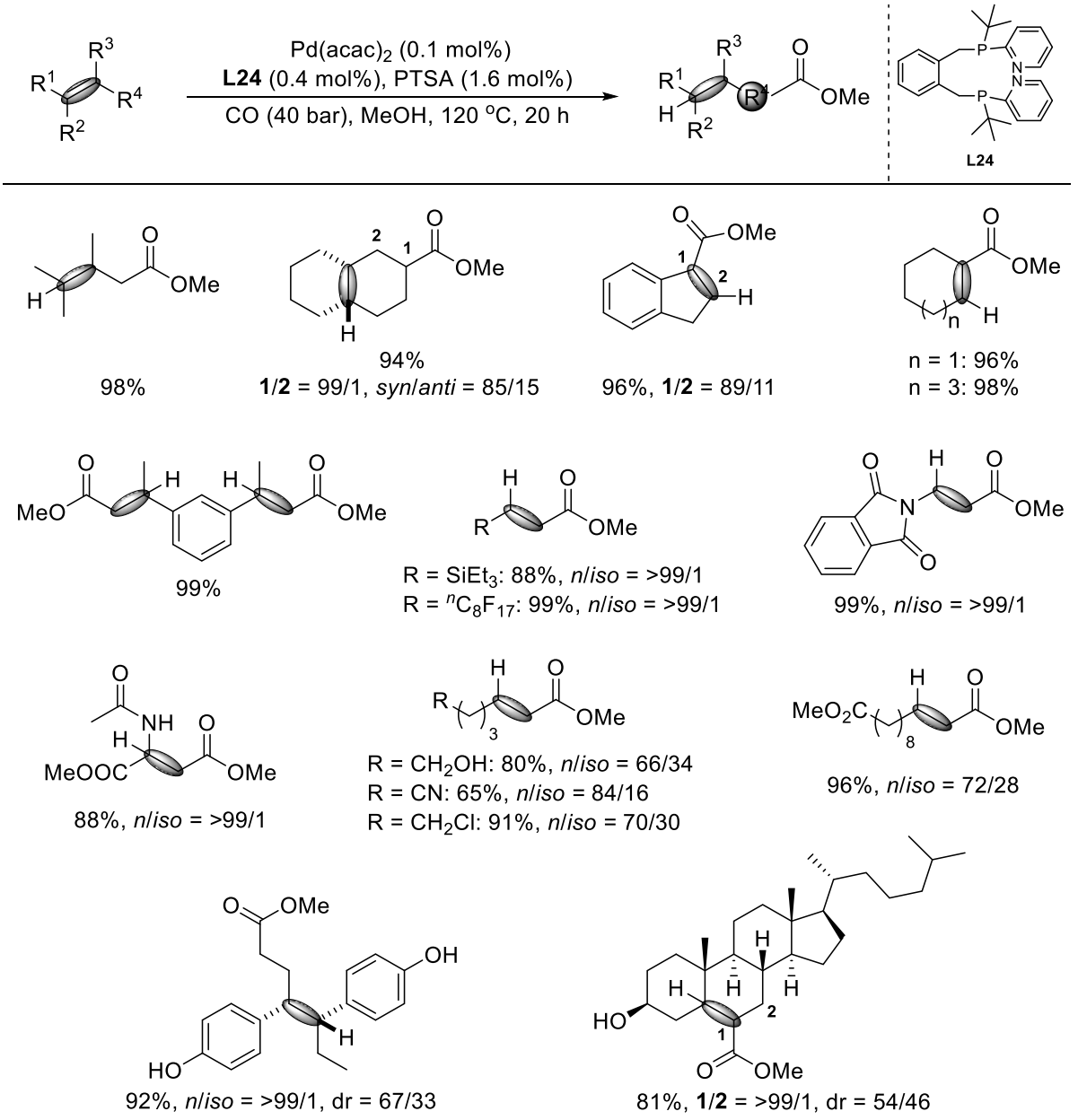
Using the catalyst system [$Pd_2(dba)_3$], d*t*bpx and methane sulfonic acid (MSA), the isomerization-methoxycarbonylation of internal alkenes to linear carboxylic acid ester was achieved. The reaction is proposed to occur via a metal-hydride mechanism with the trapping of the acyl species by methanol as the rate-determining step.This method is further extended to the isomerization/methoxycarbonylation of unsaturated carboxylates to industrially important linear α,ω-diester (Scheme 19).[159-160] Although spanning nine carbon atoms, the selectivity for the linear product remained above 90%.



Scheme 19. Palladium-catalysed isomerization-methoxycarbonylation of internal alkenes

Recently, our group designed and introduced palladium catalysts based on 1,2-bis((tert-butyl(pyridin-2-yl)phosphanyl)methyl)benzene (LIKAT ligand **I**, **L24** as shown in Scheme 21).[148, 161] Application of this condation allowed a general alkoxycarbonylation of sterically hindered olefins (Scheme 20) as well as natural products and pharmaceuticals to give the desired products in excellent yields. This transformation reflects good industrial application potential.

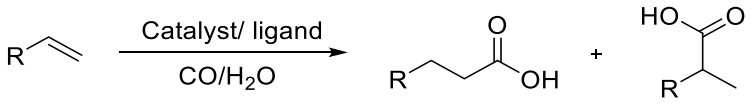
Scheme 20. Reactivity of olefins with different structures.



Scheme 21. Our group's work: new catalyst for alkoxycarbonylation.

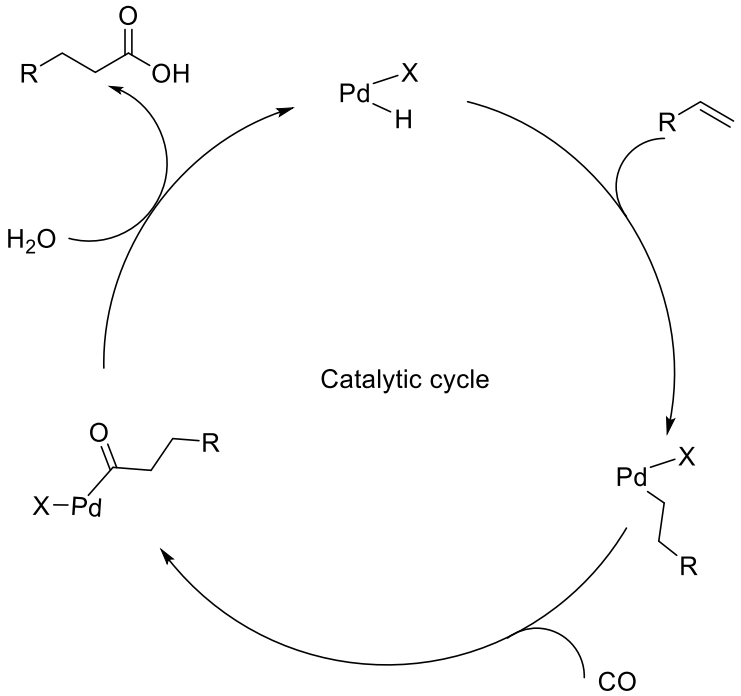
1.3.1.2. Palladium-catalyzed hydroxycarbonylation of alkenes

Hydroxycarbonylations allow to incorporate CO and H_2O into unsaturated substrates leading to carboxylic acids.[144] The representative equation is shown below (Scheme 22).



Scheme 22. Palladium-catalyzed hydroxycarbonylation of alkenes.

In 1969, Kutepow and Neubauer patented a hydroxycarbonylation process of terminal alkene using phosphine-containing palladium complexes for BASF.[162-163] Further studies by Fenton showed that $PdCl_2$ was a good precursor and the reaction parameters were optimized to obtain high conversion rates and good selectivity for the linear product.[164] Under the conditions: 7 to 55 bar pressures, 150 °C with an excess of PPh_3 as ligand, the ratio of linear to branched reached 78%. Surprisingly, when introducing some hydrogen inside, the conversion is largely improved. Based on that observation, the active catalytic species is presumably $[Pd(H)Cl(PPh_3)_2]$. We summarize the reaction mechanism in Scheme 23.



Scheme 23. Catalytic cycle of the palladium-catalyzed hydroxycarbonylation of alkenes.

Alper and co-workers discovered that, when adding copper(II) chloride and hydrochloric acid to the system, the selectivity towards the branched acid can be improved.[165] After adding Bronsted acids to the reaction system, the carbonylation could be performed even at room temperature and at low pressure of CO. Interestingly, enantioselective carbonylations can be achieved from a prochiral terminal alkene. By adding the (*R*)- or (*S*)- 1,1-binapthyl-2,2-diylhydrogenophosphate (BINPPA) as chiral ligand (Figure 7), it was possible to reach an enantiomeric excess (*ee*) up to 91%.[166] In this manner, two non-steroidal anti-inflammatory prodrugs: (*S*)-ibuprofen and (*S*)-naproxen could be synthesized from *p*-isobutylstyrene and 2-vinyl-6-methoxynaphtalene.

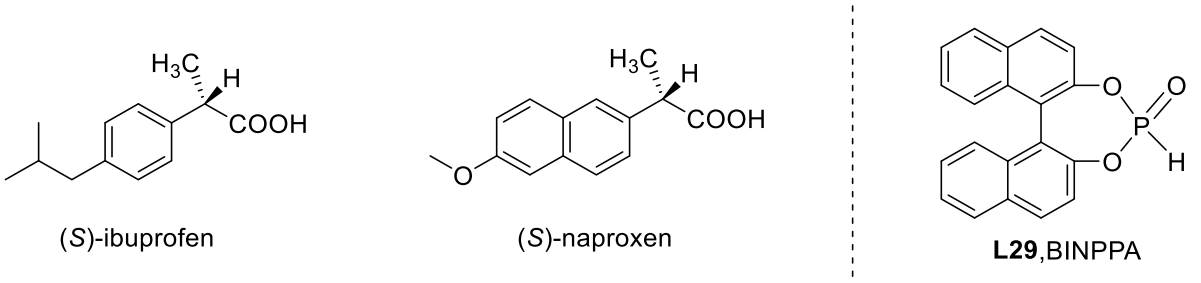
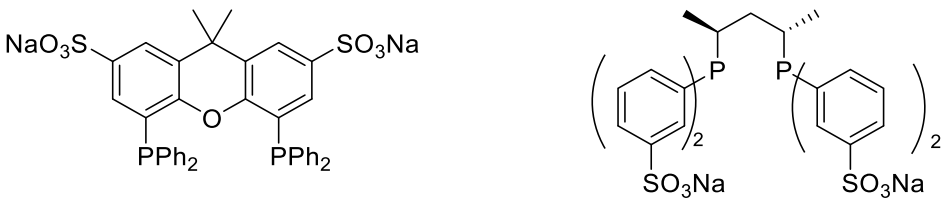


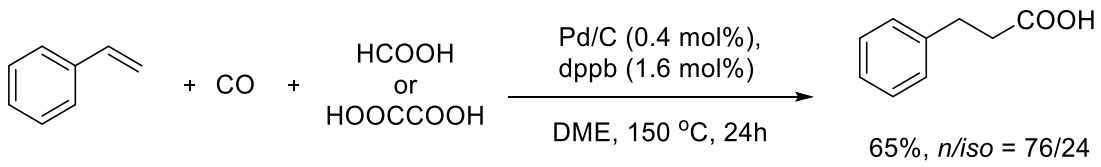
Figure 7. Enantioselective carbonylations catalyzed by BINPPA.

The selectivity of the reaction can also be controlled and high selectivity for the branched isomer was achieved using a water-soluble palladium(II) complex containing a chelating anionic ligand, such as 2-carboxylatopyridine.[167-168] Notably, lithium salt additives (LiCl or LiI) also promote the regioselectivity of the process. In 1998, van Koten and Kruis reported that ar catalyst with 2-aminophenylthiolato ligands coordinated to $PdCl_2$ moieties. Using this sytem,styrene can be converted into 2-phenylpropanoic acid with a selectivity of 99%.[169]
In order to allo carbonylations under mild conditions, a dicationic palladium catalyst coordinated by a specific bidentate diphosphine ligand (Figure 8; 2,7-bis(sulfonato)xantphos) was developed by Leeuwen and Schreuder. In the presence of p-tolylsulfonic acid as co-catalyst, the hydroxycarbonylation of ethylene, propene and styrene went smoothly and provided the products with an *n/iso* ratio of 34/66.[170] In addition, a bidentate chiral water-soluble ligand (*S*,*S*)-2,4-bis(diphenylsulfonatophosphino)butane (Figure 8; BDPPTS) has been prepared by Sinou and Serrano.[171] It's palladium complexes catalyzed the hydroxycarbonylation of various vinylarenes with *ee* values up to 43%. Furthermore, they conducted some preliminary studies on catalyst recovery. It is also possible to obtain high selectivity for the linear product. Thus in 1992, Alper reported the catalytic conversion of aromatic olefins (7 bar of CO and 150 °C). Specifically, by using a mixture of $Pd(OAc)_2$, 1,4-bis(diphenylphosphino)butane (dppb), in the presence of formic or oxalic acid (Scheme 24) α-methylstyrene was transformed into the product with a 100% selectivity and 82% yield.[172] Labeling experiments showed that the carbonyl group results from carbon monoxide and not from formic or oxalic acid.



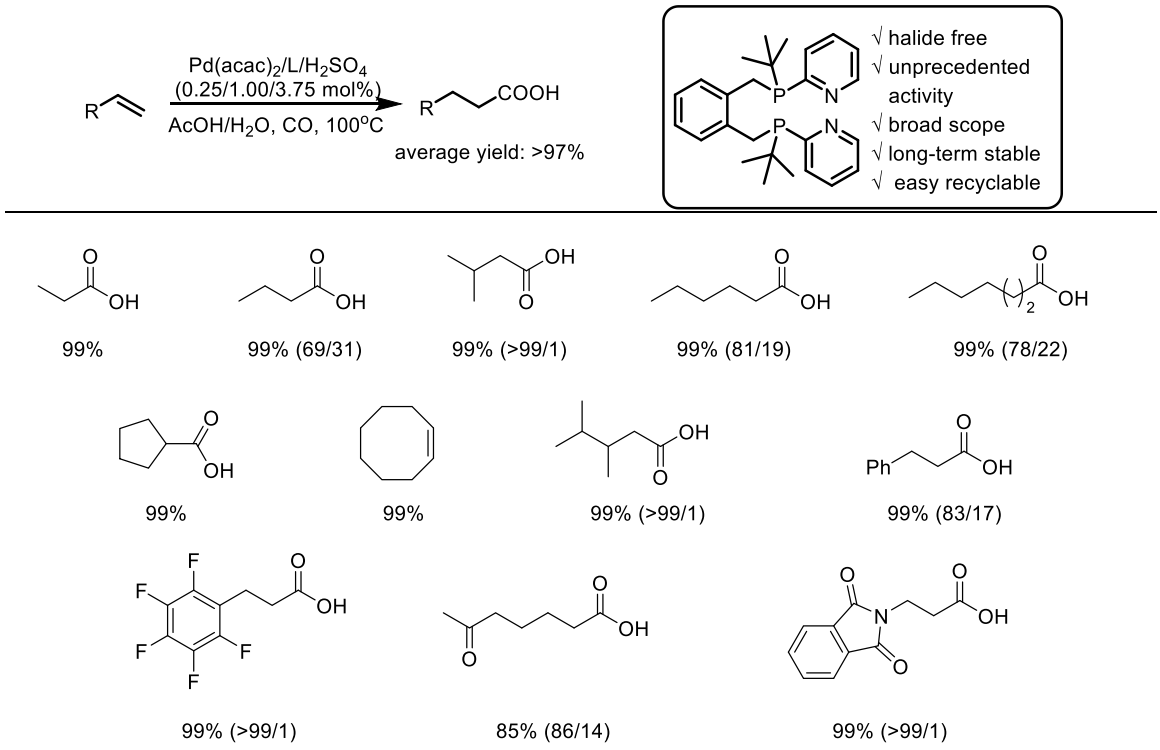
L30, 2,7-bis(sulfonato)-xantphos **L31,** BDPPTS

Figure 8. Structure of sulfonated bidentate phosphines.



Scheme 24. Alper's work: palladium catalyzed hydroxycarbonylation

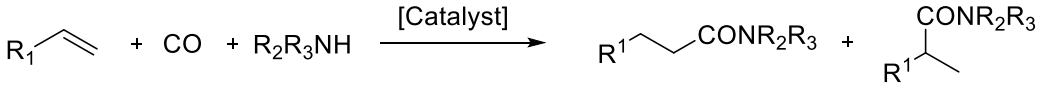
In 2019, our group reported a state-of-the-art palladium catalyst allowing production of carboxylic acids under halogen-free and relatively mild conditions (Scheme 25).[173] The catalyst showed outstanding stability and can be easily recycled from the reaction system. For ethylene, exceptionally good catalyst turnover numbers and frequencies were obtained (TON >350,000, TOF >15,000 for propionic acid). In principle, a broad range of olefins can be transformed into the corresponding products.



Scheme 25. Our group's work: Palladium catalyzed hydroxycarbonylation.

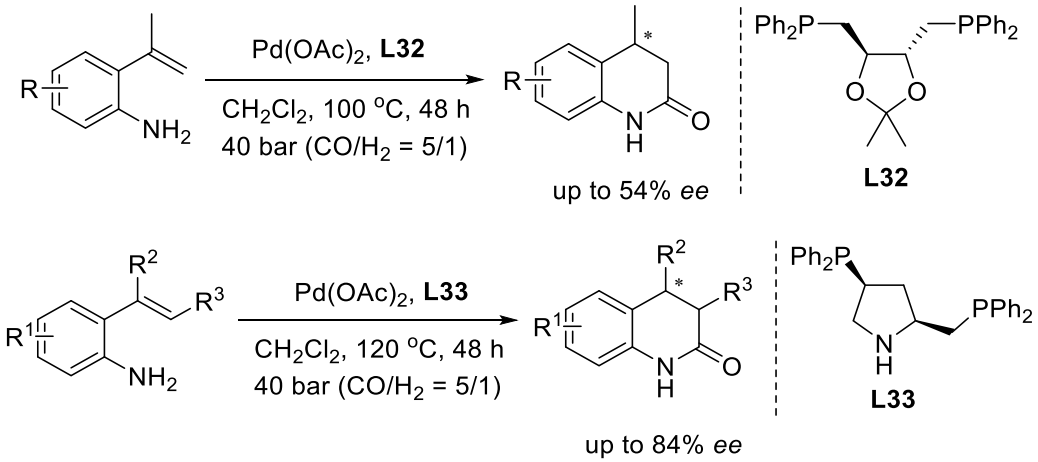
1.3.1.3. Palladium-catalyzed aminocarbonylation of alkenes

The palladium-catalyzed carbonylation of alkenes with CO and amines (aminocarbonylation) constitutes a straightforward and atom-efficient route to provide saturated carboxylic amides (Scheme 26). Compared with alkoxycarboxylations, related aminocarbonylations have attracted much less attention.[174]



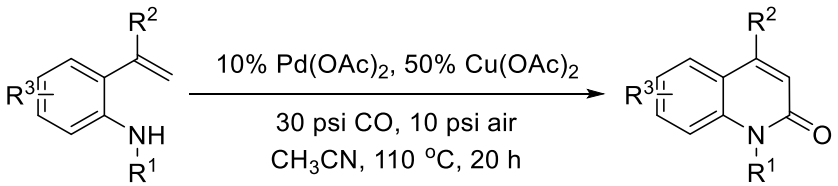
Scheme 26. Transition-metal-catalyzed aminocarbonylation of alkenes.

In early studies on aminocarbonylation of alkenes, cobalt carbonyl complexes or nickel cyanide were used as catalysts. Iron carbonyl and ruthenium chloride also showed some catalytic activity for this transformation.[175-179] However, all these reactions were carried out under relatively severe conditions (>200 °C; >150 atm). Similarly to the carbonylations *vide supra*, research in recent years has mainly focused on palladium-catalyzed aminocarbonylation reactions. In 1996, the first intramolecular aminocarbonylations of 2-aminostyrenes and 2-allylanilines were reported. In the presence of $Pd(OAc)_2$, cyclic amides with different ring size and lactams could be synthesized.[180] Notably, in 1997, excellent enantioselectivity was achieved in asymmetric aminocarbonylation reactions.[181] For example, catalyzed by $Pd(OAc)_2$ in the presence of different ligands (**L32** or **L33**), 4-methyl-3,4-dihydroquinolin-2-one derivatives can be obtained in up to 54% and 84% *ee*, respectively (Scheme 27).[182]



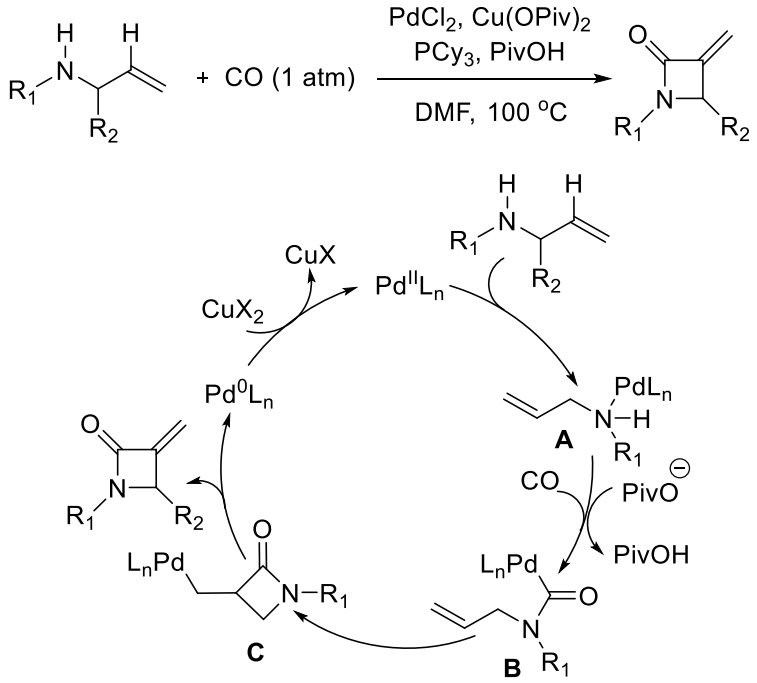
Scheme 27. Asymmetric intramolecular aminocarbonylation of 2-aminostyrene derivatives.

In 2013, Alper and co-workers developed an efficient palladium-catalyzed oxidative aminocarbonylation of *N*-monosubstituted-2-vinylanilines to prepare 2(*1H*) quinolinones in high yields (Scheme 28).[183]



Scheme 28. Palladium-catalyzed oxidative aminocarbonylation.

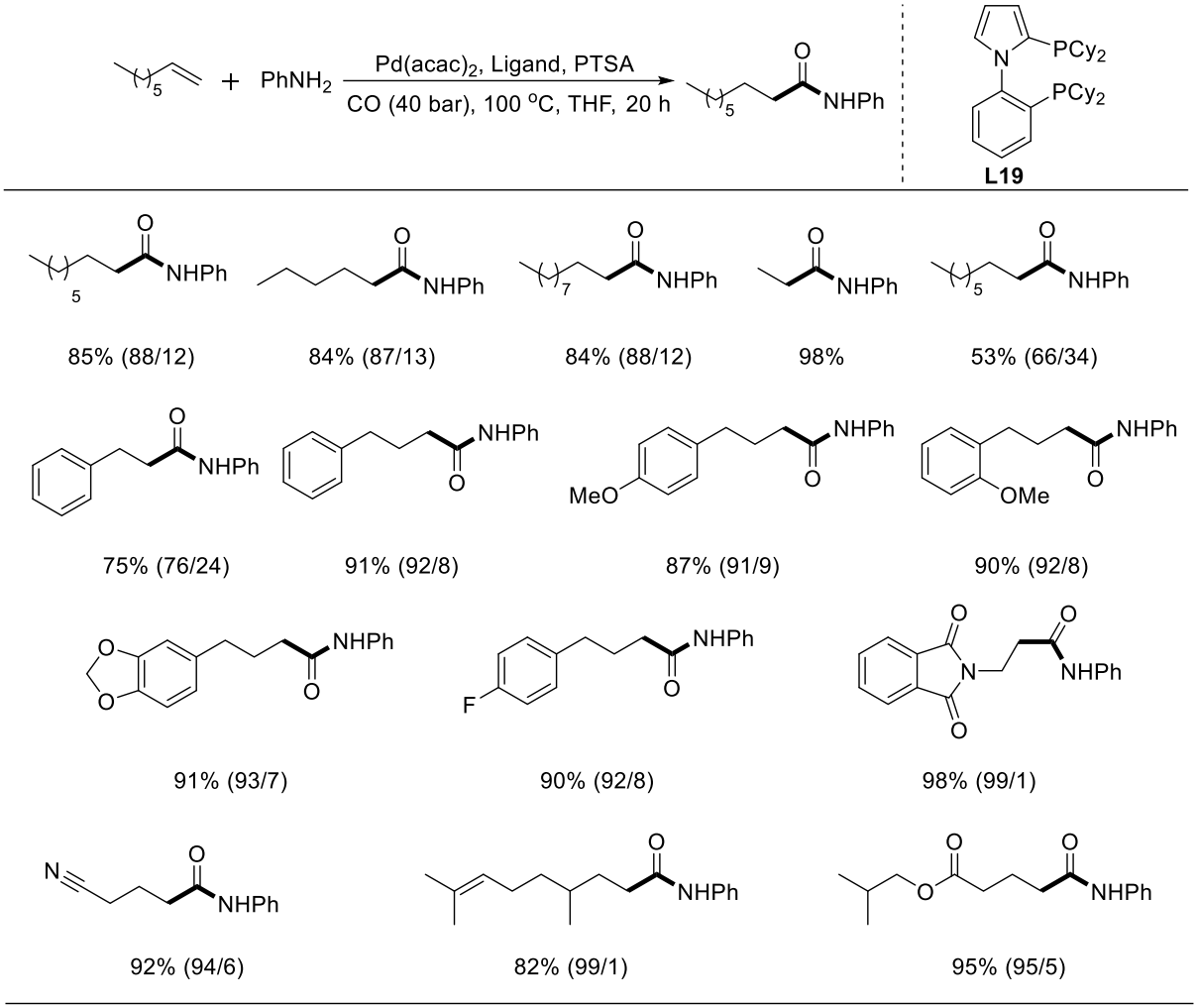
More recently, Lei and Li reported a novel palladium-catalyzed intramolecular oxidative aminocarbonylation of *N*-allylamines to form *α*-methylene-*β*-lactams.[184] A possible mechanism for this conversion is outlined in Scheme 29. The intermediate is formed by the chelation of the starting alkenylamine to palladium, and subsequent migratory insertion of the coordinated CO into the nitrogen-palladium bond. Next, olefin insertion into the acyl-palladium bond generates the intermediate C. *β*-H elimination of C affords the final product and releases a palladium hydride species which is oxidized by the copper catalyst to regenerate Pd(II) and accomplish the catalytic cycle.



Scheme 29. Palladium-catalyzed intramolecular aminocarbonylation of *N*-allylamines.

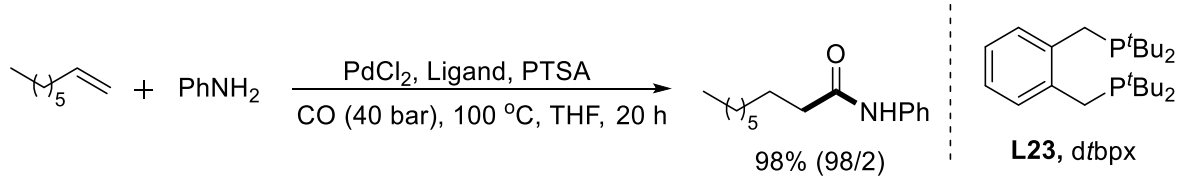
In 2013, our group reported the first palladium-catalyzed intermolecular aminocarbonylation reaction of alkenes (Scheme 30).[185] The reported catalyst system consists of an *N*-phenylpyrrole bidentate phosphorus ligand and catalytic amount of PTSA as the promoter. The reactions were performed under relatively milder conditions (100°C, 40 bar CO).

A range of alkenes bearing different functional groups were tolerated and provided the corresponding amides with good yields (up to 98%) and good linear-selectivity (*n/iso* up to 99/1). However, possibly due to the strong basicity of aliphatic amine, the reaction was hindered when using aliphatic amines as the nucleophile. Furthermore, the applicability of this methodology was demonstrated by *in-situ* generation of aniline by reduction of nitroarene using syngas (CO/H_2).



Scheme 30. Palladium-catalyzed aminocarbonylation of olefins

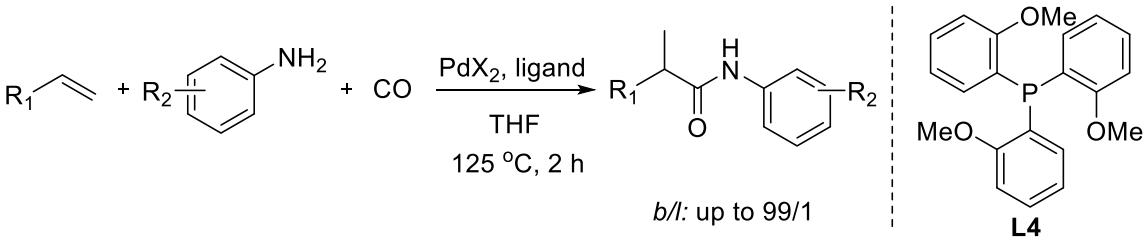
In 2014, Cole-Hamilton and co-workers reported the carbonylation of aliphatic olefins using Pd/d*t*bpx(**L23**) catalyst system (Scheme 31).[186] The application potential of this protocol was showcased by the highly linear selective aminocarbonylation of unsaturated substrates.



Scheme 31. Cole-Hamilton's work: highly linear selective aminocarbonylation

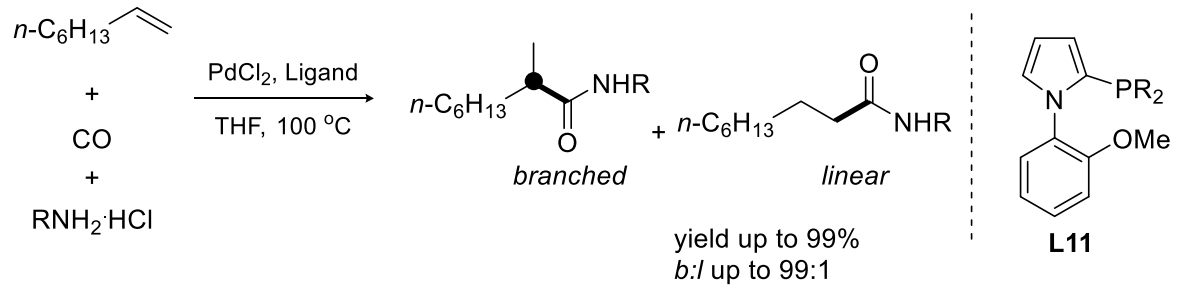
In 2014, Liu and co-workers described an efficient process for the synthesis of *N*-aryl monosubstituted carboxamides *via* the palladium-catalyzed aminocarbonylation of alkenes with CO and anilines (Scheme 32).[187] Remarkably, the catalyst does not require acid, base or

any other promoters and employs a commercially available bulky monophosphine ligand to give the branched product.



Scheme 32. Acid-free branched regioselective aminocarbonylation of alkenes.

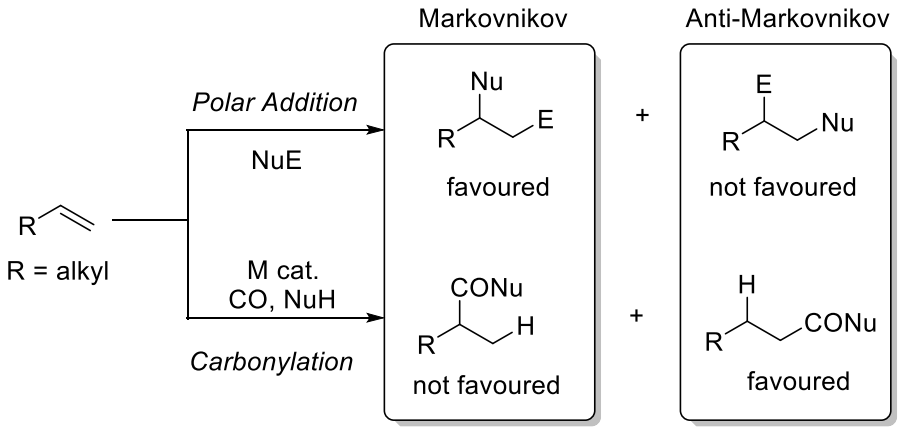
Moreover, our group recently developed the first palladium catalysed selective aminocarbonylation of alkenes with aliphatic amines (Scheme 33).[188] Applying a particular pyrrole-type ligand, a broad range of aliphatic amines and alkenes were efficiently transformed to the corresponding branched amides in excellent yields and high regioselectivity. In addition to simple aliphatic and aromatic amines, this procedure allowed the efficient aminocarbonylation of amino acids derivatives. In view of the easy availability of the substrates, this method is expected to complement the current procedures for carbonylations in organic synthesis.



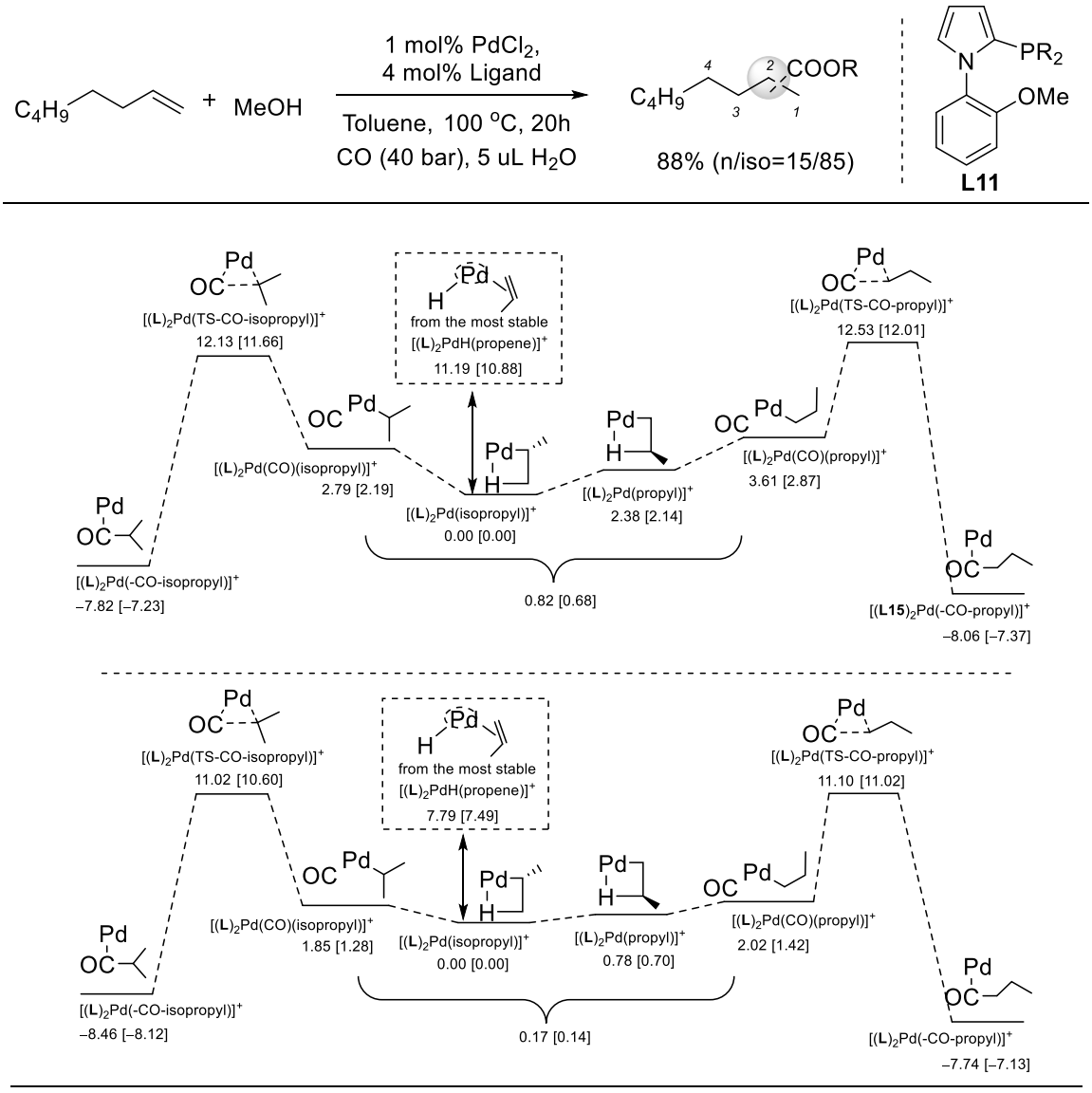
Scheme 33. Our group's work: selective palladium-catalyzed aminocarbonylation of olefins.

1.3.1.4. Branched selective carbonylation of alkenes

Selectivity control is an important issue in homogenous catalysis. The following types of selectivity can be distinguished in a chemical reaction: chemoselectivity, regioselectivity, stereoselectivity and enantioselectivity. In general, the outcome of a reaction is decided by the thermodynamics and the kinetics of the overall process, which includes the incongruent transition states, thermodynamic stability of products and equilibrium processes. Hence, the control selectivity is a challenging topic in organic synthesis.



Scheme 34. Two pathways for alkene insertion into the Pd−H bond



Scheme 35. Palladium-catalyzed Markovnikov alkoxycarbonylation of alkenes.

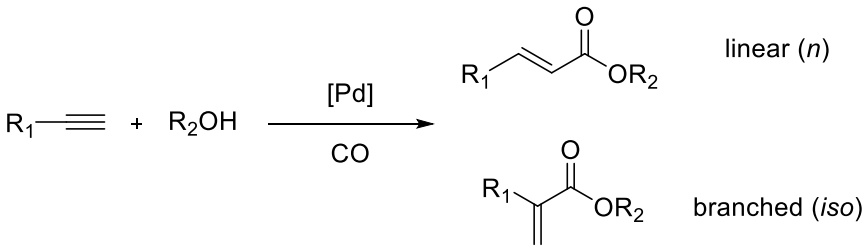
Taking Reppe carbonylation as an example, it is widely recognized that a number of efficient and highly linear-selective (*anti*-Markovnikov-selective) catalyst systems exist. However, by far

fewer studies have been reported on the branched-selective (Markovnikov-selective) carbonylation of alkenes. This is because, by reason of the increase in steric properties for the olefin insertion into the palladium-hydride bond to form the secondary carbon-palladium intermediates, the selective formation of the branched products from carbonylation reactions is more challenging (Scheme 34).

A breakthrough example on this topic was reported by our research group.[189] In 2016, we developed an efficient catalyst for Markovnikov-selective alkoxycarbonylation of aliphatic olefins (Scheme 35). In this work, our group showed for the first time that a specific Pd- catalyst system consisting of PdX_2/N-phenylpyrrole (X = halide) catalyzed the alkoxycarbonylation of numerous olefins to give the branched esters in high selectivity (*b/l* up to 91/9). The unanticipated selectivity has been rationalized by densityfunctional theory computation including dispersion correction for van der Waals interaction.

1.3.2 Palladium-catalyzed carbonylation of alkynes

Carbonylations of alkynes give access to different kinds of compounds, such as unsaturated carboxylic acid derivatives or various heterocycles.[190-196] Many of these products are interesting as fine chemicals, biologically active compounds, or intermediates in synthetic chemistry. In recent years, considerable development was made in this area. The Pd-catalyzed carbonylation of alkynes make allowance for the direct and atom-efficient preparation of α,β-unsaturated acids and esters, amides. Generally, mixtures of linear and branched products are formed. The applied catalyst, reaction conditions, and substrate can influence the regioselectivity to a different extent (Scheme 36).

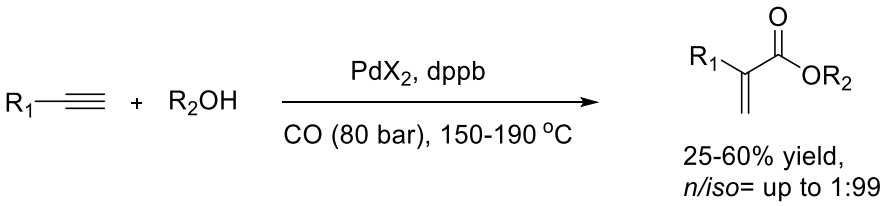


Scheme 36. Palladium-catalyzed carbonylation of alkynes.

Tsuji initially conducted the research in this area in 1966.[197-198] They reported the Pd-catalyzed (Pd/C or $PdCl_2$) carbonylation of propargyl alcohols and chlorides in different solvents.

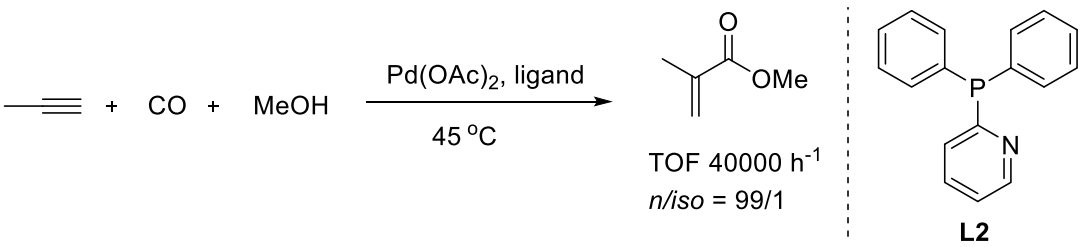
Subsequently, extensive research has been carried out in this field, where different catalysts were employed to synthesize α,β-unsaturated esters of different structures. among these products often contain linear and branched products due to selectivity.One initial research on the regioselective alkoxycarbonylation is conducted by Alper and co-workers, in their condation

$Pd(OAc)_2$ or $Pd(dba)_2$ was employed combine with the ligand dppb (Scheme 37).[199] Insufficiently, the reactions were completed under harsh conditions (150-190 °C and 80 bar CO), providing the branched products in moderate yields (25–60%).



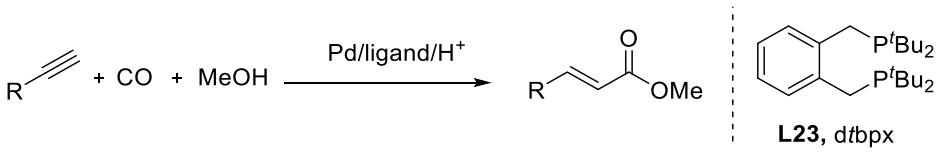
Scheme 37. Branched selective alkoxycarbonylation of terminal alkynes.

Further developments mainly focused on the effect of different ligands, But most of them show poor activity.[200-202] A great improvement was achieved by Drent in the 1990s.[203] They designed a active catalyst system containing a palladium(II) precursor, diphenyl(2-pyridyl)phosphine ligand and acid as co-catalyst. This system showed excellent activity and selectivity for terminal alkynes. As an example, propyne was transformed to the branched product methyl methacrylate (MMA) with unprecedented activity (more than 40.000 turnovers per hour) and 99% selectivity under relatively mild condition (Scheme 38). Shell conducted intense studies in this attractive conversion. Insufficiently, allene performances as an inhibitor in this condation and need to be removed from the substrates. In the chemical industry, propyne was separated as a mixture with allene from the C3 stream of a naphtha cracker. The cost of obtaining pure propyne is too high to be commercialized.



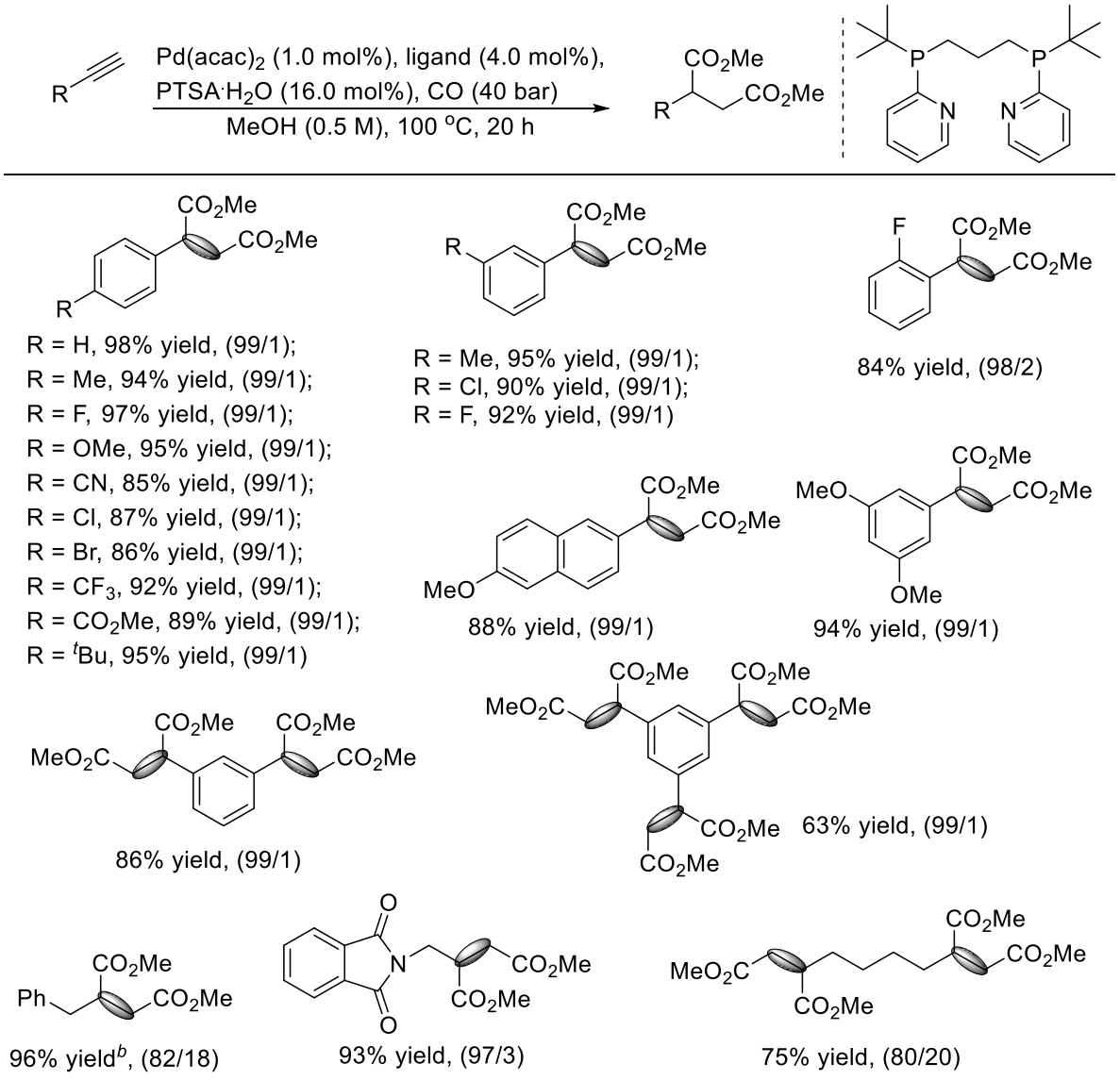
Scheme 38. Methoxycarbonylation of propyne to methyl methacrylate.

In 2010, alkoxycarbonylation of phenylacetylene was reported by Cole-Hamilton (Scheme 39). By using palladium precursor and d*t*bpx (**L**23), Methyl cinnamate can be achieved with high selectivity (96%) and excellent activity (TOF >1.700 h^{-1}).[204]



Scheme 39. Methoxycarbonylation of terminal aliphatic alkynes

The state-of-the-art system on this conversion was de by our group in 2018. We developed a class of novel diphosphine ligands bearing pyridine substituents.[205] The resulting palladium complexes achieved highly chemo- and regioselective dialkoxycarbonylation of alkynes. Kinetic studies suggested the formation of 1,4-dicarboxylic acid diesters via cascade alkoxycarbonylation of the alkynes.

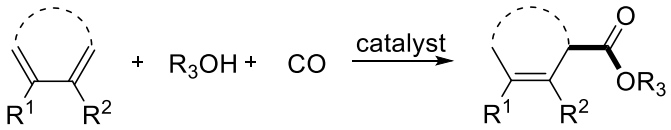


Scheme 40. State-of-the-art system for dialkoxycarbonylation of various alkynes.

1.3.3 Palladium-catalyzed carbonylation of conjugated dienes and allylic alcohols

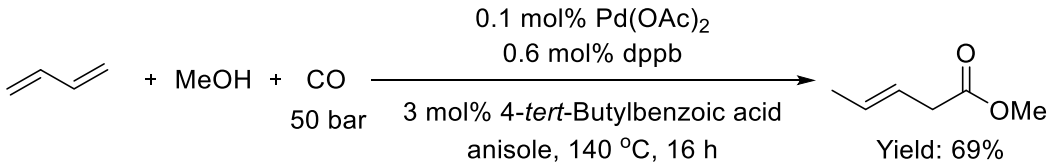
1.3.3.1. Alkoxycarbonylation of 1,3-dienes and allylic alcohols

The transition-metal-catalyzed carbonylation of 1,3-butadiene and allylic compounds is of considerable interest for the synthesis of versatile *β,γ*-unsaturated esters. In recent years, the scientist established effective carbonylation methods for the synthesis of related chemicals.[206-214] However, inadequately, stoichiometric by-products are unavoidable in this process. Apparently, the carbonylation of 1,3-dienes provide the most optimal synthesis method for *β,γ*-unsaturated esters (Scheme 41). Therefore, this conversion attracted numerous interest from industry.[215-231]



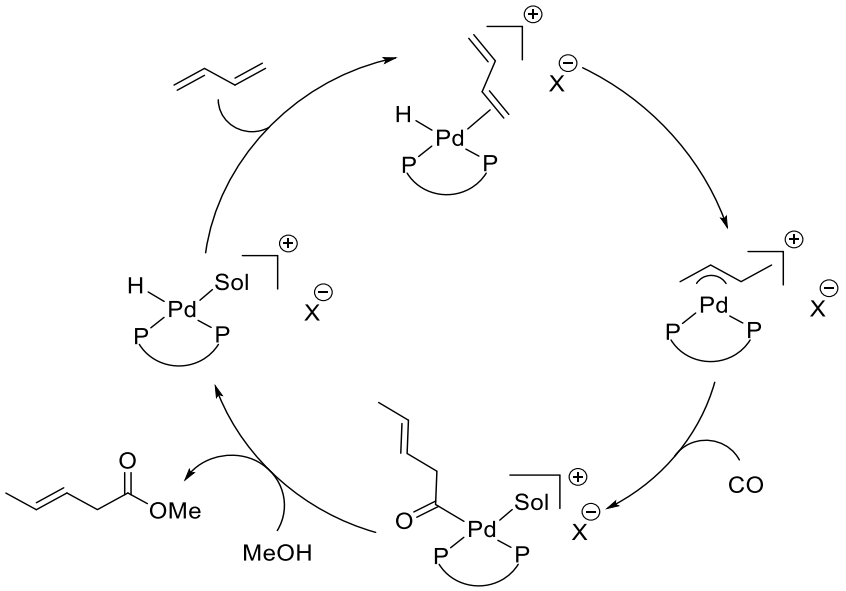
Scheme 41. Synthesis of *β,γ*-unsaturated esters *via* alkoxycarbonylation reactions.

So far, catalysts based on cobalt (mostly researched before 1990), Pd (more important since 1990), Rh, and Ir have been studied for this transformation. The carbonylation of butadiene was first reported by Reppe in the early 1940's, who obtained carbonylated vinylcyclohexene derivatives catalyzed by $Co_2(CO)_8$.[232] Afterward,
DuPont stated the alkoxycarbonylation of 1,3-butadiene to methyl pentenoate by employing a Co/Cu/Th catalyst under harsh condations (810 bar). In the late 1960's, Tsuji reported relevant conversion in the presence of Pd catalyst to give ethyl 3-pentenoate as product with 30% yield.[233]. Matsuda and co-workers demonstrated cobalt catalysts show some activity in the presence of pyridines for this reaction.[234] Nevertheless, only low turnover numbers (about 50) were accomplished under high CO pressure. Next Knifton performed a systematic investigation on the reaction of 1,3-dienes.[235] However, principally 3,8-nonadienoate esters (telomerization products) were obtained. A survey of the patent literature reveals extensive research on the catalytic methoxycarbonylation of 1,3-dienes by Shell, Du Pont, BASF, Dow and DSM. Their research revealed a helpful effect of added acids on selectivity and stability of the metal catalyst. Furthermore, a Shell patent described that by regulatory the polarity of the reaction condation higher reaction rates can be realized.
In agreement with our interest in industrially relevant carbonylation reactions, we performed a systematic research on the methoxycarbonylation of 1,3-butadiene.[236] Inspection of the effect of different reaction condations on relevant activity and selectivity, proved the necessity of chelating ligands and acids as co-catalyst with the intention of acquire satisfied outcomes. After extensive screening of ligands and other reaction conditions, Desired product was acquired in 69% yield and good selectivity under the catalytic condation (Scheme 42).



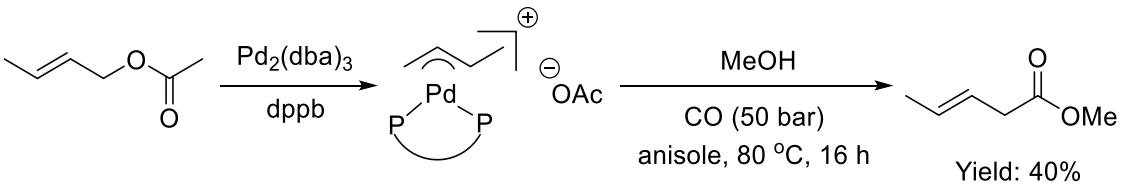
Scheme 42. Our group's work: monoalkoxycarbonylation of 1,3-butadiene.

The mechanism for monoalkoxycarbonylation of 1,3-butadiene was summarized in Scheme 43. The first stage of the conversion is the coordination of the 1,3-diene to a palladium hydride complex formed by oxidative addition of an acid to Pd center. After generation of the crotyl-palladium complex, CO insertion leads to the corresponding acyl-palladium complex. Consequent attack by the alcohol forms the product and the palladium hydride complex is regenerated.



