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Palladium/di-1-adamantyl-*n*-butylphosphine-catalyzed Carbonylation Reactions

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University of Rostock

Abstract

Palladium/di-1-adamantyl-*n*-butylphosphine-catalyzed Carbonylation Reactions

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Within this thesis several homogeneous palladium-catalyzed carbonylation reactions in the presence of carbon monoxide were investigated. In the course of our studies, the superior performance of the catalyst system palladium acetate/di-1-adamantyl-*n*-butylphosphine (cata*CX*ium® A) in comparison to established palladium catalysts was demonstrated for both reductive carbonylations and alkoxycarbonylations of aryl and vinyl bromides. Hence, a variety of (hetero)aromatic aldehydes and carboxylic acid derivatives (esters, amides, acids) were successfully synthesized, among them novel biologically interesting indolylmaleimides. Furthermore, an efficient method for the synthesis of non-steroidal anti-inflammatory drugs such as ketoprofen and suprofen was developed.

In der vorliegenden Dissertation wurden verschiedene, homogen palladiumkatalysierte Carbonylierungsreaktionen in Gegenwart von Kohlenmonoxid untersucht. Dabei konnte gezeigt werden, dass das System Palladiumacetat/Di-1-adamantyl-*n*-butylphosphin (cata*CX*ium® A) sowohl in der reduktiven Carbonylierung als auch in der Alkoxycarbonylierung von Aryl- und Vinylbromiden die bekannten Palladium-Katalysator-Systeme an Aktivität, Selektivität und Produktivität übertrifft. Eine Vielzahl von (hetero)aromatischen Aldehyden und Carbonsäurederivaten (Ester, Amide, Säuren) konnte erfolgreich hergestellt werden, darunter auch bisher nicht beschriebene biologisch interessante Indolylmaleinimide. Darüber hinaus wurde im Rahmen dieser Arbeit eine effiziente Methode zur Synthese von nicht-steroidalen, entzündungshemmenden Arzneimitteln (z.B. Ketoprofen, Suprofen) entwickelt.

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List of Abbreviations

Ac	Acetyl
BINAP	2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl
tol-BINAP	2,2′-Bis(di-*p*-tolylphosphino)-1,1′-binaphthyl
bmim	1-Butyl-3-methylimidazolium
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
*n*Bu	*n*-Butyl
*t*Bu	*tert*-Butyl
cata*CX*ium® A	Di-1-adamantyl-*n*-butylphosphine
Cy	Cyclohexyl
DABCO	1,4-Diazabicyclo[2.2.2]octane
dba	*trans,trans*-Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
dcpp	1,3-Bis(dicyclohexylphosphino)propane
deg	Degree
dippp	1,3-Bis(di-*iso*-propylphosphino)propane
DMAP	4-Dimethylaminopyridine
DME	1,2-Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
DPEphos	Bis(2-diphenylphosphinophenyl)ether
dppb	1,4-Bis(diphenylphosphino)butane
dppe	1,2-Bis(diphenylphosphino)ethane
dppf	1,1′-Bis(diphenylphosphino)ferrocene
dppm	Bis(diphenylphosphino)methane

dppp	1,3-Bis(diphenylphosphino)propane
dtbpx	1,2-Bis(di-*tert*-butyl-phosphinomethyl)benzene
equiv.	Equivalent(s)
Et	Ethyl
Fmoc	Fluorenylmethoxycarbonyl
HMDS	Hexamethyldisilazane
IL	Ionic liquid
MMA	Methyl methacrylate
Me	Methyl
MS	Molecular sieves
MW	Microwave
NHC	*N*-Heterocyclic carbene
NMDPP	Neomenthyldiphenylphosphine
Norphos	2,3-Bis(diphenylphosphino)-bicyclo[2.2.1]hept-5-ene
Nu	Nucleophile
o	Ortho
OTf	Triflate (trifluoromethanesulfonate)
OTs	Tosylate (*p*-toluenesulfonate)
p	Para
Pd/C	Palladium on carbon
Ph	Phenyl
Phanephos	4,12-Bis(diphenylphosphino)-[2.2]-paracyclophane
PMHS	Polymethylhydrosiloxane
*i*Pr	*iso*-Propyl
Py	Pyridine
R	Organic group
rac	Racemic

RT	Room temperature
SCE	Saturated calomel electrode
TBDMSOTf	*tert*-Butyldimethylsilyl triflate
Tfp	Tri(2-furyl)phosphine
THF	Tetrahydrofuran
TMEDA	*N*,*N*,*N*′,*N*′-Tetramethylethylenediamine
TMS	Trimethylsilyl
TON	Turnover number
TOF	Turnover frequency [h^{-1}]
TPPTS	Sodium salt of trisulfonated triphenylphosphine
X	Leaving group, (pseudo)halide
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

1 Preface

The development of efficient and environmentally benign synthetic processes constitutes one of the most important research targets in modern chemistry. Furthermore, the improvement of existing inefficient synthetic methodologies due to environmental and economic requirements is of major interest. In this regard, homogeneous catalysis offers a great potential for achieving these objectives and, thus, to fulfil today's demand of sustainable chemistry. Among the many different catalytic transformations, homogeneous transition metal-catalyzed carbon-carbon bond forming reactions (e.g. Heck, Suzuki, and Sonogashira reaction) have found widespread application in organic syntheses in both academic and industrial laboratories. Starting from readily available substrates, a variety of complex and structurally diverse organic compounds can be prepared with high efficiency and selectivity (chemo-, regio-, diastereo-, and enantioselectivity) as well as enhanced atom-economy compared to traditional stoichiometric reactions. In general, palladium complexes are employed as catalysts due to their better performance under mild conditions, versatility and broad tolerance towards functional groups.[1]

A reaction, which has been the subject of many patents and publications, is the palladium-catalyzed carbonylation.[2] The functionalization of organic molecules with carbon monoxide as a carbonyl source has become an important and convenient method for the selective preparation of intermediates of naturally or biologically active products, pharmaceuticals and fine chemicals. Thus, a broad range of high-valuable compounds such as aldehydes, ketones, carboxylic acid derivatives, lactones, lactames, etc., are accessible from organic halides or unsaturated substrates in one step. Although much research effort has been done in this field, there still exists considerable interest in the exploration of facile and innovative synthetic strategies.

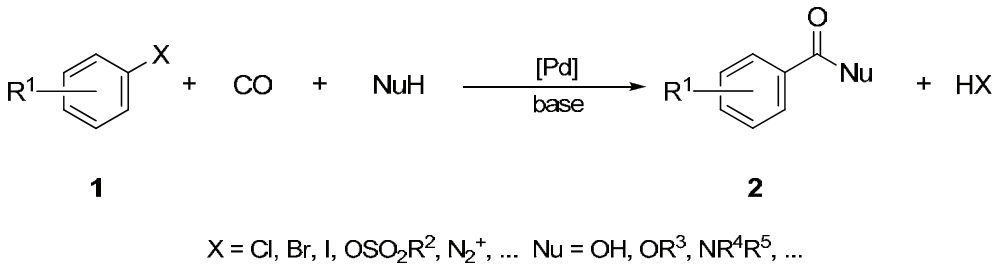
The present dissertation highlights recent achievements in palladium-catalyzed carbonylation reactions and is presented as a cumulative collection of publications which have been already released in international journals.

2 Palladium-catalyzed carbonylation reactions

With regard to the work of our research group, the following chapter tries to give an overview of recent developments in the field of palladium-catalyzed carbonylation reactions of aromatic halides (or halide equivalents), olefines, and alkynes. Due to the vast number of publications in this research area, the present review mainly comprises selected contributions published in the years 2000-2008. In addition, a brief description of recent palladium-catalyzed carbonylative cross-coupling reactions of organic electrophiles is included.

2.1 Carbonylation of aromatic (pseudo)halides

The palladium-catalyzed carbonylation of aryl-X compounds leading to carboxylic acid derivatives has become a valuable tool in organic synthesis. In general, aromatic halides are reacted with a proper nucleophile under carbon monoxide atmosphere in the presence of a palladium complex (Scheme 1). Thereby, the leaving group X is formally replaced by the nucleophile with incorporation of one or two molecules of carbon monoxide. Typically, the reaction requires at least a stoichiometric amount of base to regenerate the catalyst.



Scheme 1. General scheme for the carbonylation of aryl-X compounds.

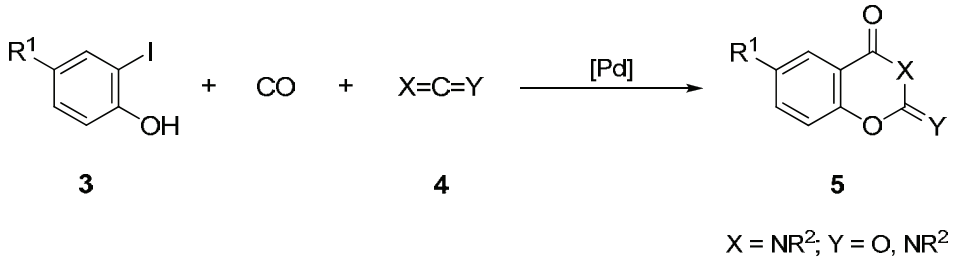
Based on the C-X bond energy, the rate of the oxidative addition of the organic halide to an electronically unsaturated metal complex decreases along the sequence:

C-I > C-OTf ≥ C-Br >> C-Cl >> C-F.[2b]

Besides (hetero)aryl halides, alkenyl-X,[3] and, in particular, steroidal[4] derivatives have successfully been employed as reagents.

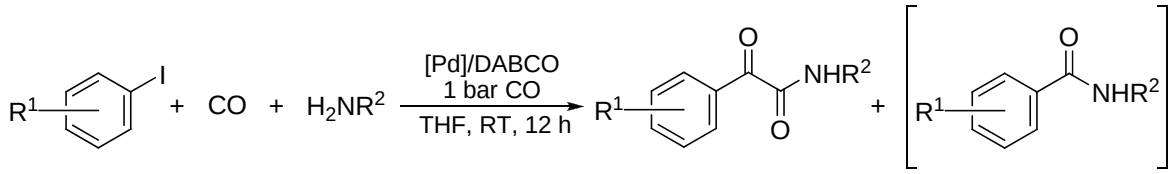
Carboxylic acids, esters, amides, anhydrides and acid fluorides are accessible straightforward via carbonylation depending on whether water (hydroxycarbonylation), alcohols (alkoxycarbonylation), amines (aminocarbonylation), carboxylate salts or fluorides are used as nucleophiles. Advantageously, with respect to compound libraries, a variety of carbonylation products can be prepared from the same aromatic substrate by simply changing the nucleophile.

In addition to intermolecular carbonylations also intramolecular reactions are known, which allow for the synthesis of different heterocycles. For example, the intramolecular amino- or alkoxycarbonylation (cyclocarbonylation) of amino- or hydroxyl-substituted aryl/vinyl halides enables the synthesis of lactones, lactams, oxazoles, thiazoles, imidazoles, etc.[5] As shown in Scheme 2, the Pd-catalyzed cyclocarbonylation of *o*-iodoanilines/*o*-iodophenols **3** with unsaturated halides/triflates or heterocumulenes **4** (isocyanates, carbodiimides, ketenimines) has been applied for the synthesis of benzoxazinones **5**.[6]



Scheme 2. Pd-catalyzed cyclocarbonylation of *o*-iodophenols with heterocumulenes to benzoxazinones.[6d]

A special carbonylation variant is the palladium-catalyzed double carbonylation. The reaction competes with monocarbonylation and usually requires elevated CO pressures. By the introduction of two molecules of carbon monoxide, α-keto acids, esters or amides are attainable from (hetero)aryl, alkenyl and alkyl halides.[6a,7] A significant improvement of the existing protocols was achieved by Uozumi and co-workers who discovered that 1,4-diazabicyclo[2.2.2]octane (DABCO) is a suitable base for the highly selective double carbonylation of aryl iodides **6** with primary amines **7** (Scheme 3).[8] Thus, the desired α-keto amides **8** were prepared under very mild conditions (1 bar CO, 25°C) in the presence of a palladium-triphenylphosphine complex.



6 **7** **8**, 46-98% **9**, 7-13%

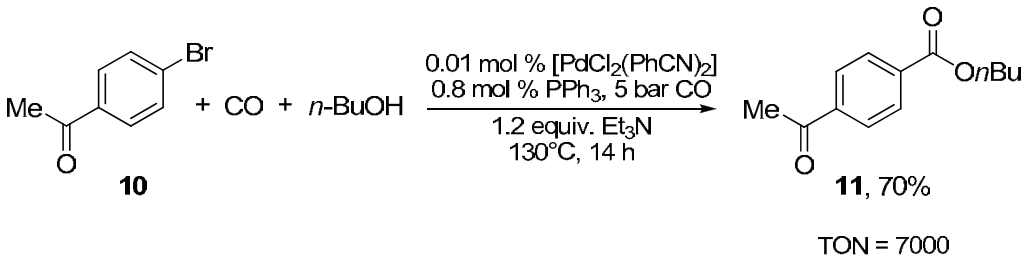
R^1 = H, 4-OMe, 4-Me, 3-Me, 2-Me; R^2 = *i*Pr, Cy, *t*Bu, *n*Bu

Scheme 3. Palladium-catalyzed double carbonylation of aryl iodides with primary amines by Uozumi et al.[8]

2.1.1 Synthesis of carboxylic acid derivatives from aryl bromides or iodides

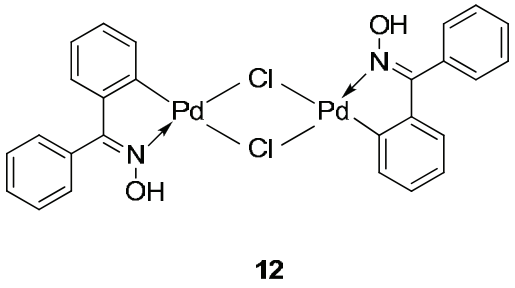
With regard to the starting material, (hetero)aromatic bromides and iodides have been most widely employed in intermolecular alkoxycarbonylation,[9,10] aminocarbonylation,[10,11] and hydroxycarbonylation reactions.[12] The first palladium-catalyzed alkoxycarbonylation was described by Heck and co-workers in 1974. In order to synthesize carboxylic acid *n*-butyl esters, aryl and vinyl iodides and bromides were reacted with carbon monoxide (1 bar) in *n*-butanol at 100°C.[13] In general, good yields were obtained in the presence of 1.5 mol % of either $[PdX_2(PPh_3)_2]$ or the respective haloarylbis(triphenylphosphine)palladium(II) complexes by adding a slight excess of tri-*n*-butylamine. Notably, the reaction with palladium acetate as catalyst was limited to aryl iodides. Since that pioneering report, major improvements concerning solvents, bases, and catalyst systems, particularly ligands, have been made.

In order to develop more productive carbonylation catalysts, the palladium-catalyzed butoxycarbonylation of 4-bromoacetophenone was investigated in detail in our group.[14] In addition to temperature, carbon monoxide pressure, solvent, and base, different catalyst precursors and the ligand to palladium ratio were studied. Almost quantitative yield of butyl ester **11** was gained at 5 bar CO and 100°C in the presence of 0.3 mol % $[Pd(PPh_3)_4]$ and 3 equivalents of Et_3N using *n*-butanol as solvent. The optimization resulted in the highest turnover number (TON = 7000) known until then for the alkoxycarbonylation of aryl halides (Scheme 4).



Scheme 4. Optimized palladium-catalyzed butoxycarbonylation of 4-bromoacetophenone.[14]

Another way to improve catalyst productivity is the use of structurally more stable catalysts. Hence, a novel, covalently bonded, cyclometallated dimeric palladium(II) catalyst was synthesized by Ramesh et al.[15] High selectivity and excellent yields (76-95%) for the reaction of various aryl iodides with aliphatic alcohols and phenols were maintained by utilizing the dimeric oxime palladacycle **12** (Figure 1). No by-products were detected and the complex was highly stable even at high temperature (120°C) and 10 bar of carbon monoxide.



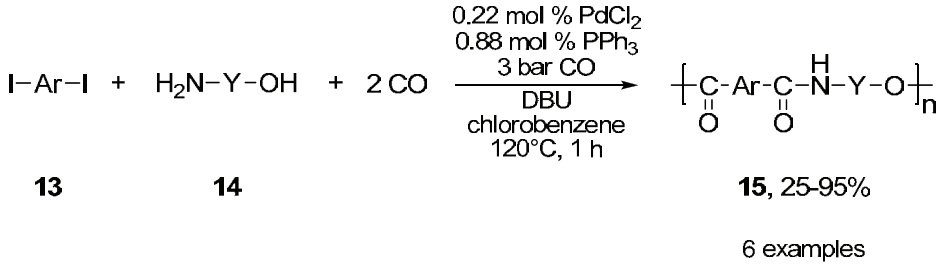
12

Figure 1. The dimeric oxime-palladium(II) catalyst **12**.[15]

Furthermore, a combined ruthenium/palladium catalyst[16] and heterogeneous palladium complexes[17] have been applied for alkoxycarbonylations of aromatic iodides. Advantageously, the heterogeneous catalyst systems were effectively removed from the reaction mixture by a simple filtration process and were reused several times with minor loss of activity. More recently, the methoxycarbonylation of bromoanisoles and unprotected bromoanilines was improved by Albaneze-Walker and co-workers.[18] By employing 3 mol % of $PdCl_2$/*rac*-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) at low pressure (4.5 bar CO, 100°C), high yields (>91%) were achieved except for *p*-bromoaniline (50%).

An interesting palladium-catalyzed carbonylation-polycondensation reaction of aromatic diiodides and aminohydroxy compounds was described by Chaudhari et al. (Scheme 5).[19]

Thus, alternating polyesteramides **15** were prepared in chlorobenzene with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as base at 3 bar of carbon monoxide and 120°C.



Scheme 5. Polyesteramide synthesis by a carbonylation-polycondensation sequence; Y = organic unit.[19]

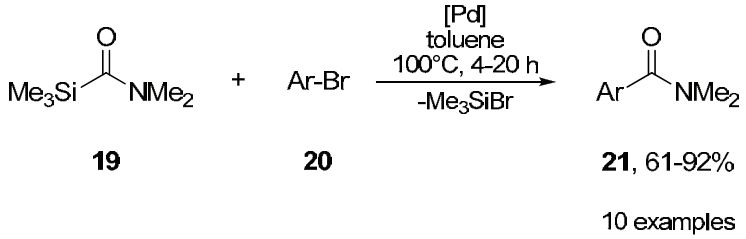
Again, Heck and co-workers developed the first Pd-catalyzed amidation reactions of aryl-X compounds. They demonstrated that secondary or tertiary amides are conveniently produced via carbonylation.[20] More specifically, (hetero)aryl bromides and vinyl iodides were reacted with primary or secondary amines under atmospheric CO pressure at 60-100°C in the presence of 1.5 mol % [$PdX_2(PPh_3)_2$]. When weakly basic amines were employed as nucleophiles, stoichiometric amounts of a tertiary amine were required to neutralize the formed acid.

An aminocarbonylation in the absence of carbon monoxide[21] and base was realized in 2002 by adding phosphoryl chloride to the reaction of aryl iodides **16** with *N*,*N*-dimethylformamide (**17**).[22] Good to high yields were obtained in toluene at 120°C utilizing 2.5 mol % [$Pd_2(dba)_3$] (dba = *trans*,*trans*-dibenzylideneacetone) (Scheme 6). The generated Vilsmeier reagent was suggested to be essential for the reaction to take place.

Scheme 6. Aminocarbonylation of aryl iodides in the absence of CO.[22]

Another example of a Pd-catalyzed CO-free carbonylation reaction was published by Cunico and Maity.[23] Depending on the substrate, 2 mol % of either [$Pd(PPh_3)_4$] or [$Pd(P^tBu_3)_2$] were used to catalyze the reaction of (hetero)aryl bromides **20** with

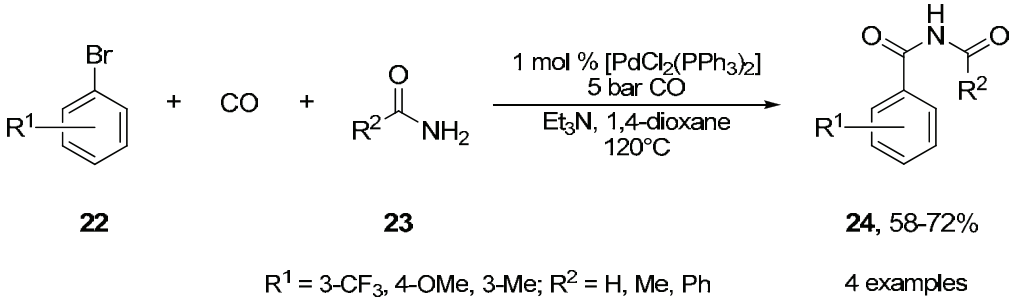
N,*N*-dimethyl-carbamoyl(trimethyl)silane (**19**) at 100°C (Scheme 7). Thus, tertiary amides **21** were prepared in good yields (61-92%) by direct carbamoylation. Notably, chlorobenzene, 1-chloro-4-methoxybenzene, and iodobenzene gave the desired products in 74%, 78%, and 60% yield, respectively.



Scheme 7. Direct carbamoylation of aryl bromides.[23]

More recently, a solid-phase palladium-catalyzed aminocarbonylation of aryl bromides or iodides utilizing molybdenumhexacarbonyl [$Mo(CO)_6$] as the carbon monoxide source was presented.[24] These reactions proceeded under mild conditions in the absence of microwave irradiation. Carbonylation reactions of ferrocene derivatives in the presence of $Pd(OAc)_2/PPh_3$ were investigated by Skoda-Földes and Kollár. They synthesized ferrocene amides and novel ferrocene α-ketoamides in good yields by Pd-catalyzed aminocarbonylation or double carbonylation of iodoferrocene at 40-50 bar CO.[25] The selectivity for the reaction with less sterically hindered secondary amines was highly dependent on the temperature. Thus, formation of double-carbonylated products was favored at 40-60°C whereas amides were produced almost exclusively at 100°C.[25b,c] Analogous aminocarbonylation reactions of 1,1′-diiodoferrocene led to diamides (70-92%), 1′-iodo-ferrocenecarboxamides (14-35%) and 1′-iodo-ferrocenylglyoxylic amides (11-40%).[25a]

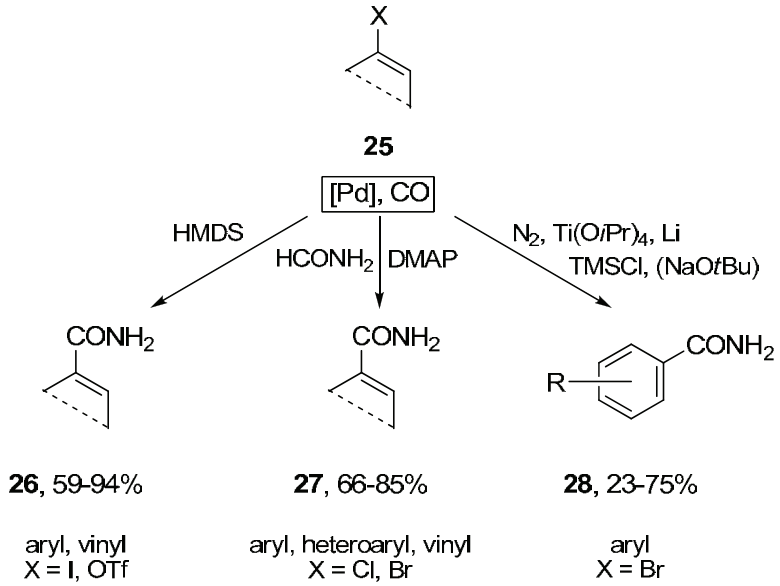
Schnyder and Indolese expanded the scope of the aminocarbonylation to the synthesis of unsymmetrical aroyl acyl imides **24** by treating aryl bromides **22** with **23** or sulfonamides under mild conditions (Scheme 8).[26] Best results were achieved with Et_3N as base (58-72%).



