Leibniz-Institut für Katalyse e.V.

an der Universität Rostock

Development of Carbonylative Synthetic Methods Towards Carboxylic Acid Derivatives and Heterocycles

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Dedicated To

My Beloved Parents

献给我亲爱的父母

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Abstract

Development of carbonylative synthetic methods towards carboxylic acid derivatives and heterocycles

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This thesis mainly describes the development of novel catalytic carbonylative transformations based on palladium catalysis, which includes the discovery of novel transformations, the catalyst-modulated selectivity and the applications of carbonylative methods. The discovery of novel reactivity focus on the synthesis of β,γ-unsaturated esters, amides and imides from 1,3-diene, under "acid-free" conditions. In addition, a highly efficient palladium-catalyzed hydroamidocarbonylation reaction of alkene has been described. Based on allylic alcohol as the organic building-block, the first palladium-catalyzed direct aminocarbonylation reaction allylic alcohol is successfully developed. The development on catalyst-controlled selective transformation is displayed through the unprecedented branched-selectivity observed towards the alkoxycarbonylation of various non-functionalized alkenes with a palladium/*N*-phenylpyrrole phosphine type ligand catalyst system. Furthermore, applications with carbonylative synthesis as the tool are showcased by synthesis of a variety of heterocycles starting from commercially available double-functionalized aromatic compounds.

Entwicklung synthetischer Carbonylierungsmethoden für die Erzeugung/zur Bildung verschiedener Carboxylsäuren und Heterozyklen.

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Die vorliegende Arbeit fokussiert sich hauptsächlich auf die Entwicklung neuer katalytischer Carbonylierungsmethoden auf Basis der Palladiumkatalyse. Dies schliesst die Entdeckung neuer synthetischer Transformationen, die katalysatorabhängige Selektivität und Anwendungsbeispiele carbonylierender Reaktionen ein. Dabei liegt ein besonderer Augenmerk der neuen synthetischen Methoden auf der Herstellung von β,γ-ungesättigten Estern, Amiden und Imiden ausgehend von 1,3-Dienen unter "säurefreien" Reaktionsbedingungen. Zusätzlich konnte eine effektive palladiumkatalysierte Hydroamidocarbonylierungsreaktion ausgehend vom Alken und die auf Allylkalkohol ersten

bekannten direkten palladiumkatalysierten Aminocarbonylierungsreaktion etabliert werden. Die katalysatorabhängige Selektivität konnte erstmals bezüglich der Alkoxycarbonylierung verschiedener unfunktionalisierter Alkene durch ein Palladium/*N*-Phenylpyrrolphosphin Katalysatorsystem gezeigt werden. Weiterhin gelang es, die gute Anwendbarkeit der Carbonylierungsreaktionen durch die Synthese einer Vielzahl von Heterozyklen, ausgehend von kommerziell erhältlichen bifunktionalisierten aromatischen Verbindungen, zu zeigen.

Table of Contents

List of Schemes

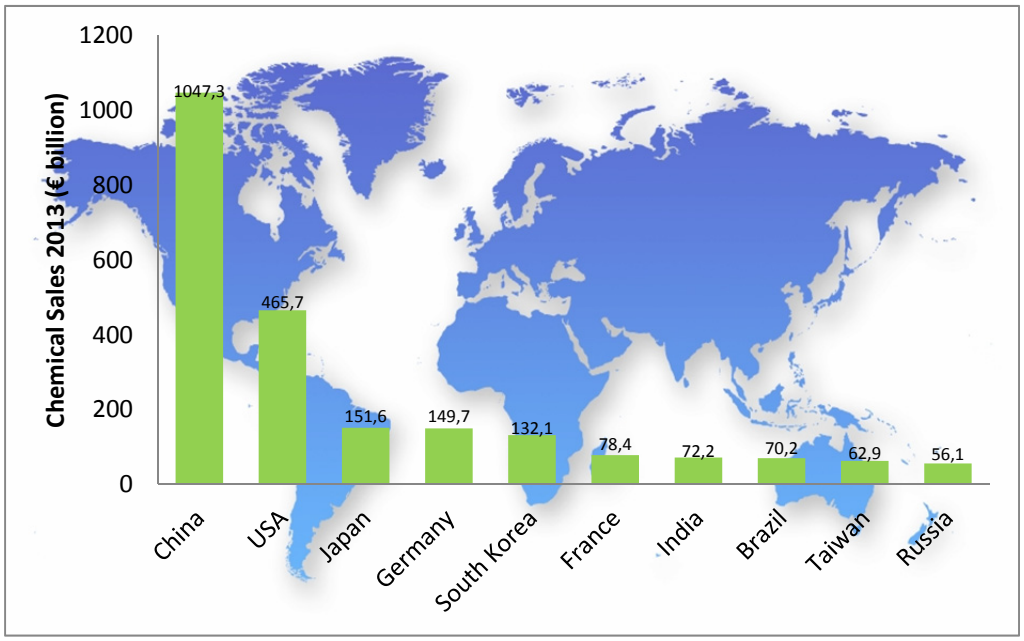
List of Abbreviations

(-)-DIOP	*(-)-2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane*
ABS	*Acrylonitrile butadiene styrene*
acac	*Acetylacetone*
Ar	*Aryl*
ArX	*Arylhalide*
atm	*atmosphere*
b	*Branched product*
BASF	*Badische Anilin- & Soda-Fabrik*
Bn	*Benzyl*
Bu	*Butyl*
BuOH	*Butanol*
BuPAd2	*Di(1-adamantyl)-n-butylphosphine*
Cat.	*Catalyst*
cataCXium PCy	*2-(dicyclohexylphosphanyl)-1-phenyl-1H-pyrrole*
CF_3	*Trifluoromethyl*
CO	*carbon monoxide*
cod	*Cycloocta-1,5-diene*
Cy	*Cyclohexyl*
d	*Day*
dba	*trans, trans-Dibenzylideneacetone*
Dipea	*N-Ethyldiisopropylamine*
DPEPhos	*(Oxydi-2,1-phenylene)bis(diphenylphosphine)*
dppb	*1,4-Bis(diphenylphosphino)butane*
dppf	*1,1'-Ferrocenediyl-bis(diphenylphosphine)*
dppp	*1,3-Bis(diphenylphosphino)propane*
dpppen	*1,5-Bis(diphenylphosphino)pentane*
dtbpx	*1,2-bis(di-tert-butyl-phophanylmethyl)benzene*
E	*Entgegen (describing the absolute stereochemistry of double bonds)*
ee	*Enantiomeric excess*
et al.	*Et alii*
Et_2O	*Diethylether*
etc.	*Et cetera*
EtOH	*Ethanol*
FG	*Functional group*
h	*Hour*
HMF	*Hydroxymethylfurfural*
iso-	*Sum of branched products*
L	*Ligand*
l	*Linear product*

MeOH	*Methanol*
MEK	*Methy ethylketone*
MMA	*Methylmethacrylate*
MSA	*Methyl sulfonicacid*
MSA	*Methanesulfonic acid*
n-	*Normal*
N-	*Nitrogen substituted*
Nf	*Nonafluoro-1-butanesulfonyl*
NBR	*Nitrile butadiene rubber*
NMP	*N-Methylpyrrolidone*
NuH	*Nucleophile*
SBR	*Styrene butadiene rubber*
TAME	*Tert-Amyl methyl ether*
OAc	*Acetate*
OH	*Hydroxy*
OMe	*Methoxy*
OTf	*Trifluoromethanesulfonyl*
Ph	*Phenyl*
Ph	*Phenyl*
PMMA	*poly(methyl methacrylate)*
p-TsOH	*para-Toluenesulfonic acid*
SHOP	*Shell higher olefin process*
tBu	*Tert-butyl*
TFA	*Trifluoroacetic acid*
THF	*Tetrahydrofuran*
TM	*Transition metal*
TMS	*Trimethylsilyl*
TON	*Turnover Number*
Xantphos	*4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene*

1 Preface

The world chemical turnover was valued at €3,156 billion in 2013, among which the European Union accounts for 16.7% of the total (Scheme 1). Compared to 2012, the global sales grew by 2.4% from 3084 billion. Chemical companies in the European Union in 2013 employed a total staff of about 1.2 million.[1] The development of chemical industry has laid the material foundation of today's human society and is extraordinarily accelerating the growth of developing countries. On the other hand, the development of chemical industry is closely related to the global environment and human life. One of the most impressive issue facing chemists is how to use chemical tool to reduce or prevent pollution during chemical production.



Scheme 1 Global chemical sales in 2013

As one of the major concerns for chemical production, the control of material and energy consumption is significantly influencing the output of industry. At the same time, the discovery and development of catalysts have greatly contributed to the success of chemical industry by significantly increasing the efficiency. Notably, the current global market of catalysts is valued at $16.3 billion and is forecasted to increase at 4.8% per year to $20.6 billion in 2018. As much as 90% of all chemical processes take use of catalysts (petroleum refining, pollution abatement and production of fuels and chemicals). About 60% of all consumer and industrial products (including fertilizers, plastics, pharmaceuticals and batteries) are at present produced using catalysts.[2]

The development of catalysis is playing more and more important role in chemical production under the request of more sustainable development.[3] Well-known catalytic processes such as Haber–Bosch process[4] for ammonia production and Fischer-Tropsch process [5]for liquid hydrocarbon production have greatly contributed to the human society and already demonstrated the power of catalysis. The gains from developing catalytic methods are both financial and environmental, leading to significant lower production cost (energy and material) and substantial reduction of harmful wastes.

Depending on whether a catalyst exists in the same phase, catalyst can be heterogeneous or homogeneous. Nevertheless, biocatalysis is often classified as a separate group. Among which, the importance of the development of homogeneous catalysis is highlighted by three Nobel prizes in chemistry in the last 15 years. In 2001, William S. Knowles, Ryoji Noyori and K. Barry Sharpless were awarded for their work on chirally catalyzed hydrogenations and oxidation reactions. In 2005, Yves Chauvin, Robert H. Grubbs and Richard R. Schrock were awarded for the development of the metathesis method in organic synthesis. In 2010, Richard F. Heck, Ei-ichi Negishi and Akira Suzuki were awarded for palladium-catalyzed cross couplings in organic synthesis.[6][7]

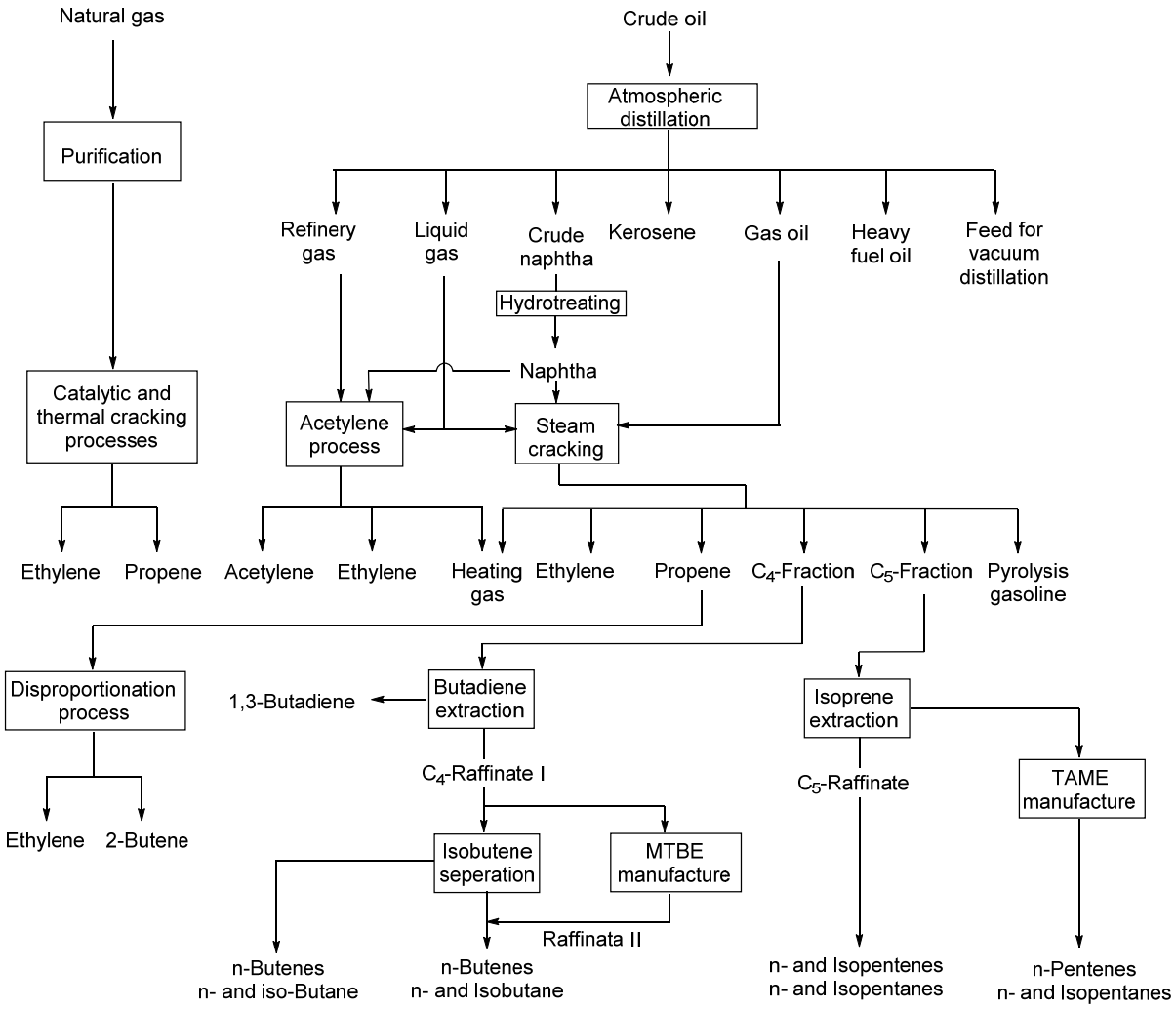
Carbonylation reactions imply the reactions that involve the introduction of carbon monoxide (CO) into organic and inorganic substrate. One obvious reason for the large application of carbonylation reactions in industry is that carbon monoxide is an abundantly available and reactive molecule. The production of carbon monoxide is done either by the combustion of carbon under insufficient amount of oxygen or by passing steam over a red-hot carbon fuel, so called “water gas”. This thesis mainly focuses on the development of carbonylative synthetic methods towards carboxylic derivatives and heterocycles catalyzed by homogeneous transition metal catalysts, with a distinct emphasis on palladium-catalyzed carbonylative transformations.

2 Carbonylation of alkenes

2.1 Research background

Olefins are one of the most important feedstocks for organic synthesis due to its abundance and availability. Lower olefins are mainly derived from cracking processes (Scheme 2).[8] In terms of quantity, ethylene and propene are among the most important

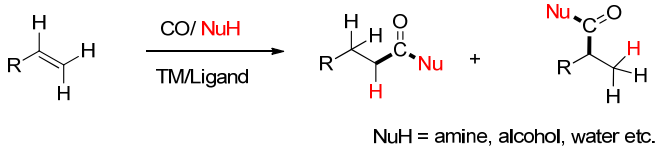
basic organic chemicals. Higher olefins can be produced by the oligomerization of ethylene, such as Ziegler process[9], Shell higher olefin process (SHOP)[10].



Scheme 2 Industrial production of alkenes

Alkene carbonylation reactions are nowadays the largest application of homogeneous catalysis in chemical industry regarding the production scale.[11] The investigation of alkene carbonylation was originated since the pioneering work on catalytic carbonylation of unsaturated compounds by Walter Reppe in BASF, who designed and invented high-pressure reactors for handling flammable gaseous reactants.[12] His pioneer work in carbonylation reactions was done in 1930s by using cobalt or 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”.[12a, 13] The need for catalyst precursors to operate under high pressure is mainly because the necessity to stabilize the two catalytic species $[CoH(CO)_4]$ or $[Ni(H)(X)(CO)_2]$. In 1938, hydroformylation

reaction (also called "oxo-synthesis") was discovered by Otto Roelen during the investigation of Fischer-Tropsch reaction in the presence of cobalt-based catalyst.[14] In 1967, von Kutepow and co-workers, patented for BASF the hydroxycarbonylation of a terminal alkene using phosphine-containing palladium complexes.[15] In late 1990s, palladium based system consisting of palladium acetate/triphenylphosphine and Brønsted acid were discovered and described in a series of patents on the alkoxycarbonylation of ethylene to generate propionate. Due to the significant better activity in carbonylation reactions of the alkenes and alkynes, the research on developing palladium based catalyst systems for carbonylation of alkene has received considerable attentions (Equation 1).[16] On the other hand, under the request for more sustainable chemical production, significant research attentions were also focused on finding suitable alternative transition metal catalysts for carbonylation reactions (especially on non-noble metal).[17]



Equation 1 General formula for carbonylation of alkene

Despite the different nature of metals, ligands and substrates, basically, two reaction mechanisms have been suggested for alkene carbonylation reactions (as depicted in Figure 1). The primary well-recognized pathway is considered to be initiated by the formation of metal hydride species (path A). By subsequent alkene coordination and insertion, the δ-alkyl-metal species could be formed, which is followed by the coordination and insertion of carbon monoxide to generate acyl-metal species. Further on, final product could be formed by the nucleophilic attack on the electron-deficient acyl metal intermediate and regenerate the catalytic active metal hydride species. Another reaction mechanism was described to start from the metalation of nucleophile. After the coordination and insertion of carbon monoxide, carboxyl-metal complex could be generated (path B). Subsequently, the coordination and insertion of alkene will generate alkyl-metal complex. In the final step, the solvolysis of the alkylmetal intermediate will afford the product and further regenerate the catalytic active species.

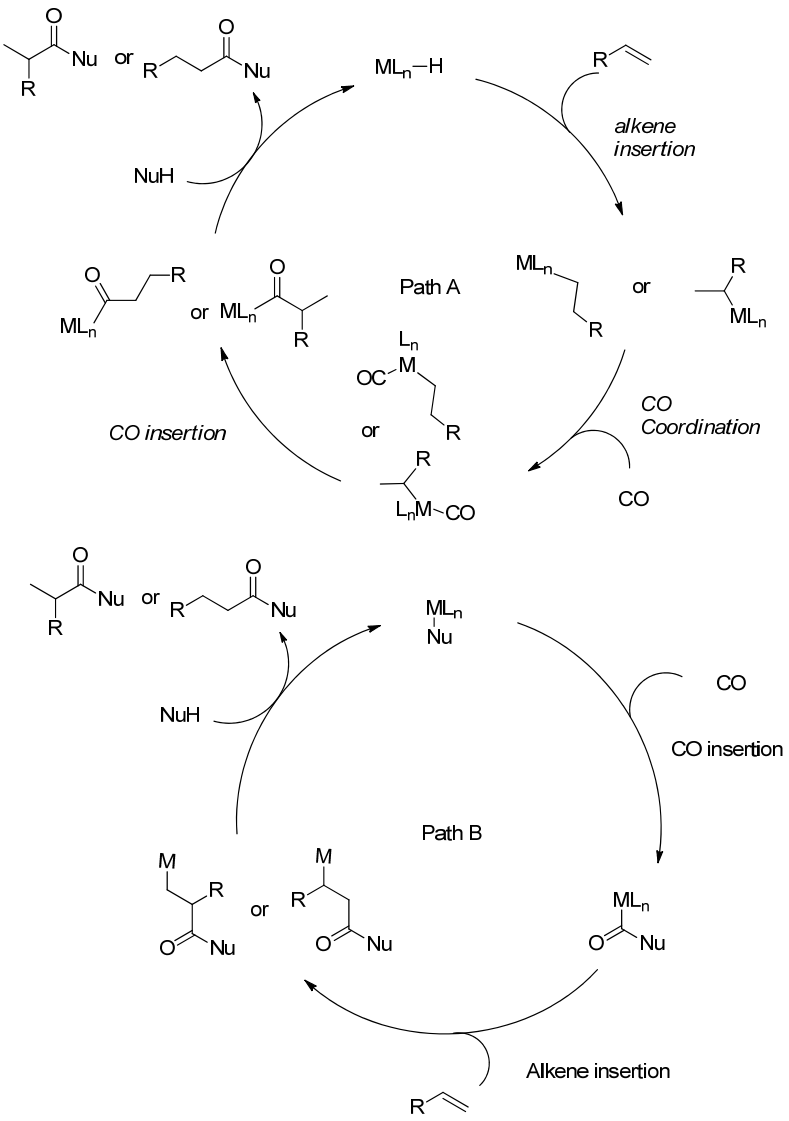
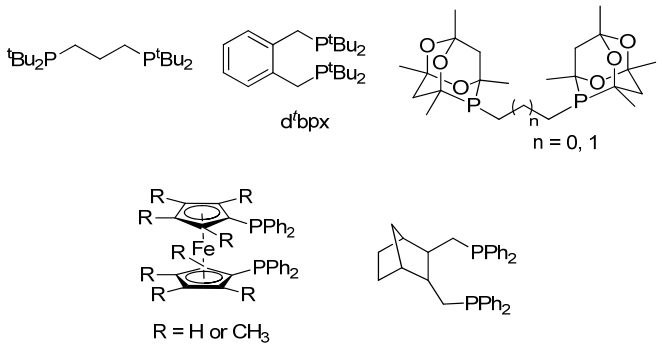


Figure 1 General catalytic cycles of carbonylation of alkenes

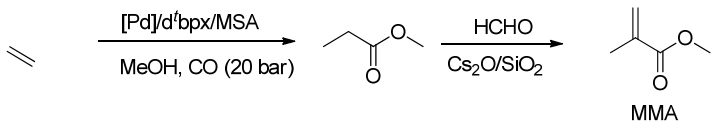
2.2 Alkoxycarbonylation of alkenes

As indicated above, the development of the alkoxycarbonylation reaction (also called hydroesterification) of alkenes is initiated by Reppe's origin report using $[Ni(CO)_4]$ as the catalyst under harsh conditions. Owing to the progresses in coordination chemistry, also by the innovation of ligands, palladium was later found to be much more efficient. Despite numerous catalyst systems have been explored for the alkoxycarbonylation of alkenes, highly linear selective catalyst systems have been established by the combination of Pd(0) or Pd(II) precursors and bulky chelating ligands, such as bis(phosphaadamantyl)alkanes[18], 1,2-bis(di-tert-butyl-phophanylmethyl)benzene(d^{t}bpx)[19], or 1,1'-bis(diphenylphosphanyl)metallocenes[20] (Scheme 3).



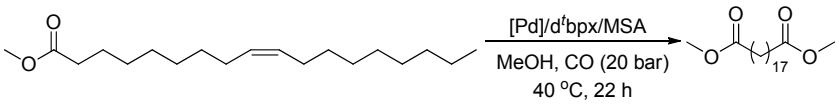
Scheme 3 Selected ligands for palladium-catalyzed linear selective alkoxycarbonylation

One important application of alkoxycarbonylation is the production of propionate from ethylene (Scheme 4), by a palladium/d^{t}bpx/acid (Lucite process).[19a, 21] Further aldol-condensation with formaldehyde using heterogeneous catalyst with cesium oxide over silica selectively to form methyl methacrylate (MMA), which is the monomer for the production of poly(methyl methacrylate) (PMMA). To note, this process is in the production scale of ca. 120,000 tons per year.[22]



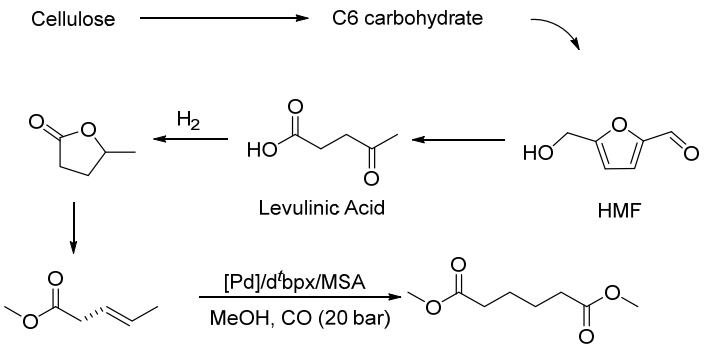
Scheme 4 Methoxycarbonylation/condensation route to MMA

Using the same catalyst system [Pd$_2$(dba)$_3$], d^{t}bpx and methane sulfonic acid provide highly active catalyst for the isomerization-methoxycarbonylation of internal alkenes to linear carboxylic acid ester. 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 carboxylate to industrially important linear α,ω-diester (Equation 2).



Equation 2 Palladium-catalyzed methoxycarbonylation of methyl oleate

Moreover, as depicted in Scheme 5, the same catalyst system is also used to transform biomass derived unsaturated aliphatic ester to synthesize methyl adipate, an important monomer for nylon-66 synthesis.[23]



Scheme 5 Synthesis of adipate based on biomass using palladium-catalyzed methoxycarbonylation reaction

2.3 Branched-selective carbonylation of alkenes

Selectivity is a major issue in organic synthesis.[24] According to the concerning discipline, definitions are invented, such as chemoselectivity, regioselectivity, stereoselectivity and enantioselectivity. In principle, the outcome of a reaction is decided by the thermodynamic and the kinetic, which may mainly involve the incongruent transition states, thermodynamic stability of products and equilibrium processes. Therefore, the catalyst-controlled selectivity in organic synthesis is considered to be extraordinary challenging.

As described above, in regard to alkoxycarbonylation, nowadays a number of efficient and highly linear-selective systems exist. Nevertheless, despite the apparent simplicity of the Markovnikov-selective carbonylation of aliphatic olefins, a general methodology is basically unknown. Branched-selective alkoxycarbonylation protocols was only achieved with specific substrates, such as vinylarene, vinylacetate, perfluoroalkene, which either takes use of special electronic property of the substrate or taking use of the stabilization effect by specific coordination mode of the substrate to the metal centre[25].

2.3.1 Branched-selective carbonylation of vinylarene

The alkoxycarbonylation of vinylarene is an important process for the production 2-arylpropanoic acid and its derivatives, which serves as nonsteroidal anti-inflammatory drugs, such as ibuprofen and naproxen. Due to the commercial and pharmaceutical importance of these products, numerous researches on their selective synthesis have been done (Figure 2).[26]

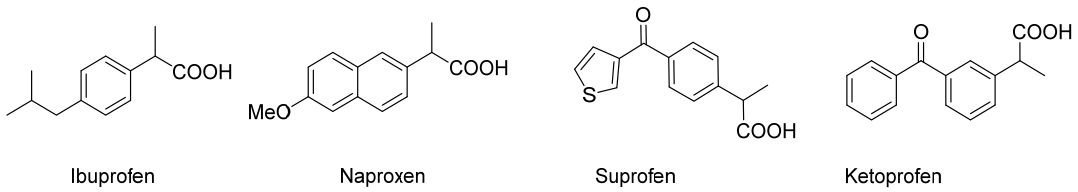
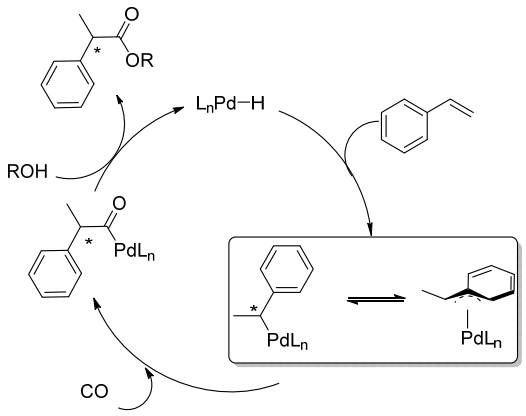


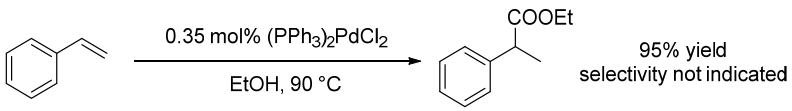
Figure 2 Selected examples of 2-aryl-propanoic acid

The origin of regioselectivity of carbonylation of vinylarenes could be accounted by the π-benzylic stabilization effect of vinylarene in the palladium hydride insertion step. (Scheme 6) The regioselectivity in the palladium-catalyzed carbonylation of styrene was mainly controlled by the auxiliary phosphorus ligand. When monophosphines are used, the branched-product is usually produced as the major product with practically complete regioselectivity. In contrast, when using di-phosphine as auxiliary ligand, the regioselectivity switches to favor the linear product. Moreover, the activity and regioselectivity of carbonylation of styrene are also sensitive to the nature of anions.[27]



Scheme 6 Proposed mechanistic cycle for branched-selective alkoxycarbonylation of vinylarene

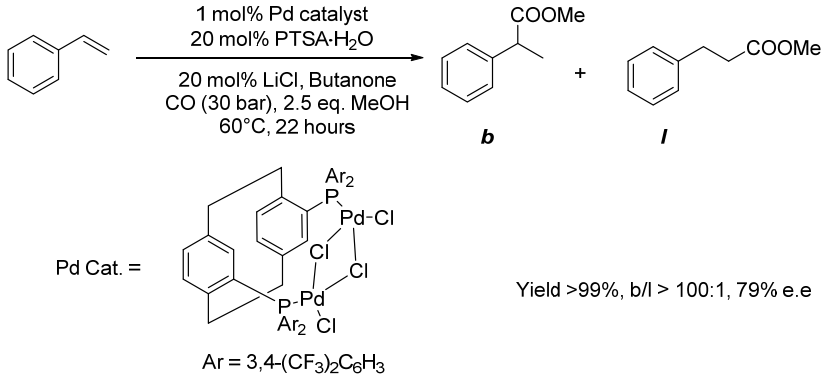
One of the first reported branched-selective styrene carbonylation reaction is included in a patent by BASF in 1963 and later published.[28] In presence of $(PPh_3)_2PdCl_2$, styrene was transformed to the corresponding branched ester with 95% yield. However, in this report, the selectivity was not indicated (Equation 3).



Equation 3 Branched-selective alkoxycarbonylation of styrene

In 1995, Howard et al. reported the alkoxycarbonylation of alkenes catalyzed by $Pd(OAc)_2$ immobilized on montmorillonite (a swelling-type smectite clay) in the presence of

triphenylphophine and an acid promoter. The observed regioselectivity was similar to homogeneous analogs (*b*:*l* = 98:2- 100:0).[26l]



Equation 4 Regio- and enantioselective alkoxycarbonylation of styrene

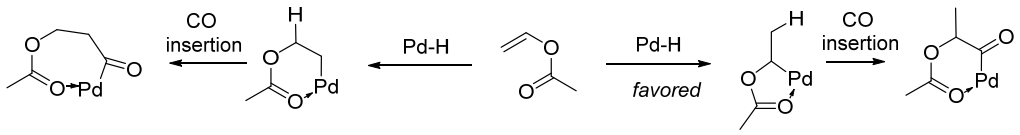
More recently, Clarke reported the use of a family of novel mononuclear and dinuclear palladium complexes, the simultaneous control of regioselectivity and enantioselectivity in the hydroxycarbonylation and alkoxycarbonylation of styrene derivatives has been for the first time realized (Equation 4).[29]

2.3.2 Branched-selective alkoxycarbonylation of vinyl acetate

Vinyl acetate is a cheap and easily available chemical, which is the precursor to polyvinyl acetate, an important polymer in industry. About 80% of the available capacity of vinyl acetate is produced by the oxidation reaction of ethylene and acetic acid with heterogeneous catalysts containing palladium. Another 20% of capacity is mainly produced by the addition of acetic acid to acetylene in the gas phase in the presence of heterogeneous catalyst containing zinc salts. [30]

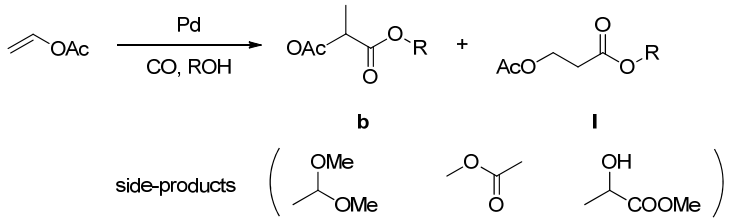
Lactic acid and its derivatives are important chemicals and synthetic building blocks for food and polymer industry (polylactide synthesis). Due to the limitation of currently performed biochemical synthetic approach, the search for alternative synthetic protocol for lactate production is desirable. In this regard, the branched-selective alkoxycarbonylation of vinyl acetate represents a promising and atom-economic route for lactate synthesis.

The regioselectivity of carbonylation of vinyl acetate is usually explained by the weak coordination of the acetyl group. As depicted in Scheme 7, a five membered palladacycle would form as a stabilized intermediate, which will lead to the formation of branched-carbonylated product as the major product.



Scheme 7 Addition of Pd-H to vinyl acetate

The first report on the alkoxycarbonylation of vinyl acetate dates back to 1992, when Drent reported the methoxycarbonylation of vinyl acetate using palladium acetate and 1,3-bis(ditertiarybutylphosphino)propane as the catalyst system.[31] In MeOH/diglyme at 75°C and 40 bar CO, the methyl ester was formed with *b:l* ratio of 2:1. In 1996, Kudo reported that $PdCl_2/PPh_3$ in the presence of 2,6-lutidine can catalyze the methoxycarbonylation of vinyl acetate at 120°C and 200 bar.[32] The major side product was observed as transesterification product methyl acetate (Equation 5).



Equation 5 Alkoxycarbonylation of vinylacetate

In 2005, Cole-Hamilton and co-workers reported that $[(d^tbpx)PdH]^+$ catalyst system is also active for the carbonylation of vinyl acetate. The selectivity to branched product achieved as high as 78% at low conversion at 25°C.[33]

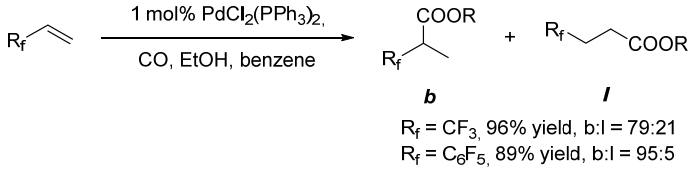
Börner and co-workers reported their study on the influence of acidic and non-acidic promoters for palladium-catalyzed alkoxycarbonylation of vinyl acetate. Up to 40:1 branched to linear ratio was achieved using a simple Pd/PPh_3 catalyst system accompanied with pyridine/p-TsOH as the additive.[34]

2.3.3 Branched-selective alkoxycarbonylation of perfluoroalkene

3,3,3-trifluoropropene and pentafluorostyrene are important organic building blocks. Fluoro-containing organic molecules are useful in agrochemical and pharmaceutical industry due to the special physiological activities displayed. Likewise, fluoro-containing materials have also found broad applications.[35]

Scheme 8 Difference in electronic property of propene and 3,3,3-trifluoropropene

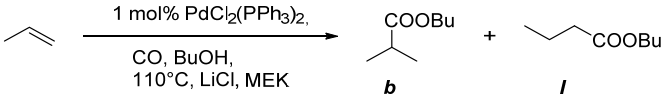
Generally, if an alkene contains an electron-withdrawing substituent attached to it, the carbonylation reaction tends to occur at its α-position (Scheme 8).[25] As early as 1983, the alkoxycarbonylation and hydroxycarbonylation of 3,3,3-trifluoropropene and pentafluorostyrene have been reported by Ojima and his co-workers.[36] Ethyl 2-methyl-3,3,3-trifluoropropionate was obtained in 96% yield with 79% branched-selectivity in the alkoxycarbonylation reaction of 3,3,3-trifluoropropene by using $PdCl_2(PPh_3)_2$ as the catalyst. Using the same catalyst system, pentafluorostyrene could be alkoxycarbonylated to the corresponding branched ester with 89% yield and 95% regioselectivity (Equation 6).



Equation 6 Branched-selective alkoxycarbonylation of perfluoroalkene

2.3.4 Branched-selective alkoxycarbonylation of propene

In 1981, Cavinato and Toniolo reported the solvent effect on the alkoxycarbonylation of propene (Equation 7).[37] In the presence of $PdCl_2(PPh_3)_2$, with LiCl as additive, using a 17.8/1 methylethylketone/butanol ratio, the reaction gave 90% yield and 81% branched-selectivity.[37]



Equation 7 Branched-selective carbonylation of propene

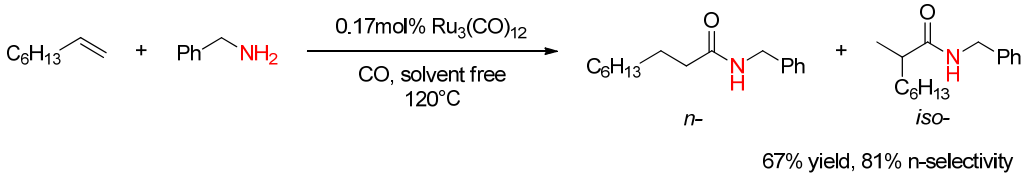
In the framework of this dissertation, we show our recent finding about a specific palladium catalyst system consisting of PdX_2/*N*-phenylpyrrole (X = halide) catalyzes the alkoxycarbonylation of various alkenes to give the branched esters in high selectivity (*b:l* up to 91:9). The observed but unexpected selectivity has been rationalized by density functional theory computation including dispersion correction for van der Waals interaction.

2.4 Carbonylation of alkenes with *N*-nucleophiles

Over the past 70 years' discovery of carbonylation reactions of alkene, specifically in palladium-catalyzed alkene carbonylation, the investigations using *O*-nucleophile (alcohol, or water) were predominant. In contrast, carbonylation reactions with other nucleophiles were relatively less studied.[38]

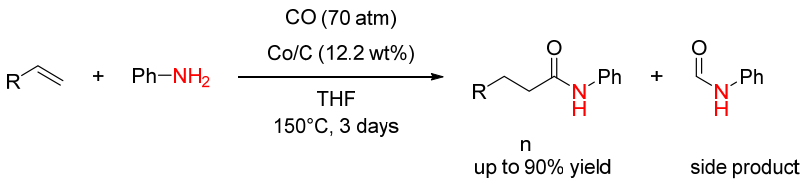
Early reports on the aminocarbonylation(also called amidation) of alkenes mainly focused on the using non-noble metal catalysts, such as Raney Co[39], nickel cyanide[40], iron carbonyl[39] complexes and ruthenium chloride[41] as the catalyst. Nevertheless, these catalysts were not efficient enough (usually performed at >200 °C, >150 bar CO).[12c, 42]

In 1986, Watanabe reported $Ru_3(CO)_{12}$ catalyzed aminocarbonylation of alkenes.[43] Starting from 1-octene and benzylamine as the substrate, in the presence of 0.17 mol% $Ru_3(CO)_{12}$, at 120 °C, the corresponding aliphatic amide could be obtained with 67% yield, with 81% linear selectivity (Equation 8). In this report, the addition of phosphite or phosphine ligand was shown to inhibit the reactivity. In the same report, Rhodium catalyst was also shown to be active for this transformation by giving 55% yield and 95% linear selectivity. In most cases, the *N*-formylation product was observed as the major byproduct. Moreover, the carbamoyl complex was isolated and proposed to be the active species. More interestingly, catalyst system for aminocarbonylation of ethylene by supported ruthenium and rhodium catayst was also reported. The increase of the acidity of the support will further dehydrate the propionamide to propiononitrile.[44]



Equation 8 Ruthenium-catalyzed aminocarbonylation of alkene

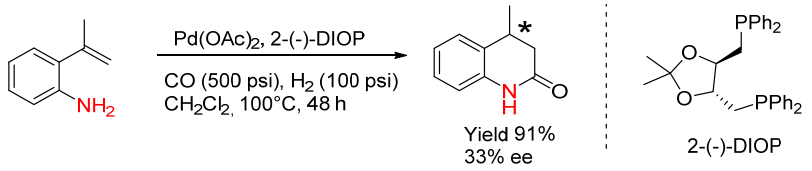
Besides, supported cobalt catalyst system was also studied by Chung in 2002.[45] Compared with the previously reported cobalt carbonyl catalyzed aminocarbonylation reaction, milder reaction conditions were used (150°C, 70 atm. CO), even though long reaction time is needed in this protocol (Equation 9).



Equation 9 Co/C catalyzed aminocarbonylation of alkene

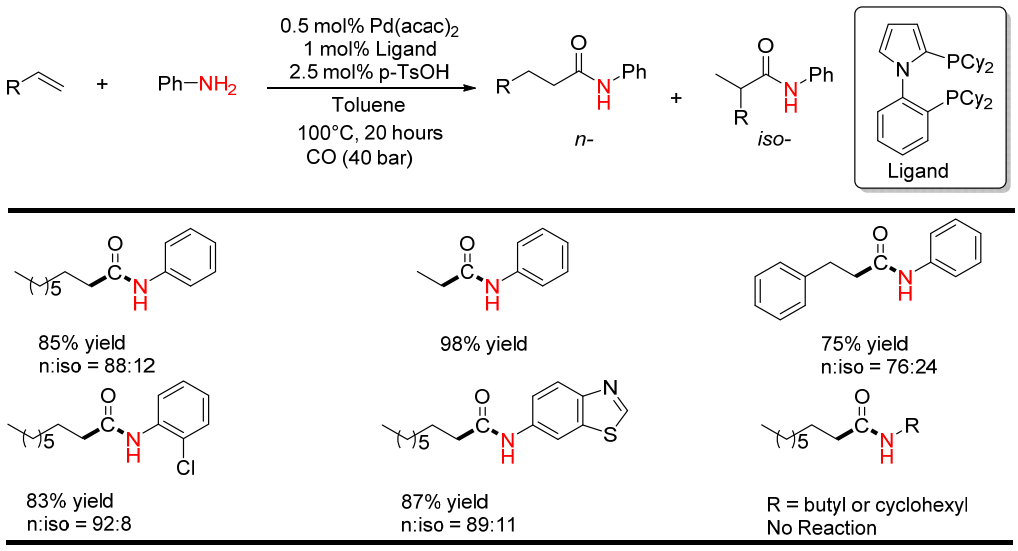
In 1997, Alper et al. reported the first intramolecular cyclocarbonylation of 2-vinylanilines catalyzed by palladium with chiral phosphines.[46] The reaction of 2-(1-

methylvinyl)aniline using a catalyst system consisting of $Pd(OAc)_2$-2(-)DIOP gave 3,4-dihydro-4-methyl-2(1H)-quinolin-2-ones in up to 54% enantiomeric excess (Equation 10).



Equation 10 Intramolecular aminocarbonylation of 2-vinylanilines

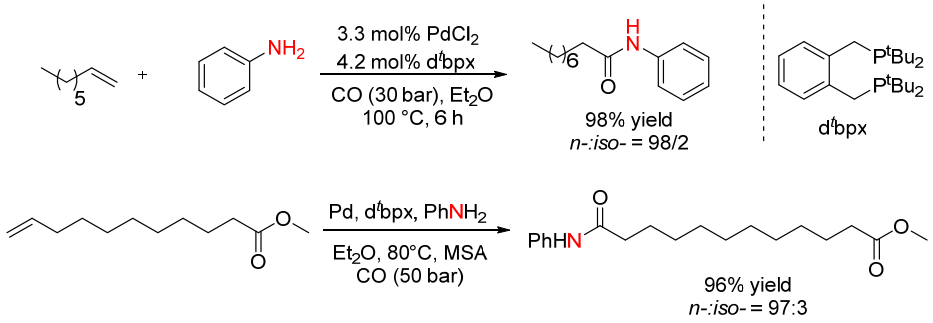
In 2013, our group reported the first palladium-catalyzed intermolecular aminocarbonylation reaction of alkenes (Scheme 9).[47] The reported catalyst system consists of an *N*-phenylpyrrole bidentate phosphorus ligand and catalytic amount of *p*-TsOH as the promoter. The reactions were performed under much milder conditions (100°C, 40 bar CO), which tolerated a much broader scope of substrates. 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 amine as the nucleophile. Furthermore, the applicability of this methodology is further demonstrated by in-situ generation of aniline by reduction of nitroarene using syngas (CO/H_2).



Scheme 9 Palladium-catalyzed aminocarbonylation of alkenes

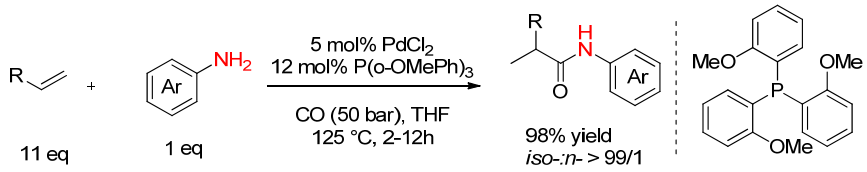
Cole-Hamilton and co-workers subsequently reported another catalyst system for the carbonylation of aliphatic olefins using Pd/d^{t}bpx catalyst system (Scheme 10).[48] The application potential of this protocol was showcased by the highly linear selective

aminocarbonylation of unsaturated aliphatic carboxylate to synthesize α,ω-ester amides. For example, starting from 10-undecenoate, under 80°C and 50 bar CO, the corresponding α,ω-ester amide was obtained with 96% yield with 97% linear selectivity.



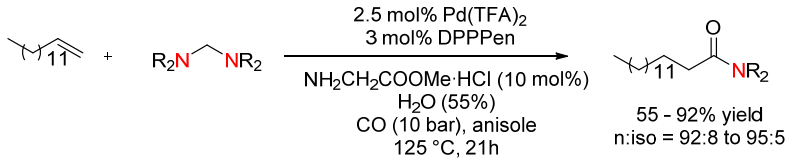
Scheme 10 Palladium/d^{t}bpx catalyst system for aminocarbonylation of alkene

More recently, Liu, Dyson and co-workers reported an efficient method for selective aminocarbonylation of alkenes which afford monosubstitued carboxamides with excellent regioselectivity (*iso-:n-* > 99:1).[49] The reported catalyst system doesn't require any additional acidic promoters, which are usually needed for alkoxycarbonylation reactions (Equation 11).



Equation 11 Acid-free branched regioselective aminocarbonylation of alkenes.

As a common drawback of all the above-mentioned palladium systems, only aromatic amines could be tolerated. When using aliphatic amine as the nucleophile, the reactivity is usually totally inhibited. Huang hypothesized that this problem is mainly owing to the strong basicity of aliphatic amine (pK_b <5) compared with aromatic amine (pK_b >9) may inhibit the formation of palladium hydride species.[50] According to this hypothesis, they reported a cooperative catalytic system operating by the synergistic combination of palladium, paraformaldehyde and acid to promote aminocarbonylation of alkenes using both aromatic and aliphatic amines (Equation 12).

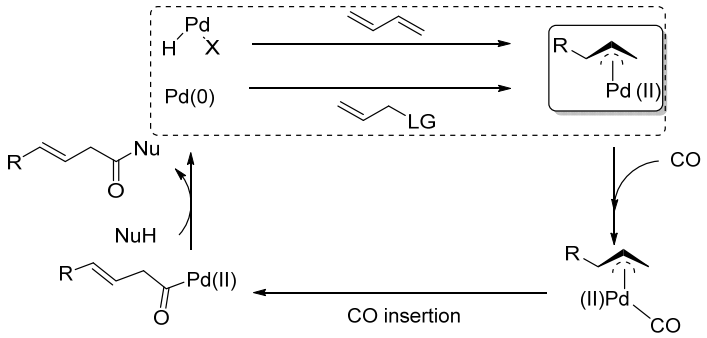


Equation 12 Aminocarbonylation of alkenes: overcoming the basicity barrier

Enlightened by the former work on the aminocarbonylation reactions of alkene using aromatic or aliphatic amines as the nucleophile, within the context of this dissertation, we show that unconventional nucleophiles amides could serve as the nucleophile using a PdX_2/DPEphos catalyst system.[51] This reaction protocol provides an atom-economic and straightforward method for straightforward imide synthesis. Furthermore, the anxiolytic drug Aniracetam was synthesized in one step in an intramolecular fashion using the developed protocol.

3 Carbonylation of conjugated dienes and allylic alcohols

3.1 Research Background



Scheme 11 General reaction mechanism for carbonylation of dienes and allylic compounds

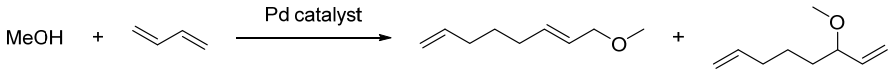
Dienes[52] and allylic alcohols[53] are two series of valuable and easily available substrates in organic synthesis. In parallel to the coupling chemistry using diene and allylic substrates (so called Tsuji-Trost allylation),[54] the carbonylation reactions of dienes and allylic compounds are generally considered to proceed *via* allyl-palladium species as the key reaction intermediate.[55]

A general reaction mechanism could be depicted as in Scheme 11. Firstly, allylpalladium species could be formed by the insertion of 1,3-diene to palladium hydride[56] or by the oxidative addition of allylic compounds to the Pd(0) center.[57] Followed by the carbon monoxide coordination and insertion to the allyl palladium intermediate, acyl palladium species could be generated. Finally, the nucleophilic attack of the nucleophile to the acyl palladium species will produce β,γ-unsaturated carboxylic derivatives and regenerate the catalytic active species.

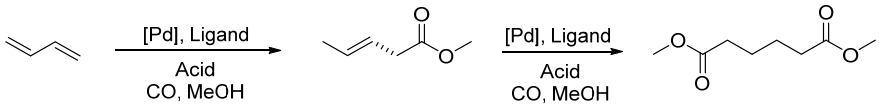
3.2 Carbonylation of 1,3-dienes

3.2.1 Alkoxycarbonylation of 1,3-dienes

In chemical industry, most butadiene is polymerized to produce synthetic rubber. Copolymerization of butadiene and styrene and/or acrylonitrile, such as acrylonitrile butadiene styrene (ABS), acrylonitrile butadiene rubber (NBR) and styrene–butadiene rubber (SBR) produces tough and/or elastic material. In transition-metal catalysis, palladium-catalyzed telomerization processes of butadiene is also recognized as a highly efficient and sustainable processes for 1,3-diene transformation (Equation 13).[58]



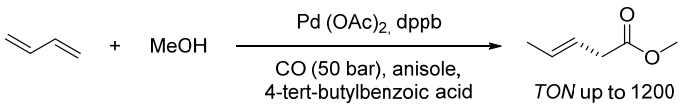
Equation 13 Palladium catalyzed telomerization of 1,3-dienes



Scheme 12 Sequential alkoxycarbonylation of butadiene to dimethyl adipate

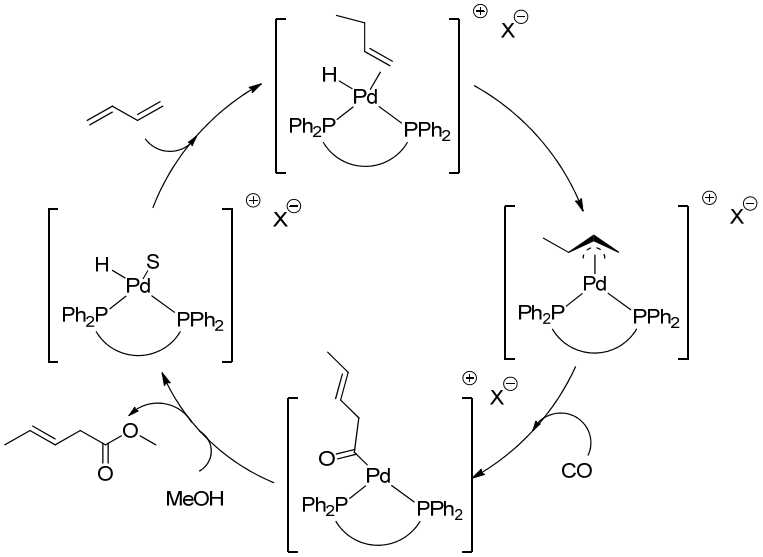
Selective transformations of 1,3-dienes into more value-added compounds are highly desirable. Specifically, the selective alkoxycarbonylation of 1,3-butadiene is of major industrial interests, which give rise to the production of adipic acid and ε-caprolactam *via* 3-pentenoic acid ester (Scheme 12). In early 1940s, Reppe reported the reaction of 1,3-butadiene to carbonylated cyclohexene using $[Co_2(CO)_8]$ as a catalyst. Later, DuPont reported the methoxycarbonylation of 1,3-butadiene to methyl pentenoate by using Co/Cu/Th catalyst at high pressure (810 bar).[59] BASF also made another patent on the alkoxycarbonylation of butadiene using Co-based catalyst in 1990s.[60] However, the conditions used were still very harsh (100–1000 bar CO with 0.1 – 10% H_2). In the late 1960s, Tsuji et al. described using $PdCl_2$ as catalyst for the alkoxycarbonylation reaction of 1,3-butadiene, however the productivity was low (at approximately 30% yield).[61] Matsuda and co-workers also demonstrated the use of cobalt catalyst for this reaction in the presence of pyridines at high CO pressure and low turnover number (TON 25- 80).[62] Later, a systematic investigation of the palladium-catalyzed carbonylation of 1,3-dienes was done by Knifton.[63] Despite variation of different ligands and solvents, mainly 3,8-nonadienoate esters (telomerization products) were obtained. A significant amount of work (mainly

included in patents) was done on the palladium-catalyzed methoxycarbonylation of 1,3-dienes by Shell[64], Du Pont, and DSM[65].