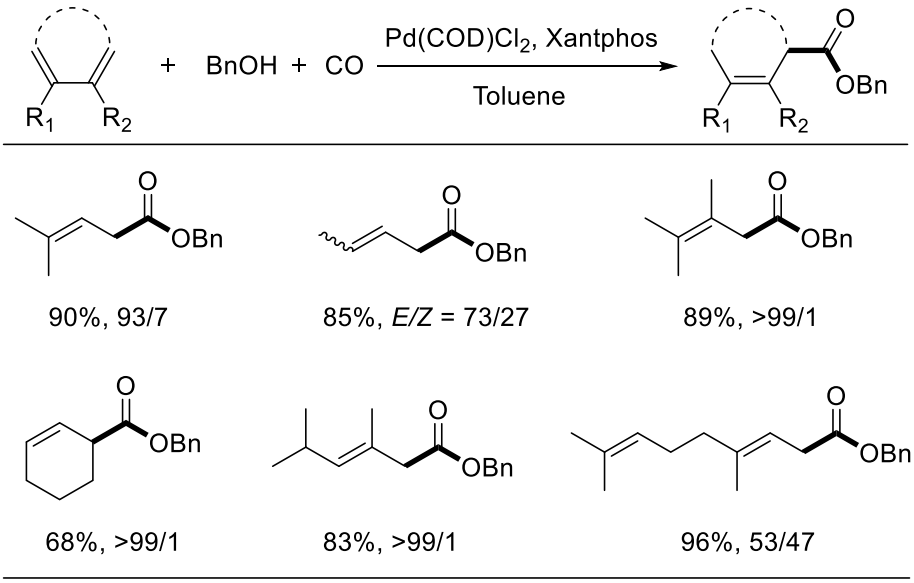
Scheme 43. Proposed catalytic cycle for methoxycarbonylation of 1,3-butadiene.

With the purpose of investigate the mechanism of the monoalkoxycarbonylation more thoroughly, well-defined intermediates in the catalytic cycle were pre-synthesised and the basic steps of the reaction were separately examined. First, cationic crotylpalladium complexes were synthesized, under standard reaction conditions, the cationic crotylpalladium acetate complex, which be similar to the actual intermediate of the catalytic cycle, provided the best yield (40%) of the anticipated product at 80 °C (Scheme 44).



Scheme 44. Mechanistic experiments for methoxycarbonylation of 1,3-butadiene.

Mechanistic research revealed that the first half of the catalytic cycle seems to be proceeding readily, although there is a adverse influence of the CO pressure on the yield of the crotylpalladium complex. Additionally, carbonylation tests of different crotylpalladium complexes displayed that the yield of monocarbonylation product depends on the ligand. In all condations, an acylpalladium complex can not be detected. The formation of these complexes might be the most difficult step under related reaction conditions.

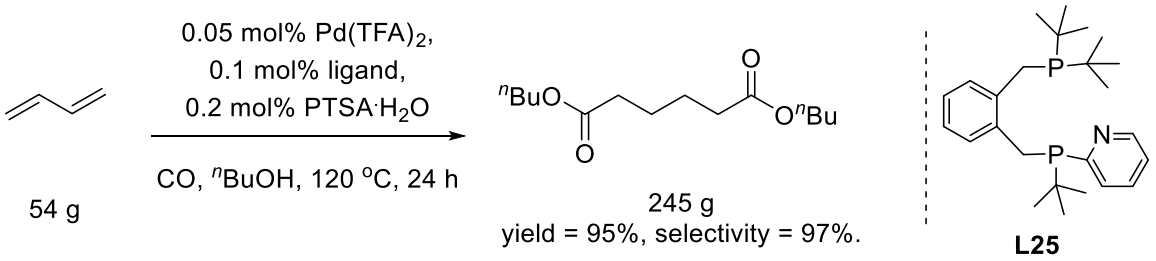


Scheme 45. Our group's work: monoalkoxycarbonylation of conjugated dienes under acid-free condition.

In 2014, our group developed a general palladium-based catalyst for the alkoxycarbonylation of conjugated dienes under acid-free conditions.[237] This highly active transformation provides effective access to various unsaturated esters in excellent yields and satisfactory selectivities (Scheme 45).

As mentioned above the direct dicarbonylation of 1,3-butadiene offers the possibility for a more effective and environmentally friendly course to industrially significant adipic acid derivatives. Yet, due to the complex reaction network of regioisomeric carbonylation and isomerization pathways, a selective practical catalyst for this process has thus far proven elusive.[238]

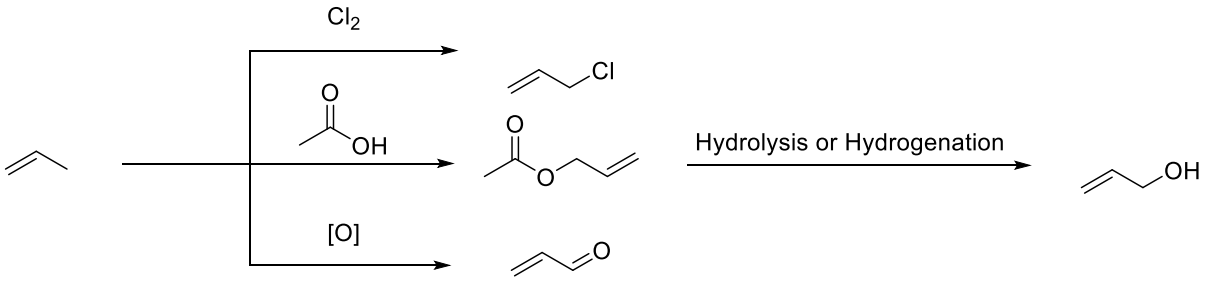
In the framework of this thesis, we designed a new pyridyl-substituted bidentate phosphine ligand (HeMaRaphos) that, upon coordination to palladium, catalyzed adipate diester formation from 1,3-butadiene, carbon monoxide, and butanol with 97% selectivity and 100% atom-economy under industrially viable and scalable conditions (turnover number > 60,000). This catalyst system also afforded access to a variety of other di- and triesters from other 1,2- and 1,3-dienes.[239]



Scheme 46. Palladium-catalyzed dialkoxycarbonylation of butadiene

Allyl alcohol was first prepared in 1856 by Cahours and Hormann by saponification of allyl iodide.[240] It is mainly converted to glycidol, which is the intermediate in the preparation of glycerol and glycidyl esters. Allyl alcohol is mainly derived from propylene.[241] Nowadays, allyl alcohol is produced by Dow and Shell through hydrolysis of allyl chloride,which comes from the chlorination of propene. An alternative route to produce allylalcohol is through the acetoxylation of propylene to allyl acetate followed by hydrolysis.[242]

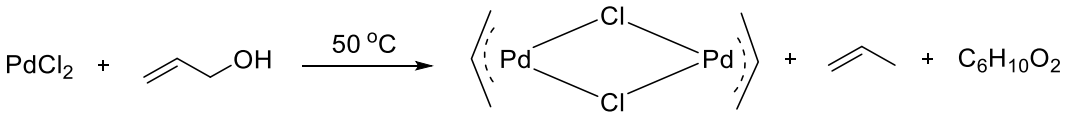
Another alternative route for allylic alcohol production is via the reduction of acrolein which is derived from the selective oxidation of propylene (Scheme 47). Besides allyl alcohol, versatile allylic alcohols are produced in a large scale, such as crotyl alcohol and prenol.[243] More remarkably, natural products such as geraniol, nerol and farnesol are also easily available from the biosynthesis of terpenes, which are broadly used in fragrance and flavor industry.



Scheme 47. Synthetic routes of allylic alcohol.

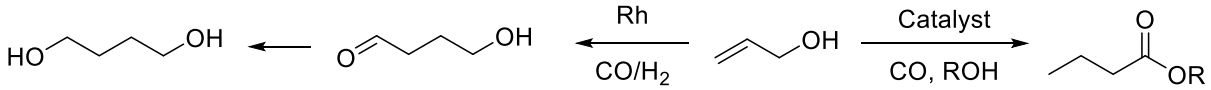
In 1959, the reaction of allylic alcohol and palladium chloride was first reported by Smidt et al., showing that the reaction of allylic alcohol with palladium chloride will generate [(allyl)PdCl]2,

propene and an unidentified oxidized $C_6H_{10}O_2$ product.(Scheme 48). In fact, this work has laid the basis of the coupling chemistry with allylic alcohol as the substrate.[244-246]



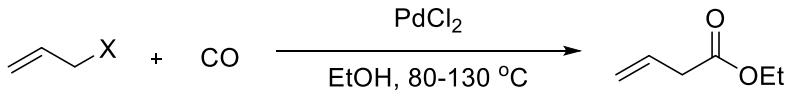
Scheme 48. The reaction of allylic alcohol and palladium chloride.

In general, allylic alcohols comprise two reactive electrophilic positions. The carbonylation of either reactive site of allylic alcohol is known, in which the chemoselectivity mainly depends on the conditions and catalyst used. As an example of the carbonylation reaction at the alkene side, allyl alcohol can be hydroformylated to produce 4-hydroxybutanal, which can be further hydrogenated to synthesize 1,4-butandiol (Scheme 49).[247]



Scheme 49. Two reaction possibilities for allyl alcohol.

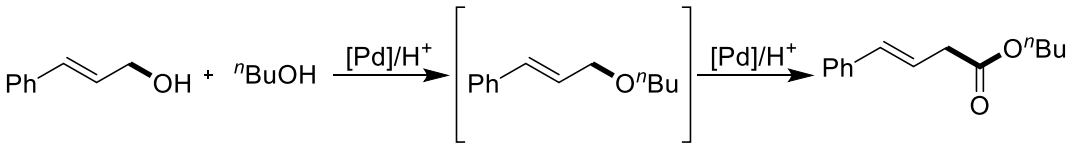
The direct carbonylation of the C-O moiety to synthesize β,γ-unsaturated carboxylic derivatives was first studied in 1964 by Tsuji.[248] In this report, various allylic compounds, including allylic chloride, allylic bromide, allylic ether and allylic alcohol were reported to be carbonylated to the corresponding β,γ-unsaturated carboxylic esters in the presence of palladium chloride under CO pressure (Scheme 50).



X = Cl, OH, OTs, OAc, OEt, OPh

Scheme 50. Tsuji's work: Carbonylation of various allylic compounds

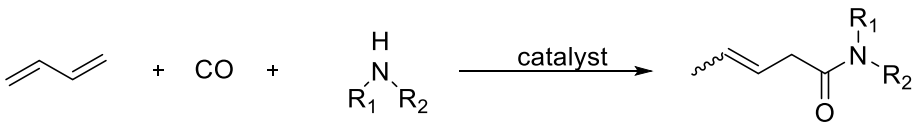
In 2013, a palladium-catalyzed carbonylation of allylic alcohols was reported by our group (Scheme 51).[249] This catalyst system consists of $Pd(OAc)_2$, phosphine ligand, such as Xantphos or $BuPAd_2$ and trifluoroacetic acid as the additive.Mechanistic studies showed that the allylic ether acts as a key intermediate in this reaction.



Scheme 51. Palladium-catalyzed carbonylation of allylic alcohols

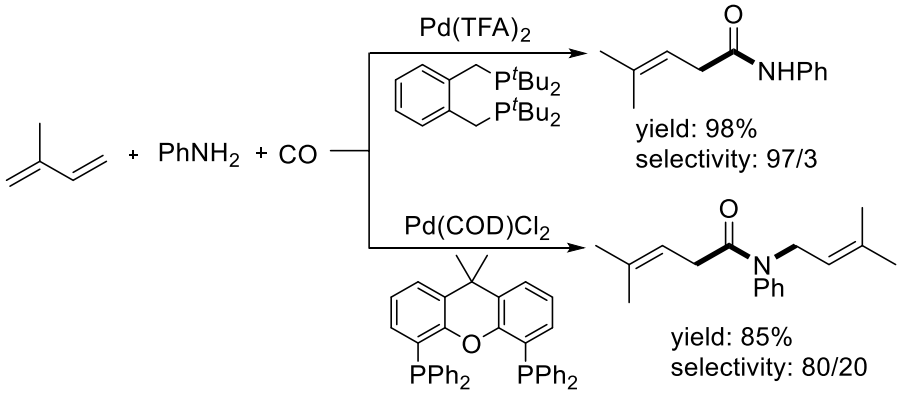
1.3.3.2. Aminocarbonylation of 1,3-dienes and allylic alcohols

Amides motifs are important in organic chemistry, which can be easily found in materials, agrochemicals and pharmaceuticals etc.. The efficient formation of amide bonds is an interesting but still challenging topic. In terms of atom-economy, the aminocarbonylation of 1,3-diene is a perfect synthetic route to synthesize β,γ-unsaturated amides (100% atom economy).[250] Nevertheless, a main challenge for the aminocarbonylation of 1,3-dienes is the corresponding competitive direct amination reaction,which generates allylic amine as the major product (Scheme 52).



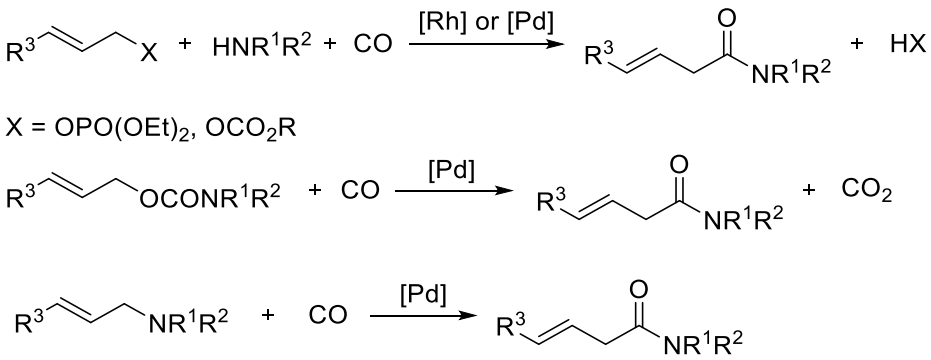
Scheme 52. Palladium-catalyzed aminocarbonylation of 1,3-dienes

To the best of our knowledge, efficient palladium catalyst systems for the aminocarbonylation reaction of diene were basically not known before our studies. In 2014, we developed the first practical aminocarbonylation transformation of 1,3-dienes (Scheme 53).[251] With different palladium phosphine complexes, carbonylation (1:1 adduct) or a selective hydroamination-carbonylation sequence (2:1 adduct) was achieved, respectively. Using diverse aromatic amines a variety of synthetically valuable β,γ-unsaturated amides are formed in good to excellent yields. Combining this process with established functionalizations allows for an efficient preparation of various heterocyclic compounds. The elevated atom economy, the additive-free reaction conditions make this procedure attractive for synthetic applications and we believe it will complement the current methodologies for carbonylations in organic synthesis.



Scheme 53. Our group's work: selective palladium-catalyzed aminocarbonylation of dienes.

Comparing to the well-studied carbonylation reaction of allyl derivatives to form *β,γ*-unsaturated esters, there are rare cases known that allow the synthesis of related *β,γ*-unsaturated amides *via* carbonylation of allyl-X compounds (Scheme 54).[252-254]



Scheme 54. Selective carbonylation of allyl-X compounds.

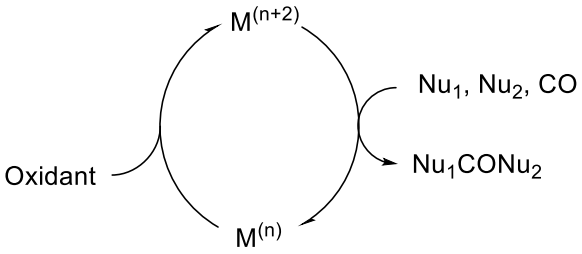
A main challenge for aminocarbonylation procedure is the competing direct amination of the substrate. In fact, such aminations of allyl-X compounds should react faster than carbonylations. Moreover, a general drawback of these reactions is the stoichiometric production of by-products (e.g. salts).

1.3.4. Palladium-catalyzed oxidative carbonylations

Oxidative carbonylations have acquired a rising importance during the last decades,[255-268] due to the progress of new and selective catalytic systems,[269] mainly based on palladium, which are able to promote ordered sequences of conversions under mild conditions with formation of highly functionalized carbonyl compounds in one step starting from very inexpensive building blocks.[269-285]

Oxidative carbonylation reactions might proceed under milder conditions as they avoid the challenging oxidative addition of metal compound to the corresponding electrophile, which is

usually repressed by the high preasure of CO in traditional carbonylation reactions.[190, 286-290] However, the metal re-oxidation procedure has always been a main problem in oxidative carbonylation. Typical oxidants applied in oxidative carbonylation reactions are organic compounds or inorganic salts, such as benzoquinone, potassium persulfate, $CuCl_2$, silver salts, etc. In some condations, hyperbaric oxygen or air have been efficiently used in oxidative carbonylation processes.[291-297] Most of the substrates of oxidative carbonylation reactions are nucleophiles, various of them are broadly available.[286, 298-299] In general, oxidative carbonylation reactions could potentially offer a more environmentally benign and efficient process to produce numerous versatile carbonyl derivatives.[300-301]

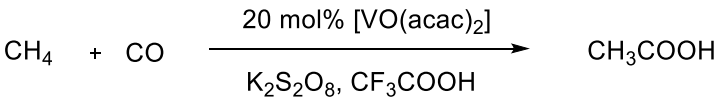


Scheme 55. Catalyst regeneration cycle.

1.3.4.1. Oxidative carbonylation reactions of alkanes

Direct functionalization of alkanes *via* C-H activation has attracted countless interest as alkanes, principally methane, is one of the most abundant natural sources. However, alkane activation/functionalization remains challenging since it is hard to cleave the C-H bond selectively while keeping the functionalized product less reactive than the starting material under the similar conversion conditions.[302]

Fujiwara made some major contributions in this regard and his earliest studies date back to the 1980s.[303-305] For example, they established highly active vanadium- and calcium-catalyzed oxidative carbonylation of methane. The $[VO(acac)_2]$ catalyst with the assistance of co-catalysts $K_2S_2O_8$ and CF_3COOH could efficiently transform methane and CO into acetic acid with satisfactory yield (Scheme 56, 93 % yield).

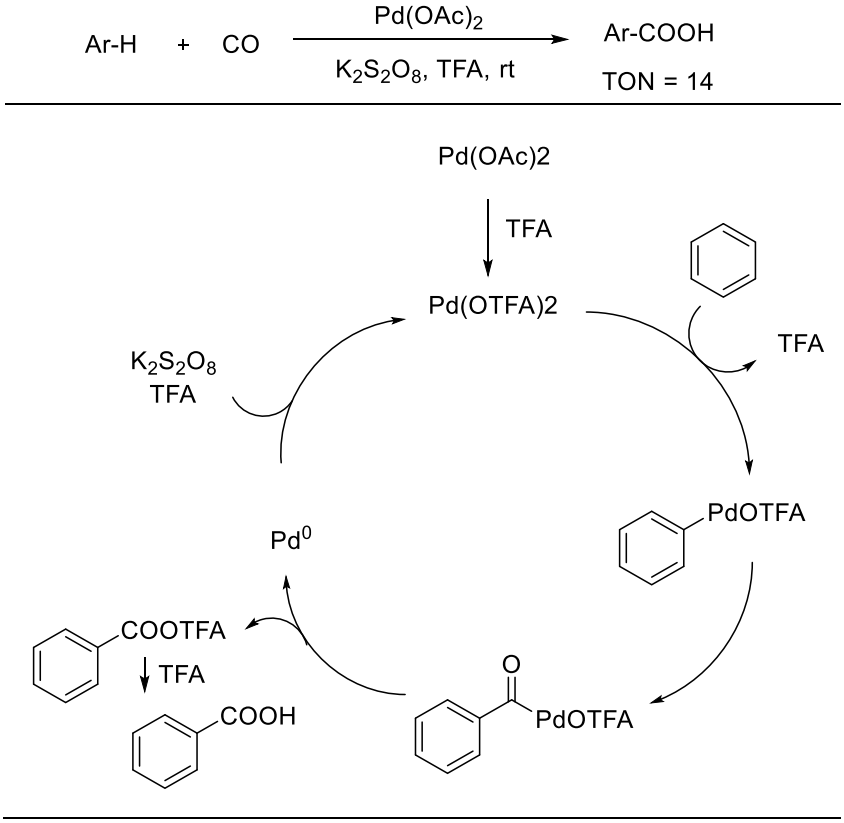


Scheme 56. Vanadium-catalyzed oxidative carbonylation of methane.

1.3.4.2. Oxidative carbonylation reactions of arenes

Direct oxidative carbonylation of arenes was also initiated by Fujiwara et al.[305] They first stated the synthesis of aromatic acid derivatives directly from simple arenes and carbon monoxide in

the presence of a stoichiometric amount of Pd(OAc)2 catalyst.[306] In the proposed mechanism, aromatic compounds undergo palladation to give the aromatic–Pd α complex, which further reacts with carbon monoxide to form an acyl palladium species. The newly shaped palladium complex then undergoes reductive elimination to yield the Pd^0 species and acetic benzoic anhydride, which additionally reacts with acetic acid to give the final product benzoic acid.

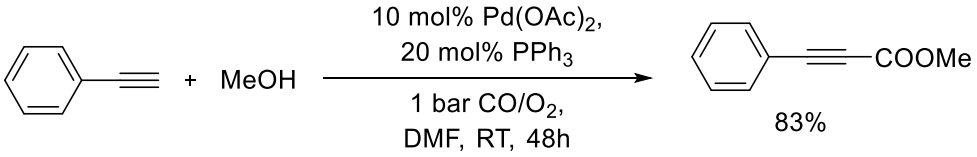


Scheme 57. $Pd(OAc)_2$/TFA-catalyzed direct oxidative carbonylation of simple arenes.

Additionally, to expand the reaction efficiency, the same researchers developed a powerful catalytic system further. A sequence of simple arenes such as benzene, toluene, chlorobenzene, anisole, and naphthalene were oxidatively carboxylated by palladium(II) acetate catalyst in the presence of $K_2S_2O_8$ as the oxidant in trifluoroacetic acid (TFA) at room temperature under a low pressure of CO. The aromatic carboxylic acids were produced in moderate yields.[307-308]

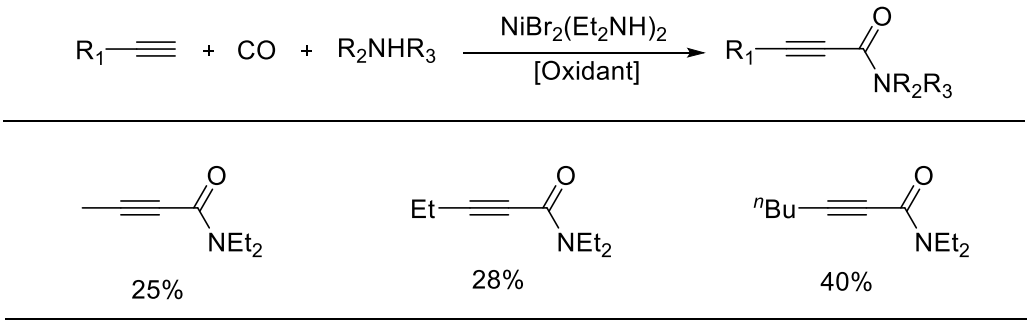
1.3.4.3. Oxidative carbonylation reactions of alkenes and alkynes

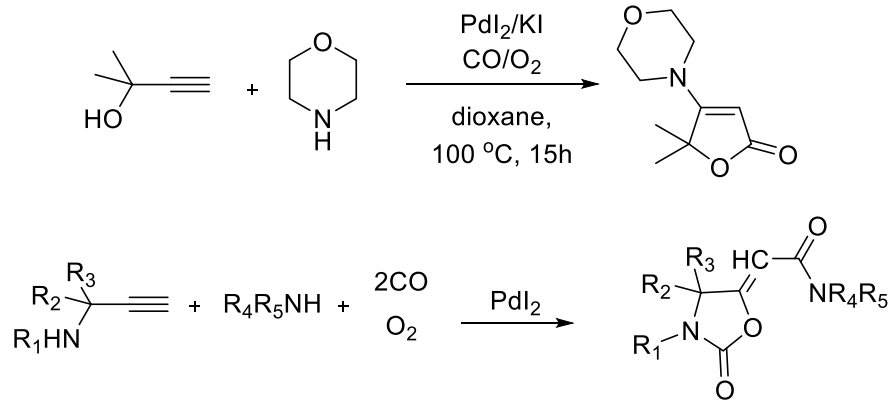
An significant type of oxidative carbonylation reaction is the oxidative carbonylation of olefines and alkynes,[165, 301, 309-314] which provide possibilities for the direct synthesis of useful acyclic and heterocylic carbonyl chemicals.



Scheme 58. Yamomoto's work: Oxidative carbonylation of alkynes.

In 2004, Yamomoto group elaborated a new process to synthesis alkyl 2-alkynoates from terminal alkynes with carbon monoxide (only 1 atm) under mild conditions using Pd/phosphine catalysts and oxygen as the green oxidant (Scheme 58).[315]

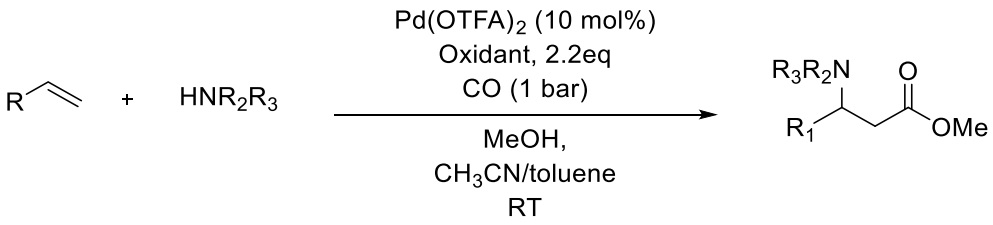




Scheme 59. Gabriele's work: Pd-catalyzed aminocarbonylation.

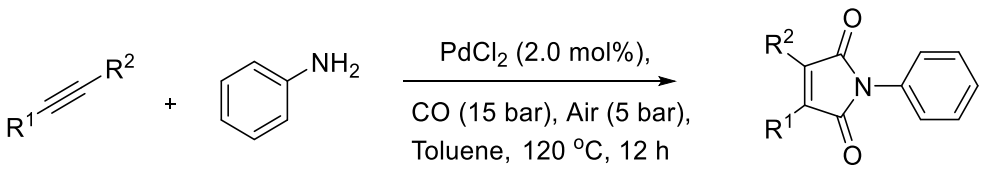
On the foundation of the behavior of typical complexes such as methoxycarbonylpalladium and alkynylpalladium complexes. The first catalytic aminocarbonylation of 1-alkynes was achieved by Gabriele.[316] Both alkyl- and arylacetylenes could be converted to the corresponding 2-ynamides effectively (Scheme 59). This procedure has been successfully applied to the direct synthesis of a variety of carbonylated heterocycles starting from terminal alkynes bearing a appropriately employed nucleophilic group.[317-320]

In 2015, Guosheng Liu's group developed a novel palladium-catalyzed intermolecular aminocarbonylation of alkenes.[321] This methodology presents a facile synthesis of β-amino acid derivatives from simple olefins (Scheme 60).



Scheme 60. Liu's work: A novel palladium-catalyzed intermolecular aminocarbonylation.

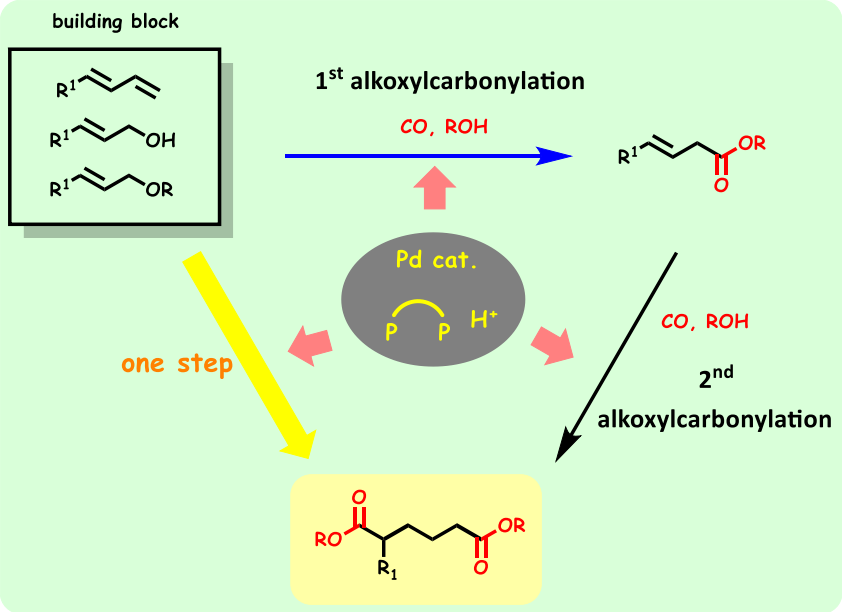
In the framework of this thesis, we present our latest research results in this field. A catalytic oxidative carbonylation reaction was developed for the synthesis of poly-substituted maleimides from alkynes and amines with air as a green oxidant by our group.[322] This novel transformation proceeds in the presence of palladium chloride without the need for expensive ligands or additives and has a broad substrate scope affording a variety of maleimides in good to high yields (Scheme 61).



Scheme 61. A catalytic oxidative carbonylation reaction with air as a green oxidant.

2. Objectives of this work

As described in the introduction, the carbonylation of easily available feedstocks such as olefins, 1,3-butadiene and alkynes with carbon monoxide as a carbonyl source represents important and convenient methods for the selective preparation of diverse fine and bulk chemicals. Although much research has been accomplished in this field, there still exists significant academic and industrial interest to increase the efficiency and selectivity of the processes through the development of new catalyst systems. Therefore, the major aim of this work was the development of novel catalysts system for carbonylation of unsaturated organic compounds to useful bulk and fine chemicals. At the same time, we aimed to simplify some current tedious synthetic methods, to make catalytic systems easier.



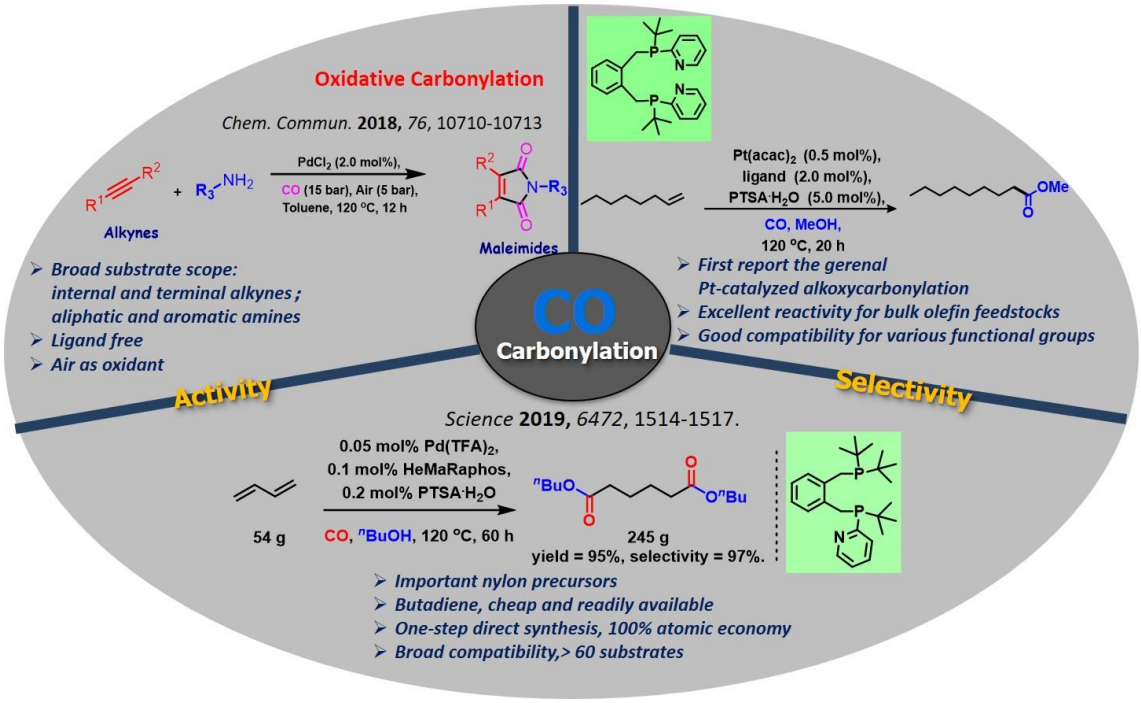
Scheme 62. Dicarbonylation of allyl alcohols, ethers and 1,3-dienes

For example, our research focused on the exploration of a more efficient method from butadiene to adipic acid diesters. By analyzing the existing catalytic procedures, we find that they are mainly based on two-step carbonylations. One step converts butadiene to methyl pentenoate through a palladium catalyst and phosphine ligand. After separation and purification, the obtained products were used for a second carbonylation step, which finally achieves the conversion of 1,3-butadiene to adipic acid diester through a multi-step reaction. Through analysis, we find that in the above conversion, the conditions for two steps are similar, but in order to obtain the target product, quick isomerization of carbon-carbon double bond is required between the first and the second step. The rate of isomerization should be faster than

the second step of carbonylation. At the same time, the catalyst should have appropriate activity to promote continuously two steps of carbonylation smoothly.

As a summary, the main goal of my PhD research was to develop an appropriate catalytic system to achieve a direct synthesis of adipic acid esters via palladium-catalyzed carbonylation of 1,3-dienes. Meanwhile, I explored some related carbonylation reactions.

3. Summary

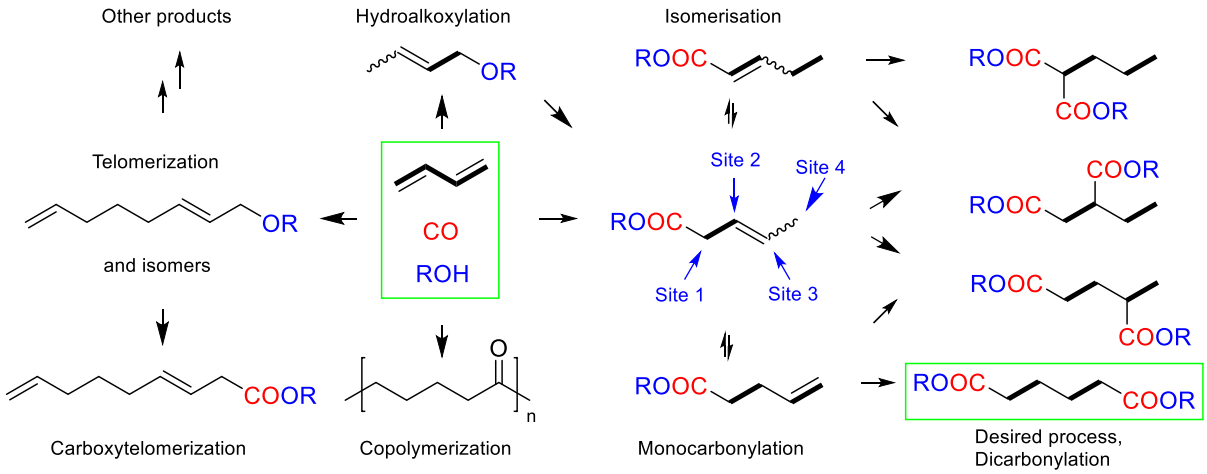


Scheme 63. Research summary.

3.1 Direct synthesis of adipic acid esters via palladium-catalyzed carbonylation of 1,3-dienes

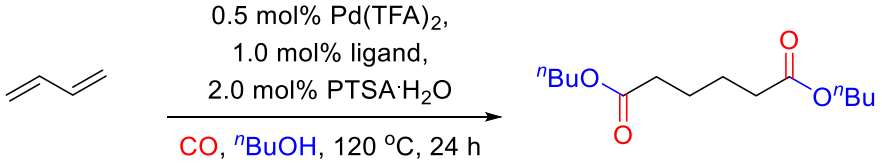
The direct carbonylation of 1,3-butadiene offers the potential of a greener and more cost-efficient route to industrially important adipic acid derivatives. Despite decades of research in academia and extensive explorations in industry, no viable straightforward process has been developed, yet. Hence, this transformation remains one of the ultimate goals of carbonylation chemistry.

As shown in Scheme 64, multiple challenges need to be resolved to achieve such a catalytic process: (a) the catalyst should be able to catalyze two different carbonylation reactions efficiently, which could not be achieved with previously known systems. (b) Secondly, as the linear dicarbonylation product is the technically desired product, the catalyst is required to have an extraordinary isomerization activity. Obviously, the isomerization of the initially formed monocarbonylation intermediate to the terminal olefin is thermodynamically particularly unfavorable. (c) In order to ensure high product yields, other typical side reactions such as telomerization,[323] hydrogenation and (co)polymerization have to be suppressed.



Scheme 64. Reaction network involved in synthesis of adipates from 1,3-butadiene.

In order to accomplish this goal, we first examined the catalytic activities of a number of known ligands. Further, through vigorous and determined attempt, we developed an improved palladium catalyst with the novel bidentate phosphine ligand (HeMaRaphos) for alkoxycarbonylation reactions. On the one hand, the di-*tert*-butylphosphino fragment with its steric hindrance and electron-richness should promote fast isomerization of carbon-carbon double bonds, while on the other hand, the *tert*-butyl-2-pyridyl phosphino group not only will facilitate the formation of the active palladium hydride complex, but also should accelerate the final methanolysis step.



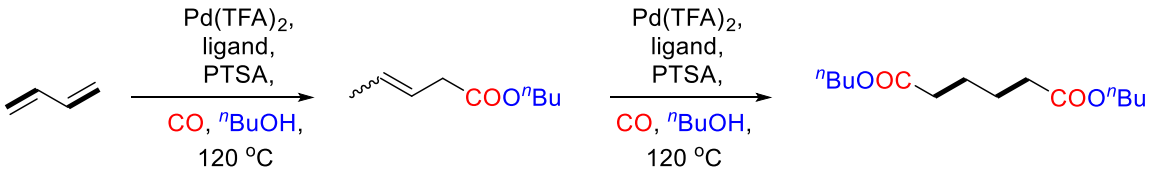
Ligand									HeMaRaphos									
Reactivity	✗	18%	✗	13%	✗	0%	–	77%	+	85%	✗	0%	✗	0%	✗	0%	✗	0%
Selectivity	+	97%	+	95%	✗	0%	–	48%	+	97%	✗	0%	✗	0%	✗	0%	✗	0%

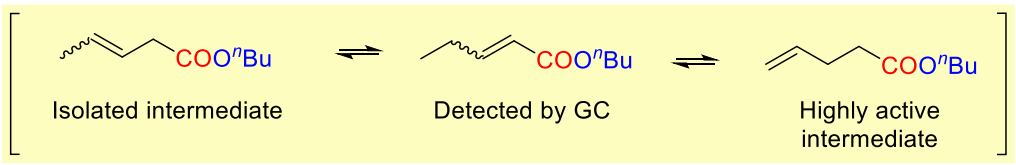
+ >80% – 40-80% ✗ <40%

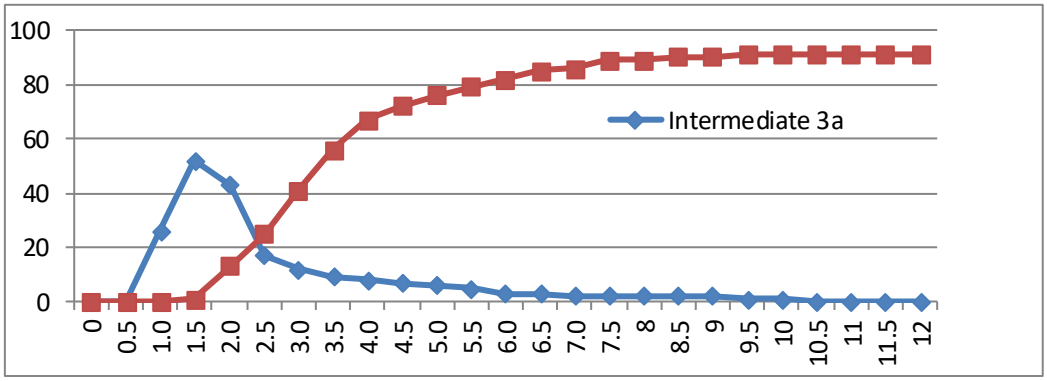
Scheme 65. Palladium-catalyzed dicarbonylation of 1,3-butadiene: Effect of ligands.

To our delight, the dicarbonylation of 1,3-butadiene proceeded in the presence of HeMaRaphos and $Pd(TFA)_2$ to adipate diester with a yield of 85% and a linear selectivity of

97%! To the best of our knowledge, this is the first report of an efficient one-pot conversion of 1,3-butadiene to adipate diesters. To understand the performance of the palladium catalyst with HeMaRaphos, kinetic monitoring experiments were conducted (Scheme 66). In the first half hour, the active hydride complex is formed from the *in situ* mixture of $Pd(TFA)_2$, ligand and PTSA. Then, alkoxycarbonylation occurred to give selectively *n*-butyl pent-3-eneoate. This intermediate continuously accumulates to reach a maximum yield of about 50% after 90 minutes. Stopping the reaction at this time, one can easily isolate the monocarbonylation product from the reaction mixture. Meanwhile, the active catalyst promotes olefin isomerization. Notably, the terminal olefin *n*-butyl pent-4-enoate could not be detected, which we explain by its fast conversion into the linear adipate diester.





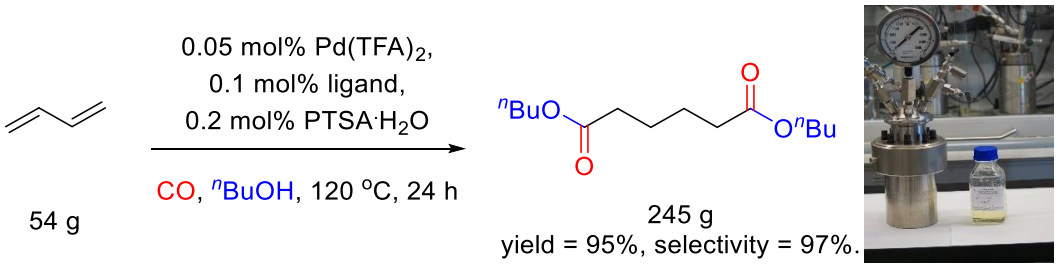


The ***X***-axis represents the reaction time and the ***Y***-axis represents the reaction yield. Reaction conditions: butadiene (20 mmol), $Pd(TFA)_2$ (0.005 mmol, 0.5 mol%), ligand (0.01 mmol, 1.0 mol%), $PTSA{\cdot}H_2O$ (2 mol%), ^{n}BuOH (25 mL), CO (40 atm), 120 °C; the GC yield were determined by GC analysis with mesitylene as the internal standard.

Scheme 66. Kinetic monitoring experiment.

Next, detailed optimization studies on the effect of palladium precursor, acid, temperature and pressure were performed to further improve the practicability of this process. In particular, excellent catalyst turnover numbers (>60.000) were obtained using the defined Pd(II)-HeMaRa-complex under optimal conditions. Finally, upscaling reactions of 1,3-butadiene with

methanol and n-butanol were carried out at low catalyst loading (<0.5 mol%). The resulting plasticizers were smoothly obtained in 88-91% yield and >97% linear selectivity. As an example, a reaction without additional solvent could be performed on >200 g-scale with a catalyst loading of only 0.05%. As shown, the desired product is attained in 95% with 97% selectivity (Scheme 67).



Scheme 67. Upscaling reactions

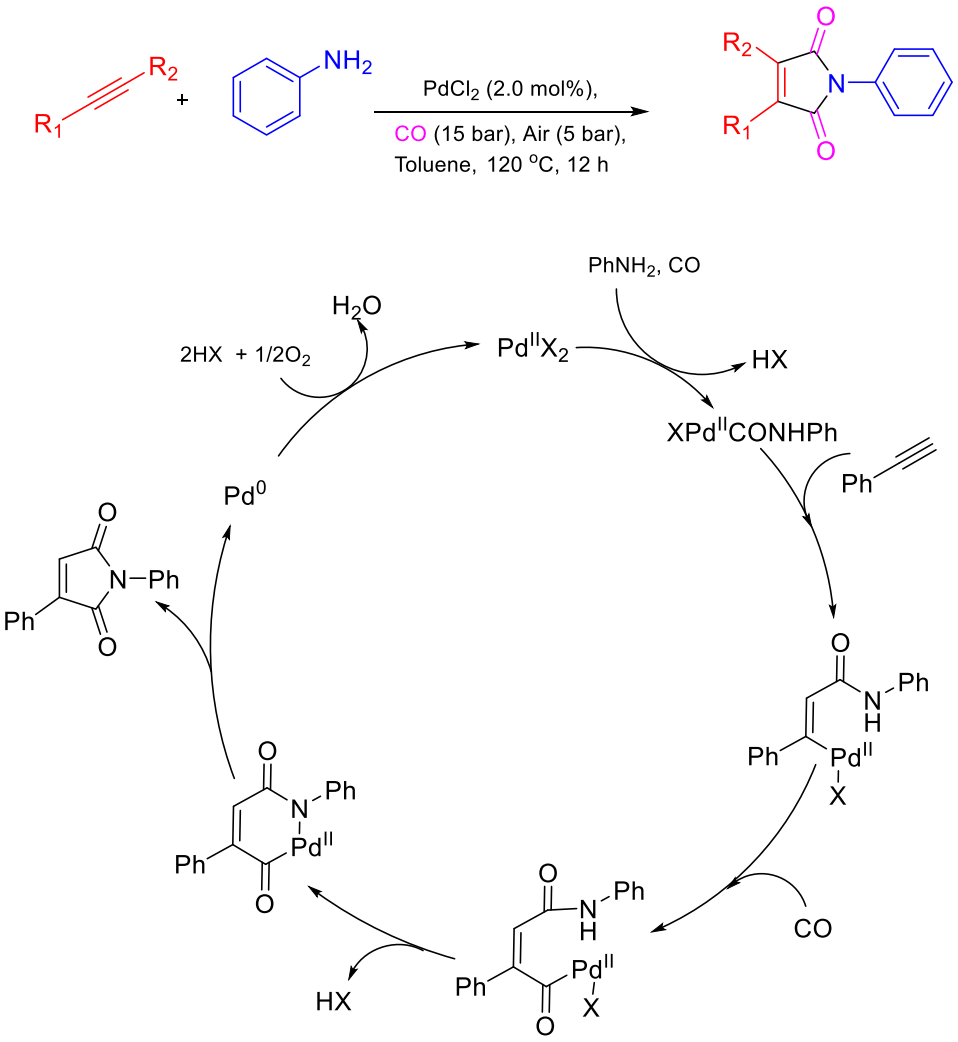
Apart from the specific importance of the dicarbonylation of 1,3-butadiene in the chemical industry, this methodology also offers interesting prospects for valorization of other dienes for fine chemical production, and even basic organic synthesis [324-326]. To show the generality of the novel catalyst system, 15 different dienes and more than 30 alcohols were converted in general in high yield and selectivity to the corresponding diesters. In summary, we have developed a novel catalytic system that can directly convert butadiene to a linear adipic acid diester in one step. This catalytic system greatly simplifies existing synthetic methods.

3.2 Palladium-catalyzed aerobic oxidative carbonylation of alkynes with amines: a general access to substituted maleimides

Substituted maleimides represent interesting building blocks, which are widely found in bioactive natural products and drug molecules. In general, traditional industrial processes for manufacturing maleimides are based on the reaction of amines with maleic anhydride. However, this methodology is especially suited to give unsubstituted or symmetrically substituted maleimides. Consequently, there is a need for the development of new synthetic procedures for the synthesis of polysubstituted maleimides.

We thought a novel convenient approach to this interesting class of products can be achieved by oxidative carbonylation of alkynes. The initial study was performed with phenylacetylene and aniline as the model substrates. After intensive investigations, we found when air (5 bar) was used as the oxidant in the presence of $PdCl_2$ (2.0 mol%) at 120 °C in toluene, the desired maleimide could be obtained in 96% GC yield with almost no by-product present.

On the basis of our results, we also proposed a possible pathway for the transformation (Scheme 68). First, the palladium acyl complex is generated from palladium(II) in the presence of aniline and CO. Subsequently, π-coordination of the carbon-carbon triple bond to the metal center, followed by the insertion of the alkyne into the palladium carbon bond, affords the corresponding palladium intermediates. Then, the palladium species undergoes CO insertion to give the acyl complex. Finally, the maleimide is eliminated through reductive elimination of intermediate to give a palladium(0) complex, which is oxidized to palladium(II) in the presence of air to finish the catalytic cycle.



Scheme 68. Proposed catalytic cycle.

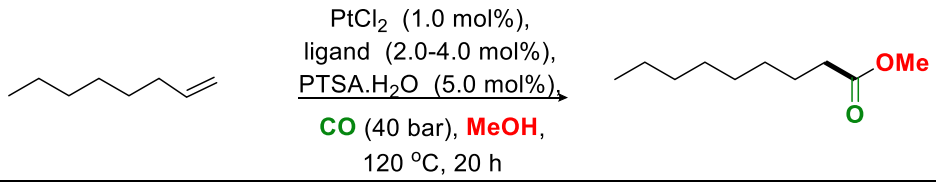
Notably, in this system, we used air as oxidant and do not added other oxidants or co-oxidants, which is environmentally friendly. At the same time, our system is relatively simple, without the need of phosphine ligands. Furthermore, the reaction has a broad substrate scope. Regarding the alkyne, both internal alkynes and terminal alkynes react well and provided the corresponding products in good to high yields (61-92%). For the amine substrates, aliphatic

and aromatic amines both are compatible with the catalyst system, affording to the products directly in excellent yields.

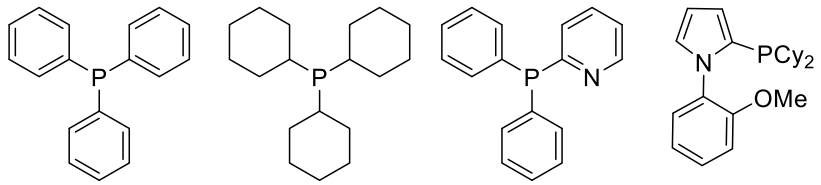
In summary, we have developed a novel oxidative carbonylation catalytic system for the synthesis of polysubstituted maleimides. This catalytic system complements the existing synthesis methods. Using environmentally friendly air as an oxidant is an additional advantage of our protocol.

3.3 A General Platinum-catalyzed Alkoxycarbonylation of Olefins

In the past decade, the price of Pd was highly dynamic and has increased significantly, due to the large demand for this metal in industrial & environmental catalysis. Thus, the current price of bulk platinum is about half of that of palladium. This situation stimulated us to to think about the possibility of using Pt complexes instead of Pd ones in carbonylation reactions.

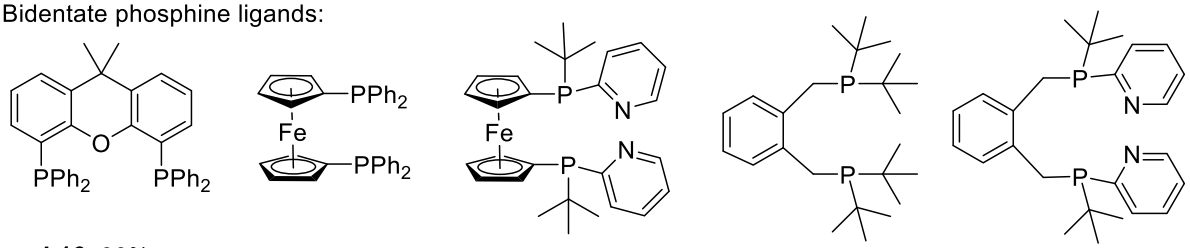


Monodentate phosphine ligands:



L1, 0% **L3**, 0% **L2**, 0% **L11,** 0%

Bidentate phosphine ligands:



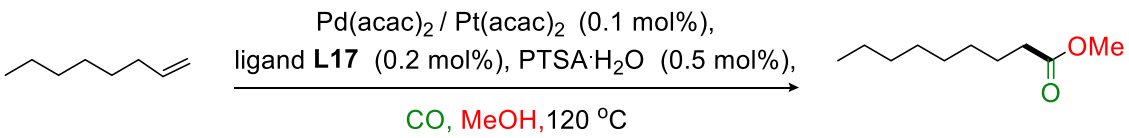
L16, 38%, (*n/iso*=78/22) **L21,** 0% **L22,** 78%, (*n/iso*=64/36) **L23,** 24%, (*n/iso*=77/23) **L24,** 95%, (*n/iso*=73/27)

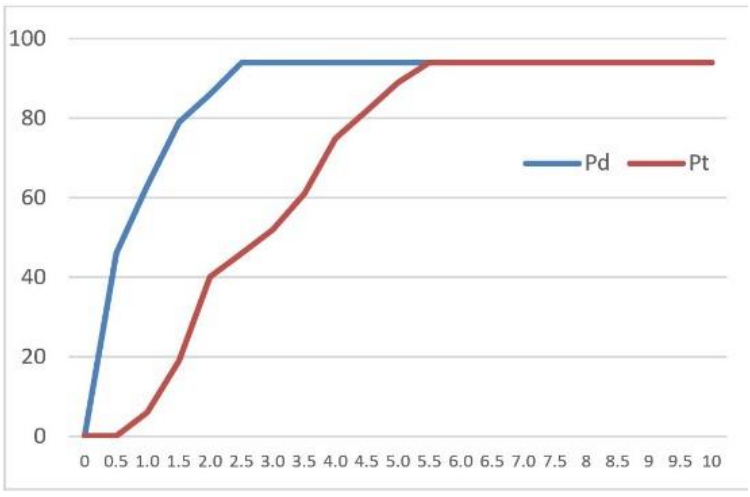
[a]. Standard reaction conditions: 1-Octene (1.0 mmol), $PtCl_2$ (0.01 mmol, 1.0 mol%), ligands (monodentate phosphine ligand: 0.04 mmol, 4.0 mol%; bidentate phosphine ligand: 0.02 mmol, 2.0 mol%), PTSA·H_2O (5.0 mol%), MeOH (2.0 mL), CO (40 atm),120 °C, 20 h; The selectivity and yield were determined by GC analysis with mesitylene as the internal standard.

Scheme 69. Pt-catalysed alkoxycarbonylation of alkenes: Ligand effect.

It is well-known, even in textbooks, that the catalytic performance of platinum complexes is poor, with rates typically four orders of magnitude lower than palladium. To solve the problems associated with Pt-catalysed carbonylation reactions, we thought that the design of an appropriate ligand might be a solution. In recent years, we developed several phosphine-based ligands (Scheme 69) bearing both sterically hindered alkyl as well as basic (pyridine) substituents on the phosphorous atom with different backbones. Mechanistic studies have shown that this basic group on the phosphine ligand not only acts as a proton shuttle for the faster formation of the corresponding palladium hydride complex, but is also able to improve the durability of the catalyst via hemilabile coordination to the metal centre in the catalytic cycle. Based on our previous works and our long-standing interest in such reactions, we started a more detailed study of platinum-catalyzed alkoxycarbonylations.

At the beginning of our investigations, 1-octene (1 mmol) and methanol were chosen as benchmark substrates (Scheme 69). Following our concept of "built-in-base" ligands, to our delight high reactivity was obtained! Specifically in the presence of ligand **L24**, the desired poduct was achieved in greater than 90% yield with the ratio of linear to branched products of approximately 3/1.





Scheme 70. Kinetic monitoring experiment.

In order to better understand the differences in catalytic activity between Pd and Pt, we monitored the product yield over time under similar conditions. To clearly reflect the catalyst differences, we reduced the metal loading to only 0.1 mol%. As shown in Scheme 70, for the Pd catalyst, the reaction showed almost no induction period, which indicated that the active

Pd−H species are generated immediately at 120 °C. In general, the reaction proceeded very quickly and was completed after about 2.5 hours with a product yield of 94%. For the Pt-based catalyst system, the reaction required an induction period of about 1 h. Then, the conversion increased, and the reaction is completed in 5.5 hours. To our delight the products were also obtained in 94% yield with 74/26 selectivity.