Scheme 8. Synthesis of aroyl acyl imides by aminocarbonylation of aryl bromides.[26]

For the first time, nonprotected bromoindoles were converted directly into the corresponding indole carboxylic amides by palladium-catalyzed carbonylation.[27] At 25 bar CO and 130°C, the use of $[PdCl_2(PhCN)_2]$/1,1′-bis(diphenylphosphino)ferrocene (dppf) and Et_3N was found to be optimal to give high yields (>90%) for the reaction of indoles with piperazine and morpholine derivatives, *n*-butylamine, and ethanol. The free carboxylic acid was also directly accessible (67%). Furthermore, potentially bioactive amphetamine analogoues were obtained in excellent yields (92-99%) by applying the optimized protocol.

Only a few routes towards primary amides have been described to date (Scheme 9). Morera and Ortar used hexamethyldisilazane (HMDS) as an ammonia source in the carbonylation of aryl iodides and triflates.[28] The desired products **26** were isolated in good to high yields (59-94%) after hydrolysis.

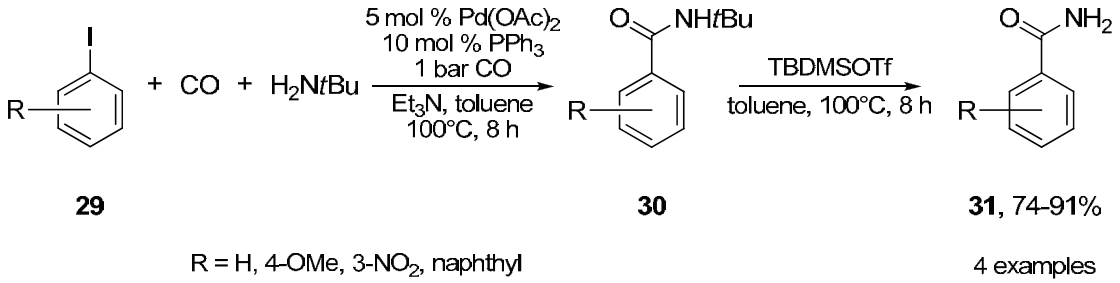


Scheme 9. Different routes towards primary amides.[28-30]

In addition, Indolese and co-workers reported the efficient aminocarbonylation of aryl bromides with formamide under 5 bar of carbon monoxide by employing 4-(dimethyl-amino)pyridine (DMAP) as base.[29] Primary benzamides **28** were also prepared from aryl bromides by using CO and a titanium-nitrogen complex in conjunction with NaO*t*Bu or in the absence of base.[30]

Furthermore, primary amides **31** and ketoamides were synthesized in good yields by a carbonylation-deprotection sequence in the presence of $Pd(OAc)_2/PPh_3$ (Scheme 10).[31] Initially, aryl iodides **29** were reacted with *tert*-butylamine at 1 bar CO. When the reaction was carried out at 60°C, ketoamides resulting from double carbonylation were mainly

produced whereas formation of the amides **30** was favored at 100°C. After isolation, the products were heated with one equivalent of *tert*-butyldimethylsilyl triflate (TBDMSOTf) in toluene at 100°C to obtain the corresponding primary derivatives **31**.



Scheme 10. Synthesis of primary amides by a Pd-catalyzed aminocarbonylation-deprotection sequence.[31]

Recently, we prepared various aromatic and heteroaromatic esters, amides, and acids from the corresponding bromoarenes by making use of a novel catalyst system consisting of $Pd(OAc)_2$ and commercially available di-1-adamantyl-*n*-butylphosphine[32] (cata*CX*ium® A, **32**; Figure 2).[33]

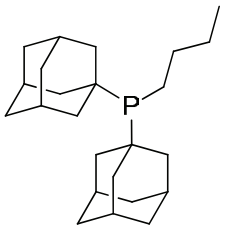


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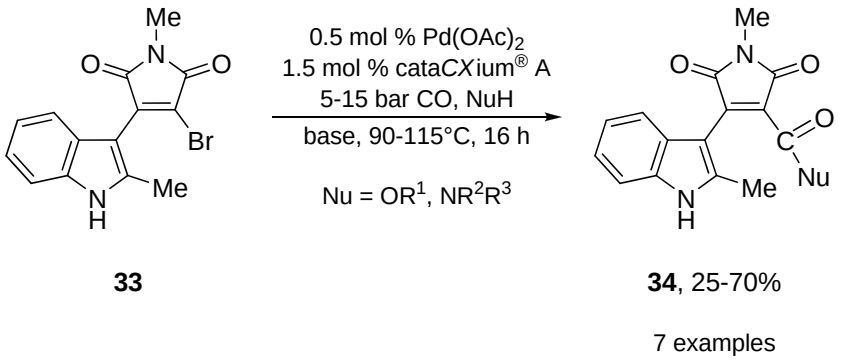
Figure 2. Di-1-adamantyl-*n*-butylphosphine: cata*CX*ium® A.

Compared to most known carbonylation protocols, the reaction was carried out at lower catalyst loadings (0.5 mol % Pd or below) in the presence of carbon monoxide (5 bar) to give the desired compounds in excellent yields (see chapter 4.2). Later on, the method was applied to synthesize novel potentially bioactive 3-alkoxycarbonyl- and 3-aminocarbonyl-4-indolylmaleimides **34** from 3-bromoindolylmaleimide **33** (Scheme 11, see chapter 4.3).[34]

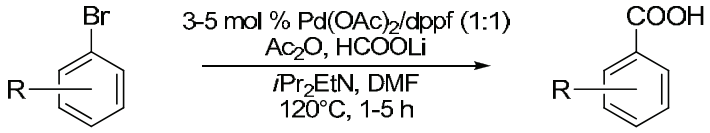


33 **34**, 25-70%

7 examples

Scheme 11. Palladium-catalyzed carbonylation of 3-bromoindolylmaleimide **33**.[34]

A novel, CO-free protocol for palladium-catalyzed hydroxycarbonylations of aryl and vinyl halides or triflates utilizing an acetic anhydride/lithium formate combination as a condensed source of carbon monoxide was published by Cacchi and co-workers.[35] The transformation was carried out under mild conditions (80°C) and tolerated a wide range of functional groups, including ether, ketone, ester, and nitro groups. In 2006, the same carbonyl source was adapted for the Pd-catalyzed hydroxycarbonylation of aryl bromides (Scheme 12).[36] The reaction of bromoarenes **35** with acetic anhydride and lithium formate proceeded smoothly in DMF at 120°C in the presence of 3-5 mol % $Pd(OAc)_2$ and dppf (Pd/P = 1/1) to provide carboxylic acids **36** in good yields (61-97%). In addition, the protocol was applied to the synthesis of terephthalic acid from 1,4-dibromobenzene (75%).[36]



35 **36**, 61-97%

R = 4-Me, 4-Ph, 4-COOEt, 4-Br, 4-Cl, 4-F, 4-CF_3, ... 12 examples

Scheme 12. Hydroxycarbonylation of aryl bromides with mixed acetic formic anhydride as carbonyl source.[36]

Subsequently, Cacchi et al. presented an efficient hydroxycarbonylation of aryl iodides using recoverable carbon aerogels doped with palladium nanoparticles as catalyst.[37] High yields (77-94%) were maintained in DMF at 100°C with acetic anhydride/lithium formate along with lithium chloride and *N,N*-diisopropylethylamine as base. Remarkably, for the reaction of *p*-iodotoluene the catalyst was reused up to 12 times without any appreciable loss of activity.

Beside methodological improvements, intermolecular carbonylation reactions of aryl iodides, bromides, and triflates[38] have been applied in numerous syntheses of biologically active compounds and natural products (Figure 3).[39] For better understanding, the bond formed by carbonylation is indicated in each case.

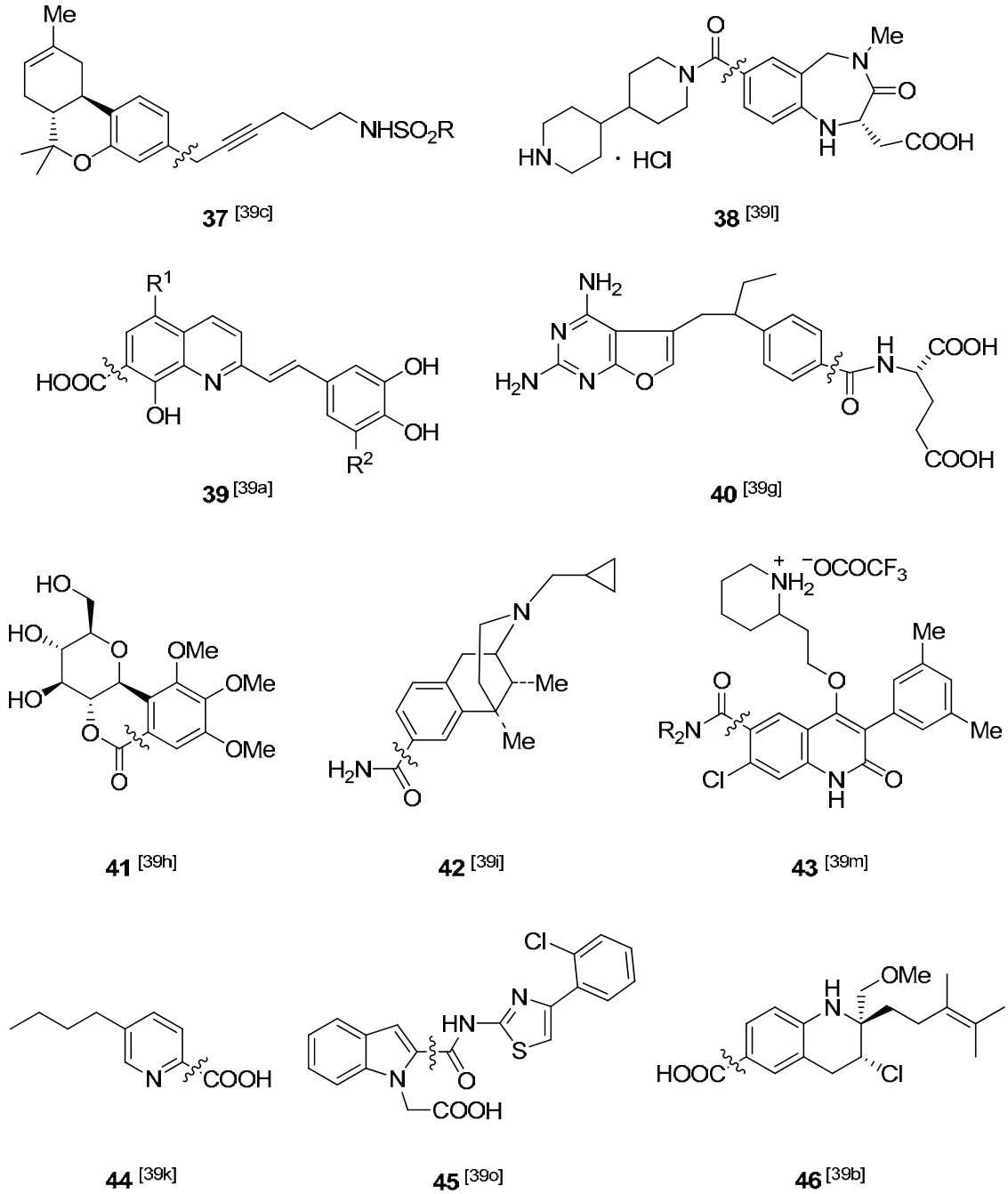
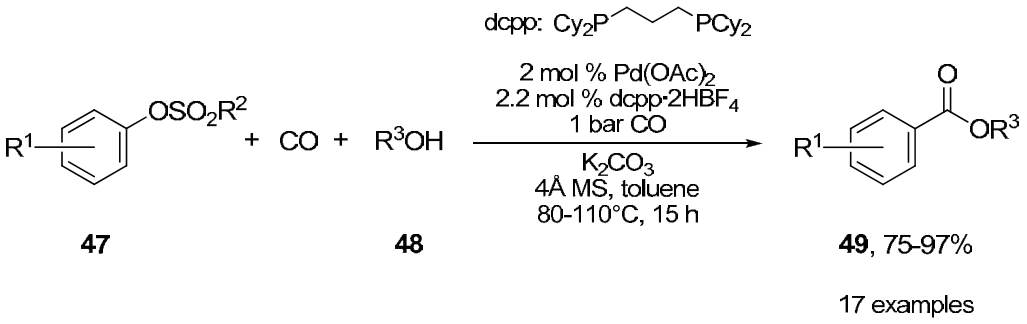


Figure 3. Examples of biologically active compounds synthesized by palladium-catalyzed alkoxy- and aminocarbonylation. (The bonds formed by carbonylation are indicated in each case.)

Palladium-catalyzed carbonylations of arene diazonium salts[40] and diaryl iodonium salts[41] are less common. Interestingly, only three palladium-catalyzed carbonylation reactions of aryl *p*-toluenesulfonates (tosylates) are known until to date.[42-44] The first successful alkoxycarbonylation of 4-substituted aryl tosylates was described by Kubota et al. in 1998.[42] Reactions were performed either in methanol or ethanol in the presence of $PdCl_2$ and 1,3-bis(diphenylphosphino)propane (dppp) at 10 bar CO and 150°C. Unfortunately, only 4-acetylphenyl tosylate gave the desired ethyl ester in satisfying yield (81%). Almost no or low conversion was observed for electron-rich or electronically neutral substrates. In 2006, Cai and co-workers utilized a catalyst system derived from $Pd(OAc)_2$ (4 mol %) and a Josiphos ligand (4.4 mol %) to synthesize ethyl benzoates from aryl arenesulfonates at 6 bar of carbon monoxide.[43] Isolated yields >90% were obtained for most aryl *p*-fluoro-benzenesulfonates. The less reactive aryl tosylates yielded ethyl benzoate, ethyl 4-methyl-benzoate, ethyl 4-acetobenzoate, and ethyl 4-cyanomethylbenzoate in 92%, 61%, 96%, and 93%, respectively.

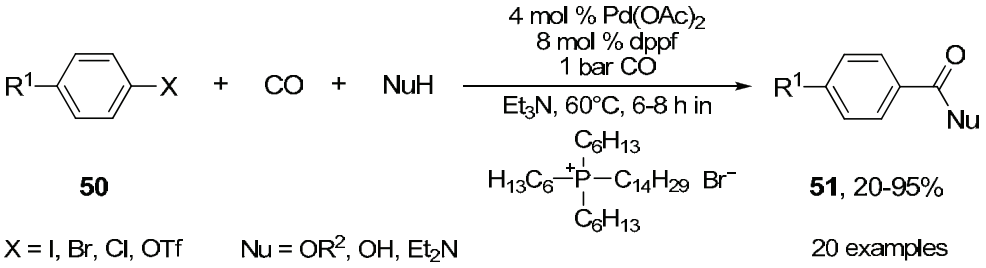
Most recently, an active and efficient catalyst for the alkoxycarbonylation of aryl tosylates was presented by the group of Buchwald (Scheme 13).[44] Under mild conditions (80-110°C, 1 bar CO), electron-rich, electron-poor, and heterocyclic tosylates **47** were reacted with several primary alcohols in the presence of $Pd(OAc)_2$ and electron-rich, chelating 1,3-bis(di-cyclohexylphosphino)propane (dcpp).



Scheme 13. Pd-catalyzed alkoxycarbonylation of aryl tosylates and mesylates by Buchwald et al.[44]

Clean conversion and no competing formation of ether by-products were observed when molecular sieves were employed. Notably, different functional groups, e.g. aldehyde, ketone, ester, or cyano were tolerated. Furthermore, the alkoxycarbonylation of aryl methylsulfonates (mesylates) was demonstrated for the first time (75-97% yield).[44]

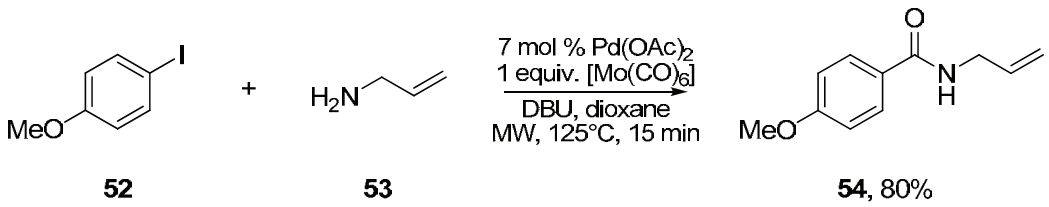
The use of non-volatile ionic liquids (ILs) as solvents in palladium-catalyzed carbonylations was demonstrated first by Tanaka.[45] Compared to standard conditions, higher yields for the alkoxycarbonylation of bromobenzene were obtained when 1-butyl-3-methylimidazolium tetrafluoroborate [bmim][BF_4] was employed as the reaction medium. Besides, the selectivity for the monocarbonylation of iodobenzene with *i*-PrOH or Et_2NH was significantly enhanced by [bmim][BF_4]. After separation of the products, the solvent-catalyst system was easily recycled and exhibited catalytic activity up to seven times. Since this report, the replacement of traditional solvents by quaternary ammonium halides, imidazolium- or pyridinium-derived ILs has gained increasing importance.[46] Recently, the phosphonium salt IL trihexyl(tetradecyl)phosphonium bromide has proven to be an effective reaction medium for different carbonylation reactions of aryl and vinyl bromides or iodides under mild conditions (Scheme 14).[47]



Scheme 14. Palladium-catalyzed carbonylation reactions in a phosphonium salt ionic liquid.[47]

Microwave-assisted palladium-catalyzed carbonylations of aryl-X compounds have been mainly reported by Larhed and co-workers.[48] Typically, these reactions were conducted in sealed vessels using microwave irradiation and either [$Mo(CO)_6$] or formic acid derivatives as CO-releasing reagents. Alternatively, alkoxy- and hydroxycarbonylations of aryl iodides with gaseous carbon monoxide have been performed by employing pre-pressurized reaction vessels in conjunction with microwave heating.[49]

Very recently, a microwave-promoted palladium-catalyzed aminocarbonylation of (hetero)aryl halides (X = I, Br, Cl) using [$Mo(CO)_6$] and allylamine (**53**) as nucleophile was described.[50] Surprisingly, no side-products resulting from the competing Heck-reaction were detected and aminocarbonylation was achieved for the first time on a larger scale (25 mmol) starting from 4-iodoanisole (**52**) (Scheme 15). Nowadays, fast and energy-efficient microwave-assisted protocols have found several applications in the synthesis of biologically active compounds.[51]



52 **53** **54**, 80%

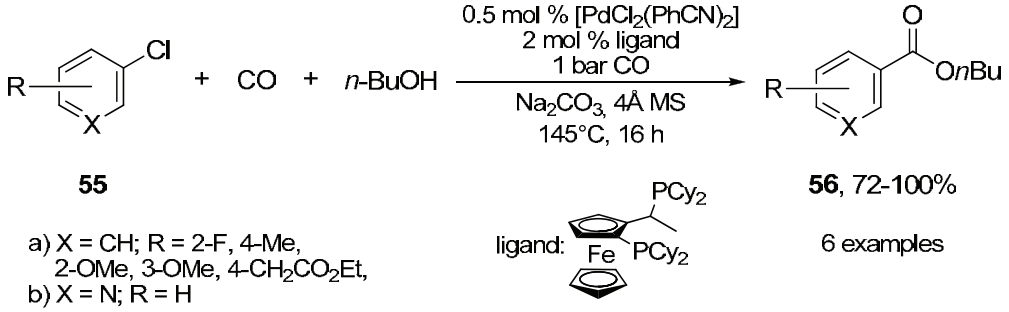
Scheme 15. Microwave-assisted aminocarbonylation on a 25 mmol scale.[50]

2.1.2 Synthesis of carboxylic acid derivatives from aryl chlorides

Among the aryl halides, chloroarenes are probably the most interesting class of starting materials. Since aromatic chlorides are often cheap, relatively inert, and moreover, widely available in bulk quantities, there still exists a significant interest in replacing aryl bromides/iodides by the corresponding chlorides. Unfortunately, chloroarenes show much lower reactivity due to the high stability of the aromatic carbon-chlorine bond. Hence, efficient catalyst systems and more severe conditions are required to activate these substrates towards oxidative addition[52] and carbonylation reactions. In the past, [(chloroarene)$Cr(CO)_3$] complexes with reduced π-electron density were employed to allow for carbonylation of aryl chlorides with alcohols or amines at high pressure.[53] Milstein and co-workers utilized in their seminal work palladium complexes of the bulky and electron-rich bidentate ligand 1,3-bis(di-*iso*-propylphosphino)propane (dippp) to synthesize carboxylic acids, esters and amides in high yields (70-89%) at 5 bar CO.[54] However, the reaction still required high temperature (150°C) and precautious handling of the pyrophoric ligand. In another approach, PCy_3 and related ligands were applied to overcome the problem of clustering and agglomeration of Pd atoms.[55] Palladium on charcoal in addition with $K_2Cr_2O_7$ afforded comparably low yields (20%) for the carbonylation of a series of chloroarenes in methanol at 200°C within 50 h.[56] A palladium-catalyzed aminocarbonylation of electron-deficient chloroarenes in the presence of 1,2-bis(diphenylphosphino)ethane (dppe) and a slight excess of sodium iodide under milder conditions was also described.[57]

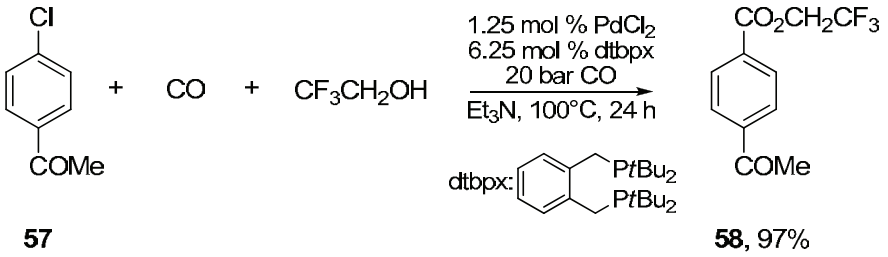
It was shown in our research group that carbonylation of electron-deficient, electronically neutral, and electron-rich aryl chlorides **55** may take place at lower carbon monoxide pressure.[58] A study of the reaction parameters and various catalyst systems revealed the advantages of cyclohexyl-substituted, bidentate ferrocenyl phosphine ligands. Thus, air-stable and commercially available 1-[2-(dicyclohexylphosphanyl)ferrocenyl]ethyldicyclohexyl-

phosphine gave quantitative conversion and good to excellent yields when *n*-butanol (Scheme 16), water or di-*n*-propylamine were applied together with Na_2CO_3 as the base.[58b] Unfortunately, an excess of ligand relative to the metal (P/Pd = 8/1) and relatively high temperatures (145°C) were required. However, a turnover number of almost 1600 was observed for the conversion of chlorobenzene to *n*-butyl benzoate with only 0.05 mol % $[PdCl_2(PhCN)_2]$, underlining the high productivity of the developed catalyst.