Equation 14 Alkoxycarbonylation of diene using benzoic acid as additive

In 2002, our group demonstrated the importance of chelating phosphine ligands and benzoic acid as additive in the palladium-catalyzed methoxycarbonylation of 1,3-butadiene(Equation 14). By using palladium catalyst system in the presence of dppb as the ligand and 4-tertbutylbenzoic acid as the catalyst, the telomerization reaction is almost completely suppressed. Relatively good productivity was obtained (*TON* up to 1200). The acyl palladium species was not observed in any cases. Thus, the formation of acylpalladium species was assumed to be the difficult step (Scheme 13).



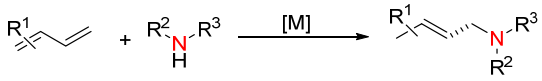
Scheme 13 Mechanistic proposal for palladium-catalyzed alkoxycarbonylation of 1,3-butadiene

In the framework of this thesis, we show a novel protocol for palladium-catalyzed alkoxycarbonylation of 1,3-dienes with enhanced substrate scope due to the absence of acidic additives. The first catalytic di- and trialkoxycarbonylations of 1,3-dienes utilizing easily accessible diols and glycerol affords potential plasticizers in a straight forward manner.

3.2.2 Aminocarbonylation of 1,3-dienes

Amides motifs are important in organic chemistry, which can be easily found in materials, agrochemicals and pharmaceuticals etc.. The efficient formation of amide bond is

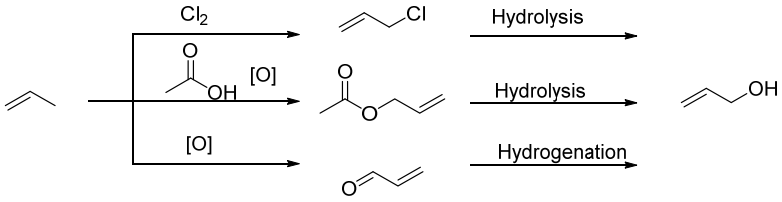
considered to be an interesting but challenging topic. In terms of atom-economy, the aminocarbonylation of 1,3-diene is a perfect synthetic route to synthesize β,γ-unsaturated amides (100% atom economy).[66] Nevertheless, a major challenge for the aminocarbonylation of diene is the corresponding competitive direct amination reaction, which generates allylic amine as the major product (Equation 15).[67]



Equation 15 Transition metal catalyzed amination of diene

To the best of our knowledge, efficient palladium catalyst system for the aminocarbonylation reaction of diene was basically not known before our study. In the framework of this study, we describe an efficient palladium based catalyst system for the efficient aminocarbonylation of 1,3-diene. The described methodology is further highlighted by the applications in heterocycle synthesis.[68]

3.3 Carbonylation of allylic alcohols

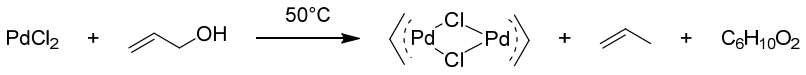


Scheme 14 Industrial routes of allylic alcohol synthesis

Allyl alcohol was first prepared in 1856 by Cahours and Hormann by saponification of allyl iodide. It is mainly converted to glycidol, which is the intermediate in the synthesis of glycerol, glycidyl ethers and esters. Allyl alcohol is mainly derived from propylene.[69] Nowadays, allyl alcohol is produced by Dow and Shell through hydrolysis of allyl chloride, which comes from the chlorination of propene.[53] An alternative route to produce allyl alcohol is through the acetoxylation of propylene to allyl acetate followed by hydrolysis. Another alternative route for allylic alcohol production is *via* the reduction of acrolein which is derived from the selective oxidation of propylene (Scheme 14).[70]

Besides allyl alcohol, versatile allylic alcohols are produced in a large scale, such as crotyl alcohol and prenol.[71] More interestingly, 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.[72]

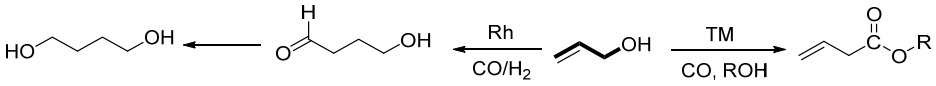
In 1959, the reaction of allylic alcohol and palladium chloride was first reported by Smidt et al., showing that the reaction of allylic alcohol with palladium chloride will generate $[(allyl)PdCl]_2$, propene and an unidentified oxidized $C_6H_{10}O_2$ product.(Equation 16) In fact, this work has laid the foundation of the coupling chemistry with allylic alcohol as the substrate.



Equation 16 Reaction of allylic alcohol with palladium

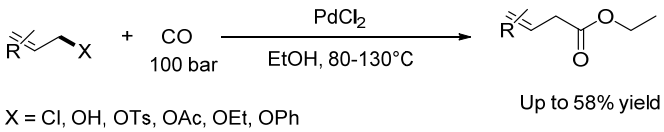
3.3.1 Alkoxycarbonylation of allylic alcohols

In principle, allylic alcohol can be considered as a reactant containing two reactive electrophilic sites. 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 at the alkene part to generate 4-hydroxybutanal, which can be further hydrogenated to synthesize 1,4-butandiol (Scheme 15).[73]



Scheme 15 Comparison of functionalization of allylic alcohol from the alkene part and alkoxy group part

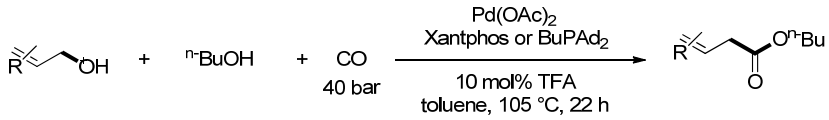
The direct carbonylation of the C-O moiety to synthesize β,γ-unsaturated carboxylic derivatives was first studied in 1964 by Tsuji.[74] In this report, various allylic compounds, including allylic chloride, allylic bromide, allylic ether and allylic alcohol were reported to be carbonylated to the corresponding β,γ-unsaturated carboxylic esters in the presence of palladium chloride under CO pressure (Equation 17).



Equation 17 Initial report of alkoxycarbonylation of allylic compounds by Tsuji

In 1980, a catalyst system in combination of palladium halide such as $PdCl_2$, $PdBr_2$, a phosphine ligand, such as PPh_3, P(*p*-Tol)$_3$ and co-catalyst $SnCl_2$ or $GeCl_2$ was disclosed by Knifton.[75] In 1992, similar work was performed by Miura and coworkers with lithium chloride and titanium isopropoxide as the reaction promoter.[76] In 1997, another example

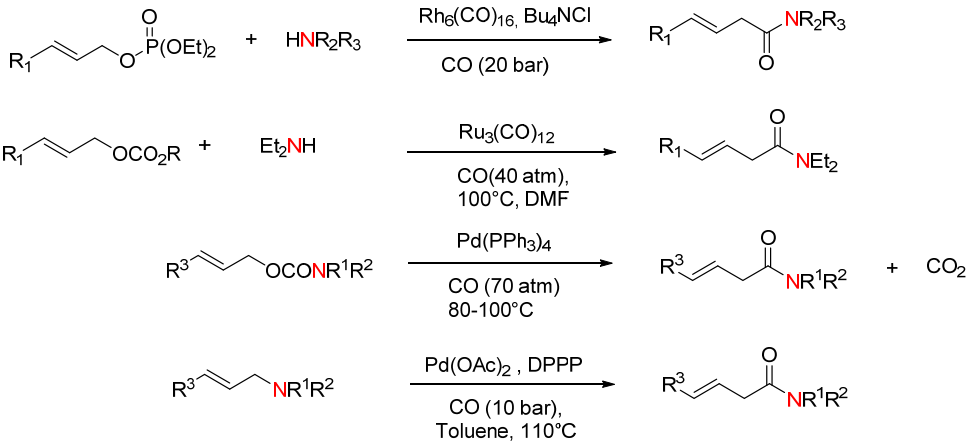
of carbonylation of allylic alcohol with phenol as the nucleophile was also reported.[77] A more general and practical procedure for the alkoxycarbonylation of allylic alcohol was recently reported in our group (Equation 18).[78] This catalyst system consists of $Pd(OAc)_2$, phosphine ligand, such as Xantphos or $BuPAd_2$ and trifluoroacetic acid as the additive. Mechanistic study showed that allylic ether acts as a key intermediate in the reaction. In all these above mentioned catalyst systems for allylic alcohol carbonylation, the C=C bond remained not carbonylated after the reaction. Only one example was reported concerning the intramolecular carbonylation of allylic alcohol in the synthesis of lactone in the presence of palladium under oxidation conditions.[79]



Equation 18 Alkoxycarbonylation carbonylation of allylic alcohol developed in our group

In the framework of this thesis, a novel straightforward method for the synthesis of industrial interested carboxylic derivatives *via* carbonylation of allylic alcohols is developed. Nevertheless, this part of results will not be disclosed in this thesis for confidentiality reasons.[80]

3.3.2 Aminocarbonylation of allylic alcohols



Scheme 16 Carbonylative methods for β,γ-unsaturated amide synthesis from allylic compounds

As mentioned above, β,γ-unsaturated amides are important synthetic intermediate in organic synthesis.[81] Therefore, the development of more efficient catalytic methods for β,γ-unsaturated amides has become one of our long-standing research interests. Alternatively, known methods for the carbonylative preparation of β,γ-unsaturated amides

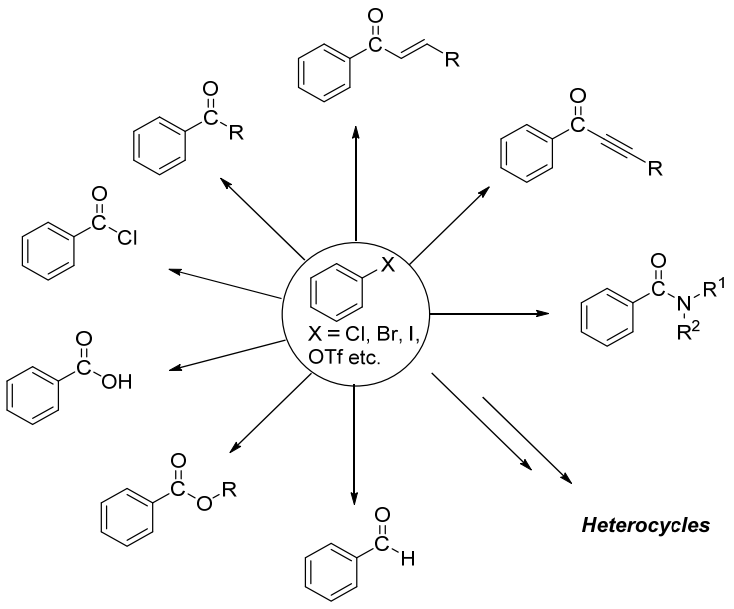
usually takes use of the carbonylation of allylic compounds (as shown in Scheme 16). For example, starting from allylphosphonate[82] or carbonate[83], in the presence of ruthenium, rhodium or palladium catalyst, the corresponding β,γ-unsaturated amides can be generated in the presence of amine and carbon monoxide. To note, in these reactions, stoichiometric amount of waste would be generated. Instead, when using carbamate as the starting material, β,γ-unsaturated amides can also be produced using palladium catalyst.[84] In addition, the carbonylation reaction of allylamines *via C-N* bond oxidative addition was also reported.[85]

After the development of the aminocarbonylation of diene, we decided to further investigate the aminocarbonylation starting from allylic alcohol, a much more stable and more easily available substrate. Moreover, the direct aminocarbonylation of allylic alcohol remains to be challenging due to the poor ability of hydroxy group to act as a leaving group.[86]

In the framework of this thesis, the direct aminocarbonylation of allylic alcohol synthesizing β,γ-unsaturated amides is developed. Mechanistic studies and control experiments show that the reaction goes through tandem allylic alcohol amination and C-N bond carbonylation reaction pathway.[87]

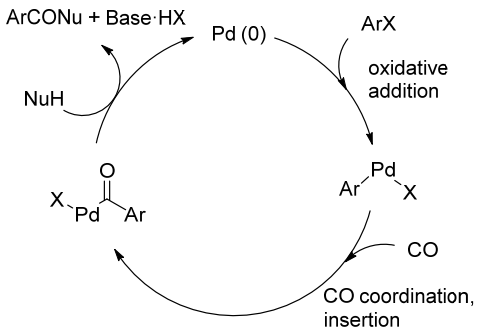
4 Carbonylation of Ar-X

4.1 Research Background



Scheme 17 Palladium-catalyzed carbonylation of aromatic halides

The development of coupling chemistry based on aryl-X (X = Cl, Br, I etc.) has witnessed the significant improvement of synthetic efficiency compared to the old fashioned coupling chemistry using stoichiometric reactions.[88] Almost in parallel with the development of the well-known Heck reaction[89], Heck found the basis of carbonylation of aryl halides by the discovery of palladium catalyzed aminocarbonylation and formylation of aryl and vinylic halide in the mid-1970s.[90] Since then, this area witnessed countless developments in the construction of all kinds of carbonyl containing compounds starting from easily available aryl halides and a suitable nucleophile (Scheme 17).[16c]



Scheme 18 General catalytic cycle for palladium catalyzed carbonylation of ArX

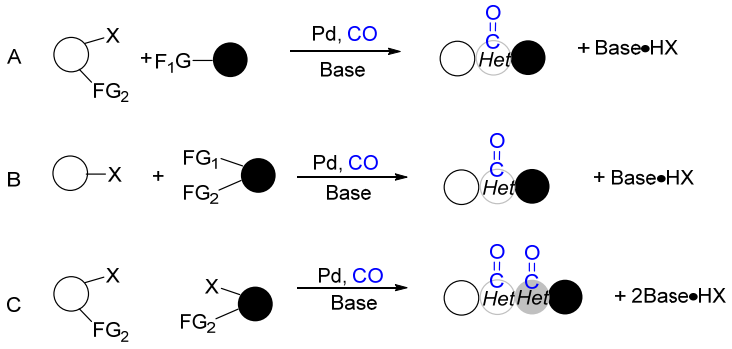
Generally, palladium catalyzed carbonylative coupling reactions start from Pd(0) as the active catalyst (Scheme 18). After the oxidative addition of ArX compounds to the palladium center, intermediate Ar-Pd-X could be generated. Further, the coordination and insertion of CO into Ar-Pd bond will generate acyl-palladium intermediate. Depending on the nature of nucleophile, the last step could occur *via* nucleophilic attack manner assisted by base (mainly with soft nucleophiles), or the transmetallation/reductive elimination sequence (usually with hard nucleophiles), or further coordination insertion of unsaturated C-C bond and subsequent β-elimination (in case of carbonylative heck reaction).

4.2 Carbonylative synthesis of heterocycles

Heterocyclic compound is defined as a cyclic compound that has atom of at least two different elements as members of its rings. Heterocyclic compounds are broadly applied, especially in material synthesis, agrochemical synthesis and pharmaceutical chemistry. To note, 45 out of the top 100 top US pharmaceutical products (by retail sales) in 2013 contains heterocyclic structure.[91]

Carbonylative coupling reactions represent facile methods to incorporate heteroatoms, especially in the formation of functional groups like amides, imides, esters,

ketones and thioester.[92] Along with the development of carbonylative coupling methods, the design of tandem reactions have found extensive applications in organic synthesis, especially in the construction of heterocycles. Excellent reviews concerning the synthesis of heterocycles using carbonylation reactions can be found in the literature.[92-93]



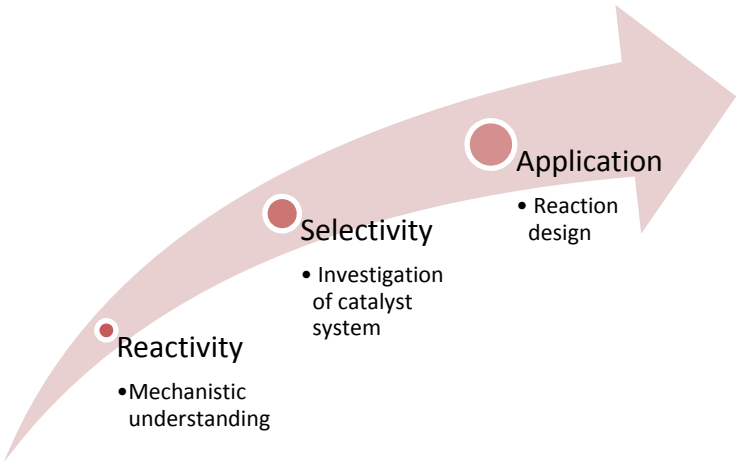
Scheme 19 Reactions models for heterocycle synthesis *via* carbonylative coupling reactions

The use of double-functionalized arenes as the building blocks for the construction of heterocycles was found to be interesting, because a number of double-functional arenes, even multi-functionalized arenes are nowadays commercially available, which give rise to the rapid synthesis of drug candidates containing heterocycles.[94] In principle, starting from functionalized aryl-X, the construction of heterocycles could be classified into three models. Firstly, starting from functionalized aryl-halide, by combination of a suitable nucleophile, heterocycle can be synthesized *via* the tandem carbonylation/cyclization reaction (Strategy A, Scheme 19). Secondly, starting from aryl halides, by coupling with double-functionalized compounds, heterocycles could also be obtained via rational carbonylative reaction design (Strategy B, Scheme 19). Moreover, in this thesis, we described the double carbonylative synthesis of heterocycles starting from two functionalized arylhalides (Strategy C, Scheme 19).

In the framework of this thesis, we demonstrated *strategies A* by the synthesis of quinazolinone[95], dihydrobenzodioxepinone[96]. Further, *strategy B* was demonstrated by the synthesis of quinazolinone *via* tandem aminocarbonylation/cyclization[97]. Further, *strategy C* is proposed and demonstrated through the first synthesis of quinazolindione[98] and isoindolinones[99] *via* double-carbonylation reactions.

5 Objectives of this work

As described above, transition metal catalyzed carbonylation reactions have attracted the research interest for academic and industrial chemists over the developments in last 70 years. Further discovery and progress of carbonylation methods is continuing to be highly desired (Scheme 20).



Scheme 20 Objectives of this work

Due to their bulk availability and relative low price, novel catalytic transformations based on feedstock chemicals, such as alkenes, dienes, and allylic alcohols will definitely renovate the classical route for chemical production. Likewise, carbonylative transformations based on these substrates are proved to be highly atom-economic and efficient, which attracted our interest to further discover unknown transformations for sustainable chemical synthesis.

In addition to the demand of novel transformations, the catalyst modulated/controlled selectivity (chemoselectivity, regioselectivity, enantioselectivity etc.) in catalytic transformations is even more challenging. As a part of this thesis, the investigation of a general and selective method based on our original catalyst system for branched-selective carbonylation of nonfunctionalized alkenes is described.

As a target of most catalytic transformations, the importance of application can never be overlooked. Since carbonylation reactions have been used to construct various carboxylic derivatives starting from easily available starting materials. The studies on rational design of tandem reactions in the concise construction of heterocycle are also conducted using carbonylation reactions.

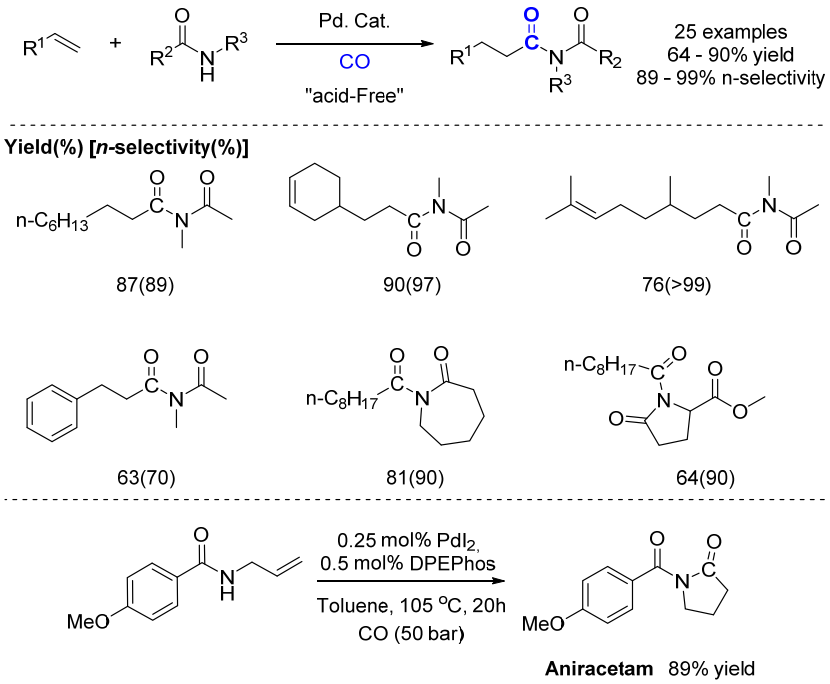
On another hand, in order to overcome the practically limitations of gaseous carbon monoxide in synthetic application, the development of CO surrogates to access safer and more operator friendly carbonylation reactions has been desirable.

Finally, the conducted research has been focused on the development of novel reactivity for palladium catalyzed carbonylations. Moreover, the combination of the known organic reactions and our developed carbonylation reactions to apply in organic synthesis has been an objective of this work.

6 Summary of publications

In conclusion, based on the understanding of fundamental organometallic chemistry and the mechanistic aspects of palladium-catalyzed carbonylations, starting from chemical feedstocks, such as alkenes, allylic alcohols and 1,3-dienes, the development of novel catalytic transformation is described in this thesis.

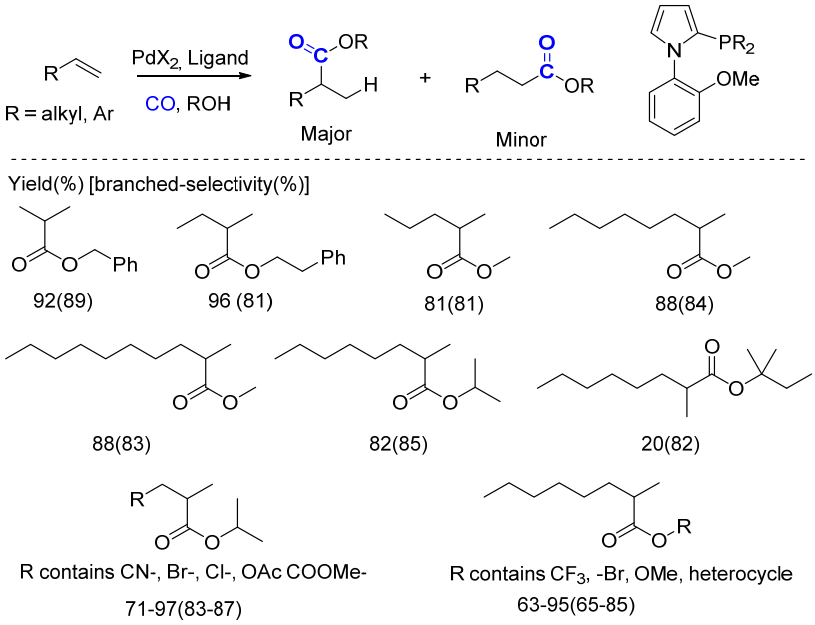
Carbonylation of alkenes: In this thesis, a novel palladium-catalyzed hydroamidocarbonylation reaction of aliphatic and aromatic alkenes using amides as nucleophile was successfully developed. This method provides an economical and sustainable synthesis of versatile imides. The optimal catalyst system (PdI_2/DPEPhos) is commercially available and is shown to be efficient and robust at relatively low catalyst loading. With respect to applications, it is noteworthy that alkenes with different structural characteristics are tolerated and the corresponding imides are produced highly selectively (89–99% n-selectivity). Moreover, various amides were tested and transformed to the corresponding imides in moderate to excellent yields (64–90%). The synthetic utility of the method is showcased by the synthesis of the anxiolytic drug Aniracetam in an atom-economic manner (Scheme 21).[51]



Scheme 21 Hydroamidocarbonylation of alkenes

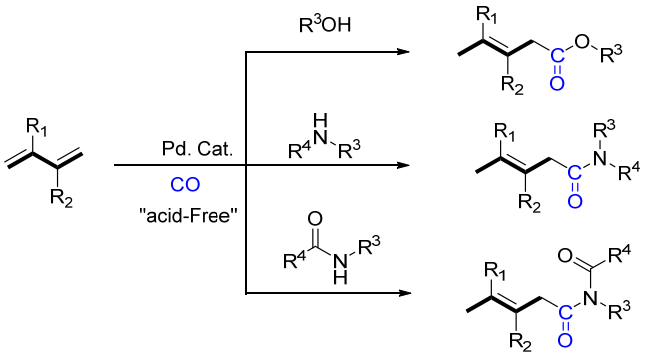
Next, we show for the first time that a specific palladium catalyst system consisting of PdX_2/*N*-phenylpyrrole (X = halide) catalyse the alkoxycarbonylation of various alkenes to

give the branched esters (Markovnikov product) in high selectivity (*b/l* up to 91/9). The observed but unexpected selectivity has been rationalized by density functional theory computation including dispersion correction for van der Waals interaction (Scheme 22).



Scheme 22 Selective palladium-catalyzed Markovnikov alkoxycarbonylation of non-functionalized alkenes

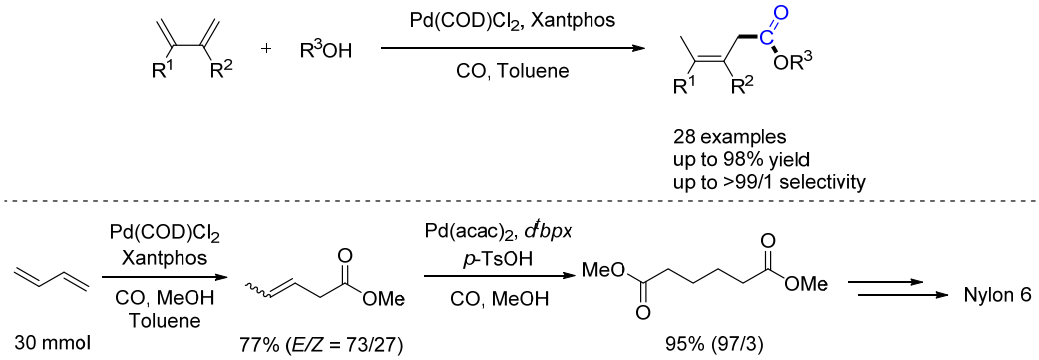
Carbonylation of dienes: In this thesis, we also described the synthesis of β,γ-unsaturated esters[100], amides[68] and imides[101], starting from 1,3-diene. (Scheme 23)



Scheme 23 overview of our work on diene carbonylation

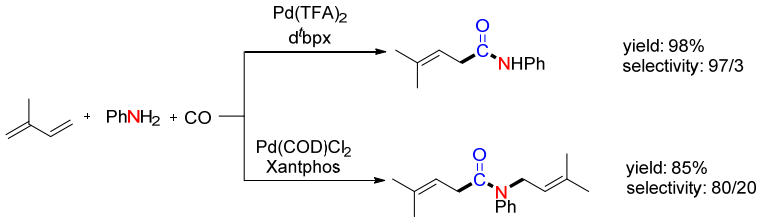
To start with, we developed a novel protocol for the palladium-catalyzed alkoxycarbonylation of conjugated 1,3-dienes to produce a variety of synthetically useful β,γ-unsaturated esters in good yields with often high selectivity. Compared to previously known procedures the substrate scope is enhanced in the absence of additives such as acids, which might cause corrosion problems. Furthermore, we reported the first catalytic di- and tri-alkoxycarbonylations of 1,3-dienes utilizing easily accessible diols and glycerol. These products are of interest as alternative plasticizers. Combining the presented

procedure with established carbonylation reactions allows for an efficient preparation of adipates (Scheme 24).



Scheme 24 Alkoxycarbonylation of 1,3-diene and potential application in Nylon-6 synthesis

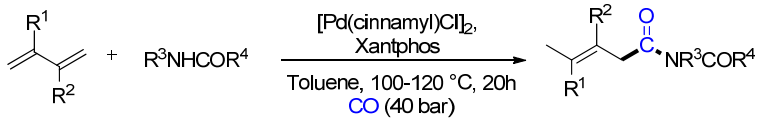
Furthermore, we developed the first general palladium-catalyzed-aminocarbonylation reactions of 1,3-dienes (Scheme 25). In the presence of different palladium phosphine complexes carbonylation (1:1 adduct) or a selective hydroamination-carbonylation sequence (2:1 adduct) was observed, respectively. Using different aromatic amines a variety of synthetically useful β,γ-unsaturated amides are produced in good to excellent yields. Combining this procedure with established functionalization allows for an efficient preparation of various heterocyclic compounds. The high atom economy, the additive-free reaction conditions make this protocol attractive for synthetic applications and we believe it will complement the current methodologies for carbonylations in organic synthesis.



Scheme 25 Palladium-catalyzed aminocarbonylation of 1,3-dienes

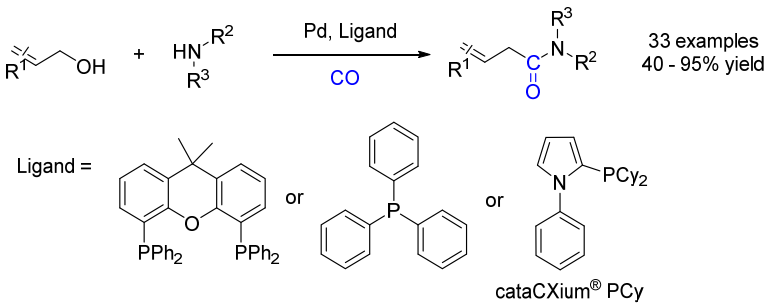
In addition, the palladium-catalyzed amidocarbonylation of dienes which leads to synthetically interesting β,γ-unsaturated imides is for the first time realized under mild reaction conditions (Equation 19).[102] Versatile amides were demonstrated to be compatible with these conditions. The generality of this reaction condition is also proved with the application of several commercially available dienes. More interestingly, industrial feedstock butadiene was found to be compatible even with lowered catalyst loading. The developed reaction is proposed to start with palladium hydride as the active species. We

believe that this synthetic protocol would be further used for more efficient complex organic synthesis.



Equation 19 Palladium-catalyzed hydroamidocarbonylation of 1,3-dienes

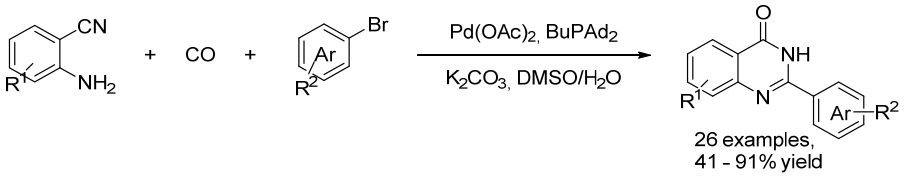
Carbonylation of allylic alcohol: As an alternatively interesting protocol for β,γ-unsaturated amides, a direct aminocarbonylation reaction of allylic alcohol is developed (Equation 20). The developed palladium-catalyst system consists of a phosphine ligand (Xantphos, PPh_3 or cataCXium® PCy). Starting from easily available allylic alcohols and aromatic amines, the synthetically useful β, γ-unsaturated amides could be obtained with good yield under mild reaction conditions. Various allylic alcohols are demonstrated to be well tolerated, including those naturally derived allylic alcohols, such as geraniol, nerol and linalool. Moreover, both catalyst systems for secondary and primary amines are disclosed, which showed excellent functional group tolerance. With the help of control experiments, a plausible reaction mechanism is proposed which involves mainly two cycles connected each other with allyl amine as a major intermediate and allyl-palladium cationic species as a major catalytic intermediate.



Equation 20 Palladium-catalyzed aminocarbonylation of allylic alcohols

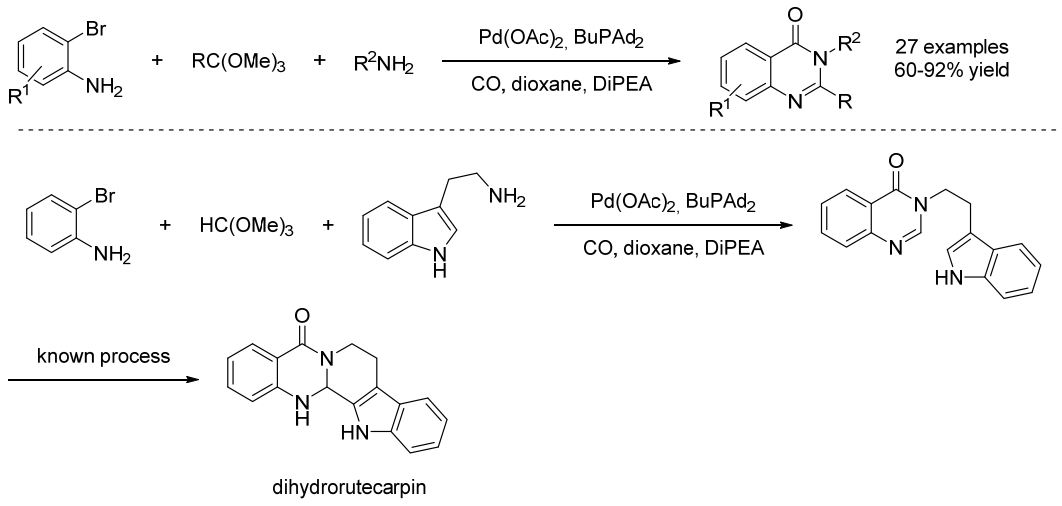
Carbonylative synthesis of heterocycles: Quinazoline[103] represents an important class of heterocyclic compounds with an array of biological activities, such as anticancer, anti-inflammatory, anti-microbial activity, etc. An interesting and straightforward procedure for the carbonylative synthesis of quinazolinones from commercially available 2-aminobenzonitriles and bromobenzenes has been developed (Equation 21).[97] Various quinazolinones were produced in moderate to excellent yields in one step. The reactions go

through aminocarbonylation of aryl bromides/hydration of nitriles/condensation cyclization sequence.



Equation 21 Palladium catalyzed carbonylative synthesis of quinazolinones

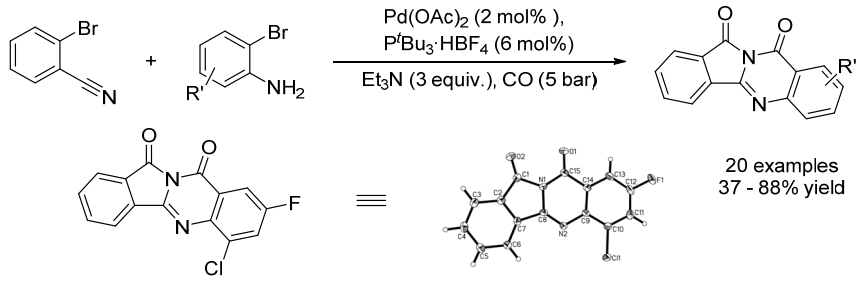
As a more convenient and more flexible protocol for the selective construction of 4(3H)-quinazolinones, we have developed a novel palladium-catalyzed four-component carbonylative coupling system in a one-pot fashion (Scheme 26). The easy generation of molecular diversity along with the importance of 4(3H)-quinazolinones in medicinal chemistry makes the reaction described herein an appropriate alternative for the synthesis of potentially bioactive compounds. In this context, and considering the simplicity of the starting materials, the reaction is suitable for the synthesis of small libraries of functionalized 4(3H)-quinazolinones. Notably, this interesting procedure can be easily scaled up and its application in the synthesis of the bioactive dihydrorutaempine precursor was successful.



Scheme 26 Palladium-catalyzed four-component carbonylative synthesis of quinazolinones

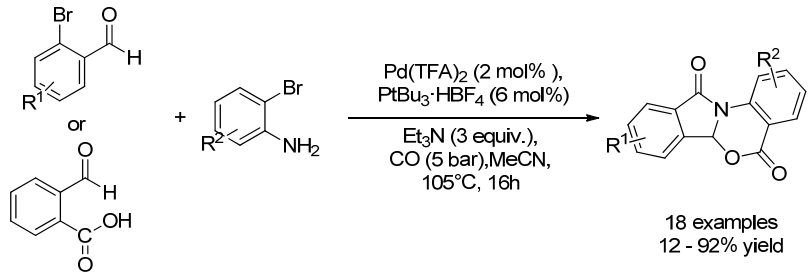
Next, we conceived the concept for double-carbonylation of two functionalized aryl-halides (Scheme 27). For the first time, we described a palladium-catalyzed double-carbonylation process for the synthesis of quinazolinediones.[98] Starting from commercially available 2-bromobenzonitriles and 2-bromoanilines a series of isoindolo[1,2-b]quinazoline-10,12-diones was straightforwardly synthesized in good isolated yields (around 20

examples). Notably, in this novel domino process both inter- and intramolecular carbonylation reactions take place and two CO molecules are incorporated in the parent product structure. Considering that at least 5 different C-C and C-N bonds are formed, each of the individual reaction steps proceeds with high selectivity and excellent yield.



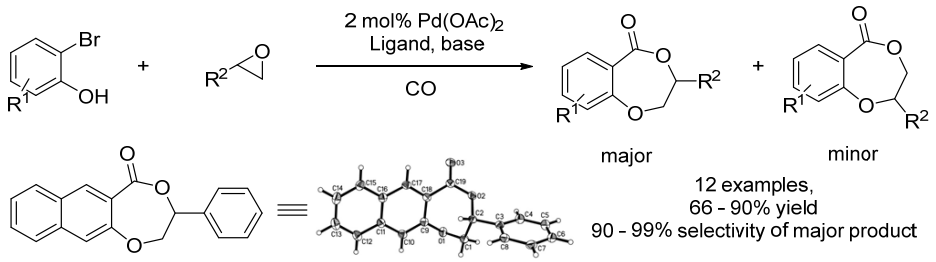
Scheme 27 Palladium-catalyzed double-carbonylative synthesis of quinazolinediones

In continuation to our study on double-carbonylative construction of heterocycles, we have developed a convenient and highly efficient cascade palladium-catalyzed carbonylative approach to functionalized isoindolinones from readily available materials. [99] The reported compounds will be a new entry into the synthesis of the isoindolinone family. Other remarkable advantages of this methodology include operationally simple, practical, high isolated yields in a one-pot fashion that allows C-C bond and C-N bond formation with excellent outcomes under relatively mild conditions (Scheme 28).



Scheme 28 Palladium-catalyzed double-carbonylative synthesis of isoindolinone

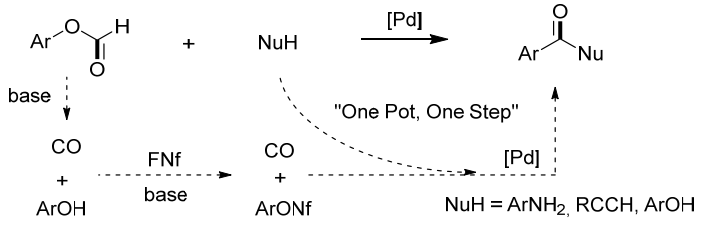
Besides, epoxide is for the first time used as a coupling partner in palladium catalyzed carbonylative coupling reaction *via* a ring-opening pathway (Scheme 29).[96] Starting from commercially available compounds, moderate to good yield of versatile desired product is obtained in a regioselective manner (major: minor > 90%) under mild conditions. This methodology is proven to be a straight forward pathway towards 2,3-dihydrobenzodioxepinones.



Scheme 29 Palladium-catalyzed carbonylative synthesis of dihydrobenzodioxepinones

"CO-Free" carbonylation:

Finally, In order to overcome the limitations of gaseous carbon monoxide in synthetic application, the development of CO surrogates to access safer and more operator friendly carbonylation reactions has been described.[104] carbonylative coupling reactions using aryl formates as the CO source and pseudohalide precursors have been developed (Scheme 30). No external carbon monoxide gas was required. The corresponding amides, alkynones, furanones, and phenyl benzoates were synthesized in good yields upon reaction with amines, alkynes and phenols, respectively.



Scheme 30 Arylformate as a bifunctional reagent for carbonylative synthesis

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8 Publications

8.1 Aryl Formate as Bifunctional Reagent: Applications in Palladium-Catalyzed Carbonylative Coupling Reactions Using In Situ Generated CO

Haoquan Li, Helfried Neumann, Matthias Beller*, Xiao-Feng Wu*

Angewandte Chemie International Edition, 2014, 3247-3250.

Contributions

In this paper, I came up with the idea, discovered the one-pot “CO-Free” reaction, planned and executed all of the optimization of the model system and also developed the substrate scope. Additionally, I wrote the major part of the corresponding manuscript, thus my overall contribution to this work approximately accounts for 70%.

Cross-Coupling

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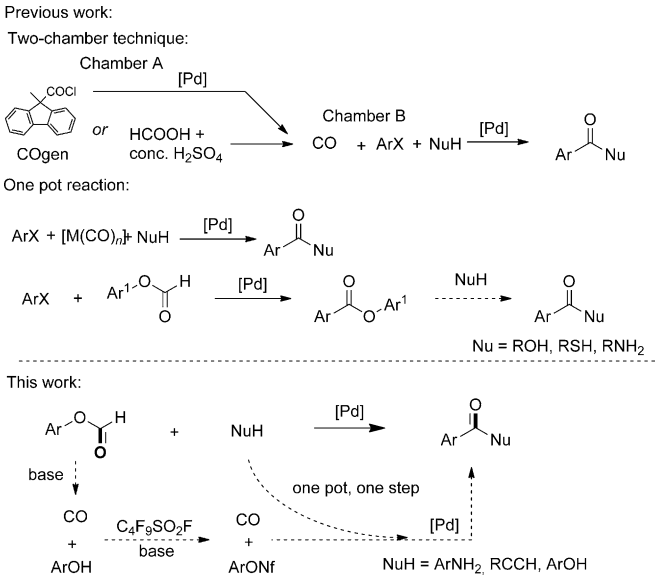
Aryl Formate as Bifunctional Reagent: Applications in Palladium-Catalyzed Carbonylative Coupling Reactions Using In Situ Generated CO**

Haoquan Li, Helfried Neumann, Matthias Beller, and Xiao-Feng Wu**

Abstract: *After decades of development, carbonylation reactions have become one of the most powerful tools in modern organic synthesis. However, the requirement of CO gas limits the applications of such reactions. Reported herein is a versatile and practical protocol for carbonylative reactions which rely on the cooperation of phenyl formate and nonaflate, and the generation of CO in situ. This protocol has a high functional-group tolerance and could be applied in carbonylations with C, N, and, O nucleophiles. The corresponding amides, alkynones, furanones, and aryl benzoates were synthesized in good yields.*

Ever since the pioneering work of Heck and Schoenberg in 1974, palladium-catalyzed carbonylative transformations of aryl halides have undergone impressive developments.[1] It has now constituted one of the most efficient and widely used methodologies for constructing carbonyl-containing compounds, such as aldehydes, amides, esters, etc.[2] However, the high toxicity, and odorless and flammable character of CO gas means that transformations using CO gas must be operated with special care. Usually, autoclaves and well-ventilated fume hoods, equipped with special CO detectors and alarms, are required for these reactions, and has actually hindered the applications of such reactions.

Given the disadvantages of using gaseous CO "CO-free" carbonylation reactions have attracted a lot of attention over the last three decades.[2b,3] To generate CO and consume CO in a closed system, a two-chamber technique was recently developed by Skrydstrup and co-workers. By using this technique, 9-methylfluorene-9-carbonyl chloride (COgen) was developed to generate CO gas with the assistance of a palladium catalyst (Scheme 1). And it was also reported to be suitable for ^{13}C-isotope labeling.[4] Notably, formic acid was also developed to generate CO through a dehydration reaction in sulfuric acid at elevated temperatures (Morgan reaction).[4b] In contrast, the in situ generation of CO from metal carbonyl complexes was proven to be compatible with a number of carbonylation reactions, both for one-pot transformations and the two-chamber technique.[5] Remarkably, alkyl formate was developed for the alkoxycarbonylation of olefins and aryl halides as well. Compared to alkyl formate, aryl formate was reported to generate CO in the presence of base under much milder reaction conditions.[6] The groups of Manabe[7] and Tsuji[8] independently reported the esterification of aryl halides using aryl formates. Also, the synthesis of amides, alkyl esters, amides, and thioesters can be achieved by a two-step process using 2,4,6-trichlorophenyl formate[7c] as a reactive intermediate. However, because of the fact that phenol could also acts as a strong nucleophile in the reaction, the choice of direct carbonylative coupling partners, such as amines, alkynes, alkenes, was limited.



Scheme 1. Comparison of the prior work to the current work.

Hydroxy groups are very useful functional groups and they are frequently converted into sulfonates, such as trifluorosulfonate (OTf), and subjected to a variety of additional transformations because of their leaving ability.[9] More recently, nonafluorobutanesulfonyl fluoride (NfF), has become a more attractive sulfonylating reagent because of its stability, reactivity, and availability.[10] Actually, it is now produced on the industrial scale by anodic fluorination of a cyclic sulfolene precursor.[11] In 2012, our group reported the palladium carbonylative synthesis of esters and amides starting from the in situ generated nonaflate under low pressure of carbon monoxide (1 bar).[12] With our continuous interest in developing carbonylation reactions, our initial idea

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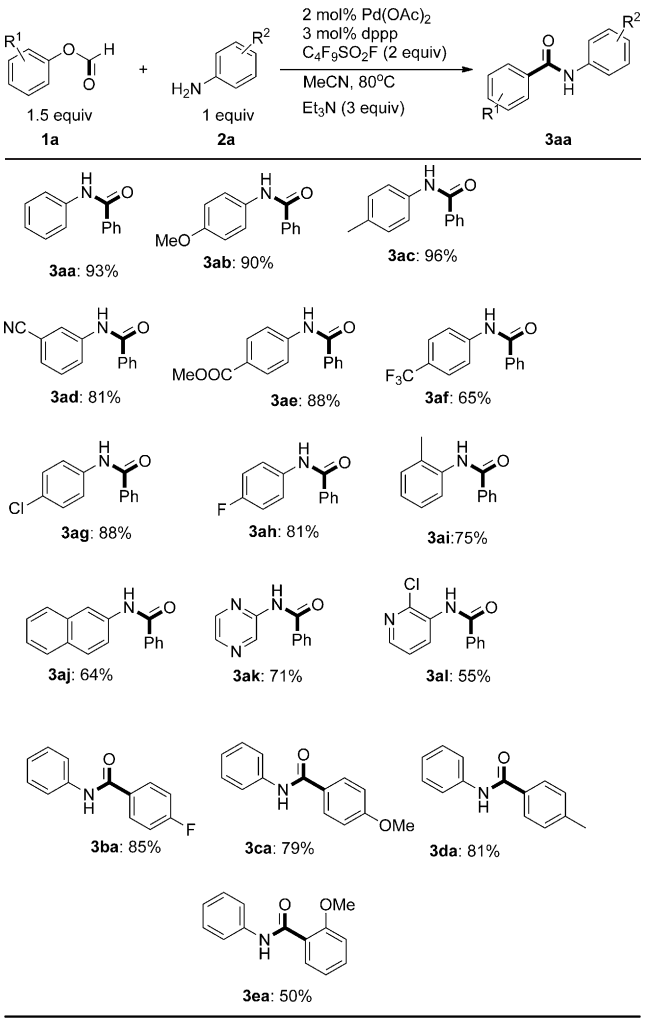
was to transform the in situ generated phenol into the aryl nonaflate, which could further act as a pseudohalide. The in situ generated CO accompanied by a nucleophile, thus furnishes carbonylation reactions without the need for external CO (Scheme 1).

We started our investigations using the following reaction conditions: aniline (0.5 mmol, 1 equiv), phenyl formate (0.5 mmol, 1 equiv), FNf (0.5 mmol, 1 equiv), with 2 mol% of $Pd(OAc)_2$, 6 mol% of $BuPAd_2$, and with 3 equivalents of Et_3N as a base in MeCN at 80°C for 24 hours. Surprisingly, 22% of benzanilide was observed and phenyl benzoate and phenylnonaflate were observed as by products. Subsequently, we tested various ligands (dppe, dppp, dppb, PPh_3, etc.) and bases, and also varied the amounts of phenyl formate and nonafluorosulfonyl fluoride used (see the Supporting Information). We identified the optimized reaction conditions to be include dppp (3 mol%) as the ligand, $Pd(OAc)_2$ (2 mol%) as the catalyst, with 1.5 equivalents of phenyl formate and 2 equivalents of FNf, which acts as the pseudohalide and as well as the CO source, and the desired benzanilide was formed in 93% yield in the presence of 1 equivalent of aniline.

With the best reaction conditions, different anilines were subjected to the reaction (Table 1). Anilines bearing electron-donating groups, such as anisidine and toluidine, resulted in excellent yields (90% and 96%, respectively). Also, many anilines bearing electron-withdrawing groups, such as the cyano, carboxylate group, chloro, and fluoro group, gave good yields of the corresponding amides (81–88%). Even the trifluoromethyl group, which is a strong electron-withdrawing group, led to moderate yield of the desired amide upon isolation (65%). Additionally, to learn about the steric effect of aniline derivatives, *ortho*-toluidine was tested, and although the conversion was lower, 75% of the product was obtained upon isolation. Naphthyl amine was then tested and moderate yield was obtained (64%). More interestingly, the reaction works well with a heteroaromatic amine such as 2-aminopyrazine, and good yield was obtained (71%). Notably, in the case of 3-amino-2-chloropyridine, the corresponding amide was isolated in 55% yield and the chloro substituent on the pyridine ring remained intact, even though it is considered to be highly reactive under palladium catalysis. However, the use of aliphatic amines such as morpholine and octylamine was not successful and afforded only the formylation product of the corresponding amines. Moreover, to learn about the electronic effects as well as the steric effect of the phenyl formate on this reaction, different formates were tested in addition. Although *ortho*-methoxy-substituted phenyl formate gave lower yield (50%), the other aryl formates showed good reactivity towards the corresponding benzanilides.