Under our optimized catalytic conditions, a variety of substituted olefins gave the corresponding esters in synthetically useful yields with often excellent regioselectivity. Mixtures of internal and terminal olefins are usually preferred as less expensive starting materials in industry. Hence, the functionalization of internal olefins with this catalyst is also noteworthy. In summary, through the rational design of the catalytic system, we demonstrate for the first time a general Pt-catalyzed alkoxycarbonylation of olefins.

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5. Publications

5.1. Direct synthesis of adipic acid esters via palladium-catalyzed carbonylation of 1,3-dienes

Ji Yang, Jiawang Liu (co-first author), Helfried Neumann, Robert Franke, Ralf Jackstell, Matthias Beller

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Contributions

In this paper, I planned, performed and analyzed most experiments for this manuscript. I have done the major part of writing of the draft for this manuscript. My contribution as co-author of this paper is approximately 60%.

ORGANIC CHEMISTRY

Direct synthesis of adipic acid esters via palladium-catalyzed carbonylation of 1,3-dienes

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The direct carbonylation of 1,3-butadiene offers the potential for a more cost-efficient and environmentally benign route to industrially important adipic acid derivatives. However, owing to the complex reaction network of regioisomeric carbonylation and isomerization pathways, a selective practical catalyst for this process has thus far proven elusive. Here, we report the design of a pyridyl-substituted bidentate phosphine ligand (HeMaRaphos) that, upon coordination to palladium, catalyzes adipate diester formation from 1,3-butadiene, carbon monoxide, and butanol with 97% selectivity and 100% atom-economy under industrially viable and scalable conditions (turnover number > 60,000). This catalyst system also affords access to a variety of other di- and triesters from 1,2- and 1,3-dienes.

Carbonylation reactions are among the most important applications of industrial catalysis (*1*–*5*): Using carbon monoxide (CO) as a highly versatile C1 building block with olefins, more than 10 million metric tons of various carbonyl compounds (aldehydes, acids, and esters) are produced annually for numerous consumer products. CO is a central intermediate in the chemical industry that can be easily produced either from fossil-based resources (coal or gas) or from renewables (CO_2 or biowaste). Despite the initial discovery of homogeneously catalyzed carbonylation processes nearly 80 years ago (*6*–*15*), several unattained objectives remain, perhaps most saliently the direct dicarbonylation of 1,3-dienes. This reaction would enable more environmentally benign, atom-economical production of adipate esters, the building blocks of polyamides and polyesters currently produced on a multimillion-metric ton scale (*16*, *17*). More specifically, adipate diesters are used for plasticizers, perfumes, lubricants, solvents, several active pharmaceutical ingredients, and, with respect to scale, most importantly for the production of nylons. Now, the main industrial route to produce adipate diesters involves oxidation of a mixture of cyclohexanol and cyclohexanone by an excess of nitric acid, followed by esterification with the corresponding alcohols (*18*–*20*). This process requires special equipment owing to the acid's corrosiveness and produces stoichiometric amounts of nitrous oxide (N_2O) (*21*), which is a major scavenger of stratospheric ozone and has nearly 300 times the atmospheric heat-trapping capacity of CO_2 (*22*).

Over several decades, numerous companies all over the world, including BASF, Dupont, Shell, Dow, Kuraray, and Sinopec, investigated the prospect of accessing adipate esters via butadiene dicarbonylation. However, despite extensive explorations, no such industrially viable transformation was developed (*23*–*38*). Some pilot tests were implemented (*23*–*36*), but those processes all involved multistep reactions with insufficient selectivity (~60 to 80%) for the desired linear diester.

Here, we present a palladium-catalyzed dicarbonylation of 1,3-butadiene that provides dialkyl adipates in ≥95% yield and ≥97% selectivity. Key to success was the ligand design. Recently, we developed bidentate phosphine ligands for palladium-catalyzed alkoxycarbonylation reactions in which basic pyridyl substituents on phosphorus proved essential for high activity (*39*). On the basis of that work and our long-standing interest in carbonylation reactions (*40*), we proceeded to investigate the dicarbonylation reaction of 1,3-butadiene with butanol as a model for the direct synthesis of adipate diesters.

As shown in Fig. 1, there are multiple challenges associated with this catalytic process: (i) The catalyst must promote two different carbonylation reactions on the diene substrate (which could not be achieved previously); (ii) the linear dicarbonylation product must be

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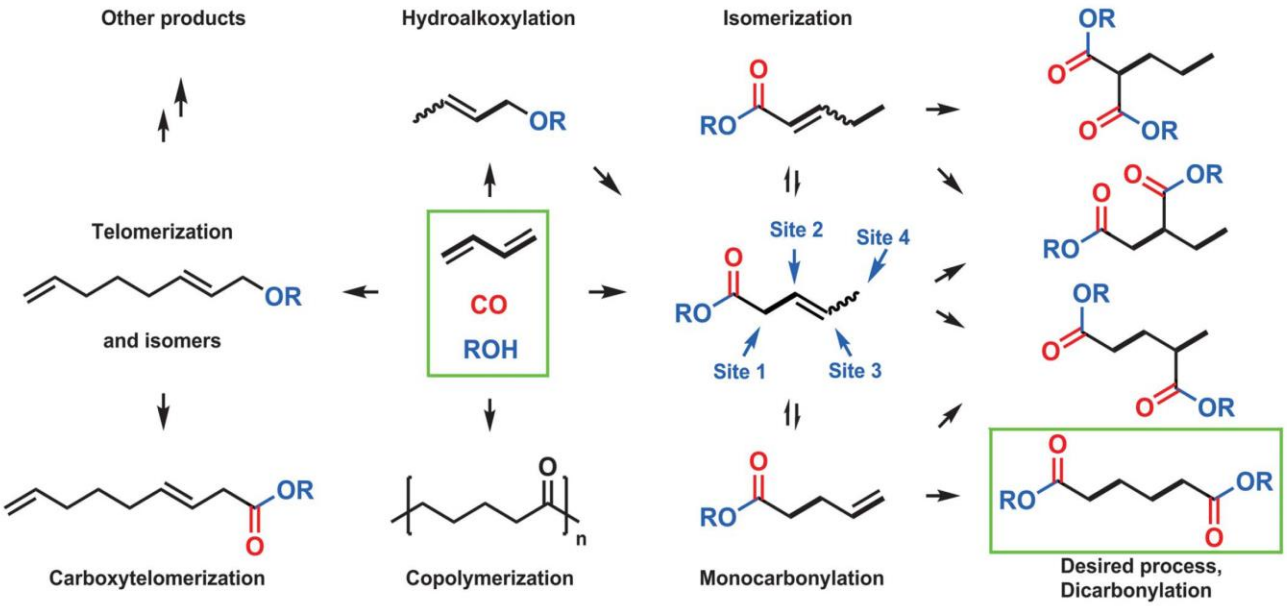

Fig. 1. Reaction network involved in synthesis of adipates from 1,3-butadienes. The green outlines indicate the starting materials (1,3-butadiene, carbon monoxide, and alcohol) and desired product adipic diester.

formed selectively, despite the fact that isomerization of the initially formed monocarbonylated intermediate to the terminal olefin is thermodynamically particularly unfavorable; and (iii) other side reactions such as telomerization (*41*), hydroalkoxylation, and (co)polymerization must be suppressed.

We sought to realize the selective dicarbonylation of 1,3-butadiene by using base-modified derivatives of the 1,2-bis[(di-*tert*-butylphosphino) methyl]benzene ligand (**L1**, dtbpx), which is used for the bulk production of methyl methacrylate (*42*). Initial optimization studies with this ligand (Fig. 2) showed slight activity but good selectivity to give the linear di-*n*-butyl adipate **4a** at 120°C and 40 bar CO with *p*-toluenesulfonic acid as a cocatalyst. To improve the catalyst performance, dtbpx derivatives **L2** and **L3** were tested. However, no increase of activity was observed. According to our hypothesis above, the incorporation of suitable basic groups on this specific ligand backbone should increase the activity of the corresponding palladium catalyst system in alkoxycarbonylation reactions. Indeed, using **L4** considerably increased activity and yield of diesters (77%) but at the expense of insufficient selectivity (48%). Considering the appropriate reactivity of **L4** and the suitable selectivity of **L1**, we designed the ligand **L5** (HeMaRaphos), which combines the two structural fragments of **L1** and **L4**: The bulky and electron-rich di-*tert*-butylphosphino fragment could promote fast isomerization of carbon-carbon double bonds (*43*–*45*) while the *tert*-butyl-2-pyridyl phosphino group facilitated formation of the active palladium hydride complex and accelerated the final alcoholysis step. Mixing **L5** and Pd(0) bis(dibenzylideneacetone) [$Pd(dba)_2$] in the presence of HCl resulted in the formation of a bright yellow palladium complex, which was suitable for x-ray crystallography (fig. S1). Although no coordination of the pyridine-N atom to the palladium center was observed in solid state, the durability of the catalyst in solution might be enhanced by such hemilabile binding. To our delight, the dicarbonylation of 1,3-butadiene proceeded in the presence of HeMaRaphos and Pd(II) trifluoroacetate [$Pd(TFA)_2$] to adipate diester with a yield of 85% and a linear selectivity of 97%. We benchmark the distinct behavior of **L5** in comparison with more than 70 other ligands, including well-known mono- and bidentate phosphines, in table S1.

To understand the performance of the palladium catalyst with HeMaRaphos, we conducted kinetic monitoring experiments (fig. S3). In the first half hour, formation of the active palladium hydride complex was observed in the in situ mixture of $Pd(TFA)_2$, **L5**, and *p*-toluenesulfonic acid (PTSA). Then, alkoxycarbonylation occurred to selectively produce *n*-butyl pent-3-enoate **3a**. This intermediate continuously accumulated to reach a maximum yield of about 50% after 90 min. Stopping the reaction at this time allowed isolation of **3a** from the reaction mixture. Meanwhile, the active catalyst also promoted olefin isomerization. The terminal olefin *n*-butyl pent-4-enoate **3c** could not be detected, which we attribute to its fast conversion into the linear adipate diester.

Next, detailed optimization studies on the effect of palladium precursor, acid, temperature, and pressure were performed to further improve the practicality of the process (tables S2 to S7). In particular, excellent catalyst turnover numbers (>60,000) were obtained using the presynthesized Pd(II)-HeMaRaphos complex under optimal conditions (table S9). Scaled-up reactions of 1,3-butadiene with methanol and *n*-butanol were then carried out at low catalyst loading [<0.5 mole % (mol %)] (table S8). The resulting esters were smoothly obtained in 88 to 95% yield and >97% linear selectivity. As an example, a reaction without additional solvent could be performed on a >200-g scale with a Pd loading of only 0.05 mol % (fig. S2 and table S8).

Beyond the specific importance of the dicarbonylation of 1,3-butadiene in the chemical industry, this methodology also offers

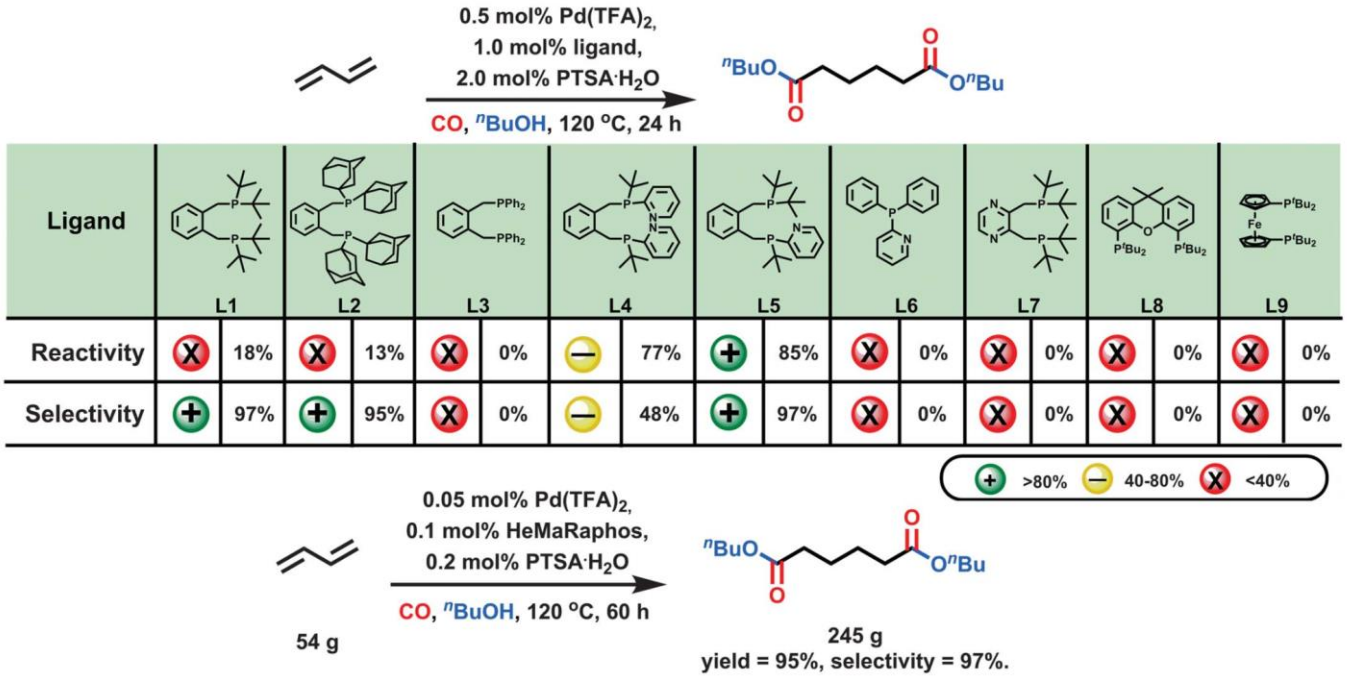

Fig. 2. Ligand optimization for palladium-catalyzed dicarbonylation of 1,3-butadiene. Reaction conditions for ligand optimization: butadiene (1.0 mmol, solution in toluene), $Pd(TFA)_2$ (0.005 mmol, 0.5 mol %), ligand (0.01 mmol, 1.0 mol %), PTSA•H_2O (2.0 mol %), ^{n}BuOH (2.0 ml), CO (40 bar), 120°C, and 24 hours; the ratio of products and yields were determined by gas chromatography analysis with mesitylene as the internal standard. Reactivity represents the yield of the diester. Selectivity represents the ratio of linear diester to all diesters. ^{n}Bu, *n*-butyl; ^{t}Bu, *tert*-butyl.

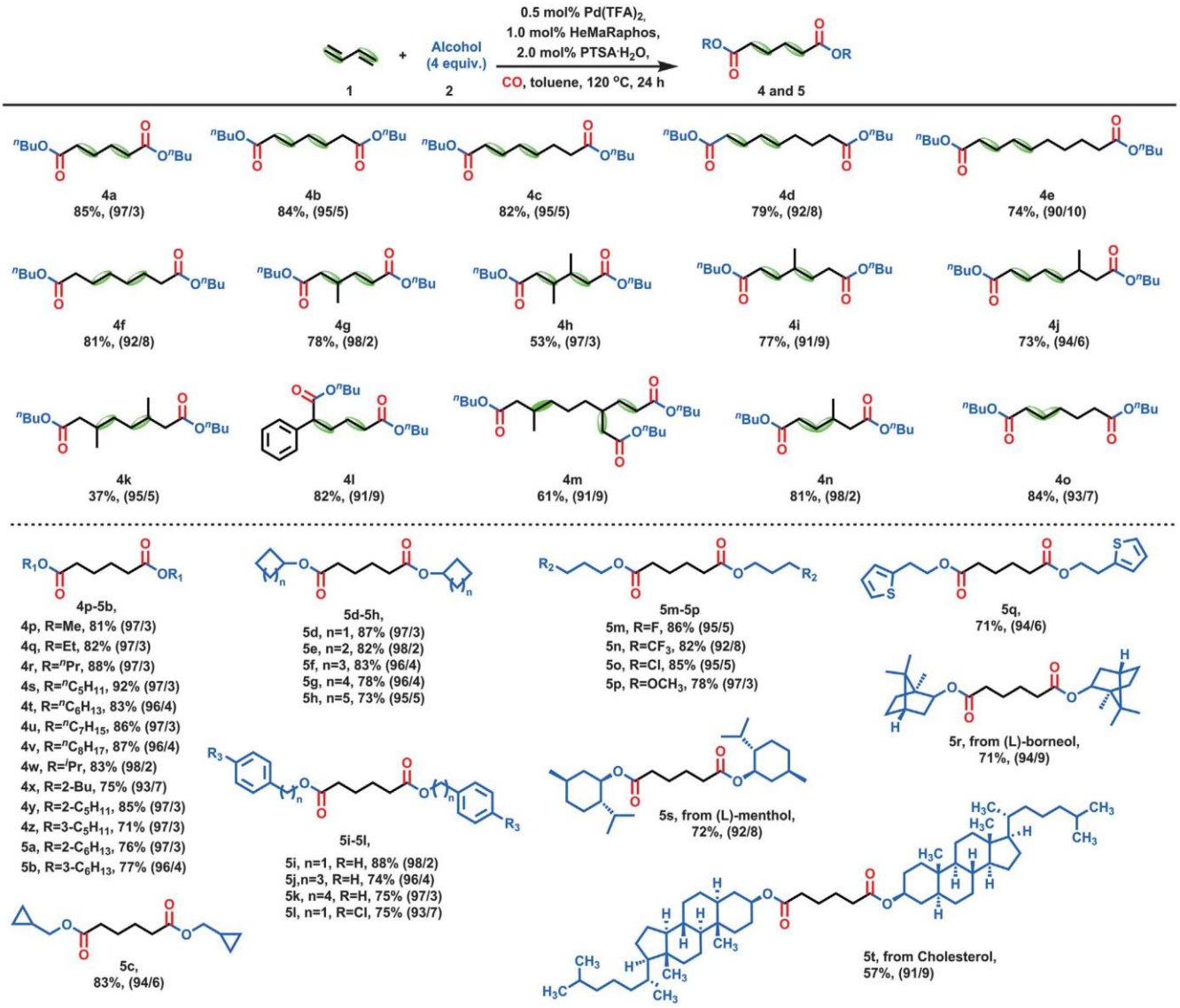

Fig. 3. Palladium-catalyzed dicarbonylation of 1,2- and 1,3-dienes. Me, methyl; Et, ethyl; ^{n}Pr, *n*-propyl; ^{i}Pr, isopropyl.

prospects for valorization of other dienes for fine chemical production (*46*–*48*). To showcase the generality of the catalyst system, 15 different dienes and more than 30 alcohols were converted in high yield and selectivity to the corresponding diesters (Fig. 3). For example, several linear conjugated dienes **1a** to **1f** showed excellent reactivity and regioselectivity. Even for internal conjugated double bonds (**1f**), isomerization reactions led preferentially to the terminal products. Increased steric hindrance on the carbon chain, including a tetra-substituted conjugated diene, influenced the reactivity; however, the regioselectivity to the corresponding linear diesters remained very high (**1g** to **1k**). 1-Phenyl–substituted 1,3-diene **1l**, for which the regioselectivity might be more difficult to control, afforded excellent 1,4-site selectivity. Using myrcene **1m** as an exemplary inexpensive, widely available natural diterpene, tri-alkoxycarbonylation was achieved smoothly. In addition to conjugated 1,3-dienes, 1,2-dienes **1n** and **1o** were converted to the corresponding linear diesters with similar activity and regioselectivity.

Numerous aliphatic alcohols (products **4p** to **4z** and **5a** to **5h**) were also tolerated by the catalyst system and gave diesters in high yields and selectivity (>93%). Various functional groups (products **5m** to **5p**)—including electron-withdrawing fluorine, chlorine, and trifluoromethyl, as well as electron-donating methoxy—were compatible. Furthermore, a heterocyclic derivative (**5q**) and hydroxylated natural products [(L)-menthol, (L)-borneol, and cholesterol] yielded the desired products with high regioselectivity.

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SUPPLEMENTARY MATERIALS

science.sciencemag.org/content/366/6472/1514/suppl/DC1
Materials and Methods
Figs. S1 to S4
Tables S1 to S9
NMR and HRMS Spectra
References (*49–52*)

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5.2. Palladium-catalyzed aerobic oxidative carbonylation of alkynes with amines: a general access to substituted maleimides

Ji Yang, Jiawang Liu (co-first author), Ralf Jackstell, Matthias Beller

Chem. Commun. **2018,** *54*, 10710.

Contributions

In this paper, I planned, performed and analyzed most experiments for this manuscript. I have done the major part of writing of the manuscript. My contribution as co-author of this paper is approximately 60%.

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Palladium-catalyzed aerobic oxidative carbonylation of alkynes with amines: a general access to substituted maleimides†

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A catalytic oxidative carbonylation reaction was developed for the synthesis of polysubstituted maleimides from alkynes and amines with air as a green oxidant. This novel transformation proceeds in the presence of palladium chloride without the need for expensive ligands or additives and has a broad substrate scope affording a variety of maleimides in good to high yields.

Substituted maleimides represent interesting building blocks which are widely found in bioactive natural products and drug molecules (Fig. 1).[1] In addition, this class of compounds are also applied in engineering,[2,3] natural rubbers,[4] resins,[5] and the aerospace industry.[6] In general, the traditional industrial process for manufacturing maleimides is the reaction of amines with maleic and related anhydrides. However, this methodology is mainly used for the preparation of non- or symmetrically substituted maleimides.[7] Consequently, there is still a need for new procedures to access polysubstituted maleimides.

As one of the most important homogenous catalytic processes, transition-metal-catalyzed carbonylation reactions allow for direct conversion of easily available feedstocks, like olefins or alkynes and carbon monoxide, into a variety of carbonylated compounds with higher value, which are useful in organic synthesis, pharmaceutical as well as medicinal chemistry.[8] In 2006, Kondo and co-workers reported an interesting ruthenium-catalyzed co-cyclization of internal alkynes, isocyanates, and CO for the synthesis of multiple substituted maleimides in excellent yields (Scheme 1a).[9a] Later on, $Fe(CO)_5$ was also found to be a good catalyst for this transformation albeit with lower yield (Scheme 1a).[9b] In the past decade, our group also developed iron and rhodium catalysts that allow for carbonylation of internal alkynes with amines, affording a variety of maleimides (Scheme 1b).[10] However, as a general drawback only internal alkynes could be applied in these methodologies.

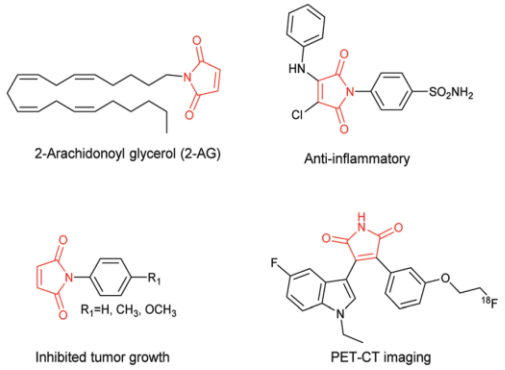
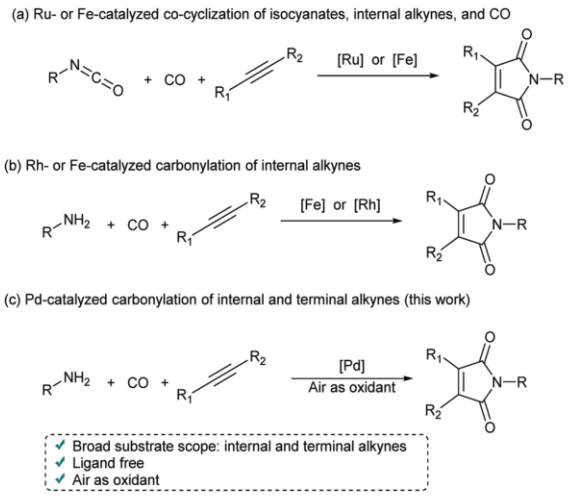


Fig. 1 Selective examples of bioactive maleimides.



Scheme 1 Synthesis of substituted maleimides *via* carbonylation reactions.

Recently, we and other groups became interested in the oxidative carbonylation of olefins and alkynes.[11] We thought the later reaction offered a more practical approach to this

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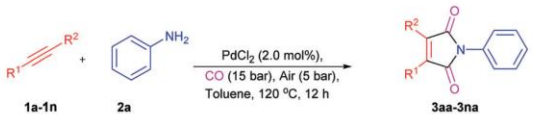
‡ These authors contributed equally to this work.

Table 1 Pd-catalyzed oxidative aminocarbonylation of alkynes: variation of alkynes[a]



1a-1n 2a 3aa-3na

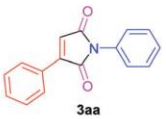
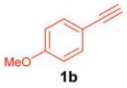
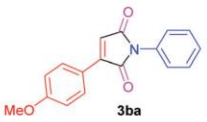
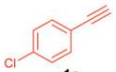
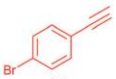
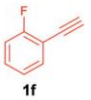
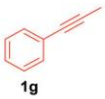
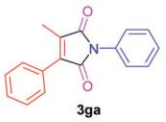
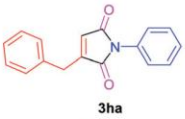
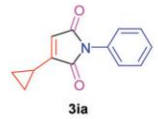
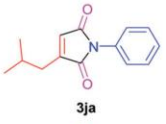
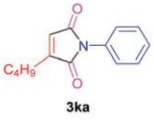
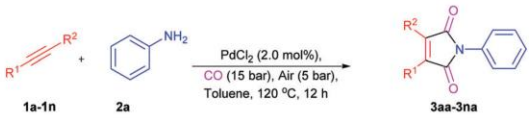
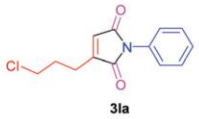
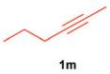
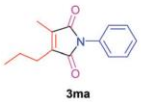
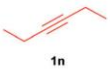
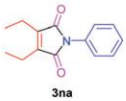
Entry	Alkynes	Products	Yield (%)
1	 1a	 3aa	92
2	 1b	 3ba	74
3	 1c	 3ca	85
4	 1d	 3da	83
5	 1e	 3ea	84
6	 1f	 3fa	87
7	 1g	 3ga	63
8	 1h	 3ha	87
9	 1i	 3ia	91
10	 1j	 3ja	92
11	 1k	 3ka	91

Table 1 (*continued*)



1a-1n 2a 3aa-3na

Entry	Alkynes	Products	Yield (%)
12	 1l	 3la	81
13	 1m	 3ma	82
14	 1n	 3na	71

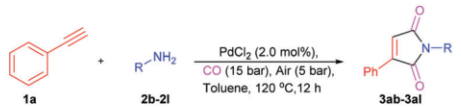
[a] Reaction conditions: **1** (1.5 mmol), **2** (1.0 mmol), $PdCl_2$ (2.0 mol%), CO (15 bar), air (5 bar), toluene (2.0 mL), 120 °C, 12 h.

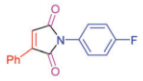
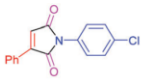
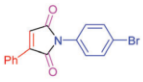
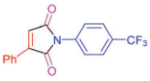
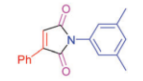
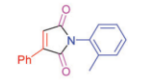
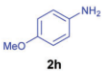
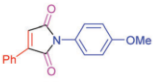
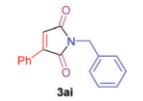
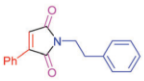
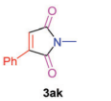
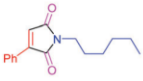
interesting class of products (Scheme 1c). Notably, oxidative carbonylations are among the most important reactions in the field of palladium catalysis, since their discovery by Tsuji and co-workers in 1964.[12] Although these transformations have found varied use,[13] the main drawback is the use of (over)-stoichiometric amounts of oxidants and/or additional copper salts. Clearly, among all the known oxidants air is the ideal, green reagent. Herein, we report the first general Pd-catalyzed oxidative carbonylation of alkynes with amines in the presence of air for the synthesis of various maleimides in high yields.

In our initial studies we investigated the oxidative carbonylation of phenylacetylene **1a** and aniline **2a** as a benchmark system. Although carbon monoxide is an abundant and inexpensive C1 source, its use under oxidative conditions requires certain safety measures. Hence, all catalytic reactions should be performed either with a diluted amount of CO or in the presence of a significant excess carbon monoxide. After variation of solvents, palladium precursors, temperature, and pressure, we found that simple $PdCl_2$ (2.0 mol%) in the presence of air (5 bar) gave the desired product 1,3-diphenyl-1*H*-pyrrole-2,5-dione **3aa** in 92% GC yield at 120 °C in toluene. Surprisingly, there is almost no by-product observed in this reaction. Obviously, a control experiment without palladium salt revealed no desired product. At the same time, we found that this transformation does not require any ligands, which makes the reaction system very convenient.

With these optimized conditions in hands, we proceeded to explore the substrate scope for this novel methodology. First, different alkynes including terminal and internal alkynes were studied with aniline as the reaction partner, affording a variety of poly-substituted maleimides in good to high yields (63–92%). As shown in Table 1, the reactions of aromatic terminal alkynes with electron-donating (**1b**) or electron-withdrawing (**1c–1f**) functional groups afforded the corresponding products in a

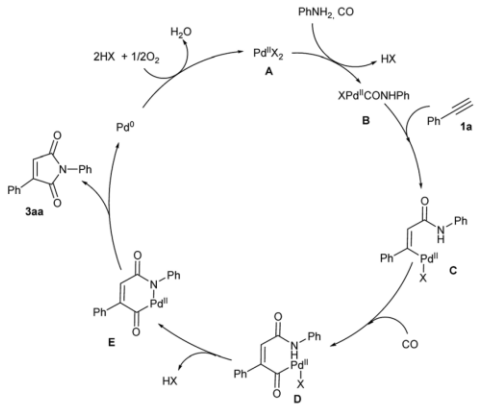
Table 2 Pd-catalyzed oxidative aminocarbonylation of alkynes: variation of amines[a]



Entry	Amines	Products	Yield (%)
1	 2b	 3ab	91
2	 2c	 3ac	84
3	 2d	 3ad	81
4	 2e	 3ae	95
5	 2f	 3af	91
6	 2g	 3ag	78
7	 2h	 3ah	71
8	 2i	 3ai	91
9	 2j	 3aj	87
10[b]	 2k	 3ak	76
11	 2l	 3al	84

[a] Reaction conditions: **1** (1.5 mmol), **2** (1.0 mmol), $PdCl_2$ (2.0 mol%), CO (15 bar), air (5 bar), toluene (2.0 mL), 120 °C, 12 h. [b] Methylamine solution, 2.0 M in THF, 1.0 mmol.

straightforward manner. Notably, this reaction tolerates halide substituents (chloride, bromide). In general, substrates bearing electron-withdrawing functional groups gave higher yields compared to electron-rich aryl acetylenes. For aromatic internal alkynes (**1g**), the yield decreased, and about 35% of the original



Scheme 2 Proposed catalytic cycle.

alkyne remained. On the other hand, aliphatic terminal alkynes with different carbon chains (**1h–1l**) afforded the desired products in good yields (81–92%). It is worth noting that internal alkynes (**1m**, **1n**) were also transformed affording the multiple-substituted maleimides in good yields.

Next, the scope with respect to amines was investigated and the results are summarized in Table 2. Aromatic amines (**2b–2h**) with either electron-donating (OMe, Me) or electron-withdrawing (F, Cl, Br, CF_3) functional groups on the phenyl ring provided the corresponding products (**3ab–3ah**) in high yields (71–95%).

Aromatic amines bearing chloro- or bromo-atoms on the phenyl ring (**2c**, **2d**), which are often sensitive to palladium catalysis, also worked well, without adverse effect on the reaction. At the same time, the steric hindrance of the substituent on the amine also has a certain influence on the reaction, the yield of 2-methylaniline (**2g**) is moderately lower than that of unsubstituted aniline. Bioactive amines (**2i**, **2j**) yielded the corresponding products in 87–91%. Similarly, for aliphatic amines (**2k**, **2l**) this transformation gave the corresponding products in high yields (76–84%).

With respect to the mechanism it is interesting to note that the groups of Gabriele,[14] Xia,[15] and Muldoon[11c] reported related carbonylations to 2-ynamides in the presence of halide additives. However, under our conditions, the corresponding ynamides were not observed by GC-MS as intermediates to a significant extent. Hence, on the basis of previous mechanistic studies for oxidative carbonylations,[16] we propose the following pathway for this transformation (Scheme 2). First, the palladium acyl complex **B** was generated from palladium(II) **A** in the presence of amine and CO. Subsequently, π-coordination of the carbon–carbon triple bond to the metal center, followed by the insertion of the alkyne into the palladium carbon bond, affords palladium intermediates **C**. Then, the palladium species **C** undergoes CO insertion to give the acyl palladium species **D**. Finally, the maleimide is eliminated through reductive elimination of intermediate **E** to give the palladium (0) which is oxidized to palladium(II) in the presence of air to finish the catalytic cycle.

In conclusion, we have developed a ligand-free palladium catalyzed oxidative carbonylation of alkynes with amines to give poly-substituted maleimides in good to high yields (63–95%). In this convenient protocol air was utilized as the terminal oxidant without other co-oxidants.[17]

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Conflicts of interest

There are no conflicts to declare.

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5.3. A General Platinum-catalyzed Alkoxycarbonylation of Olefins

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Contributions

In this paper, I planned, performed and analyzed most experiments for this manuscript. I have done the major part of writing of the manuscript. My contribution as co-author of this paper is approximately 75%.

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COMMUNICATION

A General Platinum-catalyzed Alkoxycarbonylation of Olefins

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Hydroxy- and alkoxycarbonylation reactions constitute important industrial processes in homogeneous catalysis. Nowadays, palladium complexes constitute state-of-the-art catalysts for these transformations. Herein, we report the first efficient platinum-catalysed alkoxycarbonylations of olefins including sterically hindered and functionalized ones. This atom-efficient catalytic transformation provides straightforward access to a variety of valuable esters in good to excellent yields and often with high selectivities. In kinetic experiments the activities of Pd- and Pt-based catalysts were compared. Even at low catalyst loading, Pt shows high catalytic activity.

Carbonylation processes using CO as one of the most important C1 building blocks represent industrial core reactions for converting various bulk feedstock into a diverse set of useful chemicals for our daily life.[1] Besides hydroformylation,[2] which produces over 10 million tons of oxo products every year, alkoxycarbonylation and related transformations are another important type of such reactions. They allow for the 100%-atom efficient synthesis of acids, esters, amides, etc. Without doubt, up to now palladium complexes prevail in this field based on their favourable reactivity and efficiency.[3] However, in recent years the price of Pd is highly dynamic and has increased significantly, due to the large demand for this metal in industrial & environmental catalysis. Thus, the current price of bulk platinum is about half of that of palladium (Figure 1).[4] This situation stimulated us to to think about the possibility of using Pt instead of Pd in carbonylation reactions.

It is well-known, even in textbooks, that the catalytic performance of platinum complexes is poor, with rates typically four orders of magnitude lower than palladium.[5] Thus, only scarce reports are known,[6] mainly focusing on the mechanistic aspects of such reactions. In general, the mechanism of a Pt catalysed methoxycarbonylation of alkene should follow an analogous pathway to the more active Pd systems (Scheme 1).[7] However, as pointed out by Iggo and co-workers there are some subtle differences: (a) The carbonyl hydride complex **B** is much less reactive towards alkene and this step is probably rate limiting in the Pt system. The higher affinity of Pt for CO results in the formation of the Pt hydride complex **B** from both complexes **D** and **E** presumably by the back reaction, a feature not observed in an analogous Pd system.[8]

Figure 1. Recent prices for palladium and platinum

This demonstrates the ready reversibility of the catalytic cycle in the Pt system; only in the presence of excess CO there is significant forward reaction **C** to **D** to **E** to **B** + ester product; (b) the Pt alkyl-carbonyl complex **D** converts to the acyl complex **E** in a more endothermic process and the formation of the stable carbonyl complex **D** requires a higher energy barrier compared to Pd.

To solve these problems of Pt-catalysed carbonylation reactions, we thought that the design of an appropriate ligand might be a solution. In recent years, we developed several phosphine-based ligands (Scheme 2) bearing both sterically hindered alkyl as well as basic (pyridine) substituents on the phosphorous atom with different backbones.[9] Mechanistic studies have shown that this basic group on the phosphine ligand not only

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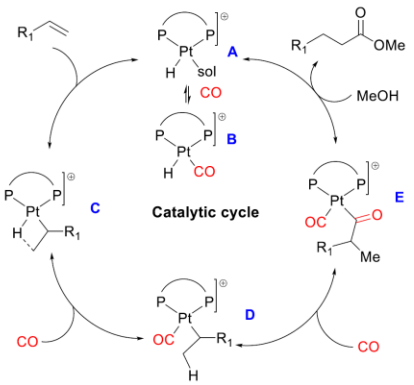
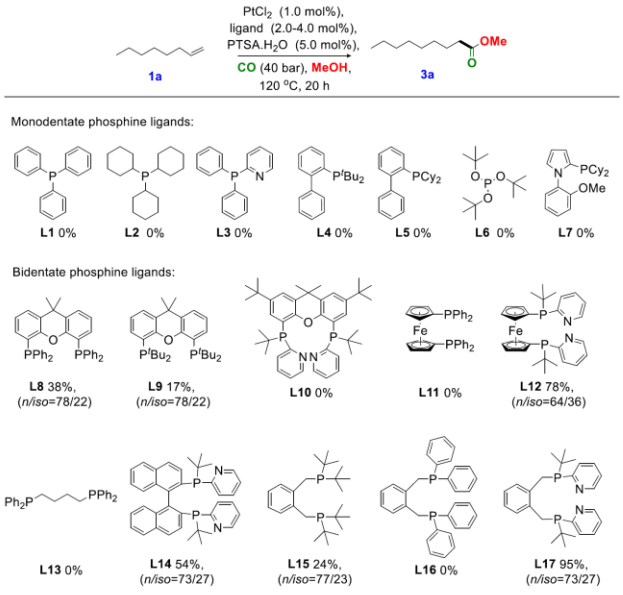
acts as a proton shuttle for the faster formation of the corresponding palladium hydride complex, but also able to improve the durability of the catalyst via hemilabile coordination to the metal centre in the catalytic cycle.



Scheme 1. Proposed mechanism for Pt catalysed methoxycarbonylation of alkenes according to literature.[5]

Based on our previous works, we became interested if these ligands will also improve the efficiency of the platinum-catalysed carbonylations. Based on our long-standing interest in such reactions,[10] we report herein the first general Pt-catalysed alkoxycarbonylation of olefins.

Scheme 2. Pt-catalysed alkoxycarbonylation of alkenes: Ligand effect.



[a]. Standard reaction conditions: 1-octene (1.0 mmol), $PtCl_2$ (0.01 mmol, 1.0 mol%), ligands (monodentate phosphine ligand: 0.04 mmol, 4.0 mol%; bidentate phosphine ligand: 0.02 mmol, 2.0 mol%), PTSA·H_2O (5.0 mol%), MeOH (2.0 mL), CO (40 atm), 120 °C, 20 h; The selectivity and yield were determined by GC analysis with mesitylene as the internal standard.

At the beginning of our studies, 1-octene (1 mmol) and methanol were chosen as benchmark substrates (Scheme 2). Initially, testing different monodentate phosphines (triphenylphosphine, tricyclohexylphosphine, diphenylpyridyl-phosphine **L1**, **L2**, **L3**) with our model substrates no target product was detected. Similarly, monodentate ligands with increased steric hindrance **L4**, **L5**, **L6**, and **L7** led not to the formation of the desired product. However, examination of various bidentate phosphine ligands including the xanthone backbone **L8**, **L9**, ferrocene backbone **L11**, flexible linear backbone **L13**, o-xylylene backbone **L15**, **L16**, showed some reactivity (0% to 38%). Following our concept of "built-in-base" ligands, to our delight high reactivity was obtained! Specifically in the presence of **L17**, **3a** was achieved in greater than 90% with the ratio of linear to branched products of approximately 3/1.

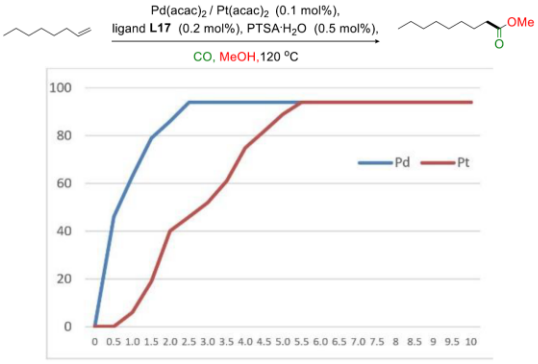


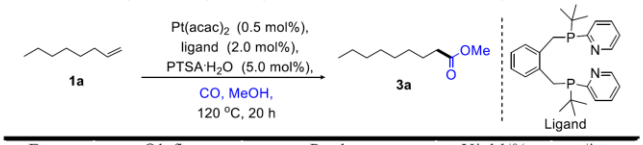
Figure 2. Kinetic monitoring experiment.

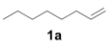
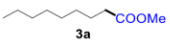
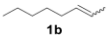
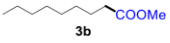
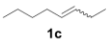
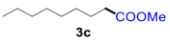
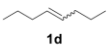
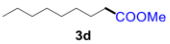
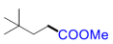
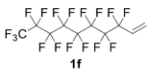
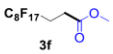
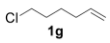
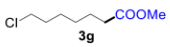
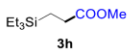
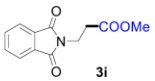
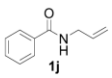
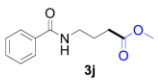
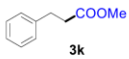
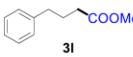
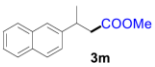
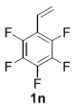
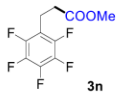
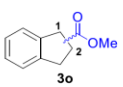
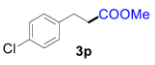
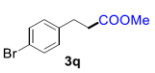
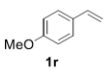
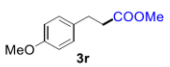
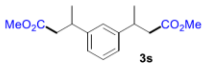
To improve this novel catalyst system further on, the effects of other critical reaction parameters such as different metal precursors, acid co-catalyst, catalyst loading and temperature were investigated carefully (see Supplementary information Table S3.2- Table S3.6 for details). Compared to $PtCl_2$, $Pt(acac)_2$ gave slightly better results under identical conditions. Acid co-catalysts with strong acidity facilitate the carbonylative conversion. The effect of reaction temperature has a noticeable influence on the rate and extent of the methoxy-carbonylation process of alkene.

In order to better understand the differences in catalytic activity between Pd and Pt, we monitored the product yield over time under similar conditions. To clearly reflect the catalyst differences, we reduced the metal loading to only 0.1 mol%. As shown in Figure 2, for the Pd catalyst, the reaction showed almost no induction period, which indicated that the active Pd–H species are generated immediately at 120 °C. In general, the reaction proceeded very quickly and was completed after about 2.5 hours with a product yield of 94%. For the Pt catalyst system, the reaction required an induction period of about 1 h. Then, the conversion increased, and the reaction is completed in 5.5 hours. To our delight the products 2a were also obtained in 94% yield with 74/26 selectivity.

With the optimized reaction conditions established, we examined the general scope and limitations of this novel catalytic process with respect to olefins (Table 1). With the optimized reaction conditions established, we examined the general scope and limitations of this novel catalytic process with respect to olefins (Table 1).

Table 1. Pt-catalysed alkoxycarbonylation of alkenes: Substrates scope.[a]



Entry	Olefin	Product	Yield/%	n/iso
1	 1a	 3a	95	74/26
2	 1b	 3b	95	57/43
3	 1c	 3c	92	49/51
4	 1d	 3d	90	47/53
5	 1e	 3e	93	>99/1
6	 1f	 3f	87	>99/1
7	 1g	 3g	87	66/34
8	 1h	 3h	82	99/1
9	 1i	 3i	77	>99/1
10	 1j	 3j	66	68/32
11	 1k	 3k	95	71/29
12	 1l	 3l	94	65/35
13	 1m	 3m	97	>99/1
14	 1n	 3n	87	>99/1
15	 1o	 3o	87	1/2= 88/12
16	 1p	 3p	89	71/29
17	 1q	 3q	86	72/28
18	 1r	 3r	85	52/48
19[b]	 1s	 3s	86	>99/1
20	 1t	3t	97	-
21	1u	3u	96	-
22	1v	3v	88	-
23	1w	3w	98	69/31
24	1x	3x	88	42/58
25	1y	3y	89	-
26[b]	1z	3z	84	78/22
27[b]	2a	4a	86	95/5
28	81% 19% 2b diisobutylene	4b	94	>99/1
29[b]	2d	4c	70	>99/1
30[b]	2e	4d	32	90/10

[a]. Standard reaction conditions: Alkene (1.0 mmol), $Pt(acac)_2$ (0.005 mmol, 0.5 mol%), ligand (0.02 mmol, 2.0 mol%), PTSA·H_2O (5.0 mol%), MeOH (2.0 mL), CO (40 atm), 120 °C, 20 h; The selectivity and yield were determined by GC analysis. [b]. Alkene (1.0 mmol), $Pt(acac)_2$ (0.01 mmol, 1.0 mol%), ligand (0.04 mmol, 4.0 mol%), PTSA·H_2O (10.0 mol%), MeOH (2.0 mL), CO (40 atm), 120 °C, 24 h.

A variety of substituted olefins gave the corresponding esters in synthetically useful yields with excellent regioselectivity. Mixtures of internal and terminal olefins are usually preferred as less expensive starting materials in industry. Delightfully, this catalytic system was able to convert those internal olefin isomers including 2-, 3-, and 4-octenes (**1b-1d**) into the corresponding methyl nonanoates with high yield and moderate selectivity. Testing different olefins with steric hindrance (**1e**, **1v**, **1y**, **2b**, **2d**, **2e**) and various functional groups gave good results, too. Notably, a broad range of functional groups were tolerated, including electron-donating (triethylsilyl **1h**, methoxy **1r** and phenolic hydroxyl group **2e**) as well as electron-withdrawing substituents (perfluoroalkyl **1f**), and reactive chloro (**1g, 1p**), imide (**1i**), amide (**1j**), cyano (**1z**), ester (**1w, 1x, 2a**) groups. Moreover, the diester (**3s**), which is potential plasticizer for polymer materials,[11] was obtained in high yield and selectivity. Cycloalkenes, which often show lower reactivity under traditional alkoxy-carbonylation conditions, are

transformed into the corresponding esters in high yields and selectivity (**1t, 1u, 1v**), too. Furthermore, internal olefins (**1w,1x**) were transformed into diester products, which might be of interest for polymers. Another potential industrial application is the alkoxycarbonylation of diisobutene (**DIB, 2b**).[12] To our delight, our catalytic system allowed complete transformation of the substrate with 91% yield. Compared to the related palladium catalyst, the Pt catalytic system is more sensitive to steric hindrance, e.g. for tetra-substituted olefins (**2d, 2e**) the yield decreased significantly. We explain observation by the lower binding affinity of these substrates towards the metal center and formation of unwanted ether by-products.[13]

In summary, we demonstrate for the first time a general Pt-catalyzed alkoxycarbonylation of olefins. By using specific ligands such as **L17** the activity of the metal center is greatly improved, and the catalyst system becomes comparable with the palladium catalyst. At the same time, this Pt catalytic system shows excellent reactivity for bulk olefin feedstocks and good compatibility for various functional groups, which provide new inspiration for platinum-catalyzed alkoxycarbonylations.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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

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

Angew. Chem., Int. Ed. **2018**, *58,* 10683

Contributions

In this paper, I performed part of the catalytic experiments. My contribution as co-author of this paper is approximately 30%.

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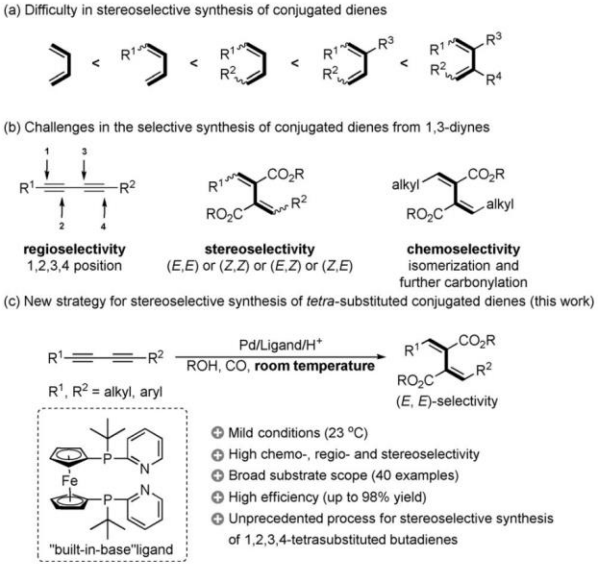
Stereoselective Synthesis of Highly Substituted Conjugated Dienes via Pd-Catalyzed Carbonylation of 1,3-Diynes

*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-tetrasubstituted 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 energy levels, which determine their transformations.[2] Hence, they serve as versatile building blocks and have 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- and trisubstituted 1,3-dienes, the tetrasubstituted counterparts contain substituents at all four positions, resulting in more difficulties in controlling the stereoselectivity (Scheme 1a). More specifically, every carbon–carbon double bond should be constructed stereoselectively and the substituents incorporated in a regioselective manner. Thus, the development of new methodologies, particularly for the stereoselective synthesis of multisubstituted conjugated dienes remains difficult.



Scheme 1. Selective synthesis of 1,2,3,4-tetrasubstituted conjugated dienes: Challenges and new method.

As one of the most important processes in homogeneous catalysis, the palladium-catalyzed carbonylation of alkynes/alkenes has been extensively investigated and applied in academia and industry for several decades.[9] Based on our continued interest in carbonylations, recently we decided 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, although they afford an easy possibility for the selective synthesis of multiply substituted conjugated dienes.[11]

Obviously, control of selectivity is a key challenge of our envisioned synthesis: 1. Carbonylation of the substrate (1,3-diynes) having two triple bonds and four active positions may result in different regioisomers (Scheme 1b, left). 2. Furthermore, four different stereoisomers of the desired tetrasubstituted conjugated dienes can be formed (Scheme 1b, middle). 3. 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 containing basic sites by introduction of pyridine substituents on the phosphorus 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

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the thought 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 1c).

At the beginning of our studies, we investigated the effect of ligands bearing *tert*-butyl and pyridine substituents on the phosphorus atom for the methoxycarbonylation of 1,4-diphenylbuta-1,3-diyne **1a** under typical alkoxycarbonylation conditions (1.0 mol% Pd catalyst, 16.0 mol% *p*-toluenesulfonic acid monohydrate (PTSA·H_2O), 40 bar CO, 120°C). When we tested the ligands 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**), we found 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 the Supporting Information).

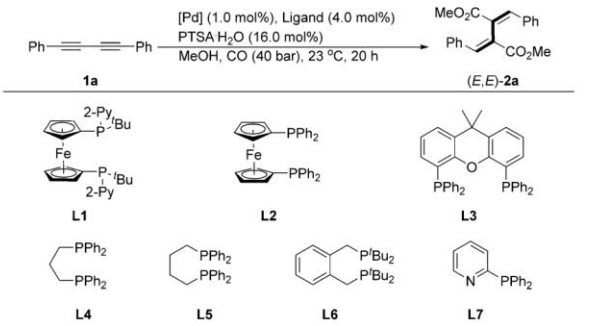
Notably, the reaction proceeded smoothly already at room temperature (23°C) in the presence of **L1**, affording **2a** in 96% (Table 1; see the Supporting Information for more details). When we tested the commercially available ligands **L2–L7**, which are commonly used in various carbonylation reactions,[15] we obtained only poor results and in all cases the desired product **2a** was obtained 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 a short time (4 h) using a lower concentration of PTSA·H_2O (Table 1, entry 13).

With the optimized reaction conditions in hand, 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.

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% yield. 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 a 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

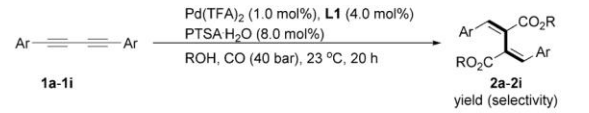
Table 1: Pd-catalyzed stereoselective carbonylation of 1,4-diphenylbuta-1,3-diyne.[a]

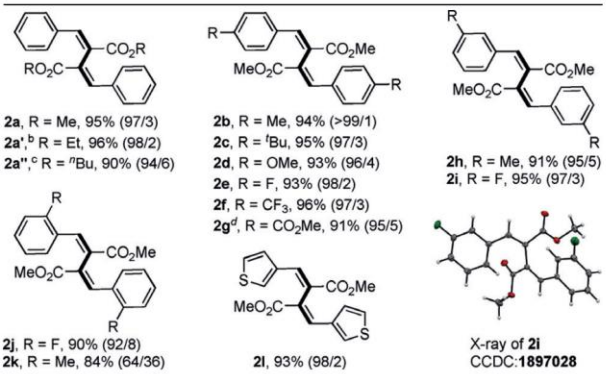


Entry	Ligand	[Pd]	Sel.[b]	Yield of **2a** [%][c]
1	**L1**	$Pd(acac)_2$	97/3	96
2	**L2**	$Pd(acac)_2$	37/63	10
3	**L3**	$Pd(acac)_2$	–/–	0
4	**L4**	$Pd(acac)_2$	–/–	0
5	**L5**	$Pd(acac)_2$	–/–	0
16	**L6**	$Pd(acac)_2$	24/76	5
7	**L7**	$Pd(acac)_2$	–/–	trace
8[d]	**L1**	$Pd(acac)_2$	97/3	96
9[e]	**L1**	$Pd(acac)_2$	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 the Supporting Information). [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] Yield of isolated product.

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

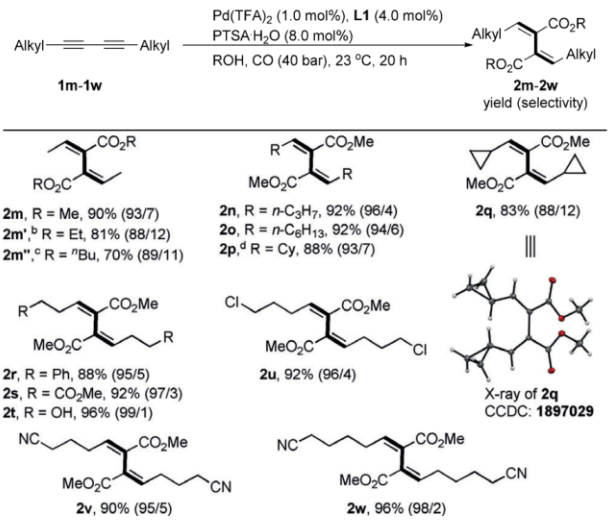




[a] Reaction conditions: Substrates (0.25 mmol), $Pd(TFA)_2$ (1.0 mol%), **L1** (4.0 mol%), PTSA·H_2O (8.0 mol%), CO (40 atm), 23°C, methanol (1.0 mL), 20 h. Yield of isolated product. The selectivity in brackets was determined by GC analysis. [b] EtOH was used. [c] *n*BuOH was used. [d] 2/8/16 mol%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

to afford various conjugated dienes in high yields (Table 3). As an example, the reaction of aliphatic substrate **2m** was 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 multiply substituted aliphatic conjugated dienes is not an easy task. In the reaction of 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.