Scheme 16. Palladium-catalyzed butoxycarbonylation of aryl chlorides.[58]

More recently, the alkoxycarbonylation of aromatic chlorides in the presence of a catalyst system based on Pd/1,2-bis(di-*tert*-butyl-phosphinomethyl)benzene (dtbpx) was investigated in detail by Cole-Hamilton et al.[59] When methanol was employed as nucleophile, only moderate yields (16-35%) were observed for strongly activated methyl 4-chlorobenzoate and 4-chlorocyanobenzene. Unfortunately, in all cases, many by-products were detected resulting from nucleophilic aromatic substitution, reduction, dehalogenation, transesterification, etc. However, the selectivity for the transformation of 4-chloroacetophenone (**57**) was improved dramatically by using less nucleophilic 2,2,2-trifluoroethanol as the nucleophile (Scheme 17).

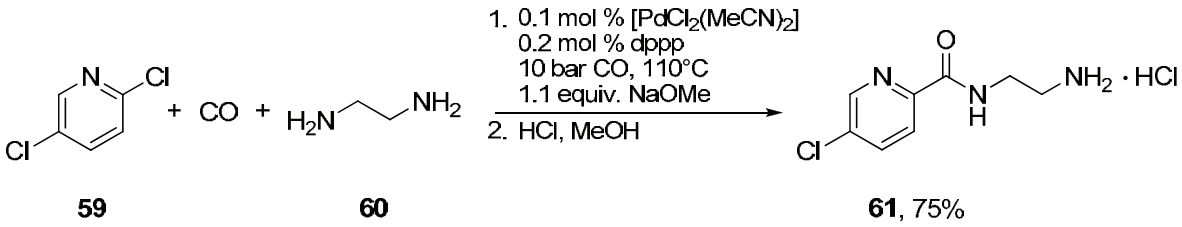


Scheme 17. Alkoxycarbonylation of 4-chloroacetophenone according to Cole-Hamilton.[59]

Activated and deactivated chloroarenes were transformed into a variety of benzamides with $[Mo(CO)_6]$ as solid carbon monoxide source and microwave irradiation (170°C).[60] The

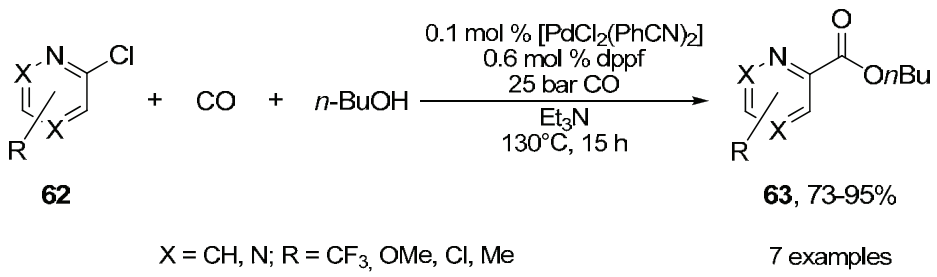
combination of Herrmann's palladacycle[61] with commercially available $[(t\text{Bu})_3\text{PH}]\text{BF}_4$ furnished useful product yields (51-91%) under non-inert conditions after only 15-25 min of heating.

From an industrial point of view, the carbonylation of heteroaryl chlorides,[62] particularly pyridine derivatives, is of special interest since the resulting products are valuable intermediates for the synthesis of biologically active compounds such as herbicides or pharmaceuticals.[63] For example, the monoaminocarbonylation of 2,5-dichloropyridine (**59**) with ethylendiamine (**60**) is applied by Hoffmann-La Roche AG for a short industrial production of Lazabemide hydrochloride (**61**), a monoamine oxidase B inhibitor (Scheme 18).[64]



Scheme 18. Synthesis of Lazabemide hydrochloride by aminocarbonylation of 2,5-dichloropyridine.[64]

In 2001, we discovered that heteroaryl chlorides could be activated towards alkoxycarbonylation in the presence of 1,4-bis(diphenylphosphino)butane (dppb) or dppf and Et_3N.[58c,65] Thus, the conversion of 2- and 4-chloropyridines, chloropyrazines, and chloroquinolines at low catalyst loadings (0.1 mol % $[\text{PdCl}_2(\text{PhCN})_2]$, 0.6 mol % dppf), 25 bar CO, 130°C led to good to excellent yields (73-95%, Scheme 19). In contrast, less activated 3-chloropyridines were carbonylated under the same conditions by employing 1,4-bis-(dicyclohexylphosphino)butane and NaOAc as base. It is important to note that for the first time a catalyst turnover number of 13000 was obtained for the reaction of 2-chloropyridine with *n*-butanol by using only 0.005 mol % $[\text{PdCl}_2(\text{PhCN})_2]$ and dppb (P/Pd = 240/1).

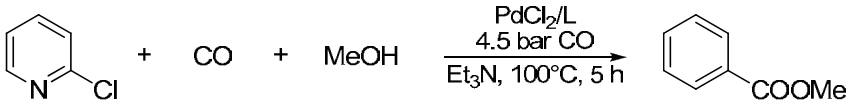


Scheme 19. Palladium-catalyzed butoxycarbonylation of *N*-heteroaryl chlorides.[65]

Bessard and co-workers presented an ethoxycarbonylation process for the preparation of pyridine mono- and dicarboxylates from 2,3-dichloro-5-(trifluoromethyl)pyridine.[66] Interestingly, the synthesis of ethyl 3-chloro-5-(trifluoromethyl)pyridine-2-carboxylate was conducted on a 0.5 mol scale. The reaction was carried out with 0.5 mol % $Pd(OAc)_2$ and 3 mol % dppf at 15 bar CO. After 5 h at 80°C, the monoester was isolated in 94% yield. The corresponding diester was produced selectively on a 10 mmol scale by increasing the temperature to 150°C. 2-Chloropyridine was used as a model substrate by Blaser and co-workers to develop a simple parallel procedure for carbonylations of aryl halides with alcohols and CO in standard autoclave equipment.[67]

The methoxycarbonylation of heterocyclic chlorides was accomplished with $PdCl_2$/(*rac*-BINAP) at 4.5 bar CO and 100 °C.[18] Due to the excellent stability of the catalyst, no side-reactions occurred and the methyl esters were isolated in good to excellent yields (60-99%). However, attempts to carbonylate chlorobenzene and 3-chloropyridine failed. The screening of diverse bidentate ligands for the reaction of 2-chloropyridine (**64**) revealed an effect of the bite angle on the rate of conversion (Table 1). Except for 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos, Table 1, entry 9), conversions higher than 85% were obtained for phosphines with a natural bite angle near 90°.

Table 1. Effect of bite angle on the conversion of 2-chloropyridine.[18]



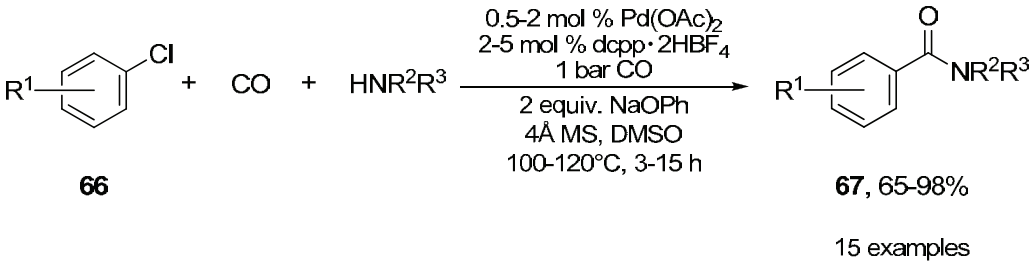
64 **65**

Entry	**Ligand L**	**Natural bite angle** [deg]	**Conversion** [%]
1	dppm	72	3
2	dppe	78	6
3	dppp	91	86
4	tol-BINAP	91	98
5	*rac*-BINAP	92	94
6	dppb	99	35
7	DPEphos	102	13
8	Phanephos	104	13
9	Xantphos	110	99
10	Norphos	123	1

[a] Reaction conditions: 0.1 mol % $PdCl_2$/L, 1.3 equiv. Et_3N, MeOH, 4.5 bar CO, 100 C, 5 h.

Recently, polychlorinated pyridines have also been carbonylated in 2-ethyl-1-hexanol under atmospheric CO pressure and in standard laboratory glassware.[68]

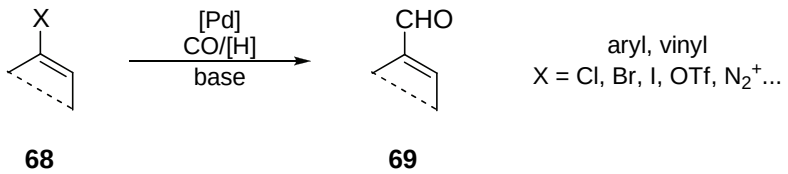
A general protocol for the aminocarbonylation of (hetero)aryl chlorides was presented by Buchwald and co-workers. In the presence of Pd/dcpp, several substituted aryl and heteroaryl chlorides **66** were reacted with primary, α-branched primary, cyclic and acyclic secondary, and aryl amines (Scheme 20).[69] The corresponding amides **67** were obtained in good to excellent yields (65-98%) when anhydrous sodium phenoxide was used as base. Advantageously, the reaction proceeded at atmospheric pressure of carbon monoxide and required relatively low temperatures (100-120°C). The authors ascribed the mild reaction conditions to the fact that the basic additive NaOPh acted as a nucleophilic catalyst. Accordingly, phenyl 3-methoxybenzoate has been identified as the key intermediate which is then converted to the desired amide product.



Scheme 20. Palladium-catalyzed aminocarbonylation of aryl chlorides according to Buchwald et al.[69]

2.1.3 Reductive carbonylations

Among the various carbonylation reactions, the reductive carbonylation (formylation) of aryl-X or vinyl-X derivatives to aromatic or α,β-unsaturated aldehydes is synthetically one of the most interesting procedures (Scheme 21).



Scheme 21. General palladium-catalyzed reductive carbonylation reaction.

The obtained aldehydes are important building blocks for the preparation of biologically active molecules and their intermediates (Figure 4) due to the fact that the carbonyl group easily undergoes a wide range of transformations (C-C and C-N-coupling reactions, reductions, etc.). Today, a variety of catalysts are available for the alkoxy- and amino-carbonylation of aryl and vinyl halides, but there are comparatively few general protocols concerning the synthetically more interesting formylation of these substrates.

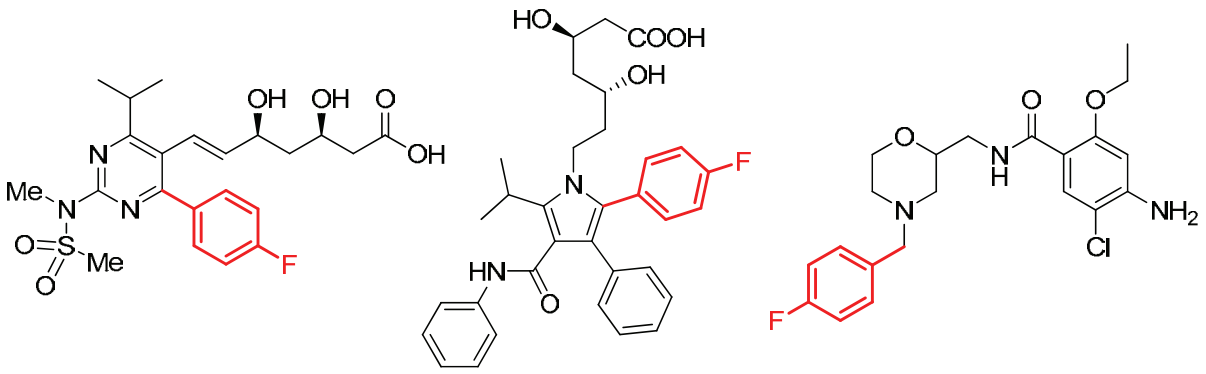
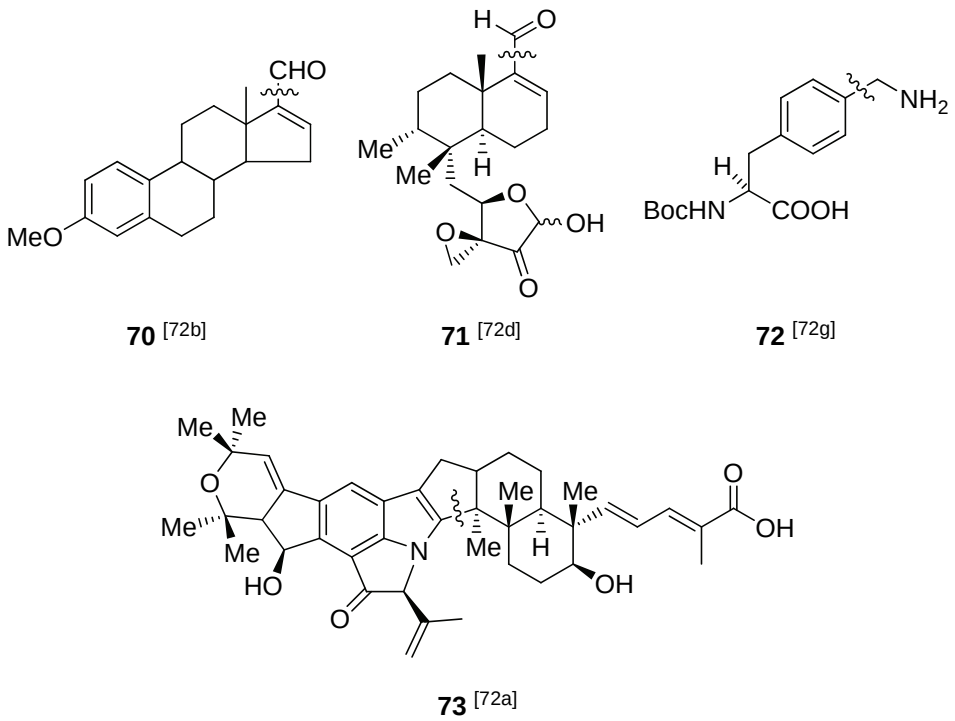


Figure 4. 4-Fluorobenzaldehyde as a building block for pharmaceuticals.

The palladium-catalyzed reductive carbonylation reaction was discovered by Schoenberg and Heck in 1974.[70] High pressures (80-100 bar) and temperatures of 80-150°C were essential to convert aryl and vinyl bromides or iodides in the presence of synthesis gas to the corresponding aldehydes. Furthermore, a comparably large amount of $[PdX_2(PPh_3)_2]$ (1-3 mol %) was required to achieve good yields (53-95%).

One decade later, this pioneering work was improved by employing metal hydrides as reducing agents. Baillargeon and Stille[71] established the use of tributyltin hydride (Bu_3SnH) in formylation reactions. Under mild conditions (50°C, 1-3 bar CO), aryl iodides, benzylic halides, vinyl iodides and triflates, and allylic halides were successfully carbonylated in 2.5-3.5 h reaction time. Since then, tin hydrides have been applied for reductive carbonylations in numerous natural product syntheses (Figure 5).[72]



70 [72b] **71** [72d] **72** [72g]

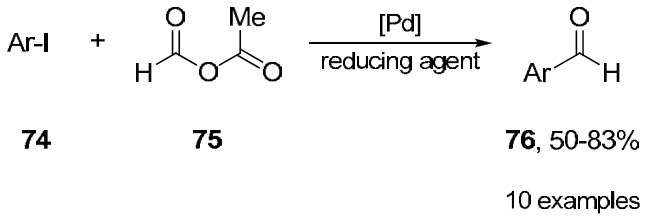
73 [72a]

Figure 5. Examples of reductive carbonylations in natural product syntheses. (The bonds formed by carbonylation are indicated in each case.)

A more convenient approach is based on the use of organosilanes in conjunction with carbon monoxide.[73,74] Lately, Ashfield and Barnard[75,55a] took up this concept by testing the practicability of different R_3SiH systems for various known palladium catalysts. They demonstrated that numerous optimization experiments are inevitable to find the appropriate parameters (catalyst, base, solvent, temperature, pressure, concentration) for the transformation of (hetero)aryl bromides and iodides. Thus, when Et_3SiH was employed under mild conditions (3 bar CO, 60-120°C), the $[PdCl_2(dppp)]$/DMF/Na_2CO_3 system gave good results for most of the substrates. In general, the desired aldehydes were obtained in 79-100% yield. However, the catalyst system failed with aryl chlorides[76] as well as sterically hindered aryl bromides and iodides. Besides, the method is inappropriate for industrial application since the reaction conditions have to be optimized for each substrate.

The use of readily available and cheap formate salts is a more benign variant to perform palladium-catalyzed reductive carbonylations.[73c,76a,77] For example, a silica-supported phosphine palladium complex (″Si″-*P*-Pd) was employed by Cai and co-workers for the formylation of aryl bromides and iodides with sodium formate at 1 bar CO and 90-110°C (45-81%).[78] The polymeric catalyst was recovered afterwards and showed comparable catalytic activity than homogeneous $[PdCl_2(PPh_3)_2]$.

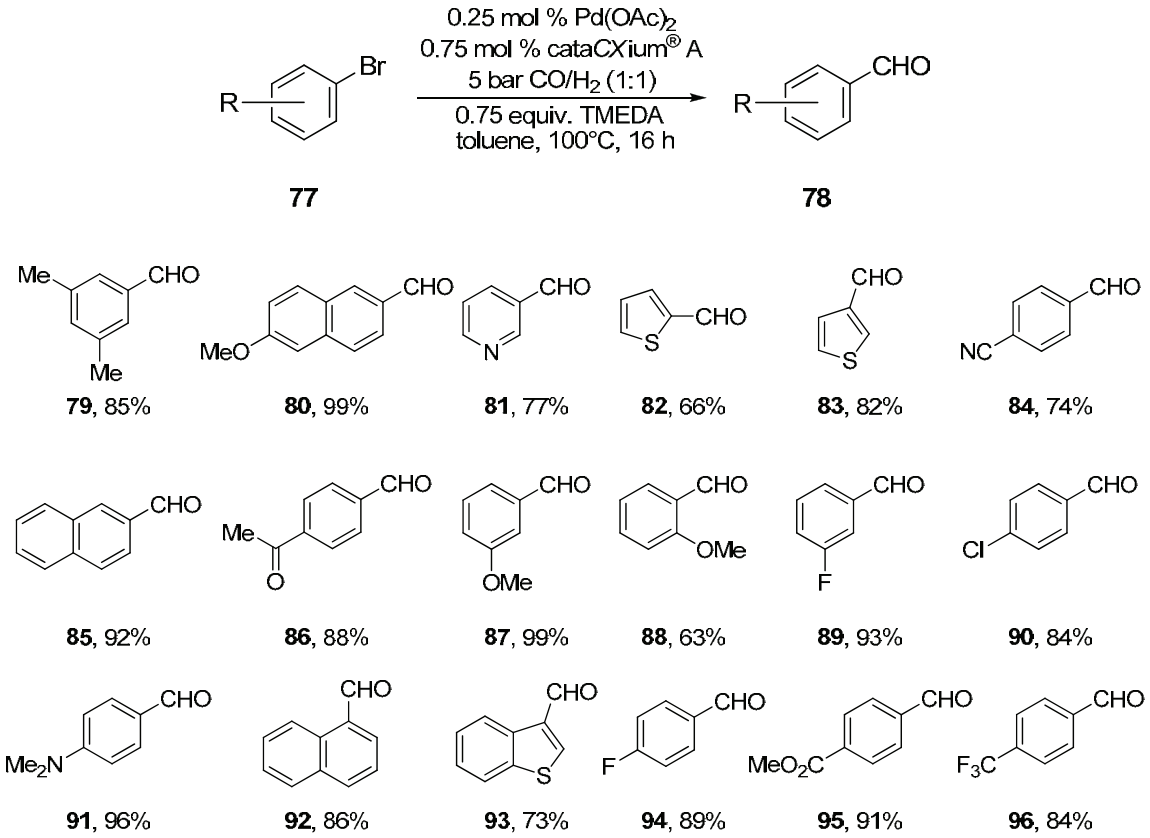
Cacchi et al. presented two generalized protocols for the synthesis of substituted benzaldehydes **76** from aryl iodides **74** (Scheme 22).[79] Depending on the electronic properties of the substrates, the reaction conditions had to be modified. Thus, neutral, electron-rich, and slightly electron-deficient aryl iodides were carbonylated in CH_3CN in the presence of $[Pd_2(dba)_3]$/dppe/*i*Pr_2EtN by applying Et_3SiH and acetic formic anhydride as in situ CO source. Electron-poor aryl iodides were reacted in DMF in an analogous manner; however, the addition of 3 equivalents of LiCl was required. Good to high yields were achieved for most educts at 60°C, and several functional groups were tolerated.