1,3-Ynones moieties are known as versatile substrates for natural product synthesis.[13] With this in mind, it would be interesting to synthesize these molecules under CO-free conditions. During the course of our reaction optimization (see Table S2 in the Supporting Information), we found that when the scale of the reaction was increased to 1 mmol, a higher pressure of generated CO was necessary to facilitate the reaction. After optimization [$Pd(OAc)_2$ (5 mol%), dppf (7.5 mol%), Et_3N (5 equiv), phenyl formate (2 equiv), NfF

Table 1: Carbonylative synthesis of amides.[a,b]

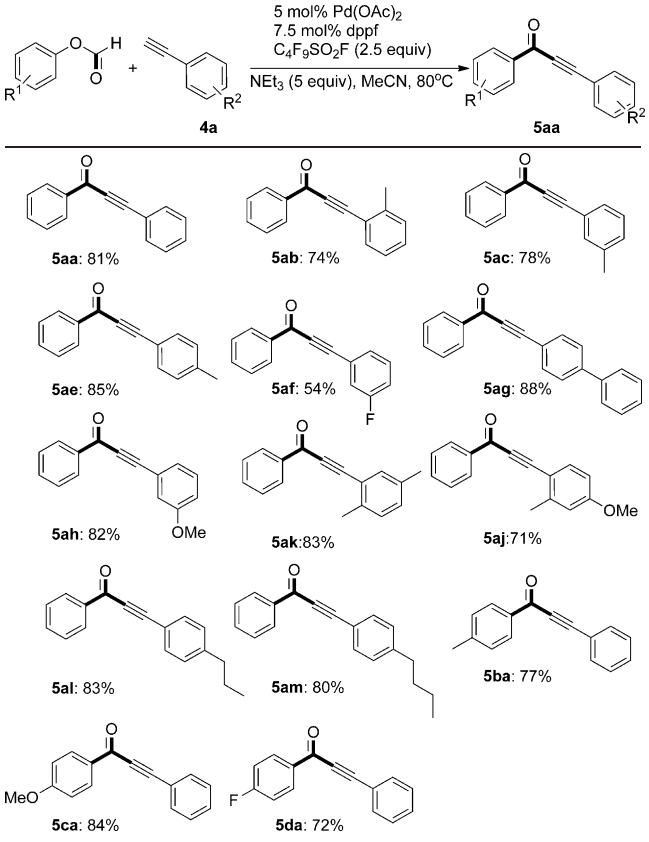


[a] Reaction conditions: Aniline (0.5 mmol), phenyl formate (0.75 mmol), $C_4F_9SO_2F$ (2 equiv), $Pd(OAc)_2$ (2 mol%), dppp (3 mol%), Et_3N (3 equiv), CH_3CN (2 mL) in a 12 mL sealed vial, 80°C, 16 h. [b] Yields of isolated products. dppp = 1,3-bis(diphenylphosphanyl)propane.

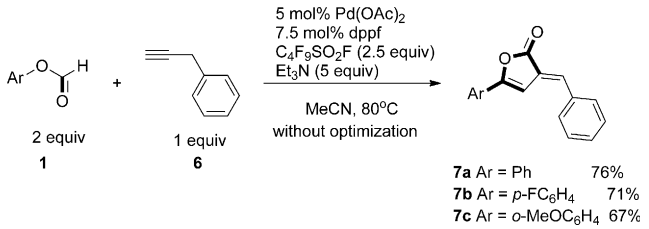
(2.5 equiv), phenylacetylene (1 equiv, 1 mmol) at 80°C for 16 h] good yield of the desired alkynone was obtained (81%; Table 2). The the scope of this transformation was then investigated, and moderate to good yields were obtained with different substituted phenylacetylenes and aryl formats under identical reaction conditions (54–88%).

Furanones represent an important family of organic compounds in natural products and bioactive derivatives. Our previous work has shown that by using a carbonylative reaction, furanones can be synthesized under palladium-catalyzed coupling reactions.[14] Surprisingly, when prop-2-yn-1-ylbenzene (**6**) was subjected to the reaction conditions, the furanone **7a** was obtained selectively with a moderate yield (76%; Scheme 2). Other phenyl formates, such as *para*-fluorophenyl formate and even the sterically hindered *ortho*-methoxy phenyl formate, were tested without further optimization and gave the desired furanones in 67–71% yields upon isolation. This reaction represents the first carbonylative synthesis of furanones in a CO-free manner.

Table 2: Carbonylative synthesis of alkynone without external CO.[a,b]



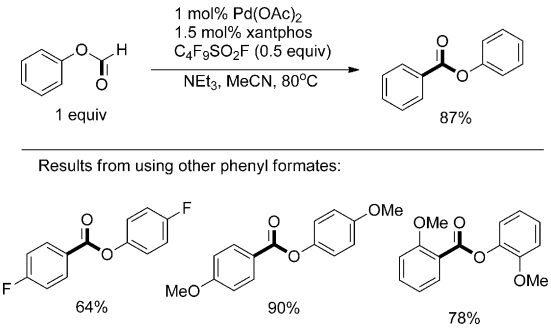
[a] Reaction conditions: Phenylacetylene (1 mmol), phenyl formate (2 mmol), $C_4F_9SO_2F$ (2.5 equiv), $Pd(OAc)_2$ (5 mol%), dppf (7.5 mol%), Et_3N (5 equiv), CH_3CN (5 mL) in a 12 mL sealed vial, 80°C, 16 h. [b] Yields of isolated products. dppf = 1,1′-bis(diphenylphosphino)ferrocene.



Scheme 2. Palladium-catalyzed carbonylative synthesis of furanone without external CO.

Based on our previous experience with the alkoxycarbonylation of phenols to give esters using in situ formed aryl nonaflates with 1 bar of external CO gas, we further extended our methodology to ester synthesis in the absence of external CO gas and using phenyl formate as the only substrate (Scheme 3). By using $Pd(OAc)_2$ (1 mol%), Xantphos (1.5 mol%), NfF (0.5 equiv), and phenyl formate (1 equiv) in acetonitrile at 80°C, phenyl benzoate was produced in 87% yield. With other phenyl formates (*p*-F, *p*-OMe, and *o*-OMe), yields from 64 to 90% were obtained.

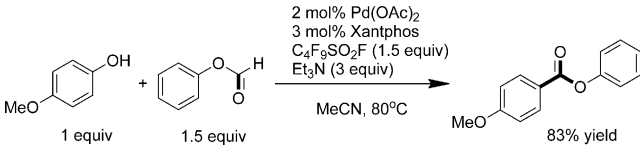
Notably, in addition to the above-mentioned symmetrical aryl benzoates, unsymmetrical phenyl benzoates can be



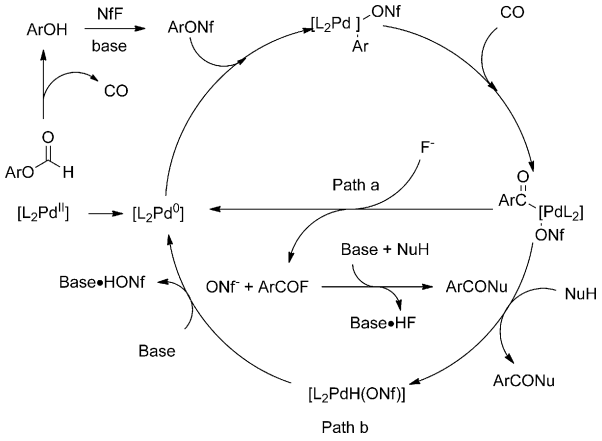
Scheme 3. Palladium-catalyzed synthesis of symmetrical phenyl benzoate derivatives without external CO. Reaction conditions: Phenyl formate (1 mmol), $C_4F_9SO_2F$ (0.5 equiv), $Pd(OAc)_2$ (1 mol%), Xantphos (1.5 mol%), Et_3N (1.5 equiv), CH_3CN (2 mL) in a 12 mL sealed vial, 80°C, 16 h. Yields are those of the isolated products. Xantphos = 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene.

produced by our procedure as well. Phenyl 4-methoxybenzoate was isolated in 83% yield from phenyl formate and *p*-methoxyphenol in a one-pot manner without further optimization (Scheme 4).

With respect to the reaction mechanism, as shown in Scheme 5, the aryl formate decomposes to generate one molecule of CO and phenol which will further react with perfluorobutanesulfonyl fluoride to generate aryl nonaflate (ArONf). Palladium acetate is reduced to Pd^0 and starts the catalytic cycle.[15] Subsequently, nonaflate will act as a pseudohalide and undergo oxidative addition with Pd^0. After the



Scheme 4. Palladium-catalyzed synthesis of unsymmetrical phenyl benzoates without external CO. Reaction conditions: *p*-methoxyphenol (0.5 mmol, 1 equiv), phenylformate (0.75 mmol), $C_4F_9SO_2F$ (1.5 equiv), $Pd(OAc)_2$ (2 mol%), Xantphos (3 mol%), Et_3N (3 equiv), CH_3CN (2 mL) in a 12 mL sealed vial, 80°C, 16 h. Yields are those of isolated products.



Scheme 5. Proposed reaction mechanism.

coordination and insertion of the in situ generated CO, an acyl palladium complex is generated as the key intermediate. Subsequently, two possible pathways to generate the target molecule could be considered. According to our analysis of the final reaction mixture, benzoyl fluoride derivatives were observed by GC-MS. A significant amount of benzoyl fluoride was observed especially when the benzene ring was bearing donating substituents. The generation of benzoyl fluoride can be explained by the nucleophilic attack of the fluoride ion on the electron poor carbonyl on the acyl palladium intermediate.[16] In this case Pd^0 can be regenerated by the decoordination of nonaflate on the palladium center (Path a). The generated benzoyl fluoride can further react with nucleophiles and produce the final product with the help of a base.[7a] Another possible pathway is go through the traditional carbonylative coupling pathway which proceeds by the nucleophilic attack of the nucleophile onto the acyl palladium intermediate and regeneration of Pd^0 with a base (Path b).

In summary, carbonylative coupling reactions using aryl formates as the CO source and pseudohalide precursors have been developed. No external carbon monoxide gas was required. The corresponding amides, alkynones, furanones, and phenyl benzoates were synthesized in good yields upon reaction with amines, alkynes and phenols, respectively. The development of this protocol with other nucleophiles and detailed mechanistic studies are underway in our group.

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8.2 Palladium-Catalyzed Hydroamidocarbonylation of Olefins to Imides

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Angewandte Chemie International Edition, 2015, 10239-10243.

Contributions

In this paper, I discovered the reaction, planned and executed most of the optimization of the model system and also developed the substrate scope. Additionally, I wrote the major part of the corresponding manuscript, thus my overall contribution to this work approximately accounts for 70%.

Synthetic Methods

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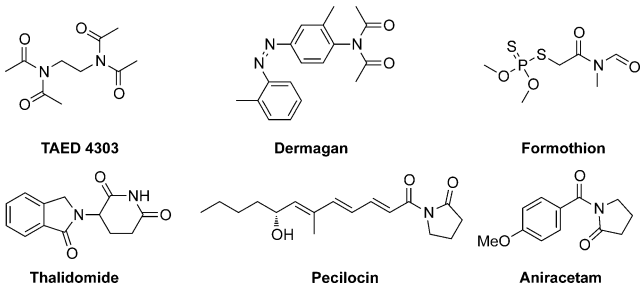
Palladium-Catalyzed Hydroamidocarbonylation of Olefins to Imides**

*Haoquan Li, Kaiwu Dong, Helfried Neumann, and Matthias Beller**

Abstract: *Carbonylation reactions allow the efficient synthesis of all kinds of carbonyl-containing compounds. Here, we report a straightforward synthesis of various imides from olefins and CO for the first time. The established hydroamidocarbonylation reaction affords imides in good yields (up to 90%) and with good regioselectivity (up to 99:1) when applying different alkenes and amides. The synthetic potential of the method is highlighted by the synthesis of Aniracetam by intramolecular hydroamidocarbonylation.*

Carbonylation reactions using carbon monoxide (CO) as one of the cheapest and most flexible C1 building blocks continues to attract significant interest in organic synthesis and from industrial chemists.[1] In terms of production scale, carbonylation reactions nowadays constitute the largest industrial applications in the area of homogeneous catalysis.[2] In addition to the well-known Monsanto[3] or Cativa process[4] which produce acetic acid by the carbonylation of methanol, carbonylative transformations of simple alkenes have been shown to be core processes in industry for the production of esters (alkoxycarbonylation)[5] and aldehydes (hydroformylation).[6] However, the related synthesis of more value added amides (aminocarbonylations) from simple alkene has been less explored.[7] In this respect, our research group recently reported a general aminocarbonylation of alkenes by using a palladium catalyst system.[7b] The aminocarbonylation of various conjugated dienes to synthesize the corresponding β,γ-unsaturated amide was also developed.[7d] Notably, all these reactions proceed with high atom economy.[8]

Apart from amides, imides also constitute an important organic moiety in fine chemicals. For example, tetraacetylethylenediamine (TAED) is used on multi-10000 ton scale as a peroxide bleach activator in detergents. Moreover, this functional group is used in the synthesis of pharmaceuticals as well as agrochemicals and various bioactive molecules. As shown in Scheme 1, selected examples include Diacetazotol (Dermagan), which stimulates wound epithelization, Formothion, a systemic and contact insecticide, Thalidomide, which shows antiangiogenic and antineoplastic properties, Pecilocin, with antifungal activity, and the anxiolytic drug Aniracetam (Ampamet).[9]



Scheme 1. Selected examples of imide-containing bioactive molecules.

Typical syntheses of imides proceed by the nucleophilic substitution of activated carboxylic acid derivatives, for example, acid chlorides or anhydrides, with amides in the presence of base under carefully controlled conditions.[10] The selective oxidation of amides to imides is also known in a few cases.[11]

Compared to the existing methods, the direct carbonylation of easily available olefins to imides would be advantageous with respect to waste formation and step economy (100% atom efficiency). Based on our continued interest and experience in carbonylation reactions, we envisioned and started to explore the synthesis of imides from alkenes and amides.[12] Herein, we report a novel palladium-catalyzed hydroamidocarbonylation of alkenes for the synthesis of various synthetically interesting imides.

At the beginning of our study, 1-octene and *N*-methylacetamide were chosen as model substrates. A variety of ligands were tested (in the case of monodentate ligands 4 mol%, in the case of bidentate ligands 2 mol%) in the presence of 1 mol% $PdCl_2$ in toluene at 105°C under a CO atmosphere (50 bar). With PPh_3 (**L1**) as ligand, a mixture of the desired linear product (*n*-) **3aa** (53%) and the corresponding branched product (iso-) **3aa′** (47%) was obtained in a yield of only a 26% (Scheme 2). No desired product was observed at all with tri(*o*-tolyl)phosphine (**L2**) and di(1-adamantyl)-*n*-butylphosphine (**L3**). However, to our delight, the use of bidentate ligands gave much better results. In fact, a 50% yield of the desired product with 73% selectivity was obtained when Xantphos **L4** was tested. Surprisingly, the use of sterically hindered *t*Bu analogues of Xantphos (**L5**) gave no desired product. A similar result was also observed with the DBFphos series (**L6** and **L7**). On the other hand, a 39% yield with 86% linear selectivity was obtained when dppf (1,1′-bis(diphenylphosphino)ferrocene) (**L8**) was used. Binap backbone bidentate ligands **L9** and **L10** were also active (34% yield, 69% selectivity and 40% yield, 87% selectivity,

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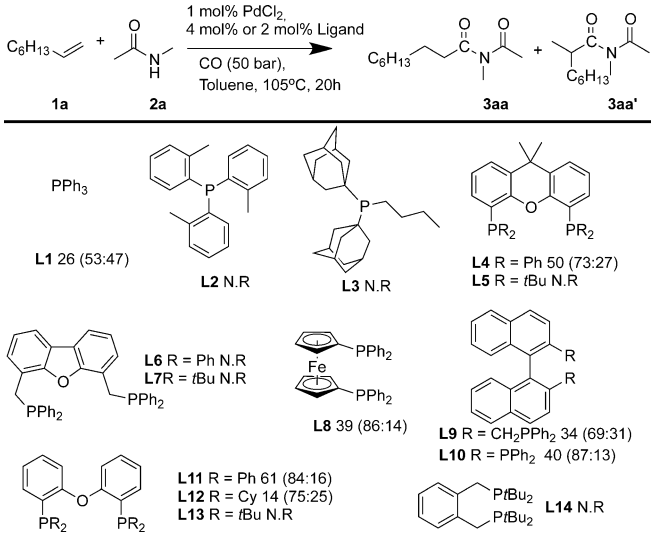


Scheme 2. Hydroamidocarbonylation of 1-octene. Reaction conditions: Ligand variation. **2a** (1.0 mmol), **1a** (1.0 mmol), $PdCl_2$ (1 mol%), monodentate ligand (4 mol%) or bidentate ligand (2 mol%), toluene (2 mL), CO (50 bar) heating at 105°C for 20 h. Yield (%) of the mixture of **3aa** and **3aa'** determined by GC using isooctane as an internal standard, the number in parenthesis indicates the **3/3'** selectivity determined by GC. N.R. indicates no observable product by GC.

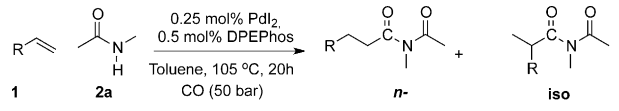
respectively). Notably, the best result (61% yield, 84% selectivity) was observed using DPEPhos [(oxydi-2,1-phenylene)bis(diphenylphosphine)] (**L11**). Thus, **L11** was chosen for further studies. Similar to the Xantphos ligand, the sterically hindered cyclohexyl and *tert*-butyl analogues of DPEPhos (**L12** and **L13**) were shown to be less reactive (14% yield, 75% selectivity and no conversion, respectively). Interestingly, the so-called d^tbpx ligand α,α′-bis(di-*tert*-butylphosphino)-o-xylene (**L14**) , which is known to be highly active for palladium-catalyzed carbonylation reactions of alkenes and for the aminocarbonylation of butadiene was shown to be completely inactive in this case.[13,7c]

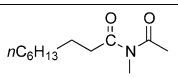
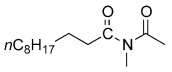
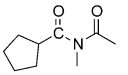
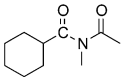
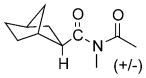
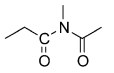
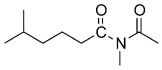
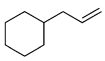
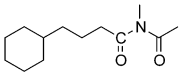
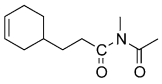
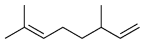
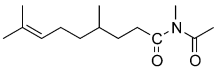
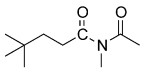
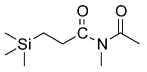
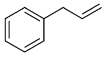
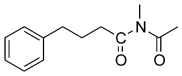
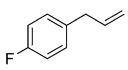
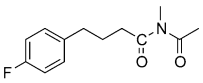
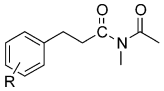
In contrast to most of the recently developed palladium-catalyzed carbonylation reactions of olefins, the presented imide formation takes place under "acid-free" conditions. Under such conditions, slow isomerization of 1-octene leads to an accumulation of internal octenes, which are not in fast equilibrium with the terminal olefin. Hence, the use of an increased amount of olefin (2 equiv) resulted in the yield of the desired terminal imide increasing to 85% with similar *n*-/iso selectivity (84%). It is noteworthy that carbonylation products derived from internal olefins are not observed under the "acid-free" conditions, which shows that the reaction rates of the terminal alkenes are much faster than the internal ones.

Next, the effect of the counterion was investigated by testing different palladium sources (see Table S1 in the Supporting Information). $[Pd(cod)Cl_2]$ and $[Pd(CH_3CN)_2Cl_2]$ resulted in similar linear selectivity, however with slightly decreased yields (Table S1, entries 3 and 4). Surprisingly, almost quantitative yields and an increased linear selectivity of the reactions were observed with both $PdBr_2$ and PdI_2 as the palladium source (85% and 88%, respectively; Table S1, entries 5 and 6). However, with $Pd(OAc)_2$ and $[Pd(acac)_2]$, only traces of product could be observed, with low conversion of **1a** (Table S1, entries 7 and 8). By using PdI_2 as the palladium source, the reaction even proceeded at 80°C, although giving a lower yield (Table S1, entry 9). In general, the catalyst system was shown to be robust and almost the same yield and selectivity (92%, 89%; Table S1, entry 11) was achieved at a lower catalyst loading (0.25 mol%). To our surprise, the addition of 0.75 mol% *p*-toluenesulfonic acid led to a significant decrease in the yield of the product (64% yield; Table S1, entry 13). Monitoring the gas consumption showed that the reaction reached over 90% conversion after 10 h (see the Supporting Information for details).

With the optimized conditions in hand, a range of easily available and structurally diverse olefins were tested (Table 1). Primarily, 1-decene (**1b**) gave a very similar result to 1-octene (**1a**, Table 1, entries 1 and 2; 87% and 88% yield of isolated **3**, 89% *n*-selectivity). To our delight, different cyclic olefins (1 equiv) also reacted smoothly. For example, the reactions with cyclopentene (**1c**) and cyclohexene (**1d**) resulted in complete conversion and good yields of the isolated products (Table 1, entries 3 and 4; 83% and 90% yield, respectively). With norbonene (**1e**) as substrate, the reaction was shown to be completely *exo*-selective, with the imide moiety in the equatorial position (58% yield; Table 1, entry 5). Interestingly, the basic industrial feedstock ethylene (**1f**) gave **3fa** in 91% yield (Table 1, entry 6). Excellent linear selectivities were observed in the case of sterically hindered 1-alkenes. For example, 4-methyl-1-pentene (**1g**) and allylcyclohexane (**1h**) led to yields of 85% and 86% of isolated product with an *n*-selectivity of 89% for **3ga** and **3ha** (Table 1, entries 7 and 8). With 4-vinylcyclohexene (**1i**) as substrate, 97% linear selectivity was obtained with a 90% yield of the isolated product (Table 1, entry 9). It is noteworthy that in this case the internal C=C bond remained intact after reaction, thus showing that the terminal alkene is much more reactive in this reaction than the cyclic internal alkene. Natural oil derived substrate citronellene (**1j**) gave a 76% yield of **3ja** with an *n*-selectivity of more than 99%. The trisubstituted internal double bond also stayed intact in this case (Table 1, entry 10). To our delight, the optimized conditions are also compatible with more bulky substrates, such as **1k** and **1l**, which resulted in 55% and 60% yields, respectively, with complete linear selectivity (Table 1, entries 11 and 12). The electronic effect of substituted allylbenzenes was also studied. The reaction between allylbenzene and *N*-methylacetamide went to complete conversion at a slightly elevated temperature (120°C), and the corresponding linear imide **3ma** was isolated in 88% yield with an *n*-selectivity of 90% (Table 1, entry 13). With 1-allyl-4-fluorobenzene (**1n**) as the substrate, the reaction was complete at 105°C and afforded **3na** in 85% yield and 88% selectivity (Table 1, entry 14). Finally, styrene was successfully employed as an example of an aromatic olefin (Table 1, entry 15; 63% yield and 70% *n*-selectivity). This system was further demonstrated to tolerate Br and Cl substituents on styrene derivatives. Under the optimized reaction conditions, low conversions were observed (28% and 31% yield of isolated product for **3pa** and **3qa**, respectively). By increasing

Table 1: Palladium-catalyzed hydroamidocarbonylation of different alkenes.

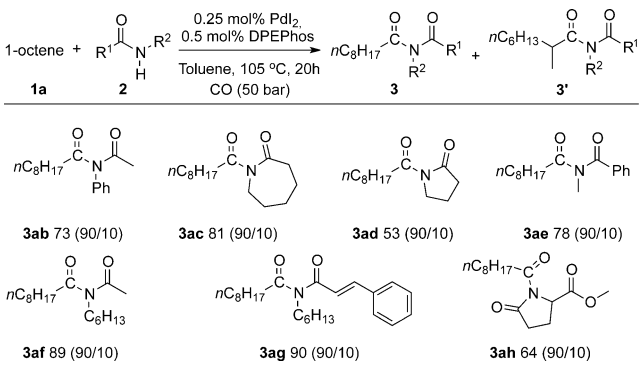


Entry[a]	1		3		Yield [%] (*n*/iso[b])
1		**1a**		**3aa**	87 (89/11) 88 (89/11)[f]
2		**1b**		**3ba**	88 (89/11)
3[c]		**1c**		**3ca**	83
4[c]		**1d**		**3da**	90
5[c]		**1e**		**3ea**	58
6[d]		**1f**		**3fa**	91
7		**1g**		**3ga**	85 (89/11)
8		**1h**		**3ha**	86 (89/11)
9		**1i**		**3ia**	90 (97/3)
10		**1j**		**3ja**	76 (>99/1)
11		**1k**		**3ka**	55 (>99/1)
12		**1l**		**3la**	60 (>99/1)
13[e]		**1m**		**3ma**	88 (90/10)
14		**1n**		**3na**	85 (88/12)
15 16[g] 17[g]		**1o** R = H **1p** R = 4-Br **1q** R = 4-Cl		**3oa** **3pa** **3qa**	63 (70/30) 60 (75/25) 67 (75/25)

[a] **1** (1.5 mmol), **2** (1 mmol), PdI_2 (0.0025 mmol, 0.25 mol%), DPEPhos (0.005 mmol, 0.5 mol%), CO (50 bar), toluene, 105 °C, 20 h. [b] Yield of isolated **3**, the number in parenthesis indicates *n*-/iso selectivity determined by gas chromatography. [c] **1** (1 mmol). [d] Reaction carried out on a 4 mmol scale with 0.5 g ethylene (ca. 4.5 equiv) in a 25 mL autoclave. [e] 120 °C. [f] Reaction carried out on a 10 mmol scale. [g] PdI_2 (0.01 mmol, 1 mol%), DPEPhos (0.02 mmol, 2 mol%).

the catalyst loading (1 mol% PdI_2, 2 mol% DPEPhos), the corresponding products **3pa** and **3qa** were isolated in 60% and 67% yield, respectively, with 75% *n*-selectivity (Table 1, entries 16 and 17).

To reveal the generality of this method, different amides were tested (Scheme 3). By using acetanilide (**2b**) under the standard conditions, **3ab** was obtained in 73% yield with 90% *n*-selectivity. Industrially important aliphatic lactams, which

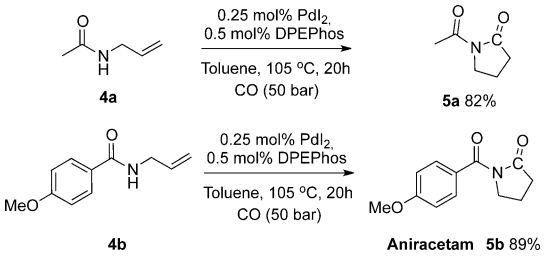


Scheme 3. Hydroamidocarbonylation with different amides as nucleophile. Reaction conditions: **1** (1.5 mmol), **2** (1 mmol), PdI_2 (0.0025 mmol), DPEPhos (0.005 mmol), CO (50 bar), toluene, 105 °C, 20 h. In each case, the yield (%) of isolated compound **3** is given, and the number in the parenthesis indicates the **3/3′** ratio.

are produced as bulk chemicals, were also tested: the use of ξ-caprolactam (**2c**) and 2-pyrolidinone (**2d**) as nucleophiles led to the corresponding imides **3ac** and **3ad** in 81% and 53% yield, respectively, with 90% *n*-selectivity. *N*-Methylbenzamide (**2e**) was also shown to be compatible, and afforded **3ae** in 78% yield and 90% *n*-selectivity. Moreover, longer aliphatic chain amides also reacted smoothly. When *N*-hexylacetamide (**2f**) was subjected to the optimized conditions, an excellent yield of **3af** was obtained. With *N*-hexylcinnamide (**2g**) as the substrate, **3ag** was obtained in an excellent yield (90% yield, 90% *n*-selectivity). More strikingly, amino acid derived methyl pyroglutamate (**2h**) also proved to be a suitable substrate and afforded **3ah** in 64% yield and 90% selectivity.

To further demonstrate the applicability of this novel method, an example of an intramolecular hydroamidocarbonylation was also investigated. Gratifyingly, carbonylation of the allylic amide **4a** occurred in a straightforward manner and afforded the expected product in 82% yield (Scheme 4). This result inspired us to synthesize Aniracetam, which is sold in Europe as a prescription drug and is considered to be more potent than the well-known Piracetam. Simply starting from *N*-allyl-4-methoxybenzamide, carbonylation proceeded at 105 °C and 50 bar of CO to give Aniracetam in 89% yield of the isolated product.[14]

Although the detailed mechanism of this reaction remains to be further elucidated, we suggest that the reaction goes through a similar reaction pathway as the well-known alkoxycarbonylation reaction mechanism, with Pd-H as the key intermediate.[15] Initially, the active Pd-H catalyst is generated from the respective Pd^{II} precursor.[16] This assumption is also supported by the alkene isomerization observed



Scheme 4. Intramolecular hydroamidocarbonylation. Reaction conditions: **4** (1 mmol), PdI_2 (0.0025 mmol), DPEPhos (**L12**, 0.005 mmol), CO (50 bar), toluene (2 mL), 105 °C, 20 h. The yield of isolated product is given.

after reaction being promoted by the Pd-H species. Notably, the role of the counterion could possibly be rationalized by the Pd-H species being generated more easily with a palladium precursor with a conjugate anion from a strong acid (eg. Cl^-, Br^-, I^-). Insertion of the alkene, followed by reaction with CO leads to the corresponding acylpalladium intermediate. Finally, nucleophilic attack of the amide affords the imide as the final product and regenerates the active species Pd-H.[7d,i] However, we are not able to exclude other mechanistic pathways.

In summary, a novel palladium-catalyzed hydroamidocarbonylation reaction of aliphatic and aromatic alkenes using amides as nucleophile was successfully developed. This method provides an economical and sustainable synthesis of versatile imides. The optimal catalyst system (PdI_2/DPEPhos) is commercially available and is shown to be efficient and robust at relatively low catalyst loading. With respect to applications, it is noteworthy that alkenes with different structural characteristics are tolerated and the corresponding imides are produced highly selectively (89–99 % *n*-selectivity). Moreover, various amides were tested and transformed to the corresponding imides in moderate to excellent yields (64–90 %). The synthetic utility of the method is showcased by the synthesis of the anxiolytic drug Aniracetam in an atom-economic manner.

Keywords: alkenes · amides · carbonylation · homogeneous catalysis · imides

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Angew. Chem. **2015**, *127*, 10377–10381

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[16] The initial reduction of Pd^{II} to Pd^{0} to form the active palladium hydride species is possible through interaction with the substrate, phosphorus ligand, or carbon monoxide in the presence of traces of H_2O. The effect of the water content was also studied. Similar results were obtained on addition of a small amount of water (2.5 $\mu L\,mL^{-1}$). However, decreased product yields were observed on increasing the water content. This can be explained by decomposition of the catalyst and/or the product in the presence of a higher concentration of water (See Figure S1 in Supporting Information for details).

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8.3 Palladium-catalysed Markovnikov Alkoxycarbonylation of Alkenes: Reaction Discovery, Scope and Mechanism

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Submitted,

Contributions

In this publication, I discovered the distinct reactivity, performed most of the experiments and participated in the mechanistic discussions. I wrote the introduction part and experimental part of the manuscript. My overall contribution to this work approximately accounts for 60%.

Palladium-catalysed Markovnikov Alkoxycarbonylation of Alkenes: Reaction Discovery, Scope and Mechanism

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Hydroesterification reactions represent a fundamental type of carbonylation reactions and constitute one of the most important industrial applications of homogeneous catalysis. Over the past 70 years, numerous catalyst systems have been developed, which allow for highly linear selective (anti-Markovnikov) reactions and are used in industry to produce linear carboxylates starting from olefins. In contrast, a general catalyst system for Markovnikov-selective alkoxycarbonylation of aliphatic olefins remains to be unknown. In this report, we show for the first time that a specific palladium catalyst system consisting of PdX_2/*N*-phenylpyrrole (X = halide) catalyse the alkoxycarbonylation of various alkenes to give the branched esters in high selectivity (*b*/*l* up to 91/9). The observed but unexpected selectivity has been rationalized by density functional theory computation including dispersion correction for van der Waals interaction.

KEYWORDS: catalysis, carbonylation, palladium, alkene functionalization, Markovnikov selectivity

Introduction

Due to the perfect atom economy, the addition of HNu (Nu = halogen, CHR_3, CN, OH, NR_2 etc.) to carbon-carbon multiple bonds is one of the most desired transformations in organic synthesis.[1] Using abundant and inexpensive starting materials a number of industrial processes are taking advantage of these methods. Well recognized examples include hydroamination, hydration, etc. In

general, most of the electrophilic addition reactions of alkenes follow the so-called Markovnikov rule (Figure 1). In the polar addition reaction of Nu-E to alkenes, the superior stability of the resulting secondary carbocation $RCHE^{+}CH_3$ compared to the primary carbocation $RCEHCH_2^{+}$ controls the regioselectivity of the process and generates the corresponding branched "Markovnikov product" after nucleophilic attack of the nucleophile.[2] Interestingly, transition metal catalysed reactions of alkenes, such as hydrocyanation and hydrosilylation, etc.[3-6] As well as carbonylation reactions (hydroformylation, alkoxycarbonylation, aminocarbonylation) offer the possibility to generate the corresponding linear products. Notably, in these latter reactions the selective formation of Markovnikov products is difficult.[7] In fact, regioselective alkene functionalization continues to be an exceedingly challenging goal for (homogeneous) catalysis.[8]

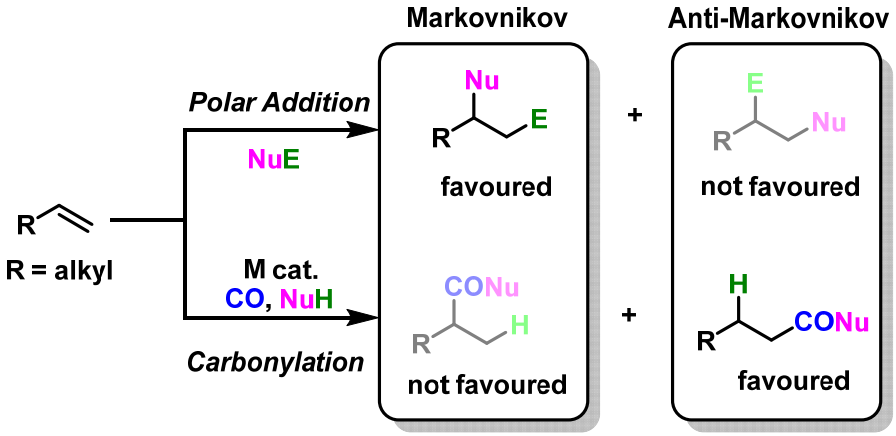
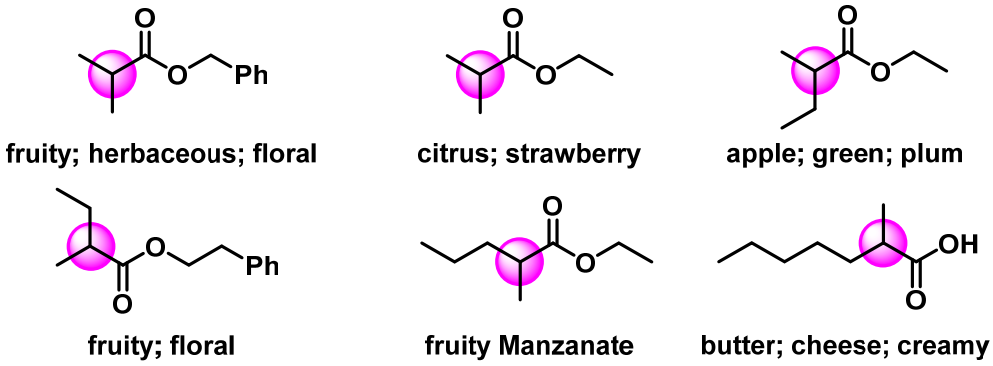


Figure 1: Comparison of general product distribution for polar addition and carbonylation reactions of alkenes

In general, carbonylation reactions constitute one of the most important alkene transformation reactions with regard to the production scale.[9-12] In this context, the direct carbonylation of abundantly available alkenes to aldehydes and carboxylic esters, so-called hydroformylation (~10 million ton/year)[13] and alkoxycarbonylation (multi-million ton/year), are two key transformations for the chemical industry.[14,15] As pointed out above, the linear product (anti-Markovnikov product) is usually favoured for alkene carbonylations developed thus far. In fact, continuing activities over the past four decades, mainly based on the (r)evolution of phosphorus ligands, established efficient and highly linear selective catalytic systems for hydroformylations and alkoxycarbonylations of aliphatic alkenes, which are applied in industry, too.[16-18]

The formation of the branched product for both hydroformylation and alkoxycarbonylation reactions is more challenging due to the increase in steric congestion for secondary carbon-metal intermediates.[19-22] Only in case of special substrates, such as allenes, vinylarenes, vinylacetate,

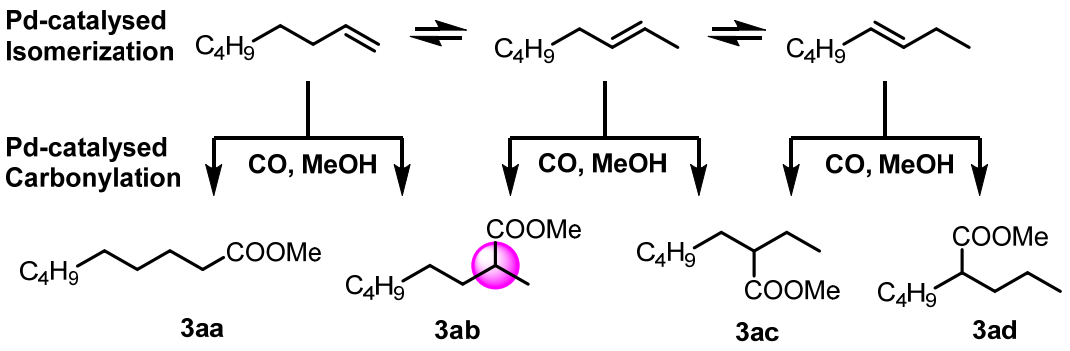
branched-selective alkoxycarbonylations can be predominant.[23-30] Hence, a convenient protocol for the Markovnikov carbonylation of alkenes is still an unsolved problem and Markovinkov-selective alkoxycarbonylation of easily available bulk olefins such as butenes, hexenes, octenes, etc. are basically unknown, despite the potential products arising from such reactions, have broad utility in the fragrance and flavor industry[31,32,33] as well as the life science industries. Moreover, branched aliphatic esters are used as important intermediates in organic synthesis.[34-37] In view of a more sustainable production for such compounds, the development of selective catalytic methodologies is highly desired.



Scheme 1 Selected examples of 2-methylcarboxylates and their organoleptic properties

Based on our long-standing interest in carbonylation reactions, we report herein our recent investigations on a general and universal method for the Markovnikov alkoxycarbonylation of aliphatic 1-alkenes.

One of the prerequisites for Markovnikov selective carbonylation of alkenes (≥ C5), is to control the isomerization reaction of the alkene (Scheme 2).[38-41] One obvious reason is the variety of esters arising from carbonylation of different internal alkenes. For example, simple 1-octene might form already 4 different regioisomeric C9-esters (**3aa** - **3ad**). In case of di-and multi-substituted olefins even more esters are formed. In order to avoid formation of such mixtures, we anticipated an “acid-free” catalyst system could prevent olefin isomerization reactions and keep the terminal alkene as a major component in the reaction media.

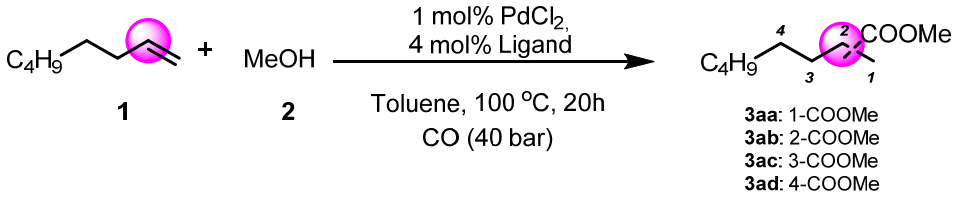


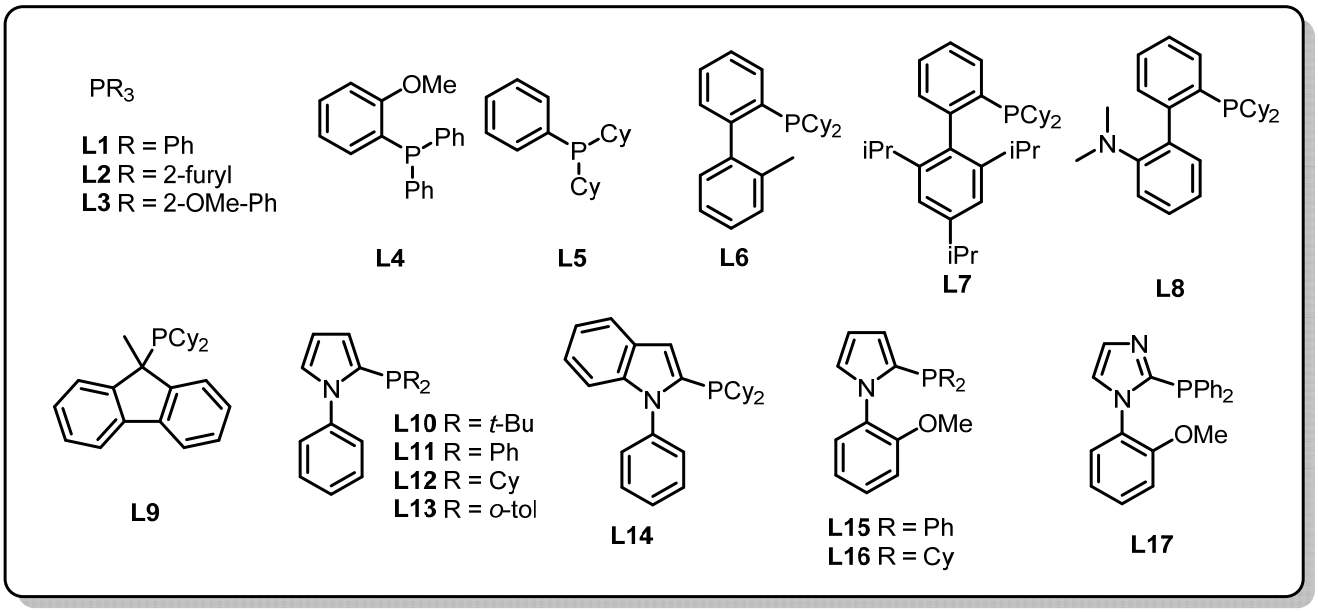
Scheme 2 Possible products from palladium-catalysed methoxycarbonylation of 1-octene

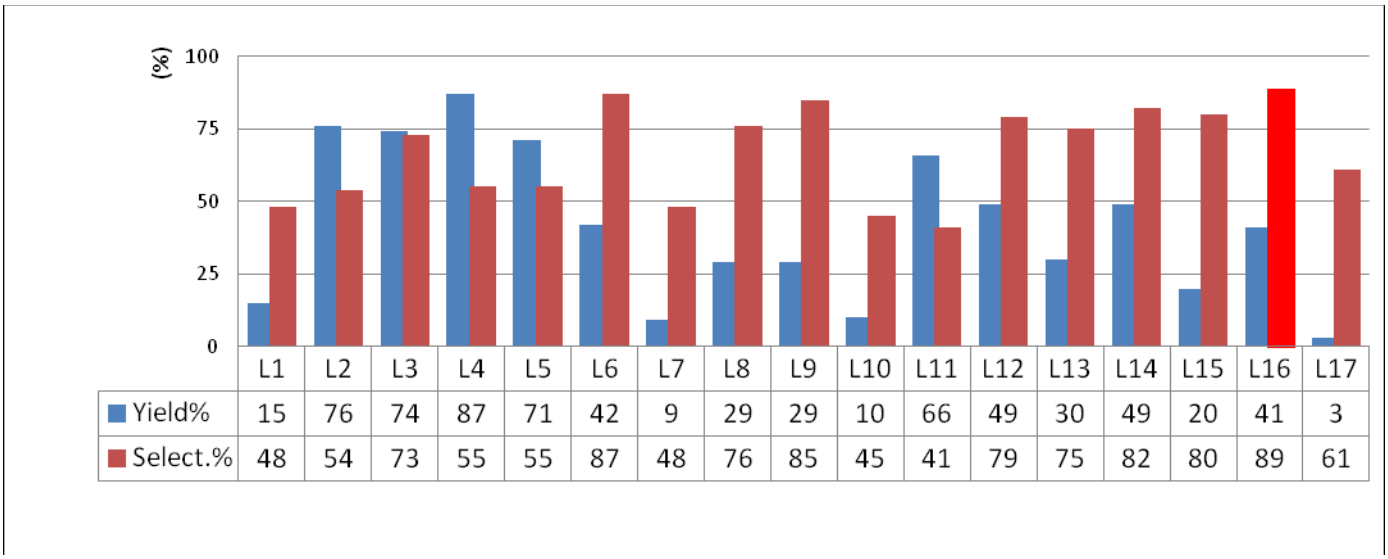
Results and discussion

Catalytic experiments: At the beginning of our study, 1-octene (1 mmol) and methanol (1 mmol) were chosen as the benchmark substrates. In order to control the regioselectivity of this transformation, carbonylation experiments in the presence of $PdCl_2$ (1 mol%) and various standard and specifically made phosphine ligands were performed. It is well known that bidentate phosphine ligands preferentially form linear esters from both internal and terminal olefins.[16,42,43] Hence, initially different monodentate phosphine ligands were tested with our model substrates (Scheme 3). Applying triarylphosphine ligands **L1**, **L2**, **L4**, almost equal amounts of branched and linear products were obtained. To our surprise, in the presence of **L3** (tris-2-methoxyphenyl)phosphine) 74% yield of C9-esters with 73% selectivity for the desired branched product was obtained. Apparently, the increased steric hindrance of the ligand due to *ortho*-substitution prefers the formation of the desired branched product. Consequently, more sterically hindered ligands such as biaryl ligands **L6**-**L17** were tested. Indeed, with the commercial available biaryl ligands which were reported to be excellent ligands for several coupling reactions, modest to good branched selectivity were observed.[44] For example, Mephos **L6** and Davephos **L8** gave 42% and 29% yield and 87% and 76% selectivity, respectively. For comparison, only 55% branched-selectivity was observed with **L5** PCy_2Ph, which clearly shows that the biaryl-function is important to obtain the desired branched-selectivity. Subsequently, different commercially available cataCXium® series ligands were tested.[45] To our delight, in the presence of the methyl-fluorenylphosphine ligand **L9**, 85% selectivity was observed. Among all the *N*-phenyl-pyrrole-based ligands tested (**L10** - **L13**), the cyclohexyl-substituted derivative **L12** gave best branched-selectivity (79%). Applying the related ligand **L14** with *N*-phenylindole backbone, a similar result was observed (49% yield and 82% branched-selectivity). Gratifyingly, with *N*-(*o*-MeO-phenyl)-pyrrole as the ligand backbone **L15**, and the commercially available ligand **L16** (cataCXium® POMeCy), high regioselectivity was observed (respectively, 20%

and 41% yield, 80% and 89% branched-selectivity). Unfortunately the analogue *N*-phenyl-imidazole ligand **L17** gave only low yield (3%).







	L1	L2	L3	L4	L5	L6	L7	L8	L9	L10	L11	L12	L13	L14	L15	L16	L17
Yield%	15	76	74	87	71	42	9	29	29	10	66	49	30	49	20	41	3
Select.%	48	54	73	55	55	87	48	76	85	45	41	79	75	82	80	89	61

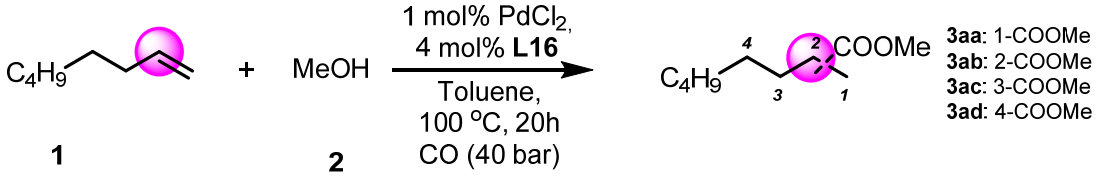
[a]Reaction conditions: **1** (1.0 mmol), **2** (1.0 mmol), $PdCl_2$ (1 mol%), Ligand (4 mol%), CO (40 bar), toluene (2 mL), 100 °C, 20 h. Yield of mixture all the C9 esters, which is determined by GC analysis using isooctane as the internal standard. Select.% = (***3ab***/(***3aa***+***3ab***)). The ratios of isomers were determined by GC analysis. In all cases, insignificant amount of **3ac** and **3ad** could be observed.

Scheme 3 Markovnikov alkoxycarbonylation of 1-octene: Variation of selected ligands

With **L16** as the ligand of choice, we tried to further improve the reactivity (Table 1, entry 2). By adding 10 μL H_2O which probably facilitates the formation of the active palladium hydride, the yield was improved to 63% with slightly decreased *iso*-selectivity (84%) and 92% of ***3ab***/*iso*- ratio.

Comparably, in the case of addition of 5 mol% of PTSA (*p*-toluenesulfonic acid monohydrate), the activity was promoted but larger amount of internal carbonylated products **3ac** and **3ad** was obtained (Table 1, entry 3). Finally, by increasing the amount of olefin to 2 equiv. an excellent yield with 83% *iso*-selectivity and 96% **3ab**/*iso*- selectivity was observed (Table 1, entries 4 and 5).

Table 1 Markovnikov alkoxycarbonylation of 1-octene: Influence of water and acid



1 **2**

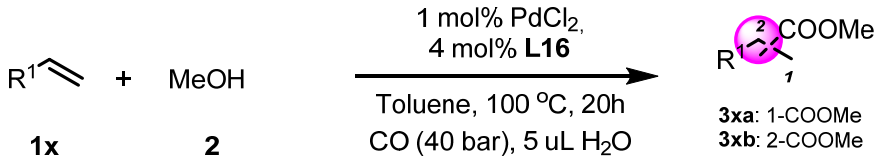
Entry[a]	**1**:**2**	Additive	Yield(%)[b]	*iso*-(%)	***3ab***/*iso*-(%)
1	1:1	/	41	89	98
2	1:1	10 µL H_2O	63	84	92
3	1:1	5 mol% PTSA	88	86	88
4	1.5:1	10 µL H_2O	86	84	94
5[d]	2:1	10 µL H_2O	>99	83	96
6	2:1	5 µL H_2O	>99	84	96
7[c]	2:1	5 µL H_2O	61	82	99
8[d]	2:1	5 µL H_2O	67	86	92
9[e]	2:1	2.5 µL H_2O	45	85	99

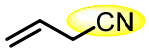
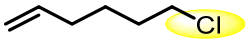
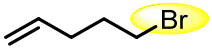
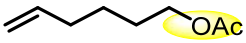
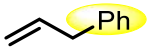
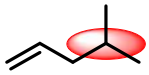
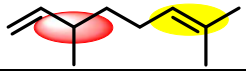
[a] General Reaction condition: **2** (1 mmol), 1-octene, $PdCl_2$ (1 mol%), cataCXium® POMecy **L16** (4 mol%), toluene (2 ml), additive, heated at 100°C under CO (40 bar) for 20 hours [b] Yield of mixture of C9 esters determined by GC with internal standard, *n*- = **3aa**, *iso*- = **3ab**+**3ac**+**3ad**, *iso*-% = *iso*-/(*iso*- + *n*-) . [c] Reaction conducted at 80°C; [d] 30 bar of CO; [e] $PdCl_2$ (0.5 mol%), cataCXium® POMecy **L16** (4 mol%).