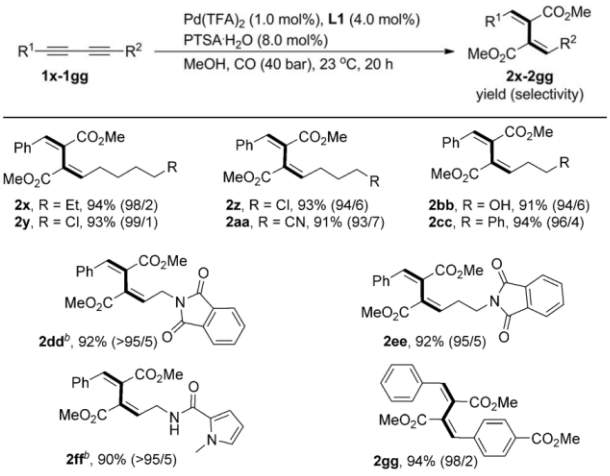
Table 3: Carbonylation of 1,4-dialkylbuta-1,3-diynes: Substrate scope.[a]



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

With respect to organic synthesis, the double carbonylation of nonsymmetric 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 selectivities of 93/7–99/1 (Table 4). Moreover, **2ff** is obtained in 90% yield which demonstrates that N-heterocycles are well-tolerated by our catalyst. Finally, product **2gg** with two different aromatic substituents was also prepared more efficiently than in a previous report.[16] It is worth mentioning that the presented

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

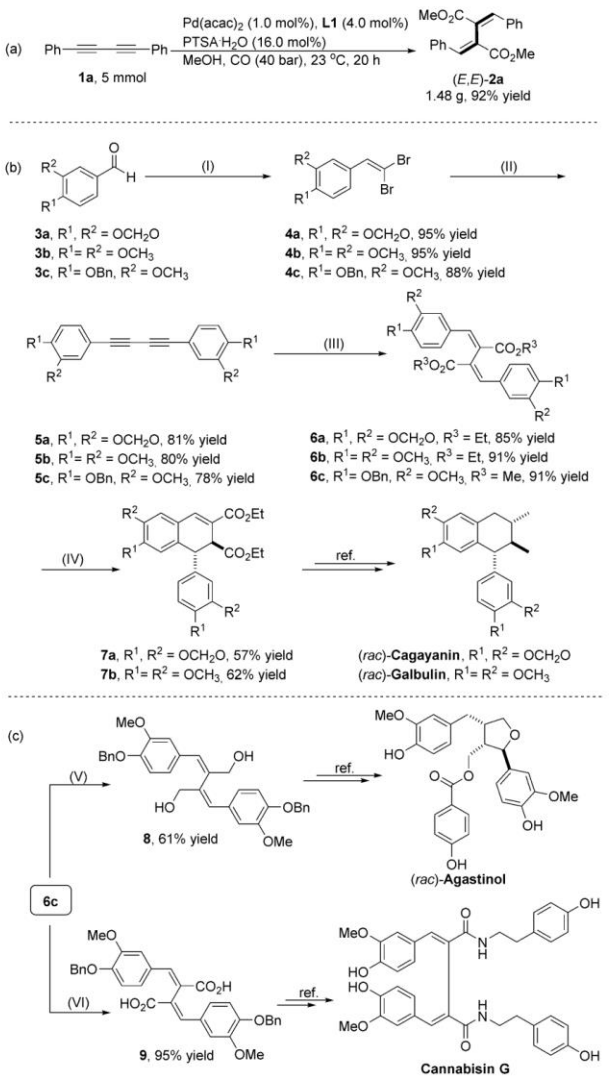


[a] Reaction conditions: substrates (0.25 mmol), $Pd(TFA)_2$ (1.0 mol%), **L1** (4.0 mol%), $PTSA{\cdot}H_2O$ (8.0 mol%), CO (40 atm), 23 °C, methanol (1.0 mL), 20 h. Yield of isolated product. The selectivity in brackets was determined by GC analysis. [b] 2/8/16 mol% Pd/**L1**/$PTSA{\cdot}H_2O$ was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

methodology can be scaled up easily. Hence, the practical gram-scale synthesis of **2a** was performed and the desired product was obtained in 92% yield (Scheme 2a).

Finally, we showed the usefulness of this protocol in the synthesis of key intermediates for pharmaceutically interesting bioactive compounds. Hence, dienes **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 key intermediates in the synthesis of the naturally occurring lignans (*rac*)-cagayanin and (*rac*)-galbulin (Scheme 2b).[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 the potential anti-apoptotic agent (*rac*)-agastinol.[17] (*E*,*E*)-2,3-Bis(4-benzyloxy-3-methoxybenzylidene)succinic acid **9** was achieved in 95% yield from **6c**, and **9** can be directly used for the synthesis of cannabisin G,[18] a compound that showed cytotoxic activity against human prostate cancer LNCaP cells (Scheme 2c).[19]

In summary, we have developed the first selective double-carbonylation reaction 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-tetrasubstituted 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]



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, 2 h. VI) $LiAlH_4$, $AlCl_3$, THF, rt, 1 h. DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene, TFA: trifluoroacetic acid, HOTf: trifluoromethanesulfonic acid.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

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

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[20] Following the advice of a referee, we also performed a few experiments using two alcohols with distinct reactivity to test 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% yields, respectively, of the mixed-ester compounds. In the future, the selectivity of the process should be improved.

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5.5. Pd-catalyzed selective carbonylation of gem-difluoroalkenes: a practical synthesis of difluoromethylated esters

Jiawang Liu, Ji Yang, Francesco Ferretti, Ralf Jackstell, Matthias Beller

Angew. Chem., Int. Ed. **2018**, *58,* 4690

Contributions

In this paper, I performed part of the catalytic experiments. My contribution as co-author of this paper is approximately 30%.

Fluoroalkenes

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Pd-Catalyzed Selective Carbonylation of *gem*-Difluoroalkenes: A Practical Synthesis of Difluoromethylated Esters

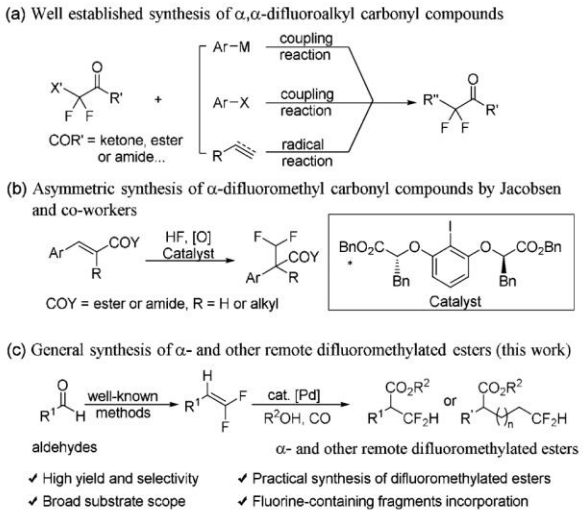
*Jiawang Liu, Ji Yang, Francesco Ferretti, Ralf Jackstell, and Matthias Beller**

Abstract: *The first catalyst for the alkoxycarbonylation of gem-difluoroalkenes is described. This novel catalytic transformation proceeds in the presence of Pd(acac)$_2$/1,2-bis((di-tert-butylphosphan-yl)methyl)benzene (btbpx) (**L4**) and allows for an efficient and straightforward access to a range of difluoromethylated esters in high yields and regioselectivities. The synthetic utility of the protocol is showcased in the practical synthesis of a Cyclandelate analogue using this methodology as the key step.*

The incorporation of fluorine or fluorinated building blocks into organic molecules has become an important tool for designing bioactive compounds and to improve the properties of functional materials.[1] Thus, in recent years the controlled introduction of these groups represents one of the most active areas in the development of novel synthetic methodologies.[2]

Among the various fluorinated moieties, the difluoromethyl group (CF_2H) is a particularly interesting one. Compared with the well-known CF_3 substituent, this group bears a slightly acidic C–H bond,[3] which is capable of hydrogen-bonding interactions to improve the binding selectivity to specific receptors.[4] Moreover, the difluoromethyl group is recognized as being isosteric and isopolar with alcohols[5] or thiols.[6] Thus, at present there is a strong interest to replace hydroxyl, amino, or thio substituents by CF_2H groups within lead structures of pharmaceuticals.[7] Although significant advancements have been made in the direct introduction of CF_2H group into organic compounds,[8] including electrophilic,[9] nucleophilic,[10] free-radical,[11] and difluorocarbene-involving[12] reactions, the preparation of functionalized difluoromethyl and α,α-difluoroalkyl carbonyl compounds is still highly desired.

Currently, transition metal catalyzed cross-coupling reactions using commercially available $BrCF_2CO_2Et$ or its analogs with organometallic regents[13] and the radical-induced functionalization of alkenes and/or alkynes[14] provide the most convenient strategies for the synthesis of α,α-difluoroalkyl carboxylic acid derivatives (Scheme 1 a).[15] Nevertheless, for the preparation of α-difluoromethyl compounds, few efficient catalytic reports exist.[16] Notably, in 2016 Jacobsen and co-workers developed the first catalytic asymmetric geminal difluorination of β-substituted styrenes to give difluoromethylated carbonyl compounds with tertiary or quaternary stereocenters (Scheme 1 b).[17] We thought a complementary practical approach to this interesting class of products can be achieved by carbonylation of *gem*-difluoroalkenes (Scheme 1 c).



Scheme 1. Synthesis of α,α-difluoroalkyl carbonyl compounds and α-difluoromethyl carbonyl compounds.

As one of the most important processes for producing carboxylic derivatives, transition metal catalyzed carbonylation reactions have been extensively investigated and applied in academia and industry for several decades.[18] In this respect, the alkoxycarbonylation represents a well-established method for the transformation of alkenes into the corresponding esters.[19] In recent years, notable advancements were achieved with respect to catalyst activity,[20] selectivity,[21] and CO surrogates.[22] To the best of our knowledge, the direct alkoxycarbonylation of such functionalized olefins to give difluoromethylated esters has not been reported yet. Obviously, a key challenge for such process is to avoid the competitive β-F elimination to form undesired byproducts.[23] Advantageously, there are many methods and reagents developed for the synthesis of *gem*-difluoroalkenes from aldehydes and ketones.[24]

Based on our continuous interest in carbonylations, herein we present the first examples of alkoxycarbonylations to construct α-difluoromethylated esters. Interestingly, using

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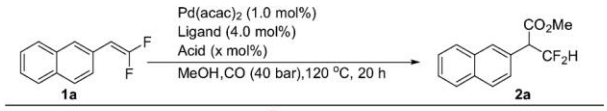
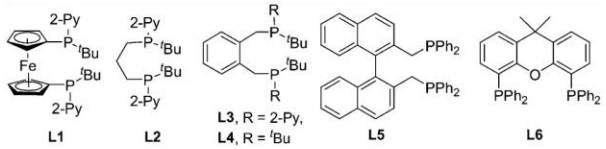
aliphatic alkenes a cascade isomerization–alkoxycarbonylation allows for remote olefin functionalization in high yield and selectivity.[27]

Recently, we demonstrated the advantage of specific phosphine ligands with built-in base function for Pd-catalyzed alkoxycarbonylations of less-reactive olefins including hindered *tetra*-substituted alkenes.[20] 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 Pd acyl complex, which can be rate-limiting step in these catalytic protocols.[25] Hence, at the start of our studies, we investigated the influence of these and related standard ligands for the methoxycarbonylation of 2-(2,2-difluorovinyl)naphthalene **1a** under typical carbonylation conditions for alkenes (Table 1).

Table 1: Pd-catalyzed alkoxcarbonylation of 2-(2,2-difluorovinyl)naphthalene: Investigation of reaction conditions.[a]





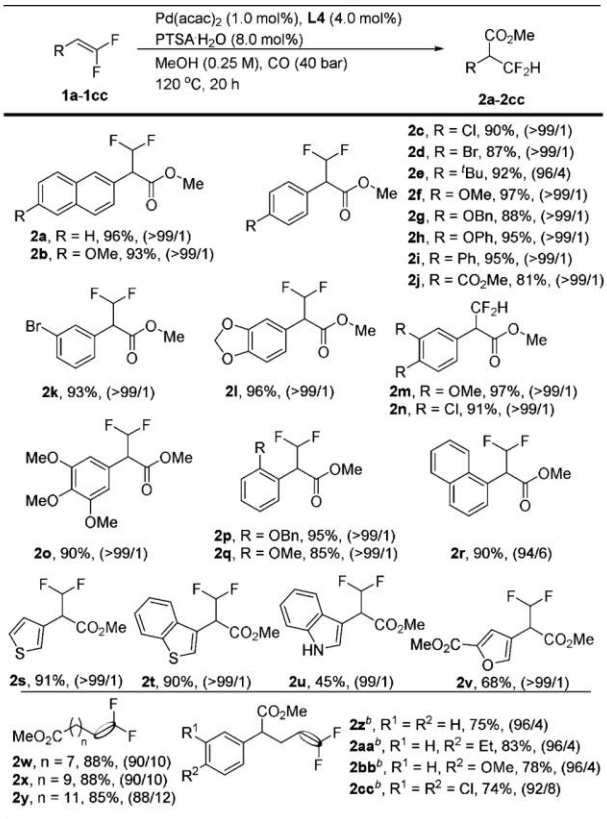
Entry	Ligand	Acid (*x*)	*b*/*l*[b]	Yield (%)[b]
1	**L1**	PTSA·H_2O (16)	98/2	18
2	**L2**	PTSA·H_2O (16)	76/24	7
3	**L3**	PTSA·H_2O (16)	93/7	72
4	**L4**	PTSA·H_2O (16)	>99/1	92
5	**L5**	PTSA·H_2O (16)	93/7	5
6	**L6**	PTSA·H_2O (16)	>99/1	9
7	**L4**	No acid	–/–	0
8	**L4**	HOAc (16)	–/–	0
9	**L4**	H_2SO_4 (8)	92/8	5
10	**L4**	HOTf (16)	>99/1	91
11	**L4**	**PTSA·H_2O (8)**	**>99/1**	**97 (96[c])**
12	**L4**	PTSA·H_2O (5)	>99/1	93

[a] Reaction conditions: **1a** (0.5 mmol), $Pd(acac)_2$ (1.0 mol%), **L** (4.0 mol%), PTSA·H_2O (16.0 mol%), CO (40 atm), 120°C in methanol (2.0 mL). [b] The ratio of branched/linear (*b*/*l*) and yield was determined by GC. [c] Yield of isolated product.

Applying 1,1′-ferrocenediyl-bis(*tert*-butyl(pyridin-2-yl)phosphine) **L1**, ester **2a** was obtained with excellent regioselectivity albeit in 18% yield. In the presence of 1,3-bis(*tert*-butyl(pyridin-2-yl)phosphanyl)propane **L2** as the ligand, the yield of the desired product was even lower. To our delight, using 1,2-bis((*tert*-butyl(pyridin-2-yl)phosphanyl)methyl)benzene **L3** the desired product **2a** was obtained in 72% yield. Surprisingly, the commercially available 1,2-bis((di-*tert*-butylphosphan-yl)methyl)benzene (btbpx) ligand **L4**[26] which has the same backbone as **L3**, gave an improved yield of 92% and >99/1 regioselecivity. Other commonly used bidentate phosphine ligands such as Naphos **L5** and Xantphos **L6** only afforded the product in poor yields. No reaction occurred without acid or with weak acid. Even sulfuric acid gave only trace amounts of **2a**, while trifluoromethanesulfonic acid afforded the desired product in 91% yield with excellent regioselectivity. Besides, the acid concentration had a significant influence on the productivity giving **2a** in 93% and 97% in the presence of 5 and 8 mol% PTSA, respectively.

With optimized reaction conditions established, we examined the substrate scope of this process. First, we studied the alkoxycarbonylations of different *gem*-difluoroalkenes, a variety of aromatic *gem*-difluoroalkenes bearing diverse substituents and heterocycles, are transformed into the corresponding products in high yields with excellent regioselectivities. More specifically, *gem*-difluoroalkenes **1a–k** with either electron-donating (OMe, OBn, OPh) or electron-withdrawing (Cl, Br, CO_2Me) groups on the phenyl ring provided the corresponding products **2a–k** in 85–98% (Table 2). Notably, in case of bromo-substituted substrates, which provide useful handles for further synthetic transformations, no dehalogenation was observed. Furthermore, substrates **1l–1o** with multiple functional groups, also give the corresponding products **2l–2o** in 90–97%. The position of substituents on the phenyl ring has no influence on the reaction outcome. Hence, *gem*-difluor-

Table 2: Substrate scope with respect to *gem*-Difluoroalkenes.[a]



[a] Reaction conditions: **1** (0.5 mmol), $Pd(acac)_2$ (1.0 mol%), **L4** (4.0 mol%), PTSA·H_2O (16.0 mol%), CO (40 atm), 120°C in methanol (2.0 mL). Yield of isolated products is reported. The ratio of branched/linear was determined by GC. [b] 3/12/12 mol% of Pd/**L4**/PTSA·H_2O and CO (50 atm).

oalkenes **1p–1r** afforded **2p–2r** in very good yields and selectivities. Interestingly, heterocycle-substituted *gem*-difluoroalkenes based on (benzo)thiophene, indole, and furan proved to be viable substrates and gave the corresponding products **2s–2v** in moderate to excellent yields. It should be noted that the product **2u** was obtained by carbonylation and deprotection of 1-(3-(2,2-difluorovinyl)-1*H*-indol-1-yl)ethan-1-one under standard conditions. Unfortunately, when other heterocycles including 2-(2,2-difluorovinyl)benzofuran and quinoline, as well as *tetra*-substituted difluoroalkenes were used, no desired product was detected (see the Supporting Information, Table S8 and *S*11).

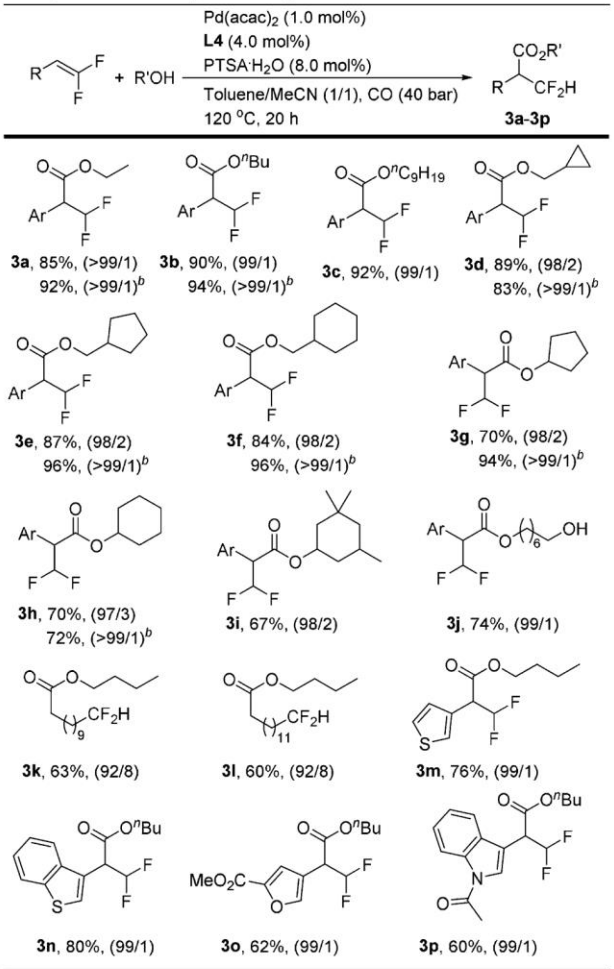
Next, we evaluated the reactivity of aliphatic *gem*-difluoroalkenes, which from the viewpoint of selectivity represent more demanding substrates as they may undergo additional isomerization reactions. Nevertheless, alkoxycarbonylations proceeded selectively to afford various difluoromethylated esters. The linear, long chain, aliphatic substrates **1w**, **1x** and **1y** without other functional groups gave the corresponding products **2w–2y** in good to high yields and selectivities. The isomerization process for those substrates takes place at a faster rate than the carbonylation in α-position explaining the selectivity towards the linear ω-ester. Reactions of 1,1-difluoro-4-arylbutenes **1z–1cc** also reacted well leading to the γ-difluoromethylated esters **2z–2cc** in good to high yields and selectivities, albeit at higher catalyst loading and higher CO pressure.

To demonstrate that this novel transformation can be applied to wider scope of alcohols, we investigated the alkoxycarbonylation of **1a** with *n*-butanol as the nucleophile. Hence, different solvents and conditions were tested using **L4** as the ligand, and the yield and selectivity was optimized to be 94% and 99/1 when a mixed solvent system of toluene and acetonitrile (v/v = 1/1) was used (see the Supporting Information for more details).

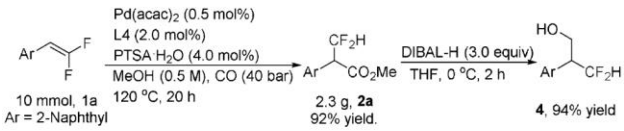
Under this optimized conditions, the scope of different alcohols with 2-(2,2-difluorovinyl)naphthalene **1a** were examined (Table 3). Gratifyingly, the corresponding esters were obtained in good to high yields, again with excellent regioselectivities. For example, primary alcohols, such as ethanol, *n*-butanol, *n*-nonanol, cyclopropylmethanol, cyclopentylmethanol, and cyclohexylmethanol, gave the desired products **3a–3f** in 84–92% yield. Similarly, carbonylations with less reactive secondary alcohols, for instance cyclopentanol, cyclohexanol and *cis*-3,3,5-trimethylcyclohexanol proceeded smoothly, providing the products **3g–3i** in 67–94% yield. Moreover, 1,7-heptanediol could also be used in this reaction to afford selectively the monoester product **3j**. Notably, in case of inexpensive alcohols (see products **3a**, **3b** and **3d–3h**) the reactions can be easily performed in neat alcohol. Furthermore, aliphatic and heterocyclic *gem*-difluoroalkenes also gave the corresponding products **3k–3p** in 60–80% yield.

A practical advantage of the presented methodology is the possibility for easy scale up. Hence, we performed the gram-scale synthesis of **2a** under 0.5 mol% Pd catalysts loading and the desired product was obtained in 92% yield (Scheme 2). Obviously, this and related esters present versatile building

Table 3: Substrate scope with respect to alcohols.[a]



[a] Reaction conditions: **1** (0.5 mmol), ROH (1.5 mmol), $Pd(acac)_2$ (1.0 mol%), **L4** (4.0 mol%), $PTSA{\cdot}H_2O$ (16.0 mol%), CO (40 atm), 120 °C in toluene/MeCN (1/1). Yield of isolated products is reported. The ratio of branched/linear was determined by GC. For **3a–3j**, Ar = 2-Naphthyl. [b] 1.0 mL alcohols were used as solvents.

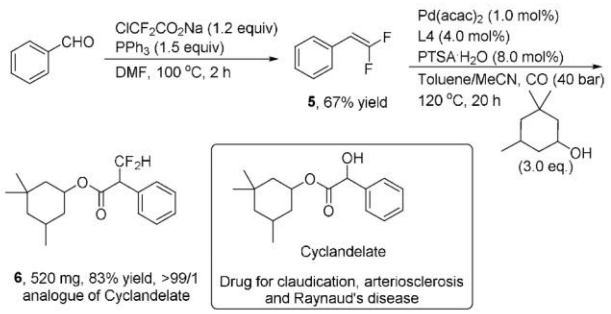


Scheme 2. Gram-scale synthesis of **2a**.

blocks which can be straightforwardly converted to interesting amides, acids, nitriles, alcohols, and so on. To showcase such possibilities, the reduction of **2a** to **4** has been performed. To explore the stability of the system, we further decreased the catalyst loading. Keeping the acid concentration constant and fixing the **L4** concentration to 2 mmol L^{-1}, at **1a**/Pd ratio > 10000, TONs up to 8400 were reached (for more details, see Table S9 in the Supporting Information).

To highlight the usefulness of our protocol further, we synthesized the analogue of Cyclandelate, which is a commonly used drug for claudication, arteriosclerosis, and

Raynaud's disease (Scheme 3). The desired product **6** was achieved in 83% yield by direct alkoxycarbonylation of *gem*-difluoroalkene **5** with 3,3,5-trimethylcyclohexanol under the optimized reaction conditions. To the best of our knowledge, this is the first example for the synthesis of this drug's analogue.



Scheme 3. Practical synthesis of cyclandelate analogue.

In summary, we have developed the first selective carbonylation of *gem*-difluoroalkenes. This catalytic protocol makes use of a Pd/**L4** catalyst and provides a variety of synthetically useful difluoromethylated esters in high yields and excellent regioselectivities. Owing to availability of starting materials and the step-economy, this procedure is efficient and easy to scale up. The straightforward synthesis of a Cyclandelate analogue demonstrates the synthetic utility of this methodology. It is expected to provide other valuable difluoromethyl-containing building blocks for modern organic synthesis and complements the currently known carbonylation methods.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: carbonylation · difluoromethylated esters · fluoroalkenes · palladium · selectivity

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[27] For more details of the mechanistic studies, see the Supporting Information.

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

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Contributions

In this paper, I performed part of the catalytic experiments. My contribution as co-author of this paper is approximately 40%.

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

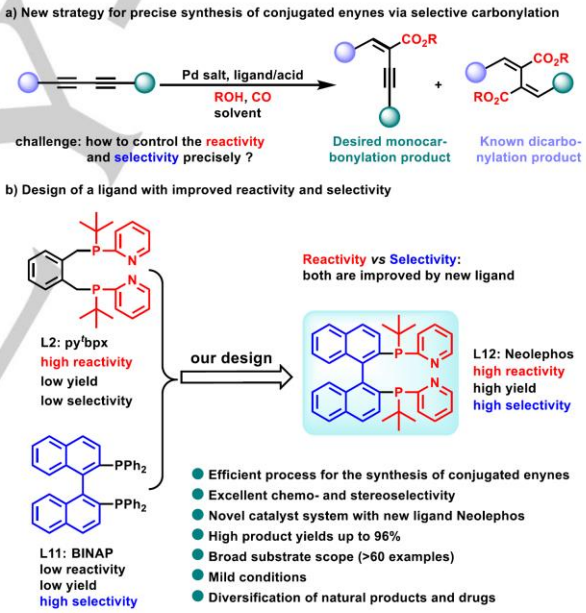
Jiawang Liu, Ji Yang, Carolin Schneider, Robert Franke, Ralf Jackstell and Matthias Beller*

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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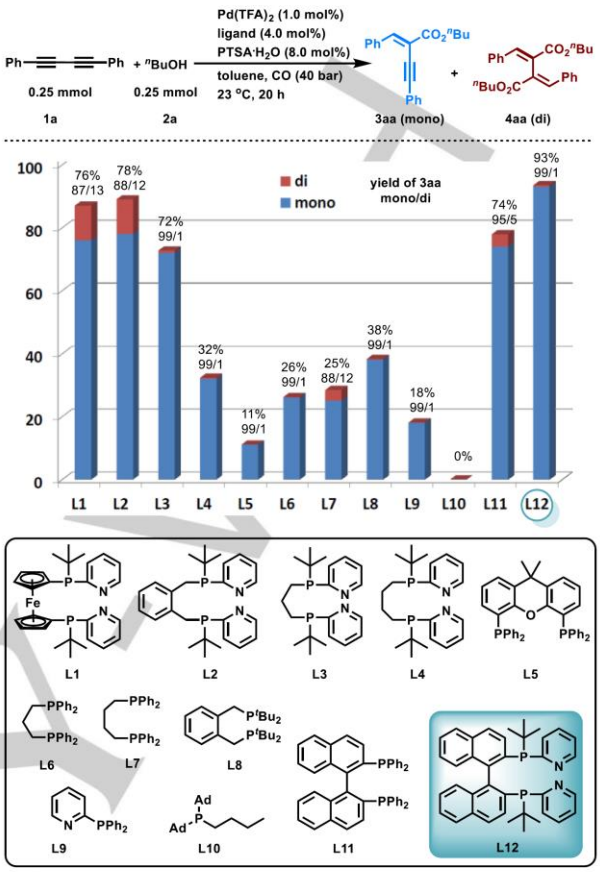
challenge for this transformation is to avoid the generation of double carbonylation products (Scheme 1, a), which could be difficult owing to the similarity between diyne and enyne. Herein, we present a solution for this problem by careful control of the reaction conditions and design of the new ligand **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

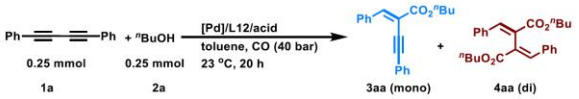
In general, for palladium-catalyzed alkoxycarbonylations the choice of ligand is crucial for controlling the selectivity and activity of the overall transformation. Thus, we investigated the effect of different phosphine ligands in the benchmark reaction of commercially available 1,4-diphenylbuta-1,3-diyne **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 $PTSA{\cdot}H_2O$ (*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**), $PTSA{\cdot}H_2O$ (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.

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-$PySO_3H$	99/1	12
5	$Pd(TFA)_2$	HOTf	99/1	45
6	$Pd(TFA)_2$	PTSA·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 ^{n}BuOH 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, ^{t}Bu) 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.

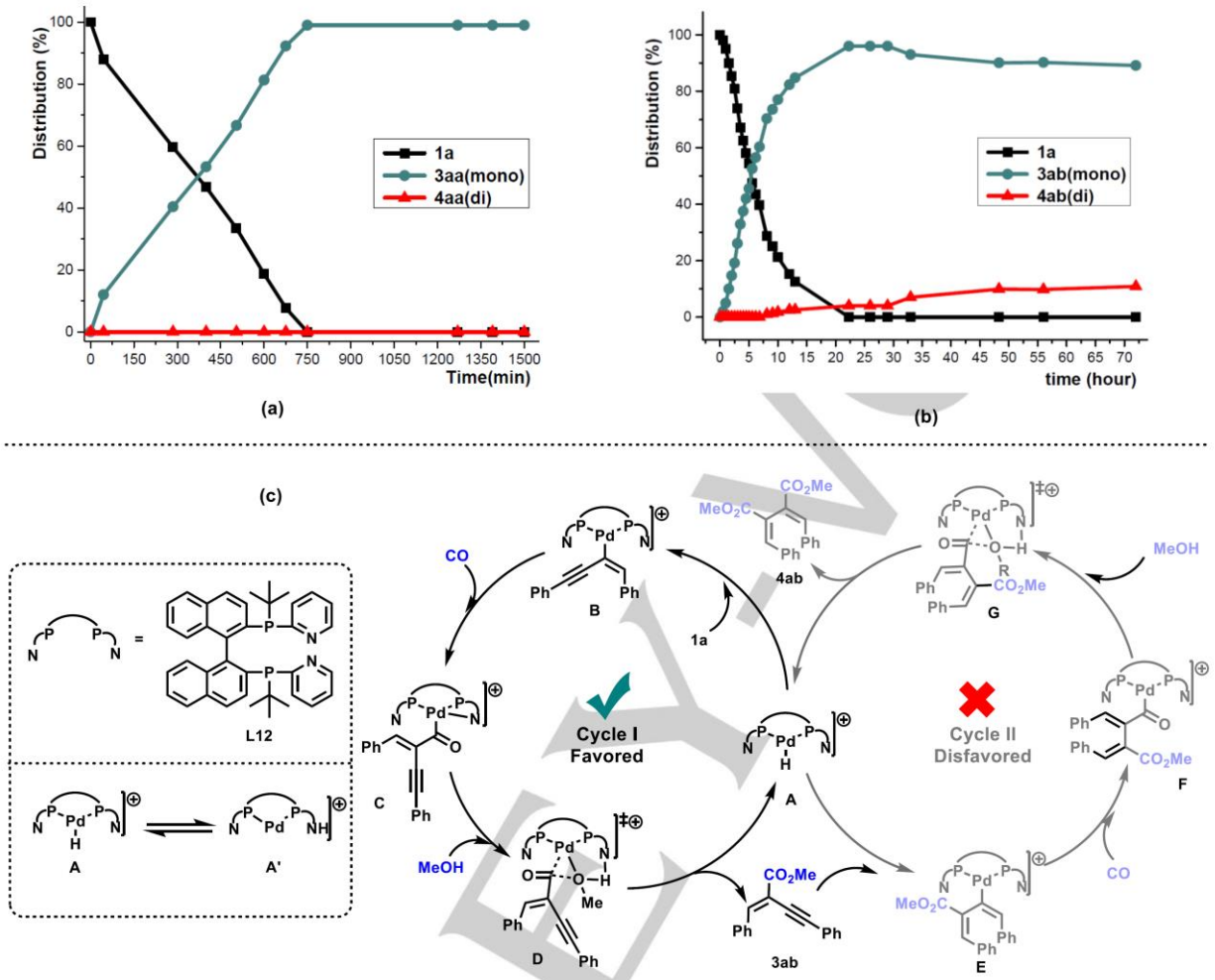
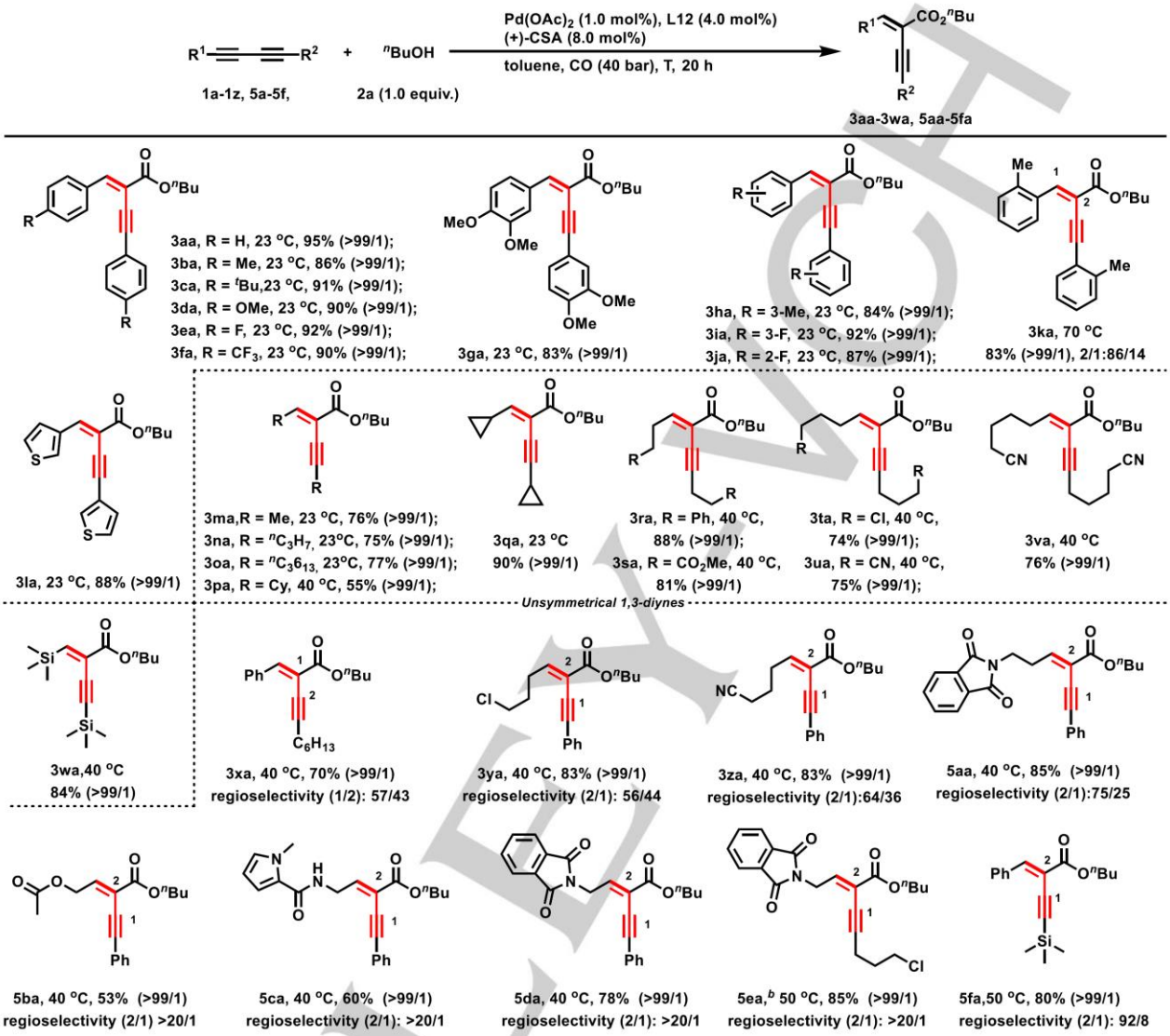


Figure 2. (a) Compounds distribution of Pd-catalyzed alkoxycarbonylation of **1a** in the presence of **L12** (reaction conditions: 1.0 mol% of Pd $(OAc)_2$, 4.0 mol% of **L12**, 8.0 mol% (+)-CSA, 5 mol of 1a, 5.0 mmol of 1-butanol, 20 mL of toluene, 23 °C). (b) Compounds distribution of Pd-catalyzed 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

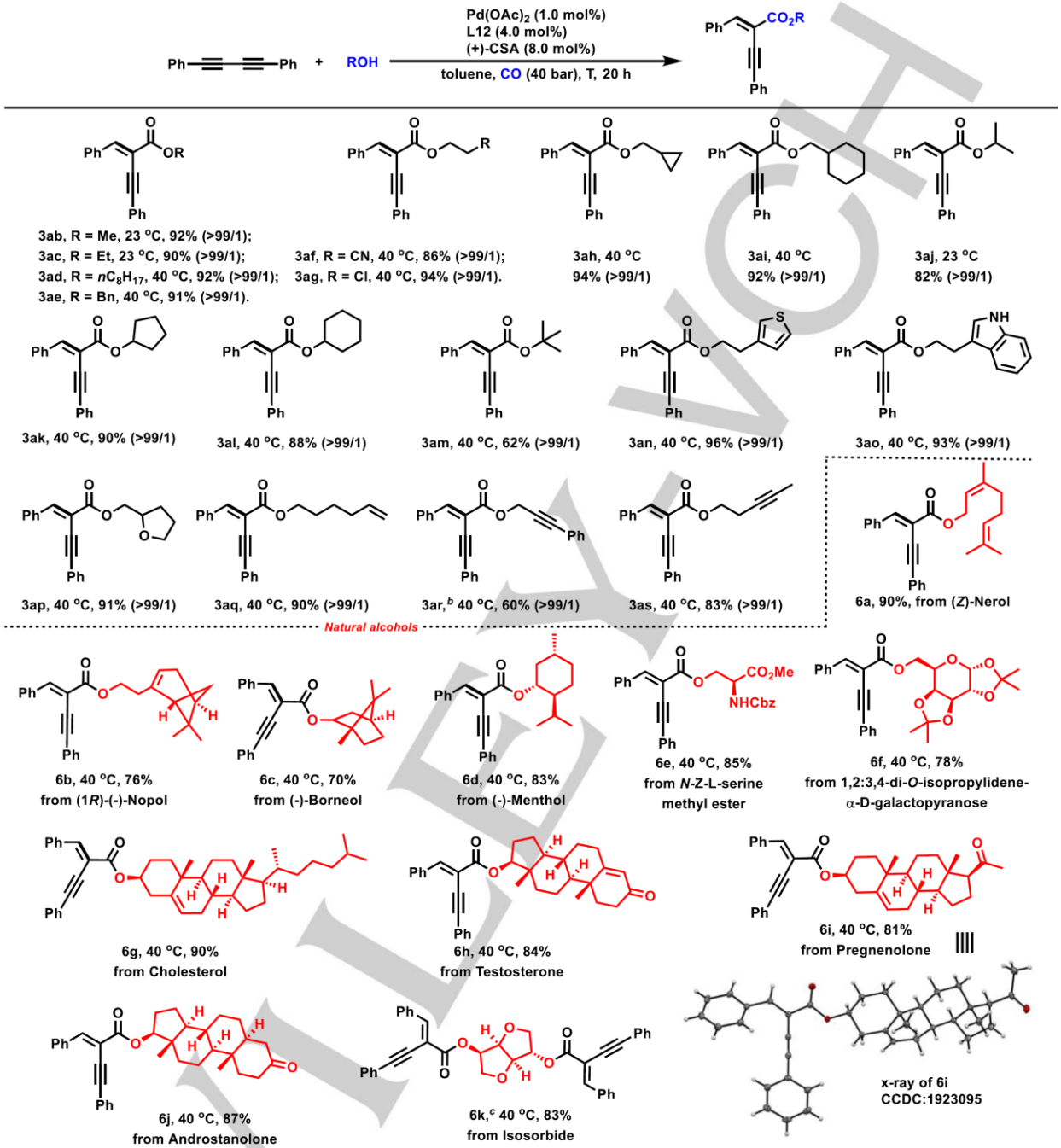
Table 2. Pd-catalyzed monocarbonylation of 1,3-diynes with *n*-butanol: Substrate scope [a]



[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*)-

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



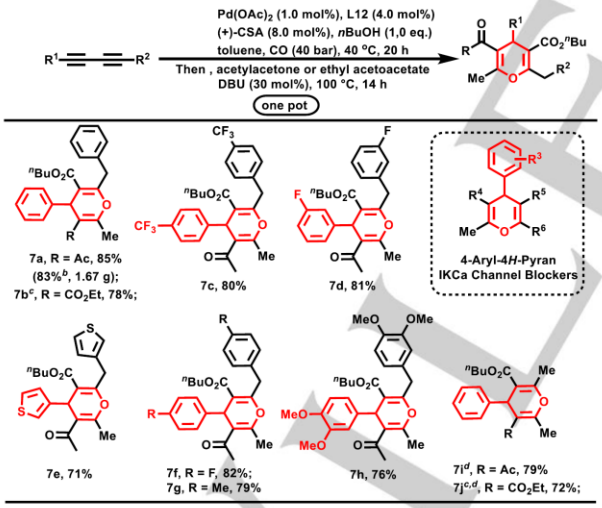
[a] Unless otherwise noted, all reactions were performed under 40 atm CO for 20 h in the presence of **1a** (0.25 mmol), alcohols (0.375 mmol), $Pd(OAc)_2$ (1.0 mol%, 0.56 mg), **L12** (4.0 mol%, 5.84 mg), (+)-CSA (8.0 mol%, 4.6 mg) in toluene (1.0 mL) at specified temperature. The yields were isolated 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

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.

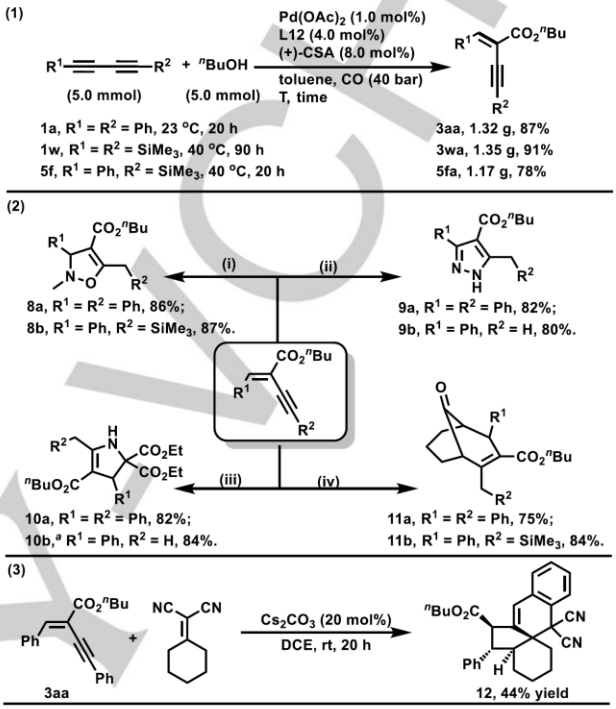
To demonstrate exemplarily the usefulness of the resulting products as intermediates in organic synthesis, we performed the effective synthesis of several 4-phenyl-4*H*-pyrans **7a**-**7j** in 71-85% yield directly from different (non)symmetrical1,3-diynes (Table 4). This novel one-pot process includes 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

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.

Acknowledgements

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

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09/2017-Present	**Doctoral research experiences** **1** Direct synthesis of adipic acid esters via palladium-catalyzed carbonylation of 1,3-dienes **2** Exploration of palladium-catalyzed aerobic oxidative carbonylation of alkynes with amines

	3 Exploration of platinum-catalyzed alkoxycarbonylation of olefins
	4 Selectively synthesis of adipic acid from allyl alcohol by palladium-catalyzed carbonylation
08/2014-06/2017	**Master research experiences**
	5 Ligand controlled cobalt catalyzed regiodivergent 1,2-hydroboration of 1,3-dienes
	6 Cobalt-catalyzed alkyne hydrosilylation and sequential vinylsilane hydroboration with markovnikov selectivity

List of Publications

1. **Yang, J**.; Liu, J. (co-first author); Neumann, H.; Franke, R.; Jackstell, R.; Beller, M., Direct synthesis of adipic acid esters via palladium-catalyzed carbonylation of 1,3-dienes. *Science* **2019,** *366,* 1514-1517.
2. **Yang, J**.; Liu, J. (co-first author); Jackstell, R.; Beller, M., Palladium-catalyzed aerobic oxidative carbonylation of alkynes with amines: a general access to substituted maleimides. *Chem. Commun.* **2018,** *54,* 10710-10713.
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4. Liu, J.; **Yang, J. (co-first author);**; Baumann, W.; Jackstell, R.; Beller, M., Stereoselective Synthesis of Highly Substituted Conjugated Dienes via Pd-Catalyzed Carbonylation of 1,3-Diynes. *Angew. Chem., Int. Ed.* **2019**, *58,* 10378.
5. Liu, J.; **Yang, J.;** Schneider, C.; Franke, R.; Jackstell, R.; Beller, M., Tailored Palladium Catalysts for Selective Synthesis of Conjugated Enynes via Monocarbonylation of 1,3-Diynes. *Angew. Chem., Int. Ed.* doi:10.1002/anie.201915386
6. Liu, J.; **Yang, J**.; Ferretti, F.; Jackstell, R.; Beller, M., Pd-Catalyzed Selective Carbonylation of gem-Difluoroalkenes: A Practical Synthesis of Difluoromethylated Esters. *Angew. Chem., Int. Ed.* **2019**, *58*, 4690-4694.
7. Peng, S.; **Yang, J. (co-first author)**; Liu, G.; Huang, Z., Ligand controlled cobalt catalyzed regiodivergent 1,2-hydroboration of 1,3-dienes. *Science China Chemistry* **2019**, 62, 336-340.
8. Zuo, Z.; **Yang, J**.; Huang, Z., Cobalt-Catalyzed Alkyne Hydrosilylation and Sequential Vinylsilane Hydroboration with Markovnikov Selectivity. *Angew. Chem., Int. Ed.* **2016**, *55,* 10839-10843.

Conference participations

[1] Poster "**Palladium-catalyzed aerobic oxidative carbonylation of alkynes with amines: a general access to substituted maleimides**"

Ji Yang, Jiawang Liu, Ralf Jackstella and Matthias Beller

at the Fifth International Conference, Catalysis of renewable resources: Fuel, energy, chemistry, Crete, Greece, September 2-6, 2019

Appendix

Supplementary Materials for

Direct synthesis of adipic acid esters via palladium-catalyzed carbonylation of 1,3-dienes

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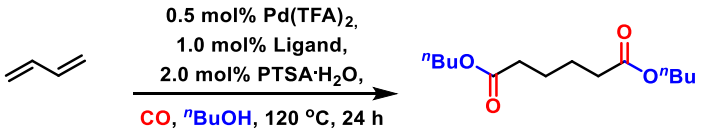
S1. General information: Materials and methods

All commercial reagents were ordered from Aldrich, TCI, Alfa, Fluka, Acros, ABCR, Fluorochem and Strem. Unless otherwise stated, commercial reagents were used without purification. Air- and moisture-sensitive syntheses were performed under argon atmosphere in heating gun vacuum dried glassware. In some experiments, we used the solution of butadiene in toluene. It is necessary to test the concentration before use, quantitative internal standard can be added, and then determining the concentration of butadiene by ^{1}H NMR. Abbreviations for some commonly used chemicals are as follows: $Pd(TFA)_2$, Palladium(II) trifluoroacetate; $PTSA{\cdot}H_2O$, *p*-toluenesulfonic acid monohydrate. Analytical data of literature known compounds were in accordance with reported data. NMR spectra were recorded on Bruker Avance 300 (300 MHz) or 400 (400 MHz) NMR spectrometers. Chemical shifts δ (ppm) are given relative to solvent: references for $CDCl_3$ were 7.26 ppm (^{1}H NMR) and 77.16 ppm (^{13}C NMR), for CD_2Cl_2 were 5.32 ppm (^{1}H NMR) and 53.84 ppm (^{13}C NMR), for d_6-benzene were 7.16 ppm (^{1}H NMR) and 128.26 ppm (^{13}C NMR), and for d_8-toluene were 2.08 ppm (^{1}H NMR) and 20.43 ppm (^{13}C NMR). Signals were assigned as s (singlet), d (doublet), t (triplet), dd (doublet of doublet), m (multiplet) and br. s (broad singlet). All measurements were carried out at room temperature unless otherwise stated. Electron impact (EI) mass spectra were recorded on AMD 402 mass spectrometer (70 eV). High resolution mass spectra (HRMS) were recorded on Agilent 6210 Time-of-Flight LC/MS (Agilent) with electrospray ionization (ESI). The data are given as mass units per charge (m/z) and intensities of signals are given in brackets. For GC analyses, HP 6890 chromatograph with a 29 m HP5 column was used.

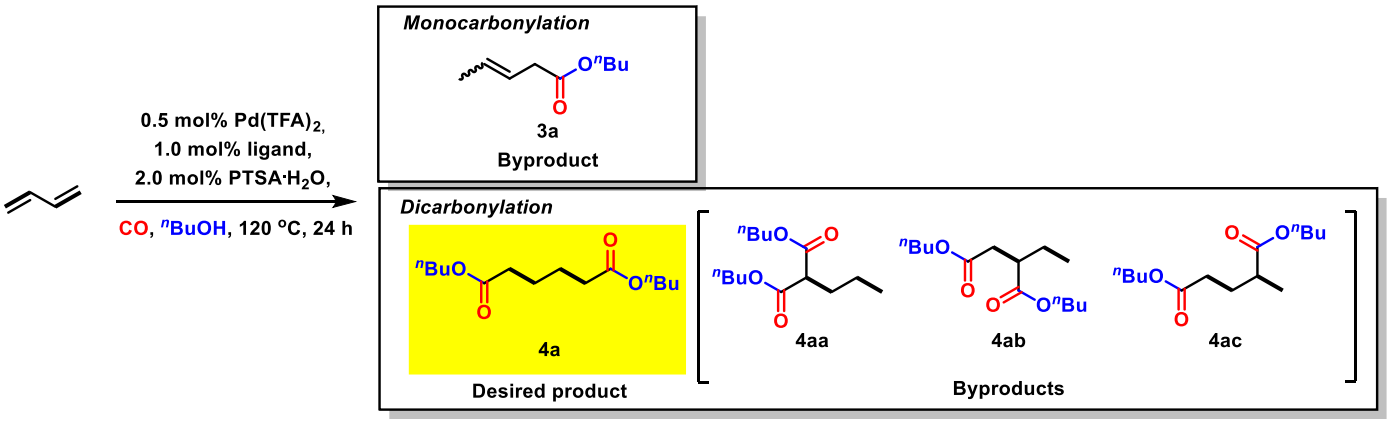
S2. General procedure of dicarbonylation of 1,3-butadiene

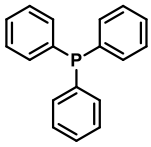


In contrast to the shown mechanism, in general in all catalytic experiments an excess of ligand was used to ensure stability of the active complex at low metal concentration. A 4 mL screw-cap vial was charged with palladium salt (0.5 mol% in terms of Pd atom), ligand (1.0 mol%), acid (2.0 mol% in terms of H atom) and an oven-dried stirring bar. The vial was closed by PTFE/white rubber septum (Wheaton 13 mm Septa) and phenolic cap, then connected with a needle to the atmosphere, the vial was evacuated under vacuum and recharged with argon for three times. After ^{n}BuOH (2.0 mL) was injected by syringe; a quantitative solution of butadiene is added to the reaction vial, the vial was fixed in an alloy plate and put into Paar 4560 series autoclave (300 mL) under argon atmosphere. At room temperature, the autoclave is flushed with carbon monoxide for three times and then carbon monoxide was charged to 40 bar. The reaction was heated under specified temperature for 24 hours. Afterwards, the autoclave was cooled to room temperature and the pressure was carefully released. Mesitylene (0.5 mmol) was added into the reaction as internal standard. A sample of the mixture was analyzed by gas chromatography. Pure product is obtained by column chromatography on silica gel (eluent: pentane/ethyl acetate = 40:1).