Scheme 22. Pd-catalyzed synthesis of benzaldehydes from aryl iodides and acetic formic anhydride.[79]

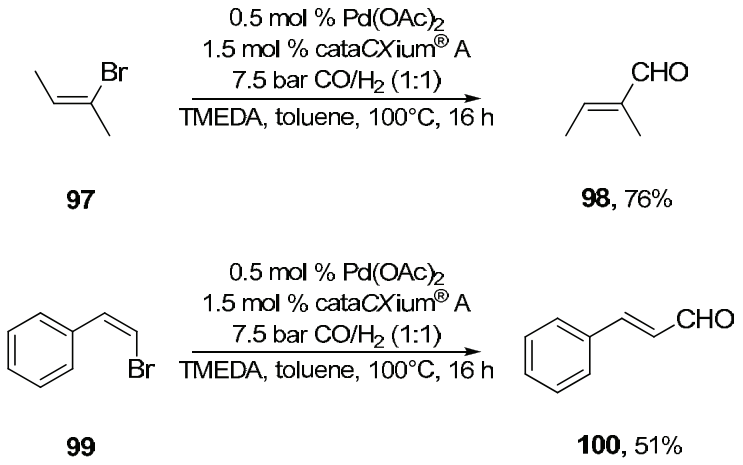
An electrochemical approach to aromatic and heteroaromatic aldehydes was presented by Chiarotto and co-workers.[80] Based on preliminary investigations,[81] the formylation of aryl iodides was accomplished in the presence of formic acid and atmospheric pressure of carbon monoxide.[80b] Formate ions were generated from HCOOH in the presence of 10 mol % palladium-phosphine complexes under electrolytic conditions (-1.2 V vs. SCE). Here, good yields were achieved for most of the substrates. The analogous electrocarbonylation of iodothiophens, iodofuran and iodopyridines in the presence of a phosphine-free palladium catalyst ($Pd(OAc)_2$/DABCO) proceeded with moderate to good yields.[80a]

Holzapfel et al. published an alternative synthesis of pyridine and quinoline carboxaldehydes by reductive carbonylation of (hetero)aryl bromides and triflates.[82] Since different hydrogen donors, e.g. Bu_3SnH or polymethylhydrosiloxane (PMHS), led to poor results or to significant amounts of by-product resulting from reductive dehalogenation, synthesis gas was used as formylation source. Thus, carbonylation in the presence of $Pd(OAc)_2/PPh_3$ and 30-40 bar CO/H_2 (1:1) furnished the favored aldehydes in 30-88% yield. However, the protocol was limited to only a few substrates. Recently, the most general and efficient palladium-catalyzed formylation procedure for the synthesis of aromatic and heteroaromatic aldehydes was developed in our research group (Scheme 23).[83]



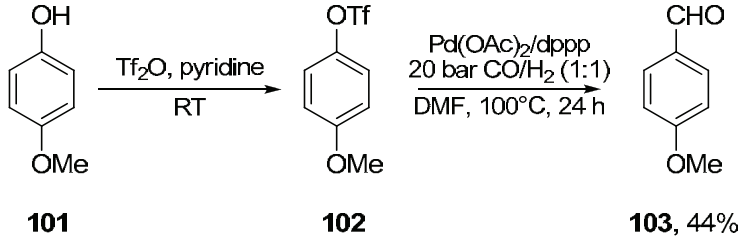
Scheme 23. Scope of the reductive carbonylation with cata*CX*ium® A.[83a]

Several (hetero)aryl bromides were successfully carbonylated with cheap and environmentally benign synthesis gas in the presence of $Pd(OAc)_2$/cata*CX*ium® A[84,85] and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) at 100°C.[83a] Advantageously, the catalyst system was active at low concentrations (0.25 mol % $Pd(OAc)_2$, 0.75 mol % cata*CX*ium® A) and at much lower pressures (5 bar) than previously reported catalysts. Besides, it was shown that vinyl halides could be formylated under similar conditions to form α,β-unsaturated aldehydes in 41-98% yield (see chapter 4.1).[86] Interestingly, the transformation of (*Z*)-2-bromo-2-butene (**97**) and *cis*-β-bromostyrene (**99**) resulted in the selective formation of the corresponding *trans*-aldehydes (Scheme 24). Notably, the catalyst system is currently employed on a multi-1000 kg-scale in the first industrial palladium-catalyzed reductive carbonylation of aryl halides due to its efficiency and easy handling (stable to air and moisture).



Scheme 24. Reductive carbonylation of vinyl halides.[86]

The first general palladium-catalyzed carbonylation of aryl triflates with synthesis gas was reported in 2007 (see chapter 4.6).[87] In contrast to aryl bromides, only the bidentate ligands dppe and dppp led to significant conversion and aldehyde formation. Under mild conditions, various aromatic aldehydes were obtained in 50-92% yield in the presence of 1.5 mol % $Pd(OAc)_2$, 2.25 mol % dppp and pyridine in DMF. In addition, it was demonstrated that 4-methoxybenzaldehyde (**103**) could be prepared directly from 4-methoxyphenol (**101**) by a one-pot sulfonylation-carbonylation sequence (Scheme 25).[87]



Scheme 25. One-pot sulfonylation-carbonylation process towards 4-methoxybenzaldehyde.[87]

2.2 Carbonylation of unsaturated compounds

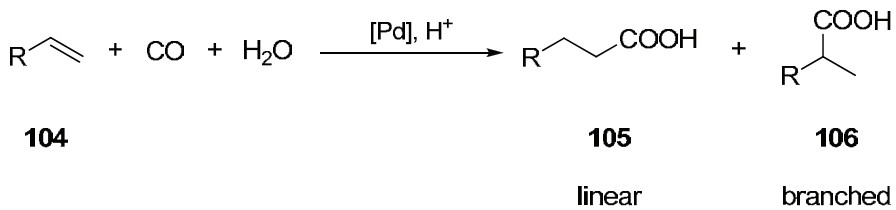
Catalytic carbonylations of unsaturated compounds are known since the pioneering work of Walter Reppe at BASF, who converted acetylene, carbon monoxide, and water to acrylic acid with $[Ni(CO)_4]$ as catalyst under drastic conditions.[88] Since then, transition metal-catalyzed carbonylation reactions have gained in importance. More specifically, the

palladium-catalyzed addition of carbon monoxide to alkenes and alkynes in the presence of an acidic hydrogen donor has received considerable attention during the last years and has been used to prepare a range of important products. For example, industrially valuable carboxylic acids such as linear fatty acids and branched 2-arylpropionic acids are directly accessible via hydroxycarbonylation or hydroesterification followed by hydrolysis. The latter compounds belong to the most important class of non-steroidal anti-inflammatory agents (e.g. ibuprofen, naproxen, and ketoprofen). An important example of an industrial application of alkyne carbonylation is the production of methyl methacrylate (MMA), a large-scale chemical intermediate for the synthesis of homopolymers and co-polymers.

It should be noted that the closely related, industrially important alkene hydroformylation (oxo synthesis) by which a formyl group and a hydrogen atom are attached to a carbon-carbon double bond is not treated in this chapter.

2.2.1 Hydroxycarbonylation of alkenes

The palladium-catalyzed carbonylation of alkenes with CO and water (hydroxycarbonylation) constitutes a straightforward and atom-efficient route to saturated carboxylic acids (Scheme 26). Since the preliminary work of von Kutepow,[89] the reaction has been extensively studied and progresses in controlling regiochemistry have been reviewed.[90]



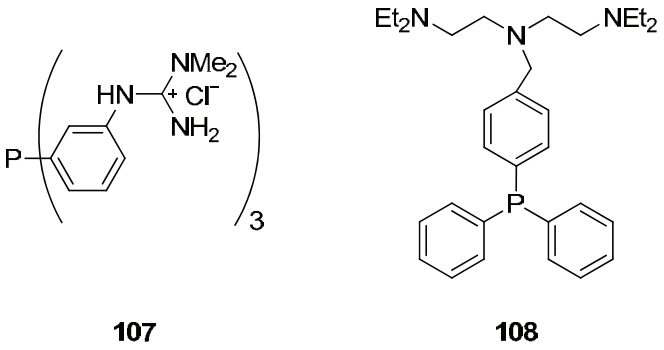
Scheme 26. Palladium-catalyzed hydroxycarbonylation of alkenes.

Different palladium precursors in combination with various promoters have been applied to achieve high catalytic activity and selectivity for the reaction of unsubstituted and functionalized olefins. For instance, Alper and co-workers described a catalyst system consisting of $PdCl_2/CuCl_2/HCl$ for the synthesis of branched acids under very mild conditions

(room temperature, 1 bar CO) in the presence of oxygen.[91] Similarly, $PdCl_2/CuCl_2/PPh_3$ was utilized for the highly regioselective synthesis of branched *o*-(4-methylphenyl)propionic acid from 4-methylstyrene.[92] Arylpropionic acids were synthesized regioselectively also by Seayad et al. by employing the simple catalyst system [Pd]/LiCl and *p*-toluenesulfonic acid (TsOH).[93] High selectivity towards linear acids was realized by using $Pd(OAc)_2$/dppb in the presence of formic acid as promoter.[94] Linear or branched products were obtained with palladium complexes in conjunction with mono- or diphosphines and oxalic acid.[95]

Notably, the hydroxycarbonylation has been performed in neat water or biphasic media resulting in high yields and selectivity.[96] The range of recoverable, water-soluble catalyst systems varies from palladium complexes of sodium trisulfonated triphenylphosphine (TPPTS)[97] in the presence of a Brønsted acid as promoter or the acid form TPPTSH[98] with acetic acid as co-catalyst to Pd-modified β-cyclodextrins as mass transfer promoters.[99] In addition, it has been reported that sulfonated chelating diphosphines efficiently catalyze the hydroxycarbonylation of ethene, propene and vinyl arenes.[100]

Recently, water-soluble palladium complexes containing more stable guanidinum phosphine ligands have been applied for the carbonylation of styrene in water.[101] In contrast to the Pd/TPPTS system, 3-phenylpropionic acid was obtained as major product (67%) when a catalyst system of $Pd(OAc)_2$ and tris(guanidinioaryl) ligand **107** (Figure 6) was employed at 20 bar of carbon monoxide and 110°C. Remarkably, 2-phenylpropionic acid was maintained predominantly (61%) by decreasing the temperature to 80°C.



107 **108**

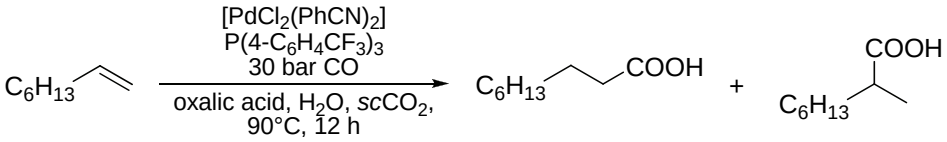
Figure 6. Alternative water-soluble phosphine ligands.[101,102]

An inverted regioselectivity compared to the TPPTS system, was also found for an amphiphilic palladium catalyst of *N*-bis-(*N′*,*N′*-diethyl-2-aminoethyl)-4-aminomethylphenyl-diphenylphosphine (**108**; Figure 6).[102] The carbonylation of styrene, 1-octene and

4-penteneoic acid in water with methanesulfonic acid (CH_3SO_3H) yielded regioselectively the corresponding linear acids at 50 bar CO and 100°C. Advantageously, the catalyst system was recovered easily via extraction of the substrate or via extraction of the catalyst into an organic solvent.[102]

The first example of an hydroxycarbonylation of terminal alkenes in environmentally friendly supercritical carbon dioxide was reported in 2006.[103] Initially, 1-octene (**109**) was reacted with oxalic acid/water in $scCO_2$ in the presence of $[PdCl_2(PhCN)_2]$ and phosphine $P(4\text{-}C_6H_4CF_3)_3$ at 90°C and 150 bar of total pressure (Table 2). Thus, 90% selectivity and 75% regioselectivity in nonanoic acid (**110**) were observed (Table 2, entry 2).

Table 2. Palladium-catalyzed hydroxycarbonylation of 1-octene in $scCO_2$.[103]



109 **110** **111**

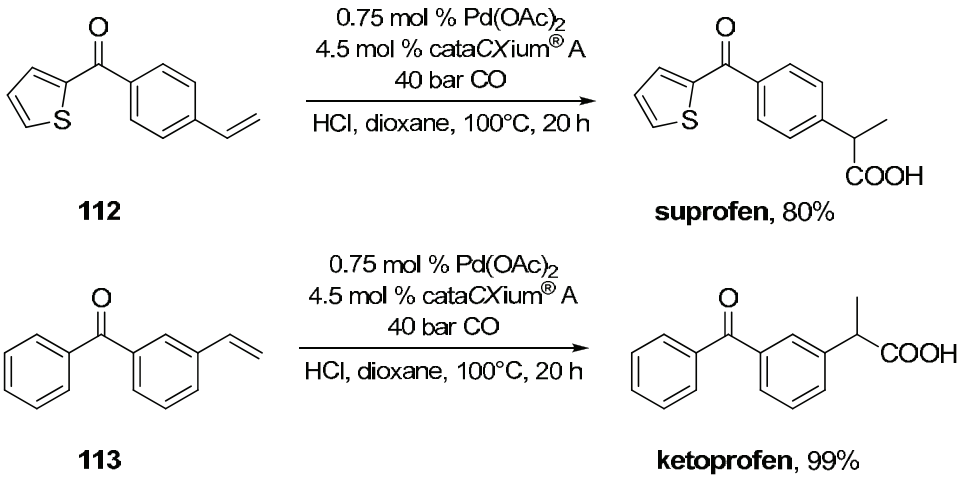
Entry	p_{total} [bar]	H_2O/Krytox®	Conversion [%]	Acid Selectivity [%]	110/111 [%]
1	203	0	6	74	60/40
2	152	0	55	90	75/25
3[b]	30	0	78	63	68/32
4	152	28	80	80	80/20
5	152	14	93	77	82/18
6	152	7	79	81	89/11
7	167	14	44	80	78/22

[a] Reaction conditions: 1.56 mmol 1-octene, 1.6 mol % $[PdCl_2(PhCN)_2]$, 6.4 mol % $P(4\text{-}C_6H_4CF_3)_3$, 1 equiv. oxalic acid, 12.5 mmol H_2O, 30.4 bar CO, 90 C, 12 h. [b] DME as the solvent, PPh_3 as the ligand.

Since the conversion was low (55%), a perfluorinated surfactant (Krytox®) was added to facilitate the mass transfer of water to the catalyst containing $scCO_2$ phase. An increase of the amount of surfactant (H_2O/Krytox® = 14/1) led to maximum conversion (93%) and 82% regioselectivity in the linear product **110** (Table 2, entry 5). Interestingly, the selectivity towards acids is higher than for organic (PPh_3) and aqueous (TPPTS) systems.

Very recently, studies of the palladium-catalyzed hydroxycarbonylation of styrene revealed the beneficial performance of the catalyst $Pd(OAc)_2$/cata*CX*ium® A.[104] Complete conversion and high regioselectivity towards the branched acid (94%) were observed in a

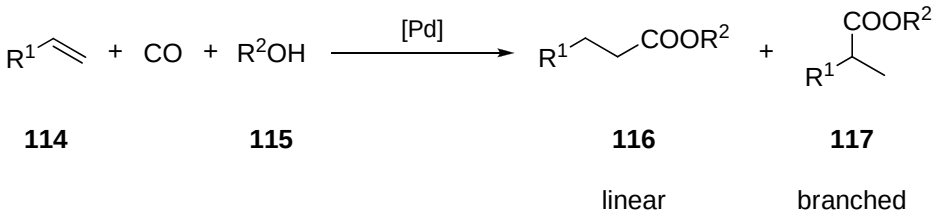
solution of dioxane and 37% hydrochloric acid at 40 bar CO. As a result, suprofen and ketoprofen were synthesized in 80% and 99% yields with excellent regioselectivity (99%) from **112** and **113**, respectively (Scheme 27). Notably, when the hydroxycarbonylation was combined with a carbonylative Suzuki reaction, different 2-arylpropionic acids were prepared in only two steps and in one pot starting from easily available aryl halides and arylboronic acids (see chapter 4.5).[104]



Scheme 27. Synthesis of suprofen and ketoprofen by Pd-catalyzed hydroxycarbonylation of vinyl arenes.[104]

2.2.2 Hydroesterification of alkenes

The palladium-catalyzed carbonylation of alkenes with CO in the presence of an alcohol (hydroesterification, alkoxycarbonylation) directly leads to the formation of industrially important carboxylic acid esters (Scheme 28). Analogous bisalkoxycarbonylation of the starting material provides a convenient route to diesters.[105] In addition to simple olefins and vinyl arenes, naturally occurring alkenes such as unsaturated steroids[106] or terpenes[107] have been carbonylated to obtain biologically active or useful organic synthetic building blocks.



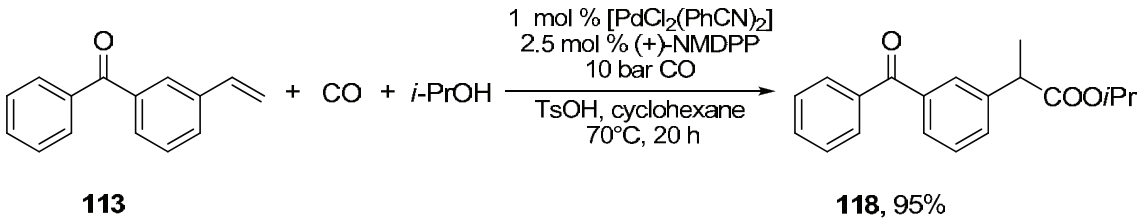
Scheme 28. Palladium-catalyzed hydroesterification of alkenes.

The monoalkoxycarbonylation usually yields a mixture of linear and branched chain esters depending on the catalytic system (nature of the phosphine ligand, bite angle, etc.) and the reaction conditions used. Thus, several mechanistic and theoretical studies have been conducted to find efficient catalyst systems affording good chemo- and regioselectivity, as well as high catalytic activity and stability.[108] Nowadays, a variety of soluble cationic as well as neutral palladium complexes are available.

Initially, several ligand-free catalyst precursors were established. For instance, the simple palladium(II) system $PdCl_2$/HCl in EtOH was applied by Tsuji et al. to synthesize carboxylic esters from olefins at 80°C and 100 bar of carbon monoxide.[109] Stille and James were able to carbonylate cyclic and acyclic alkenes with methanol at room temperature and low pressure (3 bar CO) by using the bimetallic system $PdCl_2/CuCl_2$.[110] Stoichiometric quantities of copper(II) chloride were employed to reoxidize Pd(0) which precipitated from the reaction mixture. The same catalyst was used by Alper and co-workers to react olefins with diols[111] (e.g. ethylene glycol) or formate esters[112] under oxidative and acidic conditions. Thus, mainly branched esters were obtained under atmospheric CO pressure. Almost complete conversion of 4-methylstyrene and 97% selectivity towards the branched methyl ester were achieved by adding a slight excess of triphenylphosphine to the system $PdCl_2/CuCl_2$ (41 bar CO, 100°C).[113] A versatile approach towards carboxylic esters utilized sole $[PdCl_2(PPh_3)_2]$[114] or $[PdCl_2(PPh_3)_2]$ in the presence of a co-catalyst such as HCl[89] or BF_3•OEt_2.[115] Depending on the reaction conditions, either branched or linear regioisomers were produced. Similarly, Toniolo and Cavinato employed $[PdCl_2(PPh_3)_2]$ in conjunction with a slight excess of PPh_3[116] to prevent catalyst decomposition to metallic palladium. The selectivity was oriented towards the branched isomer when the reaction was performed in an additional solvent (100-110°C, 100 bar CO). However, the transformation became highly regioselective towards the linear ester by the addition of stannous salt $SnCl_2$.[116a,117] Furthermore, it was reported that formate esters yielded linear isomers as major products in the hydroesterification of ethene and vinyl arenes.[118] In addition, catalysts containing palladium and monophosphines were used to synthesize linear carboxylic esters.[119]

Elsevier et al. applied $[Pd(0)(PPh_3)_2(alkene)]$ complexes as catalyst precursors for the methoxycarbonylation of styrene at 80°C.[120] After 90 min, 80% conversion and a branched to linear ratio of 41/59 were detected. When the reaction was carried out at 60°C, less conversion but higher selectivity (63%) towards the branched ester was found. The best regioselectivity towards ethyl 2-phenylpropionate (>98%) was accomplished by utilizing [*trans*-$PdCl_2$-(monodentate P-ligand)$_2$]-type complexes for the ethoxycarbonylation of styrene

(90 bar CO).[121] The α-arylpropionic esters of ketoprofen[122] (**118**; Scheme 29) and naproxen[123] (95% yield) have been prepared with remarkable selectivity (>99%) by employing $[PdCl_2(PhCN)_2]$/(+)-neomenthyldiphenylphosphine (NMDPP) with TsOH and $[PdCl_2(c\text{-}C_6H_{11}PPh_2)_2]$/EtOH-THF, respectively.



Scheme 29. Palladium-catalyzed hydroesterification of 3-vinylbenzophenone.[122]

Generally, the use of Pd(0) or Pd(II) precursors in combination with bulky chelating ligands such as bis(phosphaadamantyl)diphosphines,[124] dtbpx,[125] 1,1′-bis(diphenylphosphino)metallocenes[126] or other bidentate phosphines[127] resulted in a greatly improved regioselectivity towards linear esters. By contrast, an unexpected selectivity in branched-chain products was observed for vinyl arenes[127e,128] and vinyl acetate[128b,129] by using a palladium(II) and palladium(0)/ diphosphine system, respectively. For instance, van Leeuwen and co-workers presented the highly selective formation of branched esters from styrene and carbon monoxide (70 bar) by employing bis(2-diphenylphosphinophenyl)ether (DPEphos)-based diphosphines in the presence of a Brønsted acid at 100°C.[128a] The group of Tanaka used $Pd(OAc)_2$/dtbpx for the methoxycarbonylation of styrene. In the presence of (polymeric) sulfonic acid, high chemoselectivity (95-99%) and regioselectivity towards methyl 2-phenylpropionate (86-89%) were obtained at low pressure (6 bar CO) and room temperature.[128b]

In order to improve product isolation and catalyst recovery, clay- and polymer-supported palladium catalysts have been developed to realize alkoxycarbonylations of alkenes.[130]

Ionic liquids have only scarcely been used as reaction media for palladium-catalyzed hydroesterification reactions.[131-135] Thus, Monteiro and co-workers achieved excellent regioselectivity (≥99.5%) towards α-esters for the $[PdCl_2(PhCN)_2]$/(+)-NMDPP/TsOH-catalyzed alkoxycarbonylation of styrene derivatives by using a two-phase system consisting of [bmim][BF_4] and isopropanol/cyclohexane.[131] Similarly, different imidazolium-based ionic liquids were employed as solvents for the carbonylation of styrene with various alcohols at 100 bar CO and 100°C by Rangits and Kollár.[132] When the reaction was carried out in the

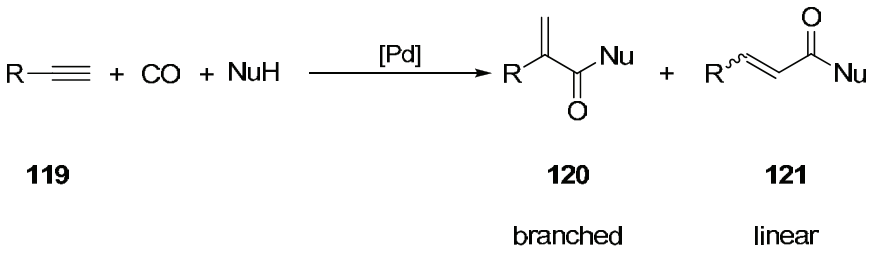
presence of $[PdCl_2(PPh_3)_2]$ in [bmim][PF_6], linear esters were formed except for *n*-propanol whereas the use of [bmim][BF_4] predominantly led to the formation of branched products. The amount of linear product was increased significantly by applying palladium-diphosphine systems. Simultaneously, Klingshirn and co-workers reported on the methoxycarbonylation of styrene, styrene derivatives and 1-octene in a range of IL's under milder conditions (14 bar CO, 90°C).[133] In the presence of $[PdCl_2(PPh_3)_2]/PPh_3$/TsOH the linear esters were observed predominantly. Although the IL/catalyst phase was recycled five times, good yields (>50%) were obtained and the linear to branched ratio even increased from 81/19 to 91/9.[133] Moreover, it was demonstrated that $[PdCl_2(PPh_3)_2]$ showed good results in the ethoxycarbonylation of styrene when the reaction was conducted in [acetonyl-mim][PF_6] or [acetonyl-mim][BF_4] at 100 bar CO (100°C).[134] Thus, ethyl 2-phenylpropionate was maintained exclusively after 24 h. Addition of the bidentate ligand dppf resulted in complete inversion of regioselectivity in [acetonyl-mim]PF_6 yielding exclusively 3-phenylpropionate. Molten ammonium and phosphonium salts were employed for the reaction of styrene with carbon monoxide (50 bar) and alcohol at 110°C. In the presence of the in situ system $PdCl_2/PPh_3/CuCl_2$ good to high regioselectivity (68-96% branched ester) depending on the halide counter ion of the ionic liquid was obtained.[135]

Asymmetric palladium-catalyzed mono- and bisalkoxycarbonylation reactions were mainly reported for styrene derivatives[136] and have been reviewed very recently.[137]

The palladium-catalyzed intramolecular alkoxycarbonylation of alkenols has been applied to synthesize cyclic esters (lactones) of different ring size in high yields.[138] Notably, good enantioselectivity was achieved in asymmetric cyclocarbonylation reactions.[139]

2.2.3 Carbonylation of alkynes

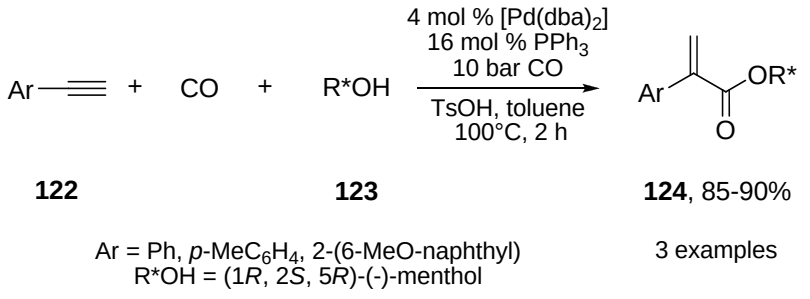
The palladium-catalyzed carbonylation of alkynes with alcohols, water, and amines normally produces mixtures of linear and branched α,β-unsaturated esters,[140] acids,[95e,141] and amides,[142] respectively (Scheme 30). The ratio of the products strongly depends on the employed catalytic system and the reaction conditions used. Thus, considerable efforts have been made to control the regio- and stereoselectivity in these reactions.