Based on these preliminary studies, the following conditions were set up for further investigations: 1 mol% $PdCl_2$, 4 mol% **L16**, 5 µL H_2O in 2 mL toluene, CO (40 bar), 100°C for 20 h. Then, different alkenes were tested (Table 2). Simple short and longer chain aliphatic olefins, *e.g.* 1-pentene or 1-decene gave good yield and good selectivity (81% and 88% yield, with 81% and 83% selectivity, respectively; Table 2, entries 3 and 4). Notably, with 2-octene as the starting substrate, 97% branched-selectivity was obtained. Among the branched products, 76.2% **3ab**, 23.0% **3ac** and 0.8% **3ad** were observed by GC analysis (Table 2, entry 2). To the best of our knowledge this constitutes the highest branched-regioselectivity reported for any non-functionalized aliphatic olefin. Furthermore, excellent functional group tolerance was observed. Alkenes bearing –CN, -Cl, -Br, -OAc, and -COOMe were shown to be compatible, and gave the corresponding ester in 71-97% yield with 83 – 87% branched-selectivity (Table 2, entries 5 - 10). Excellent branched-selectivity (>99%) was observed for styrene and the corresponding *iso*-product was isolated with 82% yield (Table 2, entry 11). Due to steric reasons, the introduction of substituents into the 3- or 4- position of a terminal olefin will increase the energy barrier for branched-selective carbonylation and thus decrease the selectivity. For example, with 4-methyl-pentene as the substrate, the branched-selectivity slightly drops to 78% (isolated yield 78%; Table 2, entry 12). Using 3-methyl-pentene the steric hindrance greatly

increased; nevertheless, 49% branched-selectivity could be observed (dr = 1:1) (Table 2, entry 13). This was also verified by using β-Citronellene as the substrate, in which a mixture of branch and linear product (52:48) was isolated with 88% yield (Table 2, entry 14). To note, the tri-substituted C=C moiety of β-Citronellene is unreactive under our reaction conditions.

Table 2 Markovnikov alkoxycarbonylation of alkenes: Substrate scope



Entry[a]	Alkene	Yield (%)[b]	*iso-* (%) [c]	*3xb/iso-* [c]
1	1-octene	88	84	86
2	2-octene	50	97	77
3	1-pentene	81	81	98
4	1-dodecene	88	83	98
5		86	85	>99
6		93	83	>99
7		71	87	>99
8		97	84	96
9		90	83	96
10		90	84	>99
11		82	>99	>99
12		78	78	>99
13		91	49	>99
14		88	52	99

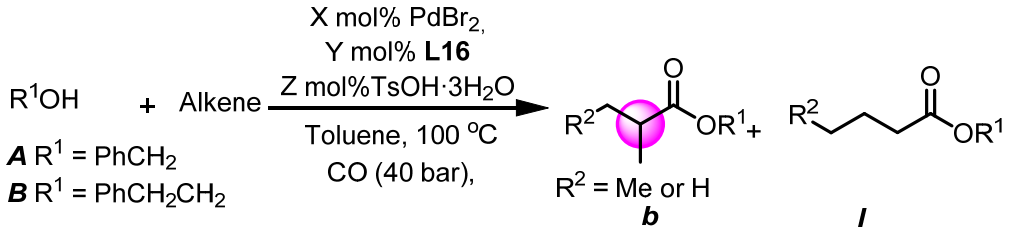
[a] Reaction condition: **1x** (2 mmol), **2** (1 mmol), $PdCl_2$ (0.01 mmol), cataCXium® POMeCy (0.04 mmol), CO (40 bar), Toluene, 100°C, 5 uL H_2O, 20 hours; [b]Yield of isolated mixture of *iso-* (major) and *n-* (minor) esters; [c] *iso-* selectivity and ***3xb****/iso-* determined by GC.

In addition to ethylene, propylene and butylene are the most important industrial olefin feedstocks, which are mainly produced today by classic cracking processes. However, emerging technologies enable the “on purpose” propylene production from more sustainable sources, such as shale gas and even biomass.[46] Butenes are produced on an industrial scale also by ethylene dimerization. New selective valorizations of these essential feedstocks are highly interesting for the chemical industry.

Clearly, single branched products could be obtained by selective alkoxycarbonylation of propylene or butylene. However, this apparently simple transformation is not realized with acceptable

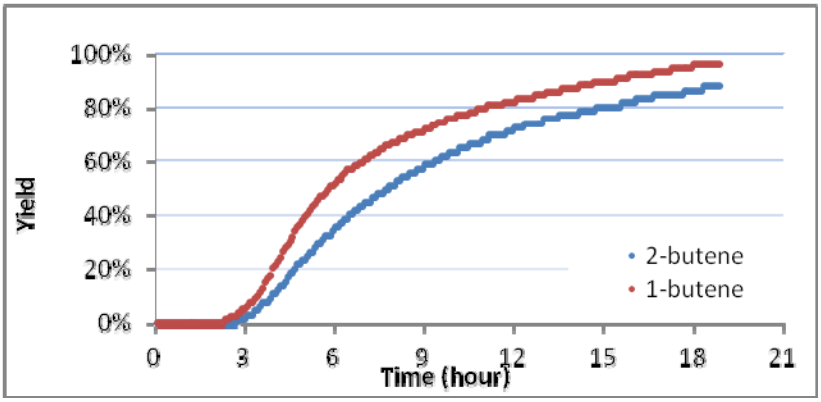
performance. In order to improve the reactivity, we performed the catalytic tests in the presence of 3 mol% of PTSA. We assumed that the additional acid will act as a more efficient reaction promoter compared to water without worrying about the formation of other internal isomeric esters. Indeed, in the presence of PTSA and $PdBr_2$ as a better palladium source improved results are obtained. With propylene and benzyl alcohol as starting material, benzyl isobutyrate (see Scheme 1) was obtained with quantitative yield with *b/l* of 88/12 (Table 3, entry 1). The catalyst loading could be further decreased to 0.05 mol% with almost quantitative yield and slightly decrease of branched-selectivity (96% yield, 84% branched-selectivity, Table 3, Entry 3). Further decrease of catalyst loading to 0.01 mol% gave 76% yield with 81% branched-selectivity (Table 3, entry 4). Moreover, decrease of reaction temperature to 80°C gave also quantitative yield at a catalyst loading of 0.5%, with 89% branched-selectivity (Table 3, entry 5).

Table 3 Markovnikov alkoxycarbonylation of propene and butenes



Entry[a]	Alkene	R^1OH	X/Y/Z	T/°C	Yield(%)[b]	*b/l*[c]	TON
1	propene	A	0.5/2/3	100	>99	88/12	200
2	propene	A	0.1/0.4/0.6	100	>99	86/14	1000
3	propene	A	0.05/0.2/0.3	100	96	84/16	1920
4	propene	A	0.01/0.06/0.06	100	76	81/19	7600
5	propene	A	0.5/2/3	80	>99	89/11	200
6	1-butene	B	0.5/2/3	100	96	81/19	192
7	2-butene	B	0.5/2/3	100	90	81/19	180
8	[d]Raffinate-1	B	0.5/2/3	100	79	81/19	158

[a]Detailed procedure see supplementary document; [b]isolated yield; [c]selectivity determined by ^{1}H-NMR. [d]Raffinate-1:mixture of isobutylene 42%, 1-butene 26%, 2- butene 17%, 1,3-butadiene 0.3%, butane/isobutane 15%.



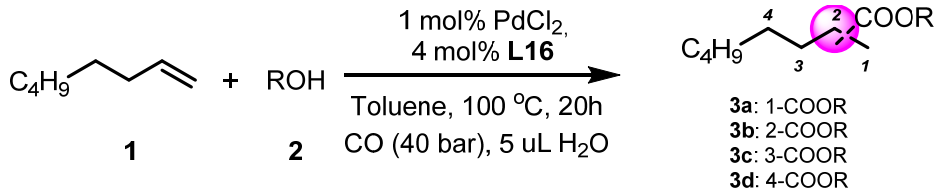
Kinetic profile is monitored by the gas consumption and further converted to yield based on the final yield.

Figure 2 Kinetic profile comparison of 2-butene and 1-butene (Table 3, entries 6, 7)

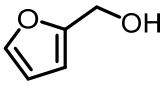
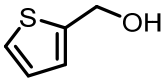
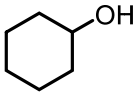
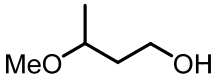
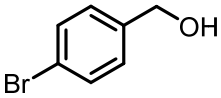
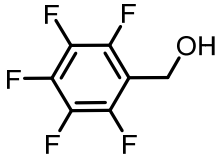
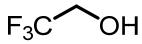
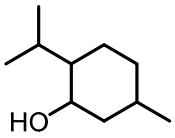
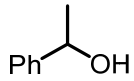
For the study of butenes, 2-phenylethanol was taken as a model substrate considering that the expected branched product phenethyl 2-methylbutyrate is used as floral and fruity organoleptic flavor and fragrance in industry. With 1-butene as substrate, 96% of yield was obtained, with 81% selectivity of the branched product. More strikingly, with 2-butene, similar yield and selectivity (90% yield, 81% branched-selectivity, Table 3) was also obtained. By comparing the reaction kinetic profile of 1-butene and 2-butene from gas consumption experiments, we can clearly see that the reaction rate of 1-butene at the beginning stage is faster than that of 2-butene, probably due to the higher concentration of 1-butene (Figure 2). In the reaction of 2-butene, we believe a majority of 2-butene is firstly isomerized to give 1-butene and further carbonylated to our desired branched product. An industrial mixture Raffinate-1 (mixture of isobutylene 42%, 1-butene 26%, 2- butene 17%, 1, 3-butadiene 0.3%, Table 2, butane/isobutane 15%) is also proved to be able to be transformed to the corresponding ester with 79% yield with 81% selectivity, with *tert*-butoxy-phenylethylether as the major by-product (Table 2, entry 8).

For various industrial applications diverse aliphatic carboxylic acid esters with different alcohols are interesting. Hence, several alcohols were tested in the alkocycarbonylation of 1-octene under the optimized conditions (Table 4). Primary alcohols such as ethanol, benzyl alcohol and nonanol gave excellent yield (88-99%) and high branched-selectivity (83-85%, Table 4, entries 1, 3, 5). Secondary alcohols such as isopropanol and cyclohexanol gave similar good results as primary alcohols (Table 4, entries 2, 9). Similarly, using more bulky substrates, e.g. menthol led to good yield and selectivity (Table 4, entry 14). However, the tertiary alcohol *t*-amyl-OH gave only 20% yield with high branched-selectivity (Table 4, entry 4). Apparently, the steric bulkiness of alcohol has no influence on the regioselectivity of the reaction, but influences the reactivity. From a synthetic point of view it is interesting to note that heteroaromatic alcohols were also tolerated. In fact, furyl- or thiophenyl-based alcohols gave ca. 80% branched-selectivity (Table 4, entries 6, 7). However, applying less basic alcohols namely phenol, pentafluorobenzyl alcohol and CF_3CH_2OH gave decreased branched-selectivity (65%, 72% and 65%, respectively; Table 4, entries 8, 12, 13). In case of (4-bromophenyl)methanol no activation of the halide was observed and high yield and branched-selectivity was obtained (Table 4, entry 11). More demanding menthol gave 82% yield and 83% branched-selectivity (Table 4, entry 14), while with 1-phenylethanol as substrate a mixture of *dr* = 1:1 product was obtained with 89% yield and 85% branched-selectivity (Table 4, entry 15).

Table 4 Alcohol substrate scope of Markovnikov alkoxycarbonylation of 1-octene



1 **2**

Entry[a]	R-OH	Yield (%)[b]	*iso*- (%) [c]	***3xb****/iso*- (%)[c]
1	EtOH	88	85	97
2	*i*-PrOH	82	85	98
3	BnOH	99	83	98
4	*t*-Amyl-OH	20	82	>99
5	Nonanol	99	84	98
6		90	80	>99
7		91	80	>99
8	Phenol	74	65	98
9		96	86	96
10		94	85	98
11		95	84	96
12		83	72	>99
13		63	65	99
14		82	83	96
15		89	85	98

[a] Reaction Conditions: **1** (2 mmol), **2** (1 mmol), $PdCl_2$ (1 mol%), **L16** (4 mol%), CO (50 bar), Toluene, 105°C, 20 hours; [b] Isolated yield; [c] iso-(%) and ***3xb****/iso*- determined by GC;

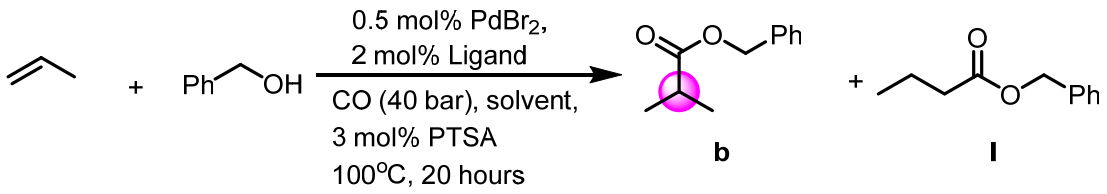
Computation studies: As shown vide supra the developed catalyst system allows for general alkoxycarbonylations of a variety of olefins and alcohols. The remarkable feature of the catalyst system is the preferred branched-selectivity of the catalyst system. To understand this observed uncommon regioselectivity in favour of the branched products we carried out computation using the range-separated hybrid WB97XD functional which includes dispersion correction.[47] Density functional theory methods including dispersion correction have been found increasingly important in describing precise ligand effects, for example studying the ligand effect on the regioselectivity of Rh-catalysed

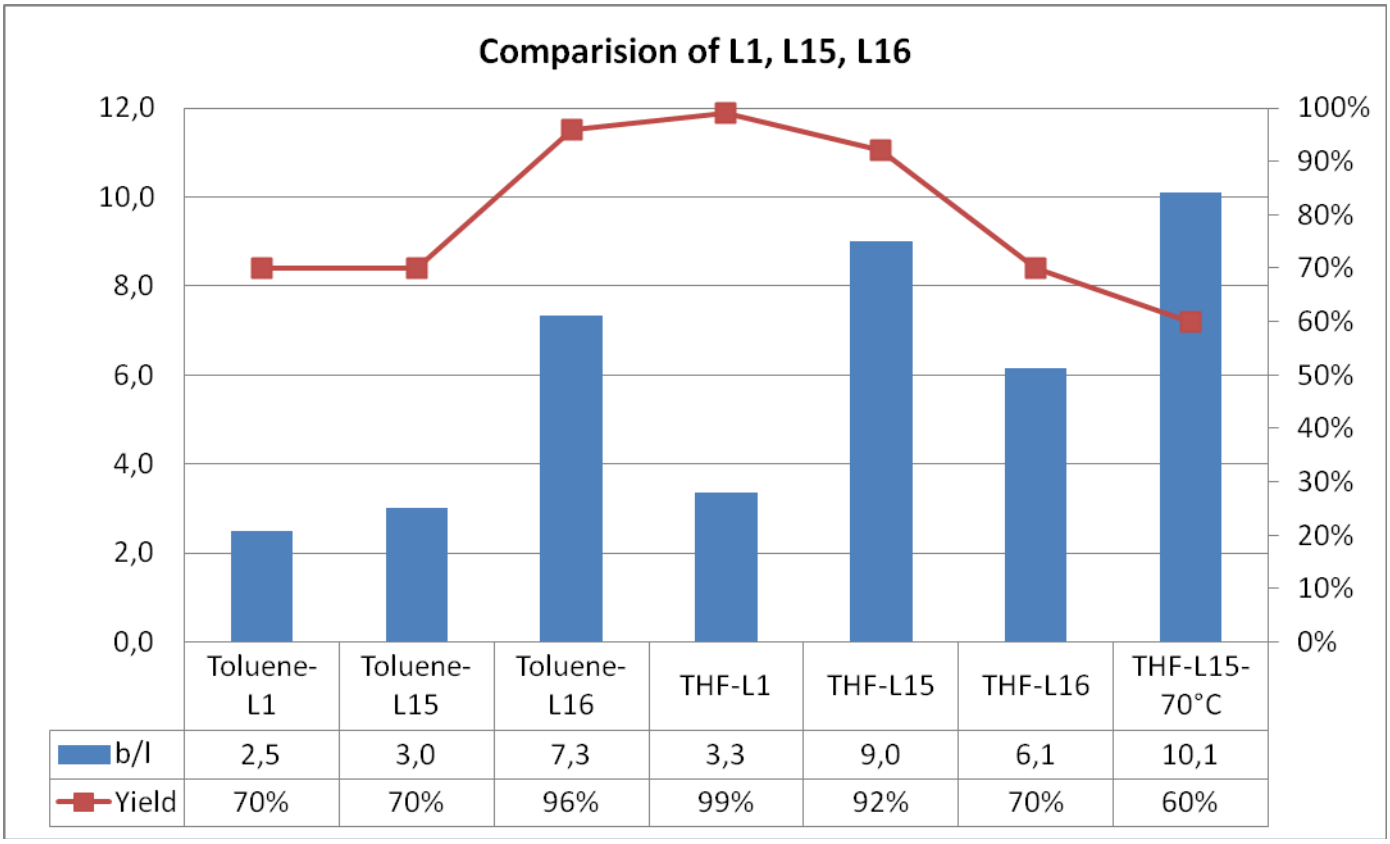
hydroformylation.[48] Here, we used the computed Gibbs free energies including solvation effect of toluene to discuss the regioselectivity (all computational details are given in the Supporting Information). In our study, we used the cationic $[L_2PdH]^+$ complex as the active catalyst and propene as model olefin. In order to differentiate the ligand effect, calculations were performed with **L1** (triphenyl phosphine) and **L15** [1-(2-methoxyphenyl)-1H-pyrrolly diphenyl phosphine]. To enable direct and systematic comparison between computation and experiment, we carried out additional catalytic experiments using both **L1** and **L15** as ligands and propene as substrate. These results are summarized in Scheme 4.

On the basis of the proposed reaction mechanism for the cationic $[L_2PdH]^+$ complexes (Scheme S1),[40] there are two elementary steps which might determine the regioselectivity. The first one is the Pd-H bond insertion into the C=C double bond of the coordinated olefin with the formation of the linear and branched alkyl complexes; and the regioselectivity can be either kinetically or thermodynamically controlled. The second possibility is the CO coordination to the alkyl complex and the subsequent CO insertion or carbonylation. Both options have been computed for comparison. The computed potential energy surfaces are shown in Figure 3.

For both **L1** and **L15** as ligands, we found stable complexes for the coordinated propene $[L_2PdH(propene)]^+$, where the C=C double bond is roughly perpendicular to the Pd-H bond. However, the corresponding transition states for the Pd-H insertion into the C=C bond by rotating the C=C bond syn to the Pd-H bond could not be located, indicating that the barrier is negligible low. Therefore, we used the relative energies of the most stable propyl $[L_2Pd(propyl)]^+$ and isopropyl $[L_2Pd(isopropyl)]^+$ complexes for discussion under the consideration that all stable $[L_2Pd(H)(propene)]^+$ complexes can form the corresponding propyl $[L_2Pd(propyl)]^+$ and isopropyl $[L_2Pd(isopropyl)]^+$ complexes.

For the reaction in the presence of **L15**, $[(\mathbf{L15})_2Pd(isopropyl)]^+$ is more stable than $[(\mathbf{L15})_2Pd(propyl)]^+$ by 2.38 kcal/mol. Considering this energy difference, the thermodynamically most stable $[(\mathbf{L15})_2Pd(isopropyl)]^+$ should lead to the branched product. However, the expected regioselectivity (96/4) is much higher than that in the catalytic experiment (75/25). For the reaction with **L1**, $[(\mathbf{L1})_2Pd(isopropyl)]^+$ is more stable than $[(\mathbf{L15})_2Pd(propyl)]^+$ by 0.78 kcal/mol. On the basis of this energy difference, the expected regioselectivity (74/26) is also much higher than that in experiment (59/41). This indicates that Pd-H insertion should not determine the regioselectivity.





	Toluene-L1	Toluene-L15	Toluene-L16	THF-L1	THF-L15	THF-L16	THF-L15-70°C
b/l	2,5	3,0	7,3	3,3	9,0	6,1	10,1
Yield	70%	70%	96%	99%	92%	70%	60%

[a] Detailed procedure mentioned above; yield of isolated product; b/l determined by ^{1}H NMR;

Scheme 4. Markovnikov alkoxycarbonylation of propene : Comparison of L1, L15 and L16

Next, we computed the reaction energy of CO coordination and the relative stability of the $[(\mathbf{L15})_2Pd(CO)(propyl)]^+$ and $[(\mathbf{L15})_2Pd(CO)(isopropyl)]^+$ complexes. It is found that $[(\mathbf{L15})_2Pd(CO)(propyl)]^+$ formation is endergonic by 1.23 kcal/mol; and $[(\mathbf{L15})_2Pd(CO)(isopropyl)]^+$ formation is endergonic by 2.79 kcal/mol. Thermodynamically, $[(\mathbf{L15})_2Pd(CO)(isopropyl)]^+$ is more stable than $[(\mathbf{L15})_2Pd(CO)(propyl)]^+$ by 0.82 kcal/mol. On the basis of this energy difference, the ratio of $[(\mathbf{L15})_2Pd(CO)(isopropyl)]^+$ and $[(\mathbf{L15})_2Pd(CO)(propyl)]^+$ is 75/25 under equilibrium. Such ratio is equal to the observed regioselectivity in favor of the branched product (Scheme 4). Starting from $[(\mathbf{L15})_2Pd(CO)(propyl)]^+$, CO insertion has barrier of 8.92 kcal/mol and is exergonic by 11.67 kcal/mol, and starting from $[(\mathbf{L15})_2Pd(CO)(isopropyl)]^+$, CO insertion has barrier of 9.34 kcal/mol and is exergonic by 11.67 kcal/mol.

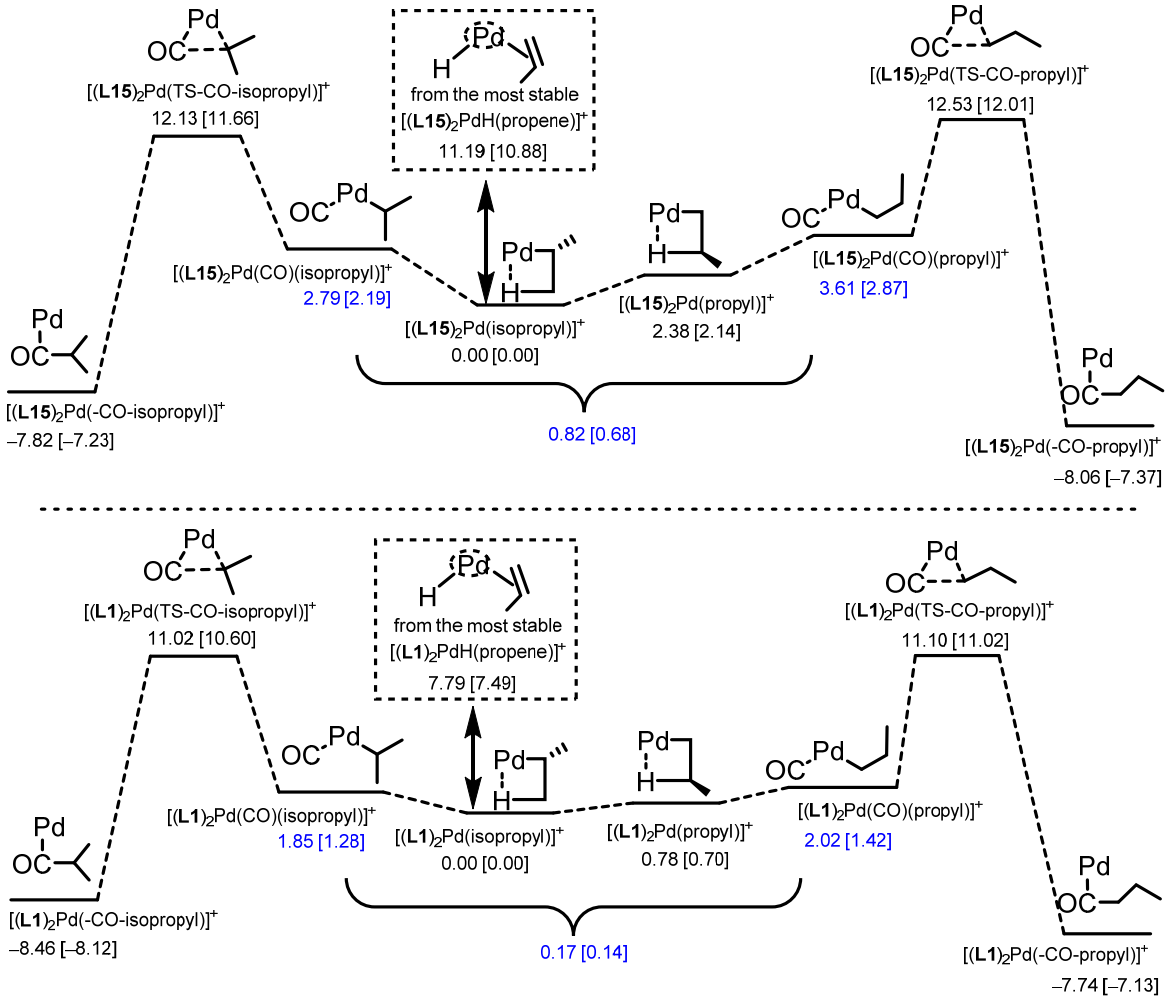


Figure 3: Gibbs free energies of Pd-H insertion and carbonylation for reaction using **L15** and **L1** on WB97XD-SCRF/TZVP//WB97XD/SVP including solvation of toluene (the WB97XD/TZVP//WB97XD/SVP gas phase values in parenthesis)

On the basis of the most stable [(**L15**)$_2$Pd(CO)(isopropyl)]$^+$, the effective free energy barrier and reaction free energy of CO insertion is 12.53 and -8.06 kcal/mol for [(**L15**)$_2$Pd(CO)(propyl)]$^+$ as well as 12.13 and -7.82 kcal/mol for [(**L15**)$_2$Pd(CO)(isopropyl)]$^+$. Since the back reaction of CO insertion has higher barrier (20.59 and 19.95 kcal/mol, for propyl and isopropyl acyl complexes, respectively), the difference in thermodynamic stability of [(**L15**)$_2$Pd(CO)(isopropyl)]$^+$ and [(**L15**)$_2$Pd(CO)(propyl)]$^+$ should determine the regioselectivity.

For **L1**, similar results are found. The formation of [(**L1**)$_2$Pd(CO)(propyl)]$^+$ and [(**L1**)$_2$Pd(CO)(isopropyl)]$^+$ is endergonic by 1.24 and 1.85 kcal/mol, respectively. Thermodynamically, [(**L1**)$_2$Pd(CO)(isopropyl)]$^+$ is more stable than [(**L1**)$_2$Pd(CO)(propyl)]$^+$ by 0.17 kcal/mol; and the expected ratio of [(**L1**)$_2$Pd(CO)(isopropyl)]$^+$ and [(**L1**)$_2$Pd(CO)(propyl)]$^+$ is 56/44 under equilibrium. Such ratio is close to the observed regioselectivity (59/41) in favor of the branched product (Scheme 4). Starting from [(**L1**)$_2$Pd(CO)(propyl)]$^+$, CO insertion has barrier of 9.08 kcal/mol and is exergonic by

9.76 kcal/mol, while starting from $[(\mathbf{L1})_2Pd(CO)(isopropyl)]^+$, CO insertion has barrier of 9.17 kcal/mol and is exergonic by 10.31 kcal/mol.

On the basis of the most stable $[(\mathbf{L1})_2Pd(CO)(isopropyl)]^+$, the effective free energy barrier and reaction free energy of CO insertion is 11.10 and -7.74 kcal/mol for $[(\mathbf{L1})_2Pd(CO)(propyl)]^+$ as well as 11.02 and -8.46 kcal/mol for $[(\mathbf{L1})_2Pd(CO)(isopropyl)]^+$. Since the back reaction of CO insertion has higher barrier (18.84 and 19.48 kcal/mol, respectively), the difference in thermodynamic stability of $[(\mathbf{L1})_2Pd(CO)(isopropyl)]^+$ and $[(\mathbf{L1})_2Pd(CO)(propyl)]^+$ should determine the regioselectivity.

All these results clearly show that the enhanced stability of the isopropyl complexes, $[(\mathbf{L15})_2Pd(CO)(isopropyl)]^+$ and $[(\mathbf{L1})_2Pd(CO)(isopropyl)]^+$, should determine the regioselectivity of the overall process. Furthermore, the reaction with **L15** is more regioselective than that with **L1**, which is in agreement with our experimental findings.

Interestingly, as shown in Figure 3 the stability of $[(\mathbf{L15})_2Pd(CO)(isopropyl)]^+$ and $[(\mathbf{L1})_2Pd(CO)(isopropyl)]^+$ can be enhanced from gas phase into toluene as solvent. Inspired by these results, we tested the solvent effect on the regioselectivity both experimentally and computationally. Indeed, using THF as solvent the experimentally observed regioselectivity increases from 75/25 to 90/10 for **L15**, as well as from 59/41 to 77/23 for **L1**. Computationally, the regioselectivity for **L15** increases from 75/25 to 83/17, however, no such effect has been found for **L1**. Additionally, we also found that the same regioselectivity for **L15** in THF can also be achieved at lower temperature (70°C) but in lower yield (92 vs. 60%). Furthermore, increase CO pressure affects neither the yield nor regioselectivity.

Summary and conclusion

In conclusion, we have discovered a PdX_2/*N*-phenylpyrrole-type catalyst system for regioselective Markovnikov alkoxycarbonylation reactions of alkenes. Notably, industrially important aliphatic olefins without further functional groups can be selectively alkoxycarbonylated to the branched products. The general applicability is demonstrated in 17 examples (71-99% yield, 49-91% branched-selectivity). Furthermore, diverse alcohols are also well tolerated (15 examples, 20–99% yield, 65–85% branched-selectivity). The applicability of this methodology is further highlighted by the employment of industrial C4 mixture in synthesis of phenethyl 2-methylbutyrate, a fruity fragrance. On the basis of density functional theory computation including dispersion correction for van der Waals interaction, the experimentally observed branched-selectivity should be determined by the enhanced

thermodynamic stability of the corresponding isopropyl $[L_2Pd(CO)(isopropyl)]^+$ complex over the propyl $[L_2Pd(CO)(propyl)]^+$ complex. Further attempts on ligand modifications are currently underway in our research group.

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Author contributions

M. B. and H. L. conceived and designed the experiments. H. L. and K. D. performed the experiments and analysed the data. H. J. performed the DFT study. H. N. and R. J. participated in the discussions and supported the project. M. B., H. J. and H. L. co-write the paper.

Additional information

Supplementary information is available in the online version of the paper. Reprints and permissions information is available online at www.nature.com/reprints. Correspondence and requests for materials should be addressed to M. B.

Competing financial interests

The authors declare no competing financial interests

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8.4 Palladium-catalyzed aminocarbonylation reaction of allylic alcohols

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Manuscript in preparation

In this publication, I discovered the distinct reactivity, performed all of the optimization, scope and mechanistic study. I prepared the manuscript. My overall contribution to this work approximately accounts for 75%.

Palladium-catalyzed Aminocarbonylation of Allylic Alcohols

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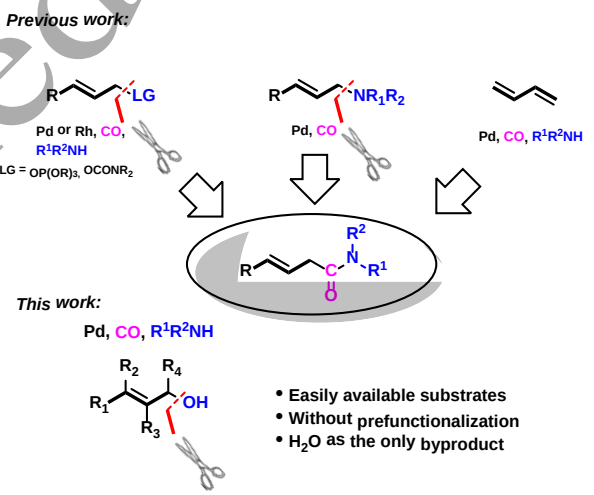
ABSTRACT: A benign and efficient palladium-catalyzed aminocarbonylation reaction of allylic alcohols is presented. The generality of this novel process is demonstrated by the synthesis of β,γ-unsaturated amides including aliphatic, cinnamyl and terpene derivatives. The choice of ligand is crucial for optimal carbonylation processes: While in most cases the combination of $PdCl_2$ with Xantphos **L15** gave best results, sterically hindered substrates performed better in the presence of simple triphenylphosphine **L1** and primary anilines gave best results using **L10**. The reactivity of the respective catalyst system is significantly enhanced by addition of small amounts of water. Mechanistic studies and control experiments revealed a tandem allylic alcohol amination/C-N bond carbonylation reaction sequence.

Allylic alcohols represent sustainable and versatile building blocks in organic synthesis.[1] Among the various allylic substrates, this motif is most common. In fact, a plethora of allylic alcohols is commercially available or can be easily synthesized by numerous methodologies.[2] Besides, naturally occurring terpenes such as phytol, geraniol, nerol, farnesol etc. are broadly used in the fragrance industry and also found elegant applications in organic synthesis. For example, the industrial manufacture of *vitamin* E3 and *vitamin* K1 are based on allylic alcohols.[4] Due to its special structure, the investigations for novel transformations of allylic alcohols have attracted significant attention from both academic and industrial researchers.[5]

Carbonylation reaction constitutes a powerful tool for the synthesis of carboxylic derivatives.[6] More specifically, the aminocarbonylation of olefins, arylhalide and even C^{sp3}-H were demonstrated to be unprecedented efficient synthetic route to construct amides moiety using CO as the building block.[7] Recently, we reported a novel aminocarbonylation reaction of dienes using a palladium/d'bpx catalyst system, which represents an atom-economic synthetic protocol to synthesize β,γ-unsaturated amide[8], a useful synthetic intermediate in organic synthesis.[9] However, the instability of most dienes and the gaseous nature of butadiene actually prompt us to further discover a more practical methodology. As an alternative efficient approach, the carbonylation of allylic compounds soon attracted our attention. To note, the carbonylation of allylic compounds with prefunctionalized allylic compounds, such as allyl phosphonate[10], carbamate[11] was known since 1990s. Obviously, significant amount of waste will be generated not only during the prefunctionalization step, but also during the reaction procedure. Moreover, the carbonylation of allylamine[12] was also known, which also suffers from limited commercialized substrates. (Scheme 1) In comparision, the direct aminocarbonylation allylic alcohol would be an ideal alternative, regarding availability and atom-economy issue (water as the only by-product). Yet, the direct carbonylation reaction of allylic alcohol is in principle more challenging due to the poor ability of hydroxyl group to serve as a leaving group.[13] Only few examples on carbonylation of allylalcohol were known.[14] Among the known cases, acidic additive is essential to induce the activity, such as lewis acids[15], brønsted acid[16], or CO_2[17].

In continuation to our long standing interest in the development of carbonylation reactions based on feedstock chemicals, we report herein the first direct aminocarbonylation of allylic alcohol.[18]

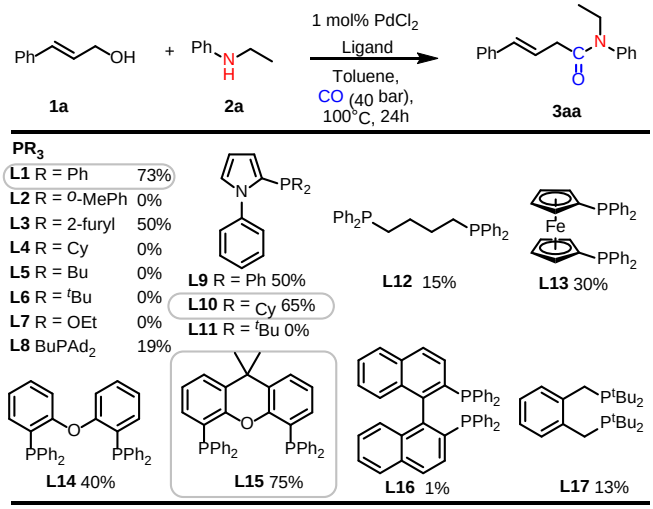
Scheme 1 Comparision of previous work and current work



At the beginning of our study, cinnamyl alcohol **1a** (1 mmol) and *N*-ethylaniline **2a** (1 mmol) were chosen as model substrate (Scheme 2). In the presence of $PdCl_2$ (1 mol%) as the catalyst precursor, a plethora of phosphine ligands (4 mol% for monodentate ligand and 2 mol% for bidentate ligand) were tested without any additive (see Scheme 1). Surprisingly, when we tested different monodentate ligands (**L1** – **L8**), simple PPh_3 **L1** gave the best result (73% yield). Next, *N*-phenylpyrrole type ligands were tested, among which cyclohexyl substituted ligand **L10** (cataCXium PCy) gave better result (65% yield) than phenyl substituted and t-Bu substituted ones (50%, 0% yield obtained, respectively). Then, different commercially available bidentate ligands were tested (**L13**-**L17**). With dppf **L13** (with bite angle 99°) as ligand, 30% of yield was obtained, DPEphos **L14** (with bite angle 104°) gave 40% yield. When Xantphos **L15** (with bite angle 108°) was tested, good yield (75%) was obtained. With binap ligand **L16** (with bite angle 93°) as the ligand, only 1% of product could be observed.[19] From the results, larger bite angle seems to be

beneficial for the reaction. Sterically hindered and electron rich d^{t}bpx ligand **L17** was finally tested, but only 13% yield was obtained.

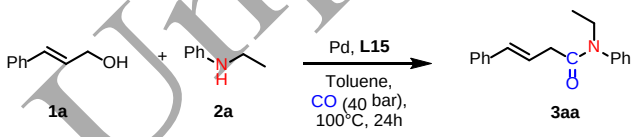
Scheme 1 Palladium catalysed aminocarbonylation of allylic alcohol: ligand screening



Reaction conditions: 1a (1 mmol), 2a (1 mmol), Ligand (**L1- L11** 4 mol%, **L12-L17** 2 mol%), Toluene (2 mL), CO (40 bar), 100°C, 24 hours; yield determined by GC analysis with isooctane as the internal standard.

With **L15** as the ligand of choice, we tried to further improve the productivity of this reaction. However, when catalyst loading was lowered to 0.5 mol%, only 19% yield was observed (Table 1, entries 2-3). Next, different additives were tested in order to improve the reactivity. With catalytic amount of TFA, LiCl, MSA and HCl added, the yield improved significantly (Table 1, entries 4 to 7). More surprisingly, with water as the only additive, which is also generated during the reaction, 80% yield was obtained (Table 1, entry 8). Further, by improving the amount of **1a** to 1.5 equiv., quantative yield was obtained (Table 1, entry 11). Furthermore, at 0.25 mol% palladium loading, the reaction was observed to be incomplete after 24 hours, in which 92% yield was obtained by elongating the reaction time to 48 hours. (Table 1, entries 12, 13) Further decrease of catalyst loading to 0.1 mol% gave only traces of desired product after 24 hours.

Table 1. Palladium-catalysed aminocarbonylation of allylic alcohol: Optimizationl

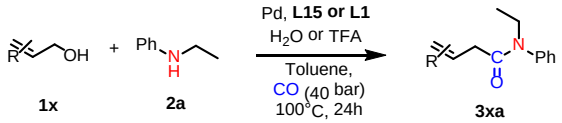


Entry	Pd (mol%)	Ligand (mol%)	additive	Yield (%)
1	$PdCl_2$(1)	L15 (2)	/	75[a]
2	$PdCl_2$(1)	L15 (1.5)	/	75[a]
3	$PdCl_2$(0.5)	L15 (0.75)	/	19[a]
4	$PdCl_2$(0.5)	L15 (0.75)	CF_3COOH (3 mol%)	75[a]
5	$PdCl_2$(0.5)	L15 (0.75)	$LiCl{\cdot}H_2O$ (10 mol%)	81[a]
6	$PdCl_2$(0.5)	L15 (0.75)	MSA (3 mol%)	84[a]
7	$PdCl_2$(0.5)	L15 (0.75)	HCl (3 mol%)	87[a]
8	$PdCl_2$(0.5)	L15 (0.75)	H_2O(10 uL)	80[a]
11	$PdCl_2$(0.5)	L15(0.75)	H_2O(10 uL)	95[b]
12	$PdCl_2$(0.25)	L15(0.375)	H_2O(10 uL)	25[b], 92[b,c]
13	$PdCl_2$(0.1)	L15(0.15)	H_2O(10 uL)	trace[b,c]

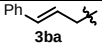
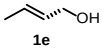
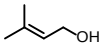
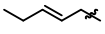
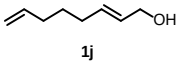
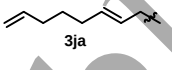
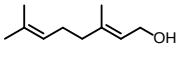
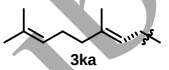
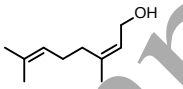
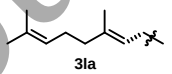
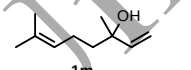
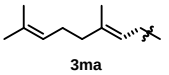
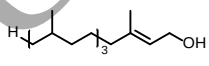
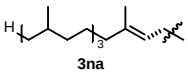
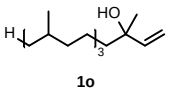
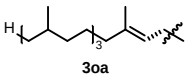
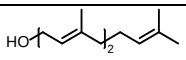
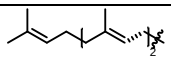
a) General conditions: **1a** (1mmol), **2a**(1 mmol), $PdCl_2$, **L15**, toluene(2 mL), 100°C, 24 hours, CO (40 bar); b) **1a** (1.5 mmol); c) 48 hours.

In order to explore the scope, a variety of allylic alcohols were tested (Scheme 3). Firstly, with 1-phenylprop-2-en-1-ol **1b** as substrate, the linear product was obtained with excellent yield (95%, Scheme 3, entry 1). This indicates that the reaction goes through allyl-palladium as the reaction intermediate. With allylic alcohol **1c** as substrate, under similar condition, an increase amount of allylic alcohol (3 equiv.) will afford 92% yield of **3ca (**Scheme 3, entry 2**)**. However, with methyl substituent on the 2-position, under standard conditions (*condition A*), no desired product was observed. With slightly modified method (TFA as additive, **L1** as ligand, 120°C see *condition B*), the corresponding product **3da** could be obtained with 40% yield (Scheme 3, entry 3). Further, good yield was obtained with crotyl alcohol **1e** as the substrate (84% yield, *E*/Z = 76/24, Scheme 3, entry 4). As expected, with but-3-en-2-ol **1f** as the substrate, same product was obtained with 87% isolated yield (Scheme 3, entry 5). Another example for 1-substituted allyl alcohol **1g** also gave linear product **3ga**, as the final product, with 84% isolated yield (Scheme 3, entry 6). With 3-substitued allyl alcohol **1h**, no product was observed using **L15** as ligand (*condition A*), even when TFA was added as additive (Scheme 3, entry 7). However, using PPh_3 **L1** as the ligand, 53% isolated yield was obtained at 100°C (*condition C*). Further increase of the reaction temperature to 120°C afford 83% isolated yield (*condition D*). Moreover, cyclic allyl alcohol cyclohex-2-enol **1i** was also shown to be compatible with our optimized *condition A*. (51% isolated yield of **3ia,** Scheme 3, entry 8). Starting from **1j**, which derives from the telomerisation of butadien 62% isolated was obtained using *condition C* (Scheme 3, entry 9).[20] To highlight the application potential of our developed method, when Geraniol **1k**, nerol **1l** and linalool **1m**, which are used in perfumery and fragrance industry, were subjected into *condition B*, quantative yield of the desired amides were obtained (Scheme 3, entries 10-12). Noticeably, the internal C=C bond was intact under such reaction conditions. Further, both phytol and isophytol, which are acyclic diterpene alcohols, were successfully transformed into the corresponding amide with good yield (respectively 95% and 90% yield, Scheme 3, entries 13-14). Farnesol **1p**, as an example of acyclic sesquiterpene, afforded 88% yield of the corresponding amide (a mixture of 8 isomers, Scheme 3, entry 15). To note, homofarnesylic acid amide **3pa** can be used for the synthesis of (±)-ambroxan via acid catalysed cyclization reaction, which is an important amber-like perfumer material.[9a]

Table Palladium-catalyzed aminocarbonylation of allylic alcohols: substrate scope



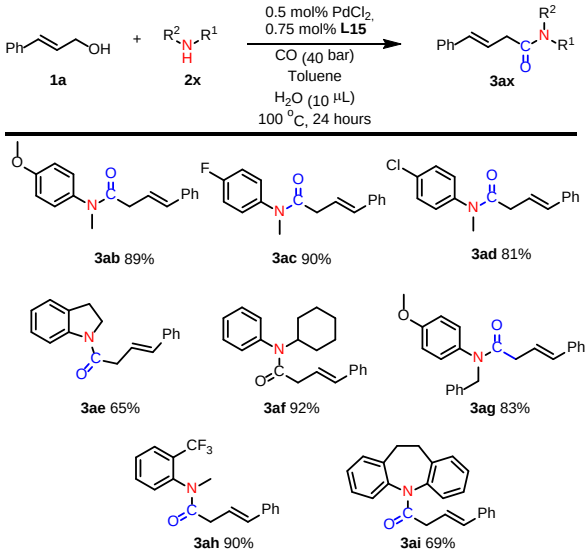
1x + 2a → 3xa

Entry[a]	1	R	Yield (%) [f]
1	 1b	 3ba	95[a]
2	 1c	 3ca	92[d]
3	 1d	 3da	0[a], 40[b]
4	 1e	 3ea	84 (E/Z = 76/24)[a]
5	 1f	 3fa	87[a]
6	 1g	 3ga	84[a]
7	 1h	 3ha	0[a], 53[c], 83[b]
8	 1i	 3ia	51[b]
9	 1j	 3ja	62[e]
10	 1k	 3ka	95[b]
11	 1j	 3la	95[b]
12	 1m	 3ma	95[b]
13	 1n	 3na	95[b]
14	 1o	 3oa	90[b]
15	 1p	 3pa	88[b]

a) General Reaction condition : 1 (1.5 mmol), 2 (1 mmol), PdCl2 (0.5 mol%, 0.005 mmol), L15 (0.75 mol%, 0.0075 mmol), H2O (10 uL) in Toluene (2 mL), CO (40 bar), 100 oC for 24 hours; b) Condition B: PdCl2 (1 mol%, 0.01 mmol), L1 (4 mol%, 0.04 mmol), TFA (5 mol%), 120oC; c) Condition C: PdCl2 (1 mol%, 0.01 mmol), L1 (4 mol%, 0.04 mmol), TFA (5 mol%), 100oC; d) Condition D: 1 (3 mmol), 2 (1 mmol), L15 (0.75 mol%, 0.0075 mmol), H2O (10 uL) in Toluene (2 mL), CO (40 bar), 100 oC for 24 hours; e) Condition E: 1 (1.5 mmol), 2 (1 mmol), PdCl2 (0.5 mol%, 0.005 mmol), L15 (0.75 mol%, 0.0075 mmol), TFA (5 mol%) in Toluene (2 mL), CO (40 bar), 100 oC for 24 hours; f) yield of isolated product.

To investigate the functional group tolerance, different *N*-substituted aniline substrates were tested (Scheme 4). With 4-methoxy-*N*-methylaniline as the substrate, **3ab** was obtained with 89% yield. With electron-withdrawing group F- and Cl-substituted *N*-methylaniline, the corresponding products **3ac** and **3ad** were obtained with good yield(respectively 90% and 81%). Next, with cyclic amine indoline and 1,2,3,4-tetrahydroquinoline tested, the corresponding **3ae** was isolated with 65% yield. More steric hindered amine substrates such as *N*-cyclohexylaniline, *N*-benzyl-4-methoxyaniline and *N*-methyl-2-(trifluoromethyl)aniline were also tolerated under this condition (respectively 92%, 83% and 90% yield). Finally, 10,11-dihydro-5H-dibenzo[b,f]azepine was also tested and afforded the corresponding product **3aj** with 69% yield.

Scheme 2 Aminocarbonylation of cinnamyl alcohols using different amines

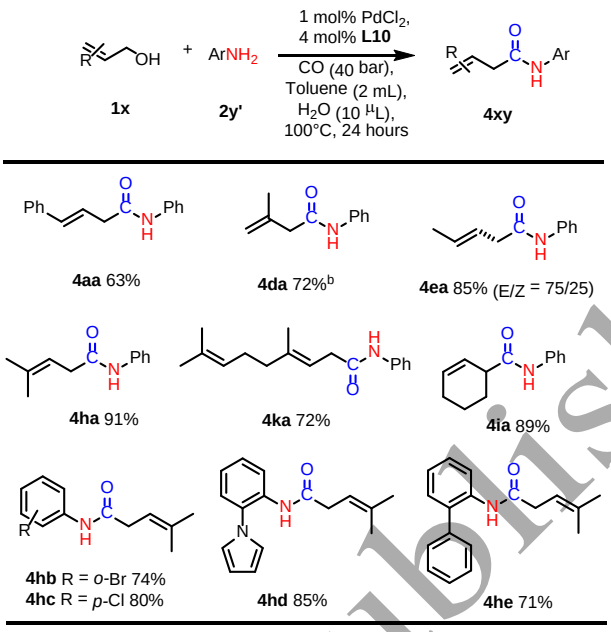


Reaction conditions: **1** (1.5 mmol), **2** (1 mmol), $PdCl_2$ (0.5 mol%, 0.005 mmol), **L15** (0.75 mol%, 0.0075 mmol), H_2O (10 uL) in Toluene (2 mL), CO (40 bar), 100 °C for 24 hours

Next, a protocol for aminocarbonylation of allylic alcohol using primary aniline derivatives was also developed. With cinnamylalcohol as the substrate, one major side reaction observed was the competitive intramolecular carbonylation at benzylic position of *N*-cinnamylaniline to afford cyclized product 1,3-diphenylpyrrolidin-2-one. After numerous trials,

the best result obtained to synthesize **4aa** starting from aniline and **1a** under the following conditions: $PdCl_2$ (1 mol%), cataCXium PCy **L10** (4 mol%), in toluene, with water as the additive, 40 bar of CO at 100 °C for 24 hours, which gave **4aa** with 63% isolated yield (Scheme 5). To our delight, with aliphatic allylic alcohols, better results were obtained. Starting from **1d** and aniline, 72% yield of **4da** was isolated after 48 hours heating. The carbonylation of crotyl alcohol (*E/Z* mixture) was also successful, 85% yield was obtained. Furthermore, good yield were also obtained when using **1h**, **1k** and cyclic allylic alcohol **1i** as the substrate (respectively 91%, 72% and 89% isolated yield for **4ha**, **4ka** and **4ia**). Additionally, other substituted aniline derivatives were also tested. With **1h** as the starting allylic alcohol, anilines bearing *ortho*-Br and para-Cl group were tolerated (74% and 80% isolated yield). More interestingly, 2-(1H-pyrrol-1-yl) aniline and 2-phenylaniline are also transformed to the corresponding product **4hd** and **4he** with good yield (85% and 71% respectively).

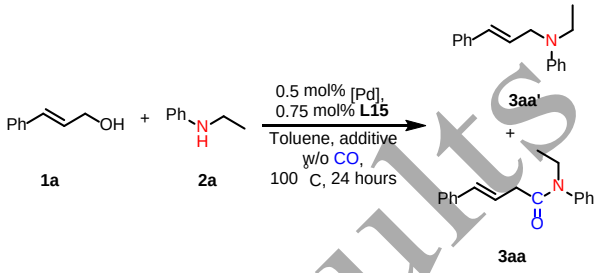
Scheme 3 Aminocarbonylation reactions using anilines



a Reaction conditions: 1 (1.1 mmol), 2 (1 mmol), PdCl2 (1 mol%, 0.01 mmol), L10 (4 mol%, 0.04 mmol), H2O (10 uL) in Toluene (2 mL), CO (40 bar), 100 oC for 24 hours. yield of isolated product. b 48h

In order to have more insight on the developed method, control experiments were conducted. To begin with, with $Pd_2(dba)_3$ and xantphos as the catalyts, additive effect was investigated without CO atmosphere. Without any additive, 15% of **4aa** was observed (Table 2, entry 1). With water added, similar result was observed (Table 2, entry 2). Increased yield was observed with the addition of 5 mol% of HCl (in Et_2O solution) (Table 2, entry 3). Using palladium chloride as the catalyst precursor, by adding 10 μL of water, 90% yield was obtained after 24 hours heating at 105°C (Table 2, entry 4). In contrast, by addition of 1 equivalent of diethyl amine, the reactivity was totally shut down. Only starting material is recovered. In this set of experiments, acid or the in-situ generated HCl will improve the amination reaction of the allylic alcohol. Under CO atmosphere, using $Pd_2(dba)_3$ as the catalyst precursor, using Xantphos as the ligand, with the addition of water as the additive, 31% of **3aa'** was observed as the product and no carbonylated **3aa** generated. Using the same catalyst, by adding 5 mol% of HCl, 77% yield of amide **3aa** was observed. By adding 10% of NaOH into the reaction, even by using $PdCl_2$ as the catalyst precursor, **3aa'** and **3aa** were totally not observed (Table 2, entry 8).