S3. Ligands screening and new ligand design

S3.1. Ligands screening





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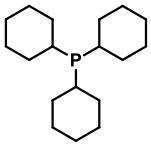

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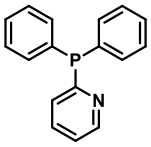

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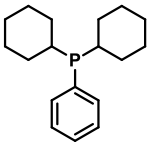

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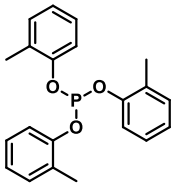

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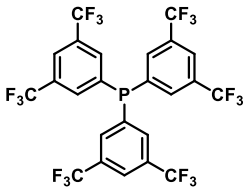

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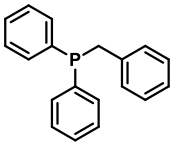
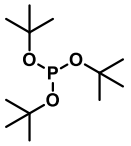
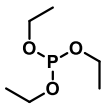


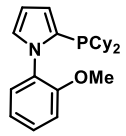
Yield (3) = 0
Yield (4) = 0



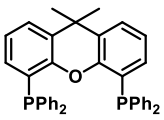
Yield (3) = 0
Yield (4) = 0



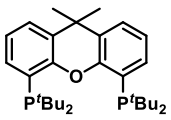
Yield (3) = 0
Yield (4) = 0



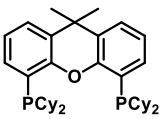
Yield (3) = 0
Yield (4) = 0



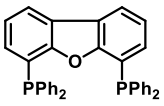
Yield (3) = 49%
Yield (4) = 25% (79/21)



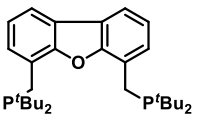
Yield (3) = 0
Yield (4) = 0



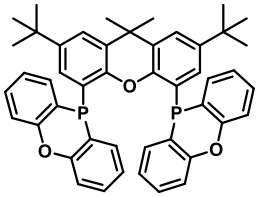
Yield (3) = 0
Yield (4) = 0



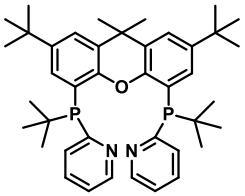
Yield (3) = 15%
Yield (4) = 0



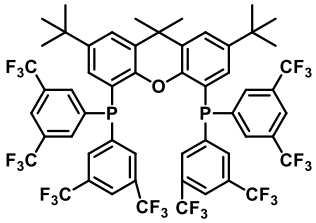
Yield (3) = 72%
Yield (4) = 4% (80/20)



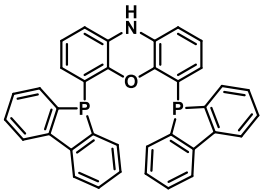
Yield (3) = 0
Yield (4) = 16% (79/21)



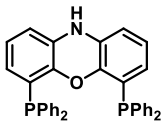
Yield (3) = 9%
Yield (4) = 0



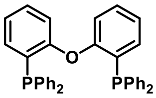
Yield (3) = 5%
Yield (4) = 31% (79/21)



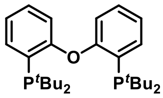
Yield (3) = 70%
Yield (4) = 0



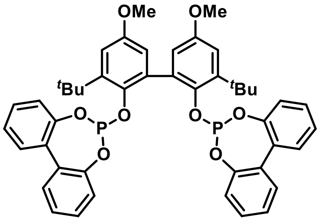
Yield (3) = 16%
Yield (4) = 0



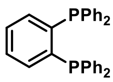
Yield (3) = 15%
Yield (4) = 0



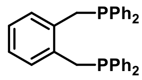
Yield (3) = 21%
Yield (4) = 0



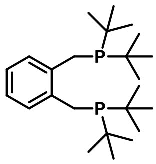
Yield (3) = 30%
Yield (4) = 0



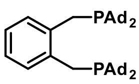
Yield (3) = 0
Yield (4) = 0



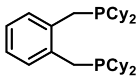
Yield (3) = 0
Yield (4) = 0



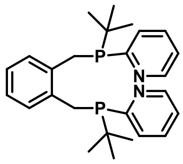
Yield (3) = 60%
Yield (4) = 18% (97/3)



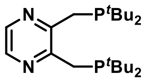
Yield (3) = 63%
Yield (4) = 13% (95/5)



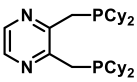
Yield (3) = 0
Yield (4) = 0



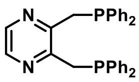
Yield (3) = 7%
Yield (4) = 77% (48/52)



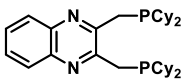
Yield (3) = 0
Yield (4) = 0



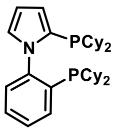
Yield (3) = 0
Yield (4) = 0



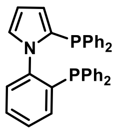
Yield (3) = 0
Yield (4) = 0



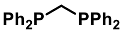
Yield (3) = 0
Yield (4) = 0



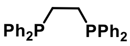
Yield (3) = 0
Yield (4) = 0



Yield (3) = 0
Yield (4) = 0

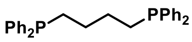


Yield (3) = 0
Yield (4) = 0

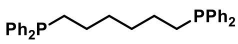


Yield (3) = 0
Yield (4) = 0

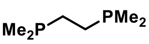
Yield (3) = 0
Yield (4) = 0



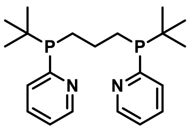
Yield (3) = 0
Yield (4) = 0



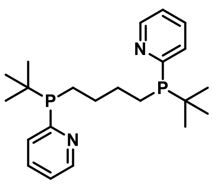
Yield (3) = 0
Yield (4) = 0



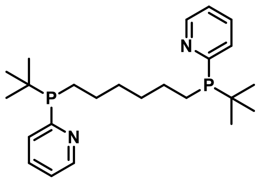
Yield (3) = 0
Yield (4) = 0



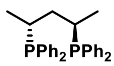
Yield (3) = 0
Yield (4) = 18% (72/28)



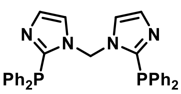
Yield (3) = 20%
Yield (4) = 0



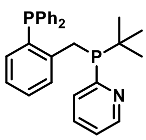
Yield (3) = 34%
Yield (4) = 5% (51/49)



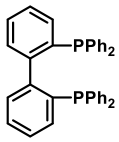
Yield (3) = 0
Yield (4) = 0



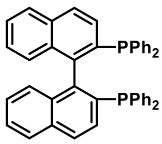
Yield (3) = 0
Yield (4) = 0



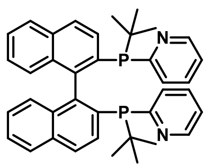
Yield (3) = 0
Yield (4) = 0



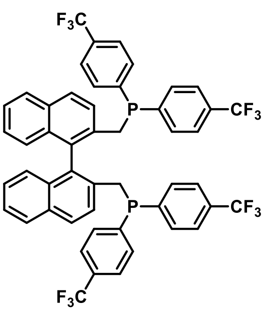
Yield (3) = 0
Yield (4) = 0



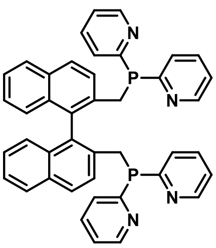
Yield (3) = 0
Yield (4) = 0



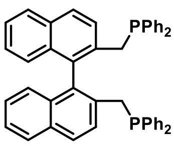
Yield (3) = 17%
Yield (4) = 0



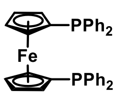
Yield (3) = 84%
Yield (4) = 0



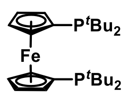
Yield (3) = 72%
Yield (4) = 0



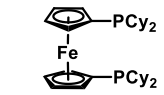
Yield (3) = 24%
Yield (4) = 0



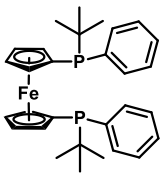
Yield (3) = 0
Yield (4) = 0



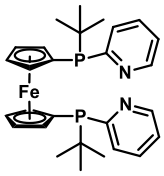
Yield (3) = 41%
Yield (4) = 0



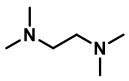
Yield (3) = 0
Yield (4) = 0



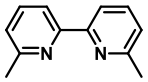
Yield (3) = 0
Yield (4) = 0



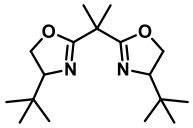
Yield (3) = 0
Yield (4) = 0



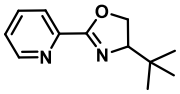
Yield (3) = 0
Yield (4) = 0



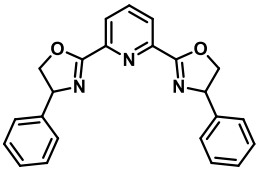
Yield (3) = 0
Yield (4) = 0



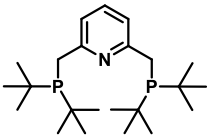
Yield (3) = 0
Yield (4) = 0



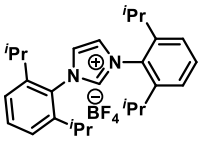
Yield (3) = 0
Yield (4) = 0



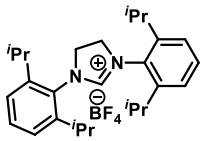
Yield (3) = 0
Yield (4) = 0



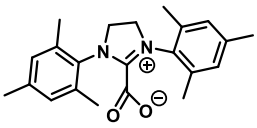
Yield (3) = 0
Yield (4) = 0



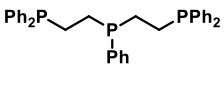
Yield (3) = 0
Yield (4) = 0



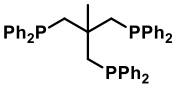
Yield (3) = 0
Yield (4) = 0



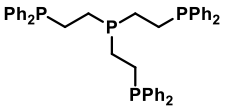
Yield (3) = 0
Yield (4) = 0



Yield (3) = 0
Yield (4) = 0



Yield (3) = 0
Yield (4) = 0

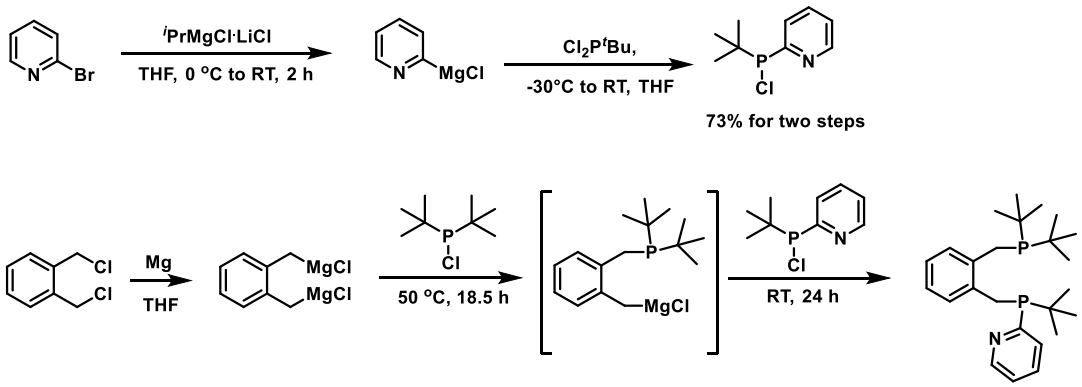


Yield (3) = 0
Yield (4) = 0

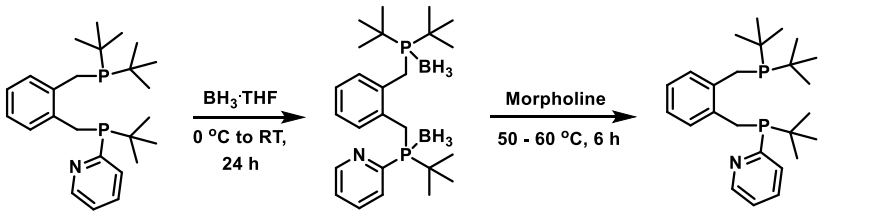
Table S1. Ligands screening. Reaction conditions: Butadiene (1.0 mmol, solution in toluene), $Pd(TFA)_2$ (0.005 mmol, 0.5 mol%), ligand (0.01 mmol, 1 mol%), $PTSA{\cdot}H_2O$ (2 mol%), ^{n}BuOH (2.0 mL), CO (40 atm), 120 °C, 24 h. The ratio of products and yields were determined by GC analysis with mesitylene as internal standard. The products selectivity is the ratio of linear diesters **4a** to branched diesters **4aa, 4ab, 4ac**.

S3.2. Synthetic route of HeMaRaphos

The new ligand HeMaRaphos was synthesized according to following procedure:



A mixture of several phosphines is obtained, followed by separation and purification:

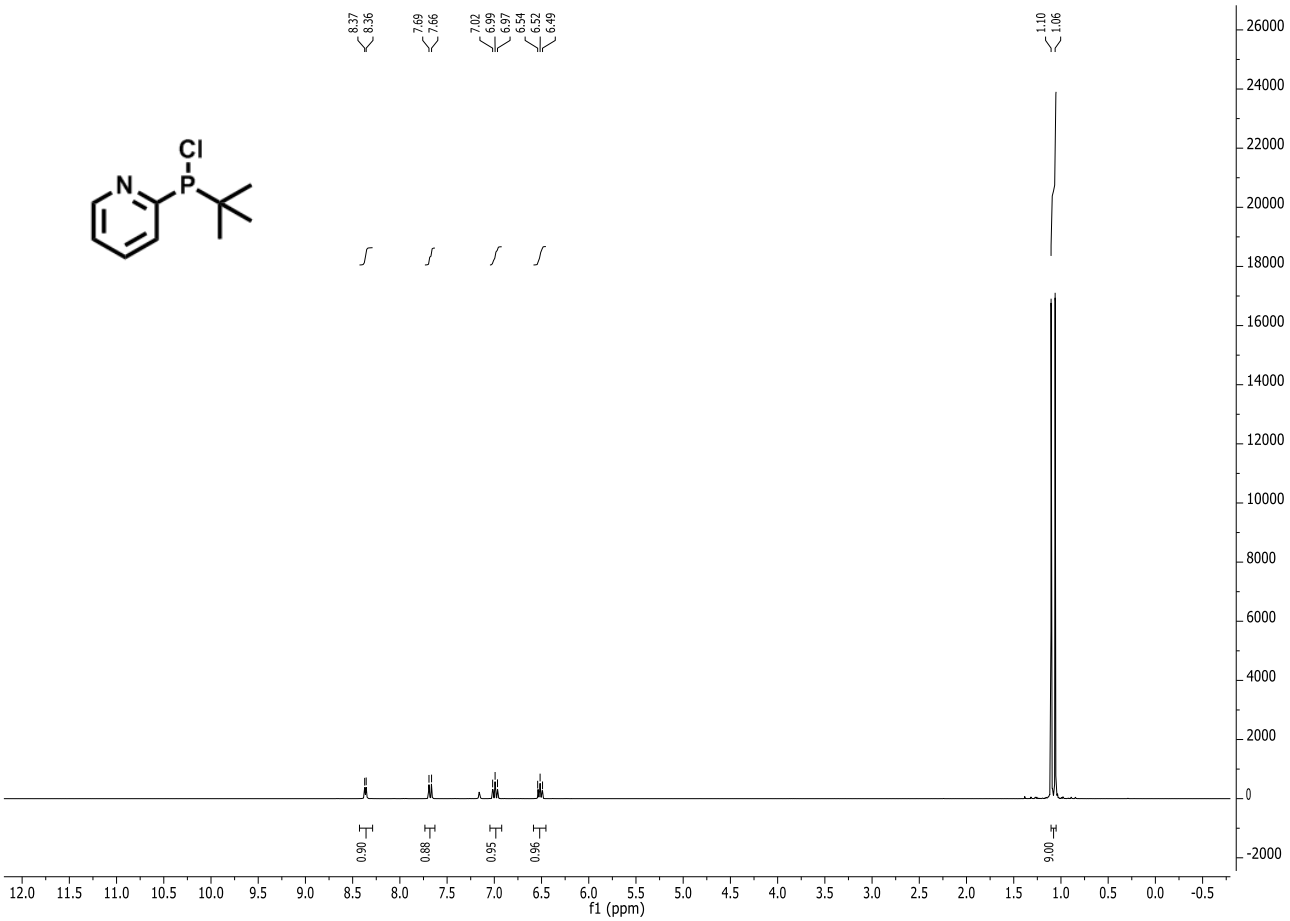


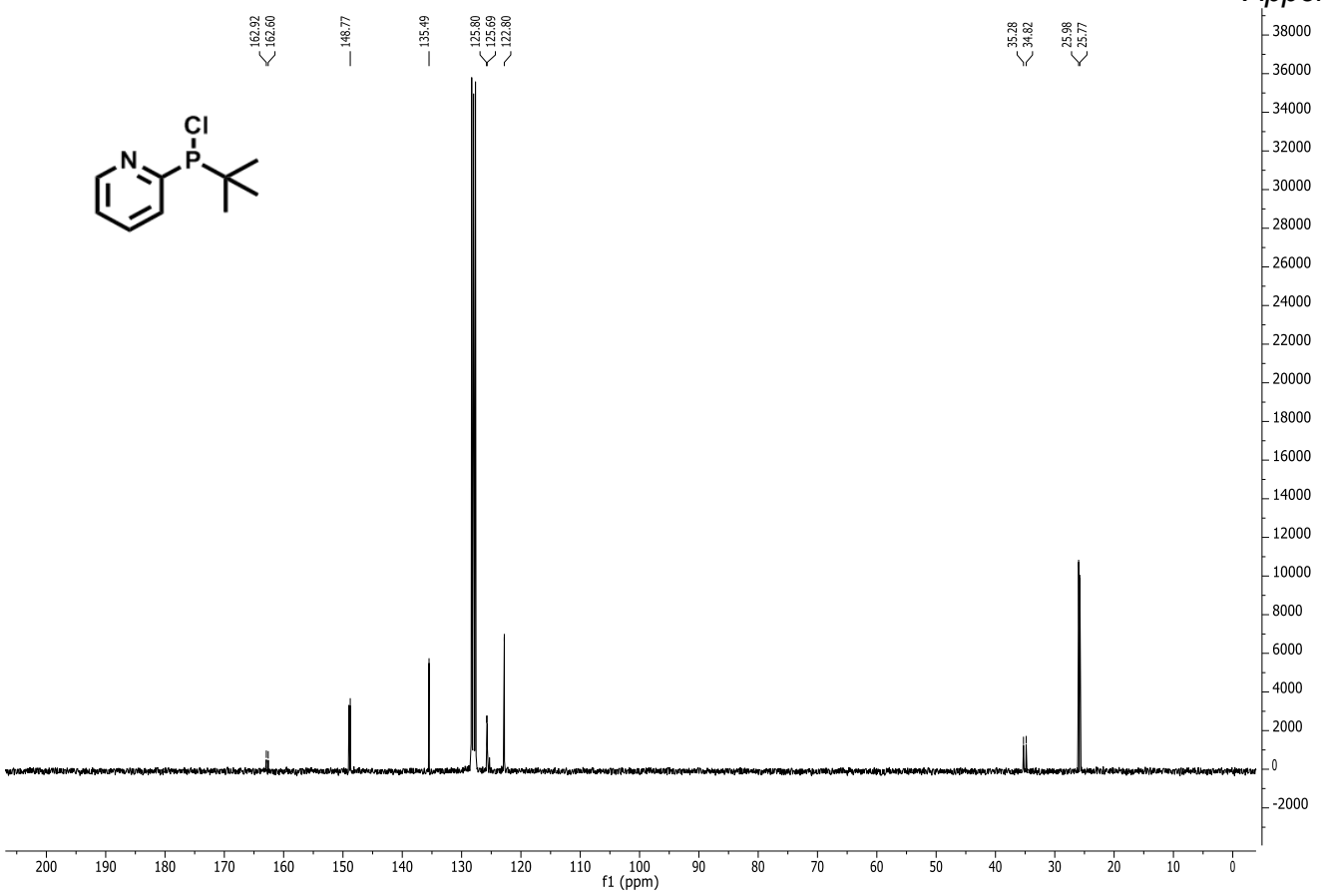
Synthesis of 2-(tert-butylchlorophosphanyl)pyridine:

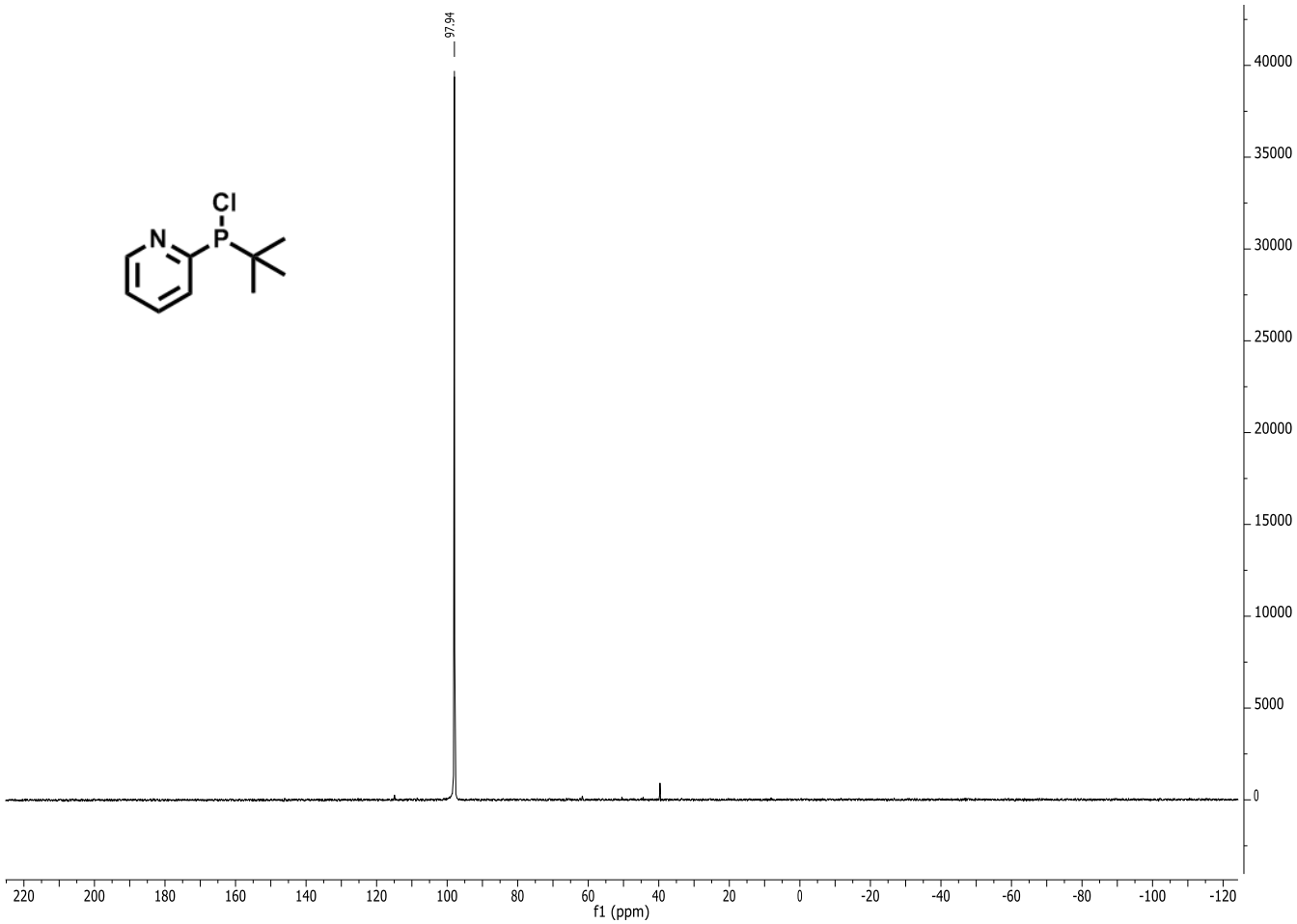
In a 2L one-neck round flask with septum, metal thermocouple and nitrogen valve, isopropylmagnesium-chloride lithiumchloride complex (800 ml, 1.3M, 1040 mmol) were given and cooled with dry ice/ethanol. Then, 2-bromopyridine (94.5 mL, 991 mmol) was dropped quickly to the solution stirred for 2 hours with cooling bath and then 2 hours at room temperature. The reaction mixture turns from yellow to a red black solution. Some additional THF was added to get a stirrable suspension. In a four-neck 4L round bottomed flask equipped with KPG-stirrer, thermocouple, nitrogen valve and septum, tert-butyldichlorophosphine solution (1090 mL, 1M, 1090 mmol) was added and cooled to about -40 °C with dry ice/ethanol. The Grignard solution was transferred in portions via a big Teflon hose to the stirred tert-butyldichlorophosphine solution. The reaction temperature shouldn't increase to more than -30 °C. the reaction was stirred overnight. Next the solvent was completely removed in high vacuum and a yellow solid was achieved. The solid was suspended in 1 L of heptane and crushed with a spatula. After stirring, the homogeneous suspension was filtered over a big fritted glass filter (diameter 10 cm) which connected to 4L three-neck round bottomed flask, the yellow precipitate was washed with 1L of heptane. Next, the heptane was removed in high vacuum and the remaining yellow liquid was transferred into a 250 mL round bottomed flask. Distillation of the crude product at 5 mbar and a transition temperature at 100 °C gave 145g (73%) of the slightly yellow 2-(*tert*-butylchloro-phosphanyl)pyridine.

^{1}H NMR (300 MHz, C_6D_6): δ 8.38-8.35 (m, 1H, Py), 7.69-7.65 (m, 1H, Py), 7.02-6.93 (m, 1H, Py), 6.55-6.46 (m, 1H, Py), 1.08 (d, J = 13.3 Hz, 9H, ^{t}Bu). **^{13}C NMR** (75 MHz, C_6D_6): δ 162.92, 162.60, 148.77, 135.49, 125.80, 125.69, 122.80,

35.28, 34.82, 25.98, 25.77. **^{31}P NMR** (121 MHz, C_6D_6) δ 97.9. **MS** (EI) *m*:*z* (relative intensity): 201 (M^+,2), 147(32), 145 (100), 109 (17), 78 (8), 57.1 (17).







Preparation of 1,2-bis (chloromagnesiomethyl) benzene:

In a 2 L round bottomed flask equipped with magnetic stirrer and nitrogen valve, magnesium powder (14.1 g, 580 mmol, 4eq) was heated at 90 °C for 45 minutes under high vacuum. After cooling to room temperature, 5 grains of iodine were added and dissolved in 60 mL of THF. The suspension was stirred for 30 minutes until the yellow color of iodine disappeared. Then, the THF solution was decanted and the activated magnesium powder was washed 6 times with 20 mL of THF. After fresh THF (250 mL) was added again, a solution of sublimated α,α'-dichloro-o-xylene (25.3 g, 144.4 mmol) dissolved in 1.2 L THF was slowly dropped via plastic hose at room temperature. The THF mixture turned slowly dark and stirred overnight. The unreacted magnesium powder was filtered off over a column with a Celite pad from the reaction mixture and a clear slightly yellow solution was achieved. Quantitative determination of the concentration of the Grignard solution: 1 mL Grignard solution was quenched with 2 mL of 0.1 M HCl and the excess acid was titrated with 0.1 M NaOH. Bromocresol purpur (0.04% in water) was used as an indicator (color change is from yellow to blue). The molarity of the solution was 0.09 M.

Synthesis of HeMaRaphos:

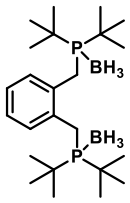
In a 1 L round bottomed flask with a nitrogen valve, metal thermocouple and oval stirrer, 1,2-bis(chloromagnesiomethyl) benzene (445 mL, 40 mmol, 0.09M) was added at room temperature. Then, di-*tert*-butylchlorophosphine (7.6 mL, 40 mmol) was dropped quickly via a syringe to the solution. The reaction mixture was warmed up at 50 °C for 18.5 h in an oil bath. The red-colored reaction solution was clear in the next day. Then, 2-Py^{t}BuPCl (8.4 mL, 40 mmol) was added to the reaction mixture at room temperature and the solution was warmed to 33 °C. The next day the solution turned to orange yellow. The solution was quenched with 8 mL degassed water and a white precipitate was formed. The solvent was removed under high vacuum and a yellow viscous residue was obtained. Then, the viscous solid was extracted with 60 mL water and 80 mL heptane. After quick phase separation, the lower aqueous phase was transferred to a 500mL round bottomed flask under argon. The organic phase was transferred into a 1 L round bottomed flask containing 8 large spoons of Na_2SO_4. The aqueous phase was washed twice with 40 mL heptane and the organic phase was also transferred to the 1 L flask with Na_2SO_4. With the cannula method, the organic phase was filtered in a 1 L round bottomed flask and washed twice with 30 mL of heptane. The heptane was removed in a high vacuum and 18.3 g of a clear viscous and yellow residue was obtained.

Protecting the crude phoshine mixture as a borane adduct is necessary for separation of the different products. After adding 160 mL THF to 18.3 g of the residue, the solution was cooled with ice and a clear solution was achieved. Then, $BH_3 \cdot$THF complex (80 mL, 80 mmol, 1M) was added rapidly. The mixture was stirred for one hour at 0 °C and then at room temperature overnight. Next, the product was separated by column chromatography. 20 large spoons (one spoon weighed about 2g) of silica gel to the borane-protected phosphine solution was added. The suspension was dried by evaporation and the remaining yellow powder was further purified by column chromatography under argon using one liter of eluent (1:20 ethyl acetate / heptane). Then, chromatography was continued with the a 1:10 ethyl acetate / heptane mixture as eluent (2 L). After that three different ligands were obtained.

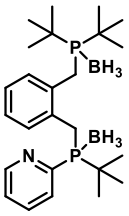
Ligand I: 2.95 g Bupox·BH_3, 18% yield, white solid.

Ligand II: 4.4 g HeMaRaphos·BH_3, 25% yield, yellow solid.

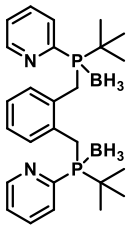
Ligand III: 1.54 g 2-PyBupox·BH_3, 8% yield, yellow solid.



Ligand I
2.95 g,
yield=18%



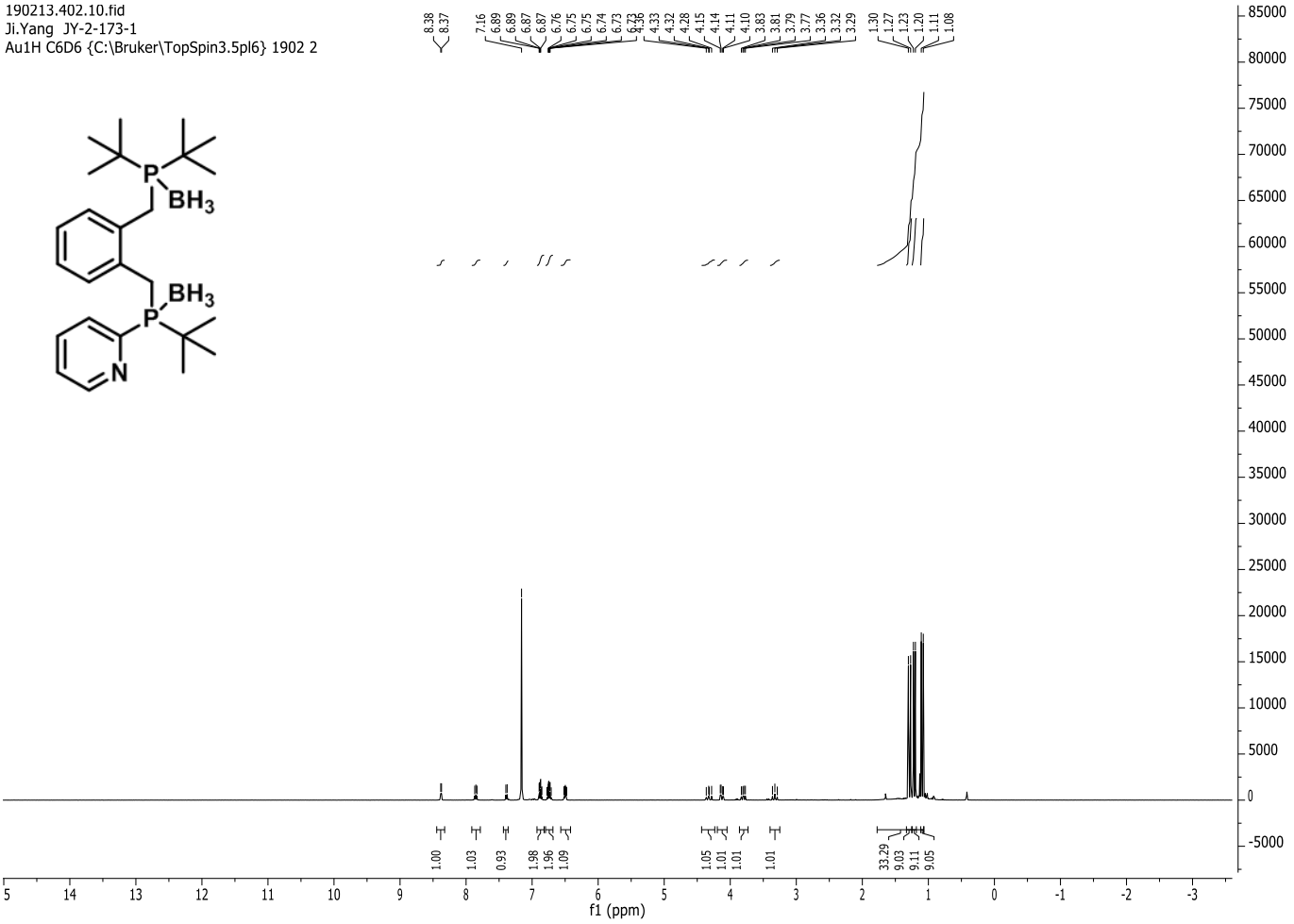
Ligand II
4.4 g,
yield=25%

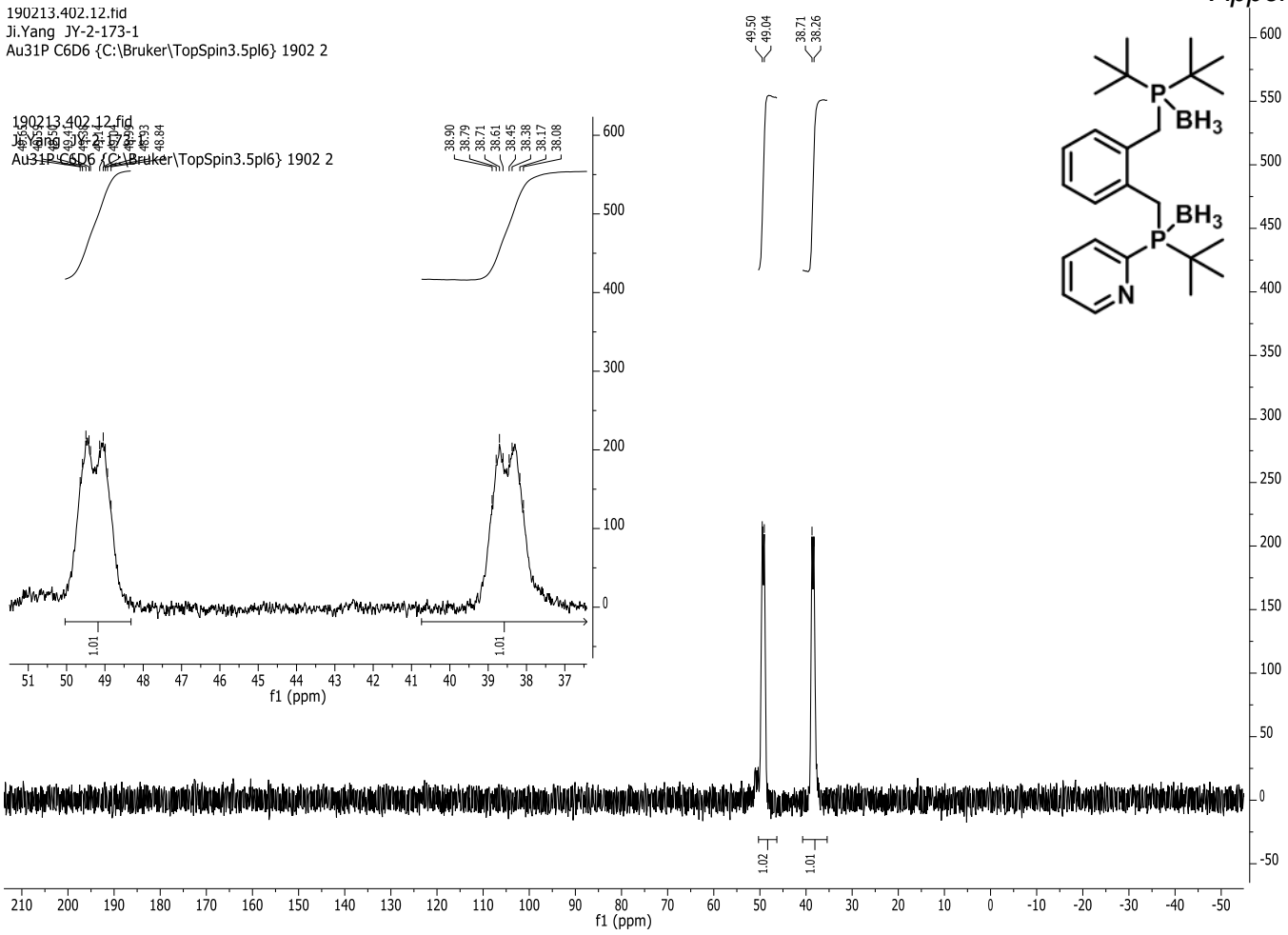


Ligand III
1.54 g,
yield=8%

Ligand II, HeMaRaphos-BH_3 complex:

^{1}H NMR (400 MHz, C_6D_6) δ 8.38 (d, *J* = 4.7 Hz, 1H), 7.91-7.78 (m, 1H), 7.39 (d, J = 7.8 Hz, 1H), 6.90-6.85 (m, 2H, py), 6.80-6.70 (m, 2H), 6.53-6.45 (m, 1H), 4.38-4.26 (m, 1H), 4.13 (dd, J = 14.4, 4.8 Hz, 1H), 3.80 (dd, J = 15.0, 9.3 Hz, 1H), 3.32 (t, J = 14.4 Hz, 1H), 1.29 (d, J = 13.5 Hz, 9H), 1.21 (d, J = 12.0 Hz, 9H), 1.09 (d, J = 12.3 Hz, 9H). 1.78-1.05 (broad, 6H, BH_3). **^{31}P NMR** (161 MHz, C_6D_6): δ 49.65-48.85 (broad), 39.10-37.77 (broad).




190213.402.12.fid
Ji.Yang JY-2-173-1
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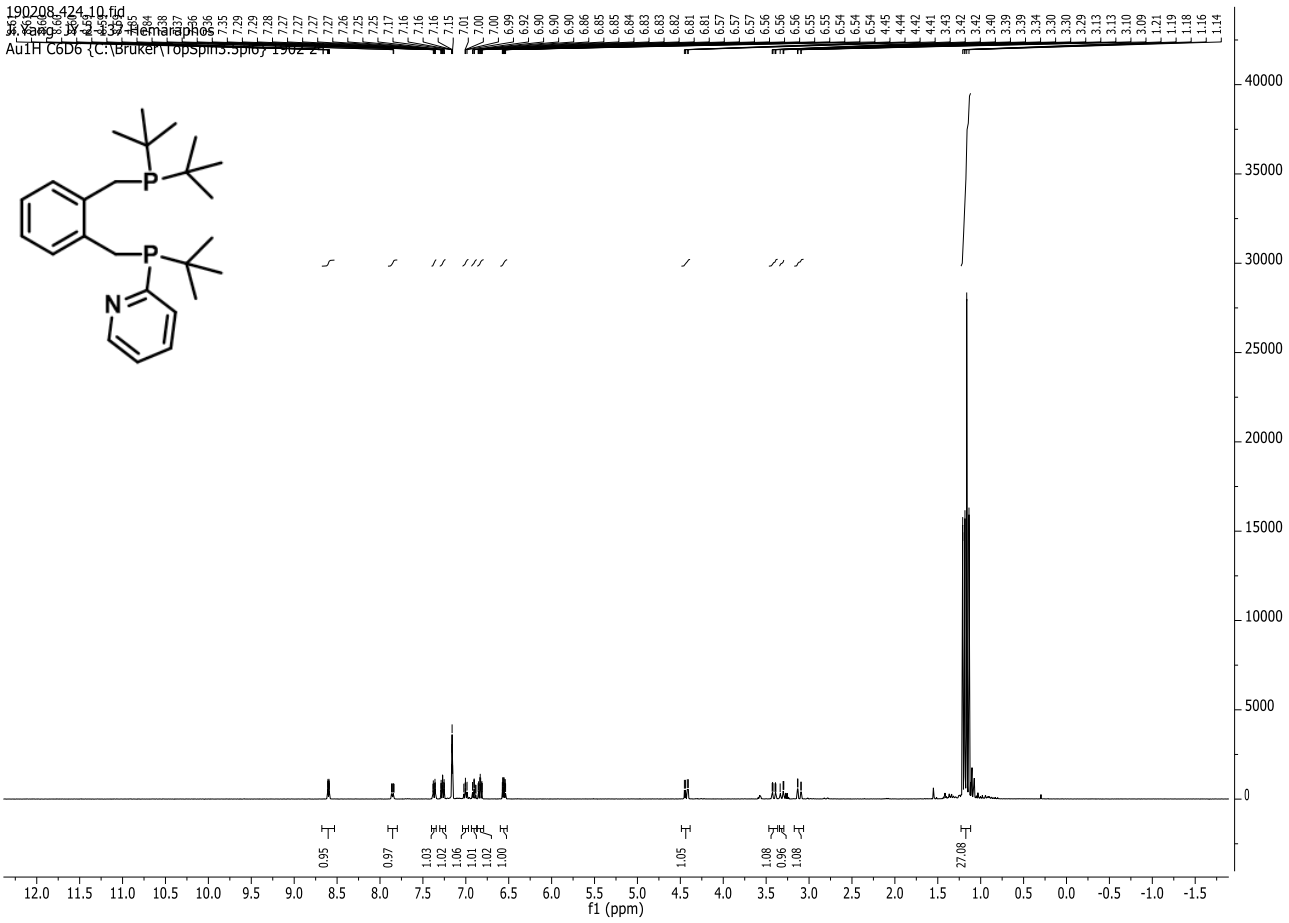
49.50
49.04
38.71
38.26
BH3
BH3
P
P
N
f1 (ppm)
1.02
1.01

Ligand deprotection:

The borane-protected unsymmetrical HeMaRaphos ligand was deprotected as follows: 3.9 g of HeMaRaphos·BH_3 adduct were transferred into a 250 mL flask with an argon valve closed by a septum. Then, 34 mL of morpholine (dried over CaH_2 and frozen out) was added and the suspension was warmed up at 50 °C over-night. Next day, a clear solution was achieved and the morpholine was removed in the vacuum. The sticky white residue was chromatographied over a column (6 cm diameter and 10.5 cm filling height of silica) with an eluent 2:1 (heptane/ethylacetate). After removing the solvent in high vacuum, 3.55 g of HeMaRaphos was obtained as a sticky colorless oil, which crystallized after some days.

^{1}H NMR (400 MHz, C_6D_6) δ 8.62-8.58(dm, J = 4.8 Hz, 1H), 7.88-7.82 (m, 1H), 7.40-7.34 (m, 1H), 7.30-7.24(tm, J = 6.2 Hz, 1H), 7.00-6.97 (m, 1H), 6.93-6.87 (m, 1H), 6.86-6.80 (tm, J = 7.7 Hz, 1H), 6.58-6.52 (m, 1H), 4.43 (dd, J = 13.5, 4.8 Hz, 1H), 3.45-3.40 (m, 1H, CH_2), 3.35-3.29 (dm, J = 13.3 Hz, 1H, CH_2), 3.14-3.05 (m, 1H, CH_2), 1.23-1.12 (m, 27H, ^{t}Bu). **^{31}P NMR** (161 MHz, C_6D_6): δ 23.50, 9.15. **HRMS** (ESI): Calcd. for $C_{25}H_{40}NP_2[M+H]^+$. 416.2636, Found:416.2636 $[M+H]^+$. **Elemental Analysis:** calcd for $C_{25}H_{39}NP_2$, C, 72.26; H, 9.46; N, 3.37; P, 14.91. Found: C, 72.48; H, 9.71; N, 3.34; P,14.72.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P
P
N
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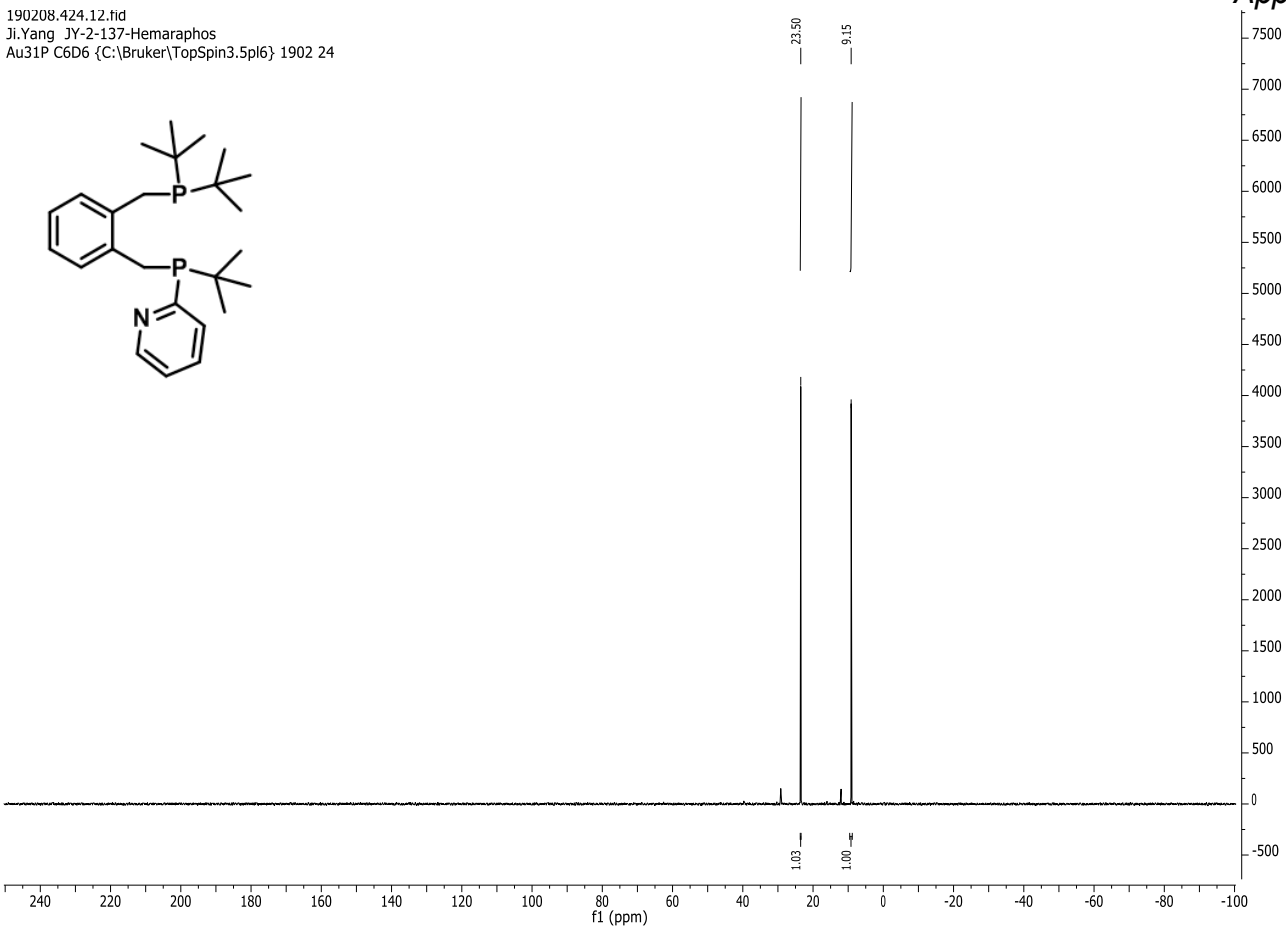
35000
30000
25000
20000
15000
10000
5000
0
0.95
0.97
1.03
1.02
1.06
1.01
1.02
1.00
1.05
1.08
0.96
1.08
27.08
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5
f1 (ppm)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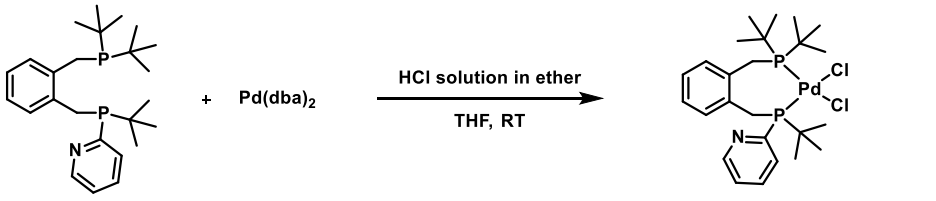
Ji.Yang JY-2-137-Hemaraphos
Au31P C6D6 {C:\Bruker\TopSpin3.5pl6} 1902 24
23.50
9.15
1.03
1.00
f1 (ppm)

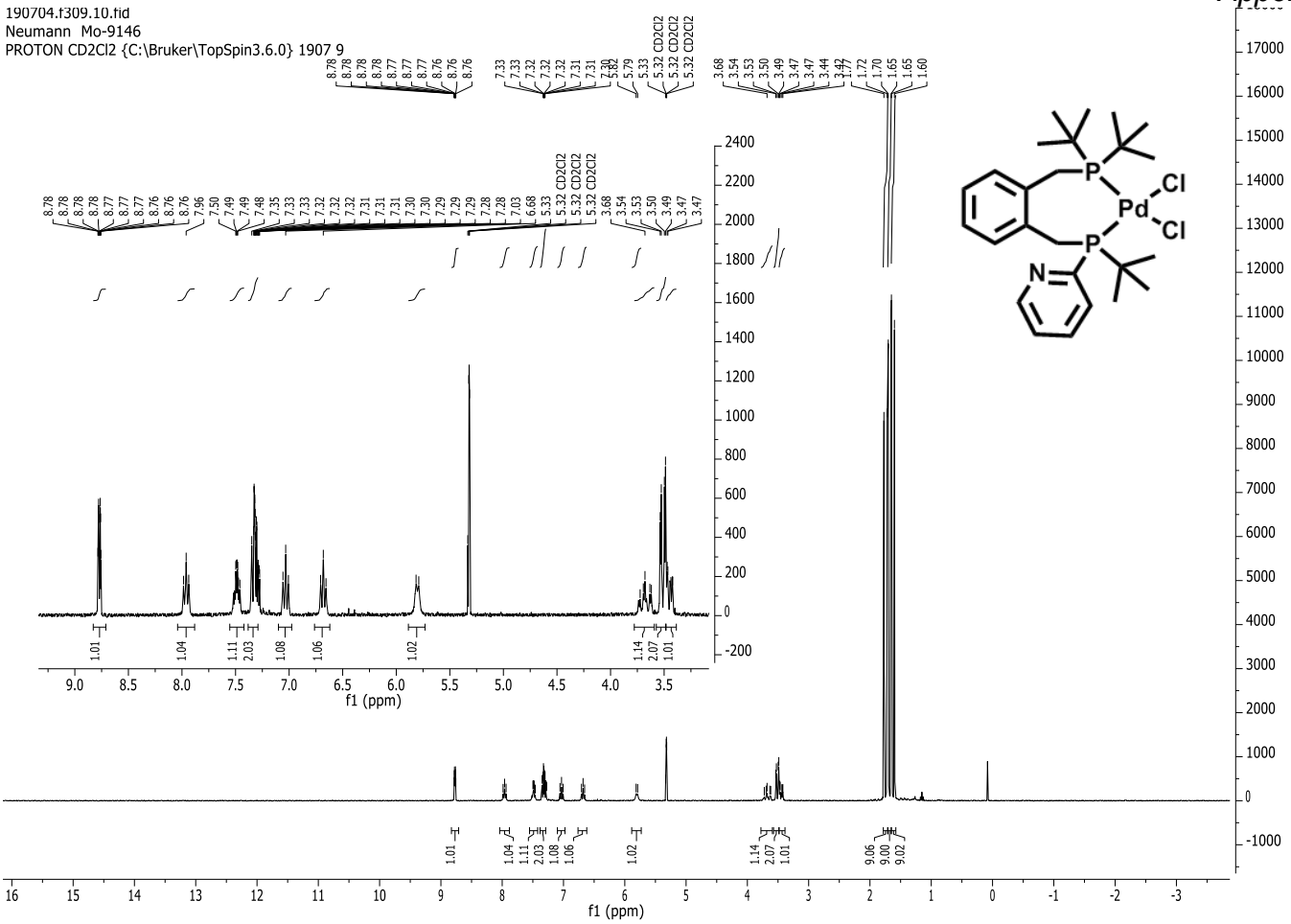
Synthesis of $PdCl_2$-HeMaRaphos complex:



Bright yellow crystal
Chemical Formula: $C_{25}H_{39}Cl_2NP_2Pd$
Exact Mass: 591,0970
Molecular Weight: 592,8615

Mixing HeMaRaphos and bis (acetonitrile) dichloro-palladium(II) complex in toluene did not result in crystals suitable for X-ray crystallography. Therefore, we developed an alternative synthesis method: In a glovebox HeMaRaphos (100 mg, 0.24 mmol) was weighed into a 25 mL round bottomed flask, which was closed with a septum. After discharging, 6 mL of THF was added and the white solid was completely dissolved. To this clear solution $Pd(dba)_2$ (138 mg, 0.24 mmol) was added. It formed a brownish orange solution, which was stirred for 2 days at room temperature. The solution was filtered using the cannula method and the residue was then washed with 2 ml of THF. The THF solution is brought to dryness in high vacuum. The yellow-brown residue was then taken up in 4 mL of ether and a dark yellow clear solution was formed. Then, HCl (200µL, 2M) solution in ether was added (the HCl solution was gently evacuated beforehand and placed in the ultrasonic bath for 10 minutes to remove the oxygen.) and an orange-red solid precipitated. Gradually, the red solid transformed into a muddy green easily stirrable suspension. The mixture was filtered using the cannula method and the precipitate was washed 3 times with 5 mL of ether each time and once with THF. After adding of 5 mL of CH_2Cl_2, the solution became green with a gray precipitate. A 5mL syringe with syringe filter (13mm syringe filter 0.2µL PTFE membrane) gave a yellow solution, which was transferred to a 25 mL round bottomed flask. The solution is concentrated and a light yellow solid was precipitated, which is placed in the refrigerator overnight. The supernatant solution is decanted and after drying 44.3 mg (31%) of a yellow solid was obtained.