Scheme 30. Palladium-catalyzed carbonylation of alkynes in the presence of a nucleophile.

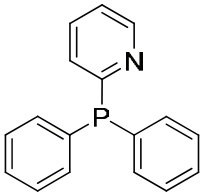
In principle, identical or slightly modified palladium catalysts are applied for the carbonylation of alkenes and alkynes. Thus, catalysts consisting of sole $PdCl_2$,[143] $PdCl_2/CuCl_2$[144] in the presence of sodium acetate,[145] or Pd/C[143,146] in conjunction with a strong acidic medium have been used successfully for alkoxycarbonylations of alkynes. Generally, product mixtures or branched-chain α,β-unsaturated esters were obtained. El Ali and Alper presented the regioselective hydroesterification of 1-alkynes with $Pd(OAc)_2$ or $[Pd(dba)_2]$ in combination with dppb.[147] The reaction proceeded smoothly at 80 bar CO and 150-190°C affording *t*-butyl ester of atropic acid in very high selectivity (up to 100%), however, the yields were only moderate (15-62%). Other regioselective carbonylations of alkynes to produce branched monoesters were realized at atmospheric pressure of CO at 100°C by utilizing catalyst systems such as $[Pd(PPh_3)_4]$ or $Pd(OAc)_2$/dppf[148] and $[Pd(dba)_2]/4PPh_3$/TsOH.[149] Unfortunately, low reaction rates were noted.

Aside from carbon monoxide, other carbonyl sources such as formate esters[150] or oxalate esters[151] have been used to transform mainly terminal alkynes. A simple and selective method for the production of chiral 2-arylpropenoic esters was presented by Monteiro et al. (Scheme 31). Thus, terminal aryl acetylenes **122** were reacted with (1*R*,2*S*,5*R*)-(-)-menthol under mild conditions in the presence of $[Pd(dba)_2]/PPh_3$/TsOH to afford the desired branched esters **124** in high yields (85-90%).[152]



Scheme 31. Synthesis of chiral 2-arylpropenoic esters.[152]

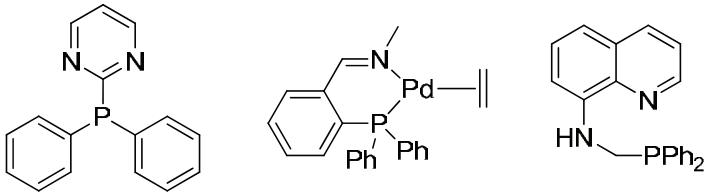
The most efficient homogeneous palladium catalyst for the carbonylation of alkynes was developed by Drent and co-workers in the early 90´s. Here, palladium acetate in combination with 2-pyridyldiphenylphosphine (**125**, (2-py)PPh_2; Figure 7) and CH_3SO_3H catalyzed the methoxycarbonylation of propyne with unprecedented activity and regioselectivity. Thus, 40000 turnovers per hour and 99.95% selectivity towards the branched product (MMA) were maintained at relatively high pressure (60 bar) and 45-60°C.[153] Later on, an investigation on the mechanism of this transformation was reported.[154]



125

Figure 7. 2-Pyridyldiphenylphosphine: (2-py)PPh_2.[153]

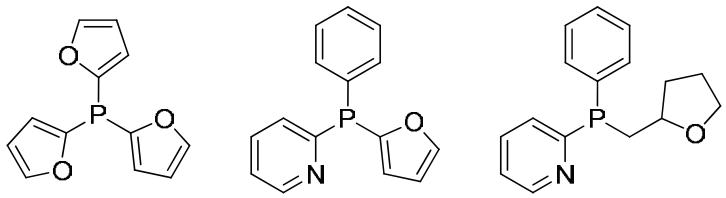
Inspired by the work of Drent, phosphine ligands bearing additional nitrogen donor atoms have been more recently employed in alkoxycarbonylation reactions of alkynes. Thus, the catalyst system $Pd(OAc)_2$/2-pyrimidyldiphenylphosphine (**126**; Figure 8) was comparably more active (97% conversion, TOF = 7000 h^{-1}) in the methoxycarbonylation of 1-hexyne as the one based on (2-py)PPh_2.[155] Unfortunately, palladium(0) complexes containing the iminophosphine ligand **127** (Figure 8) resulted in low reaction rates and moderate chemo- and regioselectivity for the reaction of phenylacetylene with methanol at 120°C.[156] When the same transformation was performed in the presence of $Pd(OAc)_2$/8-(diphenylphosphino)-methylaminoquinoline (**128**; Figure 8), modest selectivity towards the branched ester (86%) but low catalytic activity was observed.[157]



126 **127** **128**

Figure 8. Phosphine ligands with additional nitrogen donor atoms.[155-157]

The application of polydentate phosphine ligands containing oxygen and/or nitrogen donor atoms was also reported. Palladium complexes of tri(2-furyl)phosphine (**129**, Tfp; Figure 9) and CH_3SO_3H showed fairly good reaction rates and a good branched regioselectivity (around 95%) for the methoxycarbonylation of phenylacetylene at 50-80°C.[158] Under the same reaction conditions, the use of (2-furyl)phenyl(2-pyridyl)phosphine (**130**; Figure 9) resulted in a higher regioselectivity (>99%) towards the branched 2-phenyl substituted acrylic ester.[159] Remarkably, this ligand even revealed higher activity as (2-py)PPh_2 when the reaction was conducted in neat MeOH at 50°C and 40 bar CO. Furthermore, excellent selectivity (>99%) was accomplished with low ligand/Pd and acid/Pd ratios. However, only moderate activity but improved catalyst stability was noted for palladium(II) complexes of [(2-py)P(Ph)(CH_2-(thf))] (**131**; Figure 9) in the methoxycarbonylation of propyne.[160]



129 **130** **131**

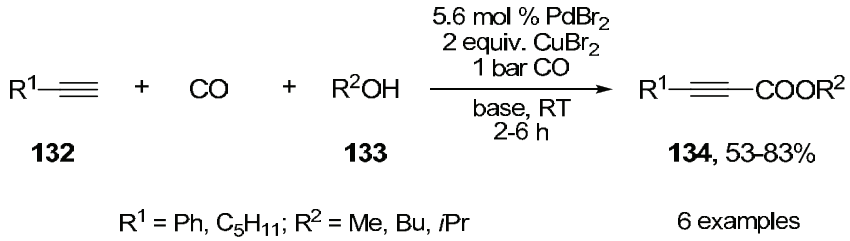
Figure 9. Polydentate phosphine ligands.[158-160]

A palladium-catalyzed electrochemical carbonylation of terminal alkynes under very mild conditions was reported in 2002.[161] Several patents and papers with respect to the synthesis of branched esters from alkynes have been published but there are only a few reports on catalysts affording selectively linear esters.[162] For example, El Ali and co-workers achieved good to high regioselectivity (57-100%) towards linear products for the conversion of terminal alkynes under neutral conditions by using a catalyst system composed of Pd(II)/dppb and synthesis gas (41 bar, CO/H_2 = 1:1).[163]

The $Pd(OAc)_2$/(2-py)PPh_2/CH_3SO_3H-catalyzed alkoxycarbonylation of 3,3,3-trifluoropropyne with methanol was optimized by Matteoli et al. Complete conversion, >99% yield and a branched to linear ratio of 73/27 were obtained in a 9:1 mixture of CH_2Cl_2 and NMP at 80°C after 24 h.[164] Later on, it was shown that $Pd(OAc)_2$ in conjunction with (6-methyl-2-pyridyl)diphenylphosphine and CH_3SO_3H leads to a highly efficient catalyst for this reaction.[165] Depending on the composition of the catalytic system and the reaction conditions

used, either branched or linear trifluoromethyl-substituted esters were maintained. Thus, high ligand/Pd (40/1) and acid/Pd ratios promoted the production of branched methyl ester at 20 bar of carbon monoxide. On the other hand, an inverted regioselectivity (up to 85%) towards the linear product was observed at 80 bar CO by employing a low ligand/Pd ratio together with a high acid/Pd ratio.[165]

A novel synthetic route to acetylene carboxylates was presented by Jiang et al. (Scheme 32).[166] The desired unsaturated esters **134** were isolated in fair to good yields (53-83%) when the palladium bromide-catalyzed carbonylation of terminal acetylenes **132** with aliphatic alcohols **133** was carried out in the presence of cupric bromide and base (NaOAc, $NaHCO_3$).



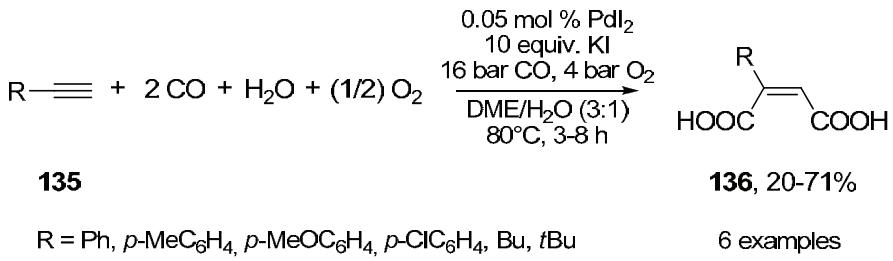
Scheme 32. $PdBr_2$-catalyzed carbonylation of terminal acetylenes to acetylene carboxylates.[166]

It was reported recently that palladium complexes derived from $Pd(OAc)_2$ and 2-[bis-{4-(trialkylsilyl)phenyl}phosphino]pyridines are highly active and selective catalysts for the methoxycarbonylation of phenylacetylene.[167] When the reaction was performed in methanol, the in situ prepared palladium catalyst displayed the same activity (TON = 4000, 50 min reaction time) and selectivity (98% towards the branched product) as the catalytic system developed by Drent.[153] However, higher activity was observed with 2-[bis{4-((2-(perfluoro-hexyl)ethyl)dimethylsilyl)phenyl}phosphino]pyridine as ligand in methanol/α,α′,α″-trifluoro-toluene (1:1). Furthermore, it was demonstrated that the zerovalent palladium complex $[Pd((2\text{-py})PPh_2)_2(c\text{-}(CH{=}CHC(O)OC(O)\text{-}))]$ was even as twice as active (TON = 8000 in MeOH) as the in situ prepared catalysts.[167]

The first insoluble polymer-bound palladium complexes of 2-pyridyldiphenylphosphine were described by Doherty and co-workers.[168] A system consisting of $Pd(OAc)_2$, polystyrene supported $(2\text{-py})PPh_2$ and CH_3SO_3H efficiently catalyzed the reaction of phenylacetylene with methanol under standard conditions (40 bar CO, 50°C) to furnish selectively methyl 2-phenylpropenoate (98%). Best results for the methoxycarbonylation of propyne (98% MMA) were achieved by utilizing a methacrylate-based homopolymer of $(2\text{-py})PPh_2$. In fact,

the immobilized catalyst systems showed nearly as high activity and selectivity towards the branched esters as those applied under homogeneous conditions.[168]

Maleic acids were synthesized directly by Pd-catalyzed oxidative dicarbonylation of 1-alkynes **135** in a 3:1 mixture of DME/H_2O (Scheme 33).[169] Fair to good yields (20-71%) for **136** were maintained under 16 bar CO and 4 bar of air at comparably low temperature (80°C) by employing PdI_2 in conjunction with an excess of KI.



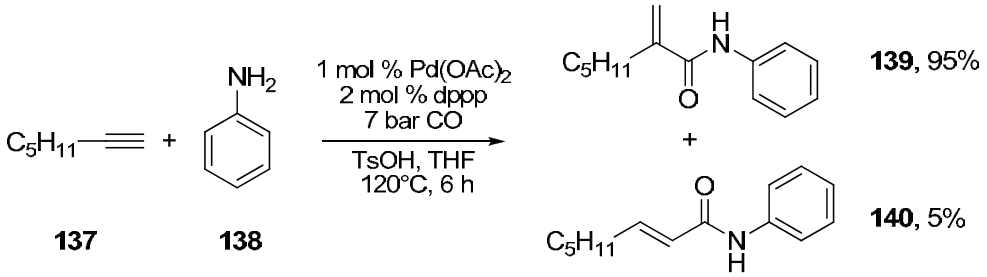
Scheme 33. Synthesis of maleic acids by palladium-catalyzed oxidative dicarbonylation of terminal alkynes.[169]

In analogous manner to dicarbonylations using water as nucleophile, the palladium-catalyzed dicarbonylation of alkynes with alcohols gives α,β-unsaturated diesters. The range of known catalyst systems varies from $PdCl_2$/HCl,[170] $PdCl_2/HgCl_2$,[105d] $PdCl_2/CuCl_2$[171] in the presence of HCl/O_2,[172] PdI_2/KI/O_2,[173] PdI_2/thiourea[174] to $PdBr_2/CuBr_2$.[175] In general, maleic acid esters (*Z*) were obtained as major products.

The regioselective intramolecular alkoxycarbonylation of terminal alkynes has proven to be one of the most important and powerful methodologies for the direct synthesis of lactones,[176] benzo[*b*]furans,[177] and furanones.[178] Besides, a variety of heterocyclic derivatives were prepared either via cyclocarbonylation[179] or cyclization-alkoxy-carbonylation of alkynes.[180]

A highly regioselective synthesis of α-methylene amides from aromatic alkynes was described by El Ali and co-workers.[181] Thus, phenylacetylene and *p*-tolylacetylene were reacted in toluene with aniline and *N*-substituted aniline derivatives in the presence of $Pd(OAc)_2$/dppb and synthesis gas (41 bar, CO/H_2 = 1:1) to give the corresponding branched acrylamides in high yields (67-95%) and with 74-100% selectivity at 110-120°C. However, improved yields (82-98%) and good regioselectivity (60-100%) towards *N*-aryl-2,3-disubstituted acrylamides were obtained by utilizing $Pd(OAc)_2$/dppp in combination with TsOH in THF (20.5 bar CO, 110°C).[182]

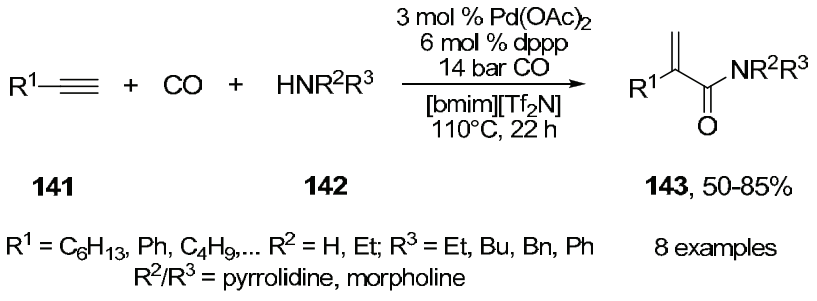
Regioselective control of the aminocarbonylation of 1-heptyne (**137**) with aniline (**138**) was achieved by using a palladium(II) precursor and bidentate phosphine ligands (Scheme 34). *N*-Phenyl-2-pentylpropeneamide (**139**) was maintained as the major product (95%) in excellent yield (95%) after 6 h by applying the approved catalyst $Pd(OAc)_2$/dppp/TsOH in THF at 7 bar CO and 120°C.[183] On the other hand, (*E*)-*N*-phenyl-2-octenamide (**140**) was formed predominantly (82%) in CH_2Cl_2 at 110°C in the presence of $Pd(OAc)_2$/dppb and synthesis gas (41 bar, CO/H_2 = 1:1). Later on, the protocol was adopted to other terminal alkyl alkynes to synthesize either linear or branched α,β-unsaturated amides.[184]



Scheme 34. Palladium-catalyzed aminocarbonylation of 1-heptyne.[183]

The aminocarbonylation of phenylacetylene catalyzed by $Pd(OAc)_2$/(2-py)PPh_2 and CH_3SO_3H was investigated in detail in 2004.[185] Best results and complete regioselectivity towards the branched amide were obtained in a 9:1 mixture of CH_2Cl_2/NMP at 20 bar CO working with an excess of phenylacetylene and an acid/Pd molar ratio of 30/1.

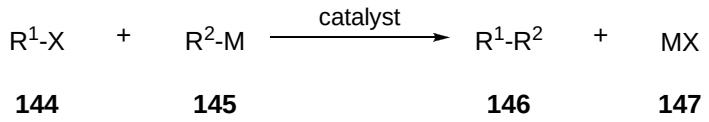
Various 2-substituted acrylamides **143** were isolated in good yields (50-85%) when the reaction of terminal alkynes **141** with primary or secondary amines **142** was carried out in the ionic liquid [bmim][Tf_2N] at 14 bar CO (Scheme 35).[186] The transformation proceeded without any acid additive. Noteworthy, the catalyst system $Pd(OAc)_2$/dppp was recycled and reused five times without losing its catalytic activity.



Scheme 35. Palladium-catalyzed regiospecific aminocarbonylation of terminal alkynes in IL.[186]

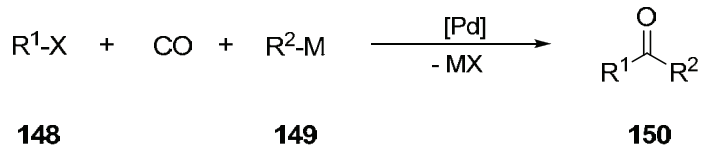
2.3 Carbonylative cross-coupling reactions

Among the many different catalytic transformations, transition metal-catalyzed cross-coupling reactions have become most popular (Scheme 36).[1] Thus, new carbon-carbon bonds are formed via cross-coupling of organic halides with either unsaturated compounds (e.g. Heck or Sonogashira reaction) or with nucleophilic metallic reagents (e.g. Kumada, Negishi, Stille or Suzuki coupling).



Scheme 36. General scheme for transition metal-catalyzed coupling reactions with organometallic compounds.

The palladium-catalyzed multi-component cross-coupling reaction of organic electrophiles, carbon monoxide, and organometallic reagents is a synthetically useful method for the preparation of (un)symmetrical ketones (Scheme 37). Carbonylative cross-coupling reactions have been reported for several metal reagents such as organoboranes or -borates,[187] organoaluminium,[188] organosilane,[189] organoantimony,[190] and organozinc[191] compounds.



Scheme 37. General scheme for the palladium-catalyzed three-component cross-coupling reaction.

2.3.1 Carbonylative Stille coupling reactions

The carbonylative Stille reaction between organic halides (or pseudohalides), carbon monoxide and stannanes has extensively been studied in the past 20 years.[192] In spite of the toxicity of the tin compounds, the Stille carbonylation has found many applications in organic synthesis because of its functional group tolerance and versatility (Figure 10).

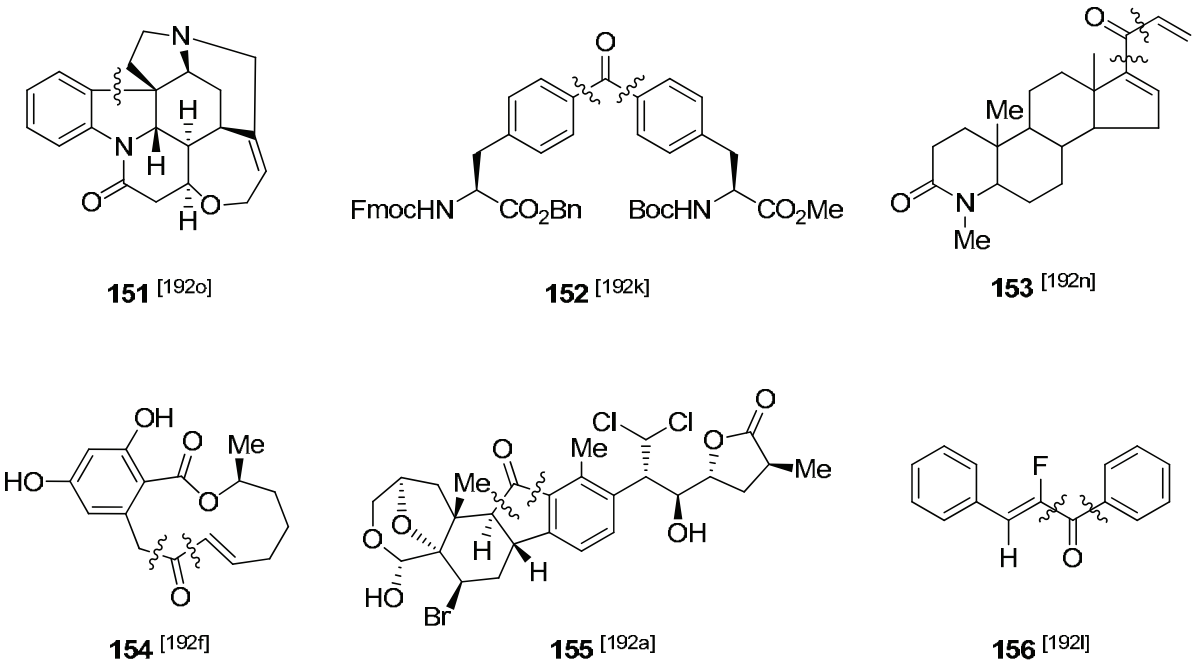
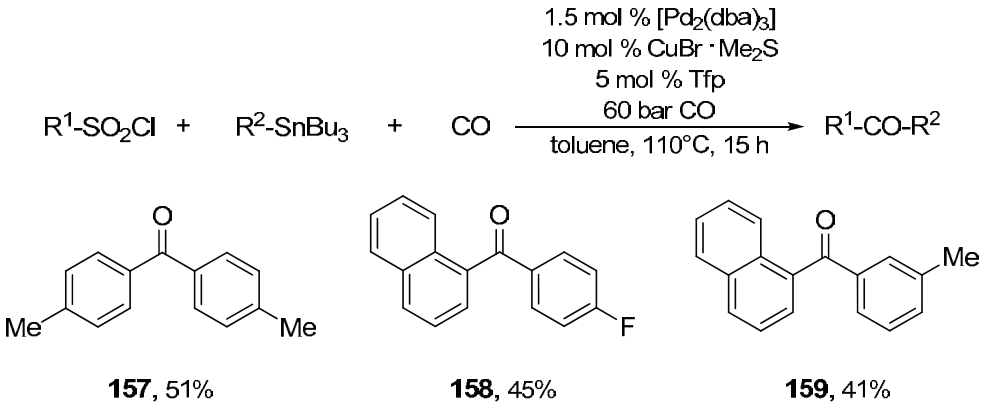


Figure 10. Examples of products from the carbonylative Stille coupling reactions in organic synthesis. (The bonds formed by carbonylation are indicated in each case.)