Table 2 Control experiments of aminocarbonylation of 1a

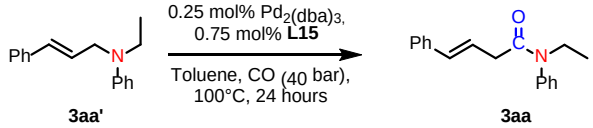


Entry	Pd	CO	Additive	3aa (%)'	3aa (%)
1	$Pd_2(dba)_3$	-	none	15	-
2	$Pd_2(dba)_3$	-	H_2O 10 uL	10	-
3	$Pd_2(dba)_3$	-	HCl (5 mol%)	64	-
4	$PdCl_2$	-	H_2O 10 uL	90	-
5	$PdCl_2$	-	Et_2NH (1 equiv.)	0	
6	$Pd_2(dba)_3$	40 bar	H_2O 10 uL	31	0
7	$Pd_2(dba)_3$	40 bar	HCl (5 mol%)	0	77
8	$PdCl_2$	40 bar	NaOH 10 mol%	0	0

Reaction conditions: **1a** (1 mmol), **2a** (1 mmol), [Pd] (0.005 mmol, 0.5 mol%), **L15** (0.0075 mmol, 0.75 mol%), CO (40 bar), 105°C, 24 hours.

Hence, we assumed that this reaction proceeds *via* allylic amine **3aa'** as a reaction intermediate. In fact, starting from **3aa'**, using $Pd_2(dba)_3$ as the catatlyst precursor, without any additive, 11% yield of **3aa** could be observed. Slightly increased yield (25%, Table 3, entry 2) was observed by adding 5 mol% of HCl into the reaction media. Surprisingly, by further adding 10 μL water, which is the byproduct of the amination reaction of allylic alcohol, the yield of **3aa** increased significantly to 93% (Table 3, entry 3). We assume that water also take the role to increase the solubility of the generated ammonium salt, which improve the ability of amine as a leaving group.

Table 3 Control experiments of aminocarbonylation of 3aa'

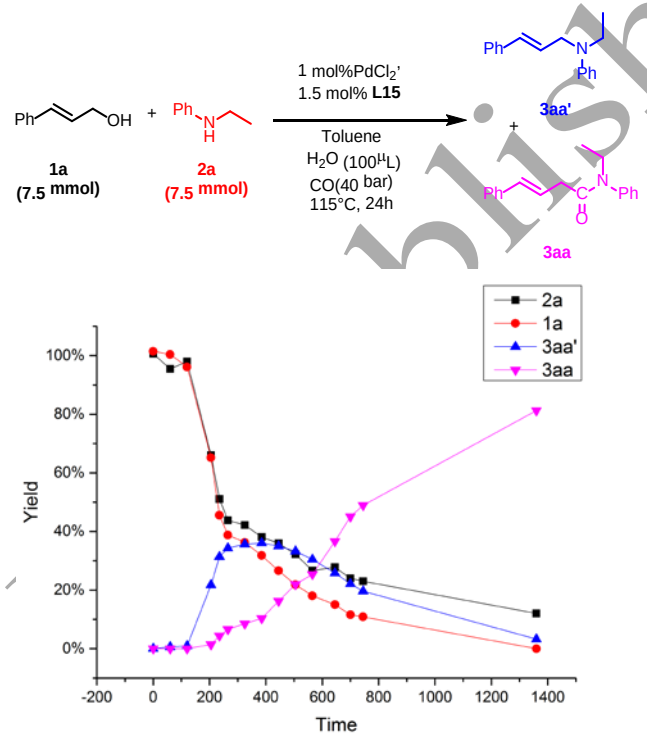


Entry	Pd/Ligand	Additive	Amide (%)
1	Pd2(dba)3, Xantphos	none	11
2	Pd2(dba)3, Xantphos	HCl (5 mol%)	25
3	Pd2(dba)3, Xantphos	HCl (5 mol%) + 10 uL H_2O	93

Reaction conditions: **3aa'** (1 mmol), $Pd_2(dba)_3$ (0.0025 mmol, 0.25 mol%), **L15** (0.0075 mmol, 0.75 mol%), CO (40 bar), 105°C, 24 hours.

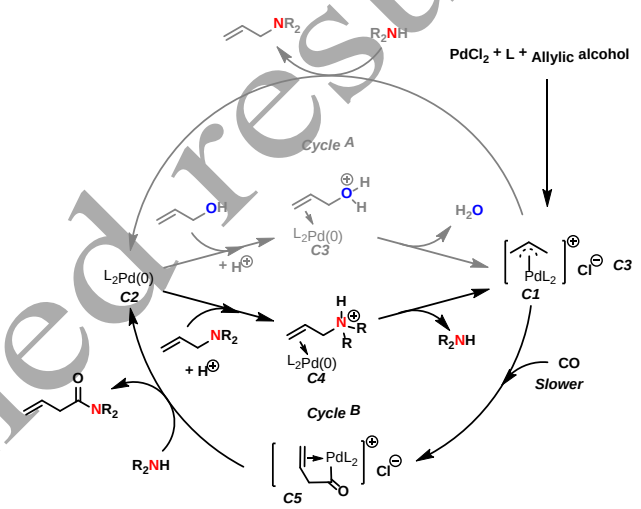
Furthermore, the progress of the aminocarbonylation of cinnamyl alcohol was monitored (due to the reason of time, reaction contidion was slightly modified, 1 mol% $PdCl_2$, 1.5 mol% Xantphos, **1a**:**2a** = 1:1, at 115°C). The reaction profile (See Figure 1) clearly showed that **1a** and **2a** were quickly consumed and transformed to **3aa'** at the first ca. 300 minutes. At the same time, less than 10% of **3aa** was formed. Then, the formation of **3aa** seemed to be accelerated probably due to the decrease of **2a** concentration and also the increase of concentration of **3aa'.** Together, the formation and consumption of **3aa'** reached equilibrium and stayed still for around 200 minutes at ca. 40% yield. Then, the concentration of **3aa'** starts to decrease along with the increase of concentration of **3aa**.

Chart 1 Reaction profile of palladium-catalyzed aminocarbonylation of allylic alcohol



Based on the previous understanding of the Tsuji-Trost type reaction of allylic alcohol, we suggest the reaction go through the mechanistic path way depicted in scheme 6 as the major reaction pathway. Basically, this reaction involves two catalytic cycles, the amination of allylic alcohol (Cycle A) and the carbonylation of allylic amine (Cycle B), which in fact correlates each other. At the beginning, as described, the catalytic active allylpalladium species ***C1*** could be generated by the reaction of $PdCl_2$ with allylic alcohol.[21] At this stage, the competition of CO coordination/insertion and nucleophilic attack of amine to allyl amine happened. This balance is mainly decided by the concentration of amine. Obviously, at the beginning of the reaction, the aminolysis of allylpalladium species is faster, which generate allylic amine and regenerate Pd(0) species ***C2***. The activation of allylic alcohol is promoted by the in-situ generated or additional acid and forms ***C1*** (Cycle A). Another cycle starts from the oxidative addition of allylamine to Pd (0) ***C2***, which is assisted by acid and water. By further CO insertion, acylpalladium species ***C5***will generate. Finally, the aminolysis of the acylpalladium will afford the final product and regenerate ***C2***.

Scheme 4 Proposed reaction pathway (phosphine ligand is omitted for clarity)



In conclusion, we developed the first palladium-catalysed aminocarbonylation reaction of allylic alcohol. The developed catalyst system consists of $PdCl_2$ and a phosphine ligand (Xantphos, PPh_3 or cataCXium PCy). In most cases, water was shown to improve the reactivity significantly and was used as the only additive. Starting from easily available allylic alcohol and aromatic amine, β, γ-unsaturated amide could be obtained with good yield under mild reaction conditions. Moreover, both catalyst systems for primary and secondary amines are described, which showed excellent functional group tolerance. With the help of control experiments, a plausible reaction mechanism is revealed involving a tandem amination/C-N bond carbonylation reaction.

ASSOCIATED CONTENT

SUPPORTING INFORMATION

Experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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8.5 Palladium-Catalyzed Alkoxycarbonylation of Conjugated Dienes under Acid-Free Conditions: Atom-Economic Synthesis of β,γ-Unsaturated Esters

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†: These authors contributed equally to the work.

Contributions

In this publication, I was involved in planning the experiments, executed a major part of the optimization reactions and major part of the scope. Additionally, I was involved in the mechanistic discussions, interpretation of results and responsible for writing part of the manuscript. My overall contribution to this work approximately accounts for 40%.

Carbonylation

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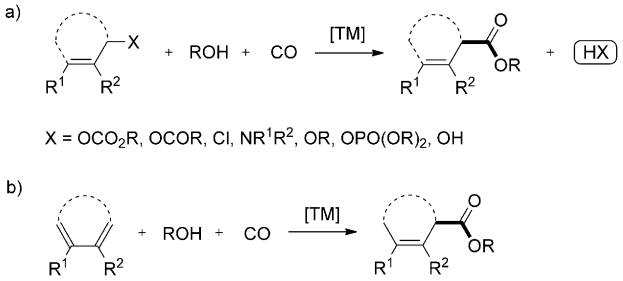
Palladium-Catalyzed Alkoxycarbonylation of Conjugated Dienes under Acid-Free Conditions: Atom-Economic Synthesis of β,γ-Unsaturated Esters**

*Xianjie Fang, Haoquan Li, Ralf Jackstell, and Matthias Beller**

Abstract: *Carbonylation reactions constitute important methodologies for the synthesis of all kinds of carboxylic acid derivatives. The development of novel and better catalysts for these transformations is of interest for both academic and industrial research. Here, a benign palladium-based catalyst system for the alkoxycarbonylation of conjugated dienes under acid-free conditions has been developed. This atom-efficient transformation provides straightforward access to a variety of β,γ-unsaturated esters in good to excellent yields and often with high selectivities. As an industrially relevant example the (formal) synthesis of dimethyl adipate and ε-caprolactam from 1,3-butadiene is demonstrated.*



Scheme 1. Synthesis of β,γ-unsaturated esters by alkoxycarbonylation reactions. TM = transition metal.

Alkene carbonylations are among the most important homogeneously catalyzed processes in industry.[1] Within this class of reactions, alkoxycarbonylations, also called hydroesterifications, represent a straightforward method for the conversion of olefins, CO, and alcohols into the corresponding esters.[2] In this respect, the transition-metal-catalyzed carbonylation of allylic compounds is of considerable interest for the synthesis of versatile β,γ-unsaturated carboxylic acid derivatives.[3] In the past, effective carbonylation methods for reactions of allylic carbonates,[4] acetates,[5] chlorides,[6] amines,[7] ethers,[8] phosphates,[5b,e,9] and alcohols[3e,6b,10] have been developed (Scheme 1a). Obviously, a general drawback of all these reactions is the stoichiometric generation of by-products. Alternatively, β,γ-unsaturated carboxylic acid derivatives can be synthesized by carbonylation of conjugated dienes (Scheme 1b). Despite the advantage of this more atom-efficient route, the carbonylation of conjugated dienes has scarcely been explored in academic laboratories. However, the selective alkoxycarbonylation of 1,3-butadiene is of major industrial interest. This substrate—produced in about 12×10^6 metric tons annually—offers the possibility to produce bulk chemicals like adipic acid and ε-caprolactam via 3-pentenoic acid esters.[11]

In the early 1940s, Reppe first reported the reaction of 1,3-butadiene to carbonylated vinylcyclohexene derivatives in the presence of $[Co_2(CO)_8]$ as a catalyst.[24] Later, Du Pont reported the methoxycarbonylation of 1,3-butadiene to methyl pentenoate by using a Co/Cu/Th catalyst at very high pressure (810 bar).[12] In the late 1960s, Tsuji et al.[13] described this reaction in the presence of a catalytic amount of palladium chloride to give ethyl 3-pentenoate. While no product yield was given in the original paper, Tsuji et al.[13b] later reported an optimized yield of approximately 30% of ethyl 3-pentenoate. Matsuda and co-workers also demonstrated the use of cobalt catalysts in the presence of pyridines for this reaction.[14] However, only low catalyst turnover numbers (25–80) were achieved and high CO pressure was needed. A systematic investigation of the palladium-catalyzed carbonylation of 1,3-dienes was done by Knifton.[15] Despite variation of different ligands and solvents, mainly 3,8-nonadienoate esters (telomerization products) were obtained. A survey of the patent literature reveals significant work on the palladium-catalyzed methoxycarbonylation of 1,3-dienes by Shell,[16] Du Pont, and DSM.[11a,17] The latter companies, as well as Rhone Poulenc[18] disclosed a positive influence of added acids or quaternary onium salts on selectivity, conversion, and stability of the palladium catalyst. In addition, a Shell patent reported that by controlling the polarity of the reaction medium higher reaction rates can be achieved.[19]

In line with our interest in industrially relevant carbonylation reactions, we performed a systematic study on the methoxycarbonylation of 1,3-butadiene.[20] Examination of the influence of different reaction parameters on product yield and selectivity demonstrated the importance of chelating phosphine ligands and benzoic acids as additives to get good results. Until today, basically all of the published catalyst systems for carbonylation of dienes suffer from drawbacks such as the need for harsh reaction conditions and/or

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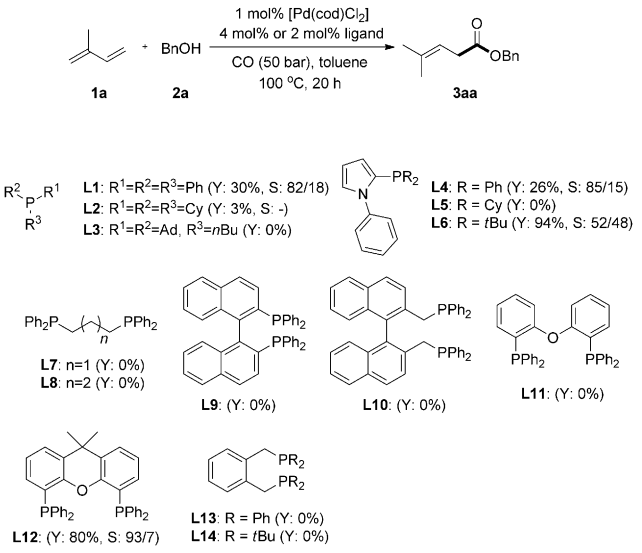
additives, for example, acids, narrow substrate scope, relatively low product yield, and limited selectivity. In this regard, the development of improved and acid-free catalyst systems for this reaction is of high importance and constitutes a challenging and relevant topic for academic and industrial research.

Herein, we present an efficient palladium-based catalyst system for the selective alkoxycarbonylation of conjugated dienes under relatively mild reaction conditions. Notably, the various mono-, di-, and tri-β,γ-unsaturated esters were obtained in high yield with good selectivity under acid-free conditions.

At the start of this study, we investigated the alkoxycarbonylation of isoprene (**1a**) and benzyl alcohol (**2a**) as a model reaction in the presence of $[Pd(cod)Cl_2]$ and different phosphine ligands (**L1**–**L14**; Scheme 2). The application of

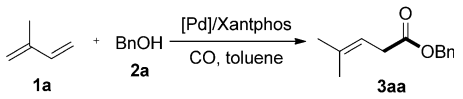


Scheme 2. Palladium-catalyzed alkoxycarbonylation of isoprene (**1a**) with benzyl alcohol (**2a**): Influence of the ligand. Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), $[Pd(cod)Cl_2]$ (1.0 mol%), monodentate Ligand (4.0 mol%), bidentate ligand (2.0 mol%), CO (50 bar), toluene (2 mL), 100°C, 20 h. Yield (Y) determined by GC analysis using isooctane as the internal standard. The ratios of isomers were determined by GC analysis. S = selectivity. Ad = adamantyl, cod = 1,5-cyclooctadiene; Cy = cyclohexyl.

the monodentate ligands **L3** and **L5**, did not lead to any conversion. Notably, using **L1**, **L2**, and **L4** provided the desired product **3aa** without acid, albeit in low yields. When commercially available cataCXium PtB **L6** was used, the desired product **3aa** was obtained in good yield, however with low selectivity. Then, commercially available bidentate ligands were tested. Interestingly, all of bidentate ligands exhibited no activity in the formation of the desired product except Xantphos (**L12**), which was identified as the most promising ligand to afford the desired product **3aa** in good yield with high selectivity.

Next, to improve the reaction, we evaluated the influence of critical reaction parameters such as the molar ratio of **1a** to **2a**, catalyst loading, palladium precursors, temperature, and gas pressure for the model reaction using Xantphos as the ligand of choice. As shown in Table 1, the yield of **3aa** was significantly affected by the molar ratio of **1a** to **2a**. Consequently, as the molar ratio of **1a** to **2a** increased to 1.2:1, the yield of **3aa** increased to 94% (entries 1 and 2). Lowering the catalyst loading revealed an optimal loading of

Table 1: Palladium-catalyzed alkoxycarbonylation of isoprene (**1a**) with benzyl alcohol (**2a**): Investigation of reaction conditions.[a]

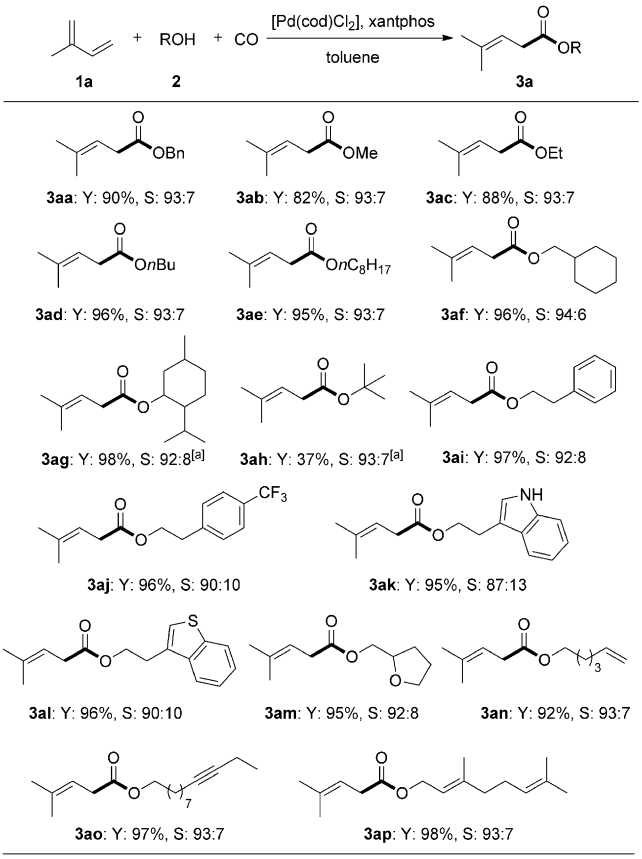


Entry	Catalyst	p_{CO} [bar]	T [°C]	Yield [%][b]	Selectivity[c]
1[d]	$[Pd(cod)Cl_2]$	50	100	80	93:7
2	$[Pd(cod)Cl_2]$	50	100	94	93:7
3[e]	$[Pd(cod)Cl_2]$	50	100	71	94:6
4	$Pd(OAc)_2$	50	100	0	–
5	$[Pd(acac)_2]$	50	100	0	–
6	$PdCl_2$	50	100	87	94:6
7	$[Pd(dba)_2]$	50	100	0	–
8	$[Pd(CH_3CN)_2Cl_2]$	50	100	91	94:6
9	$[\{Pd(cinnamyl)Cl\}_2]$	50	100	87	93:7
10	$[Pd(cod)Cl_2]$	50	80	64	97:3
11	$[Pd(cod)Cl_2]$	40	100	92	93:7
12	$[Pd(cod)Cl_2]$	20	100	80	88:12

[a] Reaction conditions: **1a** (1.2 mmol), **2a** (1.0 mmol), [Pd] (1.0 mol%), Xantphos (2.0 mol%), CO (50 bar), toluene (2 mL), 100°C, 20 h. [b] Yield determined by GC analysis using isooctane as the internal standard. [c] The ratios of isomers were determined by GC analysis. [d] **1a** (1.0 mmol). [e] [Pd] (0.5 mol%), Xantphos (1.0 mol%). acac = acetylacetonate

1 mol% of [Pd] (entry 3). Several palladium(II) and palladium(0) precursors were also investigated. Interestingly, when standard palladium precatalysts such as $Pd(OAc)_2$, $[Pd(acac)_2]$, and $[Pd(dba)_2]$ were used, no conversion was observed (entries 4, 5, and 7). However, the use of other palladium chloride precursors resulted in desired product **3aa** in 87–91% yield with high selectivity (entries 6, 8, and 9). This crucial effect of chloride ions for the successful alkoxycarbonylation is not yet completely understood. The yield of the desired ester **3aa** significantly decreased when lowering the reaction temperature (entry 10). Furthermore, lowering the CO pressure to 40 bar resulted in a similar yield and selectivity compared to 50 bar of CO, but at 20 bar CO the product yield and selectivity decreased (entries 11 and 12).

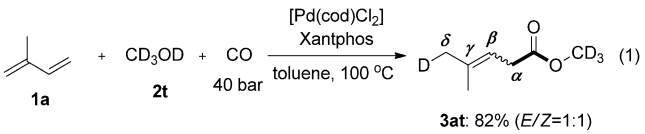
With optimized reaction conditions established (Table 1, entry 10), we examined the general scope of this acid-free alkoxycarbonylation process with respect to aliphatic alcohols (Scheme 3). A variety of substituted primary aliphatic alcohols gave the corresponding carbonylative products in excellent yields with high selectivity. Interestingly, menthol and heterocyclic alcohols proved to be efficient coupling partners and gave the corresponding esters (**3ag**, **3ak**, **3al**, and **3am**) in excellent yields with good selectivities, too. A broad range of functional groups is tolerated, including reactive alkene (**3an**), alkyne (**3ao**), and benzyl (**3aa**) groups, which provide useful handles for further synthetic



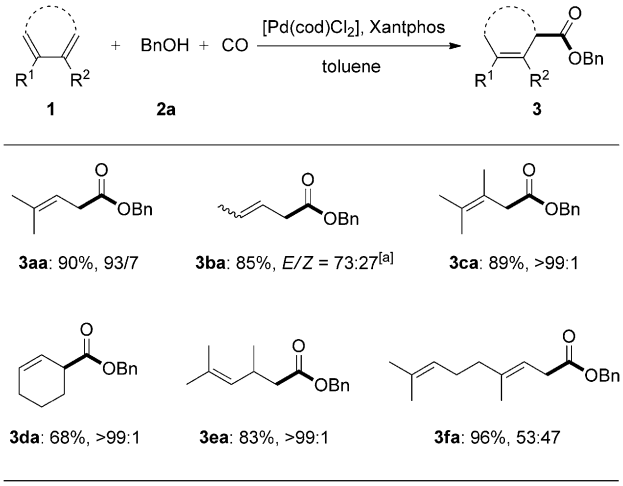
Scheme 3. Palladium-catalyzed alkoxycarbonylation of isoprene (**1a**) with aliphatic alcohols (**2**). Reaction conditions: **1a** (1.2 mmol), **2a** (1.0 mmol), [Pd(cod)Cl_2] (1.0 mol%), Xantphos (2.0 mol%), CO (40 bar), toluene (2 mL), 100°C, 20 h. Yield is that of the isolated product. The ratios of isomers were determined by GC analysis. [a] Used [Pd(cod)Cl_2] (2.5 mol%), Xantphos (5.0 mol%), 120°C.

transformations. Notably, we demonstrated the utility of our carbonylation protocol in the reaction of the allylic alcohol geraniol (**2p**), an ingredient commonly used in perfumes and flavors (**3ap**). Even tertiary alcohols underwent this transformation, although in lower yields, probably because of the increased steric effect (**3ah**).

By using the deuterated alcohol **2t** instead of MeOH, a similar yield and selectivity of the desired product was obtained under optimal reaction conditions [Eq. (1)]. Here,



the deuterium atom was found to be incorporated only at the δ-carbon atom of the product **3at**, which makes a cyclometallation mechanism more possible. However, we can exclude a selective insertion of the more sterically hindered double bond of the 1,3-diene into the Pd–D bond, which would also result in **3at**.



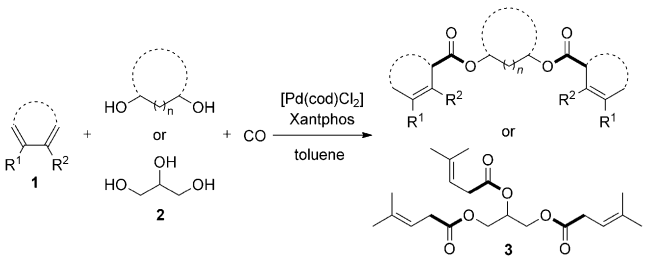
Scheme 4. Palladium-catalyzed alkoxycarbonylation of conjugated dienes (**1**) benzyl alcohol (**2a**). Reaction conditions: **1a** (1.2 mmol), **2a** (1.0 mmol), [Pd(cod)Cl_2] (1.0 mol%), Xantphos (2.0 mol%), CO (40 bar), toluene (2 mL), 100°C, 20 h. Yield is that of the isolated product. The ratios of isomers were determined by GC analysis. [a] **1b** (12 mmol), **2a** (10 mmol).

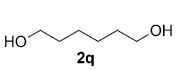
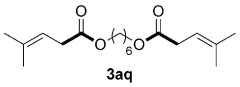
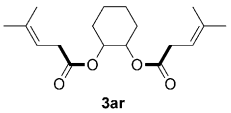
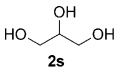
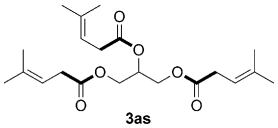
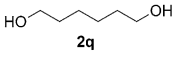
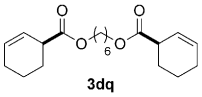
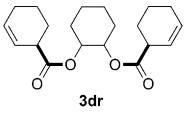
Next, we evaluated the scope of conjugated 1,3-dienes using benzyl alcohol (**2a**) as a standard coupling partner (Scheme 4). From an industrial point of view it is important that 1,3-butadiene furnish the corresponding product (**3ba**) in good yield. Furthermore, sterically crowded conjugated dienes **1c** and **1e** were smoothly transformed into the corresponding β,γ-unsaturated esters in good yields and with excellent selectivities (**3ca** and **3ea**). The cyclic conjugated diene **1d** was also efficiently transformed into the corresponding cyclic β,γ-unsaturated ester in good yield and with excellent selectivity (**3da**). Notably, the use of the renewable diene myrcene (**1f**) led to the desired functionalized β,γ-unsaturated ester in excellent yield though low selectivity (**3fa**).

Considering the importance of diesters and triesters, which are widely applied in industry as alternative plasticizers,[21] we turned our attention to this class of compounds by using diols and glycerol as coupling reagents. As shown in Table 2, the reactions of isoprene (**1a**) with the open-chain diol **2q** and cyclic diol **2r** gave the corresponding products in very good yields (entries 1 and 2). Even the triester **3as** was obtained in good yield by triple carbonylation of **1a** with glycerol **2s** (entry 3). Moreover, the cyclic diene **1d** also proved to be an efficient coupling partner for this dialkoxycarbonylation reaction and smoothly transformed into corresponding diesters in good yields (entries 4 and 5).

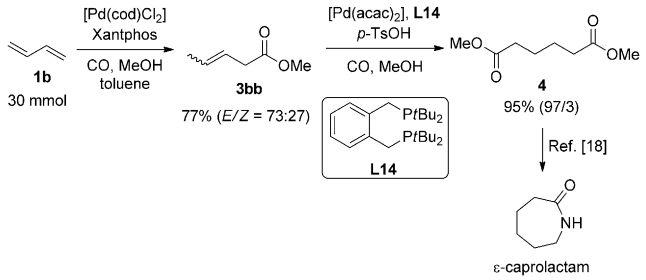
Finally, we were interested in demonstrating the usefulness of our procedure for the synthesis of adipic acid esters and caprolactam. Hence, the synthesis of **3bb** was scaled up to 30 mmol of 1,3-butadiene (**1b**; Scheme 5). Indeed, 77% yield of the corresponding β,γ-unsaturated ester was obtained. Subsequent transformation of **3bb** gave dimethyl adipate (**4**) in high yield with excellent regioselectivity.[22] It should be noted that this sequence also allows a straightforward prep-

Table 2: Palladium-catalyzed di-and trialkoxycarbonylation of 1,3-dienes (**1**) with diols and glycerol (**2**).[a]



Entry	1	2	3	Yield [%]
1	1a	 2q	 3aq	95
2[b]	1a	 2r	 3ar	98
3[c]	1a	 2s	 3as	81
4[d]	1d	 2q	 3dq	93
5[b]	1d	 2r	 3dr	77

[a] Reaction conditions: **1a** (2.4 mmol), **2a** (1.0 mmol), [Pd(cod)Cl_2] (1.0 mol%), Xantphos (2.0 mol%), CO (40 bar), toluene (2 mL), 100°C, 20 h. Yield is that of isolated product. The ratios of isomers were determined by GC analysis. [b] [Pd(cod)Cl_2] (5.0 mol%), Xantphos (10.0 mol%), 120°C. [c] **1a** (3.6 mmol), [Pd(cod)Cl_2] (5.0 mol%), Xantphos (10.0 mol%), 120°C. [d] Reaction temperature: 120°C.



Scheme 5. Straightforward synthesis of dimethyl adipate (**4**) and ε-caprolactam from 1,3-butadiene (**1b**). Ts = 4-toluenesulfonyl.

aration of ε-caprolactam, which is primarily used in the production of nylon 6 fibers and resins.[23]

In summary, we developed a novel protocol for the palladium-catalyzed alkoxycarbonylation of conjugated 1,3-dienes to produce a variety of synthetically useful β,γ-unsaturated esters in good yields with often high selectivity. Compared to previously known procedures the substrate scope is enhanced and no additives such as acids, which might cause corrosion problems are needed. Furthermore, we reported the first catalytic di- and trialkoxycarbonylations of 1,3-dienes utilizing easily accessible diols and glycerol. These products are of interest as alternative plasticizers. Combining the presented procedure with established carbonylation reactions allows an efficient preparation of adipates and ε-caprolactam. We believe these procedures will inspire chemists to use carbonylation reactions more frequently in organic synthesis.

Experimental Section

Typical procedure for the preparation of **3:** A vial (4 mL) was charged with [Pd(cod)Cl_2] (2.85 mg, 1 mol%), Xantphos (11.6 mg, 2 mol%), and a stirring bar was added. Then, toluene (2 mL), the conjugated diene **1** (1.2 mmol) and alcohol **2** (1 mmol) were injected by syringe. The vial was placed in an alloy plate, which was transferred into an autoclave (300 mL) of the 4560 series from Parr Instruments under argon atmosphere. At room temperature, the autoclave was flushed with CO three times, pressurized with CO to 40 bar, and finally the pressure was increased to 90 bar by adding nitrogen. The reaction was performed for 20 h at 100°C. After the reaction finished, the autoclave was cooled to room temperature and the pressure was carefully released and isooctane (150 μL) (internal standard) was added to the solution. The yield and selectivity were measured by GC analysis. After removing the solvent by vacuum, the residue was directly purified by flash chromatography on silica gel (eluent: heptane/ethyl acetate = 20:1) to give the desired product **3**.

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8.6 Selective Palladium-Catalyzed Aminocarbonylation of 1,3-Dienes: Atom-Efficient Synthesis of β,γ-Unsaturated Amides

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†: These authors contributed equally to the work.

Contributions

In this publication, I was involved in planning the experiments, executed a major part of the optimization reactions and major part of the scope. Moreover, I discovered the synthetic application in heterocycle synthesis. Additionally, I was involved in the mechanistic discussions, interpretation of results and responsible for writing part of the corresponding manuscript. My overall contribution to this work approximately accounts for 40%.

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Selective Palladium-Catalyzed Aminocarbonylation of 1,3-Dienes: Atom-Efficient Synthesis of β,γ-Unsaturated Amides

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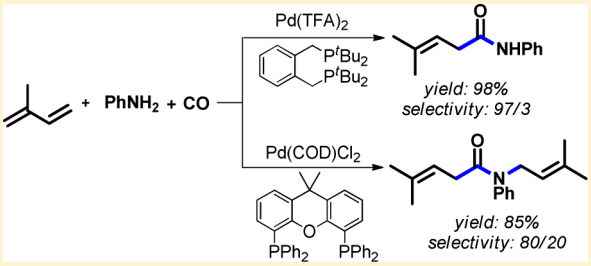
Supporting Information

ABSTRACT: Carbonylation reactions constitute important methodologies for the synthesis of all kinds of carboxylic acid derivatives. The development of novel and efficient catalysts for these transformations is of interest for both academic and industrial research. Here, the first palladium-based catalyst system for the aminocarbonylation of 1,3-dienes is described. This atom-efficient transformation proceeds under additive-free conditions and provides straightforward access to a variety of β,γ-unsaturated amides in good to excellent yields, often with high selectivities.



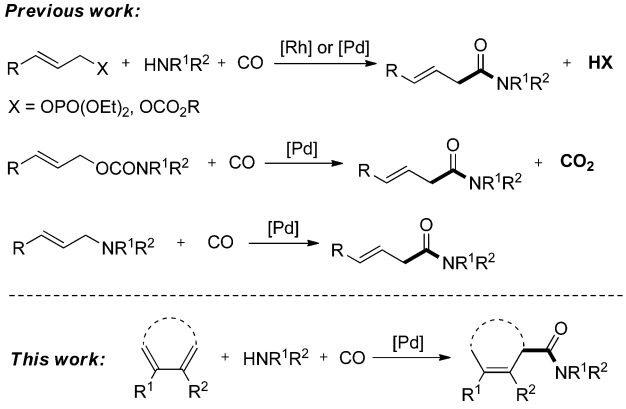
INTRODUCTION

The atom-economic synthesis of amides continues to be one of the major challenges in synthetic organic chemistry.[1] The amide bond is the key backbone of all natural peptides in biological systems and is also an important functional group in organic building blocks and industrial chemicals.[2] Traditionally, amides are synthesized by reactions of carboxylic acids and their derivatives with amines,[3] which suffers from harsh conditions. In addition, large amounts of side products are often produced. In this respect, the development of more efficient catalytic methodologies is still highly important. For example, in recent years, the palladium-catalyzed aminocarbonylation of aryl halides,[4] alkynes,[5] and alkenes[6] has become a powerful tool for the synthesis of aromatic amides, α,β-unsaturated amides, and aliphatic amides, respectively.

On the basis of our long-standing interest in transition-metal-catalyzed carbonylation reactions,[4a] we recently became interested in the carbonylation of allyl derivatives to give the corresponding homoallylic compounds, which are synthetically important but not easily accessible.[7] In the past, effective carbonylation methods for the reaction of allylic carbonates,[8] acetates,[9] chlorides,[10] amines,[11] ethers,[12] phosphates,[9b,e,13] and alcohols[14] to form β,γ-unsaturated esters have been developed. However, there are few examples known that allow the synthesis of related β,γ-unsaturated amides via carbonylation (Scheme 1).[8a,11,15]

A major problem for any aminocarbonylation methodology is the competing direct amination of the substrate. In fact, such aminations of allyl-X compounds should proceed faster than carbonylations. Moreover, a general drawback of these reactions is the stoichiometric generation of byproducts (e.g., salts). Alternatively, β,γ-unsaturated carboxylic acid derivatives might also be synthesized by carbonylation of 1,3-dienes. Despite the inherent advantage of this atom-economic green route (100% atom-efficient route), the carbonylation of 1,3-dienes has scarcely been explored in academic laboratories.[16] Compared to the well-studied alkoxycarbonylation of 1,3-dienes,[17] to the best of our knowledge comparable aminocarbonylation reactions to β,γ-unsaturated amides have not yet been reported (Scheme 1).

Scheme 1. Synthesis of β,γ-Unsaturated Amides via Carbonylation Reactions



On the basis of our previous work on the direct hydroamination of 1,3-dienes,[18] herein we describe the first general catalyst system for the direct aminocarbonylation of 1,3-dienes. Applying a variety of aromatic amines leads to β,γ-unsaturated amides in good yields and selectivities under neutral conditions.

RESULTS AND DISCUSSION

Initially, we investigated the aminocarbonylation of isoprene (**1a**) with aniline (**2a**) as a model reaction in the presence of [Pd(COD)Cl$_2$] and different phosphine ligands **L1**−**L15** (Scheme 2). In general, we observed two kinds of carbonylated products: the 1:1 adduct **3aa** and the 2:1 adduct **4aa**. In both cases, different regioisomers can be formed. Notably, a preferential

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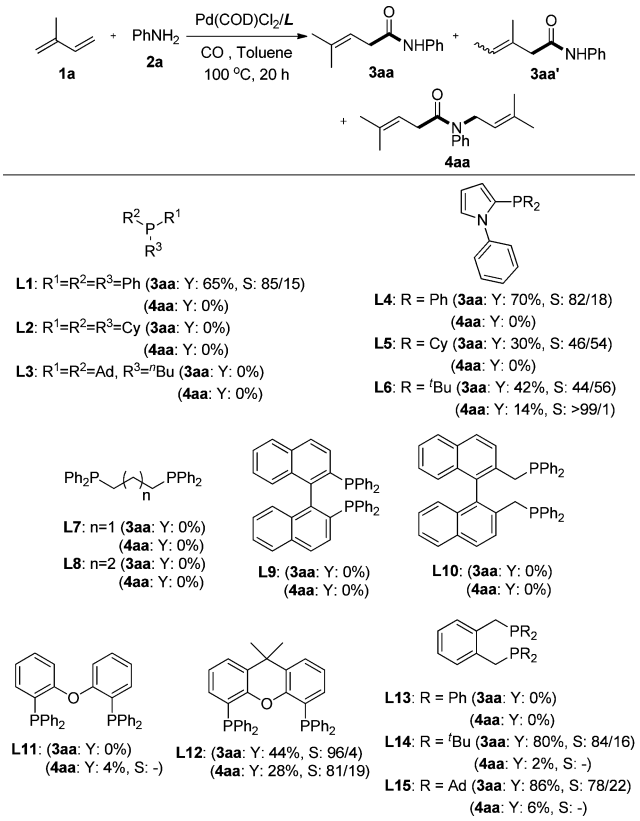
Scheme 2. Influence of the Ligand on the Palladium-Catalyzed Aminocarbonylation of Isoprene (1a) with Aniline (2a)[a]

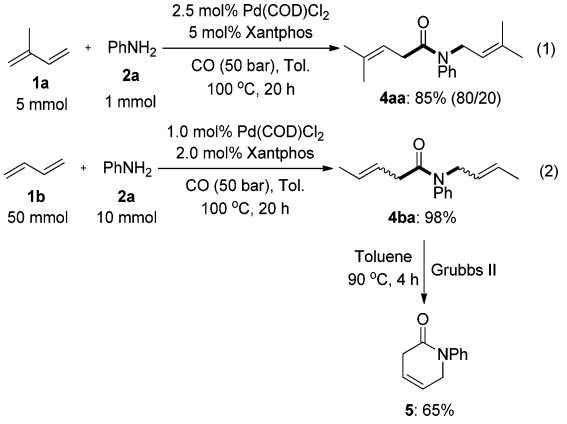


[a]Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), [Pd(COD)Cl_2] (2.5 mol %), monodentate ligand (10.0 mol %), bidentate ligand (5.0 mol %), CO (50 bar), toluene (2 mL), 100 °C, 20 h; yield and the ratios of isomers were determined by GC analysis. Y, yield; S, **3aa**/**3aa**′ ratio.

attack at the sterically less hindered position is observed. Nevertheless, minor amounts of **3aa**′ are also formed (for details, see Supporting Information).

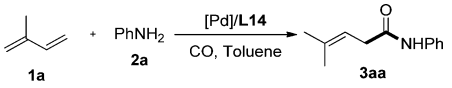
Unfortunately, the application of monodentate ligands **L2** and **L3** gave none of the desired product **3aa**. However, to our delight, **L1** and cataCXium ligands[19] **L4**–**L6** provided desired product **3aa** in moderate to good yield. Further investigations showed that selected commercially available bidentate ligands **L7**–**L11** exhibited no activity in the formation of **3aa**. However, when Xantphos (**L12**) was used, desired product **3aa** is obtained in 44% yield. In addition, significant amounts of the 2:1 adduct **4aa** are formed (yield, 28%). Next, some 1,2-bis-(phosphinomethyl)benzene ligands with different steric properties were tested, **L13**–**L15**. BuPox[20] (**L14**) was identified as the most promising ligand, and the reaction afforded desired product **3aa** in 80% yield with good selectivity.

In the presence of Xantphos (**L12**) as ligand, significant amounts of the 2:1 adduct **4aa** were obtained. Apparently, the yield of **4aa** is strongly affected by the molar ratio of **1a** to **2a**. Indeed, as the molar ratio of **1a** to **2a** increased to 5:1, the isolated yield of **4aa** increased to 85% (eq 1). From an industrial point of view, it is interesting that 1,3-butadiene (**1b**) furnished the corresponding product **4ba** in excellent yield at low catalyst loading (eq 2). Considering the 1,7-diene structural motif, product **4** provides the possibility of further transformations. Indeed, ring-closing metathesis of **4ba** occurred smoothly using Grubbs II catalyst to give 1-phenyl-1,6-dihydropyridin-2(3*H*)-one **5** in 65% yield (eq 2).



In order to improve the methodology further, we evaluated the influence of critical reaction parameters (e.g., palladium precursor, catalyst loading, temperature, CO pressure) for the model reaction using **L14** as the ligand of choice. As shown in Table 1, using typical palladium precursors such as Pd(OAc)$_2$,

Table 1. Investigation of Reaction Conditions for Palladium-Catalyzed Aminocarbonylation of Isoprene (1a) with Aniline (2a)[a]



entry	[Pd]	temp. (°C)	yield (%)[b]	sel.[c]
1	Pd(COD)Cl_2	100	80	84:16
2	Pd(OAc)$_2$	100	0	
3	Pd(acac)$_2$	100	0	
4	$PdCl_2$	100	89	84:16
5[d]	$PdCl_2$	100	19	>99:1
6	Pd(dba)$_2$	100	0	
7[e]	Pd(dba)$_2$	100	89	92:8
8[f]	Pd(dba)$_2$	100	0	
9[g]	Pd(dba)$_2$	100	0	
10[h]	Pd(dba)$_2$	100	61	94:6
11[i]	Pd(dba)$_2$	100	77	95:5
12	Pd(CH_3CN)$_2Cl_2$	100	84	87:13
13	Pd($PhCN$)$_2Cl_2$	100	70	88:12
14	[Pd(cinnamyl)Cl]$_2$	100	87	93:7
15	[Pd(allyl)Cl]$_2$	100	64	94:6
16	Pd(TFA)$_2$	100	>99	88:12
17[j]	Pd(TFA)$_2$	100	57	92:8
18[k]	Pd(TFA)$_2$	100	78	91:9
19[l]	Pd(TFA)$_2$	100	95	88:12
20[m]	Pd(TFA)$_2$	100	78	88:12
21	Pd(TFA)$_2$	80	>99	95:5
22	**Pd(TFA)$_2$**	**60**	**>99**	**97:3**
23	Pd(TFA)$_2$	40	79	>99:1

[a]Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), [Pd] (2.5 mol %), **L14** (5.0 mol %), toluene (2 mL), CO (50 bar), 20 h. [b]Yield determined by GC analysis. [c]Sel. = **3aa**/**3aa**′ ratio; the ratio of isomers was determined by GC analysis. [d]3 Å molecular sieve (200 mg). [e]TFA (10 mol %). [f]HOAc (10 mol %). [g]H_3PO_4 (10 mol %). [h]Camphorsulfonic acid (10 mol %). [i]*p*-TsOH·H_2O (10 mol %). [j][Pd] (1.5 mol %), **L14** (3.0 mol %). [k][Pd] (1.5 mol %), **L14** (3.0 mol %), TFA (10 mol %). [l]CO (40 bar). [m]CO (20 bar).

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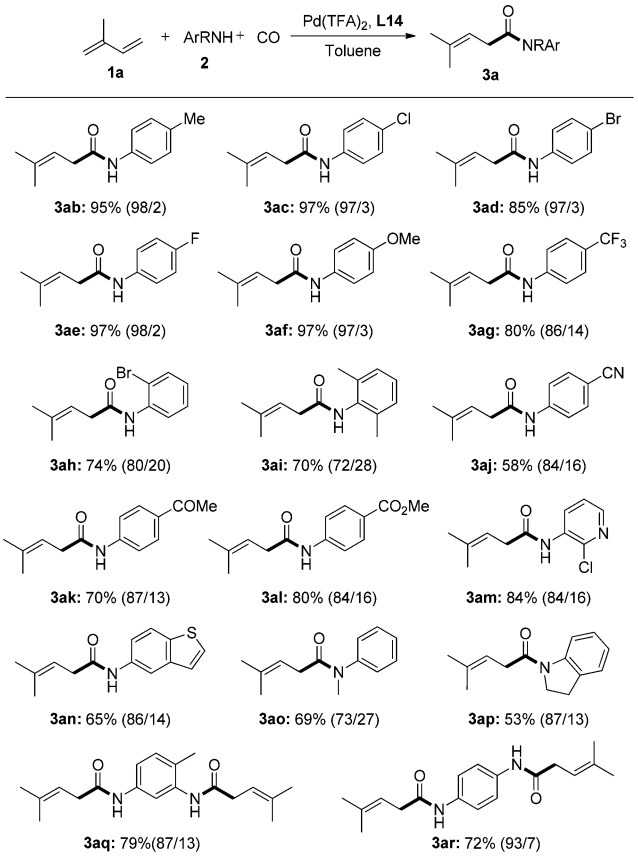
$Pd(acac)_2$, and $Pd(dba)_2$ under the standard reaction conditions, no conversion was observed (Table 1, entries 2, 3, and 6). However, using $Pd(dba)_2$ in the presence of 10 mol % of either trifluoroacetic acid, camphersulfonic acid, or *p*-toluenesulfonic acid gave the desired product in 61−89% yield (Table 1, entries 7, 10, and 11). Notably, the use of weaker acids such as acetic acid and phosphoric acid gave no product (Table 1, entries 8 and 9). Apparently, a strong acid is required to generate the catalytically active palladium species (see mechanistic discussion below). Interestingly, the addition of molecular sieves impedes the reaction, and the product yield is decreased from 89 to only 19% (Table 1, entries 4 and 5). Without molecular sieves, the use of other palladium chloride precursors resulted in the formation of desired product **3aa** in 64−89% yield with good selectivity (Table 1, entries 1, 4, and 12−15). To our delight, quantitative GC yield of desired amide **3aa** was obtained when $Pd(TFA)_2$ was used as the catalyst precursor (Table 1, entry 16). Lowering the catalyst loading revealed an optimal loading of 2.5 mol % of [Pd] (Table 1, entry 17). However, at low catalyst loading, the addition of trifluoroacetic acid also improved the conversion and restored the catalyst activity (Table 1, entry 18). The yield of desired amide **3aa** decreased when lowering the CO pressure (Table 1, entries 19 and 20). Interestingly, lowering the reaction temperature to 80 or 60 °C also resulted in full conversion and excellent chemo- and regioselectivity. Here, the regioselectivity for **3aa** increased to 97:3 (Table 1, entries 21 and 22).

With optimized reaction conditions established (Table 1, entry 22), we examined the scope of this novel aminocarbonylation process with respect to amines (Scheme 3). A variety of aromatic amines with electron-neutral, electron-deficient, and electron-rich substituents led to the corresponding carbonylative products in good yields and selectivities. Functional groups including reactive halide (**3ad** and **3ah**), nitrile (**3aj**), ketone (**3ak**), and ester (**3al**) groups, which provide useful handles for further synthetic transformations, are well-tolerated. **2i**, as an example of a bulky substrate, was smoothly transformed to the corresponding *β,γ*-unsaturated amide (**3ai**) in good yield. Interestingly, heteroaromatic amines (**3am** and **3an**) proved to be efficient coupling partners and gave the corresponding amides in decent yields with good selectivities. Even secondary aromatic amines (**2o** and **2p**) underwent this transformation and afforded the desired products in moderate to good yields (**3ao** and **3ap**). Considering the importance of diamides, which are widely applied for agrochemicals and used in the polymer industry, we tested the dicarbonylation of phenylenediamines. As shown in Scheme 3, the reactions of isoprene **1a** with *m*-phenylenediamine **2q** and *p*-phenylenediamine **2r** gave the desired diamides, again in good yields and selectivities (**3aq** and **3ar**). Unfortunately, no conversion at all was observed when benzylic amine or *n*-butylamine was used as coupling partner. Apparently, in the presence of these more basic amines, the catalyst activity disappeared.

Next, we evaluated the scope of 1,3-dienes using aniline **2a** as a standard coupling partner (Table 2). Phenyl-substituted 1,3-diene **1c** furnished the corresponding desired product in high yield with excellent regioselectivity, albeit in low stereoselectivity (Table 2, entry 2). Furthermore, sterically crowded 1,3-diene **1d** was smoothly transformed to the corresponding *β,γ*-unsaturated amide with excellent selectivity (Table 2, entry 3). The cyclic 1,3-diene **1e** was also efficiently transformed to the desired *β,γ*-unsaturated amide (Table 2, entry 4). From a synthetic point of view, the synthesis of functionalized *β,γ*-unsaturated amides from functionalized 1,3-dienes is important, which is reflected in products **3fa** and **3ga**, which are obtained

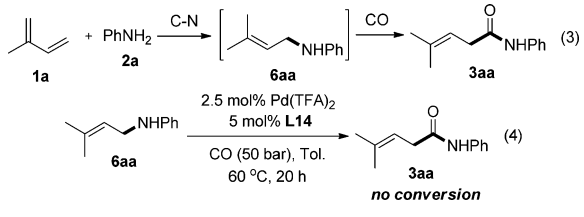
Scheme 3. Palladium-Catalyzed Aminocarbonylation of Isoprene (1a) with Aromatic Amines (2)[a]



[a]Reaction conditions: **1a** (1.0 mmol), **2** (1.0 mmol), [$Pd(TFA)_2$] (2.5 mol %), **L14** (5.0 mol %), CO (50 bar), toluene (2 mL), (**3ab**−**3ae**: 60 °C; **3af** and **3am**: 80 °C; others: 100 °C), 20 h; isolated yield; the ratio of isomers was determined by GC analysis; in the cases of **3aq** and **3ar**, a slight excess of **1a** (2.1 mmol) was used.

in a straightforward manner using our protocol (Table 2, entries 5 and 6).

On the basis of previous work on carbonylation of allylic amines[15] and alkoxycarbonylation of allylic alcohols,[14f] we initially thought that this transformation proceeds via a sequential C−N coupling/carbonylation reactions (eq 3). However, the corresponding allylamine **6aa** was not observed in the reaction mixture. In agreement with this observation, no carbonylation of the synthesized allylamine **6aa** took place under the standard conditions (eq 4). Hence, a sequential C−N coupling/carbonylation pathway seems unlikely in the present reaction process. Although the detailed mechanism of the palladium-catalyzed aminocarbonylation of 1,3-dienes is not clear, we suggest the following catalytic cycle based on our preliminary observations[17q] and previous work on aminocarbonylation of olefins[6fg] (Scheme 4).