^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.77 (d, quin, J = 4.7Hz, J = 0.9Hz, 1H), 7.96 (t, J = 7.1Hz, 1H), 7.48 (m, 1H) , 7.36-7.26 (m, 2H), 7.03 (t, J = 7.7Hz, 1H, benzene), 6.68 (t, J = 7.7Hz, 1H, benzene), 5.80 (m, 1H, benzene), 3.68 (m, 1H, CH_2), 3.56-4.40 (m, 3H, CH_2), 1.75 (d, J = 15.8Hz, 9H, ^{t}Bu), 1.67 (d, J = 15.6Hz, 9H, ^{t}Bu), 1.62 (d, J = 15.7 Hz, 9H, ^{t}Bu). **^{31}P NMR** (121 MHz, CD_2Cl_2): δ 44.82 (d, J = 8.2 Hz), 32.43 (d, J = 7.3 Hz). **Elemental Analysis**: calcd for $C_{25}H_{39}Cl_2NP_2Pd$, C, 50.65; H, 6.63; Cl, 11.96; N, 2.36; P, 10.45; Pd, 17.95. Found: C, 51.00; H, 6.15; Cl, 11.48; N, 2.29; P,10.42; Pd,17.92. **HRMS** (ESI) m/z$^+$calcd for $C_{25}H_{39}NP_2ClPd$ $(M\text{-}Cl)^+$ 556.1281; found 556.1292.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f1 (ppm)
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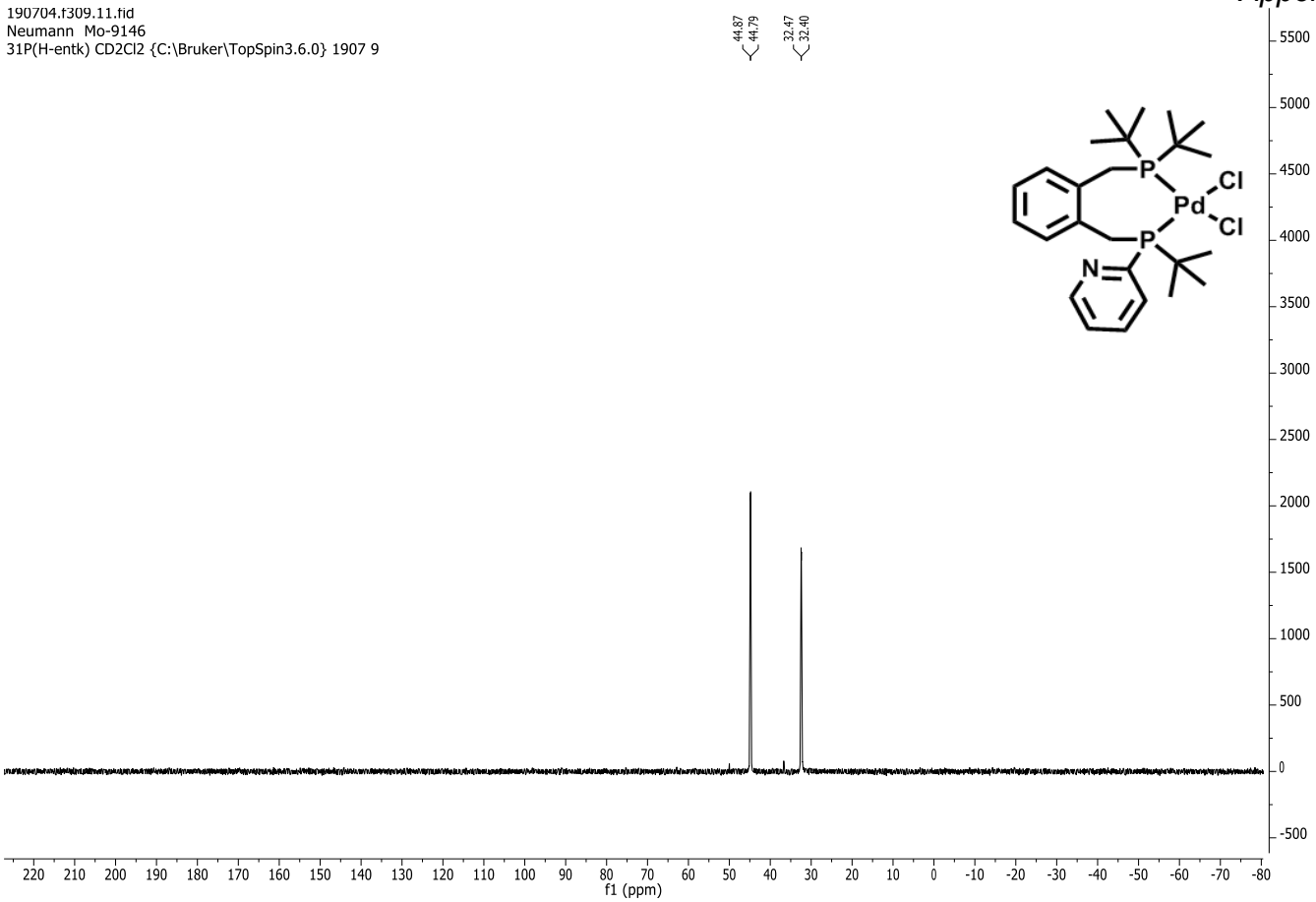
Pd
Cl
P
P
N


190704.f309.11.fid
Neumann Mo-9146
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44.79
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32.40
P
Pd
Cl
Cl
P
N
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80
f1 (ppm)

X-ray crystal structure analysis of $PdCl_2$-HeMaRaphos complex:

Data were collected on a Bruker Kappa APEX II Duo diffractometer. The structure was solved by direct methods (SHELXS-97: Sheldrick, G. M. Acta Cryst. 2008, A64, 112.) and refined by full-matrix least-squares procedures on F2 (SHELXL-2014: Sheldrick, G. M. Acta Cryst. 2015, C71, 3.). XP (Bruker AXS) was used for graphical representations.

Crystal data of ***$PdCl_2$-HeMaRaphos complex***: $C_{25}H_{39}Cl_2NP_2Pd$, M = 592.81, triclinic, space group P_1, a = 7.6882(2), b = 8.8061(2), c = 19.9191(5) Å, α = 85.0106(12), β = 89.4161(13), γ = 83.1184(13)°, V = 1333.80(6) Å^3, T = 150(2) K, Z = 2, 16530 reflections measured, 4698 independent reflections (R_{int} = 0.0432), final R values ($I > 2\sigma(I)$): R_1 = 0.0436, wR_2 = 0.1147, final R values (all data): R_1 = 0.0463, wR_2 = 0.1163, 289 parameters.
CCDC 1941490 contains the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

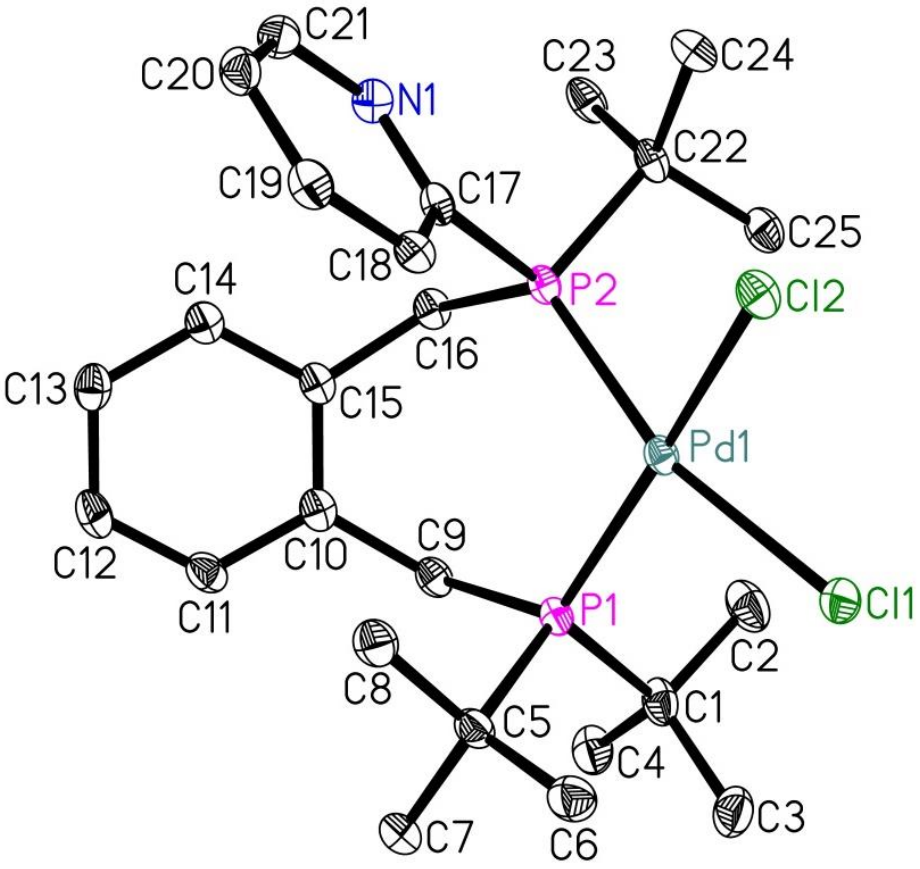
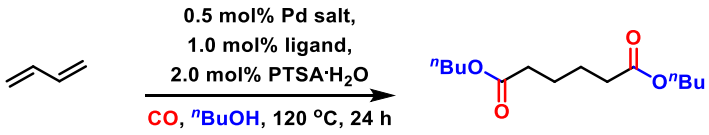


Figure S1. X-ray structures: $PdCl_2$-HeMaRaphos complex.

Molecular structure of $PdCl_2$-HeMaRaphos complex in the crystal with the atom labelling and displacement ellipsoids drawn at the 30% probability level. Hydrogen atoms are omitted for clarity.

S4. Optimization of reaction conditions

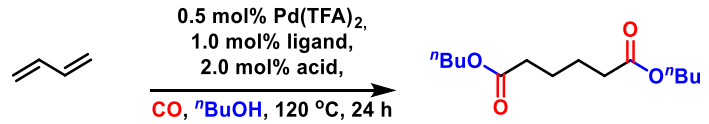
S4.1. The effect of palladium precursor



Entry	Pd salts	GC Yield of diesters (%)	Selectivity
1	$PdCl_2$	76	89/11
2	$PdBr_2$	50	63/37
3	PdI_2	0	
4	$Pd(OAc)_2$	79	97/3
5	$Pd(TFA)_2$	85	97/3
6	$Pd(acac)_2$	69	95/5
7	$Pd_2(dba)_3$	25	88/12

Table S2. Reaction conditions: Butadiene (1.0 mmol, solution in toluene), Pd salts (0.005 mmol in terms of Pd atom, 0.5 mol%), ligand (0.01 mmol, 1 mol%), PTSA·H_2O (2 mol%), ^{n}BuOH (2.0 mL), CO (40 atm), 120 °C, 24 h; the ratio of products and yield were determined by GC analysis with mesitylene as the internal standard. The products selectivity is the ratio of linear diesters to branched diesters.

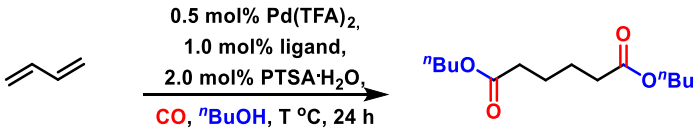
S4.2. The effect of acid



Entry	Acid	GC Yield of diesters (%)	Selectivity
1.	HCl aqueous solution	46	80/20
2.	H_2SO_4	10	93/7
3.	MSA	31	93/7
4.	CF_3COOH	17	92/8
5.	PTSA·H_2O	85	97/3
6.	H_3PO_4	0	
7.	Camphorsulfonic acid	81	93/7

Table S3. Reaction conditions: Butadiene (1.0 mmol, solution in toluene), $Pd(TFA)_2$, (0.005 mmol, 0.5 mol%), ligand (0.01 mmol, 1 mol%), acid (2 mol%), ^{n}BuOH (2.0 mL), CO (40 atm), 120 °C, 24 h; the ratio of products and yield were determined by GC analysis with mesitylene as the internal standard. The products selectivity is the ratio of linear diesters to branched diesters.

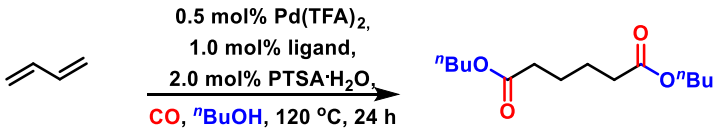
S4.3. The effect of temperature



Entry	T (°C)	GC Yield of diesters (%)	Selectivity
1	140	78	97/3
2	120	85	97/3
3	80	35	97/3
4	RT	8	

Table S4. Reaction conditions: Butadiene (1.0 mmol, solution in toluene), $Pd(TFA)_2$, (0.005 mmol, 0.5 mol%), ligand (0.01 mmol, 1 mol%), acid (2 mol%), ^{n}BuOH (2.0 mL), CO (40 atm), 24 h; the ratio of products and yield were determined by GC analysis with mesitylene as the internal standard. The products selectivity is the ratio of linear diesters to branched diesters.

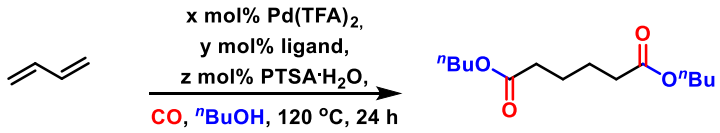
S4.4. The effect of CO pressure



Entry	CO pressure (bar)	GC Yield of diesters (%)	Selectivity
1	40	85	97/3
2	20	68	98/2

Table S5. Reaction conditions: Butadiene (1.0 mmol, solution in toluene), $Pd(TFA)_2$, (0.005 mmol, 0.5 mol%), ligand (0.01 mmol, 1 mol%), acid (2 mol%), ^{n}BuOH (2.0 mL), 120 °C, 24 h; the ratio of products and yield were determined by GC analysis with mesitylene as the internal standard. The products selectivity is the ratio of linear diesters to branched diesters.

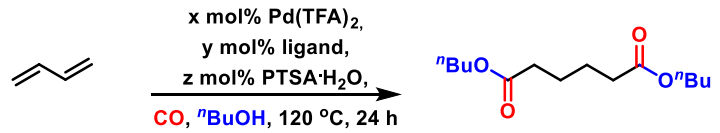
S4.5. The amount of catalyst loading



Entry	x/y/z (mol%)	GC Yield of diesters (%)	Selectivity
1.	0.1/0.2/0.4	41	93/7
2.	0.3/0.6/1.2	81	95/5
3.	0.5/1.0/2.0	85	97/3
4.	1/2/4	85	96/4
5.	2/4/8	87	96/4

Table S6. Reaction conditions: Butadiene (1.0 mmol, solution in toluene), ^{n}BuOH (2.0 mL), CO (40 atm), 120 °C, 24 h; the ratio of products and yield were determined by GC analysis with mesitylene as the internal standard. The products selectivity is the ratio of linear diesters to branched diesters.

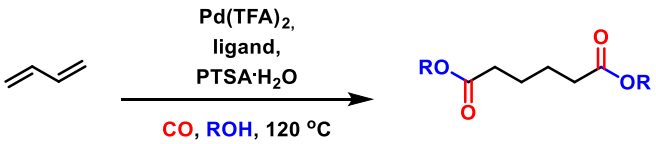
S4.6. The ratio of catalyst loading



Entry	x/y/z (mol%)	GC Yield of diesters (%)	Selectivity
1.	0.5/0.5/0.5	39	94/6
2.	0.5/0.5/1.0	51	95/5
3.	0.5/1.0/2	85	97/3
4.	0.5/2.0/4.0	86	96/4

Table S7. Reaction conditions: Butadiene (1.0 mmol, solution in toluene), ^{n}BuOH (2.0 mL), CO (40 atm), 120 °C, 24 h; the ratio of products and yield were determined by GC analysis with mesitylene as the internal standard. The products selectivity is the ratio of linear diesters to branched diesters.

S5. Upscaling reactions



Entry	Butadiene	Alcohol	Catalyst loading	Yield (%)	Selecetivity
1.	2g	MeOH	0.5 mol%	88%	97/3
2.	2g	^{n}BuOH	0.5 mol%	91%	97/3
3.	54g, 1 mol	^{n}BuOH	0.05 mol%	95%	97/3

Table S8. Upscaling reactions of 1,3-butadiene. Reaction conditions: For entry 1-2, the reaction conditions areas follows: butadiene (2g, 37 mmol), alcohol (148 mmol, 4 equiv.), toluene (15mL), $Pd(TFA)_2$ (0.185 mmol, 0.5 mol%), ligand (0.37 mmol, 1 mol%), $PTSA{\cdot}H_2O$ (0.74 mmol, 2 mol%), under 50 atm CO at 120 °C, 48 h; the ratio of products was determined by GC analysis, products were isolated by column chromatography. For entry 3, the reaction condition is: butadiene (54g, 1 mol), ^{n}BuOH (4 mol, 296g), $Pd(TFA)_2$, (0.5 mmol, 0.05 mol%, 0.166 g), ligand (1 mmol, 0.1 mol%, 0.42g), $PTSA{\cdot}H_2O$ (2 mmol, 0.2 mol%, 0.38 g), under 50 atm CO at 120 °C, 60 h; the ratio of products was determined by GC analysis, product was isolated by distillation.

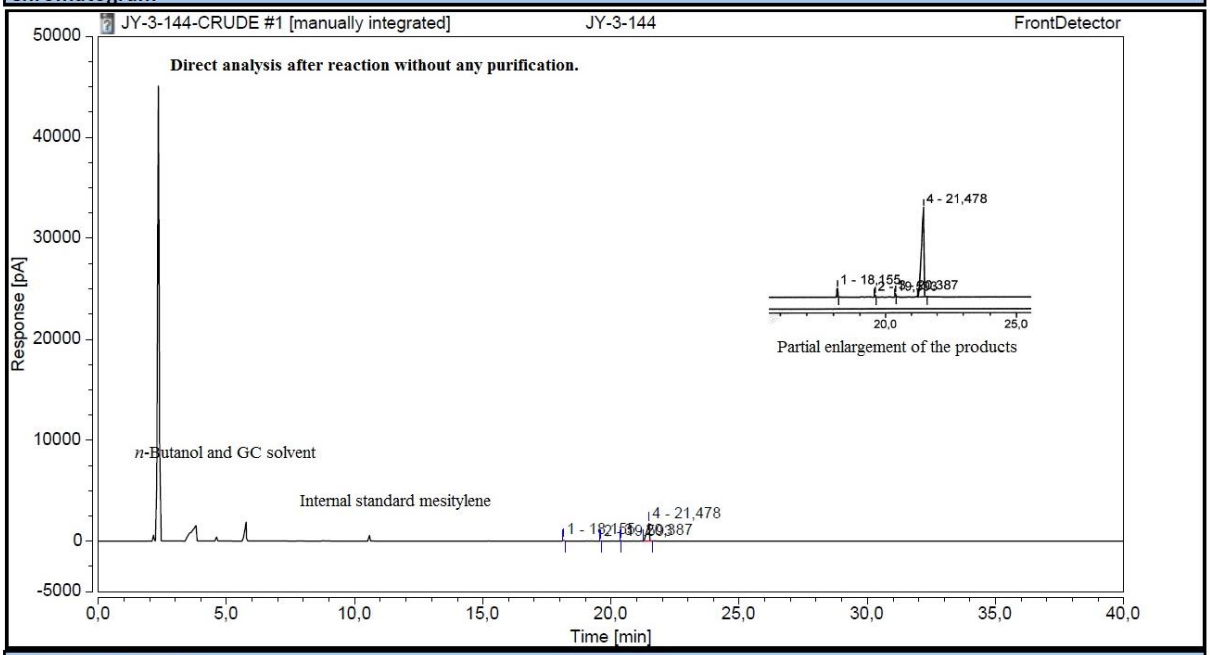
Figure S2. Upscaling reactions (for entry 3, the autoclave and product, analysis of the products).

Chromatogram and Results

Injection Details

Injection Name:	**JY-3-144**	*Run Time (min):*	**40,00**
Vial Number:	**122**	*Injection Volume:*	**2,00**
Injection Type:	**Unknown**	*Channel:*	**FrontDetector**
Calibration Level:		*Wavelength:*	**n.a.**
Instrument Method:	**dong-40min**	*Bandwidth:*	**n.a.**
Processing Method:	**dong**	*Dilution Factor:*	**1,0000**
Injection Date/Time:	**26.Jun.19 16:39**	*Sample Weight:*	**1,0000**

Chromatogram



Integration Results

No.	Peak Name	Retention Time min	Area pA*min	Height pA	Relative Area %	Relative Height %	Amount
n.a.	Component 2	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
n.a.	Component 3	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
n.a.	Component 4	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
1		18,155	3,833	162,571	2,13	8,19	n.a.
n.a.	Component 5	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
2		19,593	0,794	35,922	0,44	1,81	n.a.
3		20,387	1,062	48,146	0,59	2,43	n.a.
4		21,478	174,127	1737,416	96,84	87,57	n.a.
Total:			**179,817**	**1984,056**	**100,00**	**100,00**	

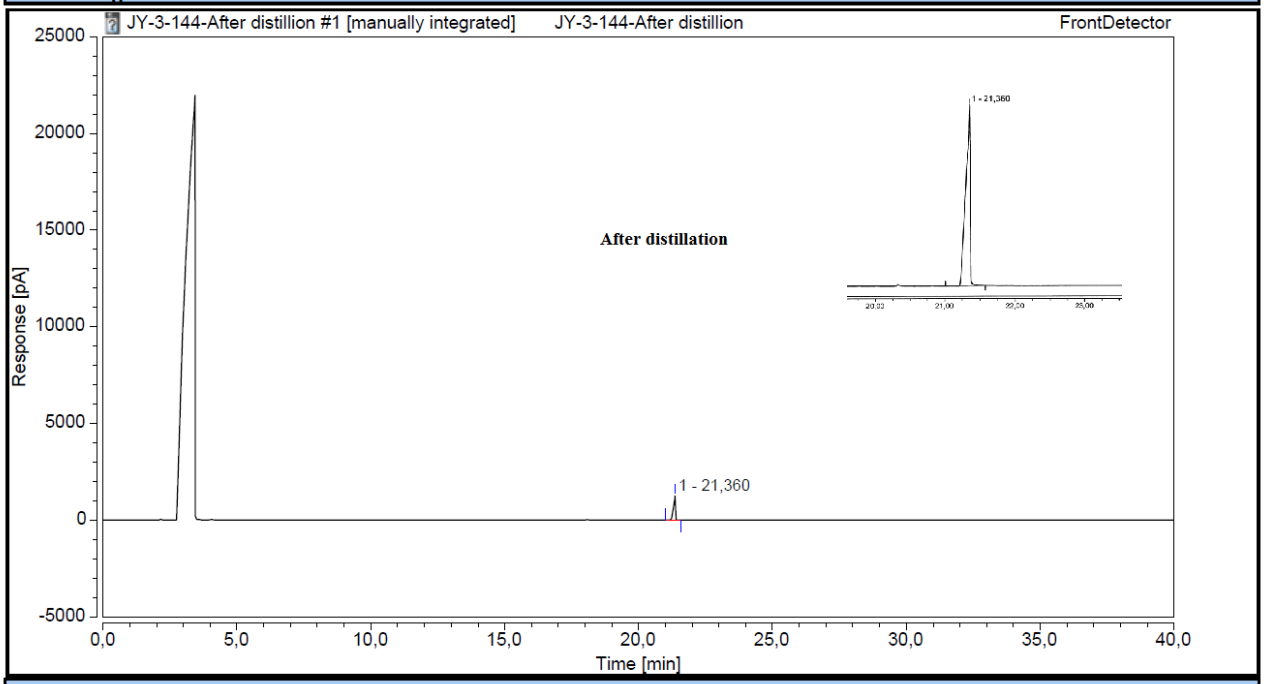
Linear product selectivity 97/3

Chromatogram and Results

Injection Details

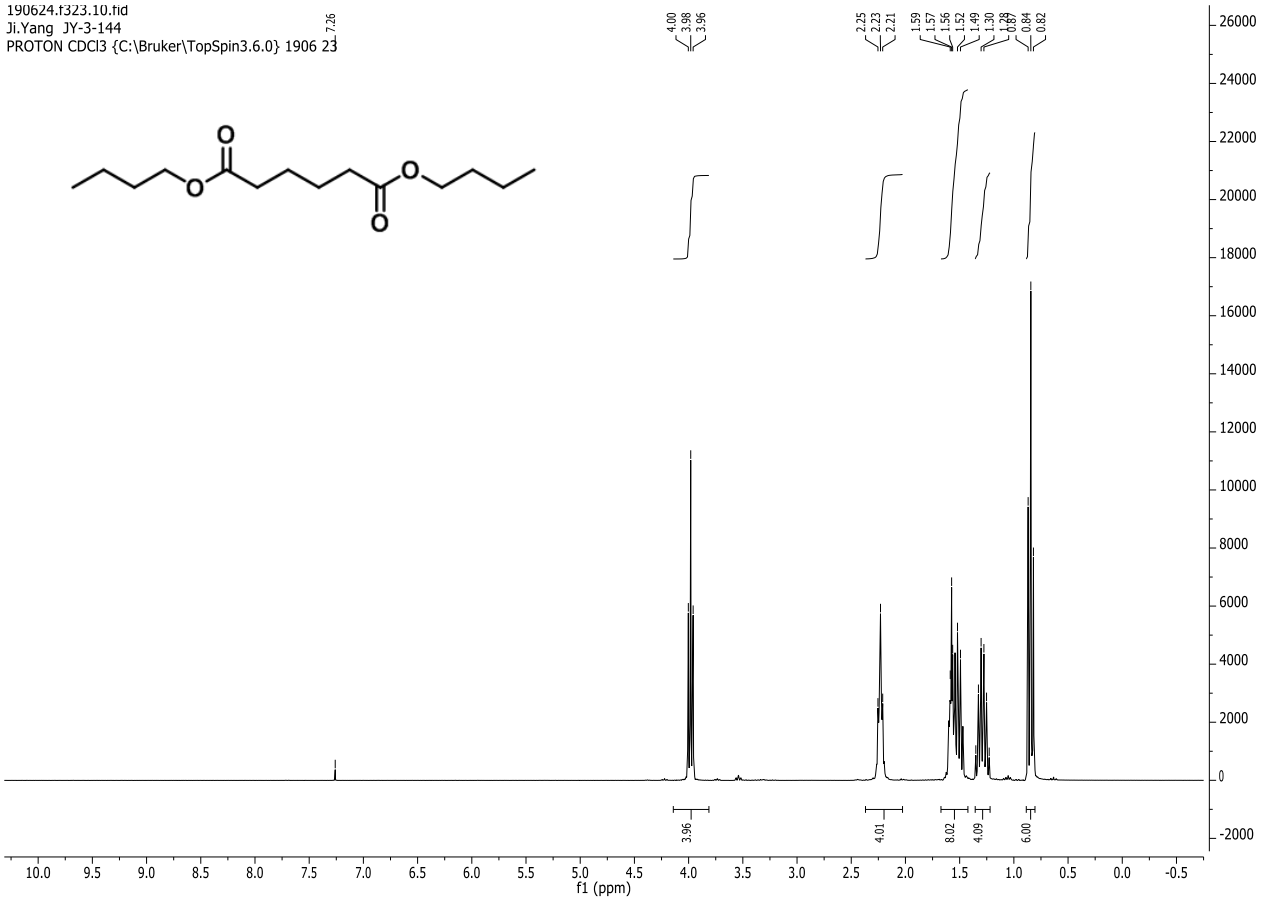
Injection Name:	**JY-3-144-After distillion**	*Run Time (min):*	**40,00**
Vial Number:	**128**	*Injection Volume:*	**2,00**
Injection Type:	**Unknown**	*Channel:*	**FrontDetector**
Calibration Level:		*Wavelength:*	**n.a.**
Instrument Method:	**dong-40min**	*Bandwidth:*	**n.a.**
Processing Method:	**dong**	*Dilution Factor:*	**1,0000**
Injection Date/Time:	**12.Jul.19 07:15**	*Sample Weight:*	**1,0000**

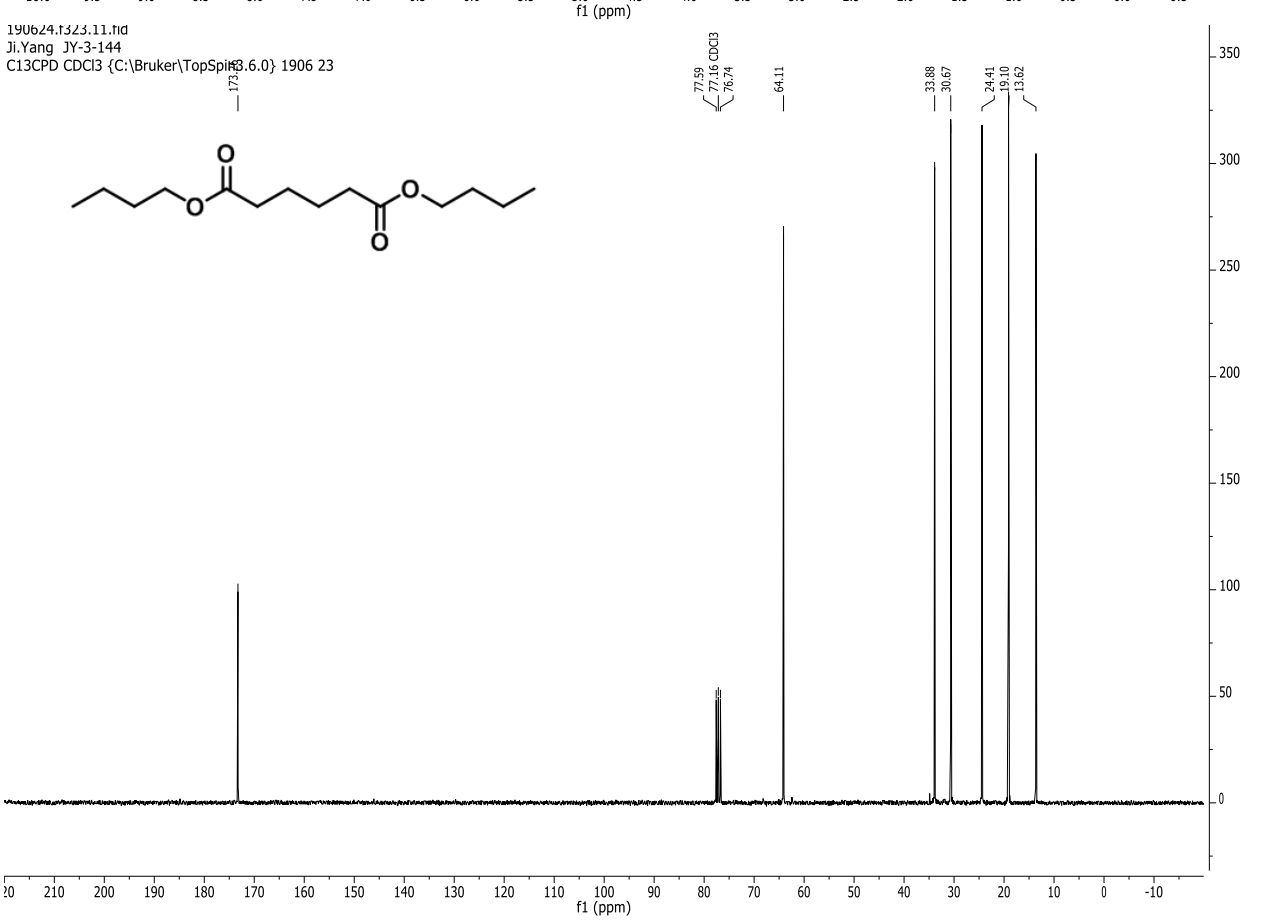
Chromatogram



Integration Results

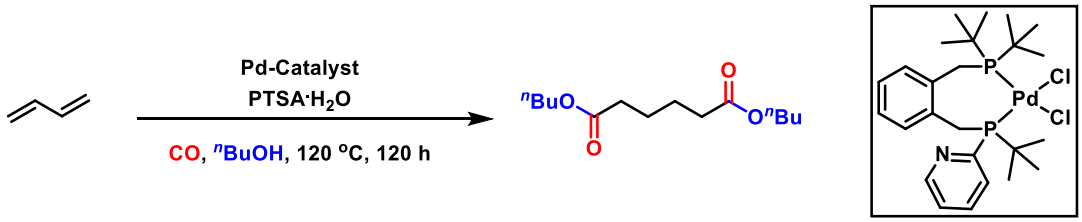
No.	Peak Name	Retention Time min	Area pA*min	Height pA	Relative Area %	Relative Height %	Amount
n.a.	Component 2	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
n.a.	Component 3	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
n.a.	Component 4	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
n.a.	Component 5	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
1		21,360	87,185	1248,081	100,00	100,00	n.a.
Total:			**87,185**	**1248,081**	**100,00**	**100,00**	


190624.f323.10.fid
Ji.Yang JY-3-144
PROTON CDCl3 {C:\Bruker\TopSpin3.6.0} 1906 23
7.26
4.00
3.98
3.96
2.25
2.23
2.21
1.59
1.57
1.56
1.52
1.49
1.30
1.28
0.87
0.84
0.82
3.96
4.01
8.02
4.09
6.00
f1 (ppm)


190624.f323.11.fid
Ji.Yang JY-3-144
C13CPD CDCl3 {C:\Bruker\TopSpin3.6.0} 1906 23
173.13
77.59
77.16 CDCl3
76.74
64.11
33.88
30.67
24.41
19.10
13.62
f1 (ppm)


190624.f323.12.fid
Ji.Yang JY-3-144
C13DEPT135 CDCl3 {C:\Bruker\TopSpin3.6.0} 1906 23
64.11
33.88
30.66
24.41
19.10
13.62
3500
3000
2500
2000
1500
1000
500
0
-500
-1000
-1500
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

S6. TON experiments



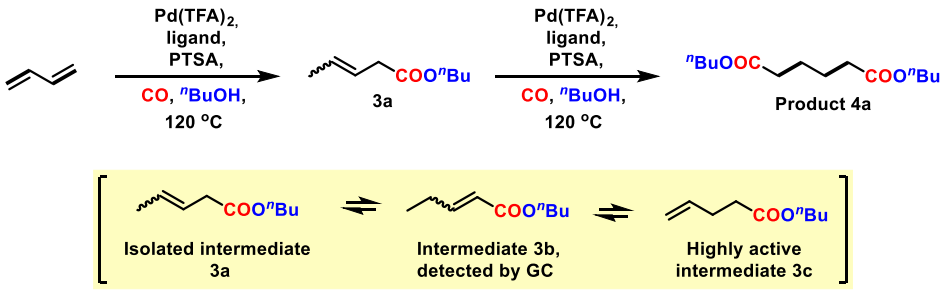
Entry	Catalyst loading	Yield (%)	Selectivity	TON
1*	10^{-4}	27	93/7	2700
2†	10^{-3}	86	89/11	860
3†	10^{-4}	86	91/9	8600
4†	10^{-5}	64	92/8	64000

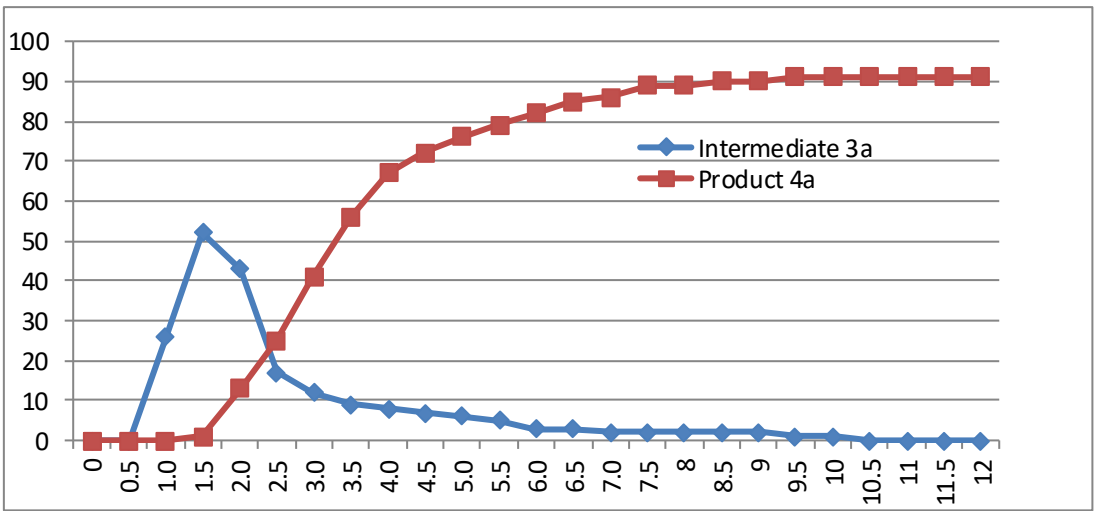
Table S9. TON Experiments. [*] For entry 1, reaction conditions: Butadiene (2.0 mmol, solution in toluene), ^{n}BuOH (3.0 mL), $PdCl_2$ (0.0002 mmol, accurately weigh 2mg $PdCl_2$, dissolved in 56.5mL ^{n}BuOH, stir well, then take 1mL of this solution add to the reaction system), HeMaRaphos (8.3 mg, 0.02 mmol), PTSA·H_2O (7.7 mg, 0.04 mmol), CO (40 atm), 120 °C, 120 h; the ratio of products and yield were determined by GC analysis with mesitylene as the internal standard. The products selectivity is the ratio of linear diesters to branched diesters. TON = turnover number = reacted butadiene (mmol) /mmol Pd. [†] Reaction conditions: Butadiene (10.0 mmol, gas), ^{n}BuOH (20.0 mL), $PdCl_2$-HeMaRaphos complex (accurately weigh 2mg $PdCl_2$-HeMaRaphos complex, dissolved in 33.7 mL ^{n}BuOH, stir well, then measure different volumes for different reactions, for example for entry 3, take 10 mL of this solution to the reaction system), PTSA·H_2O (38 mg, 0.2 mmol), CO (40 atm), 120 °C, 120 h; the ratio of products and yields were determined by GC analysis with mesitylene as the internal standard. The products selectivity is the ratio of linear diesters to branched diesters. TON = turnover number = reacted butadiene (mmol)/mmol Pd.

S7. Mechanistic studies:

S7.1. Kinetic monitoring experiment

In order to understand the process in more detail, kinetic monitoring experiments were conducted (**Figure S3**). In contrast to the shown mechanism, in general in all catalytic experiments an excess of ligand was used to ensure stability of the active complex at low metal concentration. In the first half hour, the active hydride complex is formed from the in situ mixture of $Pd(TFA)_2$, HeMaRaphos and PTSA; then, the first step alkoxycarbonylation occurred to give selectively *n*-butyl pent-3-eneoate (intermediate **3a**) which continuously accumulates to reach a maximum yield of about 50% after 90 minutes. Stopping the reaction at this time, one can easily isolate intermediate **3a** from the reaction mixture. Meanwhile, the active catalyst promotes olefin isomerization. By GC analysis we can detect the presence of *n*-butyl pent-2-eneoate intermediates **3b** (low concentration, less than 5%). Notably, the terminal olefin **3c** (*n*-butyl pent-4-enoate) could not be detected by GC, which we explain by its fast conversion into the linear adipate diester **4a**.





The ***X***-axis represents the reaction time and the ***Y***-axis represents the reaction yield. Reaction conditions: Butadiene (20 mmol), $Pd(TFA)_2$ (0.005 mmol, 0.5 mol%), ligand (0.01 mmol, 1.0 mol%), $PTSA{\cdot}H_2O$ (2 mol%), ^{n}BuOH (25 mL), CO (40 atm), 120 °C; the GC yield were determined by GC analysis with mesitylene as the internal standard.

Figure S3. Kinetic monitoring experiment.

S7.2. Catalytic mechanism

Based on previous studies, we propose the catalytic cycles as shown in **Figure S4.** We suggest the formation of a cationic Pd(II) hydride complex **A** as the key active species to initiate the following steps. First, butadiene is coordinated to the metal centre and then inserted into the Pd-H bond to form intermediate **B**. This intermediate is prone to *sigma-pi* tautomerism (**B-B'**). Next, CO insertion forms an allyl acyl compound. In general, the nitrogen atom of the ligands should improve the durability of the catalyst via hemilabile coordination to the palladium center in the catalytic cycle. Following the nucleophile ROH attack, the N on the ligand acts as a proton shuttle for the formation of the palladium hydride and assists the alcoholysis process. This process produces *n*-butyl pent-3-eneoate **3a** while regenerating the active catalyst **A**. Meanwhile, the active catalyst promotes olefin isomerization to give *n*-butyl pent-4-eneoate **3c** from *n*-butyl pent-3-eneoate **3a**, which is finally converted to the linear diester **4**.

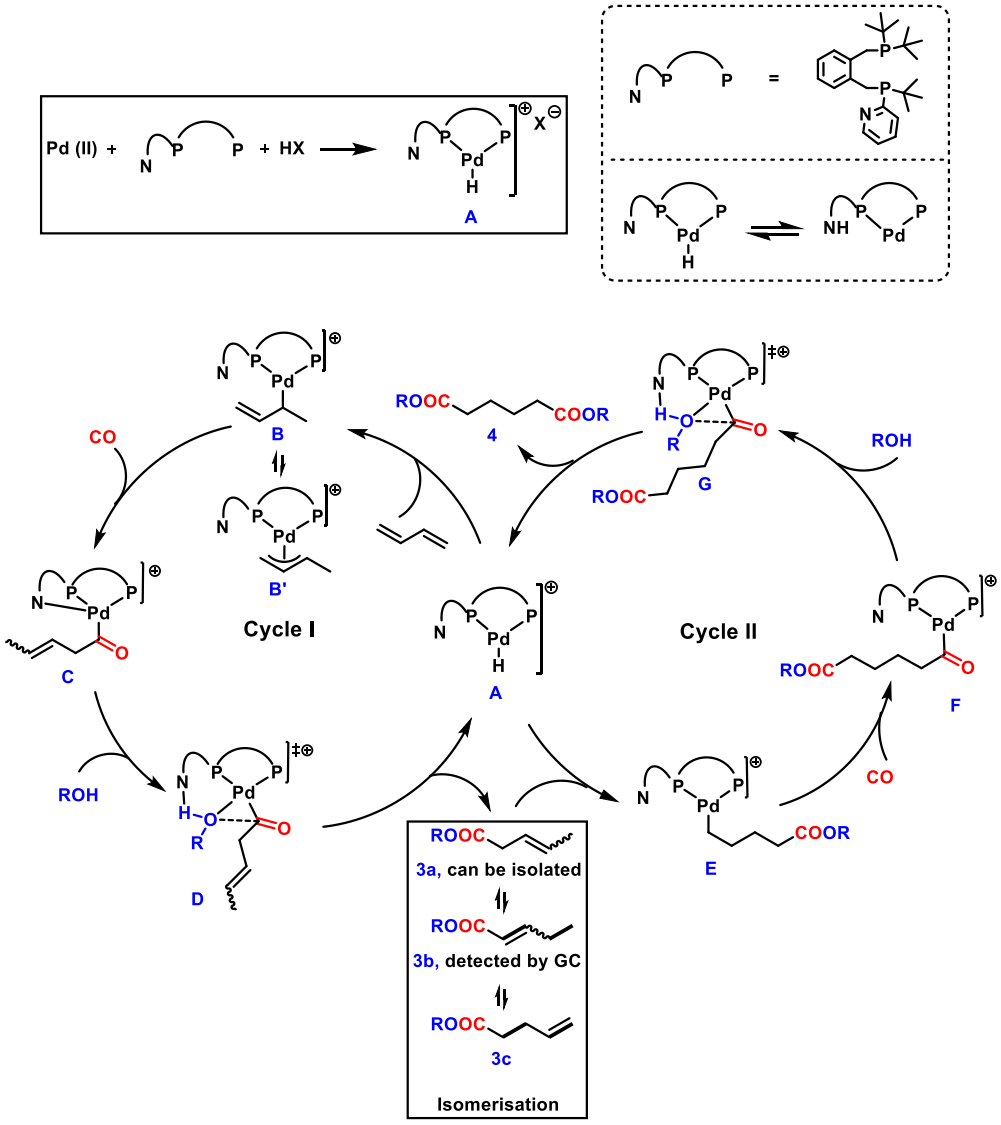
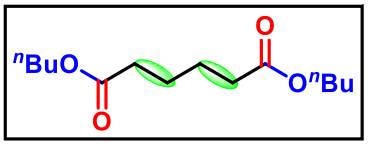


Figure S4. Proposed catalytic cycles.

S8. NMR and HRMS spectra:

Dibutyl adipate (4a)



85% yield, 219 mg, 1 mmol scale, 97% linear selectivity. Light yellow liquid. Eluent: pentane/ethyl acetate = 40/1.

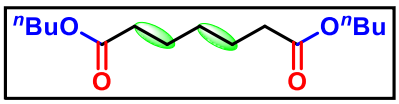
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.05 (t, *J* = 6.7 Hz, 4H), 2.40-2.17 (m, 4H), 1.74-1.45 (m, 8H), 1.46-1.25 (m, 4H), 0.91 (t, *J* = 7.3 Hz, 6H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 64.3, 34.1, 30.8, 24.6, 19.3, 13.8 ppm;

DEPT 135 NMR (75 MHz, $CDCl_3$) δ 64.3 (+), 34.1 (+), 30.8 (+), 24.6 (+), 19.3 (+), 13.8 (-) ppm;

HRMS (ESI): Calcd. for $C_{14}H_{26}O_4Na^+$: 281.1729, Found: 281.1731 $[M+Na]^+$.

Dibutyl pimelate (4b)



84% yield, 229 mg, 1 mmol scale, 95% linear selectivity. Colorless liquid. Eluent: pentane/ethyl acetate = 40/1.

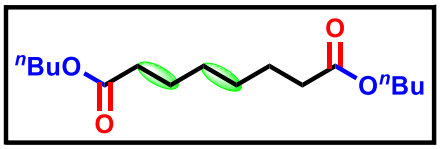
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.03 (t, *J* = 6.7 Hz, 4H), 2.27 (t, *J* = 7.5 Hz, 4H), 1.62-1.53 (m, 8H), 1.37-1.31 (m, 6H), 0.93-0.86 (t, *J* = 7.3 Hz, 6H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 64.2, 34.2, 30.8, 28.7, 24.7, 19.2, 13.8 ppm;

DEPT 135 NMR (75 MHz, $CDCl_3$) δ 64.2 (+), 34.2 (+), 30.8 (+), 28.7 (+), 24.7 (+), 19.2 (+),13.8 (-) ppm;

HRMS (EI): Calcd. for $C_{15}H_{28}O_4$: 295.1880, Found: 295.1885 $[M]^+$.

Dibutyl suberate (4c)



82% yield, 235 mg, 1 mmol scale, 95% linear selectivity. Colorless liquid. Eluent: pentane/ethyl acetate = 40/1.

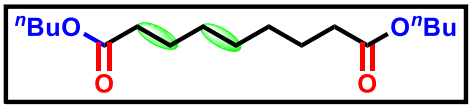
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.01 (t, *J* = 6.7 Hz, 4H), 2.23 (t, *J* = 7.5 Hz, 4H), 1.66-1.46 (m, 8H), 1.39-1.22 (m, 8H), 0.88 (t, *J* = 7.4 Hz, 6H) ppm;

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.8, 64.1, 34.3, 30.7, 28.8, 24.8, 19.2, 13.7 ppm;

DEPT 135 NMR (101 MHz, $CDCl_3$) δ 64.1(+), 34.3 (+), 30.7 (+), 28.8 (+), 24.8 (+), 19.2 (+), 13.7 (-) ppm;

HRMS (ESI): Calcd. for $C_{16}H_{30}O_4Na^+$: 309.2036, Found: 309.2047 $[M+Na]^+$.

Dibutyl sebacate (4d)



79% yield, 237 mg, 1 mmol scale, 92% linear selectivity. Colorless liquid. Eluent: pentane/ethyl acetate = 40/1.

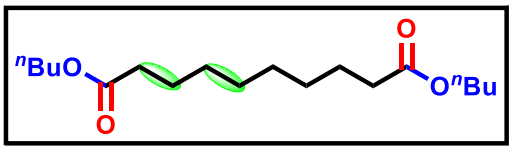
^{1}H NMR (300 MHz, $CDCl_3$) δ 3.96 (t, *J* = 6.7 Hz, 4H), 2.18 (t, *J* = 7.5 Hz, 4H), 1.64-1.41 (m, 8H), 1.35-1.14 (m, 10H), 0.83 (t, *J* = 7.4 Hz, 6H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 63.9, 34.2, 30.6, 28.9, 28.8, 24.8, 19.1, 13.6 ppm;

DEPT 135 NMR (75 MHz, $CDCl_3$) δ 63.9 (+), 34.2 (+), 30.6 (+), 28.9 (+), 28.8(+), 24.8 (+), 19.1 (+), 13.6 (-) ppm;

HRMS (ESI): Calcd. for $C_{17}H_{32}O_4Na^+$: 323.2193, Found: 323.2202 $[M+Na]^+$.

Dibutyl dodecanoate (4e)



74% yield, 232 mg, 1 mmol scale, 90% linear selectivity. Colorless liquid. Eluent: pentane/ethyl acetate = 40/1.

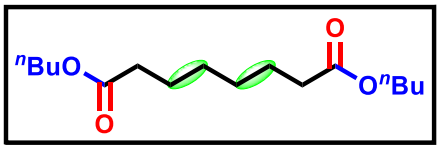
^{1}H NMR (300 MHz, $CDCl_3$) δ 3.94 (t, *J* = 6.7 Hz, 4H), 2.16 (t, *J* = 7.5 Hz, 4H), 1.60-1.38 (m, 8H), 1.37-1.07 (m, 12H), 0.81 (t, *J* = 7.4 Hz, 6H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 63.9, 34.2, 30.6, 28.9, 28.9, 24.8, 19.0, 13.6 ppm;

DEPT 135 NMR (75 MHz, $CDCl_3$) δ 63.9 (+), 34.2 (+), 30.6 (+), 28.9 (+), 28.9 (+), 24.8 (+), 19.0 (+), 13.6 (-) ppm;

HRMS (ESI): Calcd. for $C_{18}H_{34}O_4Na^+$: 337.2349, Found: 337.2357 $[M+Na]^+$.

Dibutyl suberate (4f)



81% yield, 232 mg, 1 mmol scale, 92% linear selectivity. Colorless liquid. Eluent: pentane/ethyl acetate = 40/1.

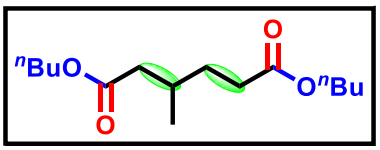
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.08-3.95 (m, 4H), 2.33-2.17 (m, 4H), 1.67-1.46 (m, 8H), 1.43-1.17 (m, 8H), 0.95-0.81 (m, 6H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 64.1, 34.3, 30.7, 28.8, 24.8, 19.2, 13.7 ppm;

DEPT 135 NMR (75 MHz, $CDCl_3$) δ 64.1 (+), 34.3 (+), 30.7 (+), 28.8 (+), 24.8 (+), 19.2 (+), 13.7 (-) ppm;

HRMS (ESI): Calcd. for $C_{16}H_{30}O_4Na^+$: 309.2036, Found: 309.2040 $[M+Na]^+$.

3-Methyl-1,6-dibutyl-hexanedioic acid diester (4g)



78% yield, 212 mg, 1 mmol scale, 98% linear selectivity. Light yellow colour liquid. Eluent: pentane/ethyl acetate = 40/1.

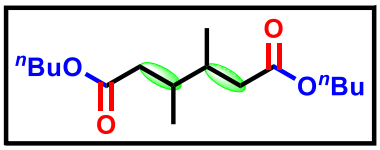
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.05 (t, J = 6.6 Hz, 4H), 2.40-1.84 (m, 5H), 1.73-1.43 (m, 6H), 1.39-1.31 (m, 4H), 0.97-0.85 (m, 9H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 172.9, 64.4, 64.3, 41.6, 32.1, 31.7, 30.8, 30.8, 30.0, 19.4, 19.3, 19.2, 13.8, 13.8 ppm;

DEPT 135 NMR (75 MHz, $CDCl_3$) δ 64.4 (+), 64.3 (+), 41.6 (+), 32.1 (+), 31.7 (+), 30.8 (+), 30.0 (-), 19.4 (-), 19.3(+), 19.2 (+), 13.8 (-) ppm;

HRMS (ESI): Calcd. for $C_{15}H_{28}O_4Na^+$: 295.1880, Found: 295.1884 $[M+Na]^+$.

3,4-Dimethyl-1,6-dibutyl-hexanedioic acid diester (4h)



53% yield, 152 mg, 1 mmol scale, 97% linear selectivity. Light yellow liquid. Eluent: pentane/ethyl acetate = 40/1.

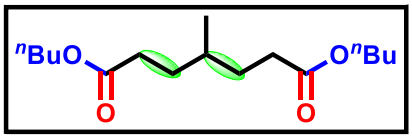
^{1}H NMR (300 MHz, $CDCl_3$) δ 3.93 (t, J = 6.7 Hz, 4H), 2.25-2.10 (m, 2H), 2.07-1.80 (m, 4H), 1.55-1.38 (m, 4H), 1.32-1.15 (m, 4H), 0.87-0.70 (m, 12H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 172.7, 63.9, 63.9, 39.4, 38.2, 34.5, 34.0, 30.6, 30.6, 19.0, 19.0, 16.4, 14.7, 13.5, 13.5 ppm;

DEPT 135 NMR (75 MHz, $CDCl_3$) δ 63.9 (+), 63.9 (+), 39.4 (+), 38.2 (+), 34.5 (-), 34.0 (-), 30.6 (+), 30.6 (+), 19.0 (+), 19.0 (+), 16.4 (-), 14.7 (-), 13.5 (-), 13.5 (-) ppm;

HRMS (ESI): Calcd. for $C_{16}H_{30}O_4Na^+$: 309.2036, Found: 309.2043 $[M+Na]^+$.

4-Methyl-1,7-dibutyl-pimelic diester (4i)



77% yield, 220 mg, 1 mmol scale, 91% linear selectivity. Light yellow liquid. Eluent: pentane/ethyl acetate = 40/1.

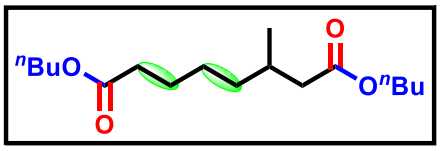
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.04 (t, *J* = 6.7 Hz, 4H), 2.45-2.13 (m, 4H), 1.74-1.24 (m, 13H), 0.93-0.84 (m, 9H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0, 64.3, 32.2, 32.1, 31.7, 30.8, 19.2, 19.0, 13.8 ppm;

DEPT 135 NMR (75 MHz, $CDCl_3$) δ 64.3 (+), 32.2 (-), 32.1 (+), 31.7 (+), 30.8 (+), 19.2 (+), 19.0 (-), 13.8 (-) ppm;

HRMS (ESI): Calcd. for $C_{16}H_{30}O_4Na^+$: 309.2036, Found: 309.2043 $[M+Na]^+$.

3-Methyl-1,8-dibutyl octanedioate (4j)



73% yield, 219 mg, 1 mmol scale, 94% linear selectivity. Light yellow liquid.

Eluent: pentane/ethyl acetate = 40/1.

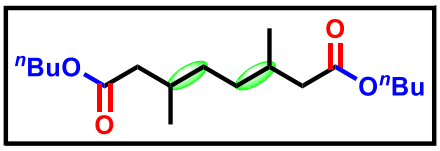
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.02 (t, *J* = 6.7 Hz, 4H), 2.34-2.00 (m, 4H), 1.97-1.85 (m, 1H), 1.62-1.47 (m, 6H), 1.40-1.15 (m, 8H), 0.94-0.85 (m, 9H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 173.3, 64.2, 64.1, 41.9, 36.3, 34.3, 30.8, 30.8, 30.3, 26.5, 25.1, 19.7, 19.2, 19.2, 13.8, 13.8 ppm;

DEPT 135 NMR (75 MHz, $CDCl_3$) δ 64.2 (+), 64.1 (+), 41.9 (+), 36.3 (+), 34.3 (+), 30.8(+), 30.8(+), 30.3 (-), 26.5 (+), 25.1 (+), 19.7 (-), 19.2 (+), 19.2 (+), 13.8 (-), 13.8 (-) ppm;

HRMS (ESI): Calcd. for $C_{17}H_{32}O_4Na^+$: 323.2193, Found: 323.2195 $[M+Na]^+$.

3,6-Dimethyl-1,8-dibutyl octanedioate (4k)



37% yield, 116 mg, 1 mmol scale, 95% linear selectivity. Light yellow liquid. Eluent: pentane/ethyl acetate = 40/1.