For example, an inverse three-component carbonylative Stille coupling on solid support was described by Yun et al.[193a] Readily available aryl bromides and iodides were coupled simultaneously with an aryl stannane, which had been immobilized on a Rink amide resin. Diarylketones with a wide range of functional groups were isolated after 18-72 h in good to excellent yields (78-99%) whereas direct cross-coupling products were not observed. Recently, a combinatorial synthesis of conjugated arene systems by sequential palladium-catalyzed coupling reactions on solid phase, including Stille carbonylation, was also developed.[193b]

The first Pd-catalyzed desulfitative coupling of arenesulfonyl chlorides and organostannanes at 60 bar CO was reported by Dubbaka and Vogel (Scheme 38).[194] The reactions were performed in toluene and required a larger amount of $CuBr \cdot Me_2S$ as co-catalyst. Unfortunately, only moderate yields (41-51%) were achieved under these conditions because of the increased formation of side-products arising from the carbonylative homo-coupling of the employed organostannanes. Interestingly, thioesters (R^1-S-CO-R^2) were obtained (32-40%) when the reaction was conducted in THF in the presence of $[Pd_2(dba)_3]$/Tfp.



Scheme 38. Palladium-catalyzed carbonylative Stille coupling reaction of sulfonyl chlorides.[194]

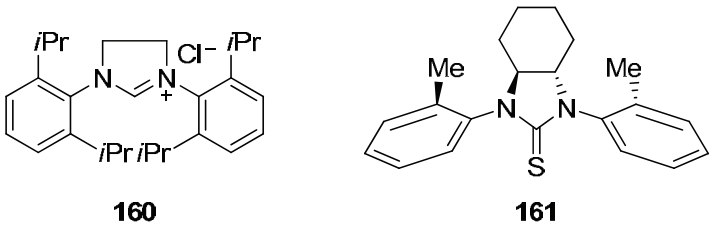
Carbonylative coupling reactions of tributyl(1-fluorovinyl)stannane with 1-iodo-2,4-dimethylbenzene were carried out under atmospheric CO pressure.[195] The desired aryl 1-fluorovinyl ketone was obtained in quantitative yield under optimized conditions (2.5 mol % $[Pd(PPh_3)_4]$, 80°C, 2 h). Hence, the carbonylative Stille reaction was applied to other 2-, 3-, or 4-substituted aryl iodides, and the corresponding fluorinated α,β-unsaturated ketones were isolated in good yields (64-99%). In contrast to the protocol of Chen et al.,[192l] the addition of copper (I) iodide or lithium chloride was not required. Some electron-deficient aryl triflates were also coupled in the presence of tetrabutylammonium iodide.

2.3.2 Carbonylative Suzuki coupling reactions

In 1993, Suzuki and co-workers successfully synthesized unsymmetrical biaryl ketones by a palladium-catalyzed cross-coupling reaction of arylboronic acids with iodoarenes in the presence of one bar of carbon monoxide (carbonylative Suzuki reaction).[196] Since their introduction 15 years ago, boronic acids have gained increasing importance compared to tin compounds as they are generally non-toxic, thermally stable, and inert to oxygen and moisture. Thus, several improvements and applications of the original synthetic protocol have been described,[192a,197] but limitations (formation of (biaryl) side-products, employment of additives, or restriction to special substrates) often remained.

In this respect, Andrus et al. have broadened the scope of the Suzuki carbonylation by using aryl diazonium tetrafluoroborate salts as coupling partners.[198] Aryl and vinyl boronic

acids were reacted with these electron-rich or -deficient substrates in dioxane at 1 bar CO and 100°C. After 5 h, the desired aryl ketones and the corresponding biaryl coupling products were isolated in 76-90% and 2-12% yield, respectively, by employing a palladium/ *N*-heterocyclic carbene (NHC) complex as catalytically active species. The catalyst was generated in situ from 2 mol % $Pd(OAc)_2$ and 2 mol % *N*,*N*-bis(2,6-diisopropylphenyl)dihydroimidazolium chloride (**160**; Figure 11).

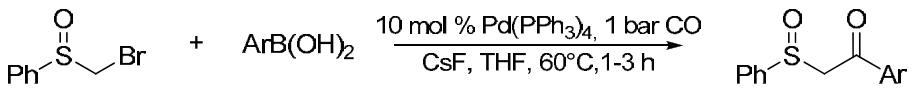


160 **161**

Figure 11. Ligands used for carbonylative cross-coupling of diazonium salts.[198,199]

Subsequently, an alternative phosphine-free palladium catalyst was reported for the carbonylative Suzuki reaction of diazonium salts. By applying the newly synthesized C_2-symmetrical and sterically bulky thiourea ligand **161 (**Figure 11), milder reaction temperatures (20 or 50°C) were achieved.[199] However, for nitrophenyldiazonium compounds the yields were lower in comparison to the method of Andrus et al.[198] The palladium/thiourea catalyst was also employed to couple (hetero)aryl iodides in satisfying yields (>70%).[199]

β-Ketosulfoxides **164** were synthesized for the first time by transformation of α-bromo sulfoxide **162** with (hetero)aryl boronic acids **163** under atmospheric CO pressure (Scheme 39).[200] Neither homo- and cross-coupling side-products nor sulfoxides resulting from dehalogenation were observed in significant amounts. Under mild conditions, aryl boronic acids with electron-withdrawing substituents were less reactive; alkyl boronic acids did not react at all. Notably, a modified reaction mechanism was supposed for the Suzuki carbonylation of α-bromo sulfoxides.[200]

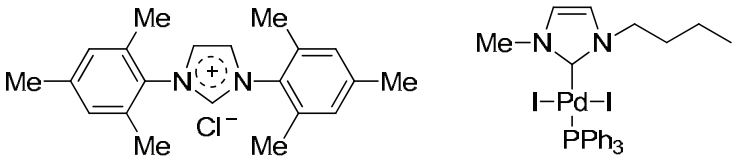


162 **163** **164**, 45-99%

12 examples

Scheme 39. First synthesis of β-ketosulfoxides by a palladium-catalyzed carbonylative Suzuki reaction.[200]

Castanet and co-workers introduced $[PdCl_2(PPh_3)_2]$ as an efficient catalyst system for carbonylative Suzuki cross-coupling reactions of mainly 2- or 4-substituted iodo- and bromopyridines.[201,202] Thus, phenyl pyridyl ketones were obtained in high yield and selectivity at 5 bar CO. Dibromopyridines furnished the corresponding dibenzoylpyridines when $[PdCl_2(PCy_3)_2]$ was used.[201,202] Shortly afterwards, the authors succeeded in extending the scope of the reaction to chloropyridines and chloroquinoline.[203] For the first time, activated aryl chlorides were directly converted to the desired benzoylpyridines by an in situ generated palladium complex based on $Pd(OAc)_2$ and imidazolium salt **165** (Figure 12). The reactions were conducted in dioxane in the presence of Cs_2CO_3 at 50 bar CO and 140°C to improve reactivity. A detailed investigation of the influence of the catalyst precursor, solvent, temperature, time and CO pressure on the Pd/NHC-catalyzed Suzuki carbonylation of pyridine halides was published recently.[204]

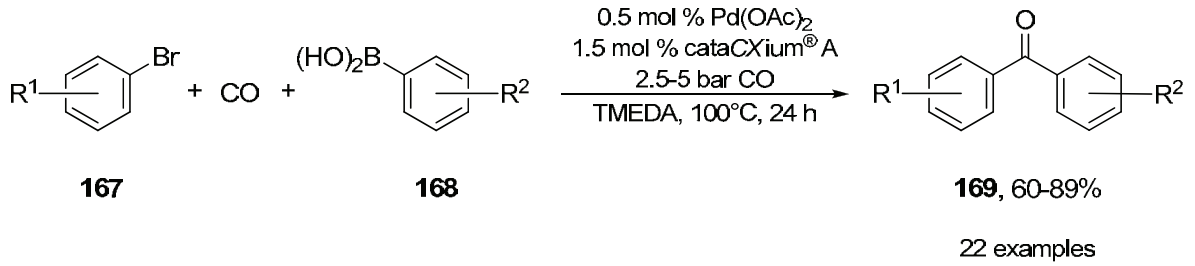


165 **166**

Figure 12. NHC ligand **165** and the palladium-carbene complex **166** used for Suzuki carbonylations.[203,205]

The Pd/NHC/phosphine complex **166** (Figure 12) was used for the carbonylative reaction of electron-rich and electron-deficient aryl iodides with phenylboronic acid or $NaBPH_4$ as cheap phenylating agent.[205] Excellent yields were achieved with K_2CO_3 as base already after 5 h under 1 bar CO at 100°C.

A general method for the synthesis of diaryl and aryl heteroaryl ketones by palladium-catalyzed Suzuki carbonylation was developed in our group (Scheme 40). A broad range of aryl and heteroaryl bromides were coupled with different aryl boronic acids at low pressure in the presence of $Pd(OAc)_2$/cata*CX*ium® A to give the corresponding ketones **169** with high selectivity (see chapter 4.4).[206]



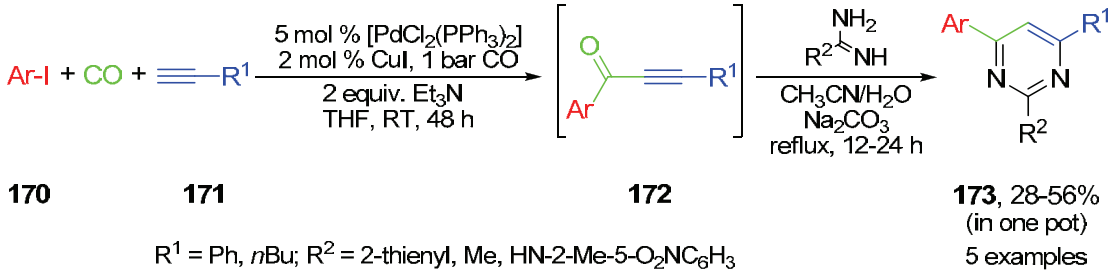
Scheme 40. General synthesis of diarylketones in the presence of $Pd(OAc)_2$ and cata*CX*ium® A.[206]

2.3.3 Carbonylative Sonogashira coupling reactions

The carbonylative three-component cross-coupling of aryl halides with terminal alkynes in the presence of amines as the base to give alkynyl ketones is known as carbonylative Sonogashira reaction and has been described in several publications.[207] Typically, the reaction requires anhydrous/anaerobic conditions, relatively high CO pressures, and a copper(I) co-catalyst. For these reasons, a variety of modifications and new procedures have been developed over the last years.

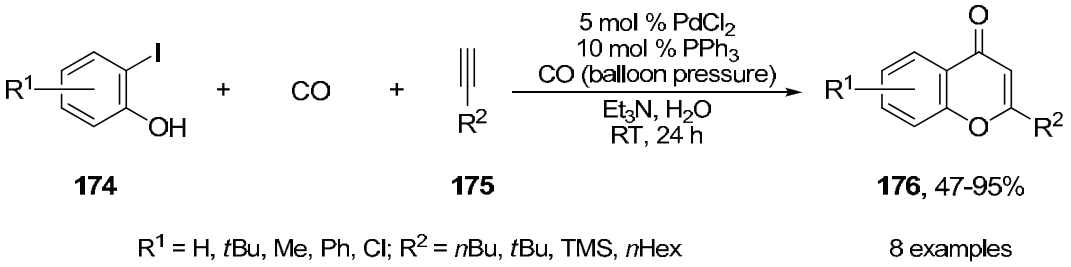
In 2003, Mohamed Ahmed and Mori reported the direct carbonylative coupling of phenylacetylene with aryl iodides by using 1 mol % $[PdCl_2(PPh_3)_2]$ and 0.5 M aqueous ammonia in THF.[208] α,β-Alkynyl ketone derivatives were isolated in 50-81% yield whereas non-carbonylative coupling products were not obtained under mild conditions (25°C, 1 bar CO) and in the absence of copper. Since the reaction was slower for alkynes bearing an alkyl substituent, higher amounts of catalyst and the addition of CuI were necessary.

Carbonylative Sonogashira reactions have been successfully employed in natural product syntheses. For example, 2,4,6-trisubstituted pyrimidines **173** have been prepared from (hetero)aryl iodides, alkynes, carbon monoxide (1 bar), and amidines by a consecutive four-component carbonylative alkynylation/cyclocondensation reaction sequence in one pot (Scheme 41).[209] Again, CuI had to be added to achieve moderate yields at room temperature. The authors also presented a two-step synthesis of pharmaceutically active meridianins and their derivatives. Carbonylative coupling of Boc-protected 3-iodoindole derivatives and trimethylsilylacetylene afforded TMS-alkynones which were subsequently treated with guanidine to give the desired indole alkaloids.



Scheme 41. One-pot four-component carbonylative coupling-cyclocondensation sequence to pyrimidines.[209]

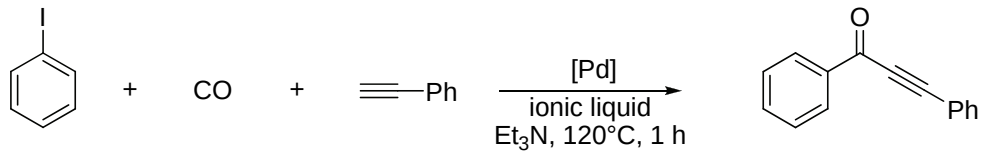
The first copper-free $PdCl_2/PPh_3$-catalyzed carbonylative Sonogashira reaction of aryl iodides using water as the solvent was published by Yang and co-workers.[210] Remarkably, both aryl- and alkyl-substituted alkynyl ketones were maintained in good to excellent yields (71-96%) when Et_3N was used as the base (1 bar CO). Due to the superior performance of the water/Et_3N system, it was supposed that Et_3N not only acted as the base but also as the co-solvent in the reaction. Furthermore, this protocol was applied to the synthesis of naturally occuring flavones **176**. Carbonylative coupling of iodophenols **174** with alkyl-substituted terminal acetylenes **175** followed by intramolecular cyclization gave the desired natural products in 47-95% yield (Scheme 42).[210]



Scheme 42. New approach towards flavones.[210]

An alternative copper-free approach to alkynyl ketones is the palladium-catalyzed carbonylative alkynylation of aryl iodides in ionic liquids.[211] The reaction of iodobenzene with phenylacetylene in the presence of CO proceeded smoothly in [bmim][PF_6] (Table 3). Thus, acetylenic ketone **178** was produced in 82% yield under 20 bar of carbon monoxide (Table 3, entry 1). A reduced pressure or amount of base and modification of the palladium species or ionic liquid did not lead to improved yields (Table 3, entries 4-7). Interestingly, the catalyst and solvent were recycled and reused with a slight decrease in efficiency (Table 3, entries 1-3).

Table 3. Palladium-catalyzed carbonylative Sonogashira coupling reaction of iodobenzene in ionic liquids.[211]



177 **178**

Entry	[Pd]	Run	CO [bar]	Et_3N [equiv.]	Ionic liquid	Isolated Yield [%][b]
1	$[PdCl_2(PPh_3)_2]$	1	20	3.6	[bmim][PF_6]	82
2		2	20	3.6	[bmim][PF_6]	68
3		3	20	3.6	[bmim][PF_6]	61
4[c]	$[PdCl_2(PPh_3)_2]$	1	20	2.0	[bmim][PF_6]	48
5	$[PdCl_2(PPh_3)_2]$	1	10	3.6	[bmim][PF_6]	52 (21)
6	$[PdCl_2(PPh_3)_2]$	1	20	3.6	[bmim][Tf_2N]	58 (24)
7	$Pd(OAc)_2$	1	20	3.6	[bmim][PF_6]	60

[a] Reaction conditions: 1 mmol iodobenzene, 1.2 mmol phenylacetylene, 1 mol % [Pd], 3 mL ionic liquid, 120 C, 1 h.
[b] Yield of isolated product. The yield of diphenylacetylene is shown in parantheses. [c] The reaction was carried out for 2 h.

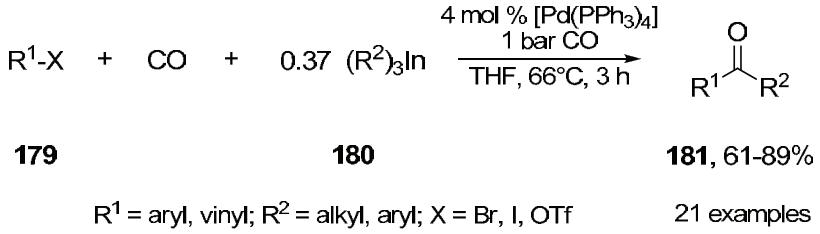
A superior selectivity and higher yields for the Sonogashira carbonylation in ionic liquids have been achieved even at low CO pressures when reactions were carried out in a continious microflow system instead of a batch reactor.[212]

Recently, the first phosphine-free, heterogeneous catalyst systems were investigated for carbonylative Sonogashira reactions.[213] Pd/C-Et_3N efficiently catalyzed the coupling reaction of various aryl halides with terminal alkynes and was easily recycled up to three times with no significant loss of catalytic activity.[213a] Only small amounts (<1%) of competing Sonogashira coupling products were observed. A magnetically separable palladium catalyst (Pd/Fe_3O_4) was reused even seven times with similar selectivity and activity. Remarkably, a turnover number of about 500 was achieved for the reaction of iodobenzene with phenylacetylene in the presence of carbon monoxide.[213b]

The first palladium-free, copper-catalyzed carbonylative Sonogashira coupling reaction of aliphatic and aromatic alkynes with iodoaryls was explored quite recently by Tambade et al.[214]

2.3.4 Indium organometallics in cross-coupling reactions

In 2003, Lee et al.[215] (Scheme 43) and Sarandeses and co-workers[216] published independently the first examples of palladium-catalyzed carbonylative cross-coupling reactions of organic electrophiles and triorganoindium compounds in the presence of carbon monoxide.



Scheme 43. Carbonylative cross-coupling with triorganoindium compounds according to Lee et al.[215]

Unsymmetrical ketones **181** were produced in good yields (61-89%) and with high atom efficiency since all organic groups attached to the metal were transferred onto the electrophile. Double carbonylative coupling provided 1,4-diacylbenzenes in 54-68% yield. The methodology was later extended by using tetraorganoindates as nucleophilic cross-coupling partners. In addition to aryl and vinyl halides, and aryl triflates, benzyl bromide and benzoyl chloride were successfully reacted with CO and various organoindates.[217] Nowadays, organoindium derivatives have become useful alternatives to other organometallic reagents in organic synthesis due to their advantageous properties such as good availability, ease of preparation and handling, high reactivity and selectivity, operational simplicity and low toxicity. [218]

2.4 References

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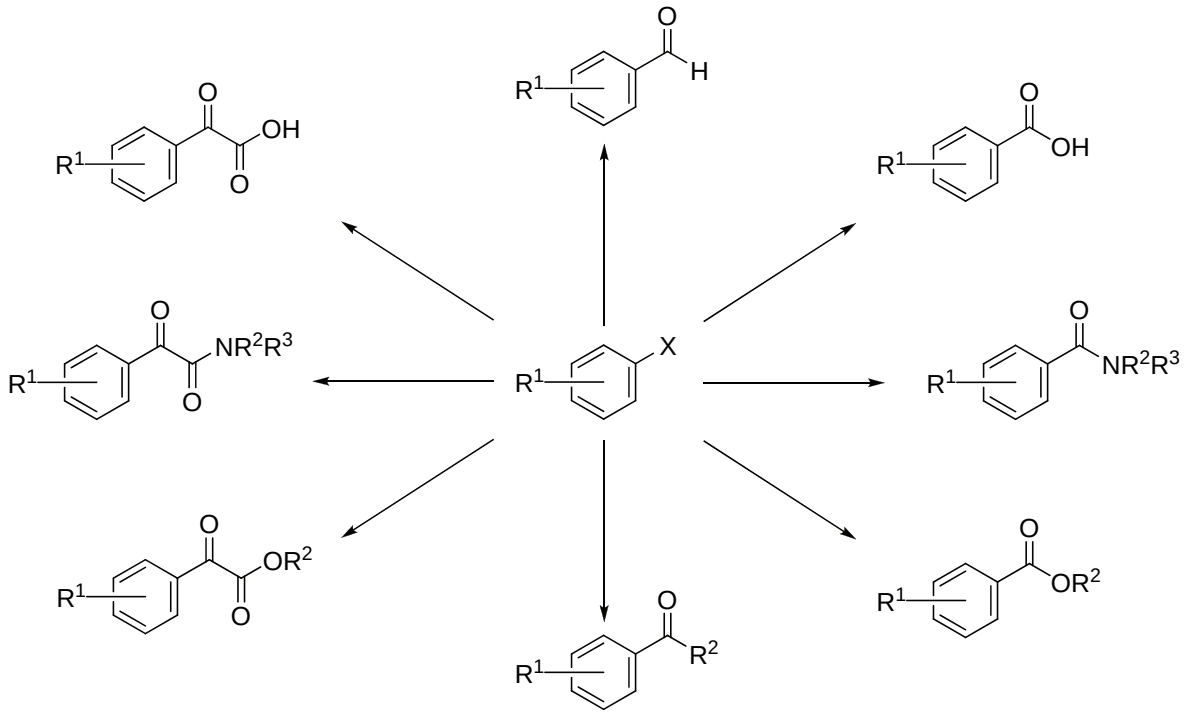
3 Objectives of this work

As pointed out in the previous chapter, the homogeneous palladium-catalyzed functionalization of organic molecules with carbon monoxide as a carbonyl source represents a constantly growing area of investigation. During the last eight years, well-established processes have been improved with respect to scope, mildness of the reaction conditions, functional group tolerance and productivity or stability of the catalyst. In addition, novel and efficient methods for the production of various carbonyl compounds have been discovered. However, further investigations are still necessary to optimize most of these synthetic protocols.



Scheme 44. Palladium-catalyzed carbonylation reactions of aryl halides.

The palladium-catalyzed carbonylation of aryl halides is a versatile reaction easily providing access to aromatic aldehydes, ketones, carboxylic acid derivatives and the corresponding α-oxo-derivatives (Scheme 44). Particularly, there has been a continuous interest in Pd-catalyzed reductive carbonylation reactions leading to benzaldehydes since

these compounds are important substrates for the preparation of numerous biologically active molecules and their intermediates. In the past, Pd-catalyzed formylation procedures often required expensive reduction reagents, high catalyst loadings or harsh reaction conditions.