Initially, the catalytic cycle should start from the cationic palladium hydride species **A**. Formation of **A** proceeds in situ

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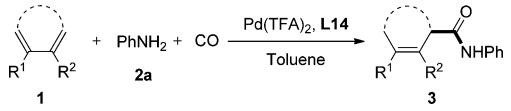
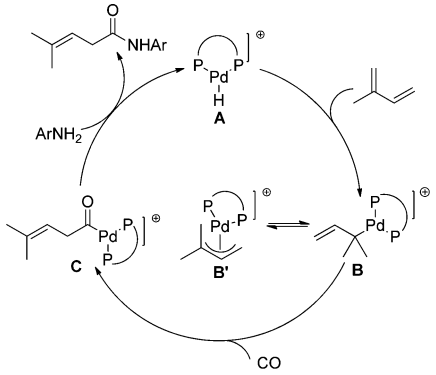
Table 2. Palladium-Catalyzed Aminocarbonylation of 1,3-Dienes (1) with Aniline (2a)[a]



Entry	1	3	Yield (selectivity)
1	1a	3aa	3aa: 98% (97/3)
2	1c	3ca	3ca: 74% (*E*/*Z*: 46/54)
3[b]	1d	3da	3da: 60%
4[c]	1e	3ea	3ea: 60%
5	1f	3fa	3fa: 83% (*E*/*Z*: 44/56)
6	1g	3ga	3ga: 72% (*E*/*Z*: 73/27)

[a]Reaction conditions: **1** (1.0 mmol), **2a** (1.0 mmol), [Pd(TFA)$_2$] (2.5 mol %), **L14** (5.0 mol %), CO (50 bar), toluene (2 mL), 60 °C, 20 h; isolated yield; the ratio of isomers was determined by GC analysis. [b]**1d** (2.0 mmol), 100 °C. [c]**1e** (5.0 mmol), [Pd(COD)Cl$_2$] (2.5 mol %), **L12** (5.0 mol %), 100 °C.

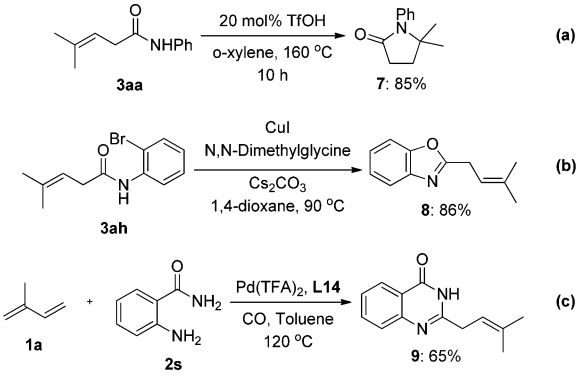
Scheme 4. Proposed Catalytic Cycle



by reaction of palladium(II) trifluoroacetate and aniline in the presence of the ligand. Notably, no formation of the corresponding hydride is observed at room temperature. However, heating this mixture at 60 °C for 6 h led to the formation of the respective hydride (for details, see the Supporting Information). In agreement with previous investigations on 1,3-diene amination, insertion of isoprene into the H-palladium bond of the active cationic palladium hydride species **A** will lead to π-allyl-Pd complex **B**′.[18a,b] Then, CO addition and insertion to give the corresponding acyl palladium complex **C** takes place. Finally, aminolysis of intermediate **C** leads to the desired product and regenerates the palladium hydride species **A**. With respect to the formation of the active catalyst, it should be noted that catalysis does not proceed at room temperature.

Finally, it should be noted that this novel procedure for the preparation of all kinds of β,γ-unsaturated amides also provides convenient access to important heterocyclic compounds. For example, intramolecular hydroamination of **3aa** occurred smoothly under acidic conditions to give γ-lactam **7** in good yield (Scheme 5a). In addition, substituted benzoxazoles are

Scheme 5. Synthetic Applications



easily available. This is exemplified by the reaction of **3ah** to **8** via a Cu-catalyzed C−O coupling reaction[21] (Scheme 5b). Interestingly, 2-allyl quinazolinone **9** was directly produced using 2-aminobenzamide **2s** as the coupling partner. This one-pot transformation proceeds by a sequential aminocarbonylation/condensation pathway (Scheme 5c).

CONCLUSIONS

In summary, we developed the first general aminocarbonylation reactions of 1,3-dienes. In the presence of different palladium phosphine complexes, carbonylation (1:1 adduct) or a selective hydroamination−carbonylation sequence (2:1 adduct) was observed. Using different aromatic amines, a variety of synthetically useful β,γ-unsaturated amides are produced in good to excellent yields. Combining this procedure with established functionalizations allows for an efficient preparation of various heterocyclic compounds. The high atom economy and additive-free reaction conditions make this protocol attractive for synthetic applications, and we believe it will complement the current methodologies for carbonylations in organic synthesis.

ASSOCIATED CONTENT

Supporting Information

Experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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8.7 Cascade synthesis of quinazolinones from 2-aminobenzonitriles and aryl bromides *via* palladium-catalyzed carbonylation reaction

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Green Chemistry, 2014, 16, 1336-1343.

Contributions

In this paper, I discovered the tandem reaction, planned and executed the optimization of the model system and also developed the substrate scope. I also wrote the major part of the corresponding manuscript, thus my overall contribution to this work approximately accounts for 70%.

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Cascade synthesis of quinazolinones from 2-aminobenzonitriles and aryl bromides *via* palladium-catalyzed carbonylation reaction†

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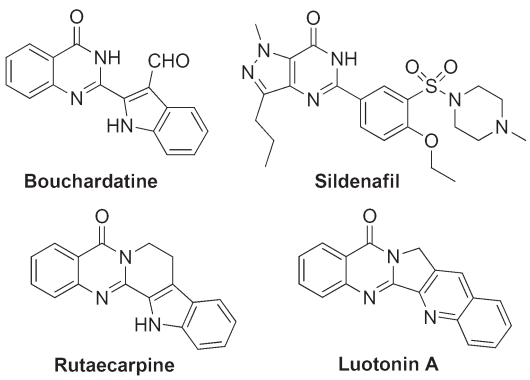
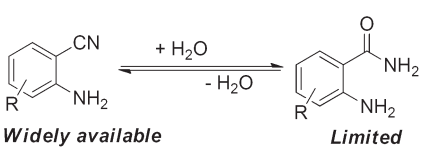
A cascade synthesis of quinazolinones from 2-aminobenzonitriles and aryl bromides through a palladium-catalyzed carbonylation reaction has been developed. Various quinazolinones were produced in moderate to excellent yields. The reactions go through aminocarbonylation of aryl bromides–hydration of nitriles–cyclization sequence. Notably, all the products were isolated by recrystallization.

Under the requests of sustainable development and green chemistry, cascade reactions have reached a pivotal role in organic synthesis.[1] Performing multiple reactions simultaneously in a single reaction vessel offers the opportunity of building up complex molecules from simple and easily available substrates with exceptional synthetic efficiency. In this sense, it is not a surprise that many valuable heterocyclic compounds are the products of cascade reactions. Among them, 2-aryl quinazolin-4(3*H*)-ones (quinazolinones) are an important class of fused heterocycles with an array of biological activities such as inhibition of human erythrocyte purine nucleoside anticancer, antiviral, anti-inflammatory, anti-microbial activity, *etc.* (Scheme 1).[2] Additionally, the applications of quinazolinones as ligands for benzodiazepine and AMPA receptors in the CNS system or as DNA binders were reported as well.[3]



Scheme 1 Selected examples of bio-active quinazolinones.

Based on the mentioned remarkable importance of quinazolinones, many useful synthetic procedures have been developed for their preparation.[4,5] Among all the reported methodologies, the reactions of 2-aminobenzamide with benzyl alcohols, acyl chlorides or their analogues are the typical approaches. But the limited commercial availability of 2-aminobenzamide derivatives limited their product diversity and further prevented the applications of these procedures. Alternatively, an interesting palladium-catalyzed intramolecular oxidative carbonylation of *N*-arylamidines was reported by Zhu and co-workers.[5p] The reactions were carried out in acetic acid, under one bar of CO together with one equivalent of CuO, various quinazolinones were produced from *N*-arylamidines in good yields. Recently, Willis and co-workers developed a novel palladium-catalyzed carbonylative cyclization of *N*-(*o*-halophenyl)imidates with amines.[5q] Under atmospheric pressure of CO, 2,3-disubstituted quinazolinones were produced in good to excellent yields. The preparation of quinazoline derivatives from 2-iodoanilines and five-membered lactams or *N*-acyl-*o*-iodoanilines was developed as well.[5r] More recently, our group described a palladium-catalyzed carbonylative synthesis of quinazolinones from aryl bromides and 2-aminobenzamide.[5s] Unfortunately, the variation of the 2-aminobenzamide part was still very limited. From a synthetic point of view, a methodology with widely available substrates as starting materials is more attractive and necessary (Scheme 2).



Scheme 2 Functional group transformations.[6]

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†Electronic supplementary information (ESI) available. See DOI: 10.1039/c3gc42089b

As an appealing alternative to 2-aminobenzamide, 2-aminobenzonitrile derivatives are broadly available.[6] It will be interesting if these compounds can be applied as substrates in quinazolinones synthesis *via in situ* hydration of the nitrile group.[7] Here, the challenges are obviously: (1) the competition reaction between low nucleophilicity and steric hindered amines and water with the acylpalladium intermediate; (2) the difficulty in hydration of 2-aminobenzonitriles; (3) the hydroxylation of aryl halides with water in the presence of base and palladium catalyst. On the other hand, one prominent potential advantage of this methodology is the easy installation of ^{18}O labelling in quinazolinones by using $H_2{}^{18}O$ instead of H_2O, as quinazolinones are biologically active molecules and ^{18}O labelled analogues are even more important in medical study.

Additionally, palladium-catalyzed carbonylation reactions have already become a powerful toolbox in modern organic synthesis.[8,9] By carbonylation reactions, carbonyl containing compounds can be easily prepared by introducing one or even more CO units (one of the cheapest *C*1 sources) inside, the carbon chain of the parent molecules can be easily prolonged and readied for further modifications while carbonylated compounds hold their own important applications in organic synthesis and advanced materials. If ^{13}CO was applied, ^{13}C labelled products can be easily prepared.[10] Due to the documented advantages of carbonylation reactions and the importance of heterocycles, it is interesting to apply carbonylations in heterocyclic compound preparation. Following this idea, we succeeded in preparation of furanones, benzoxazinones, flavones and a number of other heterocycles by carbonylation reactions.[11] As our on-going curiosity in this area, we wish to report here a convenient procedure for the synthesis of quinazolinones from readily available 2-aminobenzonitriles and aryl bromides. Various quinazolinones were produced in good yields using K_2CO_3 as an inexpensive base in aqueous solution under the assistance of a palladium catalyst.

The first set of reactions was carried out with the testing of bases. Six different types of bases were investigated with bromobenzene (1.1 mmol), 2-aminobenzonitrile (1 mmol), Pd(OAc)$_2$ (2 mol%), BuPAd$_2$ (6 mol%), in DMSO–H_2O (v/v = 1 : 1; 2 mL), under 10 bar of CO, at 120 °C. No desired product was formed with DiPEA (2.5 mmol; diisopropylethylamine), DBU (2.5 mmol; 1,8-diazabicycloundec-7-ene), and NEt_3 (2.5 mmol) as the base. Only *N*-(2-cyanophenyl)benzamide as the intermediate was formed. To our delight, 85% of 2-phenyl quinazolin-4(3*H*)-one was isolated with total conversion of substrate when 2.5 mmol of K_2CO_3 was used as the base, while decreased yield was observed when K_3PO_4 or Na_2CO_3 was applied.[7q] Then attempts in solvent replacment were carried out. DMF, dioxane, and MeCN with water and also pure water were tested as the reaction media, the conversion cannot be completed in all the cases. Afterwards, we used DMSO–H_2O (v/v = 1 : 1; 2 mL) and K_2CO_3 to check ligands. DPPP [1,3-bis(diphenylphosphino)propane], DPPB [1,4-bis(diphenylphosphino)butane], or PPh_3 all resulted in decreased yields. The attempts of decreasing temperature (100 °C) or CO pressure (5 bar) were not successful either. *N*-(2-Cyanophenyl)benzamide was observed in all the above mentioned cases.

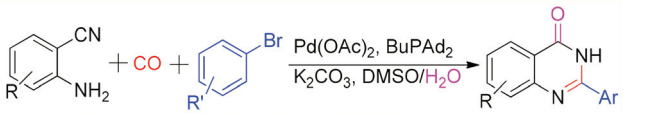
With the best reaction conditions in hand [Pd(OAc)$_2$ (2 mol%), BuPAd$_2$ (6 mol%), K_2CO_3 (2.5 mmol), DMSO–H_2O (v/v = 1 : 1; 2 mL), CO (10 bar), 120 °C, 16 h], the generality testing of this convenient methodology was subsequently carried out (Tables 1 and 2).

As shown in Table 1, substituents on 2-aminobenzonitriles were studied in the first stage. Methyl-, methoxy-, fluoro-, chloro-substituted quinazolinones were produced in good yields from their parent substrates under identical conditions (55–87%). Unfortunately, only around 10% of the desired product was isolated in the case of 2-amino-5-nitrobenzonitrile with bromobenzene. The main reason for this result is the reduction of the nitro functional group and then side reactions were induced.

A number of aryl bromides with various functional groups were tested subsequently. Methyl-, methoxy-, *tert*-butyl-, methylsulfanyl-, and *N*,*N*-dimethylamino- as typical electron-donating functional groups were checked at the beginning, and the corresponding quinazolinones were produced in 74–91% yields (Table 2, entries 1–6). 1-Bromonaphthalene can be applied as a substrate as well and gave the corresponding 2-(naphthalen-1-yl)quinazolin-4(3*H*)-one in 74% isolated yield, while 2-bromonaphthalene gave 78% of the corresponding quinazolinone (Table 2, entries 7 and 8). Electron-withdrawing substituted bromoarenes are challenging substrates in carbonylative coupling reactions, additionally, fluoro- or trifluoromethyl-substituted compounds are important as well.[12] Four interesting examples of activated bromoarenes were applied under our standard conditions. To our delight, 61–73% of the desired products were isolated without further optimization (Table 2, entries 9–12). Remarkably, two representative examples of heteroaryl bromides were successfully applied in this transformation as well (Table 2, entries 13 and 14), as 61–71% of the desired quinazolinones were produced. 2-Chloro-6-methoxypyridine as an example that shows chloroheteroarenes can be transformed under identical conditions and give 30% of the desired product (Table 2, entry 15). The yield can be improved slightly by decreasing the temperature to 100 °C. However, in the case of strongly activated organohalides, such as 2-chloropyrimidine or 2-chloropyridine, no desired product can be isolated, as the substrates reacted much faster with water in the presence of base.

A most possible reaction mechanism has been proposed in Scheme 3. The reaction started with the reduction of Pd(II) to Pd(0), then followed by the oxidative addition of bromobenzene to Pd(0) and give the organopalladium species. After the coordination and insertion of CO, the key intermediate acylpalladium complex was formed. *N*-(2-Cyanophenyl)benzamide was eliminated after nucleophilic attack of 2-aminobenzonitrile to the acylpalladium complex. Pd(0) can be regenerated under the assistance of base, ready for the next catalytic cycle. In the presence of water and base, *N*-(2-cyanophenyl)benzamide was hydrolysed into the corresponding *N*-(2-carbamoylphenyl)benzamide which goes to the terminal quinazolinone

Table 1 Palladium-catalyzed carbonylative synthesis of quinazolinones with 2-aminobenzonitriles[a]



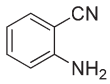
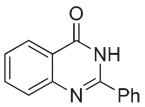
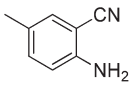
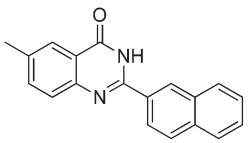
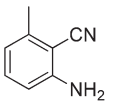
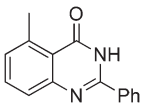
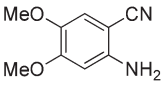
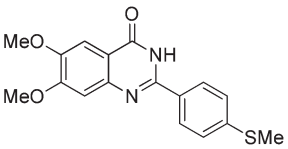
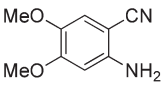
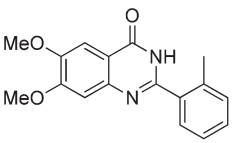
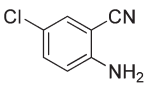
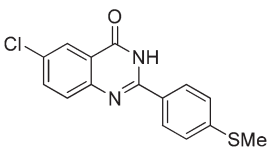
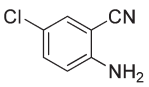
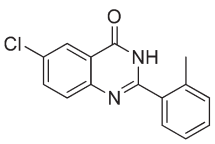
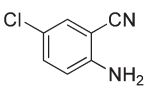
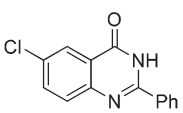
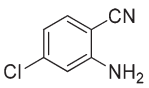
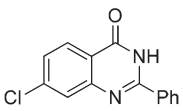
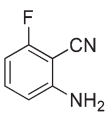
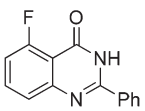
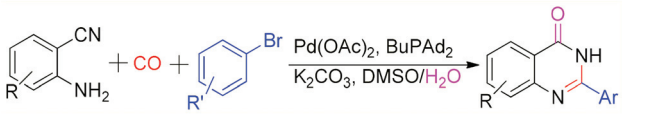
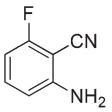
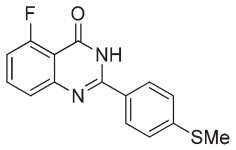
Entry	Aryl bromides	Product	Yield[b]
1			85%
2			70%
3			75%
4			73%
5			75%
6			87%
7			86%
8			80%
9			55%
10			81%

Table 1 *(Contd.)*



Entry	Aryl bromides	Product	Yield[b]
11			82%

[a] Aryl bromide (1.1 mmol), 2-aminobenzonitriles (1.0 mmol), $Pd(OAc)_2$ (2 mol%), $BuPAd_2$ (6 mol%), DMSO (1 mL), H_2O (1 mL), K_2CO_3 (2.5 mmol), 120 °C, CO (10 bar), 16 h. [b] Isolated yields.

after intramolecular condensation and thermal 1,3-proton shift.[13] The hydration of the cyano-group is a base induced transformation, and the palladium in this system might behave as a Lewis acid to further assistant K_2CO_3 in achieving the nitrile hydration. In addition, palladium may promote the condensation to give the final product as well. The thermal 1,3-proton shift can be verified by repeating the experiment in D_2O. No D was found to be incorporated into the terminal product, proving the amide proton comes from the NH_2– in anilines.

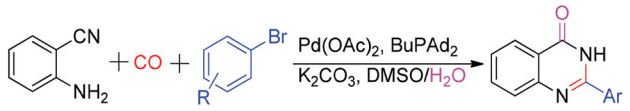
In conclusion, an interesting and straightforward procedure for the carbonylative synthesis of quinazolinones from commercially available 2-aminobenzonitriles and bromobenzenes has been developed. Various quinazolinones were produced in moderate to excellent yields under identical reaction conditions. The reactions go through aminocarbonylation of aryl bromides-hydration of nitriles-cyclization sequence. Notably, all the products are isolated by recrystallization, no column chromatography was required.

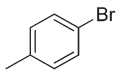
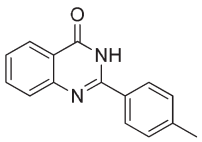
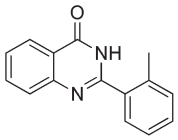
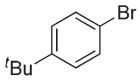
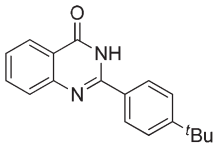
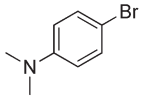
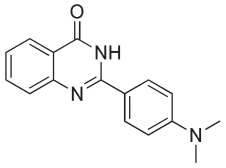
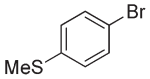
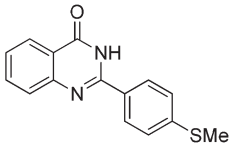
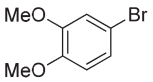
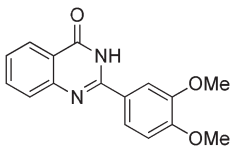
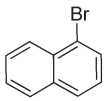
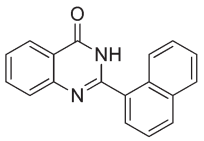
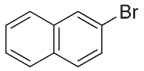
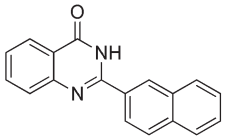
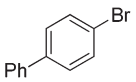
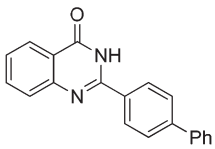
Experimental section

Typical reaction procedure for the synthesis of 2-phenyl quinazolin-4(3*H*)-one

A 12 mL vial was charged with $Pd(OAc)_2$ (2 mol%), $BuPAd_2$ (6 mol%), 2-aminobenzonitrile (1 mmol), K_2CO_3 (2.5 mmol), and a stirring bar. Then, 1 mL DMSO, 1 mL H_2O, and 1.1 mmol of bromobenzene were injected by syringe under argon. The vial (or several vials) was placed in an alloy plate, which was transferred into a 300 mL autoclave of the 4560 series from Parr Instruments® under argon atmosphere. After flushing the autoclave three times with CO, a pressure of 10 bar CO was adjusted at ambient temperature. Then, the reaction was performed for 16 hours at 120 °C. After the reaction is finished, the autoclave was cooled down to room temperature and the pressure was released carefully. The pure product can be isolated by either washing with water, ethyl acetate and finally hexane or recrystallized from MeOH.

Table 2 Palladium-catalyzed carbonylative synthesis of quinazolinones with aryl bromides[a]



Entry	Aryl bromides	Product	Yield[b]
1			88%
2			75%
3			74%
4			91%
5			89%
6			75%
7			74%
8			78%
9			67%

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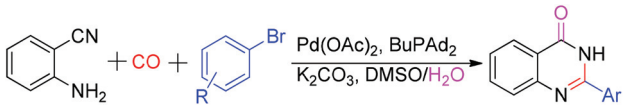
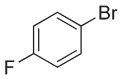
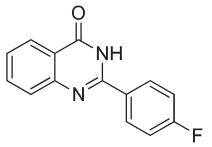
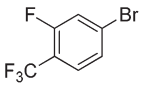
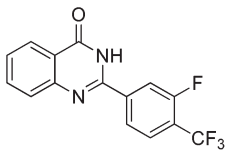
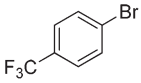
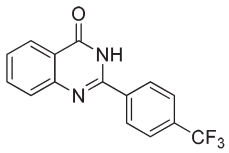
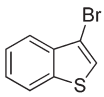
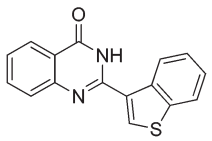
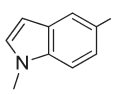
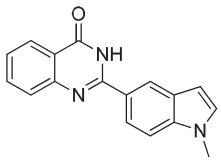
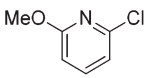
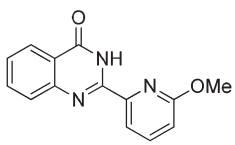


Entry	Aryl bromides	Product	Yield[b]
10			73%
11			71%
12			61%
13			72%
14			80%
15			30% 41%[c]

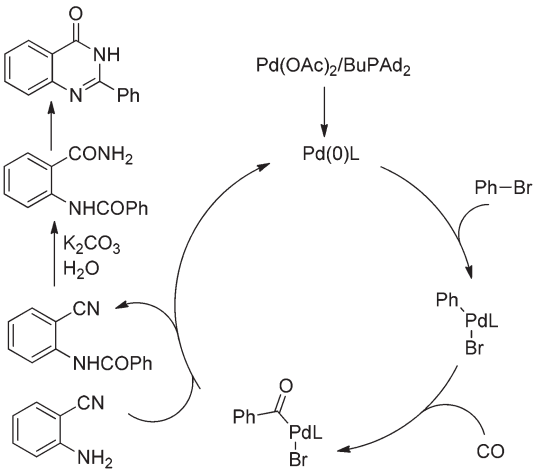
[a] Aryl bromide (1.1 mmol), 2-aminobenzonitriles (1.0 mmol), $Pd(OAc)_2$ (2 mol%), $BuPAd_2$ (6 mol%), DMSO (1 mL), H_2O (1 mL), K_2CO_3 (2.5 mmol), 120 °C, CO (10 bar), 16 h. [b] Isolated yields. [c] 100 °C.

2-Phenylquinazolin-4(3*H*)-one

^{1}H NMR (300 MHz, DMSO-d_6) δ = 12.51 (s, 1H), 8.21 (s, 3H), 7.96–7.69 (m, 2H), 7.57 (h, J = 7.2, 4H). **^{13}C NMR (75 MHz, DMSO-d_6)** δ = 162.28, 152.30, 148.78, 134.65, 132.68, 131.43, 128.52, 127.82, 127.42, 126.41, 125.70, 120.99. **GC-MS (EI, 70 eV):** m/z(%) = 222 (M^+, 100).

6-Chloro-2-phenylquinazolin-4(3*H*)-one

^{1}H NMR (300 MHz, DMSO-d_6) δ = 12.71 (s, br, 1H), 8.16 (d, 2H, J = 6.51 Hz), 8.09 (d, 1H, J = 2.4 Hz), 7.88–7.84 (dd, 1H, J = 8.9, 2.4 Hz), 7.75 (d, 1H, J = 8.7 Hz), 7.61–7.54 (m, 3H). **^{13}C NMR (75 MHz, DMSO-d_6)** δ = 161.9, 153.4, 147.9, 135.2, 133.0, 132.1,



Scheme 3 Proposed reaction mechanism.

131.3, 130.2, 129.2, 128.4, 125.4, 122.7. **GC-MS (EI, 70 eV):** *m*/*z* (%) = 256 (M^+, 100).

5-Fluoro-2-phenylquinazolin-4(3*H*)-one

^{1}H NMR (300 MHz, DMSO-d_6) δ = 12.58 (s, br, 1H), 8.18 (d, 2H, *J* = 6.6 Hz), 7.78–7.85 (m, 1H), 7.54–7.62 (m, 4H), 7.24–7.30 (m, 1H). **^{13}C NMR (75 MHz, DMSO-d_6)** δ = 161.8, 159.5, 153.3, 150.9, 135.2, 135.1, 132.2, 131.7, 128.6, 127.9, 123.6, 113.0, 112.8, 110.5. **GC-MS (EI, 70 eV):** *m*/*z*(%) = 240 (M^+, 100).

6-Methyl-2-phenylquinazolin-4(3*H*)-one

^{1}H NMR (300 MHz, DMSO-d_6) δ = 12.47 (s, br, 1H), 8.15 (d, 2H, *J* = 5.1 Hz), 7.94 (s, 1H), 7.63 (s, 2H), 7.51–7.56 (m, 3H) 2.44 (s, 3H). **^{13}C NMR (75 MHz, DMSO-d_6)** δ = 162.1, 151.4, 146.7, 136.2, 135.8, 132.7, 131.1, 128.5, 127.6, 127.3, 125.2, 120.7, 20.8. **GC-MS (EI, 70 eV):** *m*/*z*(%) = 236 (M^+, 100).

5-Methyl-2-phenylquinazolin-4(3*H*)-one

^{1}H NMR (300 MHz, DMSO-d_6) δ = 12.47 (s, br, 1H), 8.15 (d, 2H, *J* = 5.1 Hz), 7.94 (s, 1H), 7.63 (s, 2H), 7.51–7.56 (m, 3H) 2.44 (s, 3H). **^{13}C NMR (75 MHz, DMSO-d_6)** δ = 162.1, 151.4, 146.7, 136.2, 135.8, 132.7, 131.1, 128.5, 127.6, 127.3, 125.2, 120.7, 20.8. **GC-MS (EI, 70 eV):** *m*/*z*(%) = 236 (M^+, 100).

6-Chloro-2-(*o*-tolyl)quinazolin-4(3*H*)-one

^{1}H NMR (300 MHz, DMSO-d_6) δ = 12.62 (s, br, 1H), 8.10 (s, 1H), 7.97–7.62 (m, 2H), 7.61–7.08 (m, 4H), 7.51–7.56 (m, 3H) 2.38 (s, 3H). **^{13}C NMR (75 MHz, DMSO-d_6)** δ = 161.3, 155.3, 147.9, 136.7, 134.9, 134.4, 131.3, 131.0, 130.5, 130.0, 129.6, 126.1, 125.2, 122.7, 20.0. **GC-MS (EI, 70 eV):** *m*/*z*(%) = 270 (M^+, 100).

6-Chloro-2-(4-(methylthio)phenyl)quinazolin-4(3*H*)-one

^{1}H NMR (300 MHz, DMSO-d_6) δ = 12.62 (s, br, 1H), 8.13 (d, 2H, *J* = 8.4 Hz), 8.06 (d, 1H, *J* = 2.4 Hz), 7.83 (dd, 1H, *J* = 8.8 Hz, 2.4 Hz), 7.73 (d, 1H, *J* = 8.8 Hz), 7.40 (d, 2H, *J* = 8.5 Hz), 2.55 (s, 3H). **^{13}C NMR (75 MHz, DMSO-d_6)** δ = 161.8, 152.8, 147.9, 143.8, 135.1, 131.0, 130.0, 128.8, 128.6, 125.6, 125.3, 122.6, 14.5. **GC-MS (EI, 70 eV):** *m*/*z*(%) = 302 (M^+, 100).

6-Methyl-2-(naphthalen-2-yl)quinazolin-4(3*H*)-one

^{1}H NMR (300 MHz, DMSO-d_6) δ = 12.58 (s, br, 1H), 8.86–8.75 (m, 1H), 8.36–8.24 (m, 1H), 8.15–7.93 (m, 4H), 7.76–7.57 (m, 4H), 2.49 (s, 3H). **^{13}C NMR (75 MHz, DMSO-d_6)** δ = 162.7, 151.9, 147.2, 136.8, 136.4, 134.5, 132.8, 130.5, 129.4, 128.6, 128.4, 128.3, 128.1, 127.8, 127.3, 125.8, 124.9, 121.3, 21.3. **GC-MS (EI, 70 eV):** *m*/*z*(%) = 286 (M^+, 100).

6,7-Dimethoxy-2-(*o*-tolyl)quinazolin-4(3*H*)-one

^{1}H NMR (300 MHz, DMSO-d_6) δ = 12.25 (s, br, 1H), 7.52–7.44 (m, 2H), 7.43–7.36 (m, 1H), 7.35–7.24 (m, 2H), 7.15 (s, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 2.38 (s, 3H). **^{13}C NMR (75 MHz, DMSO-d_6)** δ = 162.2, 155.0, 154.1, 148.9, 145.5, 136.5, 135.3, 130.9, 123.0, 129.6, 126.1, 114.4, 108.5, 105.4, 56.4, 56.2, 20.1. **GC-MS (EI, 70 eV):** *m*/*z*(%) = 296 (M^+, 100).

6,7-Dimethoxy-2-(4-(methylthio)phenyl)quinazolin-4(3*H*)-one

^{1}H NMR (300 MHz, DMSO-d_6) δ = 12.311 (s, br, 1H), 8.12 (d, 2H, *J* = 8.4 Hz), 7.46 (s, 1H), 7.37 (d, *J* = 8.57 Hz), 7.17 (s, 1H), 3.92 (s, 3H), 3.88 (s, 3H), 2.54 (s, 3H). **^{13}C NMR (75 MHz, DMSO-d_6)** δ = 162.1, 155.2, 150.8, 148.9, 145.3, 142.9, 129.3, 128.2, 125.6, 114.3, 108.6, 105.5, 56.4, 56.2, 14.6. **GC-MS (EI, 70 eV):** *m*/*z*(%) = 328 (M^+, 100).

5-Fluoro-2-(4-(methylthio)phenyl)quinazolin-4(3*H*)-one

^{1}H NMR (300 MHz, DMSO-d_6) δ = 12.47 (s, br, 1H), 8.14 (d, 2H, *J* = 8.1 Hz), 7.80–7.70 (m, 1H), 7.50 (d, 1H, *J* = 8.29 Hz), 7.37 (d, *J* = 8.1 Hz), 7.23–7.15 (m, 1H), 2.54 (s, 3H). **^{13}C NMR (75 MHz, DMSO-d_6)** δ = 161.1 (d, *J* = 261.5 Hz), 160.5 (d, *J* = 3.7 Hz), 159.3, 153.64, 151.57, 143.74, 135.33 (d, *J* = 10.8 Hz), 129.0, 128.6, 125.5, 123.8 (d, *J* = 3.7 Hz), 112.9 (d, *J* = 20.9 Hz), 110.8 (d, *J* = 6.3 Hz), 14.6. **GC-MS (EI, 70 eV):** *m*/*z*(%) = 286 (M^+, 100).

7-Chloro-2-phenylquinazolin-4(3*H*)-one

^{1}H NMR (300 MHz, DMSO-d_6) δ = 12.71 (s, br, 1H), 8.17 (m, 3H), 7.81 (m, 1H), 7.63–7.52 (m, 4H). **^{13}C NMR (75 MHz, DMSO-d_6)** δ = 162.2, 154.4, 150.4, 139.6, 132.9, 132.2, 129.1, 128.4, 128.4, 127.2, 127.0, 120.3. **GC-MS (EI, 70 eV):** *m*/*z*(%) = 256 (M^+, 100).

2-(*p*-Tolyl)quinazolin-4(3*H*)-one

^{1}H NMR (300 MHz, DMSO-d_6) δ = 12.44 (s, 1H), 8.15 (d, *J* = 7.6 Hz, 1H), 8.11 (d, *J* = 8.0 Hz, 2H), 7.83 (t, *J* = 7.6 Hz, 1H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.51 (t, *J* = 8.0 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 2H), 2.40 (s, 3H). **^{13}C NMR (75 MHz, DMSO-d_6)** δ = 163.0, 153.0, 149.3, 141.8, 134.9, 130.6, 129.6, 128.1, 127.7, 126.7, 126.3, 121.4, 21.4. **GC-MS (EI, 70 eV):** *m*/*z*(%) = 236 (M^+, 100).

2-(*o*-Tolyl)quinazolin-4(3*H*)-one

^{1}H NMR (300 MHz, DMSO-d_6) δ = 12.46 (s, br, 1H), 8.19–8.10 (m, 3H), 7.85–7.76 (m, 1H), 7.74–7.67 (m, 1H), 7.53–7.45 (m, 1H), 7.42–7.35 (m, 2H), 2.54 (s, 3H). **^{13}C NMR (75 MHz, DMSO-**

***d*$_6$)** δ = 162.8, 152.3, 149.2, 143.5, 135.0, 129.2, 128.5, 127.8, 126.8, 126.3, 125.6, 121.4, 14.6. **GC-MS (EI, 70 eV):** *m*/*z*(%) = 236 (M^+, 100).

2-(4-(*tert*-Butyl)phenyl)quinazolin-4(3*H*)-one

^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ = 12.47 (s, br, 1H), 8.25–8.02 (m, 3H), 7.88–7.76 (m, 1H), 7.75–7.63 (m, 1H), 7.62–7.42 (m, 3H), 1.32 (s, 9H). **^{13}C NMR (75 MHz, DMSO-*d*$_6$)** δ = 162.9, 154.7, 152.8, 149.3, 135.0, 130.5, 128.0, 127.8, 126.8, 126.3, 125.9, 121.4, 35.1, 31.4. **GC-MS (EI, 70 eV):** *m*/*z*(%) = 278 (M^+, 100).

2-(4-(Dimethylamino)phenyl)quinazolin-4(3*H*)-one

^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ = ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ = 12.17 (s, 1H), 8.10 (s, 3H), 7.86–7.34 (m, 3H), 6.78 (d, 2H, *J* = 3.1 Hz), 2.99 (s, 6H). **^{13}C NMR (75 MHz, DMSO-*d*$_6$)** δ = ^{13}C NMR (75 MHz, DMSO) δ = 162.4, 152.2, 149.4, 134.4, 128.9, 127.0, 125.8, 125.4, 120.4, 118.8, 39.7. **GC-MS (EI, 70 eV):** *m*/*z* (%) = 265 (M^+, 100).

2-(4-(Methylthio)phenyl)quinazolin-4(3*H*)-one

^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ = 12.47 (s, 1H), 8.16 (d, *J* = 8.4, 3H), 7.77 (dd, *J* = 26.5, 7.6, 2H), 7.50 (t, *J* = 7.3, 1H), 7.40 (d, *J* = 8.4, 2H), 2.55 (s, 3H). **^{13}C NMR (75 MHz, DMSO-*d*$_6$)** δ = 162.8, 152.3, 149.2, 143.5, 135.0, 129.1, 128.5, 127.8, 126.8, 126.3, 125.6, 121.3, 14.6. **GC-MS (EI, 70 eV):** *m*/*z*(%) = 268 (M^+, 100).

2-(3,4-Dimethoxyphenyl)quinazolin-4(3*H*)-one

^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ = ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ = 12.42 (s, 1H), 8.15 (d, *J* = 7.3, 1H), 7.98–7.61 (m, 4H), 7.47 (t, *J* = 6.7, 1H), 7.07 (s, 1H), 3.90 (s, 3H), 3.85 (s, 3H). **^{13}C NMR (75 MHz, DMSO-*d*$_6$)** δ = 162.41, 151.84, 151.57, 148.95, 148.54, 134.44, 127.25, 126.05, 125.83, 124.76, 121.15, 120.70, 111.30, 110.67, 55.63. **GC-MS (EI, 70 eV):** *m*/*z*(%) = 282 (M^+, 100).

2-(Naphthalen-1-yl)quinazolin-4(3*H*)-one

^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ = 12.68 (s, 1H), 8.82 (s, 1H), 8.21 (d, *J* = 7.7, 2H), 8.04 (dd, *J* = 17.5, 8.7, 3H), 7.84 (dt, *J* = 14.5, 7.3, 2H), 7.70–7.50 (m, 3H). **^{13}C NMR (75 MHz, DMSO-*d*$_6$)** δ = 162.2, 152.3, 148.7, 134.6, 134.1, 132.3, 123.0, 130.0, 129.0, 128.1, 128.1, 128.0, 127.6, 127.6, 126.9, 126.6, 125.9, 124.5, 121.1. **GC-MS (EI, 70 eV):** *m*/*z*(%) = 272 (M^+, 100).

2-(Naphthalen-2-yl)quinazolin-4(3*H*)-one

^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ = 12.69 (s, 1H), 8.85 (s, 1H), 8.33 (dd, *J* = 8.7, 1.8, 1H), 8.21 (d, *J* = 6.9, 1H), 8.15–7.96 (m, 3H), 7.92–7.75 (m, 2H), 7.73–7.49 (m, 3H). **^{13}C NMR (75 MHz, DMSO-*d*$_6$)** δ = 162.2, 152.2, 148.8, 132.3, 129.9, 128.9, 128.1, 128.1, 127.9, 127.6, 127.6, 126.9, 126.6, 125.9, 124.5, 121.1. **GC-MS (EI, 70 eV):** *m*/*z*(%) = 272 (M^+, 100).

2-(4-(Trifluoromethyl)phenyl)quinazolin-4(3*H*)-one

^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ = 12.75 (s, 1H), 8.38 (d, *J* = 8.2, 2H), 8.18 (d, *J* = 7.9, 1H), 8.00–7.70 (m, 4H), 7.56 (t, *J* = 7.4, 1H). **^{13}C NMR (75 MHz, DMSO-*d*$_6$)** δ = 162.13, 151.19, 148.38, 136.58, 134.67, 131.53 (q, *J* = 34.5 Hz), 130.88, 127.61, 127.06, 125.87, 125.45 (q, *J* = 3.7 Hz), 123.94 (q, *J* = 270.2 Hz), 121.18. **GC-MS (EI, 70 eV):** *m*/*z*(%) = 290 (M^+, 100).

2-(4-Fluorophenyl)quinazolin-4(3*H*)-one

^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ = 12.59 (s, 1H), 8.42–8.06 (m, 3H), 8.00–7.67 (m, 2H), 7.64–7.31 (m, 3H). **^{13}C NMR (75 MHz, DMSO-*d*$_6$)** δ = 164.0 (d, *J* = 243.0 Hz), 162.3, 151.4, 148.6, 134.6, 130.3 (d, *J* = 9.2 Hz), 129.2 (d, *J* = 3.1 Hz), 127.4, 126.6, 125.8, 120.9, 115.6 (d, *J* = 21.8 Hz). **GC-MS (EI, 70 eV):** *m*/*z*(%) = 240 (M^+, 100).

2-(Benzo[*b*]thiophen-3-yl)quinazolin-4(3*H*)-one

^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ = 12.52 (s, br, 1H), 9.03–9.00 (d, 1H, *J* = 8.1 Hz), 8.80 (s, 1H), 8.18 (d, 1H, *J* = 8.10 Hz), 8.10 (d, 1H, *J* = 7.5 Hz), 7.93–7.76 (m, 2H), 7.64–7.42 (m, 3H). **^{13}C NMR (75 MHz, DMSO-*d*$_6$)** δ = 162.5, 149.2, 149.1, 140.2, 137.0, 135.1, 132.9, 128.6, 128.0, 127.2, 126.3, 125.9, 125.7, 125.6, 123.4, 121.7. **GC-MS (EI, 70 eV):** *m*/*z*(%) = 278 (M^+, 100).

2-(1-Methyl-1*H*-indol-5-yl)quinazolin-4(3*H*)-one

^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ = 12.40 (s, br, 1H), 8.51 (s, 1H), 8.23–7.97 (m, 2H), 7.88–7.64 (m, 2H), 7.63–7.52 (m, 1H), 7.52–7.36 (m, 2H), 6.59 (m, 1H), 3.84 (s, 3H). **^{13}C NMR (75 MHz, DMSO-*d*$_6$)** δ = 163.0, 154.0, 149.6, 138.4, 134.9, 131.7, 128.2, 127.6, 126.3, 124.0, 121.4, 121.3, 121.1, 110.3, 102.2, 33.2. **GC-MS (EI, 70 eV):** *m*/*z*(%) = 275 (M^+, 100).

2-(6-Methoxypyridin-2-yl)quinazolin-4(3*H*)-one

^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ = 11.81 (s, br, 1H), 8.20 (d, 1H, *J* = 8.2 Hz), 8.06 (d, 1H, *J* = 7.5 Hz), 7.99–7.91 (m, 1H), 7.91–7.83 (m, 1H), 7.79 (d, 1H, *J* = 8.2 Hz), 7.61–7.53 (m, 1H), 7.07 (d, *J* = 8.2 Hz), 4.09 (s, 3H).

Notes and references

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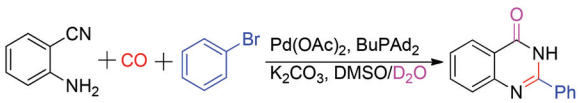

8.8 Regioselective synthesis of 2,3-dihydrobenzodioxepinones from epoxides and 2-bromophenols *via* palladium-catalyzed carbonylation

Haoquan Li, Anke Spannenberg , Helfried Neumann , Matthias Beller*, Xiao-Feng Wu*
Chemical Communications, 2014, 50, 2114-2116.

Contributions

In this paper, I discovered the tandem reaction, planned and executed the optimization of the model system. I also developed the substrate scope. I prepared suitable material for X-ray crystallography. I also wrote the major part of the corresponding manuscript, thus my overall contribution to this work approximately accounts for 70%.

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A highly regioselective cascade synthesis of 2,3-dihydrobenzodioxepinone from 2-bromophenols and epoxides has been developed. The reactions go through nucleophilic ring-opening of epoxides and subsequent palladium-catalyzed intramolecular alkoxylcarbonylation.

Palladium-catalyzed carbonylation reactions are of broad interest in both academic research and pharmaceutical applications. Ever since the pioneering work from Heck and co-workers in 1974,[1] palladium-catalyzed carbonylations have experienced impressive progress and have already become one of the most efficient tools in modern organic synthesis.[2] The most obvious advantages of carbonylative transformation are two but not least: (1) carbon monoxide is an inexpensive and easily available C1 building block; (2) carbonyl containing molecules such as aldehydes, amides, esters, ketones, alkynones *etc.* can be obtained efficiently by varying the coupling partners, which are valuable compounds themselves and ready for further modification as well.

Epoxides are widely available compounds, generally obtained from an intramolecular S_N2 substitution reaction or epoxidation of olefins.[3] Additionally, epoxides are an important class of chemicals with broad applications in organic synthesis and advanced materials.[4] Notably, a chiral center can be easily introduced into the parent molecules by applying chiral epoxides as substrates, which are readily available by asymmetric epoxidation of the corresponding alkenes. Among all the types of reactions, the ring-opening reaction of epoxides is one of the most straightforward routes for the utilization of epoxides. In general, it undergoes the S_N1 type reaction under acidic conditions and nucleophilic attack takes place at the more substituted position, while nucleophiles attack occurs at the less hindered carbon under the S_N2 type mechanism under basic conditions.

To the best of our knowledge, no example was reported for the carbonylative cross-coupling reaction with epoxides until now.[5] Due to our continual interest in palladium-catalyzed carbonylative synthesis of heterocycles, we report herein our recent results on the synthesis of benzodioxepinones which are valuable analogues of seven-membered lactones.[6] The reaction started from commercially available 2-bromophenols and epoxides *via* the cascade ring-opening reaction and palladium-catalyzed carbonylative transformation. The desired products were produced in a highly selective manner in high yields.

The first test of the reaction was carried out with 2-bromophenol (0.5 mmol), styrene oxide (0.55 mmol), 2 mol% $Pd(OAc)_2$, 3 mol% dppf, in MeCN (2 mL) under 15 bar of CO, 7% yield of **3a** was observed at 100 °C. **3a′** which originated from the nucleophilic attack at the benzylic position, was observed as well, and the ratio between **3a** and **3a′** was 68 : 32 (Table 1, entry 1). At this point, we found carbonylation to be the rate-determining step for this reaction as 2-bromophenoxy-phenylethanol was observed as the main by-product. Then different ligands were tested to promote the carbonylation step; no desired product was formed with monodentate ligands (6 mol%) such as $BuPAd_2$ and PPh_3. To our delight, 27% yield of **3a** was observed with binap as the ligand and which was chosen for further optimizations (Table 1, entry 2). In solvent testing, moderate yields of the target molecule can be obtained in DMF or DMSO (40% and 34% respectively, with **3a** : **3a′** as 85 : 15 and 86 : 14 respectively; Table 1, entries 9 and 10). In toluene, *t*BuOH and water, low or no reactivity was observed (Table 1, entries 11–14). The pressure of CO was varied as well, but no effects were observed for this transformation (Table 1, entry 15). In the end, the yield of **3a** was successfully increased to 80% with a ratio between **3a** and **3a′** of 85 : 15 by increasing the amount of styrene oxide to 1.5 equiv. (Table 1, entry 16). Among all the tested bases, NaOAc and organic base such as Et_3N and DBU gave only trace amounts of the product; moderate yield (72%) was produced with the use of 1.1 equiv. of KOH, and the best result was obtained with K_3PO_4 as the base (90%, **3a** : **3a′** = 90 : 10; Table 1, entries 16–21). Interestingly, the selectivity was reversed by adding 30 mol% of $ZnBr_2$ as the Lewis acid

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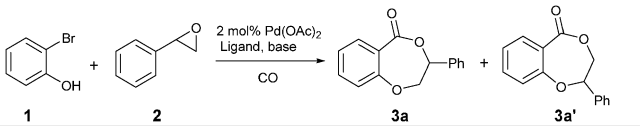
Table 1 Benzodioxepinone synthesis: optimization[a]



1 2 3a 3a'

Entry	2 : 1	Ligand	Base	Solvent	Yield[b]	3a : 3a′
1	1.1	dppf	K_2CO_3	MeCN	7	68 : 32
2	1.1	binap	K_2CO_3	MeCN	27	74 : 26
3	1.1	xantphos	K_2CO_3	MeCN	N.R	—
4	1.1	dppe	K_2CO_3	MeCN	17	76 : 24
5	1.1	dppp	K_2CO_3	MeCN	18	72 : 28
6	1.1	dppb	K_2CO_3	MeCN	24	74 : 26
7	1.1	dpppe	K_2CO_3	MeCN	N.R	—
8	1.1	DPEPhos	K_2CO_3	MeCN	13	81 : 19
9	1.1	binap	K_2CO_3	DMF	40	85 : 15
10	1.1	binap	K_2CO_3	DMSO	34	86 : 14
11	1.1	binap	K_2CO_3	Dioxane	N.R	—
12	1.1	binap	K_2CO_3	Toluene	9	40 : 60
13	1.1	binap	K_2CO_3	*t*BuOH	N.R	—
14	1.1	binap	K_2CO_3	H_2O	N.R	—
15[c]	1.1	binap	K_2CO_3	DMF	47	84 : 16
16[c]	1.5	binap	K_2CO_3	DMF	80	85 : 15
17[c]	1.5	binap	NaOAc	DMF	<5	—
18[c]	**1.5**	**binap**	**K_3PO_4**	**DMF**	**90**	**90 : 10**
19[c,d]	1.5	binap	KOH	DMF	72	91 : 9
20[c]	1.5	binap	Et_3N	DMF	<5	—
21[c]	1.5	binap	DBU	DMF	<5	—
22[c,e]	1.5	binap	K_3PO_4	H_2O	50	15 : 85

[a] $Pd(OAc)_2$ (2 mol%), ligand (3 mol%), **1** (0.5 mmol, 1 equiv.), **2** (0.75 mmol, 1.5 equiv.), base (2 equiv.) CO (15 bar), at 100 °C, 20 hours. [b] Yield was determined by GC with hexadecane as the internal standard. [c] CO (5 bar). [d] KOH (1.1 equiv.). [e] $ZnBr_2$ (30 mol%). dppf = 1,1′-bis(diphenylphosphino)-ferrocene, binap = 1,1′-binaphthalene-2,2′-diyl)bis(diphenylphosphine, xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene, dppe = ethylenebis(diphenylphosphine), dppp = 1,3-bis(diphenylphosphino)-propane, dppb = 1,4-bis(diphenylphosphino)butane, dpppe = 1,5-bis-(diphenylphosphino)pentane, DPEPhos = (oxydi-2,1-phenylene)bis-(diphenylphosphine), DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

in H_2O (Table 1, entry 22). From those primary results, we found that the properties of base and solvent were the two main factors which influenced the regioselectivity between **3a** and **3a′** and the yield.

In order to confirm the molecule structure, one of the products has been analyzed using X-ray diffraction (Fig. 1). Considering the reaction pathway for this cascade reaction, the most plausible mechanism for this transformation has been given in Scheme 1. Under basic conditions, the S_N2 type nucleophilic attack at the less hindered site of the epoxide and generation of the corresponding 2-(2-bromophenoxy)ethan-1-ol was the initial step. This was followed by the oxidative

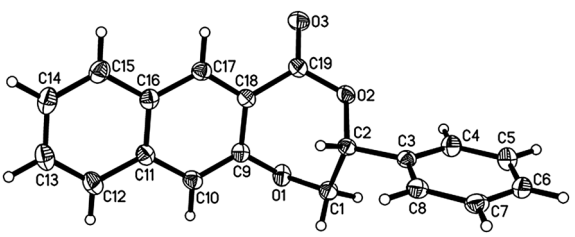
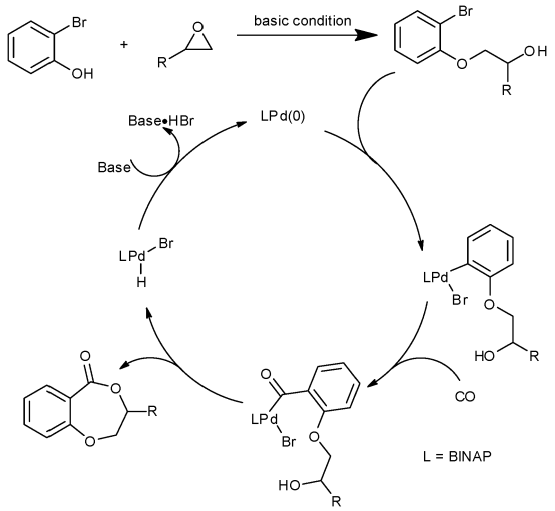


Fig. 1 Molecular structure of **3m**. Displacement ellipsoids are drawn at the 50% probability level.