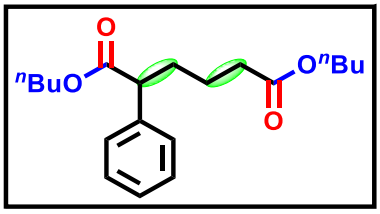
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.05 (t, *J* = 6.7 Hz, 4H), 2.32-2.23 (m, 2H), 2.14-2.05 (m, 2H), 1.96-1.86 (m, 2H), 1.64-1.54 (m, 4H), 1.43-1.21 (m, 8H), 0.97-0.87 (m, 12H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 173.4, 64.2, 64.2, 42.1, 41.9, 34.1, 34.0, 30.8, 30.8, 30.7, 30.6, 19.9, 19.7, 19.3, 19.3, 13.8, 13.8 ppm;

DEPT 135 NMR (75 MHz, $CDCl_3$) δ 64.2 (+), 64.2 (+), 42.1 (+), 41.9 (+), 34.1 (+), 34.0 (+), 30.8 (+), 30.8 (+), 30.7 (-), 30.6 (-), 19.9 (-), 19.7 (-), 19.3 (+), 19.3 (+), 13.8 (-), 13.8 (-) ppm;

HRMS (ESI): Calcd. for $C_{18}H_{34}O_4Na^+$: 337.2349, Found: 337.2360 $[M+Na]^+$.

1-Phenyl-1,8-dibutyl adipate (4l)



82% yield, 274 mg, 1 mmol scale, 91% linear selectivity. Light yellow liquid. Eluent: pentane/ethyl acetate = 40/1.

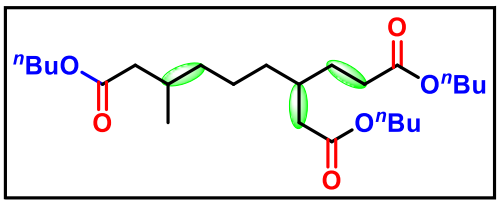
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.20 (m, 5H), 4.20-3.89 (m, 4H), 3.56 (t, J = 7.7 Hz, 1H), 2.40-1.78 (m, 4H), 1.65-1.50 (m, 6H), 1.39-1.28 (m, 4H), 0.98-0.85 (m, 6H) ppm;

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.9, 173.4, 139.0, 128.7, 128.0, 127.3, 64.7, 64.3, 51.6, 34.1, 32.9, 30.8, 30.7, 23.1, 19.2, 19.1, 13.8, 13.7 ppm;

DEPT 135 NMR (101 MHz, $CDCl_3$) δ 128.7 (+), 128.0 (+), 127.3 (+), 64.7 (-), 64.3 (-), 51.6 (+), 34.1 (-), 32.9 (-), 30.8 (-), 30.7 (-), 23.1 (-), 19.2 (-), 19.1 (-), 13.8 (+), 13.7 (+) ppm;

HRMS (ESI): Calcd. for $C_{20}H_{30}O_4Na^+$: 357.2036, Found: 357.2042 $[M+Na]^+$.

1,10-Dibutyl 7-(2-butoxy-2-oxoethyl)-3-methyldecanedioate (4m)



61% yield, 270 mg, 1 mmol scale, 91% linear selectivity. Light yellow liquid. Eluent: pentane/ethyl acetate = 20/1.

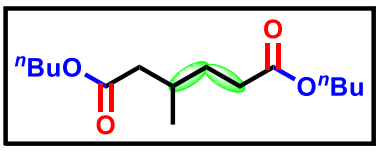
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.05 (t, J = 6.7 Hz, 6H), 2.39-2.17 (m, 5H), 2.12-2.03 (m, 1H), 1.93-1.85 (m, 2H), 1.65-1.50 (m, 8H), 1.43-1.20 (m, 12H), 0.98-0.87 (m, 12H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 173.4, 173.2, 64.4, 64.3, 64.2, 42.0, (38.9, 38.9, one carbon) 37.0, 34.7, 33.9, 31.8, 30.8, 30.8, 30.8, 30.4, (29.1, 29.0, one carbon), (24.0, 23.9, one carbon), 19.8, 19.3, 19.3, 19.3, 13.8, 13.8, 13.8 ppm;

DEPT 135 NMR (75 MHz, $CDCl_3$) δ 64.4 (+), 64.3 (+), 64.2 (+), 42.0 (+), (38.9 (+), 38.9 (+), one carbon), 37.0 (+), 34.7 (-), 33.9 (+), 31.8 (+), 30.8 (+), 30.8 (+), 30.8 (+), 30.4 (-), (29.1 (+), 29.0 (+), one carbon), (24.0 (+), 23.9 (+), one carbon), 19.8 (-), 19.3 (+), 19.3 (+), 19.3 (+), 13.8 (-), 13.8 (-), 13.8 (-) ppm;

HRMS (ESI): Calcd. for $C_{25}H_{46}O_4Na^+$: 465.3186, Found: 465.3195 $[M+Na]^+$.

3-Methyl-1,6-dibutyl-hexanedioic acid diester (4n)



81% yield, 220 mg, 1 mmol scale, 98% linear selectivity. Colorless liquid. Eluent: pentane/ethyl acetate = 40/1.

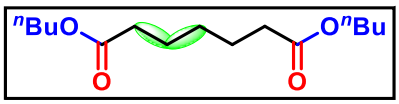
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.09-4.00 (m, 4H), 2.43-2.03 (m, 4H), 2.00-1.88 (m, 1H), 1.70-1.46 (m, 6H), 1.43-1.26 (m, 4H), 0.99-0.84 (m, 9H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 172.9, 64.3, 64.2, 41.6, 32.0, 31.7, 30.8, 30.8, 30.0, 19.4, 19.2, 19.2, 13.8, 13.8 ppm;

DEPT 135 NMR (75 MHz, $CDCl_3$) δ 64.3 (+), 64.2 (+), 41.6 (+), 32.0 (+), 31.7 (+), 30.8 (+), 30.8 (+), 30.0 (-), 19.4 (-), 19.2 (+), 19.2 (+), 13.8 (-), 13.8 (-) ppm;

HRMS (ESI): Calcd. for $C_{15}H_{28}O_4Na^+$: 295.1880, Found: 295.1888 $[M+Na]^+$.

Dibutyl pimelate (4o)



84% yield, 229 mg, 1 mmol scale, 93% linear selectivity. Colorless liquid. Eluent: pentane/ethyl acetate = 40/1.

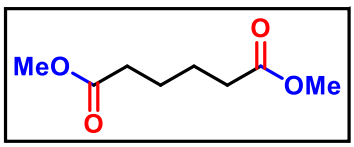
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.04-3.98 (m, 4H), 2.27-2.22 (m, 4H), 1.62-1.25 (m, 14H), 0.90-0.83 (m, 6H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 64.1, 34.1, 30.7, 28.6, 24.7, 19.2, 13.7 ppm;

DEPT 135 NMR (75 MHz, $CDCl_3$) δ 64.1 (+), 34.1 (+), 30.7 (+), 28.6 (+), 24.7 (+), 19.2 (+), 13.7 (-) ppm;

HRMS (EI): Calcd. for $C_{15}H_{28}O_4$: 295.1880, Found: 295.1886 $[M]^+$.

Dimethyl adipate (4p)



81% yield, 141 mg, 1 mmol scale, 97% linear selectivity. Colorless liquid. Eluent: pentane/ethyl acetate = 40/1.

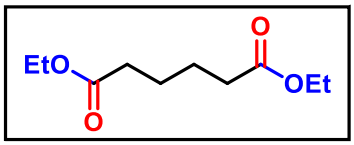
^{1}H NMR (300 MHz, $CDCl_3$) δ 3.52 (s, 6H), 2.23-2.16 (m, 4H), 1.57-1.47 (m, 4H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 51.3, 33.4, 24.2 ppm;

DEPT 135 NMR (75 MHz, $CDCl_3$) δ 51.3 (+), 33.4 (-), 24.2 (-) ppm;

HRMS (ESI): Calcd. for $C_8H_{14}O_4Na^+$:197.0784, Found:197.0784 $[M+Na]^+$.

Diethyl adipate (4q)



82% yield, 166 mg, 1 mmol scale, 97% linear selectivity. Colorless liquid. Eluent: pentane/ethyl acetate = 40/1.

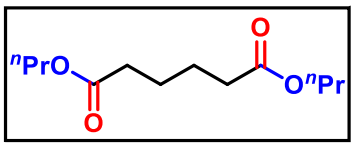
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.11 (q, *J* = 7.1 Hz, 4H), 2.35-2.25 (m, 4H), 1.70-1.58 (m, 4H), 1.24 (t, *J* = 7.1 Hz, 6H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 60.4, 34.1, 24.5, 14.4 ppm;

DEPT 135 NMR (75 MHz, $CDCl_3$) δ 60.4(+), 34.1 (+), 24.5 (+), 14.4 (-) ppm;

HRMS (ESI): Calcd. for $C_{10}H_{18}O_4Na^+$:225.1097, Found:225.1102 $[M+Na]^+$.

Dipropyl adipate (4r)



88% yield, 203 mg, 1 mmol scale, 97% linear selectivity. Colorless liquid. Eluent: pentane/ethyl acetate = 40/1.

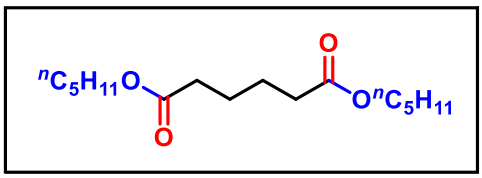
^{1}H NMR (300 MHz, $CDCl_3$) δ 3.96 (t, *J* = 6.7 Hz, 4H), 2.30-2.20 (m, 4H), 1.67-1.47 (m, 8H), 0.87 (t, *J* = 7.4 Hz, 6H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 65.9, 33.9, 24.5, 22.0, 10.4 ppm;

DEPT 135 NMR (75 MHz, $CDCl_3$) δ 65.9 (+), 33.9 (+), 24.5 (+), 22.0 (+), 10.4 (-) ppm;

HRMS (ESI): Calcd. for $C_{12}H_{22}O_4Na^+$:253.1410, Found:253.1415 $[M+Na]^+$.

Dipentyl adipate (4s)



92% yield, 263 mg, 1 mmol scale, 97% linear selectivity. Colorless liquid. Eluent: pentane/ethyl acetate = 40/1.

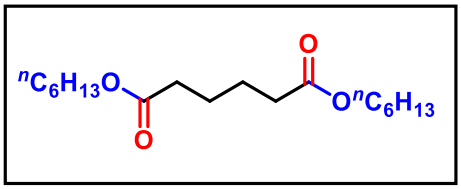
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.01 (t, *J* = 6.8 Hz, 4H), 2.33-2.22 (m, 4H), 1.67-1.52 (m, 8H), 1.30-1.26 (m, 8H), 0.90-0.81 (m, 6H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 64.5, 34.0, 28.4, 28.1, 24.5, 22.4, 14.0 ppm;

DEPT 135 NMR (75 MHz, $CDCl_3$) δ 64.5 (+), 34.0 (+), 28.4 (+), 28.1 (+), 24.5 (+), 22.4 (+), 14.0 (-) ppm;

HRMS (ESI): Calcd. for $C_{16}H_{30}O_4Na^+$:309.2036, Found:309.2041 $[M+Na]^+$.

Dihexyl adipate (4t)



83% yield, 261 mg, 1 mmol scale, 96% linear selectivity. Colorless liquid. Eluent: pentane/ethyl acetate = 40/1.

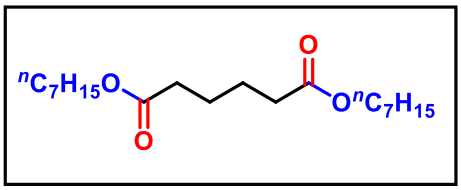
^{1}H NMR (300 MHz, $CDCl_3$) δ 3.97 (t, J = 6.7 Hz, 4H), 2.28-2.20 (m, 4H), 1.64-1.45 (m, 8H), 1.31-1.14 (m, 12H), 0.86-0.74 (m, 6H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 64.4, 33.9, 31.4, 28.6, 25.6, 24.4, 22.5, 13.9 ppm;

DEPT 135 NMR (75 MHz, $CDCl_3$) δ 64.4 (+), 33.9 (+), 31.4 (+), 28.6 (+), 25.6 (+), 24.4 (+), 22.5 (+), 13.9 (-) ppm;

HRMS (ESI): Calcd. for $C_{18}H_{34}O_4Na^+$: 337.2349, Found: 337.2354 $[M+Na]^+$.

Diheptyl adipate (4u)



86% yield, 294 mg, 1 mmol scale, 97% linear selectivity, Light yellow liquid. Eluent: pentane/ethyl acetate = 50/1.

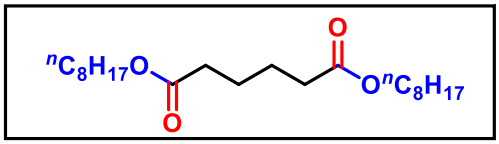
^{1}H NMR (300 MHz, $CDCl_3$) δ 3.96 (t, J = 6.0 Hz 4H), 2.40-2.00 (m, 4H), 1.65-1.38 (m, 8H), 1.34-1.08 (m, 16H), 0.86-0.65 (m, 6H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 64.4, 33.8, 31.7, 28.9, 28.6, 25.8, 24.4, 22.5, 14.0 ppm;

DEPT 135 NMR (75 MHz, $CDCl_3$) δ 64.4 (+), 33.8 (+), 31.7 (+), 28.9 (+), 28.6 (+), 25.8 (+), 24.4 (+), 22.5 (+), 14.0 (-) ppm;

HRMS (ESI): Calcd. for $C_{20}H_{38}O_4Na^+$: 365.2662, Found: 365.2662 $[M+Na]^+$.

Dioctyl adipate (4v)



87% yield, 322 mg, 1 mmol scale, 96% linear selectivity. Colorless liquid. Eluent: pentane/ethyl acetate = 40/1.

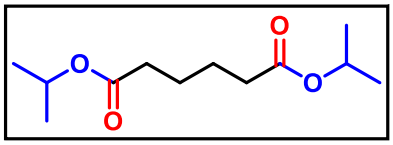
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.03 (t, *J* = 6.0 Hz 4H), 2.35-2.25 (m, 4H), 1.65-1.55 (m, 8H), 1.30-1.26 (m, 20H), 0.86-0.75 (m, 6H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 64.6, 34.1, 31.9, 29.3, 29.3, 28.7, 26.0, 24.6, 22.7, 14.2 ppm;

DEPT 135 NMR (75 MHz, $CDCl_3$) δ 64.6 (+), 34.1 (+), 31.9 (+), 29.3 (+), 29.3 (+), 28.7 (+), 26.0 (+), 24.6 (+), 22.7 (+), 14.2 (-) ppm;

HRMS (ESI): Calcd. for $C_{22}H_{42}O_4Na^+$:393.2975, Found:393.2968 $[M+Na]^+$.

Diisopropyl adipate (4w)



83% yield, 191 mg, 1 mmol scale, 98% linear selectivity. Colorless liquid. Eluent: pentane/ethyl acetate = 40/1.

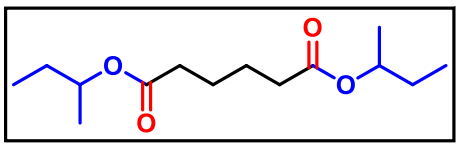
^{1}H NMR (300 MHz, $CDCl_3$) δ 5.06-4.93 (m, 2H), 2.31-2.24 (m, 4H), 1.66-1.60 (m, 4H), 1.22 (d, *J* = 6.3 Hz, 12H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 67.7, 34.5, 24.6, 22.0 ppm;

DEPT 135 NMR (75 MHz, $CDCl_3$) δ 67.7 (+), 34.5 (-), 24.6 (-), 22.0 (+) ppm;

HRMS (EI): Calcd. for $C_{12}H_{22}O_4Na^+$: 253.1416, Found:253.1422 $[M+Na]^+$.

Di-2-butyl adipate (4x)



75% yield, 194 mg, 1 mmol scale, 93% linear selectivity. Colorless liquid. Eluent: pentane/ethyl acetate = 40/1.

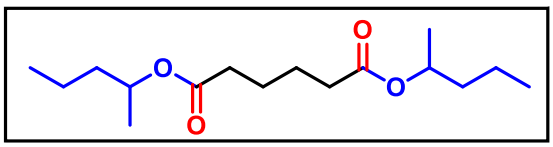
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.80-4.82 (m, 2H), 2.36-2.20 (m, 4H), 1.69-1.43 (m, 8H), 1.17 (d, *J* = 6.3 Hz, 6H), 0.86 (t, *J* = 7.5 Hz, 6H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 72.2, 34.4, 28.9, 24.6, 19.6, 9.8 ppm;

DEPT 135 NMR (75 MHz, $CDCl_3$) δ 72.2 (-), 34.4 (+), 28.9 (+), 24.6 (+), 19.6 (-), 9.8 (-) ppm;

HRMS (ESI): Calcd. for $C_{14}H_{26}O_4Na^+$:281.1723, Found:281.1728 $[M+Na]^+$.

Di-2-pentyl adipate (4y)



85% yield, 243 mg, 1 mmol scale, 97% linear selectivity. Colorless liquid. Eluent: pentane/ethyl acetate = 40/1.

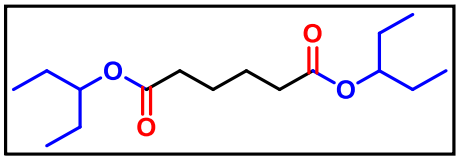
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.85-4.89 (m, 2H), 2.32-2.16 (m, 4H), 1.66-1.21 (m, 12H), 1.15 (d, *J* = 6.3 Hz, 6H), 0.86 (t, *J* = 7.2 Hz, 6H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 70.7, 38.1, 34.4, 24.6, 20.1, 18.7, 14.0 ppm;

DEPT 135 NMR (75 MHz, $CDCl_3$) δ 70.7 (+), 38.1 (-), 34.4 (-), 24.6 (-), 20.1 (+), 18.7 (-), 14.0 (+) ppm;

HRMS (ESI): Calcd. for $C_{16}H_{30}O_4Na^+$:309.2036, Found:309.2043 $[M+Na]^+$.

Di-3-pentyl adipate (4z)



71% yield, 203 mg, 1 mmol scale, 97% linear selectivity. Colorless liquid. Eluent: pentane/ethyl acetate = 40/1.

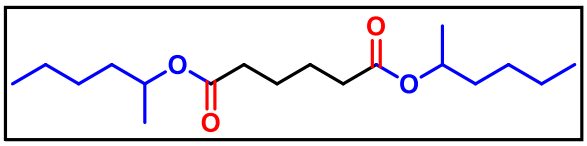
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.77-4.61 (m, 2H), 2.34-2.22 (m, 4H), 1.70-1.41 (m, 12H), 0.83 (t, *J* = 7.5 Hz, 12H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 76.6, 34.3, 26.5, 24.7, 9.7 ppm;

DEPT 135 NMR (75 MHz, $CDCl_3$) δ 76.6 (+), 34.3 (-), 26.5 (-), 24.7 (-), 9.7 (+) ppm;

HRMS (ESI): Calcd. for $C_{16}H_{30}O_4Na^+$:309.2036, Found:309.2043 $[M+Na]^+$.

Di-2-hexyl adipate (5a)



76% yield, 239 mg, 1 mmol scale, 97% selectivity of linear product, Colorless oil. Eluent: pentane/ethyl acetate = 30/1.

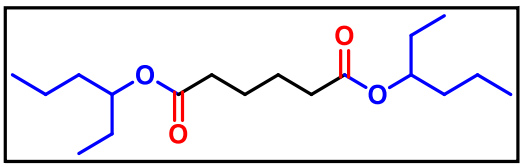
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.84 (m, 2H), 2.24 (m, 4H), 1.60 (m, 4H), 1.56-1.18 (m, 12H), 1.14 (d, *J* = 6.3 Hz, 6H), 0.83 (t, *J* = 6.7 Hz, 6H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 70.9, 35.7, 34.3, 27.6, 24.5, 22.5, 20.0, 14.0 ppm;

DEPT 135 NMR (75 MHz, $CDCl_3$) 70.9 (+), 35.7 (-), 34.3(-), 27.6 (-), 24.5 (-), 22.5 (-), 20.0 (+), 14.0 (+) ppm;

HRMS (ESI): Calcd. for $C_{18}H_{34}O_4Na^+$: 337.2349, Found: 337.2354 $[M+Na]^+$.

Di-3-hexyl adipate diester (5b)



77% yield, 242 mg, 1 mmol scale, 96% selectivity of linear product, Colorless liquid. Eluent: pentane/ethyl acetate = 30/1.

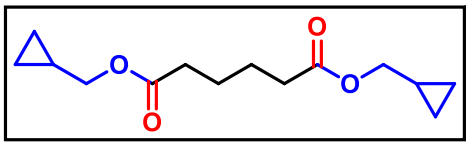
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.83-4.75 (m, 2H), 2.34-2.21 (m, 4H), 1.70-1.57 (m, 4H), 1.57-1.37 (m, 8H), 1.34-1.16 (m, 4H), 0.91-0.77(m, 12H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 75.2, 35.9, 34.3, 27.1, 24.7, 18.7, 14.0, 9.6 ppm;

DEPT 135 NMR (75 MHz, $CDCl_3$) δ 75.2 (-), 35.9 (+), 34.3 (+), 27.1 (+), 24.7 (+), 18.7 (+), 14.0 (-), 9.6 (-) ppm;

HRMS (ESI): Calcd. for $C_{18}H_{34}O_4Na^+$: 337.2349, Found: 337.2357 $[M+Na]^+$.

Dicyclopropanemethyl adipate (5c)



83% yield, 211 mg, 1 mmol scale, 94% linear selectivity. Colorless liquid. Eluent: pentane/ethyl acetate = 40/1.

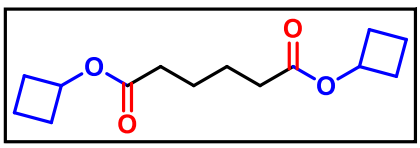
^{1}H NMR (300 MHz, $CDCl_3$) δ 3.76 (d, J = 7.3 Hz, 4H), 2.24-2.19 (m, 4H), 1.57-1.52 (m, 4H), 1.01-0.95 (m, 2H), 0.51-0.30 (m, 4H), 0.23-0.05 (m, 4H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 68.9, 33.8, 24.3, 9.7, 3.1 ppm;

DEPT 135 NMR (75 MHz, $CDCl_3$) δ 68.9 (+), 33.8 (+), 24.3 (+), 9.7 (-), 3.1 (+) ppm;

HRMS (ESI): Calcd. for $C_{14}H_{22}O_4Na^+$:277.1410, Found:277.1412 $[M+Na]^+$.

Dicyclobutyl adipate (5d)



87% yield, 221 mg, 1 mmol scale, 97% linear selectivity. Colorless liquid. Eluent: pentane/ethyl acetate = 40/1.

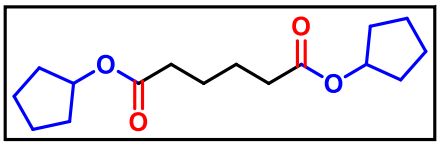
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.97-4.82 (m, 2H), 2.32-2.18 (m, 8H), 2.04-1.90 (m, 4H), 1.77-1.50 (m, 8H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 68.6, 33.9, 30.3, 24.3, 13.5 ppm;

DEPT 135 NMR (75 MHz, $CDCl_3$) δ 68.6 (-), 33.9 (+), 30.3 (+), 24.3 (+), 13.5 (+) ppm;

HRMS (ESI): Calcd. for $C_{14}H_{22}O_4Na^+$:277.1410, Found:277.1416 $[M+Na]^+$.

Dicyclopentyl adipate (5e)



82% yield, 231 mg, 1 mmol scale, 98% linear selectivity. Colorless liquid. Eluent: pentane/ethyl acetate = 40/1.

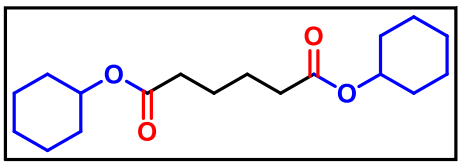
^{1}H NMR (300 MHz, $CDCl_3$) δ 5.14-5.08 (m, 2H), 2.29-2.15 (m, 4H), 1.91-1.75 (m, 4H), 1.69-1.51 (m, 16H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 77.0, 34.3, 32.7, 24.5, 23.8 ppm;

DEPT 135 NMR (75 MHz, $CDCl_3$) δ 77.0 (-), 34.3 (+), 32.7 (+), 24.5 (+), 23.8 (+) ppm;

HRMS (ESI): Calcd. for $C_{16}H_{26}O_4Na^+$:305.1723, Found:305.1731 $[M+Na]^+$.

Dicyclohexyl adipate (5f)



83% yield, 257 mg, 1 mmol scale, 96% linear selectivity. Colorless liquid. Eluent: pentane/ethyl acetate = 40/1.

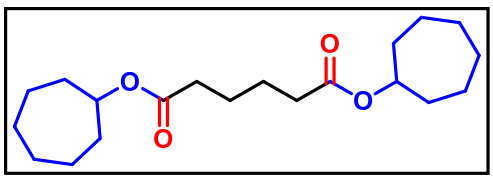
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.76-4.67 (m, 2H), 2.33-2.18 (m, 4H), 1.83-1.20 (m, 24H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 72.5, 34.4, 31.7, 25.5, 24.6, 23.8 ppm;

DEPT 135 NMR (75 MHz, $CDCl_3$) δ 72.5 (-), 34.4 (+), 31.7 (+), 25.5 (+), 24.6 (+), 23.8 (+) ppm;

HRMS (ESI): Calcd. for $C_{18}H_{30}O_4Na^+$:333.2036, Found:333.2038 $[M+Na]^+$.

Dicycloheptyl adipate (5g)



78% yield, 264 mg, 1 mmol scale, 96% linear selectivity. Colorless liquid. Eluent: pentane/ethyl acetate = 40/1.

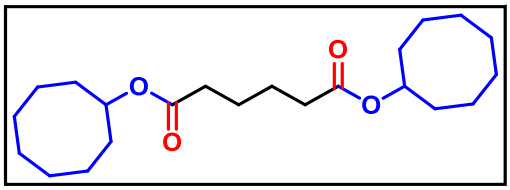
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.89-4.81 (m, 2H), 2.27-2.14 (m, 4H), 1.87-1.72 (m, 4H), 1.68-1.24 (m, 24H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 74.9, 34.3, 33.8, 28.2, 24.5, 22.9 ppm;

DEPT 135 NMR (75 MHz, $CDCl_3$) δ 74.9 (-), 34.3 (+), 33.8 (+), 28.2 (+), 24.5 (+), 22.9 (+) ppm;

HRMS (ESI): Calcd. for $C_{20}H_{34}O_4Na^+$:361.2349, Found:361.2354 $[M+Na]^+$.

Dicyclooctyl adipate (5h)



73% yield, 267 mg, 1 mmol scale, 95% linear selectivity. Colorless liquid. Eluent: pentane/ethyl acetate = 40/1.

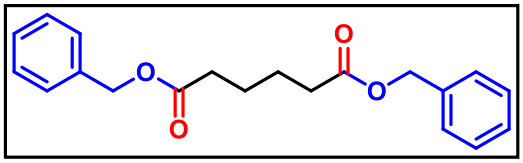
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.81-4.85 (m, 2H), 2.16-2.19 (m, 4H), 1.71-1.34 (m, 32H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 74.7, 34.3, 31.4, 27.0, 25.3, 24.4, 22.8 ppm;

DEPT 135 NMR (75 MHz, $CDCl_3$) δ 74.7 (-), 34.3 (+), 31.4 (+), 27.0 (+), 25.3 (+), 24.4 (+), 22.8 (+) ppm;

HRMS (ESI): Calcd. for $C_{22}H_{38}O_4Na^+$:389.2662, Found:389.2664 $[M+Na]^+$.

Dibenzyl adipate (5i)



88% yield, 287 mg, 1 mmol scale, 98% linear selectivity. Colorless liquid. Eluent: pentane/ethyl acetate = 40/1.

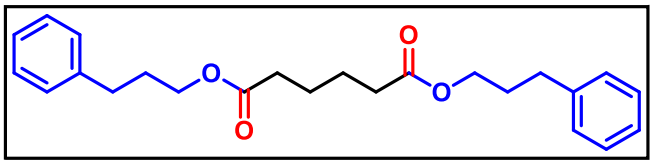
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79-6.97 (m, 10H), 5.13 (s, 4H), 2.49-2.31 (m, 4H), 1.79-1.64 (m, 4H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 136.0, 128.6, 128.2, 128.2, 66.2, 33.9, 24.4 ppm;

DEPT 135 NMR (75 MHz, $CDCl_3$) δ 128.6 (+), 128.3 (+), 128.3 (+), 66.2(-), 33.9 (-), 24.4 (-) ppm;

HRMS (ESI): Calcd. for $C_{20}H_{22}O_4Na^+$:349.1410, Found:349.1420 $[M+Na]^+$.

Di-(3-phenyl-1-propyl) adipate (5j)



74% yield, 283 mg, 1 mmol scale, 96% linear selectivity. Light yellow powder. Eluent: pentane/ethyl acetate = 40/1.

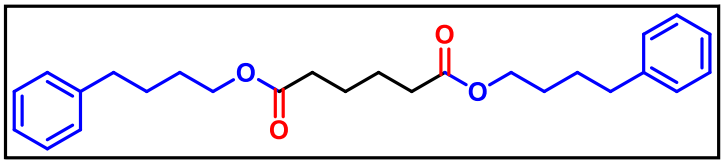
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49-7.07 (m, 10H), 4.16 (t, J = 6.6 Hz, 4H), 2.87-2.65 (m, 4H), 2.49-2.30 (m, 4H), 2.1-1.91 (m, 4H), 1.85-1.63 (m, 4H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 141.1, 128.4, 128.4, 126.0, 63.7, 33.9, 32.2, 30.2, 24.4 ppm;

DEPT 135 NMR (75 MHz, $CDCl_3$) δ 128.4 (+), 128.4 (+), 126.0 (+), 63.7(-), 33.9 (-), 32.2 (-), 30.2 (-), 24.4 (-) ppm;

HRMS (ESI): Calcd. for $C_{24}H_{30}O_4Na^+$:405.2036, Found:405.2043 $[M+Na]^+$.

Di-(4-phenyl-1-butyl) adipate (5k)



75% yield, 308 mg, 1 mmol scale, 97% linear selectivity. Light yellow powder. Eluent: pentane/ethyl acetate = 40/1.

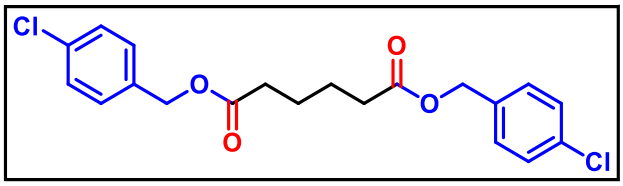
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64-7.29 (m, 10H), 4.46-4.16 (m, 4H), 2.85-2.78 (m, 4H), 2.55-2.45 (m, 4H), 1.95-1.82 (m, 12H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 141.8, 128.2, 128.2, 125.7, 64.0, 35.3, 33.7, 28.1, 27.6, 24.3 ppm;

DEPT 135 NMR (75 MHz, $CDCl_3$) δ 128.2 (+), 128.2 (+), 125.7 (+), 64.0 (-), 35.3 (-), 33.7 (-), 28.1 (-), 27.6 (-), 24.3 (-) ppm;

HRMS (ESI): Calcd. for $C_{26}H_{34}O_4Na^+$:433.2349, Found:433.2350 $[M+Na]^+$.

Di-(4-chlorobenzyl) adipate (5l)



75% yield, 296 mg, 1 mmol scale, 93% linear selectivity. White powder. Eluent: pentane/ethyl acetate = 40/1.

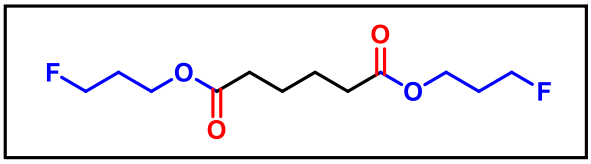
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.23 (m, 8H), 5.06 (s, 4H), 2.43-2.30 (m, 4H), 1.72-1.59 (m, 4H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 134.6, 134.1, 129.6, 128.8, 65.4, 33.8, 24.3 ppm;

DEPT 135 NMR (75 MHz, $CDCl_3$) δ 129.6 (+), 128.8(+), 65.4 (-), 33.8 (-), 24.3 (-) ppm;

HRMS (ESI): Calcd. for $C_{20}H_{20}Cl_2O_4Na^+$:417.0630, Found:417.0639 $[M+Na]^+$.

Di-(3-Fluoro-1-propyl) adipate (5m)



86% yield, 229 mg, 1 mmol scale, 95% linear selectivity. Colorless liquid. Eluent: pentane/ethyl acetate = 30/1.

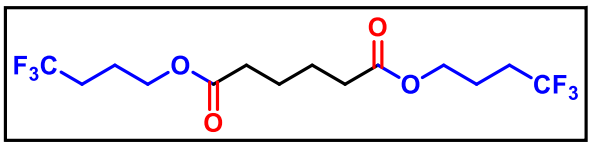
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.49 (dt, *J* = 47.0, 5.8 Hz, 4H), 4.17 (t, *J* = 6.3 Hz, 4H), 2.36-2.24 (m, 4H), 1.97 (dq, *J* = 24.9, 6.1 Hz, 4H), 1.67-1.58 (m, 4H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 81.8, 79.6, 60.4, 60.3, 33.8, 29.9, 29.7, 24.4 ppm;

DEPT 135 NMR (75 MHz, $CDCl_3$) δ 81.8 (+), 79.6 (+), 60.4 (+), 33.8 (+), 29.9 (+), 29.7 (+), 24.4 (+) ppm;

HRMS (ESI): Calcd. for $C_{12}H_{20}O_4F_2Na^+$:289.1227, Found:289.1233 $[M+Na]^+$.

Di-(4,4,4-trifluoro-1-butyl) adipate (5n)



82% yield, 300 mg, 1 mmol scale, 92% linear selectivity. Colorless liquid. Eluent: pentane/ethyl acetate = 30/1.

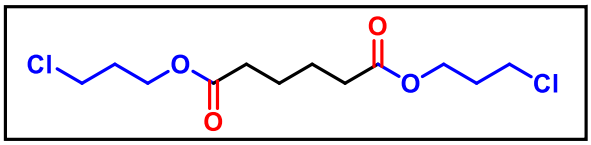
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.12 (t, *J* = 6.3 Hz, 4H), 2.41-2.26 (m, 4H), 2.26-2.03 (m, 4H), 1.99-1.81 (m, 4H), 1.74-1.54 (m, 4H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 128.8, 62.7, 33.8, 31.4, 24.4, 21.7 ppm;

DEPT 135 NMR (75 MHz, $CDCl_3$) δ 62.7 (+), 33.8 (+), 30.6 (+), 24.4 (+), 21.7 (+) ppm;

HRMS (ESI): Calcd. for $C_{14}H_{20}O_4F_6Na^+$:389.1158, Found:389.1165 $[M+Na]^+$.

Di-(3-chloro-1-propyl) adipate (5o)



85% yield, 254 mg, 1 mmol scale, 95% linear selectivity. Colorless liquid. Eluent: pentane/ethyl acetate = 20/1.

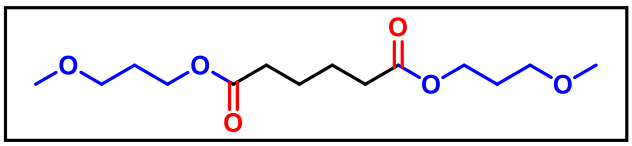
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.18 (t, *J* = 6.4 Hz, 4H), 3.57 (t, *J* = 6.4 Hz, 4H), 2.35-2.25 (m, 4H), 2.10-2.01 (m, 4H), 1.67-1.58 (m, 4H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 61.1, 41.4, 33.8, 31.6, 24.4 ppm;

DEPT 135 NMR (75 MHz, $CDCl_3$) δ 61.1 (+), 41.3 (+), 33.8 (+), 31.6 (+), 24.4 (+) ppm;

HRMS (ESI): Calcd. for $C_{12}H_{20}O_4Cl_2Na^+$:321.0636, Found:321.0640 $[M+Na]^+$.

Di-(3-methoxy-1-propyl) adipate (5p)



78% yield, 226 mg, 1 mmol scale, 97% linear selectivity. Colorless liquid. Eluent: pentane/ethyl acetate = 20/1.

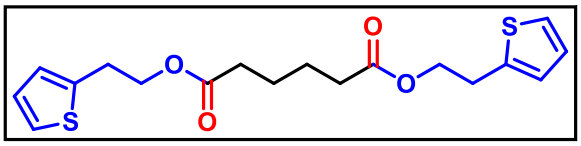
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.15 (t, *J* = 6.5 Hz, 4H), 3.43 (t, *J* = 6.3 Hz, 4H), 3.32 (s, 6H), 2.32-2.29 (m, 4H), 1.88 (m, 4H), 1.66 (m, 4H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 69.3, 61.7, 58.8, 34.0, 29.1, 24.5 ppm;

DEPT 135 NMR (75 MHz, $CDCl_3$) δ 69.3 (+), 61.7 (+), 58.8 (-), 34.0 (+), 29.1 (+), 24.5 (+) ppm;

HRMS (ESI): Calcd. for $C_{14}H_{26}O_6Na^+$:313.1621, Found:313.1628 $[M+Na]^+$.

Di-(2-thiopheneethyl) adipate (5q)



71% yield, 260 mg, 1 mmol scale, 94% linear selectivity. Light yellow solid. Eluent: pentane/ethyl acetate = 20/1.

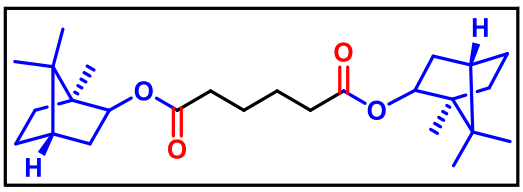
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (dd, *J* = 4.9, 2.9 Hz, 2H), 7.08-7.02 (m, 2H), 6.99 (dd, *J* = 4.9, 1.3 Hz, 2H), 4.32 (t, *J* = 6.9 Hz, 4H), 2.99 (t, *J* = 6.9 Hz, 4H), 2.37-2.28 (m, 4H), 1.67-1.61 (m, 4H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 138.0, 128.2, 125.6, 121.5, 64.1, 33.9, 29.6, 24.3 ppm;

DEPT 135 NMR (75 MHz, $CDCl_3$) δ 128.2 (-), 125.6 (-), 121.5 (-), 64.1 (+), 33.9 (+), 29.6 (+), 24.3 (+) ppm;

HRMS (ESI): Calcd. for $C_{18}H_{22}O_4S_2Na^+$:389.0851, Found:389.0858 $[M+Na]^+$.

Di-(L-bornyl) adipate (5r)



71% yield, 297 mg, 1 mmol scale, 94% linear selectivity. White solid. Eluent: pentane/ethyl acetate = 20/1.

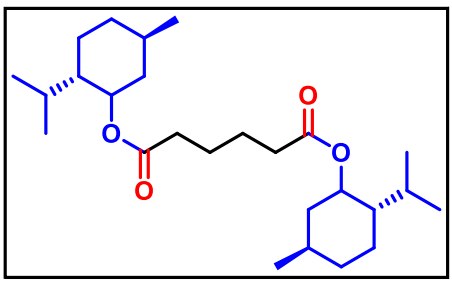
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.86 (m, 2H), 2.44-2.24 (m, 6H), 1.90 (m, 2H), 1.77-1.59 (m, 8H), 1.31-1.17 (m, 4H), 0.92 (dd, *J* = 13.7, 3.5 Hz, 2H), 0.88-0.76 (m, 18H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 79.8, 48.8, 47.9, 45.0, 36.9, 34.4, 28.1, 27.2, 24.7, 19.8, 18.9, 13.6 ppm;

DEPT 135 NMR (75 MHz, $CDCl_3$) δ 79.8 (-), 45.0 (-), 36.9 (+), 34.4 (+), 28.1 (+), 27.2 (+), 24.7 (+), 19.8 (-), 18.9 (-), 13.6 (-) ppm;

HRMS (ESI): Calcd. for $C_{26}H_{42}O_4Na^+$:441.2975, Found:441.2979 $[M+Na]^+$.

Di-(L-menthyl) adipate (5s)



72% yield, 304 mg, 1 mmol scale, 92% linear selectivity. White solid. Eluent: pentane/ethyl acetate = 30/1.

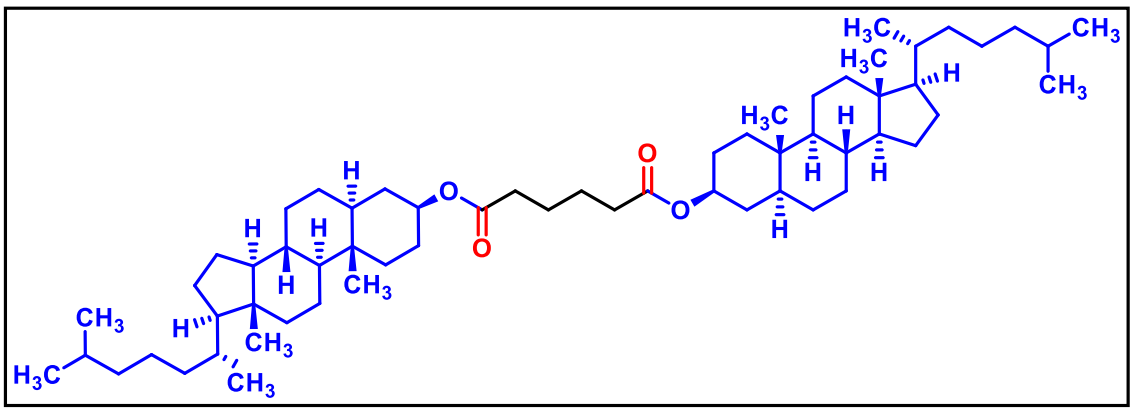
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.67 (td, *J* = 10.9, 4.4 Hz, 2H), 2.30 (m, 4H), 2.02-1.76 (m, 4H), 1.66 (m, 8H), 1.52-1.23 (m, 6H), 1.08-0.92 (m, 4H), 0.89 (dd, J = 6.8, 2.7 Hz, 12H), 0.75 (d, J = 7.0 Hz, 6H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 74.2, 47.2, 41.1, 34.5, 34.4, 31.5, 26.5, 24.7, 23.6, 22.2, 20.9, 16.5 ppm;

DEPT 135 NMR (75 MHz, $CDCl_3$) δ 74.2 (-), 47.2 (-), 41.1 (+), 34.5 (+), 34.4 (+), 31.5(-), 26.5 (-), 24.7 (+), 23.6 (+), 22.2(-), 20.9 (-), 16.5 (-) ppm;

HRMS (ESI): Calcd. for $C_{26}H_{46}O_4Na^+$:445.3288, Found:445.3296 $[M+Na]^+$.

Dicholesteryl adipate (5t)



57% yield, 505 mg, 1 mmol scale, 91% linear selectivity. White powder. Eluent: pentane/ethyl acetate = 20/1.

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.71-4.60 (m, 2H), 2.24 (s, 4H), 1.99-1.89 (m, 2H), 1.81-1.40 (m, 24H), 1.35-0.95 (m, 40H), 0.88-0.76 (m, 24H), 0.64-0.58 (m, 6H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 73.6, 56.5, 56.4, 54.3, 44.7, 42.7, 40.1, 39.6, 36.8, 36.3, 35.9, 35.6, 35.5, 34.4, 34.1, 32.1, 28.7, 28.3, 28.1, 27.6, 24.6, 24.3, 24.0, 22.9, 22.7, 21.3, 18.8, 12.3, 12.2 ppm;

DEPT 135 NMR (75 MHz, $CDCl_3$) δ 73.6 (+), 56.5 (+), 56.4 (+), 54.3 (+), 44.7 (+), 40.1 (-), 39.6 (-), 36.8 (-), 36.3 (-), 35.9 (+), 35.6 (+), 34.4 (-), 34.1 (-), 32.1 (-), 28.7 (-), 28.3 (-), 28.1 (+), 27.6 (-), 24.6 (-), 24.3 (-), 24.0 (-), 22.9 (+), 22.7 (+), 21.3 (-), 18.8 (+), 12.3 (+), 12.2 (+) ppm;

HRMS (EI): Calcd. for $C_{60}H_{102}O_4$: 886.77726, Found: 886.77626 $[M]^+$.

Supporting Information

Palladium-Catalyzed Aerobic Oxidative Carbonylation of Alkynes with Amines: A General Access to Substituted Maleimides

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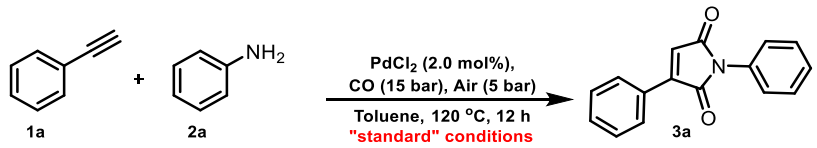
General Considerations

All commercial reagents were ordered from Alfa Aesar, Aldrich, TCI or Strem. Unless otherwise statement, commercial reagents were used without purification. Air- and moisture-sensitive syntheses were performed under argon atmosphere in heating gun vacuum dried glassware. Analytical data of literature known compounds were in accord with reported data. NMR spectra were recorded on Bruker Avance 300 (300 MHz) NMR spectrometers. Multiplets were assigned as s (singlet), d (doublet), t (triplet), dd (doublet of doublet), m (multiplet) and br. s (broad singlet). All measurements were carried out at room temperature unless otherwise stated. Electron impact (EI) mass spectra were recorded on AMD 402 mass spectrometer (70 eV). High resolution mass spectra (HRMS) were recorded on Agilent 6210 Time-of-Flight LC/MS (Agilent) with electrospray ionization (ESI). The data are given as mass units per charge (m/z) and intensities of signals are given in brackets. For GC analyses, HP 6890 chromatograph with a 29 m HP5 column was used.

Experimental sections

Preparation of Poly-substituted Maleimides

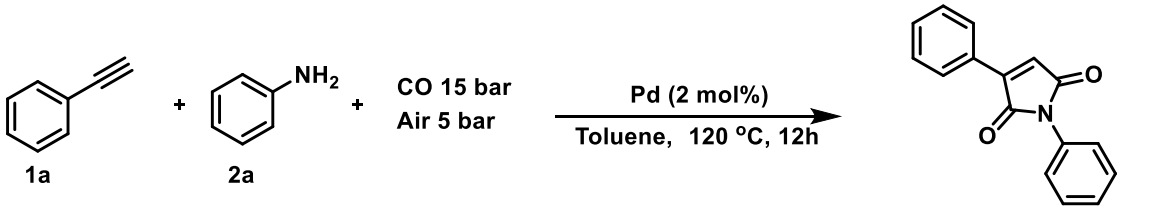


A 4 mL screw-cap vial was charged with palladium salt (2.0 mol%)), toluene (2.0 mL), amine (1.0 mmol), alkyne (1.5 mmol) and a stirring bar. The vial was closed by PTFE/white rubber septum (Wheaton 13 mm Septa) and phenolic cap and connected with atmosphere with a needle. Then, the vial was fixed in an alloy plate and put into a Paar 4560 series autoclave (300 mL). At room temperature, the autoclave is flushed with air (5 bar) and carbon monoxide (15 bar; total pressure = 20 bar).

The reaction was heated at the specified temperature (usually 120 °C) for 12 hours. Afterwards, the autoclave was cooled to room temperature and the pressure was carefully released. Isooctane (0.5 mmol) was added into the reaction as internal standard. A sample of the mixture was analyzed by gas chromatography. Pure product could be obtained by column chromatography on silica gel (eluent: pentane/ethyl acetate = 20:1).

Optimization of reaction conditions.

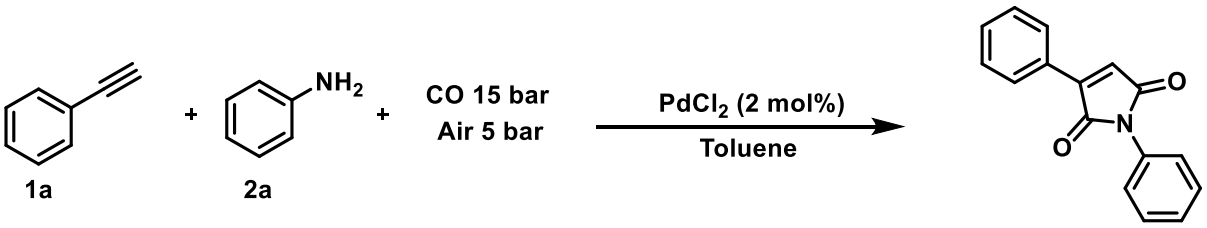
The effect of palladium precursors.



Entry	Add in reaction	Conversions [%]	Yield [%]	Notes
1	$Pd(acac)_2$	>99	trace	Ph—≡—≡—Ph by product yield 95%
2	$Pd(acac)_2$, Xantphos, LiI, H_2O	>99	95	
3	$Pd(acac)_2$, LiI, H_2O	>99	96	
4	$PdCl_2$	>99	96	
5	PdI_2	>99	96	

Reaction conditions:1a (0.75 mmol), 2a (0.5 mmol), Pd (2.0 mol%), ligand (2.0 mol%), CO (15 bar), air (5 bar), toluene (2.0 mL), H_2O (0.1 mL), 120 °C, 12 h. Yields were determined by GC analysis using isooctane as the internal standard.

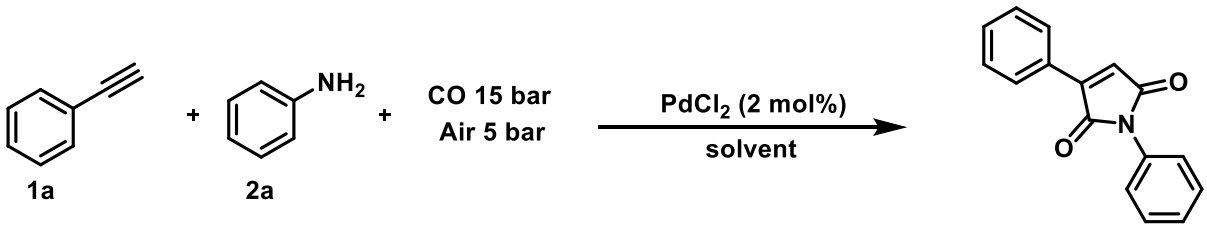
The effect of temperature.



Entry	Temperature [°C]	Conversions [%]	Yield [%]
1	125	>99	96
2	120	>99	96
3	100	>99	82
4	80	77	60
5	60	34	32

Reaction conditions:1a (1.5 mmol), 2a (1.0 mmol), $PdCl_2$ (2 mol%), CO (15 bar), air (5 bar), toluene (2.0 mL), 12 h. Yields were determined by GC analysis using isooctane as the internal standard.

The effect of solvent.



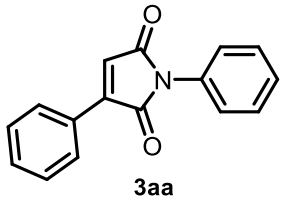
1a 2a

Entry	Solvent	Conversions [%]	Yield [%]
1	THF	>99	81
2	toluene	>99	82
3	Anisole	>99	69
4	MeCN	>99	42
5	Diglyme	>99	78
6	DMF	>99	26
7	1,4-dioxane	>99	77

In order to better investigate the difference between different solvents, we reduced the reaction temperature to 100 ^{o}C.

Reaction conditions:1a (1.5 mmol), 2a (1.0 mmol), $PdCl_2$ (2 mol%), CO (15 bar), air (5 bar), solvent (2.0 mL), 100 ^{o}C, 12 h. Yields were determined by GC analysis using isooctane as the internal standard.

Characterization of products



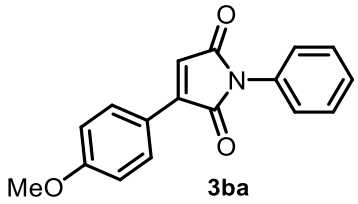
3aa

1,3-diphenyl-1H-pyrrole-2,5-dione:

229.1 mg, 92% yield, yellow solid, 1 mmol scale substrate.

^{1}H NMR (300MHz , $CDCl_3$) δ 7.89-7.85 (m, 2H), 7.40-7.34 (m, 5H), 7.30-7.25 (m, 3H), 6.75 (s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 169.44, 169.17, 143.69, 131.54, 131.38, 129.13, 129.05, 128.83, 128.61, 127.89, 126.26, 124.09.



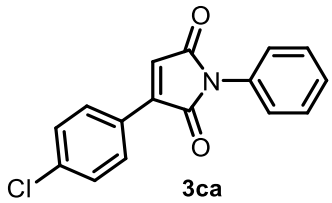
3ba

3-(4-methoxyphenyl)-1-phenyl-1H-pyrrole-2,5-dione:

206.5 mg, 74% yield, yellow solid, 1 mmol scale substrate.

^{1}H NMR (300 MHz , $CDCl_3$) δ 7.92-7.80 (m, 2H), 7.42-7.32(m, 2H), 7.31-7.24 (m, 3H), 6.90-6.84 (m, 2H), 6.61 (s, 1H), 3.74 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 169.73, 169.43, 162.14, 143.04, 131.61, 130.58, 128.99, 127.68, 126.19, 121.20, 120.95, 114.51, 77.48, 77.06, 76.64, 55.39.



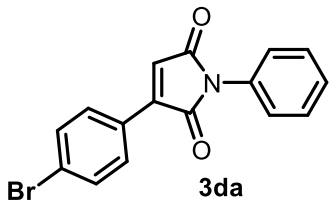
3ca

3-(4-chlorophenyl)-1-phenyl-1H-pyrrole-2,5-dione:

240.6 mg, 85% yield, yellow solid, 1 mmol scale substrate.

^{1}H NMR (400 MHz , $CDCl_3$) δ 7.84-7.78 (m, 2H), 7.37-7.26 (m, 6H), 6.74 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.15, 168.80, 142.34, 137.64, 131.33, 130.00, 129.30, 129.08, 127.91, 126.94, 126.14, 124.13.



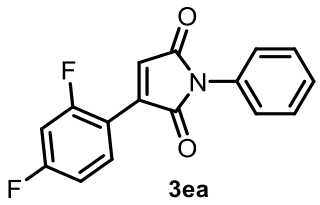
3da

3-(4-bromophenyl)-1-phenyl-1H-pyrrole-2,5-dione:

240.6 mg, 83% yield, yellow solid, 1 mmol scale substrate.

^{1}H NMR (400 MHz , $CDCl_3$) δ 7.90-7.83 (m, 2H), 7.65-7.59 (m, 2H), 7.52-7.45 (m, 2H), 7.41-7.35 (m, 3H), 6.88 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.15, 168.85, 142.56, 132.36, 131.36, 130.20, 129.14, 127.99, 127.41, 126.28, 126.20, 124.25.



3ea

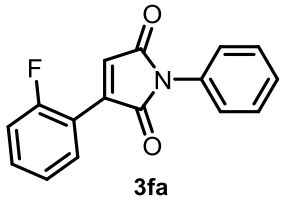
3-(2,4-difluorophenyl)-1-phenyl-1H-pyrrole-2,5-dione:

239.4 mg, 84% yield, yellow solid, 1 mmol scale substrate.