In order to overcome the limitations of known processes, we started to study the potential of various palladium catalysts and ligands in formylation reactions in the presence of synthesis gas. As a result, we revealed the superior performance of palladium acetate/di-1-adamantyl-*n*-butylphosphine (cata*CX*ium® A).[83] Hence, the primary focus of this dissertation was the exploration of the scope and limitations of the catalyst system for the reductive carbonylation of (hetero)aryl halides. Besides, the approved protocol should be extended to other classes of starting material. In addition, we wanted to investigate the catalytic activity of palladium acetate/cata*CX*ium® A compared to other palladium catalysts in alkoxy-, amino-, and hydroxycarbonylation reactions in order to demonstrate the versatility and efficiency of our catalyst. Finally, a further aim of the present thesis was the development of novel synthetic protocols for the production of important carbonyl compounds.

4 Publications

4.1 Palladium/di-1-adamantyl-*n*-butylphosphine-catalyzed reductive carbonylation of aryl and vinyl halides

Anne Brennführer, Helfried Neumann, Stefan Klaus, Thomas Riermeier, Juan Almena, Matthias Beller*, *Tetrahedron* **2007**, *63*, 6252-6258.

Contributions

In this paper, I performed the experiments on the reductive carbonylation of vinyl halides (Table 3 and 4), the Hammett-Plot (Figure 3) and the extension of the general scope of the catalyst system for the reductive carbonylation of (hetero)aryl halides (Table 2, entries 3-4, 10, 19). I wrote the manuscript, compiled the experimental data and was involved in discussions. My contribution as co-author of this paper is approximately 50%.

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Palladium/di-1-adamantyl-*n*-butylphosphine-catalyzed reductive carbonylation of aryl and vinyl halides

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Abstract A general and efficient palladium catalyzed reductive carbonylation with low catalyst loadings (0.5 mol % Pd or below) has been developed. The formylation of aryl and heteroaryl bromides proceeds smoothly in the presence of palladium/di 1 adamantyl *n* butylphos phine at ambient pressure of synthesis gas to afford the corresponding aromatic aldehydes in good yields and excellent selectivity. In addition, vinyl halides react under similar conditions to form α,β unsaturated aldehydes in good yield.

1. Introduction

The palladium-catalyzed carbonylation of aryl and hetero-aryl halides is a versatile reaction and easily provides access to aromatic ketones,[1] carboxylic acids,[2] esters,[3] amides,[4] and the corresponding α-*oxo*-derivatives.[5] With respect to the different variants of carbonylations aromatic aldehydes are probably the most useful class of products, as the highly reactive aldehyde group can be easily employed in numerous C C- and C N-coupling reactions, reductions as well as other transformations (Scheme 1). Obviously, the resulting substituted benzaldehydes are important substrates for the preparation of numerous biologically active molecules and their intermediates. Although the first palladium-catalyzed formylation was reported by Heck et al. already in 1974,[6] still this method had several limitations until very recently. In the past, often the use of expensive reduction reagents such as silicon[7] and tin[8] hydrides was necessary to achieve the formylation at lower pressures of CO. A more economical method to perform palladium-catalyzed reductive carbonyl-ations is based on the use of readily available formate salts[9] or acetic formic anhydride.[10] However, also these formylation procedures require the use of high catalyst loadings.

In addition, most palladium-catalyzed formylations are ac-companied by side reactions, especially the reductive deha-logenation of the aryl halide. In order to overcome the limitations of known procedures, we started a joint program between industry and academia to explore the potential of various palladium catalysts and ligands. After an initial com-munication,[11] here we describe a full account of our investi-gations, which led to the most general, active, and productive palladium catalyst known to date for reductive carbonyl-ations of aryl and vinyl halides.

2. Results and discussion

Based on our experience in palladium-catalyzed coupling[12] and carbonylation reactions,[13] the formylation of 4-bromo-anisole with synthesis gas to give 4-methoxybenzaldehyde was tested in the presence of 20 different phosphine ligands. Selected results are shown in Table 1. Apart from standard phosphines, ligands developed in our group such as di-1-adamantylalkylphosphines[14] and *N*-arylated heteroaryldial-kylphosphines[15] were compared under identical conditions (100 °C; 5 bar CO/H_2). In order to ensure a more rapid test-ing all experiments were carried out in a modified sixfold parallel autoclave (reaction volume 4 mL). To our surprise under these conditions only one ligand (di-1-adamantyl-*n*-butylphosphine; cata*CX*ium® A) permits efficient formyl-ation of the model substrate (92%, Table 1, entry 10). Typical bidentate ligands such as 1,3-bis(diphenylphosphino)-propane (dppp), 1,4-bis(diphenylphosphino)butane (dppb) or 1,1′-bis(diphenylphosphino)ferrocene (dppf) did not lead to significant conversion and 4-methoxybenzaldehyde formation (Table 1, entries 1 4). Triarylphosphines and dialkylheteroarylphosphines were less active or nearly inactive (Table 1, entries 5 and 6, entries 13 19). The electron rich and sterically bulky ligands such as

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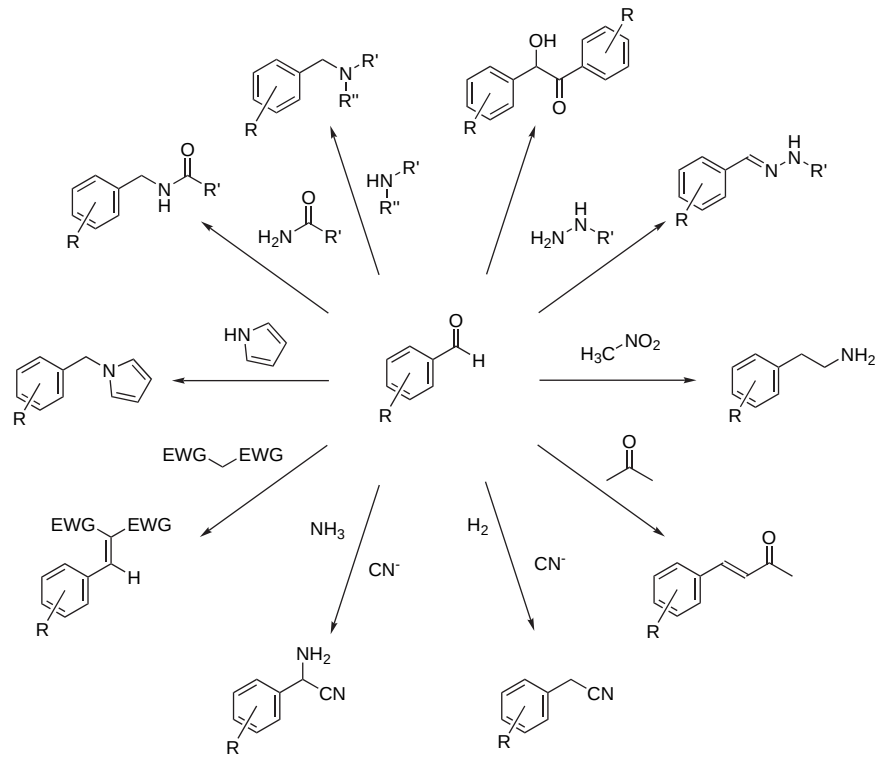
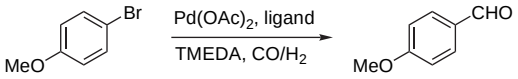
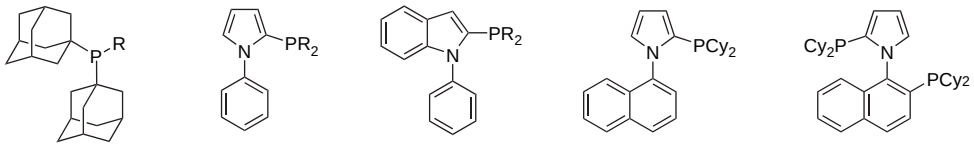


Scheme 1. Synthetic application of aromatic aldehydes.

Table 1. Effect of ligands on the formylation of 4 methoxybromobenzene





1a, R=*n* Bu
1b, R=Bn
1c, R=H

2a, R=Cy
2b, R=*t* Bu
2c, R=Ad

3a, R=Cy
3b, R=*t* Bu

4

5

Entry	Ligand	Ligand [mol %]	Conversion[a] [%]	Yield[a] [%]	Selectivity[a] [%]
1	dppp	0.75	3	0	0
2	dppp	0.375	2	1	50
3	dppb	0.75	9	7	78
4	dppf	0.375	6	3	50
5	PPh_3	0.75	2	0	0
6	P(*o* Tol)$_3$	0.75	1	0	0
7	P(*n* Bu)$_3$	0.75	1	0	0
8	P(*t* Bu)$_3$	0.75	22	18	82
9	PCy_3	0.75	13	11	85
10	**1a**	0.75	97	92	95
11	**1b**	0.75	26	19	73
12	**1c**	0.75	7	4	57
13	**2a**	0.75	9	6	67
14	**2b**	0.75	2	0	0
15	**2c**	0.75	2	1	50
16	**3a**	0.75	4	2	50
17	**3b**	0.75	1	0	0
18	**4**	0.75	13	9	69
19	**5**	0.375	3	0	0

Reaction conditions: 2 mmol 4 bromoanisole, 0.25 mol % $Pd(OAc)_2$, 0.75 equiv TMEDA, 0.2 equiv hexadecane (internal standard), 2 mL toluene, 5 bar CO/H_2 (1:1), 100 °C, 16 h.

[a] Determined by gas chromatography.

di-1-adamantylbenzylphosphane (**1b**) and P(*t*-Bu)$_3$, which can be compared to cata*CX*ium® A, also gave only low yields of the desired product (<20%, Table 1, entries 8 and 11).

Next to the ligand screening, we studied the influence of different solvents, pressure, and bases. In general, *N*-methylpyrrolidinone (NMP), 1,2-dimethoxyethane, and acetonitrile were less suitable compared to toluene. It is important to note that a low synthesis gas pressure (<5 bar) is necessary in order to achieve complete conversion. Obviously, a higher CO concentration leads to deactivation of the catalyst system. In Figure 1, the influence of carbon monoxide pressure on the yield of 4-methoxybenzaldehyde is shown in detail for seven different bases. For all tested bases the maximum yield of 4-methoxybenzaldehyde is achieved at a total pressure of about 5 bar (CO/H_2=1:1). Due to the low solubility and competing formation of 4-methoxybenzoic acid, inorganic bases, for example, K_2HPO_4, were less effective compared to organic nitrogen bases such as DABCO, TMEDA, NEt_3, and N(*n*-Bu)$_3$. Notably, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) has been rarely used as a base for palladium-catalyzed coupling reactions, but is the most active base for our model substrate.

Among the different palladium sources tested, $Pd(OAc)_2$ proved to be the best since it is better soluble in toluene than, for example, $PdBr_2$ or $Pd_2(dba)_3$. With respect to minimization of the catalyst loading, one should note that high conversion and good yield of 4-methoxybenzaldehyde are already obtained at a palladium concentration of 0.25 mol % (Fig. 2).

To prevent the formation of palladium carbonyl clusters and to stabilize the palladium catalyst, a threefold excess of the ligand (P/Pd=3:1) is necessary. The amount of palladium can be reduced at constant ligand concentration by raising the temperature from 100 °C to >120 °C. Typically a higher reaction temperature increased the conversion, but sometimes diminished the chemoselectivity of the reaction, since reductive dehalogenation of the aryl bromide becomes faster. On the other hand, decreasing the temperature retarded the conversion but increased the chemoselectivity.

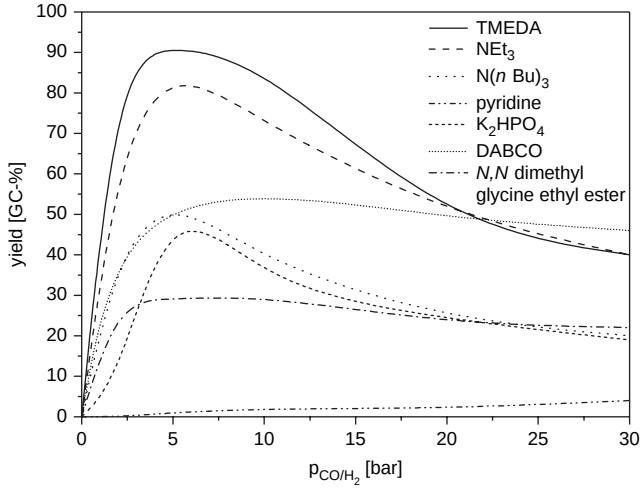


Figure 1. Influence of base and carbon monoxide pressure on the yield of 4 methoxybenzaldehyde. Reaction conditions: 2 mmol 4 bromoanisole, 0.33 mol % $Pd(OAc)_2$, 1 mol % cata*CX*ium® A, 1.5 equiv base, 0.2 equiv hexadecane (internal standard), 2 mL toluene, 100 °C, 16 h.

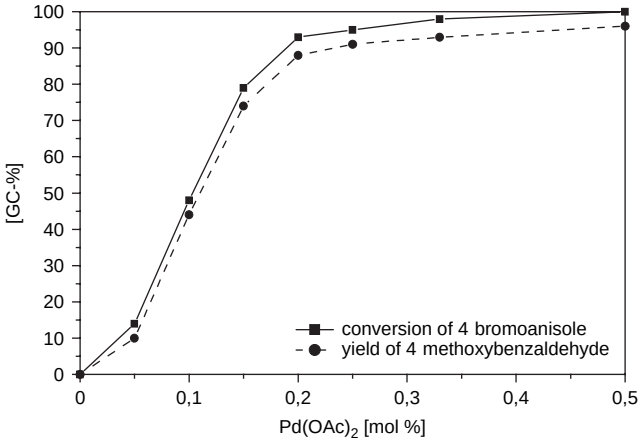


Figure 2. Influence of catalyst concentration on conversion and yield of the model reaction. Reaction conditions: 2 mmol 4 bromoanisole, $Pd(OAc)_2$/cata*CX*ium® A 1:3, 0.75 equiv TMEDA, 0.2 equiv hexadecane (internal standard), 2 mL toluene, 5 bar CO/H_2 (1:1), 100 °C, 16 h.

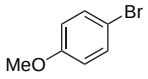
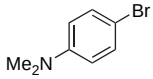
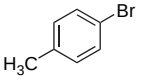
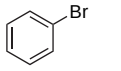
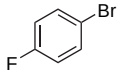
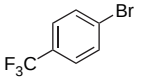
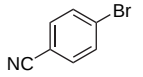
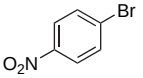
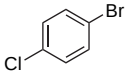
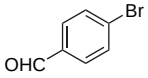
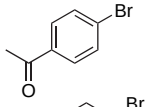
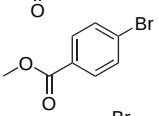
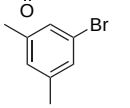
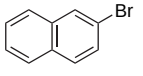
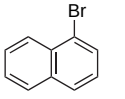
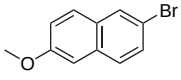
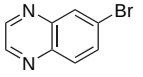
The promising results obtained with di-1-adamantyl-*n*-butylphosphine (cata*CX*ium® A) encouraged us to study the general scope and limitations of this catalyst system for the formylation of different aryl and heteroaryl bromides (Table 2).

High conversion and excellent selectivity (>90%) are observed for the formylation of various monosubstituted aryl bromides such as 4-bromoanisole, 4-bromofluorobenzene, 4-bromobenzonitrile, 4-(dimethylamino)bromobenzene, methyl 4-bromobenzoate, 4-bromoacetophenone, and 4-bromochlorobenzene (Table 2, entries 1, 5, 7, 2, 14, 13, and 9). Problematic is the carbonylation of 4-bromonitrobenzene due to deactivation of the catalyst. The formylation protocol works well also with 1-bromo-3,5-xylene, different bromonaphthalenes (Table 2, entries 15 18), and heteroaryl halides such as 3-bromothiophene and 3-bromopyridine (Table 2, entries 11 and 12). This is of special importance since heteroaromatic aldehydes are particularly useful intermediates for the synthesis of a number of biologically active molecules.[16] In case of 2-bromopyridine the catalyst seems to be deactivated by the formation of inactive dimers after the oxidative addition step.

Since all experiments shown in Table 2 were performed under similar conditions no significant difference in the rate of electron-rich substrates (e.g., 4-bromoanisole, 4-(dimethylamino)bromobenzene) and electron-deficient educts (e.g., 4-bromobenzonitrile, 4-bromoacetophenone) was observed. Thus, we conducted competition experiments in order to investigate the effect of electron-withdrawing and electron-donating substituents. Equimolar amounts of bromobenzene and the corresponding *para*-substituted derivatives were reacted with synthesis gas for 2 h. For data interpretation, we employed the Hammett equation

$$\log\frac{k}{k_0} = \sigma\rho$$

Table 2. Scope and limitations of the $Pd(OAc)_2$/di 1 adamantyl *n* butyl phosphine (cata*CX*ium® A) catalyst system

Entry	(Hetero)aryl bromide	Conversion[a] [%]	Yield[a] [%]	Selectivity[a] [%]
1		98	94	95
2		99	98	99
3		74	71	96
4		95	95	99
5		98	89	91
6		100	84	84
7		99	74	75
8		8	0	0
9		100	89	89
10		100	87	87
11		97	82	85
12		97	77	79
13		100	88	88
14		100	91	91
15		85	85	>99
16		100	92	92
17		100	86	86
18		100	99	99
19		100	85	85

Reaction conditions: 2 mmol (hetero)aryl bromide, 0.25 mol % $Pd(OAc)_2$, 0.75 mol % cata*CX*ium® A, 0.75 equiv TMEDA, 0.2 equiv hexadecane (internal standard), 2 mL toluene, 5 bar CO/H_2 (1:1), 100 °C, 16 h.
[a] Determined by gas chromatography.

where k is the rate constant of the reaction of the substituted compound, k_0 is the value for bromobenzene, σ is a constant characteristic of the substituent, and ρ is the specific reaction constant. For six different substituents the Hammett σ-values were linearly correlated with the change in relative rate constants.[17]

As shown in Figure 3, the reaction mechanism is consistent for the different substituted bromoarenes. The relative rate constant increases with increasing σ, reflecting a reaction rate that is enhanced by a decreased electron density of the aromatic ring. As a result it is likely that the oxidative addition of the active palladium species to the aryl halide constitutes the rate-determining step.

Next, we studied the reductive carbonylation of vinyl halides in the presence of different catalyst systems. Here, the formylation of (*E*)-2-bromo-2-butene was investigated as a model system in the presence of six different phosphines (Table 3, entry 1, entries 7 11).

In agreement with the results obtained for aryl bromides only cata*CX*ium® A permitted an efficient formylation of our model system (yield: 98%; Table 3, entry 1). Triphenylphosphine, the standard bidentate ligand 1,4-bis(diphenylphosphino)butane, and P(*t*-Bu)$_3$ gave only low yields of *trans*-2-methyl-2-butenal (1 12%) (Table 3, entries 7, 8, 11). On the other hand, PCy_3 and 1,1′-bis(diphenylphosphino)ferrocene (dppf) gave slightly higher, but no sufficient yields (22 30%) of the desired product (Table 3, entries 9 10).

After the ligand screening, the influence of different solvents, pressure, and bases (Table 3, entries 1 6) has also been studied. In general, we obtained similar trends as for the formylation of (hetero)aryl bromides. Toluene and THF gave better results than the more polar solvents DMF, *N*,*N*-dimethylacetamide, and NMP. *N*,*N*,*N*′,*N*′-Tetramethylethylenediamine (TMEDA) is again the most active base

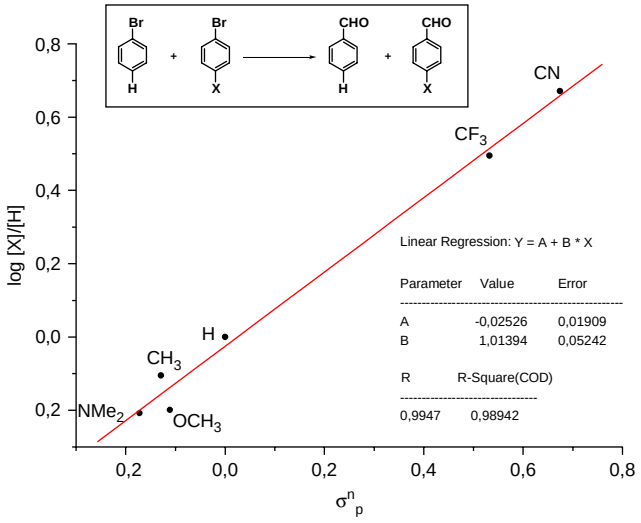
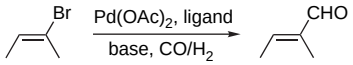


Figure 3. Relationship between rate constant and Hammett σ values for *para* substituents. Reaction conditions: 1 mmol bromobenzene, 1 mmol *para* substituted bromobenzene, 0.25 mol % $Pd(OAc)_2$, 0.75 mol % cata*CX*ium® A, 0.75 equiv TMEDA, 0.2 equiv hexadecane (internal standard), 2 mL toluene, 5 bar CO/H_2 (1:1), 100 °C, 2 h.

Table 3. Palladium catalyzed formylation of (*E*) 2 bromo 2 butene



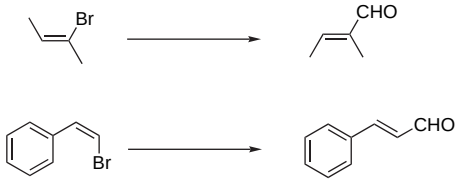
Entry	Ligand	Base	CO/H_2 [bar]	*T* [°C]	Conversion[a] [%]	Yield[a] [%]	Selectivity[a] [%]
1	cata*CX*ium® A	TMEDA	7.5	100	100	98	98
2		NEt_3	7.5	100	88	48	54
3		DABCO	7.5	100	88	50	56
4		$(CH_3)_2NCH_2COOC_2H_5$	7.5	100	89	19	22
5		K_2CO_3	7.5	100	99	46	46
6		K_2HPO_4	7.5	100	52	1	1
7	PPh_3	TMEDA	7.5	100	86	1	1
8	P(*t* Bu)$_3$	TMEDA	7.5	100	40	12	30
9	PCy_3	TMEDA	7.5	100	51	22	44
10	dppf	TMEDA	7.5	100	98	30	31
11	dppb	TMEDA	7.5	100	46	9	19

Reaction conditions: 2 mmol (*E*) 2 bromo 2 butene, 0.5 mol % $Pd(OAc)_2$, 1.5 mol % cata*CX*ium®A, 0.75 equiv TMEDA, 0.2 equiv dodecane (internal stan dard), 2 mL toluene, 16 h.
[a] Determined by gas chromatography.

for the model substrate. Complete conversion and excellent yield (>98%) are obtained at a synthesis gas pressure of 7.5 bar.

Finally, the scope of the optimized catalyst system for the reductive carbonylation of vinyl halides was tested with eight different substrates (Table 4). In addition to 2-bromo-2-butene, 1-chloro-1-cyclopentene, 1-bromostyrene, and 2-bromo-3-methyl-2-butene yielded the corresponding α,β-unsaturated aldehydes in mediocre to very good yield (41 98%). Unfortunately, no desired reaction is observed applying 1-bromo-1-propene and methyl 2-bromoacrylate as substrates. Noteworthy, the formylation of (*Z*)-2-bromo-2-butene and *cis*-β-bromo-styrene[18] gave selectively the corresponding *trans*-aldehydes (Scheme 2).