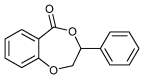
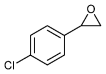
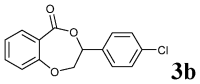
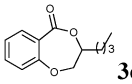
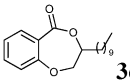
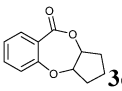
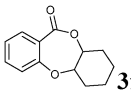
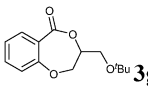
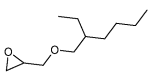
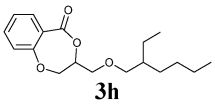
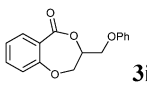
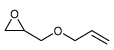
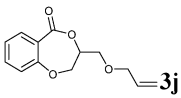
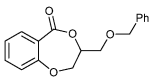
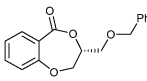
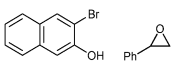
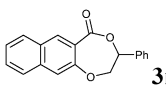
Scheme 1 Proposed reaction mechanism.

addition of the Ar–Br bond to the Pd(0) center, and the benzoyl palladium complex was produced as the key intermediate after the subsequent coordination and insertion of CO. Finally, by the intramolecular nucleophilic attack of the hydroxyl group, the seven-membered ring was eliminated as the final product and palladium(0) was regenerated under assistance of base.

With the optimized reaction conditions in hand [2 mol% $Pd(OAc)_2$, 3 mol% binap, 0.5 mmol of 2-bromophenol, 0.75 mmol of epoxide, in DMF as the solvent, with 3 equiv. of K_3PO_4 as the base, under 5 bar of CO, at 100 °C for 16 hours], we carried out the generality testing (Table 2).

Initially, different epoxides were examined with 2-bromophenol as the model substrate. Firstly, 4-chloro-styreneoxide was tested, 4,5-dihydrobenzo[*c*]oxepinone was obtained with a ratio between 3-substituted (**3c**) and 4-substitued (**3c′**) compounds of 90 : 10 and **3c** was isolated in 85% yield (Table 2, entry 2). Epoxides with aliphatic chains, 2-butyloxirane and 2-octyloxirane were subjected to the optimized conditions, moderate yields (respectively 79% and 79%) were obtained with better regioselectivity (95 : 5; Table 2, entries 3 and 4). With cyclopentene oxide as the starting substrate, the reaction also proceeded well and **3e** was isolated as a single diastereoisomer in 70% yield (Table 2, entry 5). However, when using cyclohexene oxide as the starting substrate, the product was isolated as a mixture of diastereoisomers in a diastereoisomeric ratio of 75 : 25 which might be explained by the co-existence of S_N1 and S_N2 mechanisms as the presence of palladium acetate as the Lewis acid and K_3PO_4 as base (Table 2, entry 6). With these results in hand, we then tested different glycidyl ethers under our best conditions (Table 2, entries 7–12). Notably, glycidyl ethers are another important class of epoxides and have become commercially available since the late 1940s, which are used as components of epoxy resins. Generally, different glycidyl ethers bearing aliphatic and aromatic glycidyl ethers gave moderate to good yields (66–88%). Moreover, the regioselectivity of the ring-opening reaction of glycidyl ethers are proved to be better than other aliphatic and aromatic substituted epoxides in which the selectivity is more

Table 2 Scope of the reaction under optimized conditions[a]

Entry	1	2	Product	Yield[b] (3 : 3′)[c]
1	1a		 3a	90 (90 : 10)
2	1a		 3b	85 (90 : 10)
3	1a		 3c	79 (95 : 5)
4	1a		 3d	79 (95 : 5)
5	1a		 3e	70 (dr > 99 : 1)[d]
6	1a		 3f	77 (dr: 75 : 25)[d]
7	1a		 3g	66 (>99 : 1)
8	1a		 3h	88 (>99 : 1)
9	1a		 3i	66 (98 : 2)
10	1a		 3j	79 (>99 : 1)
11	1a		 3k	85 (98 : 2)
12	1a		 3l	98% ee[e]
13			 3m	85 (90 : 10)

[a] General conditions: $Pd(OAc)_2$ (2 mol%), binap (3 mol%), **1** (0.5 mmol, 1 equiv.), **2** (0.75 mmol, 1.5 equiv.), K_3PO_4 (1.5 mmol, 3 equiv.), in DMF (2 mL), CO (5 bar), at 100 °C for 16 hours. [b] Isolated yield of **3a–m**. [c] Determined by GC. [d] Analyzed using NMR of the purified compound. [e] Analyzed using gas chromatography equipped with a chiral column of the crude product.

than 98 : 2. Remarkably, this catalytic system is proven to be tolerable towards the allyl group as 79% of **3j** was isolated by using allyl glycidyl ether as the starting material (Table 2, entry 10). In the cases of 9-oxabicyclo[6.1.0]nonane and ethyl 3-phenyloxirane-2-carboxylate, no desired products were detected.

As the achievements in asymmetric epoxidation of alkenes have been acknowledged by the Nobel Prize in 2001 and several name reactions, asymmetric epoxides are becoming readily available. It will be highly interesting if we can keep the chiral centre of the epoxide in the final products under our conditions. To our delight, when *S*-(–)-benzyl glycidyl ether was subjected to the optimized conditions, 98% of ee was obtained in the final products. Moreover, the substrate scope could also be extended to 3-bromonaphthalen-2-ol under the same conditions, which also yields the corresponding product in 85% yield (Table 2, entry 13).

In summary, a highly regioselective cascade synthesis of 2,3-dihydrobenzodioxepinone from 2-bromophenols and epoxides has been developed. Starting from commercially available substrates, moderate to good yields of versatile desired products are obtained in a regioselective manner (major product > 90%) under mild conditions.

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8.9 A Novel Domino Synthesis of Quinazolinediones by Palladium-Catalyzed Double Carbonylation

Haoquan Li, Wanfang Li, Anke Spannenberg, Wolfgang Baumann, Helfried Neumann, Matthias Beller*, Xiao-Feng Wu*

Chemistry- a European Journal, 2014, 20(28), 8541-8544.

Contributions

In this paper, I discovered the tandem reaction, planned and executed the optimization of the model system and also developed the substrate scope. Furthermore, I prepared suitable crystals for X-ray crystallography. I also wrote the major part of the corresponding manuscript, thus my overall contribution to this work approximately accounts for 70%.

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Heterocycles

A Novel Domino Synthesis of Quinazolinediones by Palladium-Catalyzed Double Carbonylation

Haoquan Li, Wanfang Li, Anke Spannenberg, Wolfgang Baumann, Helfried Neumann, Matthias Beller,* and Xiao-Feng Wu*[a]

Abstract: Combining commercially available bromoanilines and bromobenzonitriles in a novel double carbonylation process allows for a straightforward synthesis of isoindolo[1,2-b]quinazoline-10,12-diones. At least five different C–C and/or C–N bonds are selectively formed in this 3-component reaction, which likely proceeds through sequential carbonylation–cyclization–isomerisation–carbonylation steps. Notably, two molecules of CO are inserted in this highly efficient palladium-catalyzed process.

The efficient synthesis of heterocycles represents one of the most important targets for organic synthesis, because of their broad applications in pharmaceuticals, agrochemicals, and special materials.[1] Notably, seven out of the top ten pharmaceutical products by worldwide sales in 2009 are heterocyclic compounds.[2] Among the multitude of heterocycles known, quinazolinediones have an interesting fused nitrogen-containing organic framework.[3] Their derivatives display attractive biological activities, including anorexic as well as antihypertensive effects, and several drugs with related structures are applied in therapy.[4] Due to this importance, a number of procedures for the synthesis of quinazolinediones have been developed in the past decades.[5] In general, these protocols are based on the reaction of anthranilamide with phthalic anhydride or the reductive coupling of N-substituted 2-nitrobenzamides and 2-formylbenzoic acids. Although efficient, several substitution patterns cannot be easily accessed from these substrates. Thus, multi-step procedures are also used.

Domino reactions, in which the subsequent reaction step is a consequence of the functional group formed in the previous step, have become a key tool for improving the efficiency of organic synthesis. Advantageously, domino processes often allow for improved atom economy and circumvent isolating several intermediates and thus avoid waste generation.[6] Interestingly, the integration of modern palladium-catalyzed coupling reactions into domino processes enables the creation of significantly increased structural diversity from easily available building blocks. In this respect, carbonylative coupling reactions allow for the construction of a variety of carbonyl-containing compounds, as well as a number of important heterocycles.[7] Notably, CO is one of the cheapest C1 feedstocks available. While the advantages of incorporating one CO molecule are well-demonstrated, the incorporation of two CO molecules into the parent structure in a one-pot manner is even more appealing but still challenging.[8]

Based on our continuing interest in the carbonylative synthesis of heterocycles,[9] herein we wish to report a novel reaction cascade to give isoindolo[1,2-*b*]quinazoline-10,12-dione (**3**) through a palladium-catalyzed double-carbonylation process. Starting from commercially available substrates, at least five bonds were efficiently created during the reaction in a one-pot process, and two CO molecules were incorporated.

Initially, we investigated the palladium-catalyzed carbonylation of 2-bromobenzonitrile **1a** and 2-bromobenzamide **2a**. To our surprise, the fused heterocyclic product **3a** was formed containing an isoindolinone and also a quinazolinone ring. Later on, NMR spectroscopic assignments of the product structure were confirmed by the crystal structure of **3ad** (Figure 1).

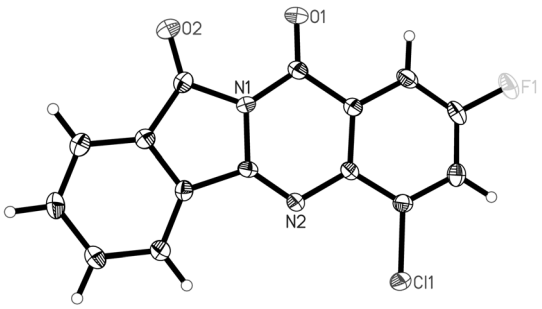

Figure 1. X-ray structure of compound **3ad**. Displacement ellipsoids are drawn at the 50% probability level. Only one of the two molecules of the asymmetric unit is shown.

In order to optimize the reaction conditions, various phosphine ligands were tested in the presence of 2 mol% of $Pd(OAc)_2$ as catalyst precursor. In general, trialkylphosphines such as $BuPAd_2$, and PCy_3 gave better yields compared to PPh_3, DPPF (1,1′-bis(diphenylphosphino)ferrocene), and DPPP (1,3-bis(diphenylphosphino)propane). Finally, $PtBu_3{\cdot}HBF_4$ was found to be the most suitable ligand for this reaction. After further testing of the effect of different solvents (DMF, 1,4-dioxane, and toluene) and bases (K_2CO_3, DiPEA, DBU, and Et_3N), toluene

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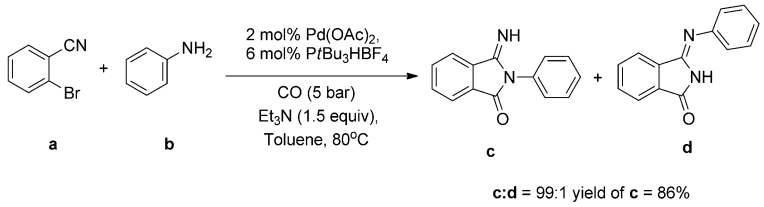
as the reaction media and Et_3N as the base was found to be the most suitable combination. Hence, we succeeded in obtaining **3aa** in 83% isolated yield under our optimized conditions (**1** (1 equiv), **2** (1.05 equiv), 2 mol% $Pd(OAc)_2$, 6 mol% $PtBu_3{\cdot}HBF_4$, 3 equiv of Et_3N, toluene, 100 °C, 5 bar of CO).

To reveal the reaction pathway, aniline was reacted under similar conditions with 2-bromobenzonitrile under a carbon monoxide atmosphere; compound **c** was obtained as the major component and **d** was observed as well. After optimization, **c** could be obtained with 86% yield (Scheme 1, for detail, please see the Supporting Information).



Scheme 1. Reaction between 2-bromobenzonitrile and aniline.

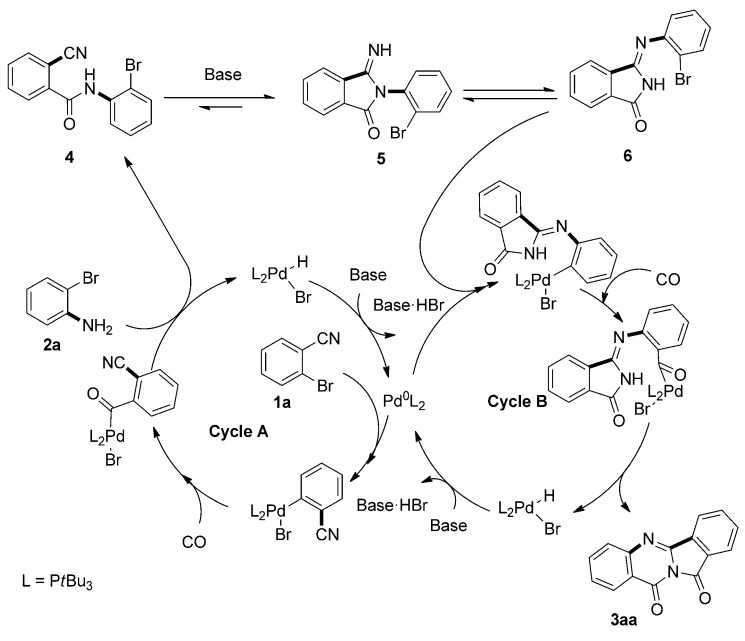
Based on the structural determination of the final product, a likely reaction pathway is given in Scheme 2. Starting from 2-bromoaniline **2a** and 2-bromobenzonitrile **1a**, the first aminocarbonylation occurred forming amide **4** (cycle A). It should be noted that the oxidative insertion of the active palladium species occurrs preferentially at **1a** due to the higher reactivity. Next, base-catalyzed isomerization–cyclization should form the iminoisoindolinone **5**.[10] Interestingly, **5** does not undergo another carbonylation reaction, instead the unexpected isomerization of **5** to **6** occurs, probably due to steric effects. Subsequent intramolecular carbonylative coupling forms **3aa** as the final product (cycle B).

Next, we investigated the generality and limitations of this methodology. Hence, without further optimization, the reaction of 2-bromobenzonitrile with nine different bromoanilines **2b**–**2j** was tested. When **2b** was used, the chloro substituent was found to stay intact under these conditions, and a good yield (70%) of **3ab** was obtained (Table 1, entry 2). Anilines with electron-withdrawing substituents gave the desired products (**2c**, **2d**, and **2f**) in 57–63% yield. Gratifyingly, when **2e** was subjected to the reaction conditions, the acetyl group was found to be well-tolerated, leading to **3ae** in 87% isolated yield! Similarly, 82% of the desired product was produced by using the corresponding cyano-substituted 2-bromoaniline as a substrate (Table 1, entry 7). Furthermore, the methyl-substitued 2-bromoanilines (**2h** and **2i**), worked quite well, and the corresponding quinazolinediones were obtained in 73 and 61% yield, respectively. Considering the broad applications of the trifluoromethyl group in bioactive compounds, **2j** was tested as well. However, in this latter case only 37% of the corresponding product **3aj** was obtained. Despite the lower yield, isolation of **3aj** was easy. More specifically, the purification of all the products was facile and no column chromatography was necessary. The pure compounds were obtained by simply recrystallizing the crude reaction mixture from ethanol. This simple isolation certainly adds to the value of the synthetic methodology.

To further demonstrate the applicability of our procedure, we then performed coupling reactions of 2-bromoaniline with ten different 2-bromobenzonitriles **1b**–**1i**.

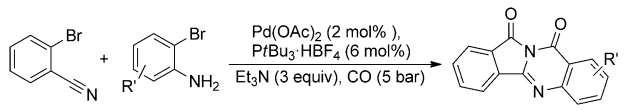
As shown in Table 2, no obvious steric effects on the 2-bromobenzonitrile ring were observed. Thus, good yields (75–87%) of the respective quinazolinediones were obtained with either 3-, 4- or 5-methyl-substituted 2-bromobenzonitriles as substrates (Table 2, entries 1–3). Also, a similar yield was obtained by using 5-methoxy-2-bromobenzonitrile as the starting material (88%; Table 2, entry 4). 63–76% of the desired prodcuts were successfully isolated using 4- and 6-fluoro-substitued 2-bromobenzonitriles **1f** and **1g**. When changing the bromo substituent to a iodo leaving group, the reaction proceeded slightly better (72% isolated yield), and the identical product was obtained. Finally, satisfactory results were achieved in the carbonylative coupling of **1b** with **2h**, **2g**, and **2e** without any further optimization (82, 79, and 84%, respectively).

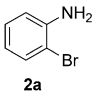
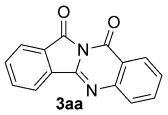
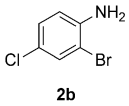
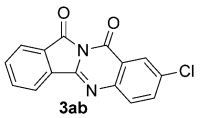
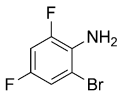
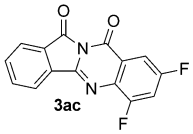
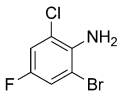
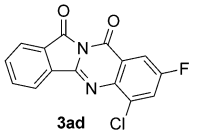
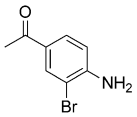
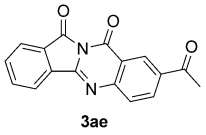
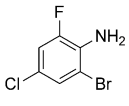
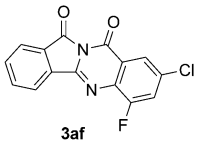
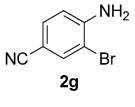
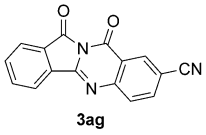
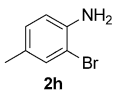
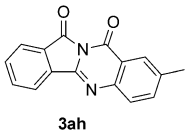
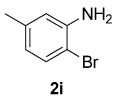
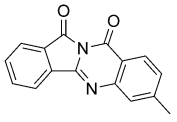
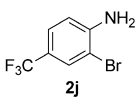
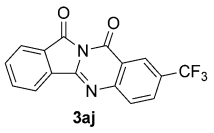
Comparing the NMR spectra of the different products, the similar heterocyclic core is unambiguously proven. For example, in the ^{13}C NMR spectrum of **3ga**, the fluorine atom has a smaller coupling constant with the carbonyl carbon ($^4J_{C-F} = 2.6$ Hz) compared to the imidamido carbon ($^3J_{C-F} = 4.8$ Hz), which also matches the 2D-NMR analysis of compound **3ca**, in which the methyl substituent that is originally at the *ortho*-position to the bromo substituent ends up in the *ortho*-position of the amido carbon on the isoindolinone ring.



Scheme 2. Proposed reaction mechanism.

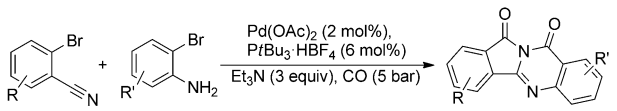
Table 1. Pd-catalyzed carbonylative synthesis of quinazolinediones from different 2-bromoaniline derivatives and 2-bromobenzonitrile.[a]

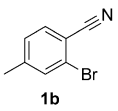
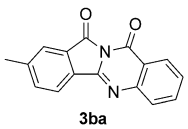
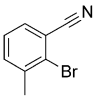
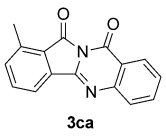
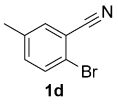
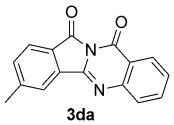
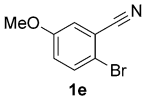
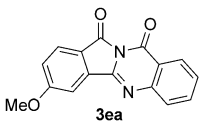
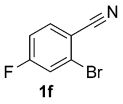
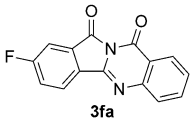
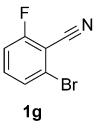
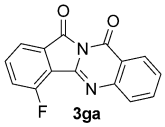
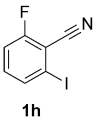
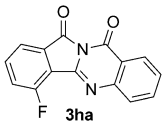
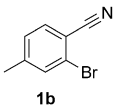
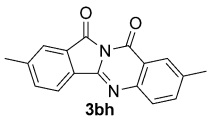
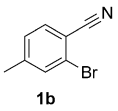
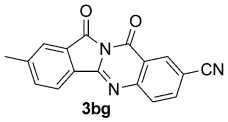


Entry	2-Bromoanilines	Product	Yield [%][b]
1	 **2a**	 **3aa**	83
2	 **2b**	 **3ab**	70
3	 **2c**	 **3ac**	63
4	 **2d**	 **3ad**	57
5	 **2e**	 **3ae**	87
6	 **2f**	 **3af**	60
7	 **2g**	 **3ag**	82
8	 **2h**	 **3ah**	73
9	 **2i**	 **3ai**	61
10	 **2j**	 **3aj**	37

[a] 2-Bromobenzonitrile (1 mmol), 2-bromoaniline (1.1 mmol), CO (5 bar), $Pd(OAc)_2$ (2 mol%), $PtBu_3{\cdot}HBF_4$ (6 mol%), toluene (4 mL), Et_3N (3 mmol), 100 °C, 20 h. [b] Isolated yields.

Table 2. Pd-catalyzed carbonylative synthesis of quinazolinediones from 2-bromoanilines and different 2-bromobenzonitriles.[a]



Entry	2-Bromoanilines	Product	Yield [%][b]
1	 **1b**	 **3ba**	78
2	 **1c**	 **3ca**	75
3	 **1d**	 **3da**	87
4	 **1e**	 **3ea**	88
5	 **1f**	 **3fa**	76
6	 **1g**	 **3ga**	63
7	 **1h**	 **3ha**	72
8[c]	 **1b**	 **3bh**	82
9[d]	 **1b**	 **3bg**	79
10[e]	**1b**	**3be**	84

[a] 2-Bromobenzonitrile derivatives (1 mmol), 2-bromoaniline (**2a**) (1.1 mmol), CO (5 bar), $Pd(OAc)_2$ (2 mol%), $PtBu_3{\cdot}HBF_4$ (6 mol%), toluene (4 mL), Et_3N (3 mmol), 100 °C, 20 h. [b] Isolated yields. [c] **2h** instead of **2a**. [d] **2g** instead of **2a**. [e] **2e** instead of **2a**.

In summary, the first palladium-catalyzed double-carbonylation process for the synthesis of quinazolinediones has been developed. Starting from commercially available 2-bromobenzonitriles and 2-bromoanilines a series of isoindolo[1,2-b]quinazoline-10,12-diones was synthesized in a straightforward manner with good isolated yields (around 20 examples). Notably, in this novel domino process, both inter- and intramolecular carbonylation reactions take place, and two CO molecules are incorporated in the parent product structure. Considering that at least 5 different C–C and C–N bonds are formed, each of the individual reaction steps proceeds with high selectivity and excellent yield. Further applications of this methodology are currently underway in our laboratory.

Experimental Section

General procedure for the synthesis of compound 3

An oven-dried 12 mL vial with stir bar was charged with 2-bromobenzonitrile (1.0 mmol, 1 equiv), 2-bromoaniline (1.1 mmol, 1.1 equiv), $Pd(OAc)_2$ (0.02 mmol, 2 mol%), and $PtBu_3{\cdot}HBF_4$ (0.06 mmol, 6 mol%) and was put into a 25 mL Schlenk and then evacuated and refilled with argon three times. Then, toluene (3 mL), Et_3N (3 mmol, 3 equiv) were injected into the vial under argon flow sequentially. The vial (or several vials) was placed in an alloy plate, which was transferred into a 300 mL autoclave of the 4560 series from Parr Instruments® under an argon atmosphere. After flushing the autoclave three times with CO, a pressure of 5 bar CO was adjusted at ambient temperature. The reaction mixture was heated overnight (20 h) at 100 °C. After the reaction finished, the autoclave was cooled down to room temperature and the pressure was released carefully. The crude reaction mixture was transferred into a 50 mL beaker with 20 mL of water. After vigorous stirring for 1 min, the crude product was obtained, filtered and washed with 10 mL of 5:1 pentane/EtOAc, and dried under vacuum. Pure compound was obtained after recrystallization in EtOH. For some of the compounds, that is, those of low solubility, pure compound could also be obtained by combining the crude product and ethanol and heating to the boiling point of ethanol, followed by cooling down and filtration.

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Keywords: carbonylation · coupling · domino reactions · multicomponent reactions · palladium

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8.10 Selective ruthenium-catalyzed methylation of 2-arylethanols using methanol as C1 feedstock

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Contributions

In this paper, I was involved in part of the optimization of the model system and also developed the substrate scope. Additionally, I was involved in the mechanistic discussion, interpretation of results. I also wrote a minor part of the corresponding manuscript, thus my overall contribution to this work approximately accounts for 30%.

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Selective ruthenium-catalyzed methylation of 2-arylethanols using methanol as C1 feedstock†

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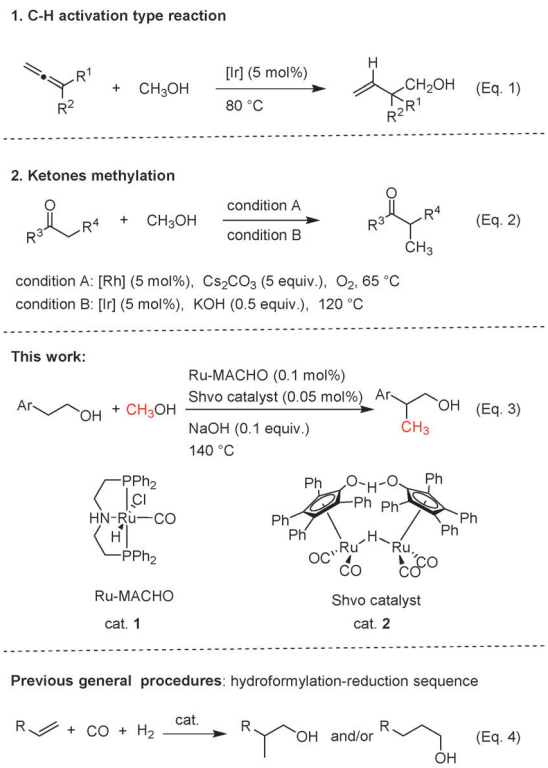
We describe the selective cross coupling of methanol and 2-arylethanols using a combination of Ru-MACHO (RuHCl(PNP^{Ph})CO) and Shvo's diruthenium complex as catalysts. The desired domino transformation takes place *via* so-called borrowing hydrogen methodology, which constitutes an ideal example of green chemistry.

Borrowing hydrogen methodologies are of increasing importance in organic synthesis and catalysis as they represent prime examples of green chemistry.[1] In general, they allow for highly atom economic formation of C–C and C–N bonds with easily available alcohols. Among the various alcohols available for borrowing hydrogen reactions methanol is the most abundant, and potentially renewable chemical feedstock, which is produced in about 100 million metric tons per year.[2,3] Despite its use in bulk applications,[4] such as the methanol-to-olefins process and carbonylations (acetic acid derivatives),[5] its application in fine chemical synthesis is underdeveloped.[6] Hence, only a few hydrogen borrowing reactions using methanol to construct C–C bonds have been reported.[7] Notably, methanol dehydrogenation is significantly higher in energy (ΔH = +84 kJ mol^{-1}) compared to the dehydrogenation of higher alcohols and even ethanol (ΔH = +68 kJ mol^{-1}).[8] Nevertheless, some pioneering works in transfer hydrogenations using methanol for C–C bonds formation were developed in recent years.[7] For example, Krische and coworkers reported an iridium-catalyzed C–C coupling of methanol and allenes (eqn (1)).[7f] Moreover, the groups of Donohoe and Obora demonstrated methylation of ketones in the presence of rhodium- or iridium-complexes, respectively (eqn (2)).[7g,h]

Based on the recent development of catalytic MeOH dehydrogenation,[9] we envisioned the possibility of a highly challenging cross coupling of methanol and primary alcohols (Scheme 1, eqn (3)). To the best of our knowledge there is only one example of this type of reaction known for the synthesis of iso-butanol.[7a–d]



Scheme 1 MeOH as C1 feedstock in borrowing hydrogen reactions for C–C bond formation.

However, drastic reaction conditions (200 °C; 1.6 equiv. of NaOMe) had to be used in order to achieve sufficient conversion. Herein, we apply MeOH as C1 feedstock for methylation of various 2-arylethanols in the presence of a bimetallic system. Key to success is the cooperative catalysis of the combination of Ru-MACHO[10,11] and Shvo's diruthenium complex[12] (eqn (3)). Under optimized conditions, only catalytic amounts of base (0.1 equiv.) are required for the desired alkylation process. In the past, the most general procedure for preparing this kind of compounds was the hydroformylation-reduction sequence (eqn (4)).[13] Compared with

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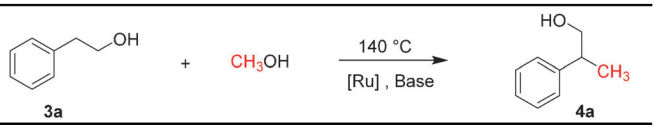
this methodology, our present protocol has advantages such as avoiding toxic CO and does not require any extra H_2 source or high pressure infrastructure.

In our initial experiments, the alkylation of 2-phenylethanol (**3a**) was selected as a model system. Here, various Ru and Ir pincer-type catalysts were tested due to their known activities in dehydrogenation reactions of alcohols.[9a,c,d,14] Gratifyingly, it was found that using Ru-MACHO (cat. **1**, 0.1 mol%) as a catalyst in the presence of NaOMe (10 mol%), the desired compound **4a** was obtained in 13% yield with 21% conversion (Table 1, entry 1). However, despite extensive variation of key reaction parameters, such as different kinds of catalyst, substrate concentration, and the base, no major increase of conversion and yield was obtained.

Considering that the mechanism involves at least six different reaction steps (two times dehydrogenation, enolization, nucleophilic addition, dehydration and hydrogenation; Scheme 2), control experiments were performed to gain some insights for

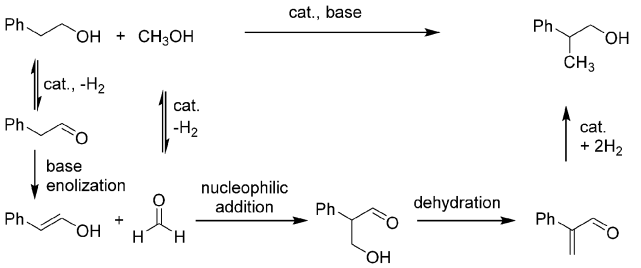
Table 1 Ruthenium-catalyzed methylation of 2-arylethanols: variation of reaction conditions



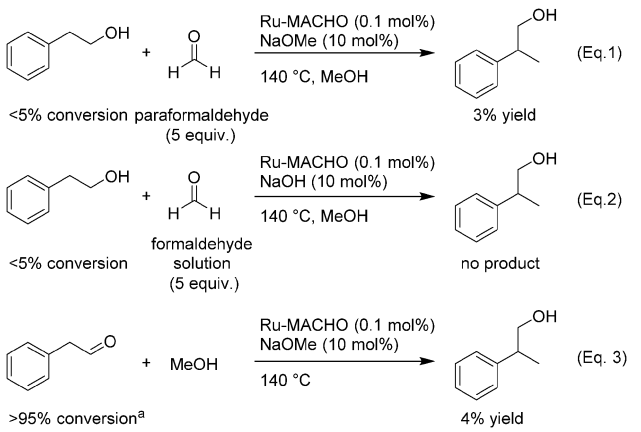
3a 4a

Entry	Catalyst	Base	Time (h)	Conversion[c] (%)	Yield[c] (%)
1	cat. **1** (0.1%)	NaOMe (10%)	17	21	13
2	cat. **1** (0.1%), cat. **2** (0.05%)	NaOMe (10%)	17	47	31
3	cat. **2** (0.05%)	NaOMe (10%)	17	<5	—
4	cat. **1** (0.1%), cat. **2** (0.05%)	NaOMe (10%)	45	53	34
5	cat. **1** (0.1%), cat. **2** (0.15%)	NaOMe (10%)	17	58	40
6	cat. **1** (0.3%), cat. **2** (0.05%)	NaOMe (10%)	17	35	19[d]
7	cat. **1** (0.1%), cat. **2** (0.05%)	NaOMe (10%)	28[a]	78	55
8	cat. **1** (0.1%), cat. **2** (0.05%)	NaOMe (10%)	45[b]	>95	73
9	$Pd(dppe)Cl_2$ (0.2%)	NaOMe (10%)	45[b]	20	—
10	cat. **1** (0.1%), cat. **2** (0.05%)	NaOH (10%)	45[b]	>95	75[e]
11	cat. **1** (0.1%), cat. **2** (0.05%)	KOH (10%)	45[b]	>95	76
12	cat. **1** (0.1%), cat. **2** (0.05%)	NaOH (5%)	45[b]	93	68
13	cat. **1** (0.07%), cat. **2** (0.035%)	NaOH (10%)	45[b]	92	71
14	cat. **1** (0.05%), cat. **2** (0.025%)	NaOH (10%)	45[b]	88	68
15	cat. **1** (0.03%), cat. **2** (0.015%)	NaOH (10%)	45[b]	66	39

Reactions were performed on the 2.5 mmol scale of **3a** in MeOH (2 mL) in a stainless steel sealed tube (40 mL).[a] After heating for 17 h, the sealed tube was removed by heating and cooling to rt. Then the pressure of the sealed tube was released to 1 atm and the reaction was continued. [b] The operation of pressure release was performed at after heating for 17 h, 28 h respectively. [c] GC conversion and yield were reported as the average of two runs. [d] Reported yield is based on the average of 2 reactions. [e] These conditions were used for other substrates. 87% isolated yield was obtained as an average of 2 reactions. The GC samples directly from the reaction mixture contained some suspension, which should contribute to the lower GC yield than isolated yield.



Scheme 2 Possible reaction mechanism.



Scheme 3 Control experiments. ([a] By-products are caused by aldol condensation reactions.)

the optimization of the process. In the presence of additional paraformaldehyde or formaldehyde solution in the reaction mixture (Scheme 3, eqn (1) and (2)), less than 5% conversion was observed, respectively. These results suggest that the Ru-MACHO catalyst does not favour the dehydrogenation of 2-phenylethanol, which is a key step to obtain high conversion and yield. Indeed, MeOH reacted with phenylacetaldehyde instead of 2-phenylethanol (Scheme 3, eqn (3)). Although more than 95% conversion of phenylacetaldehyde occurred, less than 5% yield of the desired product was obtained due to unwanted aldol-type side reactions. This experiment clearly indicates that enough formaldehyde should be generated from methanol before the dehydrogenation of 2-phenylethanol takes place.

With these considerations in mind, we imagined addition of a second catalyst, which promotes selectively the dehydrogenation of 2-phenylethanol. As a result higher reaction yields could be achieved. Hence, combinations of Ru-MACHO with different catalysts, which are active in borrowing hydrogen reactions, were tried. Indeed, addition of the well-known Shvo diruthenium complex as a second catalyst improved the product yield to 31% (Table 1, entry 2). No product was observed using the Shvo catalyst alone (Table 1, entry 3). Prolonging reaction time or higher catalyst loadings of the Shvo catalyst slightly improved the product yield further to 34% and 40%, respectively (Table 1, entries 4 and 5). Interestingly, using a higher concentration of the Ru-MACHO complex (0.3 mol%) in the presence of the Shvo complex decreased the reaction yield somehow (Table 1, entry 6).

This strange phenomenon is explained by the deactivation of the catalysts in the presence of an increased amount of hydrogen. Based on this assumption, the pressure of the reactor was released at room temperature after heating for 17 h. Then, the reaction was continued for another 11 h. To our delight, the yield of **4a** was increased from 31% to 55% (Table 1, entry 7). After another pressure release the product yield reached 73% with more than 95% conversion (Table 1, entry 8). In the presence of other bases, such as sodium hydroxide, potassium hydroxide, the same level of yields was obtained (Table 1, entries 10 and 11).

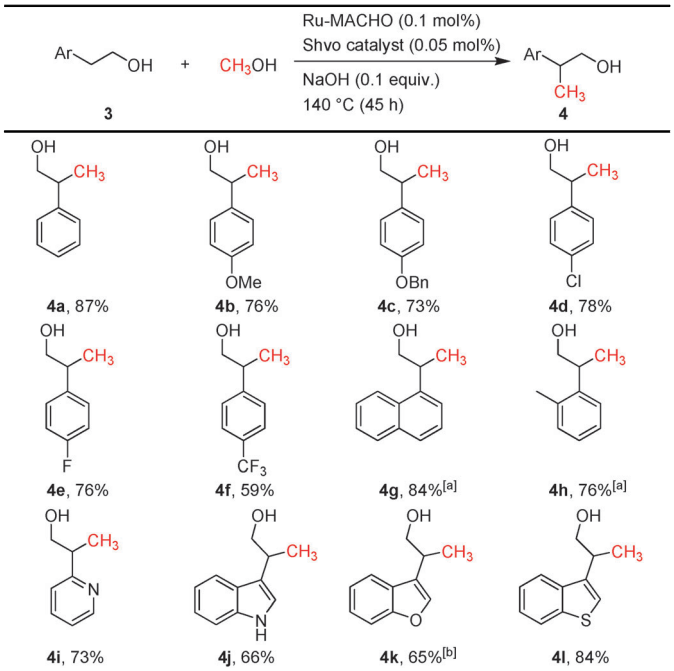
Thus, sodium hydroxide was selected as the best choice (Table 1, entry 10). A reduced amount of base (5 mol%) led to a slightly lower yield (Table 1, entry 12). When the catalyst loading was decreased from 0.1 mol% for Ru-MACHO and 0.05 mol% for the Shvo catalyst to 0.03 mol% and 0.015 mol%, obvious lower yield was detected (Table 1, entry 15). It should be noted that using Pd(dppe)Cl_2, which showed high activity for the synthesis of iso-butanol from propanol and methanol, no product **4a** was observed at all (Table 1, entry 9).[7c]

With the optimized reaction conditions in hand, the substrate scope was investigated. No matter whether electron-donating or electron-withdrawing groups are present on the phenyl ring, the reactions showed high efficiency (Table 2, **4b–4f**). Notably, the benzyl protection group survived under the conditions, although it is easily removed in the presence of a hydrogen atmosphere and transition metal catalysts (Table 2, **4c**).[15] The tolerance of halide substituents (Table 2, **4d**) affords the opportunity for further functionalization. Moreover, the compatibility of trifluoromethyl groups indicates the potential application in preparing bioactive compounds.[16] When substrates with the naphthalene ring (Table 2, **4g**) and the 2-methyl phenyl group (Table 2, **4h**) were tried, a longer reaction time was required to obtain good to excellent yields, which might be explained by the steric factor. Satisfyingly, substrates containing pyridine, protection free indole and benzofuran scaffolds displayed good reactivity, too (Table 2, **4i** to **4k**). Furthermore, the benzothiophene derivative demonstrated high efficiency (Table 2, **4l**). To demonstrate further functional group tolerance, a mixture of 2-phenylethanol and methyl benzoate was reacted with methanol under the standard reaction conditions. In fact, 92% recovery of methyl benzoate showed that an ester group is compatible with these conditions. However, using 4′-hydroxyphenyl-2-ethanol only low conversion was observed, probably due to the acidity of the phenolic hydroxyl group. Finally, 4′-aminophenyl-2-ethanol resulted in *N*-methylation reactions.

To gain some insights into the cooperative effects of the two catalysts, the benchmark reaction was performed in the presence of the same concentrations of the Ru-MACHO (cat. **1**), and the Shvo catalyst (cat. **2**), as well as their mixture (cat. **1** and cat. **2**). As shown in Fig. 1 and Table S1 (ESI†) the higher product yields using the combination of both catalysts do not result from the simple addition of the yields obtained in the presence of one catalyst. Apparently, the Ru-MACHO complex catalyzed all the necessary individual steps in the catalytic cycle, however the synergistic effect of the Shvo complex results from the accelerated dehydrogenation of 2-phenylethanol derivatives *vide supra*. Notably, the different (de)hydrogenation reactions in hydrogen borrowing methodologies proceeded best with a specific catalyst. Applying bi- or even multi-metallic catalyst systems offers a tool for improving such reactions.

Another key factor for the success of these transformations is the release of hydrogen, thereby shifting the equilibrium towards the aldol product. As shown in Fig. 1, the increasing yields *versus* reaction time disclosed that the reaction almost reached equilibrium after 17 h. Under optimized conditions without the release of pressure during the reaction, 11.9 bar, 12.0 bar and 12.2 bar of pressure was detected at 17 h, 18 h and 45 h, respectively (Fig. S1, ESI†). At the same time 36% yield and 38% yield were obtained in 17 h and 45 h. Furthermore, the reaction of 2-phenylethanol with $^{13}CH_3OH$ was performed.

Table 2 Substrate scope of methylation of 2-arylethanols



Reactions were performed on the 2.5 mmol scale under optimized reaction conditions. Isolated yields are reported. [a] Another 17 h of heating is required after 45 h of heating with 3 times pressure release. [b] The reaction was performed on the 1.17 mmol scale.

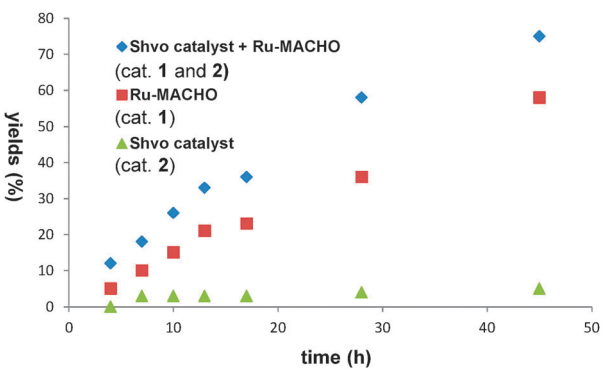
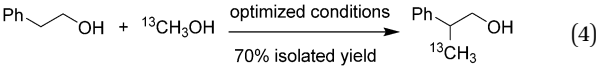


Fig. 1 Experiments with model substrate using cat. **1**, cat. **2**, the mixture of cat. **1** and cat. **2** under optimized conditions.

The signal of ^{13}C NMR spectrum disclosed unambiguously that the carbon of the methyl group in the product comes from methanol (eqn (4)). This agrees with the proposed reaction mechanism of two continuous dehydrogenation reactions, selective aldol reaction, subsequent dehydration and the final hydrogenation step (Scheme 2).



(4)

Finally, few methylation experiments were performed using 1-butanol as an example of a bulk aliphatic alcohol. Indeed, methylation also proceeded with catalyst turnover numbers of 55 at 140 °C and 100 at 160° (see ESI†). Further optimization of this reaction and other aliphatic alcohols is currently in progress.

In conclusion, we developed an efficient methylation of 2-arylethanols using methanol as C1 feedstock. Key to success is the combination of two different ruthenium complexes, namely the Ru-MACHO and the Shvo catalyst. Applying this catalyst system under optimal conditions a good substrate scope with pyridine, protection-free indole, benzofuran and benzothiophene scaffolds was achieved. At the same time, kinetic experiments disclosed that for hydrogen borrowing reactions improved product yields can be obtained by using bimetallic systems. Notably, this methodology affords products which alternatively have to be prepared by hydroformylation-reduction sequences. Obvious advantages of the presented straightforward approach are the avoidance of toxic CO and extra hydrogen as well as the necessity to use high pressure infrastructure.

This work has been supported by the state of Mecklenburg-Vorpommern, the BMBF and the BMWi (IGF 16634 BG). We acknowledge Mr Xianjie Fang, Dr Yuehui Li, Dr Lin He for helpful discussion. Yang Li acknowledges Leibniz fellowship.

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8.11 Palladium-Catalyzed Carbonylation of 2-Bromoanilines with 2-Formylbenzoic Acid and 2-Halobenzaldehydes: Efficient Synthesis of Functionalized Isoindolinones

Kishore Natte, Jianbin Chen, Haoquan Li, Helfried Neumann, Matthias Beller*, Xiao-Feng Wu*

Chemistry-A European Journal, 2014, 20 (144), 14184 -14188.

Contributions

In this paper, I came up with the idea and discovered the tandem reaction. I fully characterized the structure of the product of the model reaction. I planned and executed the original part of the optimization. Thus my overall contribution to this work approximately accounts for 30%.

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Palladium-Catalyzed Carbonylation of 2-Bromoanilines with 2-Formylbenzoic Acid and 2-Halobenzaldehydes: Efficient Synthesis of Functionalized Isoindolinones

Kishore Natte, Jianbin Chen, Haoquan Li, Helfried Neumann, Matthias Beller, and Xiao-Feng Wu*[a]

Abstract: A concise and highly versatile method for the synthesis of functionalized isoindolinones is reported. Various 2-bromoanilines undergo palladium-catalyzed carbonylation with 2-formylbenzoic acid under a convenient and mild procedure to give good to excellent yields of the corresponding isoindolinones. Additionally, 2-halobenzaldehydes can be applied as substrates in palladium-catalyzed double-carbonylation to provide identical compounds in moderate to good yields.

Cascade reactions have attracted considerable attention in organic synthesis due to the fact that complex molecules can be easily prepared from simple or commercially available compounds in a one-pot manner. In addition, heterocycles represent one of the most important targets in organic synthesis, because of their broad applications in pharmaceuticals, agrochemicals, and organic materials.[1] Of all the nitrogen-containing heterocycles, isoindolinones have been found to be a structural unit or key intermediate of many naturally occurring substances[2] and additionally they have demonstrated a remarkably wide variety of pharmacological activities, including anti-inflammatory,[3] antihypertensive and antipsychotic,[4] vasodilatory,[5] and anticancer (Figure 1).[6]

Ever since the pioneering work of Heck and Schoenberg in 1974, palladium-catalyzed carbonylations using CO enabled the synthesis of a variety of highly valued compounds.[7] Nowadays, these reactions are routinely applied for constructing carbonyl-containing compounds, such as aldehydes, amides, esters, etc.[8] Notably, CO is one of the cheapest C1 feedstocks available.[9] Although the advantages of incorporating one CO molecule are well established, the incorporation of two CO molecules into the parent structure in a one-pot fashion is even more attractive but challenging.[10]

Due to the wide range and applicability of isoindolinones and its related derivatives in medicinal and pharmaceutical industry, their synthesis has drawn the interest of many organic chemists and has become the subject of intense research. However, the development of general, simple, new, and efficient synthetic methods to produce isoindolinones derivatives are still needed. Traditionally, the most common approach for the synthesis of isoindolinones is a Diels–Alder cycloaddition[11] and Wittig reagents.[12] However, these methods generally require multiple reaction steps and are unsatisfactory both in yield and generality. Recently, Cooper and co-workers reported an efficient method for N-substituted isoindolinones by aza-Wittig/cyclization reactions.[13] In 2011, Beller and co-workers found isoindolinones can be produced by monoreduction of phthalimide using polymethylhydrosiloxane and fluoride ions as the catalyst system.[14] Moreover, C–H functionalization by using transition metals as catalysts has also been reported as an efficient synthetic method for the production of isoindolinones.[15] Alper and co-workers described two efficient synthetic approaches for the construction of isoindolinone derivatives in phosphonium salt ionic liquids through Pd-catalyzed carbonylation hydroamination reactions of 1-halo-2-alkynylbenzene and amines.[16] Massa and co-workers reported the first organocatalytic asymmetric synthesis of 3-substituted isoindolinones.[17] Recently, Lin and co-workers reported an efficient three-component reaction of 2-formylbenzoic acid, ammonia, and 4-hydroxycoumarin or indole in water, which leads to the formation of 3-heterocyclic-substituted isoindolinones in good yields.[18]

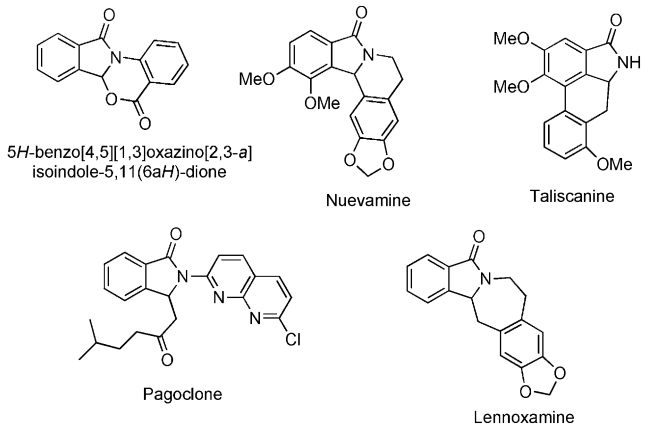

Figure 1. Selected examples of bioactive isoindolinones.

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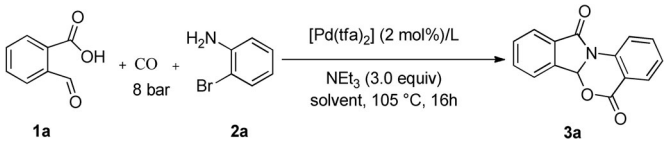
Over the last five years, we have been interested in applying carbonylation procedures to the preparation of heterocyclic compounds.[19] Several procedures have been developed for the synthesis various heterocycles. More recently, we documented an efficient synthesis of N-substituted aminopyridine pthalimides through palladium-catalyzed double carbonylation of *o*-bromobenzenes. We also synthesized a thalidomide drug in excellent yield in a one-pot manner, which is known as an inhibitor for the production of TNF.[19j] Inspired by these results and our continued interest in palladium-catalyzed carbonylative heterocycles synthesis and as well the importance of isoindolinones, we wondered whether we could obtain isoindolinones, simply by doing carbonylation of 2-bromoanilines with 2-formylbenzoic acid and 2-bromobenzaldehydes. In this report, we describe a convenient and straightforward palladium-catalyzed procedure for the synthesis of functionalized isoindolininones. To the best of our knowledge, there is no brief report existing for the synthesis of new functionalized isoindolinone molecules.