^{1}H NMR (400 MHz , $CDCl_3$) δ 8.42-8.18 (m, 1H), 7.45-7.35 (m, 2H), 7.32-7.26 (m, 3H), 6.97 (d, J = 2.8 Hz, 1H), 6.95-6.83 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.35, 169.23, 166.06 (d, *J* = 12.3 Hz), 164.52 (d, *J* = 11.8 Hz), 162.67 (d, *J* = 12.3 Hz), 161.10 (d, *J* = 11.8 Hz), 132.67 (dd, *J* = 10.0, 3.2 Hz), 131.32, 129.15, 128.02, 127.59 (dd, *J* = 14.3, 2.4 Hz), 126.24, 112.20 (dd, *J* = 21.2, 3.6 Hz), 104.98 (t, *J* = 25.8 Hz).

HRMS (ESI) calculated for $C_{16}H_9F_2NO_2(M+H)^+$: 286.0680; found: 286.0668.



3fa

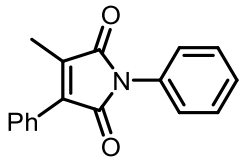
3-(2-fluorophenyl)-1H-pyrrole-2,5-dione,

232.3 mg, 87% yield, yellow solid, 1 mmol scale substrate.

^{1}H NMR (300 MHz , $CDCl_3$) δ 8.20 (td, J = 7.7, 1.7 Hz, 1H), 7.40-7.23 (m, 6H), 7.20-7.05 (m, 2H), 6.99 (d, J = 2.6 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 169.29, 162.08 (d, *J* = 255.5 Hz), 136.98, 132.58 (d, J = 9.1 Hz), 131.34, 131.22, 129.06, 128.30 (d, *J* = 14.0 Hz), 127.88, 126.19, 124.57 (d, *J* = 3.7 Hz), 116.91 (d, *J* = 11.0 Hz), 116.17 (d, *J* = 22.0 Hz).

HRMS (ESI) calculated for $C_{16}H_{10}FNO_2$ $(M+H)^+$: 268.0774; found: 268.0758.



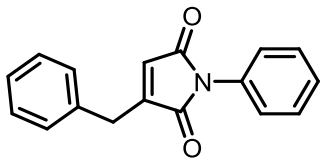
3ga

3-methyl-1,4-diphenyl-1H-pyrrole-2,5-dione:

168.3 mg, 63% yield, yellow solid, 1 mmol scale substrate.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60-7.50 (m, 2H), 7.45-7.30 (m, 7H), 7.30-7.20 (m, 1H), 2.20 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.74, 169.74, 137.17, 136.79, 131.85, 129.77, 129.64, 129.03, 128.81, 128.62, 127.60, 125.98, 10.15.



3ha

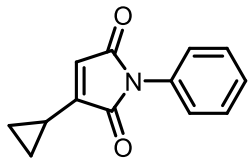
1-phenyl-3-phenylmethyl-1H-pyrrole-2,5-dione:

228.8 mg, 87% yield, yellow solid, 1 mmol scale substrate.

^{1}H NMR (300 MHz , $CDCl_3$) δ 7.40-7.14 (m, , 10H), 6.16 (t, J = 1.9 Hz, 1H), 3.73 (d, *J* = 1.9 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.08, 169.34, 149.23, 135.66, 131.54, 129.10, 129.05, 129.00, 127.70, 127.45, 127.30, 125.87, 32.00.

HRMS (ESI) calculated for $C_{17}H1_3NO_2$ $(M+H)^+$: 264.1025; found: 264.1016.



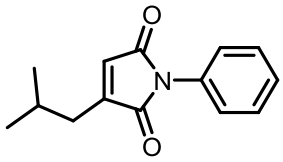
3ia

3-cyclopropyl-1-phenyl-1H-pyrrole-2,5-dione,

193.8 mg, 91% yield, yellow solid, 1 mmol scale substrate.

^{1}H NMR (300 MHz , $CDCl_3$) δ 7.40-7.30 (m, 2H), 7.28-7.22(m, 3H), 6.02(s, 1H), 1.90-1.82 (m, 1H), 1.15-1.10 (m,2H), 1.00-0.94 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 169.63, 169.16, 153.44, 131.54, 128.94, 127.54, 125.92, 120.65, 12.00, 8.38.



3ja

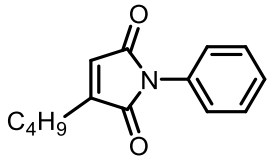
***3-(2-methylpropyl)-1-phenyl-1H-pyrrole-2,5-dione*:**

210.7 mg, 92% yield, yellow solid, 1 mmol scale substrate.

^{1}H NMR (300 MHz , $CDCl_3$) δ 7.40-7.33 (m, 2H), 7.29-7.20 (m, 3H), 6.34 (t, J = 1.5 Hz, 1H), 2.32 (dd, J = 7.0, 1.5 Hz, 2H), 2.05-1.80 (m, 1H), 0.92 (d, J = 6.7 Hz, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.50, 169.65, 148.90, 131.63, 128.98, 127.57, 127.20, 125.84, 34.30, 27.18, 22.43.

HRMS (ESI) calculated for $C_{14}H_{15}NO_2$ $(M+H)^+$: 230.1181; found: 230.1173.



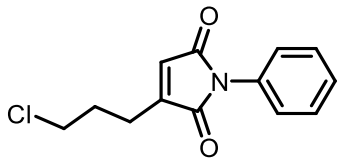
3ka

3-butyl-1-phenyl-1H-pyrrole-2,5-dione:

208.4 mg, 91% yield, yellow solid, 1 mmol scale substrate.

^{1}H NMR (300 MHz , $CDCl_3$) δ 7.50-7.42 (m,2H), 7.38-7.30 (m, 3H), 6.43 (t, J = 1.8 Hz, 1H), 2.57-2.50 (m, 2H), 1.70-1.55 (m, 2H), 1.50-1.40 (m, 2H), 0.97 (t, J = 7.3 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.49, 169.80, 150.41, 131.67, 129.10, 127.70, 126.37, 125.97, 29.22, 25.27, 22.40, 13.80.



3la

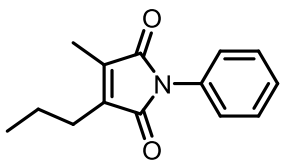
3-(3-chloro-propyl)-1-phenyl-1H-pyrrole-2,5-dione:

201.7 mg, 81% yield, yellow solid, 1 mmol scale substrate.

^{1}H NMR (400 MHz , $CDCl_3$) δ 7.50-7.40 (m, 2H), 7.40-7.29 (m, 3H), 6.48-6.45 (m, 1H), 3.61 (t, *J* = 6.3 Hz, 2H), 2.73-2.63 (m, 2H), 2.18-2.06 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.02, 169.25, 148.37, 131.46, 129.04, 127.72, 125.85, 77.48, 77.06, 76.64, 43.78, 29.72, 22.99.

HRMS (ESI) calculated for $C_{13}H_{12}ClNO_2$ $(M+H)^+$: 250.0635; found: 250.0626.



3ma

3-methyl-1-phenyl -4-propyl -1H-pyrrole-2,5-dione:

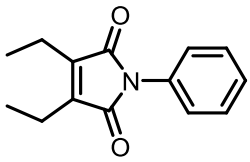
187.8 mg, 82% yield, yellow solid, 1 mmol scale substrate.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.15(m, 5H), 2.45-2.30 (m, 2H), 1.98 (s, 3H), 1.60-1.50 (m, 2H),

0.91 (t, J = 7.4 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.01, 170.71, 141.10, 137.49, 131.99, 128.96, 127.36, 125.75, 25.74, 21.62, 14.06, 8.92.

HRMS (ESI) calculated for $C_{14}H_{15}NO_2$ $(M+H)^+$: 230.1181; found: 230.1178.



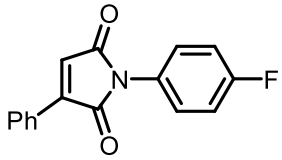
3na

3,4-diethyl-1-phenyl-1H-pyrrole-2,5-dione:

162.6 mg, 71% yield, yellow solid, 1 mmol scale substrate.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48-7.40 (m, 2H), 7.40-7.30 (m, 3H), 2.51 (q, J = 7.6 Hz, 4H), 1.21 (t, J = 7.6 Hz, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.71, 141.94, 131.98, 128.97, 127.36, 125.78, 17.18, 13.38.



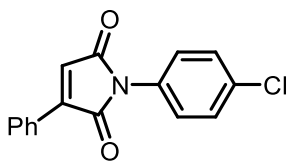
3ab

1-(4-fluorophenyl)-3-phenyl-1H-pyrrole-2,5-dione:

243.0 mg, 91% yield, , yellow solid, 1 mmol scale substrate.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00-7.95 (m, 2H), 7.52-7.46 (m,*3*H), 7.41-7.35 (m, 2H), 7.20-7.13 (m, 2H), 6.87 (s, 1H), 3.05 (t, *J* = 7.0 Hz, 2H)

^{13}C NMR (75 MHz, $CDCl_3$) δ 169.34, 169.03, 161.75 (d, *J* = 247.8 Hz), 143.77, 131.45, 129.05, 128.77, 128.46, 128.04 (d, *J* = 8.7 Hz), 127.39 (d, *J* = 3.2 Hz), 123.95, 116.08 (d, J = 22.9 Hz).



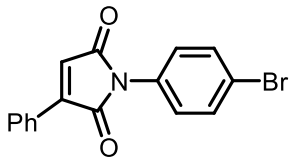
3ac

1-(4-chlorophenyl)-3-phenyl-1H-pyrrole-2,5-dione:

237.7 mg, 84% yield, yellow solid, 1 mmol scale substrate.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00-7.93 (m, 2H), 7.52-7.40 (m, 5H), 7.42-7.33 (m, 2H), 6.87 (s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ169.12, 168.82, 143.88, 133.53, 131.53, 130.03, 129.29, 129.08, 128.81, 128.41, 127.29, 124.02.



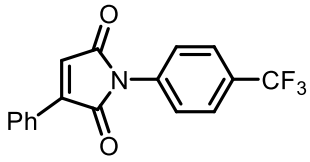
3ad

1-(4-bromophenyl)-3-phenyl-1H-pyrrole-2,5-dione:

265.7 mg, 81% yield, yellow solid, 1 mmol scale substrate.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00-7.93 (m, 2H), 7.63-7.55 (M, 2H), 7.53-7.45 (m, 3H), 7.35-7.30 (m, 2H), 6.87 (s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 169.05, 168.74, 143.87, 132.26, 131.54, 130.58, 129.09, 128.82, 128.40, 127.56, 124.04, 121.51.



3ae

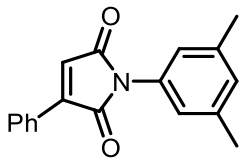
1-(4-(trifluoromethyl)phenyl)-3-phenyl-1H-pyrrole-2,5-dione:

301.2 mg, 95% yield, yellow solid, 1 mmol scale substrate.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00-7.95 (m, 2H), 7.75 (d, J = 8.4 Hz, 2H), 7.61 (d, J = 8.9 Hz, 2H), 7.55-7.45 (m, 3H), 6.90 (s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 168.91, 168.56, 144.03, 134.74, 131.67, 129.53 (d, J = 32.9 Hz), 128.99 (d, J = 28.8 Hz), 128.29, 126.21 (q, *J* = 3.7 Hz), 125.93, 124.09, 123.82 (CF_3, d, J = 272.2 Hz), 119.76.

HRMS (ESI) calculated for $C_{17}H_{10}F_3NO_2$ $(M+H)^+$: 318.0742; found: 318.0738.



3af

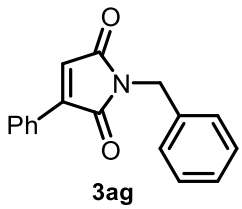
1-(3,5-dimethylphenyl)-3-phenyl-1H-pyrrole-2,5-dione:

252.1 mg, 91% yield , yellow solid, 1 mmol scale substrate.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00-7.95 (m, 2H), 7.52-7.45 (m, 3H), 7.02 (d, J = 11.0 Hz, 1H), 6.85 (s, 1H), 2.38 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) 169.65, 169.38, 143.61, 138.91, 131.31, 131.21, 129.89, 129.02, 128.81, 128.69, 124.21, 124.06, 21.34.

HRMS (ESI) calculated for $C_{18}H_{15}NO_2$ $(M+H)^+$: 278.1181; found: 278.1175.



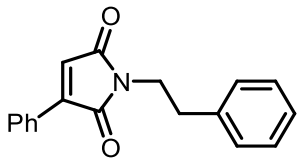
3ag

3-phenyl-1-(phenylmethyl)-1H-pyrrole-2,5-dione:

239.3 mg, 91% yield, yellow solid, 1 mmol scale substrate.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85-7.78 (m, 2H), 7.40-7.33 (m, 5H), 7.33-7.15 (m, 3H), 6.63 (s, 1H), 4.64 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.37, 170.01, 143.82, 136.40, 131.17, 128.94, 128.73, 128.71, 128.63, 128.52, 127.85, 123.91, 41.60.



3ah

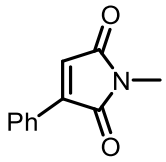
3-phenyl-1-(2-phenylethyl)-1H-pyrrole-2,5-dione:

241.0mg, 87% yield, yellow solid, 1 mmol scale substrate.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85-7.75 (m, 2H), 7.40-7.34 (m, 3H), 7.24-7.18 (m, 2H), 7.17-7.12 (m, 3H), 6.60 (s, 1H), 3.80-3.70 (m, 2H), 2.90-2.83 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.45, 170.16, 143.68, 138.00, 131.09, 128.93, 128.86, 128.76, 128.59, 128.57, 126.65, 123.84, 39.29, 34.62.

HRMS (ESI) calculated for $C_{18}H_{15}NO_2$ $(M+H)^+$: 278.1181; found: 278.1176.



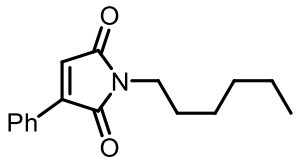
3ai

1-methyl-3-phenyl-1H-pyrrole-2,5-dione:

142.1 mg, 76% yield, yellow solid, 1 mmol scale substrate.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95-7.90 (m, 2H), 7.50-7.40 (m, 3H), 6.73 (s, 1H), 3.07 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.75, 170.45, 143.94, 131.10, 128.94, 128.76, 128.57, 123.91, 23.88.



3aj

1-pentyl-3-phenyl-1H-pyrrole-2,5-dione:

215.9 mg, 84% yield, yellow solid, 1 mmol scale substrate.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00-7.90 (m, 2H), 7.48-7.44 (m, 3H), 6.71 (s, 1H), 3.60-3.54 (m, 2H), 1.64-1.60 (m, 2H), 1.29-1.33 (m, 6H), 0.85-0.92 (m , 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.76, 170.51, 143.63, 132.51, 131.04, 128.93, 128.60, 123.87, 38.10, 31.37, 28.57, 26.49, 22.54, 14.04.

Supporting Information

A General Platinum-catalyzed Alkoxycarbonylation of Olefins

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Robert Franke, Helfried Neumann, Ralf Jackstell, and Matthias Beller*

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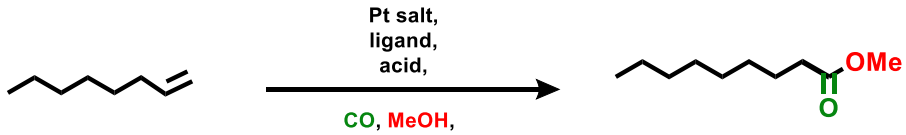
S1. General information: Materials and methods

All commercial reagents were ordered from Alfa Aesar, Aldrich, TCI or Strem. Unless otherwise stated, commercial reagents were used without purification. Air- and moisture-sensitive syntheses were performed under argon atmosphere in heating gun vacuum dried glassware. Analytical data of literature known compounds were in agree with reported data. NMR spectra were recorded on Bruker Avance 300 (300 MHz) or 400 (400 MHz) NMR spectrometers. Chemical shifts δ (ppm) are given relative to solvent: references for $CDCl_3$ were 7.26 ppm (^{1}H NMR) and 77.16 ppm (^{13}C NMR), for CD_2Cl_2 were 5.32 ppm (^{1}H NMR) and 53.84 ppm (^{13}C NMR), for d_6-benzene were 7.16 ppm (^{1}H NMR) and 128.26 ppm (^{13}C NMR), and for d_8-toluene were 2.08 ppm (^{1}H NMR) and 20.43 ppm (^{13}C NMR). Signals were assigned as s (singlet), d (doublet), t (triplet), dd (doublet of doublet), m (multiplet) and br. s (broad singlet). All measurements were carried out at room temperature unless otherwise stated. Electron impact (EI) mass spectra were recorded on AMD 402 mass spectrometer (70 eV). High resolution mass spectra (HRMS) were recorded on Agilent 6210 Time-of-Flight LC/MS (Agilent) with electrospray ionization (ESI). The data are given as mass units per charge (m/z) and intensities of signals are given in brackets. For GC analyses, HP 6890 chromatograph with a 29 m HP5 column was used.

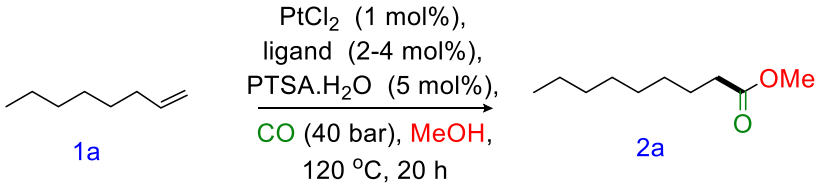
S2. General procedure of platinum catalysed alkoxycarbonylation of alkenes



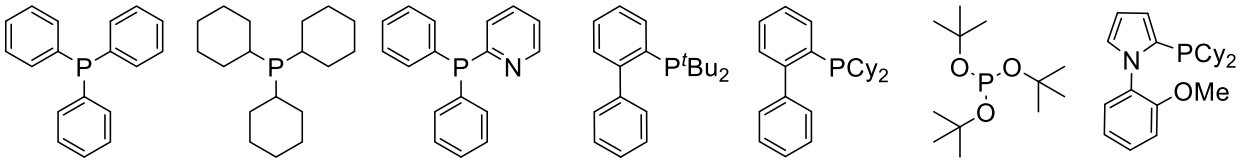
A 4 mL screw-cap vial was charged with platinum salt, ligand, acid, and an oven-dried stirring bar. The vial was closed by PTFE/white rubber septum (Wheaton 13 mm Septa) and phenolic cap and connected with atmosphere with a needle. Then, the vial was evacuated under vacuum and recharged with argon for three times. After MeOH and **1** were injected by syringe; the vial was fixed in an alloy plate and put into Paar 4560 series autoclave (300 mL) under argon atmosphere. At room temperature, the autoclave was flushed with carbon monoxide for three times and carbon monoxide was charged. The reaction was heated at the specified temperature. Afterwards, the autoclave was cooled to room temperature and the pressure was carefully released. Mesitylene was added into the reaction as internal standard. A sample of the mixture was analysed by gas chromatography. Pure products were obtained by column chromatography on silica gel.

S3. Optimisation of reaction conditions

Table S3.1. The effect of ligand [a]

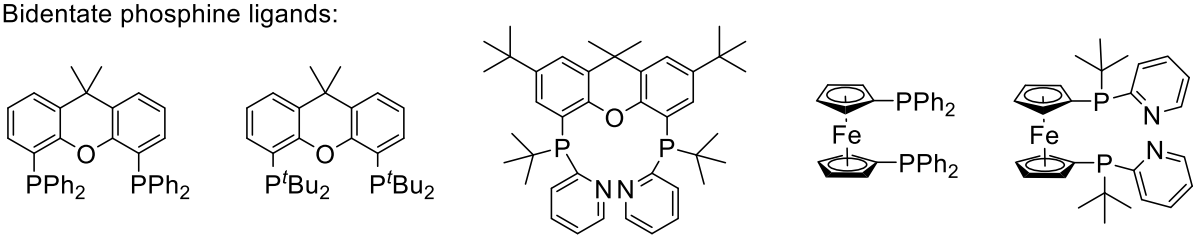


Monodentate phosphine ligands:



L1 0% L2 0% L3 0% L4 0% L5 0% L6 0% L7 0%

Bidentate phosphine ligands:



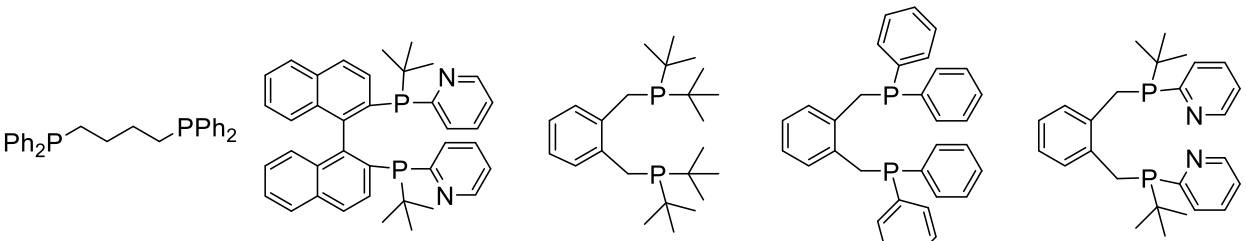
L8 38%, (*n/iso*=78/22)

L9 17%, (*n/iso*=78/22)

L10 0%

L11 0%

L12 78%, (*n/iso*=64/36)



L13 0%

L14 54%, (*n/iso*=73/27)

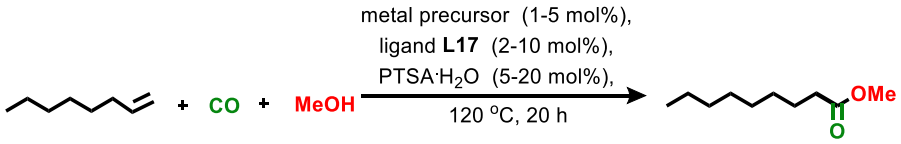
L15 24%, (*n/iso*=77/23)

L16 0%

L17 95%, (*n/iso*=73/27)

[a]. Standard reaction conditions: 1-Octene (1.0 mmol), $PtCl_2$ (0.01 mmol, 1.0 mol%), ligands (for monodentate phosphine ligand: 0.04 mmol, 4.0 mol%; for bidentate phosphine ligand: 0.02 mmol, 2.0 mol%), PTSA·H_2O (5.0 mol%), MeOH (2.0 mL), CO (40 atm), 120 °C, 20 h; The selectivity and yield were determined by GC analysis with mesitylene as the internal standard.

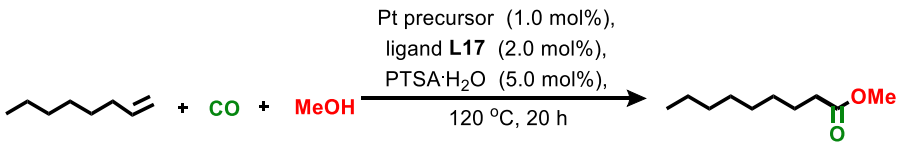
Table S3.2. The effect of different metal catalyst precursors



Entry	Metal precursor	Yield (%)	Selectity (*n/iso*)
1.	$Fe_3(CO)_{12}$ [a]	0	
2.	$Cu(CH_3CN)_4PF_6$ [a]	0	
3.	$[Ru(p\text{-}cym)Cl_2]_2$ [b]	0	
4.	Rh(cod)(acac) [b]	0	
5.	$PdCl_2$ [b]	96	72/28
6.	$PtCl_2$ [b]	95	73/27

[a]. Reaction conditions: 1-Octene (1.0 mmol), metal precursor (refer to Fe or Cu, 0.05 mmol, 5.0 mol%), ligand (0.1 mmol, 10.0 mol%), PTSA·H_2O (20.0 mol%), MeOH (2.0 mL), CO (40 atm), 120 °C, 20 h; the selectivity and yield were determined by GC analysis with mesitylene as the internal standard. [b]. reaction conditions: 1-Octene (1.0 mmol), metal precursor (refer to Ru, Rh, Pd or Pt, 0.01 mmol, 1.0 mol%), ligand (0.02 mmol, 2.0 mol%), PTSA·H_2O (5.0 mol%), MeOH (2.0 mL), CO (40 atm), 120 °C, 20 h; the selectivity and yield were determined by GC analysis with mesitylene as the internal standard.

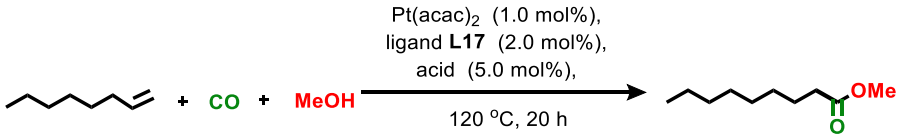
Table S3.3. The effect of Pt precursors



Entry	Pt precursor	Yield	Selectity (*n/iso*)
1.	$PtCl_2$	95	73/27
2.	$PtBr_2$	58	68/32
3.	$Pt(acac)_2$	98	79/21
4.	$Pt(cod)Cl_2$	63	68/32

[a]. reaction conditions: 1-Octene (1.0 mmol), Pt precursor (0.01 mmol, 1.0 mol%), ligand (0.02 mmol, 2.0 mol%), PTSA·H_2O (5.0 mol%), MeOH (2.0 mL), CO (40 atm), 120 °C, 20 h; the selectivity and yield were determined by GC analysis with mesitylene as the internal standard.

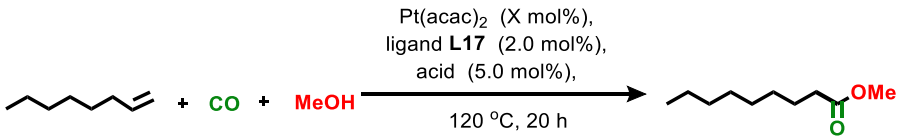
Table S3.4. The effect of acid [a]



Entry	Acid	Yield	Selectity (*n/iso*)
1.	HCl, aqueous solution	65	70/30
2.	CF_3COOH	72	69/31
3.	MSA	93	77/23
4.	CSA	90	68/32
5.	PTSA	98	79/21
6.	H_2SO_4	67	71/29

[a]. reaction conditions: 1-Octene (1.0 mmol), $Pt(acac)_2$ (0.01 mmol, 1.0 mol%), ligand (0.02 mmol, 2.0 mol%), acid (5.0 mol%), MeOH (2.0 mL), CO (40 atm), 120 °C, 20 h; the selectivity and yield were determined by GC analysis with mesitylene as the internal standard.

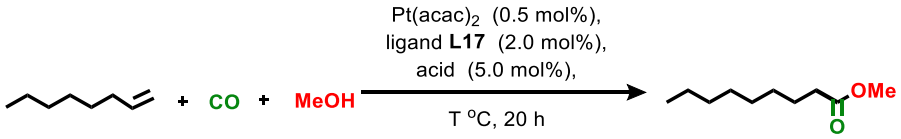
Table S3.5. The effect of catalyst loading [a]



Entry	Catalyst loading (Pt)	Yield	Selectity (*n/iso*)
1.	0.1 mmol%	54	79/21
2.	0.2 mmol%	57	79/21
3.	0.5 mmol%	95	79/21
4.	1.0 mmol%	98	79/21

[a]. reaction conditions: 1-Octene (1.0 mmol), $Pt(acac)_2$ (0.001-0.01 mmol, 0.1-1.0 mol%), ligand (0.02 mmol, 2.0 mol%), PTSA·H_2O (5.0 mol%), MeOH (2.0 mL), CO (40 atm), 120 °C, 20 h; the selectivity and yield were determined by GC analysis with mesitylene as the internal standard.

Table S3.6. The effect of tempature [a]



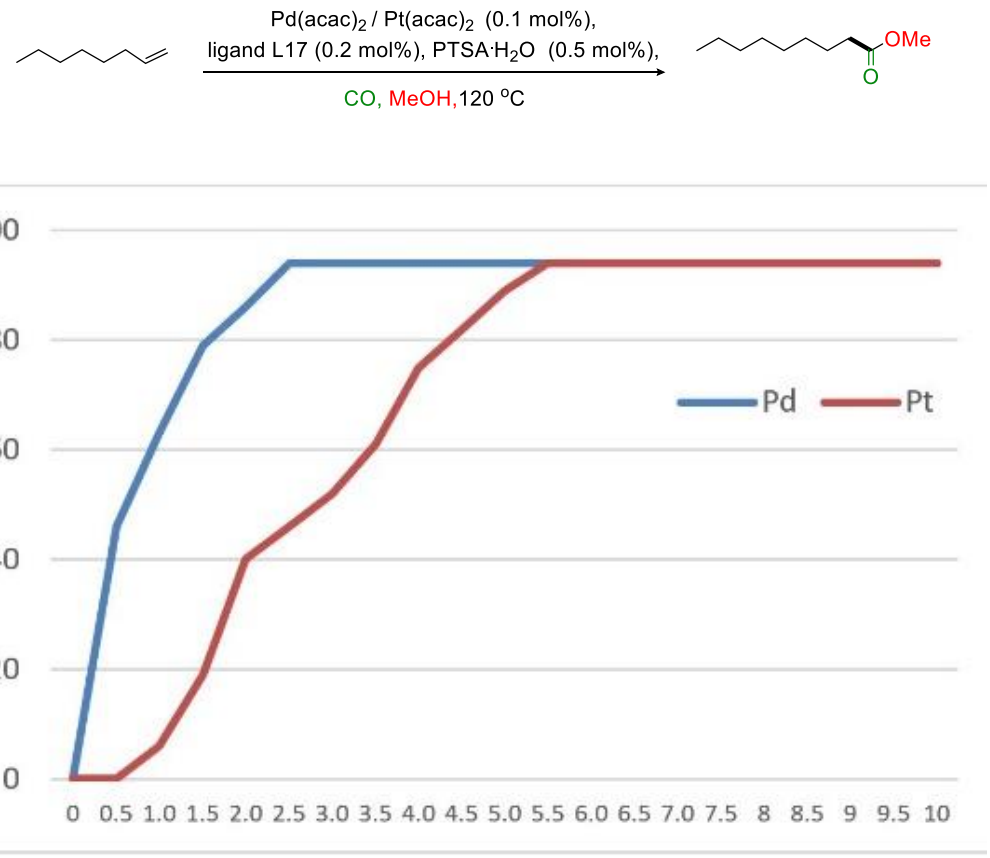
Entry	Temperature (°C)	Yield	Selectity (*n/iso*)
1	120 °C	95	79/21
2	60 °C	trace	

[a]. reaction conditions: 1-Octene (1.0 mmol), $Pt(acac)_2$ (0.005 mmol, 0.5 mol%), ligand (0.02 mmol, 2.0 mol%), PTSA·H_2O (5.0 mol%), MeOH (2.0 mL), CO (40 atm), 20 h; the selectivity and yield were determined by GC analysis with mesitylene as the internal standard.

S4. Kinetic monitoring experiment

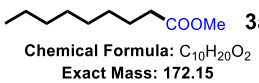
In order to understand the process in more detail, kinetic monitoring experiments were conducted. In general, all catalytic experiments an excess of ligand was used to ensure stability of the active complex at low metal concentration. By comparison, we observe that the Pd catalysed reaction is basically completed in about 2.5 hours; the rate of Pt-catalysed reaction is slower. It takes about 5.5 hours to complete the reaction. However, for 1-octene, the final yield of the product is the same for both catalysts.

Figure S4. Kinetic monitoring experiment.



The ***X***-axis represents the reaction time and the ***Y***-axis represents the reaction yield. Reaction conditions: 1-Octene (20 mmol), $Pd(acac)_2$ or $Pt(acac)_2$ (0.02 mmol, 0.1 mol%), ligand (0.04 mmol, 0.2 mol%), $PTSA{\cdot}H_2O$ (0.5 mol%), MeOH (30 mL), CO (40 atm), 120 °C; the GC yield were determined by GC analysis with mesitylene as the internal standard.

S5. Characterization of the products



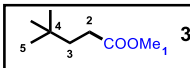
Chemical Formula: $C_{10}H_{20}O_2$
Exact Mass: 172.15

Colorless oil, 95% yield, *n*/*iso* = 74/26.

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.66 (s, 3H), 2.34-2.24 (m, 2H), 1.67-1.54 (m, 2H), 1.34-1.19 (m, 10H), 0.92-0.79 (m, 3H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) δ 174.5, 51.6, 34.2, 32.0, 29.4, 29.3, 29.3, 25.1, 22.8, 14.2.

DEPT135-^{13}C NMR (75 MHz, $CDCl_3$) δ 51.6 (-), 34.3, 31.9, 29.4, 29.3, 29.3, 25.1, 22.8, 14.2 (-).



methyl 4,4-dimethylpentanoate
Chemical Formula: $C_8H_{16}O_2$
Exact Mass: 144.12

Colorless oil, 93% yield, *n*/*iso* > 99/1.

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.65 (s, 3H), 2.31-2.21 (m, 2H), 1.58-1.48 (m, 2H), 0.88 (s, 9H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) δ 175.0, 51.6, 38.7, 30.2, 30.0, 29.1.

DEPT135-^{13}C NMR (75 MHz, $CDCl_3$) δ 51.6, 38.7 (-), 30.0 (-), 29.1.

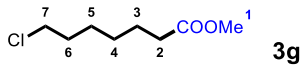
methyl 4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoroundecanoate
Chemical Formula: $C_{12}H_7F_{17}O_2$
Exact Mass: 506.02

Colorless oil, 87% yield, *n*/*iso* > 99/1.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.67 (s, 3H), 2.62-2.52 (m, 2H), 2.51-2.32 (m, 2H) ppm;

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.7, 120.7, 118.8, 118.1, 116.0, 113.8, 111.4, 111.1, 108.9, 108.5, 106.2, 52.0, 26.7, 25.3.

DEPT135-^{13}C NMR (101 MHz, $CDCl_3$) δ 52.0, 26.7 (-), 25.3 (-).



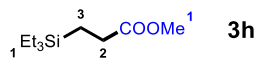
methyl 7-chloroheptanoate
Chemical Formula: $C_8H_{15}ClO_2$
Exact Mass: 178.08

Colorless oil, 87% yield, *n*/*iso* = 66/34.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.59 (s, 3H), 3.49-3.39 (t, *J* = 6.7 Hz, 2H), 2.30-2.19 (m, 2H), 1.76-1.25 (m, 8H) ppm;

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.0, 51.4, 44.9, 33.9, 32.4, 28.4, 26.5, 24.7.

DEPT135-^{13}C NMR (101 MHz, $CDCl_3$) δ 51.4, 44.9 (-), 33.9 (-), 32.4 (-), 28.4 (-), 26.5 (-), 24.7 (-).



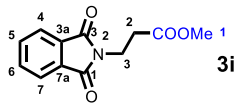
methyl 3-(triethylsilyl)propanoate
Chemical Formula: $C_{10}H_{22}O_2Si$
Exact Mass: 202.14

Colorless oil, 82% yield, *n*/*iso* = 99/1.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.64 (s, 3H), 2.32-2.18 (m, 2H), 1.02-0.77 (m, 11H), 0.58-0.44 (q, *J* = 7.9 Hz, 6H) ppm;

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.6, 51.6, 28.6, 7.3, 6.6, 3.1.

DEPT135-^{13}C NMR (101 MHz, $CDCl_3$) δ 51.6, 28.6 (-), 7.3, 6.6 (-), 3.1 (-).



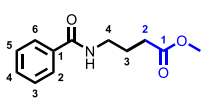
methyl 3-(1,3-dioxoisoindolin-2-yl)propanoate
Chemical Formula: $C_{12}H_{11}NO_4$
Exact Mass: 233.07

White solid, 77% yield, n/iso > 99/1.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83-7.70 (m, 2H), 7.70-7.58 (m, 2H), 3.96-3.84 (t, *J* = 7.2 Hz, 2H), 3.60 (s, 3H), 2.73-2.60 (t, *J* = 7.2 Hz, 2H) ppm;

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2, 167.9, 134.0, 132.0, 123.3, 51.9, 33.8, 32.8.

DEPT135-^{13}C NMR (101 MHz, $CDCl_3$) δ 134.0, 123.3, 51.9, 33.8 (-), 32.8 (-).



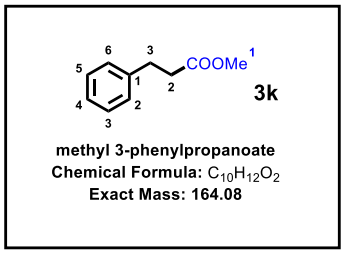
methyl 4-benzamidobutanoate
Chemical Formula: $C_{12}H_{15}NO_3$
Exact Mass: 221.11

Colorless oil, 66% yield, *n*/*iso* = 68/32.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79-7.70 (m, 2H), 7.43-7.24 (m, 4H), 3.56 (s, 3H), 3.45-3.32 (m, 2H), 2.38-2.27 (t, *J* = 7.2 Hz, 2H), 1.93-1.78 (m, 2H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9, 167.7, 134.4, 131.1, 128.2, 126.9, 51.5, 39.4, 31.5, 24.4.

DEPT135-^{13}C NMR (75 MHz, $CDCl_3$) δ 131.1, 128.2, 126.9, 51.5, 39.4 (-), 31.5 (-), 24.4 (-).

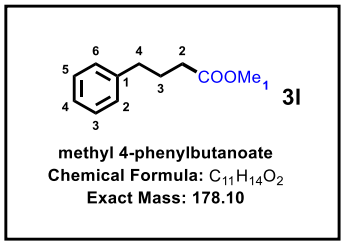


Colorless oil, 95% yield, *n*/*iso* = 71/29.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.24 (m, 5H), 3.71 (s, 3H), 3.07-2.95 (t, *J* = 7.8 Hz, 2H), 2.73-2.64 (m, 2H) ppm;

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.1, 140.5, 128.4, 128.2, 126.2, 51.4, 35.6, 30.9.

DEPT135-^{13}C NMR (101 MHz, $CDCl_3$) δ 128.4, 128.2, 126.2, 51.4, 35.6 (-), 30.9 (-).

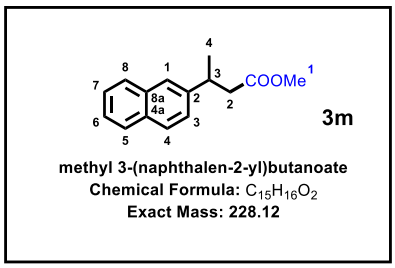


Colorless oil, 94% yield, *n*/*iso* = 65/35.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.22 (m, 5H), 3.70 (s, 3H), 2.75-2.62 (m, 2H), 2.45-2.33 (t, *J* = 7.5 Hz, 2H), 2.08-1.96 (m, 2H) ppm;

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.7, 141.3, 128.4, 128.3, 125.9, 51.3, 35.1, 33.3, 26.4.

DEPT135-^{13}C NMR (101 MHz, $CDCl_3$) δ 128.5, 128.4, 126.0, 51.5, 35.2 (-), 33.4 (-), 26.6 (-).

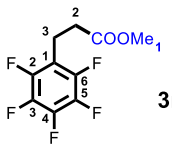


Light yellow solid, 97% yield, *n*/*iso* > 99/1.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93-7.82 (m, 3H), 7.78-7.72 (m, 1H), 7.57-7.40 (m, 3H), 3.68 (s, 3H), 3.64-3.48 (m, 1H), 2.89-2.67 (m, 2H), 1.52-1.44 (d, *J* = 7.0 Hz, 3H) ppm;

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.7, 143.1, 133.6, 132.3, 128.2, 127.6, 127.6, 125.9, 125.4, 125.4, 124.9, 51.4, 42.6, 36.5, 21.8.

DEPT135-^{13}C NMR (101 MHz, $CDCl_3$) δ 128.2, 127.6, 127.6, 125.9, 125.4, 125.4, 124.9, 51.4, 42.6 (-), 36.5, 21.8.



3n

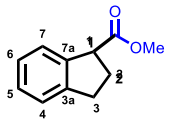
methyl 3-(perfluorophenyl)propanoate
Chemical Formula: $C_{10}H_7F_5O_2$
Exact Mass: 254.04

Colorless oil, 87% yield, *n*/*iso* > 99/1.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.65 (s, 3H), 3.03-2.95 (t, *J* = 7.7 Hz, 2H), 2.63-2.54 (t, *J* = 7.7 Hz, 2H) ppm;

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.1, 146.5, 144.0, 141.3, 138.8, 136.3, 113.5, 51.8, 32.9, 18.0.

DEPT135-^{13}C NMR (101 MHz, $CDCl_3$) δ 51.8, 32.9 (-), 18.0 (-).



3o

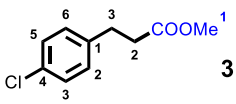
methyl-2,3-dihydro-1*H*-indene-1-carboxylate
Chemical Formula: $C_{11}H_{12}O_2$
Exact Mass: 176.08

Colorless oil, 87% yield, *1:2* = 88:12.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55-7.46 (m, 1H), 7.39-7.22 (m, 3H), 4.20-4.10 (m, 1H), 3.82 (s, 3H), 3.24-2.95 (m, 2H), 2.60-2.37 (m, 2H) ppm;

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.2, 144.0, 140.6, 127.5, 126.4, 124.7, 124.6, 51.9, 50.0, 31.7, 28.7.

DEPT135-^{13}C NMR (101 MHz, $CDCl_3$) δ 127.5 (-), 126.4 (-), 124.7 (-), 124.6 (-), 51.9 (-), 50.0 (-), 31.7, 28.7.



3p

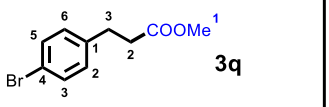
methyl 3-(4-chlorophenyl)propanoate
Chemical Formula: $C_{10}H_{11}ClO_2$
Exact Mass: 198.04

Colorless oil, 89% yield, *n*/*iso* = 71/29.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.21 (m, 2H), 7.15-7.09 (m, 2H), 3.65 (s, 3H), 2.91 (t, *J* = 7.7 Hz, 2H), 2.60 (t, *J* = 7.7 Hz, 2H) ppm;

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.9, 138.9, 132.0, 129.6, 128.5, 51.5, 35.4, 30.2.

DEPT135-^{13}C NMR (101 MHz, $CDCl_3$) δ 129.6, 128.5, 51.5, 35.4 (-), 30.2 (-).



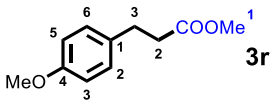
methyl 3-(4-bromophenyl)propanoate
Chemical Formula: $C_{10}H_{11}BrO_2$
Exact Mass: 241.99

Colorless oil, 86% yield, *n*/*iso* = 72/28.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.34 (m, 2H), 7.09-7.03 (m, 2H), 3.65 (s, 3H), 2.89 (t, *J* = 7.7 Hz, 2H), 2.60 (t, *J* = 7.7 Hz, 2H) ppm;

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.8, 139.4, 131.4, 130.0, 120.0, 51.5, 35.3, 30.2.

DEPT135-^{13}C NMR (101 MHz, $CDCl_3$) δ 131.4, 130.0, 51.5, 35.3 (-), 30.2 (-).



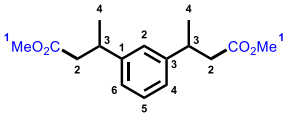
methyl 3-(4-methoxyphenyl)propanoate
Chemical Formula: $C_{11}H_{14}O_3$
Exact Mass: 194.09

Colorless oil, 85% yield, *n*/*iso* = 52/48.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17-7.09 (m, 2H), 6.91-6.86 (m, 2H), 3.78 (s, 3H), 3.68 (s, 3H), 2.92 (t, *J* = 7.8 Hz, 2H), 2.62 (t, *J* = 7.8 Hz, 2H) ppm;

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.3, 158.0, 132.5, 129.2, 113.8, 55.1, 51.4, 35.9, 30.0.

DEPT135-^{13}C NMR (101 MHz, $CDCl_3$) δ 129.2, 113.8, 55.1, 51.4, 35.9 (-), 30.0 (-).



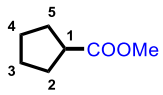
dimethyl 3,3'-(1,3-phenylene)dibutyrate
Chemical Formula: $C_{16}H_{22}O_4$
Exact Mass: 278.15

Colorless oil, 86% yield, *n*/*iso* > 99/1.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.19 (m, 1H), 7.12-7.01 (m, 3H), 3.63 (s, 6H), 3.36-3.19 (m, 2H), 2.70-2.46 (m, 4H), 1.30 (d, *J* = 7.0 Hz, 6H) ppm;

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.8, 145.9, 128.7, 125.4, 124.7, 51.5, 42.8, 36.5, 21.7.

DEPT135-^{13}C NMR (101 MHz, $CDCl_3$) δ 128.7 (-), 125.4 (-), 124.7 (-), 51.5 (-), 42.8, 36.5(-), 21.7 (-).

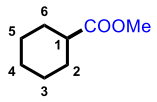


3t

methyl cyclopentanecarboxylate
Chemical Formula: $C_7H_{12}O_2$
Exact Mass: 128.08

Colorless oil, 97% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.65 (s, 3H), 2.79-2.63 (m, 1H), 1.93-1.48 (m, 8H) ppm;
^{13}C NMR (75 MHz, $CDCl_3$) δ 177.4, 51.7, 43.8, 30.1, 25.9.
DEPT135-^{13}C NMR (75 MHz, $CDCl_3$) δ 51.7 (-), 43.8 (-), 30.1, 25.9.



3u

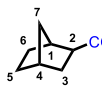
methyl cyclohexanecarboxylate
Chemical Formula: $C_8H_{14}O_2$
Exact Mass: 142.10

Colorless oil, 96% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.60 (s, 3H), 2.32-2.17 (m, 1H), 1.92-1.76 (m, 2H), 1.74-1.13 (m, 8H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) δ 176.5, 51.4, 43.1, 29.1, 25.8, 25.5.

DEPT135-^{13}C NMR (75 MHz, $CDCl_3$) δ 51.4 (-), 43.1 (-), 29.1, 25.8, 25.5.



3v

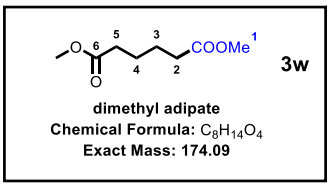
methyl (1*S*,4*R*)-bicyclo[2.2.1]heptane-2-carboxylate
Chemical Formula: $C_9H_{14}O_2$
Exact Mass: 154.10

Colorless oil, 88% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.61 (s, 3H), 2.48-2.39 (m, 1H), 2.32-2.19 (m, 2H), 1.85-1.72 (m, 1H), 1.54-1.36 (m, 4H), 1.22-1.06 (m, 3H) ppm;

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.5, 51.6, 46.4, 41.0, 36.5, 36.1, 34.2, 29.5, 28.7.

DEPT135-^{13}C NMR (101 MHz, $CDCl_3$) δ 51.6 (-), 46.4 (-), 40.9 (-), 36.5, 36.1 (-), 34.2, 29.5, 28.7.

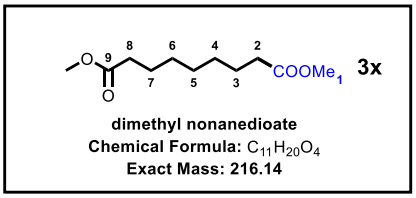


Colorless oil, 98% yield, *n*/*iso* = 69/31.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.65 (s, 6H), 2.36-2.27 (m, 4H), 1.68-1.60 (m, 4H), ppm;

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.9, 77.5, 77.2, 76.8, 51.7, 33.8, 24.5.

DEPT135-^{13}C NMR (101 MHz, $CDCl_3$) δ 51.7 (-), 33.8, 24.5.

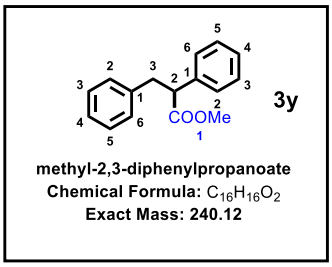


Colorless oil, 88% yield, *n*/*iso* = 42/58.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.56 (s, 6H), 2.20 (t, *J* = 7.5 Hz, 4H), 1.52 (m, 4H), 1.28-1.17 (m, 6H) ppm;

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.0, 51.3, 33.9, 28.9, 28.8, 24.8.

DEPT135-^{13}C NMR (101 MHz, $CDCl_3$) δ 51.3, 33.9 (-), 28.8 (-), 24.8 (-).

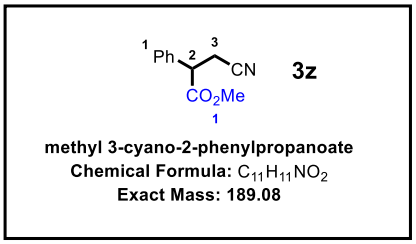


Light yellow solid, 89% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-6.95 (m, 10H), 3.78 (dd, *J* = 8.8, 6.7 Hz, 1H), 3.52 (s, 3H), 3.40-3.27 (m, 1H), 2.95 (dd, J = 13.7, 6.7 Hz, 1H) ppm;

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.9, 139.2, 138.8, 129.0, 128.8, 128.5, 128.1, 127.5, 126.5, 53.7, 52.1, 40.0.

DEPT135-^{13}C NMR (101 MHz, $CDCl_3$) δ 129.0, 128.8, 128.5, 128.1, 127.5, 126.5, 53.7, 52.1, 39.9 (-).

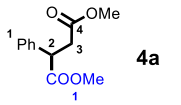


Colorless oil, 84% yield, *n*/*iso* = 78/22.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.21 (m, 5H), 3.97 (t, *J* = 7.6 Hz, 1H), 3.74 (s, 3H), 3.05 (dd, *J* = 16.8, 7.5 Hz, 1H), 2.82 (dd, *J* = 16.8, 7.6 Hz, 1H) ppm;

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5, 135.8, 129.3, 128.6, 127.6, 117.6, 52.8, 47.6, 21.7.

DEPT135-^{13}C NMR (101 MHz, $CDCl_3$) δ 129.3, 128.6, 127.6, 52.8, 47.6, 21.7 (-).



4a

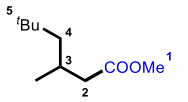
dimethyl (*R*)-2-phenylsuccinate
Chemical Formula: $C_{12}H_{14}O_4$
Exact Mass: 222.09

Colorless oil, 86% yield, 2:3 = 95:5.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.20 (m, 5H), 4.15-4.05 (m, 1H), 3.66 (s, 6H), 3.27-3.14 (m, 1H), 2.67 (dd, *J* = 17.0, 5.2 Hz, 1H) ppm;

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4, 171.9, 144.1, 128.9, 127.7, 127.6, 52.3, 51.8, 47.1, 37.6.

DEPT135-^{13}C NMR (101 MHz, $CDCl_3$) δ 128.9, 127.7, 127.6, 52.3, 51.5, 46.3, 37.6 (-).



4b

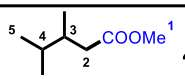
methyl 3,5,5-trimethylhexanoate
Chemical Formula: $C_{10}H_{20}O_2$
Exact Mass: 172.15

Colorless oil, 94% yield, *n*/*iso* > 99/1.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.63 (s, 3H), 2.33-2.23 (m, 1H), 2.15-2.06 (m, 1H), 2.06-1.93 (m, 1H), 1.21 (dd, *J* = 14.0, 4.0 Hz, 1H), 1.09 (dd, *J* = 14.1, 6.3 Hz, 1H), 0.97-0.92 (d, 3H), 0.88 (s, 9H) ppm;

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.7, 51.4, 50.6, 43.9, 31.2, 30.0, 27.1, 22.8.

DEPT135-^{13}C NMR (101 MHz, $CDCl_3$) δ 51.4, 50.6 (-), 43.9 (-), 30.0, 27.1, 22.8.



4c

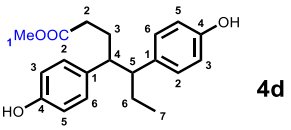
methyl 3,4-dimethylpentanoate
Chemical Formula: $C_8H_{16}O_2$
Exact Mass: 144.12

Colorless oil, 70% yield, *n*/*iso* > 99/1.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.63 (s, 3H), 2.32 (dd, *J* = 14.6, 5.2 Hz, 1H), 2.05 (dd, *J* = 14.6, 9.1 Hz, 1H), 1.92-1.75 (m, 1H), 1.62- 1.45 (m, 1H), 0.89- 0.77 (m, 9H) ppm;

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.3, 51.5, 39.1, 36.0, 32.2, 19.9, 18.4, 15.9.

DEPT135-^{13}C NMR (101 MHz, $CDCl_3$) δ 51.5, 39.1 (-), 36.0, 32.2, 19.9, 18.3, 15.9.



methyl 4,5-bis(4-hydroxyphenyl)heptanoate
Chemical Formula: $C_{20}H_{24}O_4$
Exact Mass: 328.17

White solid, 32% yield, *n/iso* = 90/10.

For this product, linear and branched products were not easily separated by column chromatography and we obtained a mixture of products. The ratio of linear and branched products is determined by GC. Corresponding low-resolution mass spectra, ^{13}C characteristic peaks were compared to the known spectra. For the ^{1}H spectrum, here we list the spectrum of the mixture products.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98-6.82 (m, 6H), 6.76-6.52 (m, 8H), 4.12-3.99 (m, 1H), 3.58-3.47 (s, 1.45 H), 3.47-3.35 (s, 2.94H), 2.70-2.31 (m, 3.04H), 2.15-1.78 (m, 5.62H), 1.24-1.11 (m, 3.38H), 0.67-0.59 (t, J = 7.2 Hz, 1H), 0.51-0.40 (t, J = 7.3 Hz, 3H) ppm;

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.7, 175.6, 154.4, 154.2, 154.1, 153.8, 135.6, 135.0, 134.1, 133.3, 130.1, 130.0, 129.3, 115.5, 115.3, 114.8, 114.6, 77.5, 77.2, 76.8, 61.0, 53.6, 52.7, 51.9, 51.8, 51.0, 50.0, 32.6, 32.1, 29.7, 28.2, 27.4, 26.0, 21.1, 14.1, 12.4, 12.2.

DEPT135-^{13}C NMR (101 MHz, $CDCl_3$) δ 130.1, 130.0, 129.3, 115.5, 115.3, 114.8, 114.6, 61.0, 53.6, 52.7, 51.9, 51.8, 51.0, 50.0, 32.6, 32.6, 29.7, 28.6, 27.4, 26.0, 21.1, 14.1, 12.4, 12.2.

Universität Rostock
Dezernat 1
Referat 1.2

Doktorandinnen/Doktoranden-Erklärung gemäß § 4 Absatz 1 Buchstaben g und h der Promotionsordnung der Mathematisch-Naturwissenschaftlichen Fakultät der Universität Rostock

Name Ji Yang
.....
(Name, Vorname)

Anschrift Bergstraße 7A, 18057, Rostock.
.....
(Straße, PLZ, Wohnort)

Ich habe eine Dissertation zum Thema

Palladium-Catalyzed Carbonylation of Unsaturated Carbon-Carbon Bonds

.....

.....

an der Mathematisch-Naturwissenschaftlichen Fakultät der Universität Rostock angefertigt. Dabei wurde ich von Frau/Herrn

Prof. Dr. Matthias Beller
.....
betreut.

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Ji Yang .....
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