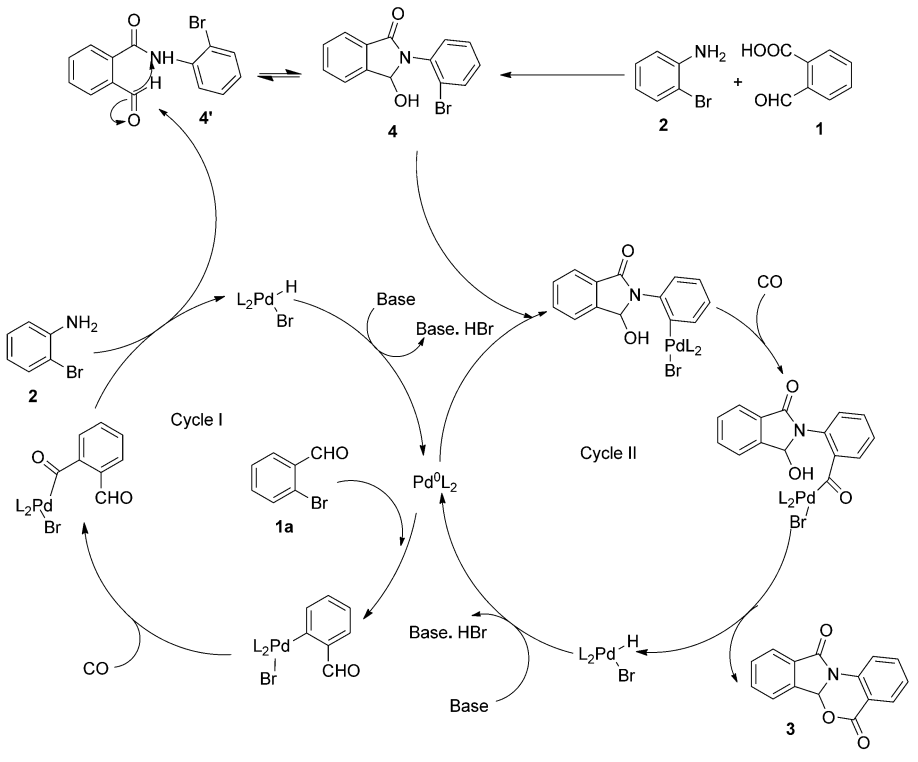
As the starting point for the optimization, we chose the reaction of 2-formylbenzoic acid (**1a**) with 2-bromoaniline (**2a**) as the model reaction. Various phosphine ligands were tested in the presence of 2 mol% of $[Pd(tfa)_2]$ (tfa = trifluoroacetic acid).as the catalyst precursor. Among seven different commonly used trialkylphosphine ligands, $BuPAd_2$ (Table 1, entry 4) gave a moderate yield compared to the other phosphine ligands (entries 1–3, 5–7). Eventually, $PtBu_3{\cdot}HBF_4$ was found to be the most suitable ligand for this carbonylative coupling reaction due to its high electron-donating ability and steric properties (entry 8). Then, different solvents (CH_3CN, DMF, THF, 1, 4-dioxane) were also screened. More specifically, acetonitrile provided the best result compared to all the other tested solvents with NEt_3 as the base. Temperature is very crucial for this reaction, when we performed the reaction at 80 °C (entry 12), only 44% of isolated desired product was obtained, the rest of the compound was formed as an intermediate (Scheme 1, intermediate 4; 2-(2-bromophenyl)-3-hydroxyisoindolin-1-one). At last, we succeeded in obtaining **3a** in 86% isolated yield under our optimized conditions (entry 8) (**1a** (1.2 equiv), **2a** (1 equiv), $[Pd(tfa)_2]$ (2 mol%), $PtBu_3{\cdot}HBF_4$ (6 mol%), Et_3N (3 equiv), toluene, CH_3CN (2 mL), 106 °C, 8 bar of CO). These promising results encouraged us to study the general scope and limitations for the carbonylation of 2-bromoaniline with 2-formylbenzoic acid.

Table 1. Optimization of the palladium-catalyzed carbonylation of 2-bromoanilines with 2-formyl benzoic acid.[a]



Entry	Ligand	Solvent	**3a** Yield [%][b]
1	dppe (3 mol%)	acetonitrile	12
2	dppb (3 mol%)	acetonitrile	16
3	dppf (3 mol%)	acetonitrile	11
4	$BuPAd_2$ (6 mol%)	acetonitrile	45
5	Xantphos (3 mol%)	acetonitrile	19
6	PPh_3 (6 mol%)	acetonitrile	27
7	PCy_3 (6 mol%)	acetonitrile	14
8	$PtBu_3{\cdot}HBF_4$ (6 mol%)	acetonitrile	90 (86)
9[c]	$PtBu_3{\cdot}HBF_4$ (6 mol%)	acetonitrile	83 (71)
10[d]	$PtBu_3{\cdot}HBF_4$ (6 mol%)	acetonitrile	75 (66)
11[e]	$PtBu_3{\cdot}HBF_4$ (6 mol%)	acetonitrile	78
12[f]	$PtBu_3{\cdot}HBF_4$ (6 mol%)	acetonitrile	(44)
13	$PtBu_3{\cdot}HBF_4$ (6 mol%)	DMF	35
14	$PtBu_3{\cdot}HBF_4$ (6 mol%)	THF	47
15	$PtBu_3{\cdot}HBF_4$ (6 mol%)	1,4 dioxane	28

[a] Reaction conditions: **1a** (0.6 mmol), **2a** (0.5 mmol), NEt_3 (1.5 mmol), solvent (2 mL), 105 °C, CO (8 bar), time (16 h). [b] GC yield using hexadecane as internal standard, isolated yields are in written in brackets. [c] 1.5 mmol of **2a**, [d] 2 mol% $Pd(OAc)_2$, [e] 5 mol% $Pd(OAc)_2$, 10 mol% $PtBu_3{\cdot}HBF_4$, [f] 80 °C. NEt_3: triethylamine. Yields were calculated based on **2**. dppe = 1,2-bis(diphenylphosphino)ethane; dppb = 1,4-bis(diphenylphosphino)butane; dppf = 1,1′-bis(diphenylphosphino)ferrocene.



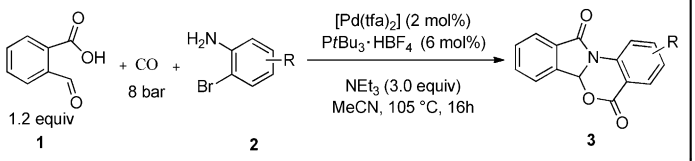
Scheme 1. Proposed reaction mechanism.

Various 2-haloanilines were tested at the first stage. Notably, carbonylation of 2-iodoaniline with **1a** led to an 88% yield of the desired product (Table 2, entry 3). When changing the iodo/bromo substituent to chloro, unfortunately, a low yield of the desired product was formed (entry 2), most of the 2-chloroaniline remained in the reaction solution. Furthermore, we also conducted an experiment with 3-amino-2-chloropyridine; however, unfortunately, only 12% of the desired product was obtained (entry 4). To our delight, different substituted 2-bromoanilines were successfully transformed and gave the corresponding valuable isoindolinones in good to excellent yields. An excellent yield was observed with chloro-substituted 2-bromoaniline (entry 5). Remarkably, methyl-substituted 2-bromoanilines can be applied as substrates in this reaction as well and succeeded in providing the desired products in excellent yields (entries 7 and 8). Noticeably, electron-withdrawing acetyl-substituted 2-bromoaniline was well-tolerated and obtained in good isolated yield (entry 11). Considering the broad applications of the fluoro group in bioactive compounds, different fluoro-substituted 2-bromoanilines were tested and good yields of the corresponding products were obtained (entries 6, 9–10).

To further demonstrate the applicability of our procedure, we then performed carbonylative coupling reactions of three different 2-bromoaniline substrates with 2-bromobenzaldehyde. As shown in Table 3, good yields of the respective isoindolinones were obtained. Noteworthy, the reaction takes place through a palladium-catalyzed double-carbonylation process. In this reaction, at least two new C–N and C–O bonds are formed. When changing the bromo substituent to an iodo leaving group, the reaction proceeded slightly better (66%), and an identical desired product was obtained (Table 3, entry 2). Furthermore, when 2-idodobenzaldehyde undergoes palladium-catalyzed double carbonylation with chloro-substituted 2-bromoaniline, 70% of the desired product was obtained (entry 4). By observing these results, we can deduce that the double carbonylation with 2-iodobenzaldehyde is more efficient than 2-bromobenzaldehyde. Nevertheless, different substituted 2-bromobenzaldehydes like 6-bromoveratraldehyde, 6-bromo-1-3-benzodioxole-5-carboxaldehyde, 5-bromo-1-3-benzodioxole-5-carboxaldeyhde, 2-bromo-5-fluorobenzaldehyde, etc. were also tested under our developed optimized reaction conditions, but unfortunately very poor yields were obtained, which demonstrates the challenging nature of this double carbonylative coupling reaction.

Based on previous mechanistic studies and our own understanding, a plausible reaction pathway is given in Scheme 1. Starting from 2-bromoaniline **2** and 2-bromobenzaldehyde **1**, the first aminocarbonylation occurred and provides amide **4′** (cycle I). It should be noted that the oxidative insertion of the active palladium species occurs preferentially at **1a** due to their higher reactivity. Next, base-catalyzed isomerization–cyclization should form the bromo-hydroxy isoindolinone **4** as the key intermediate that was detected in the optimization process as well (Scheme 1).

Table 2. Carbonylative reactions of 2-formylbenzoic acid with various 2-bromo anilines.[a]



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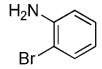
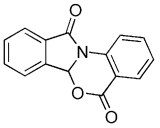
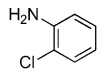
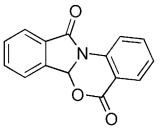
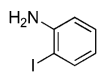
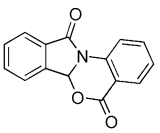
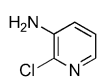
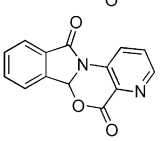
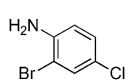
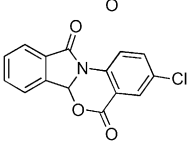
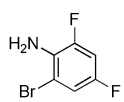
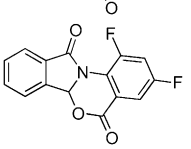
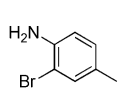
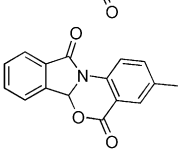
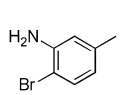
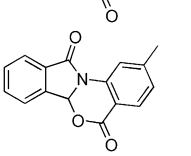
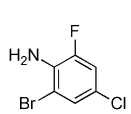
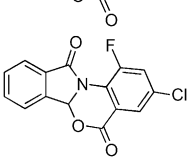
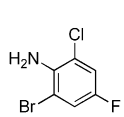
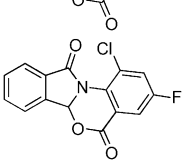
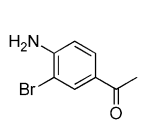
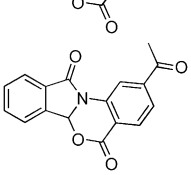
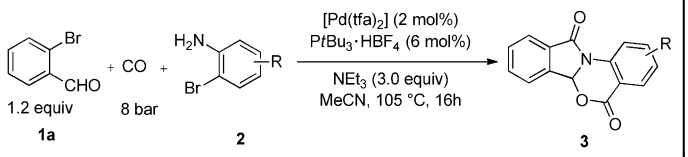
1			86
2[c]			22
3[c]			88
4[d]			12
5			85
6			83
7			86
8			92
9			72
10			73
11			81

[a] Reaction conditions: **1** (0.6 mmol), **2** (0.5 mmol), NEt_3 (1.5 mmol), acetonitrile (2 mL), 105 °C, CO (8 bar), time (16 h). [b] Isolated yields. [c] GC yield. [d] Yield determined by GCMS. Yields were calculated based on **2a**.

Table 3. Carbonylative reactions of 2-bromobenzaldeyhde with various 2-bromo anilines.[a]



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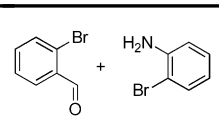
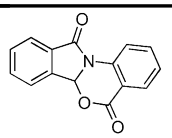
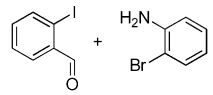
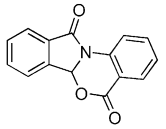
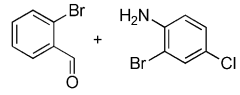
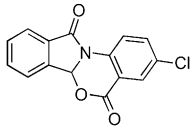
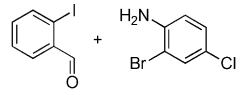
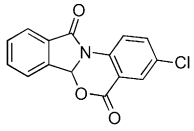
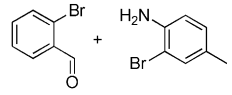
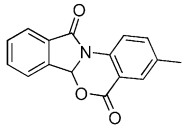
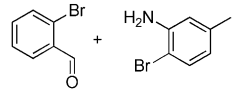
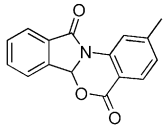
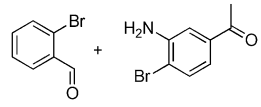
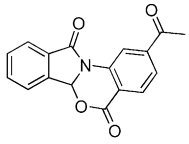
1			53
2			66
3			49
4			70
5			38
6			45
7			32

[a] Reaction conditions: **1a** (0.6 mmol), **2** (0.5 mmol), NEt_3 (1.5 mmol), acetonitrile (2 mL), 105 °C, CO (8 bar), time (16 h). [b] GC yields. Yields were calculated based on **2**.

This intermediate readily undergoes an intramolecular carbonylative cyclization reaction to provide the final product **3** (cycle II).

In conclusion, we have developed a convenient and highly efficient cascade palladium-catalyzed carbonylative approach to functionalized isoindolinones from readily available materials. The reported compounds will be a new entry into the synthesis of the isoindolinone family. Other remarkable advantages of this methodology include operationally simple, practical, high isolated yields in a one-pot fashion that allows C–C bond and C–N bond formation with excellent outcomes under relatively mild conditions.

Experimental Section

General

An oven-dried vial (12 mL) with a stir bar was charged with 2-bromoaniline (0.5 mmol, 1 equiv), 2-formylbenzoic acid (1.2 mmol, 1.2 equiv), $[Pd(TFA)_2]$ (0.02 mmol, 2 mol%), and $PtBu_3{\cdot}HBF_4$ (0.06 mmol, 6 mol%) and was put into a 25 mL Schlenk flask, which was subsequently evacuated and refilled with argon three times. Then, acetonitrile (2 mL) and Et_3N (1.5 mmol, 3 equiv) were sequentially injected into the vial under argon flow. The vial (or several vials) was placed in an alloy plate, which was transferred into a 300 mL autoclave of the 4560 series from Parr Instruments under an argon atmosphere. After flushing the autoclave three times with CO, a pressure of 8 bar CO was adjusted at ambient temperature. The reaction mixture was heated overnight (16 h) at 105 °C. After the reaction had finished, the autoclave was cooled down to room temperature and the pressure was carefully released. The product was extracted with ethyl acetate (5×3 mL). The organic layers were washed with brine, dried over Na_2SO_4, and evaporated to yield the crude reaction mixture. The purification was carried out by combi falsh machine flash chromatography on silica gel (eluent: heptane/EtOAc 60:40).

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Keywords: carbonylation · cascade reactions · heterocycles · isoindolinones · palladium

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8.12 Highly Efficient Four-Component Synthesis of 4(3*H*)-Quinazolinones: Palladium-Catalyzed Carbonylative Coupling Reactions

Lin He, Haoquan Li, Helfried Neumann, Matthias Beller,* and Xiao-Feng Wu*

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Contributions

In this paper, I was involved in part of the optimization of the model system and also developed part of the substrate scope. Thus my overall contribution to this work approximately accounts for 30%.

Multicomponent Reactions

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Highly Efficient Four-Component Synthesis of 4(3*H*)-Quinazolinones: Palladium-Catalyzed Carbonylative Coupling Reactions**

Lin He, Haoquan Li, Helfried Neumann, Matthias Beller, and Xiao-Feng Wu**

Abstract: *Given the importance of quinazolinones and carbonylative transformations, a palladium-catalyzed four-component carbonylative coupling system for the synthesis of diverse 4(3H)-quinazolinone in a concise and convergent fashion has been developed. Starting from 2-bromoanilines (1 mmol), trimethyl orthoformate (2 mmol), and amines (1.1 mmol), under 10 bar of CO, the desired products were isolated in good yields in the presence of $Pd(OAc)_2$ (2 mol %), $BuPAd_2$ (6 mol %) in 1,4-dioxane (2 mL) at 100 °C, using N,N-diisopropylethylamine (2 mmol) as the base. Notably, the process tolerates the presence of various reactive functional groups and is very selective for quinazolinones, and was used in the synthesis of the precursor to the bioactive dihydrorutaempine.*

The pursuit of sustainable chemistry has stimulated the development of new strategies and technologies for the synthesis of useful products in a safe, compact, and energy-efficient manner. In this regard, multicomponent reactions (MCRs)[1] which directly yield the target products by domino or cascade reaction sequences offer significant advantages over conventional linear-step syntheses. The resulting reduced number of synthetic and purification steps for a given molecule increases the attractiveness and practicability of the process.[2] In the ideal situation, a MCR occurs when the different transformations are mediated by the same catalytic precursor in a one-pot, one-step operation. Significant success has been achieved under this paradigm as illustrated by the growing number of processes for three-component reactions.[3] In contrast, a rather limited number of MCRs involving four or more reagents have thus far proved to be reliable enough to be among the usual synthetic tools.[4] This clearly demonstrates the increasing difficulty in finding a suitable catalytic system when increasing the number of components. Not surprisingly though, the balance between activity and selectivity is generally hard to achieve, as a sharp penalty has to be paid because of side reactions. Thus, the implementation of a straightforward MCR strategy with efficient catalytic control remains a formidable challenge.

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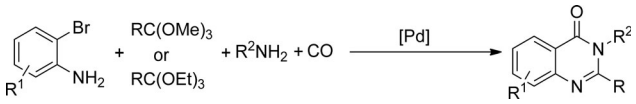
Over the years, the transition-metal-catalyzed MCRs have emerged as a powerful approach for the construction of C–X (X = C, N, O, etc.) bonds.[5] One representative example is the palladium-catalyzed carbonylative reactions, which hold an important status because of the high levels of selectivity generally observed, and the variety of bond-forming processes available.[6] Furthermore, concomitant incorporation of CO (one of the cheapest C1 source) into the final products may contribute to increasing the diversity of accessible compounds in many ways. Indeed, many elegant three-component carbonylative coupling reactions have been developed, thus providing rapid and convergent syntheses of complex organic molecules from readily available starting materials.[7] In this contribution, our laboratory and other research groups have presented several strategic options for the preparation of various heterocycles.[8,9] In pursuing our interest in finding more sophisticated MCRs, we sought to use palladium-catalyzed carbonylative reactions for the concise one-pot, four-component synthesis of valuable N-containing heterocyclic compounds. To date, only rare examples of such reactions (mainly performed in two steps manner) have been reported.[10]

As one of the most frequently encountered heterocycles in medicinal chemistry, 4(3*H*)-quinazolinones are present in a large family of products with broad pharmacological properties including antimalarial, antitumor, anticonvulsant, fungicidal, antimicrobial, and anti-inflammatory.[11] Furthermore, the heterocyclic core constitutes more than 40 alkaloids isolated from natural products.[12] In view of their importance, a number of methods for 4(3*H*)-quinazolinone preparation have been developed. These routes, however, mainly rely on using anthranilic acid or its derivatives as the starting materials, and generally suffer from low yields, multistep reactions, or harsh reaction conditions.[13] Recently, Willis and co-workers reported a straightforward procedure for the synthesis of quinazolinones.[14] They used *N*-(*o*-halophenyl)-imidates as their substrates, and the desired products were produced in good yields. Herein, we wish to report our new achievement in the carbonylative synthesis of quinazolinones. We started from commercially available 2-bromoanilines, amines, and *ortho*-esters, and various 4(3*H*)-quinazolinones were isolated in moderate to excellent yields from palladium-catalyzed aminocarbonylation reactions (Scheme 1).

Initially, the reaction was carried out with 2-bromoaniline (1 mmol), aniline (1.1 mmol), CO (10 bar), and triethyl orthoformate (2 mmol) in the presence of $Pd(OAc)_2$ (2 mol %), $BuPAd_2$ (CataCXium A, 6 mol %) at 120 °C for 16 hours. The expected four-component reaction occurred and 3-phenyl-4(3*H*)-quinazolinone (**1**) was formed as the major product (63 % GC yield) by using NEt_3 (2 mmol) as the

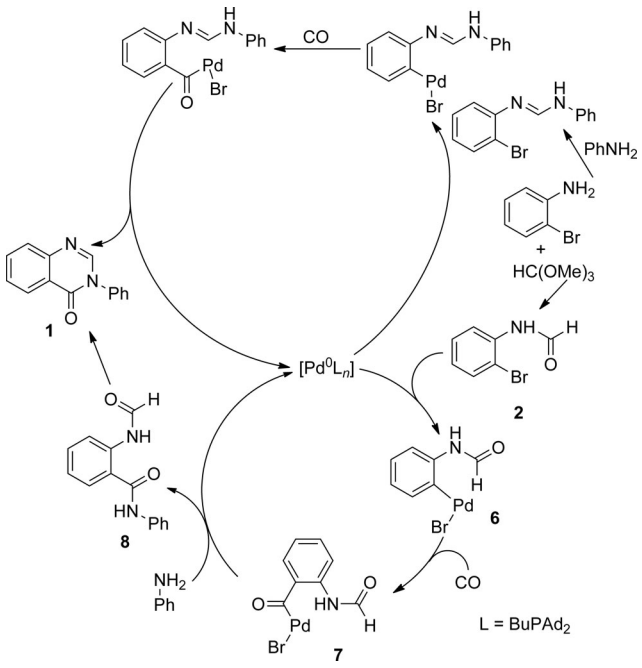


Scheme 1. Concept of the catalytic multicomponent coupling reaction for the synthesis of 4(3*H*)-quinazolinones.

base in 1,4-dioxane (2 mL). Among numerous by-products, four of them, namely *N*-(2-*b*romophenyl)formamide (**2**), *N*-phenylformamide (**3**), ethyl 2-aminobenzoate (**4**), and ethyl 2-formamidobenzoate (**5**) were identified by GC-MS (6–9% yield). This result was encouraging, since it is not easy to avoid side reactions for a reaction of such complexity. To our delight, by replacing triethyl orthoformate with trimethyl orthoformate, the desired 4(3*H*)-quinazolinone can be obtained in remarkably high yield (86% yield upon isolation, 94% GC yield). The yield of the isolated product could be further improved to 92% by using 2 mmol of DIPEA (*N*,*N*-diisopropylethylamine) as a base under milder reaction conditions (100 °C), whereas a decreased yield was observed when either K_3PO_4 or Na_2CO_3 was used. In the presence of DIPEA, the air-stable $BuPAd_2$ showed superior performance compared to ligands such as PPh_3 and DPPP. The high selectivity of the present four-component system, coupled with its ability to react under mild reaction conditions, significantly improves the economic and environmental impacts of this palladium-catalyzed carbonylative coupling process.

To gain insight into a reaction mechanism, control experiments were conducted. It was confirmed that the direct conversion of 2-bromoaniline and *N*-phenylformamide (**2**) under 10 bar of CO afford the desired product, while the combination of aniline, CO (10 bar), and *N*-(2-bromophenyl)formamide (**3**), which is the condensation product of 2-bromoaniline with trimethyl orthoformate through an ether cleavage of the imidate motif, led to **1** in near quantitative yield (95% GC yield) under the optimized reaction conditions. On the basis of the above observations and the known chemistry of the palladium-catalyzed carbonylative cyclizations, a possible reaction mechanism has been proposed in Scheme 2. Initially, the reaction of 2-bromoaniline with trimethyl orthoformate gave **2** as the intermediate. Then, oxidative addition of the in situ generated active Pd^0 complex to **2** results in the arylpalladium complex **6**. After the coordination and insertion of CO, the acylpalladium complex **7** is produced. After nucleophilic attack of aniline on the acylpalladium complex, **8** was eliminated and gave the terminal product **1** after intramolecular condensation. Pd^0 can be regenerated with the assistance of a base and thus starts the next catalytic cycle. A catalytic cycle involving (*E*)-*N*′-(2-bromophenyl)-*N*-phenylformimidamide as an intermediate cannot be excluded.

With these findings in hand, we extended this straightforward synthesis of 4(3*H*)-quinazolinones to a wider range of amines and 2-bromoanilines. As depicted in Table 1 and Table 2, the present $Pd(OAc)_2$/$BuPAd_2$ catalytic system was surprisingly versatile. Structurally diverse amines, including aromatic and aliphatic ones react with 2-bromoaniline to give

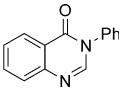
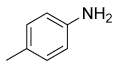
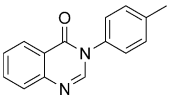
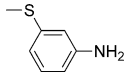
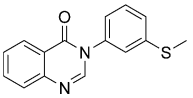
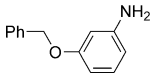
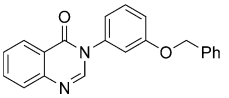
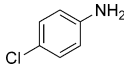
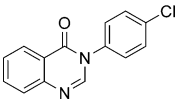
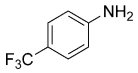
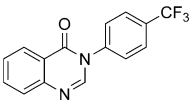
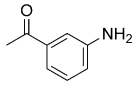
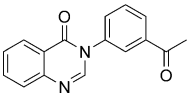
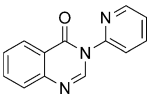
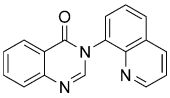
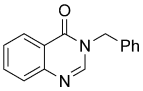
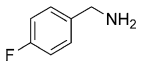
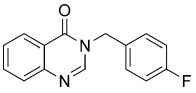
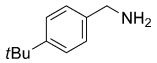
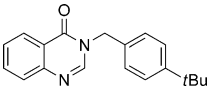
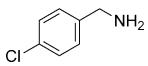
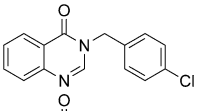
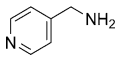
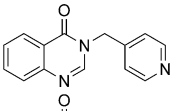
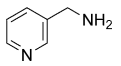
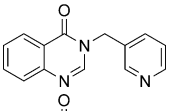
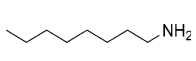
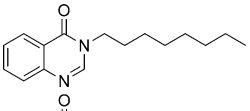
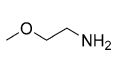
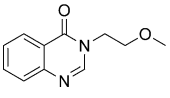


Scheme 2. Proposed reaction mechanism.

the desired products in good to excellent yields (Table 1, entries 1–17). Various anilines, regardless of the presence of electron-donating or electron-withdrawing groups reacted smoothly to give 71–92% yields of the isolated products (entries 2–7). Strikingly, a wide range of synthetically useful functional groups including thioether, benzyloxy, halide, and trifluoromethyl groups, as well as ketone moieties remained intact during the reaction. Also, the present system shows excellent promise for the transformation of heteroaromatic amines (entries 8 and 9). Notably, the notoriously difficult benzylamines were successfully converted into the corresponding 4(3*H*)-quinazolinones (60–73% yields; entries 10–15). When alkylamines were employed, it was found that N-alkylquinazolinones could be obtained in excellent yields (80–84%, entries 16 and 17). More importantly, this one-pot, four-component synthesis of 4(3*H*)-quinazolinone could be easily scaled up. For example, by using DIPEA (20 mmol) as a base, the direct conversion of 2-bromoaniline (10 mmol), aniline (11 mmol), triethyl orthoformate (20 mmol), and CO (10 bar) in the presence of $Pd(OAc)_2$ (2 mol%), and $BuPAd_2$ (Cata-CXium A, 6 mol%) proceeded smoothly in 1,4-dioxane (20 mL) at 120 °C, thus affording 3-phenyl-4(3*H*)-quinazolinone in 70% yield within 24 h (Table 1, entry 1).

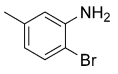
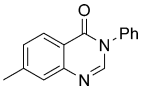
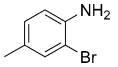
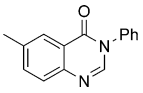
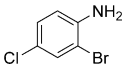
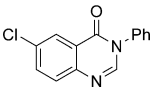
To further demonstrate the general applicability of this procedure, we then choose aniline as a standard substrate to perform the test reactions with different 2-bromoanilines (Table 2). Both electron-donating and electron-withdrawing substituents are tolerable under the present reaction conditions (Table 1, entries 1–9). Of particular note is the utility of our method for the preparation of fluorinated 4(3*H*)-quinazolinones from commercially available 2-bromoanilines. It is well known that fluorine-containing functional groups can drastically change both the biological and physical properties of organic molecules.[15] We were pleased to find

Table 1: Palladium-catalyzed carbonylative coupling of various amines with 2-bromoanilines, trimethyl orthoformate, and CO.[a]

Entry	Amine	Product	Yield [%][b]
1			92 70[c]
2			81
3			82
4			71
5			83
6			85
7			79
8			68
9			80
10			60[d]
11			71[d]
12			68[d]
13			67[d]
14			73[d]
15			69[d]
16			84[d]
17			80[d]

[a] 2-Bromoaniline (1 mmol), trimethyl orthoformate (2 mmol), amine (1.1 mmol), CO (10 bar), $Pd(OAc)_2$ (2 mol%), $BuPAd_2$ (6 mol%), 1,4-dioxane (2 mL), DIPEA (2 mmol), 100°C, 16 h. [b] Yields of isolated products. [c] 10 mmol scale. [d] NEt_3 (2 mmol), 120°C.

Table 2: Palladium-catalyzed carbonylative coupling of various 2-bromoanilines with trimethyl orthoformate, aniline, and CO.[a]

Entry	2-Bromoaniline	Product	Yield [%][b]
1			70
2			73
3			72
4			84
5			69
6			65
7			75
8			80
9			85

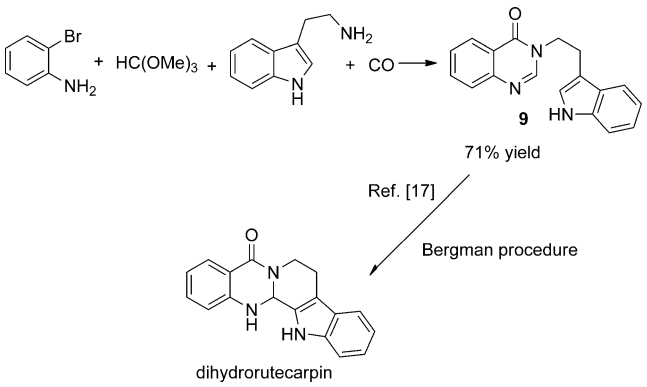
[a] 2-Bromoaniline (1 mmol), trimethyl orthoformate (2 mmol), aniline (1.1 mmol), $Pd(OAc)_2$ (2 mol%), $BuPAd_2$ (6 mol%), 1,4-dioxane (2 mL), DIPEA (2 mmol), 100°C, CO (10 bar), 16 h. [b] Yields of isolated products.

that all five 2-bromoanilines bearing fluoro, trifluoromethyl, and trifluoromethoxyl groups are suitable substrates for this procedure (65–84% yields of isolated products, entries 4–8). As a representative example of a heterocycle, 3-bromopyridin-2-amine can also be used as a substrate and resulted in the desired products in 85% yield. This result is remarkable, considering that the strong coordinating capability of such generally makes the reaction more difficult to proceed.

Besides trimethyl orthoformate, other *ortho* esters including trimethyl orthoacetate, trimethyl orthopropionate, and trimethyl orthobenzoate can also be used in the process. However, the yields of the corresponding 4(3*H*)-quinazolinones were around 15% under standard reaction conditions. The yields can be improved to 30–35% by using 2 equivalents of 2-bromoaniline.

Given the importance of the 4(3*H*)-quinazolinone nucleus in many natural products, we wanted to demonstrate the utility of this method for the synthesis of a pharmaceutically relevant alkaloids. One such target with fundamental biological interest is dihydrorutecarpin, a quinazolino carboline alkaloid which was used for more than 2000 years in Chinese

medical practice as a remedy for gastrointestinal disorders (abdominal pain, dysentery), headache, amenorrhea, and postpartum hemorrhage.[16] By the present convergent synthetic approach, carbonylative coupling of 2-bromoaniline and trimethyl orthoformate with tryptamine under 10 bar of CO provides 3-[2-(3-indolyl)ethyl]-4(3*H*)-quinazolinone (**9**) in 71% yield (Scheme 3). The treatment of **9** with trifluoroacetic anhydride effected cyclization to (trifluoroacetyl)-13*b*,l4-dihydrorutaecarpin, which can be readily hydrolyzed to the desired dihydrorutaempine according to the Bergman procedure.[17]



Scheme 3. Palladium-catalyzed four-component carbonylative coupling reaction for the synthesis of dihydrorutecarpin.

In summary, we have developed a novel palladium-catalyzed four-component carbonylative coupling system for the selective construction of 4(3*H*)-quinazolinones in a one-pot fashion. The easy generation of molecular diversity along with the importance of 4(3*H*)-quinazolinones in medicinal chemistry makes the reaction described herein an appropriate alternative for the synthesis of potentially bioactive compounds. In this context, and considering the simplicity of the starting materials, the reaction is suitable for the synthesis of small libraries of functionalized 4(3*H*)-quinazolinones. Notably, this interesting procedure can be easily scaled up and its application in the synthesis of the bioactive dihydrorutaempine precursor was successful.

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8.13 Palladium-Catalyzed Aminosulfonylation of Aryl Iodides by using Na_2SO_3 as the SO_2 Source

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European Journal of Organic Chemistry, 2014, 15, 3101-3103.

Contributions

In this paper, I was involved in the discussion and interpretation of the results. Thus my overall contribution to this work approximately accounts for 10%.

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SHORT COMMUNICATION

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Palladium-Catalyzed Aminosulfonylation of Aryl Iodides by using Na_2SO_3 as the SO_2 Source

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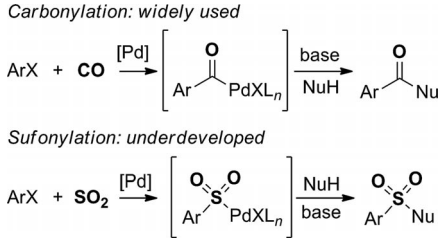
Keywords: Synthetic methods / Cross-coupling / Aminosulfonylation / Palladium / Sulfur

We realized an interesting palladium-catalyzed aminosulfonylation of aryl iodides by using Na_2SO_3 as a cheap SO_2 source. In most cases, the yields were comparable to those reported by using the 1,4-diazabicyclo[2.2.2]octane bis(sulfur dioxide) adduct (DABCO·2SO_2, DABSO) as the SO_2 source.

Introduction

Over the past decades, carbon monoxide has evolved in metal-catalyzed carbonylation reactions as an inexpensive and clean C1 source.[1] The most important catalytic transformation of CO is its insertion into metal–carbon bonds to generate acyl metal intermediates, which can be trapped by various nucleophiles. Having certain similarities in coordination chemistry with CO, SO_2 also undergoes many insertion reactions to form sulfinato metal complexes.[2] However, these complexes, especially those with transition metals, cannot easily be attacked by nucleophiles as acyl metal intermediates can (Scheme 1).[3] Incorporation of SO_2 into organic molecules is of great interest, as the sulfonyl moiety (–SO_2–) occurs in many useful organic compounds.[4] Traditionally, the introduction of a sulfonyl group is realized by using sulfuric acid, oleum, or chlorosulfonic acid.[5] The direct utilization of SO_2 as a sulfonyl source would be an extremely efficient method.



Scheme 1. Pd-catalyzed carbonylation and sulfonylation reactions.

The insertion of SO_2 into R–M bonds (in which M = Mg, Li) has been reported for the synthesis of sulfonamides and sulfones.[6] However, similar processes proved to be unsuccessful in transition-metal-catalyzed sulfonylations. This may be attributed to the multiple coordination patterns of SO_2 with transition metals.[2a] As a pilot exploration, Willis and co-workers realized the aminosulfonylation of aryl halides by using DABSO as a SO_2 equivalent (DABSO = 1,4-diazabicyclo[2.2.2]octane bis(sulfur dioxide) adduct, DABCO·2SO_2).[7] Afterwards, many sulfonylation reactions were developed with DABSO[8] and $K_2S_2O_5$[9] as SO_2 sources. DABSO is a stable solid at room temperature; thus, it is easy to handle if used as a surrogate for toxic SO_2 gas in many cases.[10] It is now commercially available but still relatively expensive.[11] Moreover, its preparation also employs a large over amount of SO_2.[12] In view of the accumulated experience in catalytic manipulations of CO, H_2, and CO_2 in our group, we started a project to investigate the catalytic transformation of SO_2 into sulfonyl-containing compounds.

Results and Discussion

For safety and convenience issues, we used the cheap and widely available raw materials sodium sulfite (Na_2SO_3) and concentrated sulfuric acid (H_2SO_4) to produce SO_2 at room temperature. Our reaction set up is depicted in Figure 1. For palladium-catalyzed carbonylation reactions, such a two-chamber reactor has already gathered more attention.[13] In tube A, the SO_2 gas is generated ex situ and conducted into reaction tube B through a poly(propene) pipe. The drying tube between A and B was omitted because moisture was reported to accelerate SO_2 insertion reactions.[14] Before the reactants and catalyst were loaded, the whole system was evacuated through the Schlenk line, and thus, the SO_2 gas would fill the two tubes (see the Supporting Information for details). The SO_2 pressure was roughly calculated to be approximately 150 kPa on the basis of the amount of sodium sulfite and the system volume. Besides, SO_2 is highly soluble in organic solvents; thus, the actual pressure should be lower and safe enough for the reaction.[15]

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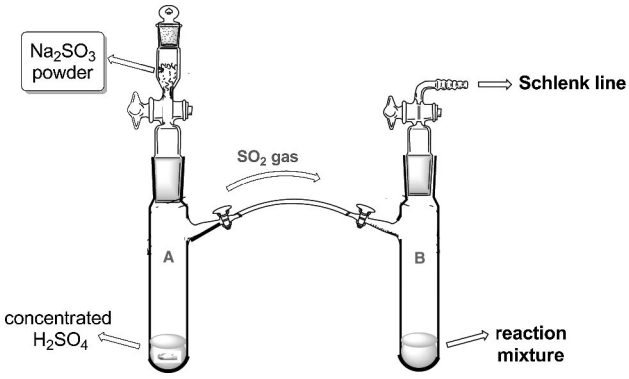
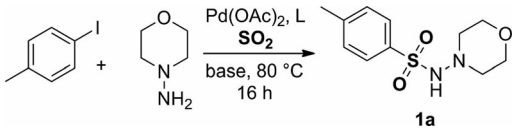


Figure 1. Ex situ generation of SO_2 for aminosulfonylation.

In the initial report by Willis,[7] they stated that gaseous SO_2 failed to give the desired aminosulfonylation products by using a variety of nucleophiles and catalysts. Herein, we found that under similar reaction conditions, gaseous SO_2 could also be directly used to synthesize sulfonamides.

We started our initial studies with 4-iodotoluene and *N*-aminomorpholine. First, triphenylphosphine (PPh_3) was used as the ligand and DABCO was used as the base, but only 7% yield of **1a** was obtained (Table 1, entry 1). Upon using Cs_2CO_3, the yield increased significantly to 44% (Table 1, entry 3). The nature of the base clearly affected the reaction (Table 1, entries 4–10). To our delight, the product was isolated in 93% yield if $P(t\text{Bu})_3$ was used as the ligand and Cs_2CO_3 was used as the base (Table 1, entry 10).

Table 1. Optimization of the aminosulfonylation of 4-iodotoluene.[a]



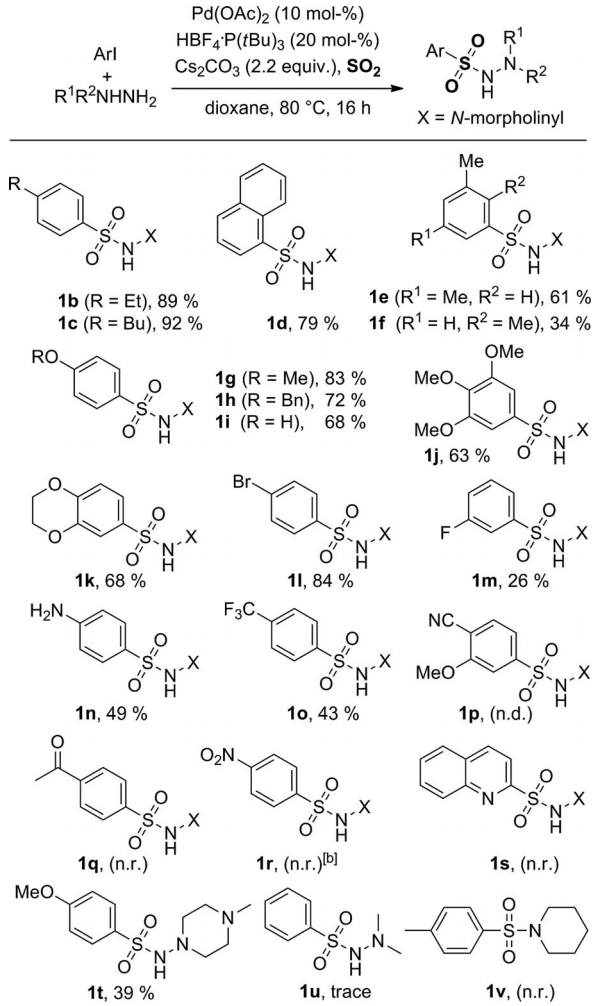
Entry	Ligand	Base	Yield[b] [%]
1	PPh_3	DABCO	7
2	PCy_3	DABCO	15
3	PPh_3	Cs_2CO_3	44
4	$P(t\text{Bu})_3{\cdot}HBF_4$	DABCO	23
5	$P(t\text{Bu})_3{\cdot}HBF_4$	DABCO (1 equiv.)	54
6	$P(t\text{Bu})_3{\cdot}HBF_4$	CsF	52
7	$P(t\text{Bu})_3{\cdot}HBF_4$	KF	34
8	$P(t\text{Bu})_3{\cdot}HBF_4$	NaOAc	–
9	$P(t\text{Bu})_3{\cdot}HBF_4$	KOH	44
10	$P(t\text{Bu})_3{\cdot}HBF_4$	Cs_2CO_3	93 (75)[c]
11	$P(t\text{Bu})_3{\cdot}HBF_4$	Cs_2CO_3 (1.2 equiv.)	21
12[d]	$P(t\text{Bu})_3{\cdot}HBF_4$	Cs_2CO_3	41
13[e]	dppp	Cs_2CO_3	60
14	$BuPAd_2$	Cs_2CO_3	56
15[f]	$P(t\text{Bu})_3{\cdot}HBF_4$	Cs_2CO_3	53
16[g]	$P(t\text{Bu})_3{\cdot}HBF_4$	Cs_2CO_3	22

[a] Reaction conditions: 4-Iodotoluene (0.25 mmol), *N*-aminomorpholine (1.5 equiv.), $Pd(OAc)_2$ (10 mol-%), ligand (20 mol-%), base (2.2 equiv.), 1,4-dioxane (1 mL), 80 °C, 16 h. Cy = cyclohexyl, dppp = 1,3-bis(diphenylphosphino)propane, Ad = adamantyl. [b] Yield of isolated product. [c] Yield in parentheses was obtained by using DABSO. [d] $Pd(OAc)_2$ (1 mol-%) and ligand (2 mol-%), 24 h. [e] Ligand (10 mol-%). [f] In DCE. [g] In DMF.

Notably, if DABCO (2.2 equiv.) was used as the base, the product was obtained in only 23% yield. This implied that DABSO might be more than a surrogate for SO_2, but a detailed reaction mechanism has not been mentioned in previous studies. Other ligands, for example, dppp and $BuPAd_2$ only gave moderate yields. Upon lowering the catalyst loading to 1 mol-%, the yield dropped to 41% after 24 h (Table 1, entry 12). Other solvents such as DMF and 1,2-dichloroethane (DCE) also gave lower yields (Table 1, entries 15 and 16). Therefore, the optimized conditions were assigned as the following: $P(t\text{Bu})_3$ as the ligand, Cs_2CO_3 as the base, and 1,4-dioxane as the solvent.

Having the optimized reaction conditions in hand, we next extended the aminosulfonation reaction to other substrates (Table 2). In most cases, the yields were moderate to good. Alkyl groups in the *ortho* and *meta* positions led to a clear decrease in the yield. For example, an *ortho*-methyl group led to 34% yield of **1f**. In general, electron-donating

Table 2. Pd-catalyzed aminosulfonation of aryl halides by using gaseous SO_2.[a]



[a] Yield of isolated product; n.t.: not detected owing to unselective reactions. n.d.: not detected owing to unreactive reactions; n.r.: no reaction. [b] 4-Nitro-1-iodobenzene was recovered for an unknown reason.

groups on the phenyl rings gave better yields. 4-Bromo-1-iodobenzene gave desired product **1l** in 84% yield, and bromobenzene was correspondingly unreactive even under harsher conditions. For cyano (see **1p**) and acetyl groups (see **1q**) on the aryl iodides, unselective reactions were observed. The use of a single N-heterocycle was attempted, but unfortunately formation of **1s** was not observed. Other nucleophiles such as morpholine, piperidine, and aniline were also used in the reaction, but the desired products were not detected.[7,8b]

Conclusions

In summary, we realized the first palladium-catalyzed aminosulfonylation of aryl iodides by using ex situ generated SO_2. In most cases, the yields were comparable to those reported by using DABSO as the SO_2 source. This success promises rich chemistry in palladium-catalyzed sulfonylation reactions by using SO_2, just as the use of CO did in carbonylation reactions. More sulfonylation reactions with the use of this simple, cheap, and safe method for the generation of SO_2 are underway in our laboratory.

Experimental Section

General Procedure: Two Schlenk tubes (10 mL) were connected by a short plastic pipe through their side arms (Figure 1). Concentrated sulfuric acid (0.5 mL) was added into tube A and Na_2SO_3 (500 mg) was put in the funnel. The air in the funnel was excluded by argon flow. Then, the whole system was vacuumed through the Schlenk line, and the stopcock of Schlenk tube B was closed. Next, the aryl iodide (0.25 mmol), $Pd(OAc)_2$ (5.61 mg, 25 μmol), $HP(tBu)_3BF_4$(14.51 mg, 50 μmol), Cs_2CO_3 (171 mg, 0.525 mmol), and 1,4-dioxane (1 mL) were added under an atmosphere of argon. Then, 4-aminomorpholine (36 μL, 0. 375 mmol) was added, and the argon gas in tube B was carefully removed by the Schlenk line. Finally, the stopcocks of the funnel and Schlenk tube B were opened slowly, and the whole system was filled with SO_2. Schlenk tube B was immersed in an oil bath, and the contents were stirred at 80 °C for 16 h. After cooling to room temperature, the mixture was filtered through Celite and then purified by flash column chromatography to give the pure product.

Supporting Information (see footnote on the first page of this article): Experimental details, characterization data, and copies of the ^1H NMR and ^{13}C NMR spectra of all final products.

Acknowledgments

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9 Miscellaneous

9.1 Curriculum Vitae

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Date of Birth: 10. Sept. 1988

● Education:

2013.7-Present Ph.D candidate, Leibniz-Institute for Catalysis, University of Rostock, Rostock, Germany

2011-2013.7 M. Sc., International Master in Molecular Catalysis and Green Chemistry, University of Rennes1, UMR CNRS 6226, Rennes, France (Graduation with level Très Bien)

2007.9-2011.6 B. Sc., Applied Chemistry, Huazhong University of Science and Technology, Wuhan, P. R. China

● Research Experience:

Since 2013.7 Research topics “Palladium catalyzed carbonylation reactions” (Supervisor: Prof. Dr. Matthias Beller.)

2011.9-2013.7 Research training on “Well defined iron complexes catalyzed hydrosilylation reactions” (Supervisors: Prof. Dr. Christophe Darcel and Dr. Jean-Baptiste Sortais)

2009.12-2011.6 Research training on “Novel synthetic methodologies on constructing and the ring-opening reaction of 3,4-dihydropyran” (supervisor: Prof. Dr. Yanlong Gu)

● Relevent Skills

- Organic and organometallic synthesis, eg. Kugelrohr distillation, Air-free techniques (Schlenk, glovebox etc.)
- Proficient with high-pressure equipment.
- Skilled in operation of analytical instrucments and data analysis, for example GC, GC-MS, NMR, IR etc.
- Excellent skills with MS Office, Chemdraw, Sci-Finder, Reaxys, NMR analysis

software (MestRenova, NMR notebook), Origin etc.

● Scholarships and Awards

2014	Chinese Government Award for Outstanding Self-Financed Graduate Students Abroad
2013.7	Leibniz Fellowship.
2011.9	Scholarship "La Fondation Rennes 1"
2011.7	Outstanding Graduate of Huazhong University of Science and Technology
2010.9	Scholarship from Shengyi Technology Co., Ltd.
2008.11	Scholarship from Eternal Chemical Co., Ltd.
2008.3	Scholarship of "Outstanding Academic Performance" **.**

● Language Skills:

Cantonese (*mother language*), Mandarin (*native*), English (*fluent*), French (*basic, CEFR-A2*), German (*intermediate, CEFR-B1*), Japanese (*JLPT-2),*

9.2 List of Publications

- Publications in peer-reviewed journals

1. **Haoquan Li**, Kaiwu Dong, Haijun Jiao, Helfried Neumann, Ralf Jackstell, Matthias Beller, Palladium-catalyzed Markovnikov Alkoxycarbonylation of Alkenes: Reaction Discovery, Scope and Mechanism, *Submitted.*
2. **Haoquan Li**, Kaiwu Dong, Helfried Neumann, Matthias Beller, Palladium-Catalyzed Hydroamidocarbonylation of Olefins to Imides, *Angew. Chem. Int. Ed.* **2015**, 54, 10239-10243; *Angew. Chem.* **2015**, *127*, 10377-10381.
3. **Haoquan Li**, Helfried Neumann, Matthias Beller, Xiao-Feng Wu, Aryl Formate as Bifunctional Reagent: Applications in Palladium-Catalyzed Carbonylative Coupling Reactions Using In Situ Generated CO, *Angew. Chem. Int. Ed.* **2014**, 53, 3183-3186; *Angew. Chem.* **2014**, *126*, 3247-3250.
4. **Haoquan Li**, Luis C. Misal Castro, Jianxia Zheng, Thierry Roisnel, Vincent Dorcet, Jean-Baptiste Sortais, Christophe Darcel, Selective Reduction of Esters to Aldehydes under the Catalysis of Well-Defined NHC–Iron Complexes, *Angew. Chem. Int. Ed.* **2013**, 52, 8045-8049; *Angew. Chem.* **2013**, *125*, 8203-8207 (*Taken as Research Highlight in Nature Chemistry*)
5. Xianjie Fang[+], **Haoquan Li**[+], Ralf Jackstell, Matthias Beller, Selective Palladium-Catalyzed Aminocarbonylation of 1,3-Dienes: Atom-Efficient Synthesis of β,γ-Unsaturated Amides, *J. Am. Chem. Soc.* **2014**, *136 (45)*, 16039-16043. *(+ equal contribution)*
6. Xianjie Fang[+], **Haoquan Li**[+], Ralf Jackstell, Matthias Beller, Palladium-Catalyzed

Alkoxycarbonylation of Conjugated Dienes under Acid-Free Conditions: Atom-Economic Synthesis of β,γ-Unsaturated Esters, *Angew. Chem. Int. Ed.* **2014**, *53*, 9030-9034; *Angew. Chem.* **2014**, *126*, 9176-9180 *(+ equal contribution)*

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- Patents

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- Posters presented in scientific conferences

1. Hassen Jaafar, **Haoquan Li**, Luis C. Misal Castro, Jiangxia Zheng, Jean-Baptiste Sortais, and Christophe Darcel, Phosphino-Pyridine Iron Complexes and Application on Hydrosilylation Catalyzed Reactions, International Green Catalysis Symposium, Rennes, France, 7-9, March, 2012.
2. **Haoquan Li**, Helfried Neumann, Xiao-Feng Wu, Matthias Beller, Arylformate as Bifunctional Reagent for Carbonylative Synthesis Without External CO, 8th Asian-European Symposium on Metal-Mediated Efficient Organic Synthesis, Çeşme, Turkey, 8-10, September, 2014.

- Participation in scientific workshop

Drug Discovery Workshop, , Organized by Lilly S.A., Alcobendas, Madrid, Spain, 18. Nov. 2015 – 20. Nov. 2015.

9.3 Selbstständigkeitserklärung

Universität Rostock
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Doktorandinnen/Doktoranden-Erklärung gemäß § 4 Absatz 1 Buchstaben g und h der Promotionsordnung der Mathematisch-Naturwissenschaftlichen Fakultät der Universität Rostock

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Ich habe eine Dissertation zum Thema

Development of Carbonylative Synthetic Methods Towards Carboxylic Acid Derivatives and Heterocycles

an der Mathematisch-Naturwissenschaftlichen Fakultät der Universität Rostock angefertigt. Dabei wurde ich von Frau/Herrn

Prof. Dr. Matthias Beller

betreut.

Ich gebe folgende Erklärung ab:

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