Apparently, the initially generated oxidative addition product is not stable under these conditions and rearranges to the thermodynamically more stable *trans*-product. This is in contrast with other palladium-catalyzed coupling reactions of vinyl halides.[19]

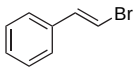
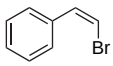


Scheme 2. Reductive carbonylation leading to α,β unsaturated *trans* aldehydes.

3. Conclusion

In conclusion, we presented a general reductive carbonylation procedure for the synthesis of aromatic and heteroaromatic aldehydes, as well as α,β-unsaturated aldehydes.

Table 4. Reductive carbonylation of different vinyl halides

Entry	Vinyl halide	$Pd(OAc)_2$ [mol %]	cata*CX*ium® A [mol %]	Conversion[a] [%]	Yield[a] [%]	Selectivity[a] [%]
1		0.5	1.5	100	98	98
2[b]		0.5	1.5	92	76	82
3		0.5	1.5	96	87	91
4		0.5	1.5	100	59	59
5[c]		0.5	1.5	100	51	51
6		0.5	1.5	64	41	59

Reaction conditions: 2 mmol vinyl halide, 0.75 equiv TMEDA, 0.2 equiv dodecane (internal standard), 2 mL toluene, 7.5 bar CO/H_2 (1:1), 100 °C, 16 h.
[a] Determined by gas chromatography.
[b] As product only *trans* 2 methyl 2 butenal is formed.
[c] Only *trans* cinnamaldehyde is observed.

Advantageously, the most simple and environmentally benign formylation source synthesis gas can be used at ambient pressure and low catalyst concentration. The ligand di-1-adamantyl-*n*-butylphosphine (cata*CX*ium® A) leads to a highly active catalyst species, but is comparably stable to air and moisture, and thus easy to handle. Due to its superior performance compared with other palladium catalysts, this system is employed for the industrial production of a drug intermediate on multi-1000 kg scale.

4. Experimental section

4.1. General remarks

All reactions were performed using standard Schlenk techniques (argon). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker ARX 300 spectrometer. Chemical shifts (δ) are given in ppm and refer to the residual solvent as the internal standard ($CDCl_3$: 7.26/77.0). Gas chromatography was performed on a Hewlett Packard HP 6890 chromatograph with a HP1 column. Chemicals were purchased from Fluka, Aldrich, and Strem, and used as received. The cata*CX*ium® A ligand is available from Strem or directly from Degussa. Solvents were distilled from sodium and benzophenone.

4.2. General procedure for the formylation of (hetero)-aryl bromides and vinyl halides

A 50 mL Schlenk flask was charged with $Pd(OAc)_2$ (11.2 mg, 0.25 mol %), cata*CX*ium® A (53.8 mg, 0.75 mol %), and toluene (20 mL). Subsequently, hexadecane (1.17 mL, internal GC standard) and TMEDA (*N*,*N*,*N*′,*N*′-tetramethylethylenediamine) (2.25 mL, 15 mmol) were added. About 2.34 mL of this clear yellow stock solution was transferred to six vials (4 mL reaction volume) equipped with a septum, a small cannula, a stirring bar, and 2 mmol of the corresponding (hetero)aryl bromide. The vials were placed in an alloy plate, which was transferred to a 300 mL autoclave of the 4560 series from Parr Instruments® under argon atmosphere. After flushing the autoclave three times with CO/H_2 (1:1), the appropriate synthesis gas pressure was adjusted to ambient temperature and the reaction was performed for 16 h at 100 °C. Before and after the reaction an aliquot of the reaction mixture was subjected to GC analysis for determination of yield and conversion.

4.2.1. Quinoxaline-6-carbaldehyde. R_f (SiO_2, *n*-heptane/EtOAc=3:1): 0.1. Yield: 85%. Yellow solid, mp 130 131 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ=10.28 (s, 1H, CHO), 9.09 (m, 2H, NCH CHN), 8.71 (s, 1H, OHCCC*H*CN), 8.22 (m, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ=192.8 (C O), 148.0 (CH), 147.1 (CH), 145.0, 141.9, 136.8, 134.5 (CH), 130.4 (CH), 126.6 (CH). MS (EI, 70 eV): *m*/*z* (%)=158 (100) M^+, 129 (49) $[M-CHO]^+$, 103 (32), 75 (23), 50 (13). IR (KBr): 1697 (vs) [C O], 1353 (s), 1226 (m), 1142 (m), 1118 (s), 1024 (s), 960 (s), 914 (s), 880 (m), 832 (m), 774 (s), 760 (m) cm ^{1}. HR-MS (EI): calcd for $C_9H_6N_2O$: 158.0475; found: 158.04706 $[M]^+$.

4.2.2. 1-Cyclopentene-1-carbaldehyde. Yield: 87%. Colorless liquid, bp 47 48 °C (14 Torr).[20] ^{1}H NMR (300 MHz, $CDCl_3$): δ=9.78 (s, 1H, CHO), 6.87 (m, 1H, C*H* CCHO), 2.60 (m, 2H, CH_2), 2.51 (m, 2H, CH_2), 1.99 (m, 2H, $CH_2CH_2CH_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ=189.9 (C O), 153.2 (CH), 147.9, 33.7 (CH_2), 28.3 (CH_2), 22.9 (CH_2). MS (EI, 70 eV): *m*/*z* (%)=96 (62) M^+, 67 (100) $[M-CHO]^+$, 41 (29), 39 (30). IR (capillary): 2957 (m), 2714 (w), 1679 (vs) [C O], 1615 (m) cm ^{1}. HR-MS (EI): calcd for C_6H_8O: 96.0570; found: 96.0571 $[M]^+$.

4.2.3. 2,3-Dimethyl-2-butenal. Yield: 41%. Colorless liquid, bp 57 °C (20 Torr).[21] ^{1}H NMR (300 MHz, $CDCl_3$): δ=10.12 (s, 1H, CHO), 2.19 (m, 3H, CH_3), 1.96 (m, 3H, CH_3), 1.74 (m, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=191.2 (C O), 155.0, 132.6, 23.8 (CH_3), 19.4 (CH_3), 11.0 (CH_3). MS (EI, 70 eV): *m*/*z* (%)=98 (100) M^+, 69 (45) $[M-CHO]^+$, 55 (45), 41 (79), 39 (30). IR (capillary): 1671 (vs) [C O], 1635 (s) [C C] cm ^{1}. HR-MS (EI): calcd for $C_6H_{10}O$: 98.0726; found: 98.0720 $[M]^+$.

Acknowledgements

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4.2 Efficient carbonylation of aryl and heteroaryl bromides using a palladium/diadamantylbutylphosphine catalyst

Helfried Neumann, Anne Brennführer, Peter Groß, Thomas Riermeier, Juan Almena, Matthias Beller*, *Adv. Synth. Catal.* **2006**, *348*, 1255-1261.

Contributions

In this paper, I performed experiments on the minimization of catalyst loading (Table 2, entries 1-3) and on the investigation of the general scope of the catalyst system (Table 2, entries 5, 8, 17). I was involved in the preparation of the manuscript, the compilation of experimental data, and I contributed to discussions. My contribution as co-author of this paper is approximately 20%.

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Efficient Carbonylation of Aryl and Heteroaryl Bromides using a Palladium/Diadamantylbutylphosphine Catalyst

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Abstract: A general palladium-catalyzed alkoxycarbonylation of aryl and heteroaryl bromides has been developed in the presence of bulky monodentate phosphines. Studies of the butoxycarbonylation of three model substrates revealed the advantages of di-1-adamantyl-*n*-butylphosphine compared to other ligands. In the presence of this catalyst system various bromoarenes provided the corresponding benzoic acid derivatives (ester, amides, acids) in excellent yield at low catalyst loadings (0.5 mol% Pd or below).

Keywords: alkoxycarbonylation; aryl halides; benzoic acid esters; carbonylation; monodentate ligands

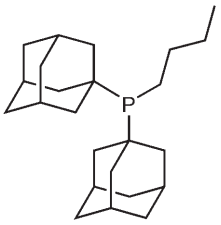
Introduction

Palladium-catalyzed carbonylations of aryl halides (or halide equivalents) represent a valuable tool for the selective introduction of carboxylic acid derivatives onto aromatic frameworks.[1] Originally, these reactions were established in the mid-1970s by the pioneering work of R. F. Heck and co-workers.[2] Since that time, carbonylations of haloarenes have found a number of applications in organic synthesis,[3] and even related industrial processes, such as the alkoxycarbonylation of a benzylic alcohol toward ibuprofen, have been realized on a multi-1000 ton scale.[4]

In the last decade, significant progress with respect to the development of more general and productive palladium catalysts for various coupling reactions has been reported. On the other hand, fewer improvements are known regarding the carbonylation of aryl halides. This is demonstrated by comparing known catalyst productivity (turnover number, TON), e.g., for a simple Suzuki reaction (in general TON = 100,000 to 1,000,000) and the carbonylation of bromoanisole (typically TON = 100).

The difficulty of more efficient palladium catalysis in the presence of a large excess of carbon monoxide is a result of the π-acceptor character of CO. Here, the activity of the catalyst towards oxidative addition is reduced, due to the binding of carbon monoxide to the metal centre. Moreover, clustering and agglomeration of Pd atoms is facile in the presence of CO, leading to non-active palladium species.[5] A solution to these problems can be the use of palladium catalysts containing the highly basic bidentate[6] or monodentate phosphines.[7] The drawbacks of these catalyst systems for larger scale applications are, however, the difficult synthesis and the highly sensitive nature of the often pyrophoric ligands.

For some time we have been involved in the development of novel palladium catalysts for various coupling reactions of aryl halides, which should be also applicable on an industrial scale.[8,9] Recently developed ligands from our side which fulfill this requirement include di-1-adamantylalkylphosphines,[10] and *N*-arylated 2-heteroaryldialkylphosphines.[11] The corresponding phosphines lead to highly active catalysts, but are comparably stable to air and moisture, and thus easy to handle. Based on our experience in carbonylation chemistry,[12] we started a program to explore the potential of these ligands in different carbonylation reactions of aryl halides. Initial results demonstrated the superiority of di-1-adamantylbutylphosphine (cata*CX*ium® A; Scheme 1) in formylation reactions with synthesis gas.[13] Here, we describe for the first time the use of these ligands in carbonylations, which led to a general and efficient palladium



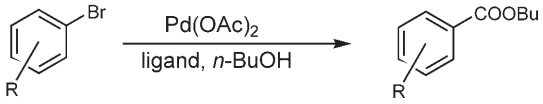
Scheme 1. Structure of di 1 adamantylbutylphosphine (cata*CX*ium® A).

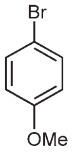
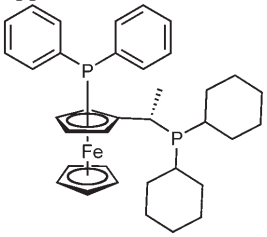
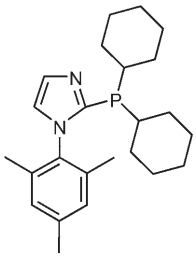
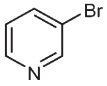
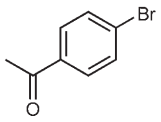
catalyst for alkoxy-, amino-, and hydroxycarbonylations of aryl and heteroaryl bromides.

Results and Discussion

Initially, the alkoxycarbonylation of 4-bromoanisole (deactivated aryl bromide) with *n*-butanol was investigated in the presence of nine different phosphines (Table 1, entries 1–9). Typically all experiments were carried out in a 6-fold parallel autoclave (reaction volume 4 mL), which allows fast testing of catalysts and variation of reaction conditions. In order to ensure reproducibility some experiments have been repeated on a 300 mL scale. For practical relevance the carboxylation experiments were carried out with 0.5 mol% catalyst loading at 115 °C and 20 bar of carbon monoxide. For the stabilization of the palladium catalyst and to prevent the formation of palladium

Table 1. Butoxycarbonylation in the presence of different ligands.[a]



Entry	(Hetero)aryl bromide	Ligand	TMEDA [equivs.]	Time [h]	Conversion by GC [%]	Yield by GC [%]
1		cata*CX*ium® A	0.6	18	96	94
2		PPh_3	0.6	18	18	18
3		P(*t* Bu)$_3$	0.6	18	100	93
4		PCy_3	0.6	18	2	2
5		dppf	0.6	18	97	84
6		dppp	0.6	18	32	29
7		dppb	0.6	18	34	30
8			0.6	18	46	40
9			0.6	18	79	70
10		cata*CX*ium® A	0.75	12	86	69
11		P(*t* Bu)$_3$	0.75	12	74	56
12		cata*CX*ium® A	0.75	12	88	79
13		P(*t* Bu)$_3$	0.75	12	80	65

[a] *Reaction conditions:* 2 mmol bromo(hetero)arene, 0.5 mol% $Pd(OAc)_2$, 1.5 mol% ligand, 2 equivs. hexadecane (internal standard), 2 mL *n* butanol, 20 bar CO, 115 °C.

carbonyl clusters a three-fold excess of the ligand (P/Pd = 3:1) was used.

As shown in Table 1 di-1-adamantyl-*n*-butylphosphine (cata*CX*ium® A) and P(*t*-Bu)$_3$ permit efficient butoxycarbonylation of 4-bromoanisole (93–94%; Table 1, entries 1, 3). 1,1′-Bis(diphenylphosphino)ferrocene (dppf) and the dicyclohexyl-2-(*N*-mesityl)imidazolylphosphine gave slightly lower yields (70–84%) of the desired product (Table 1, entries 5, 9). On the other hand PPh_3, PCy_3 and standard bidentate ligands such as 1,3-bis(diphenylphosphino)propane (dppp) or 1,4-bis(diphenylphosphino)butane did not lead to high conversion (<50%) and ester formation (2–30%) (Table 1, entries 2, 4, 6, 7). Comparing entries 4 and 9 demonstrates the importance of sterically hindered substituents on the phosphorus atom. Due to the similar performance of di-1-adamantylbutylphosphine and P(*t*-Bu)$_3$ both ligands were tested further with 3-bromopyridine and 4-bromoacetophenone. Here a higher yield of the corresponding ester was obtained with di-1-adamantylbutylphosphine as ligand. Interestingly aryl keto esters resulting from double carbonylations were observed as side products (5–10%) in these reactions. Therefore, we studied the influence of the carbon monoxide pressure more closely (Figure 1).

Excellent conversion (97%) and selectivity (>99%) is obtained already at 5 bar.[14] High conversion is seen up to 50 bar, however the selectivity is continuously decreased due to the formation of the double carbonylated product. At higher CO pressure also deactivation of the catalyst becomes more pronounced.

Next, we investigated the general scope of our catalyst system for the alkoxycarbonylation of different aryl and heteroaryl bromides (Table 2). High conversion (>95%) and excellent selectivity (>98%) were observed for the alkoxycarbonylation of various mono-

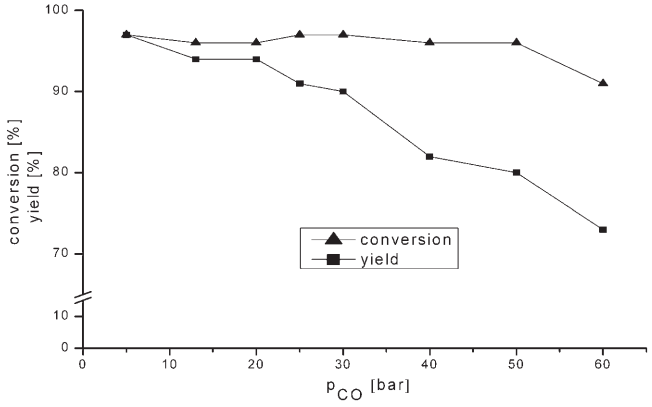


Figure 1. Influence of the carbon monoxide pressure on conversion and yield. *Reaction conditions:* 2 mmol 4 bromoanisole, 0.5 mol% $Pd(OAc)_2$, 1.5 mol% cata*CX*ium® A, 0.6 equivs. TMEDA, 0.2 equivs. hexadecane (internal standard), 0.3 mL *n* BuOH, 115 °C, 16 h.

substituted aryl bromides such as 3-[12c] and 4-bromoanisoles, 4-bromobenzonitrile, 4-(dimethylamino)-bromobenzene, 4-bromo-chlorobenzene, and 3,4,5-trifluorobenzene (Table 2, entries 3, 4, 6, 9, 15, 16). In general, there is no difference between electron-rich substrates (bromoanisoles, bromoaniline) and electron-deficient ones (bromobenzonitrile). 2-Bromobenzonitrile (86%), 1-bromo-3,4-methylendioxobenzene (83%), and 2,5-bis(trifluoromethyl)benzene (71%) also reacted well. The method works also with different heteroaryl halides (3-bromothiophene, 3-bromobenzothiophene, 2-[15] and 3-bromopyridine[12c], 6-bromoquinoxaline). At this point it is important to note that heteroaromatic carboxylic acid derivatives are particularly useful intermediates for the synthesis of a number of agrochemicals.[16] With respect to minimization of the catalyst loading one should note that the model reaction of 4-bromoanisole works well at a 0.05 mol% Pd loading, however, a further decrease of palladium resulted in a significant decrease of conversion.

Finally, we also studied the reaction of 4-bromoanisole with different nucleophiles (Table 3). In addition to methanol, ethanol, primary and secondary amines, as well as pyrrole and water led to good yield (64–89%) and good to excellent selectivity (73–>99%).

Conclusions

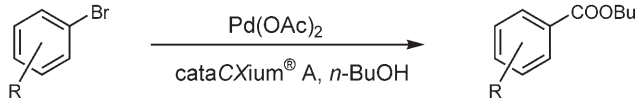
In conclusion, we have presented a general carbonylation procedure for the synthesis of aromatic and heteroaromatic esters, amides, and acids from the corresponding bromides. Best results are obtained at comparatively low pressure (5 bar) using cata*CX*ium® A as ligand. Due to the efficiency and easy handling of the catalyst we believe that this novel carbonylation protocol will allow one to perform such reactions on an industrial scale.[17]

Experimental Section

General Remarks

Butanol and toluene were purified by distillation from CaH_2 and from Na. Unless otherwise noted, all reagents were used as received from commercial suppliers. Silica gel column chromatography was performed with 230 400 mesh ASTM silica gel from Merck. Melting points were recorded on a Galen III (Cambridge Instruments) and are uncorrected. IR spectra of solids were recorded using KBr plates or KBr pellets on a Nicolet Magna 550. Mass spectra were obtained on an AMD 402/3 of AMD Intectra (EI, 70 eV). NMR data were recorded on a Bruker ARX 400 with a QNP probe head (^{1}H, 400.13 MHz; ^{13}C, 100.61 MHz) at 25 °C. GC analyses were performed on an HP 6890 equipped with a HP 5 capillary column (5% diphenylsiloxane,

Table 2. Butoxycarbonylation of various aryl and heteroaryl bromides.[a]



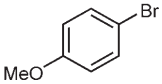
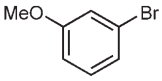
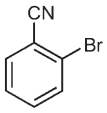
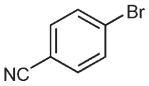
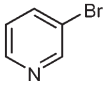
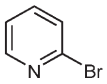
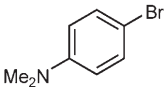
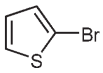
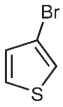
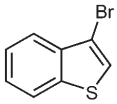
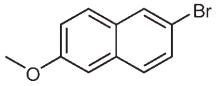
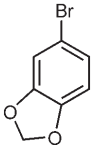
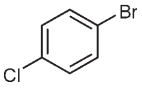
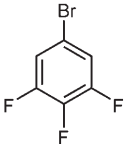
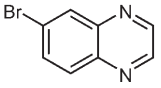
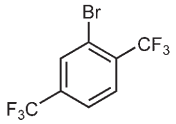
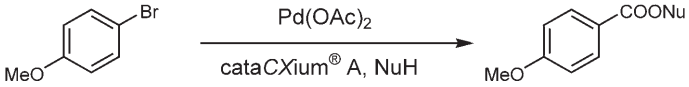
Entry	Bromo(hetero)arene	$Pd(OAc)_2$ [mol%]	cata*CX*ium® A [mol%]	Temperature [°C]	Conversion[b] [%]	Ester[b] [%]	Selectivity[b] [%]
1		0.01	1	125	39	34	87
2		0.05	1	125	85	82	96
3		0.5	1.5	115	97	97	100
4		0.5	1.5	115	100	99	99
5		0.5	1.5	115	100	86	86
6		0.5	1.5	115	100	98	98
7		0.5	1.5	115	100	91	91
8		0.5	1.5	115	100	99	99
9		0.5	1.5	125	100	99	99
10		0.5	1.5	115	69	52	75
11		0.5	1.5	115	100	84	84
12		0.5	1.5	115	100	99	99
13		0.5	1.5	115	100	99	99
14		0.5	1.5	115	86	83	96
15		0.5	1.5	115	100	99	99
16		0.5	1.5	115	96	94	98
17		0.5	1.5	115	100	98	98

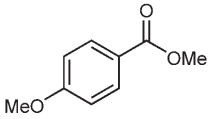
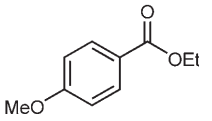
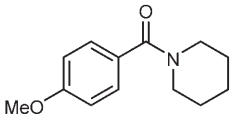
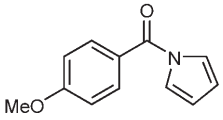
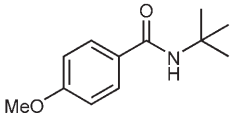
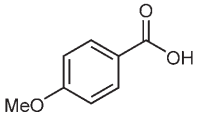
Table 2. (Continued)

Entry	Bromo(hetero)arene	$Pd(OAc)_2$ [mol%]	cata*CX*ium® A [mol%]	Temperature [°C]	Conversion[b] [%]	Ester[b] [%]	Selectivity[b] [%]
18		0.5	1.5	115	82	71	87

[a] *Reaction conditions:* 2 mmol bromo(hetero)arene, 0.75 equivs. TMEDA, 0.2 equivs. hexadecane (internal standard), 2 mL *n* butanol, 5 bar CO, 16 h.
[b] Determined by GC.

Table 3. Carbonylation of 4 bromoanisole with different nucleophiles.[a]



Entry	Nucleophile	Temperature [°C]	Product	Yield by GC [%]	Selectivity by GC [%]
1	MeOH	115		78	99
2	EtOH	115		86	99
3	piperidine	115		63	85
4	pyrrole	125		64	80
5	*t* butylamine	115		73	73
6	H_2O[b]	115		89	98

[a] *Reaction conditions:* 2 mmol 4 bromoanisole, 0.5 mol% $Pd(OAc)_2$, 1.5 mol% cata*CX*ium® A, 0.75 equivs. TMEDA, 0.2 equivs. hexadecane (internal standard), 0.2 mL toluene, 1.8 mL nucleophile, 5 bar CO, 30 bar N_2, 16 h.
[b] 0.4 mL H_2O in 1.6 mL 1,4 dioxane.

95% dimethylsiloxane, L = 30 m, d = 250 μm, d_{film} = 0.25 μm) and an FID detector. Quantitative GC analyses were referenced to internal hexadecane. All new compounds were characterized by ^1H and ^{13}C NMR spectroscopy, IR, and high resolution MS (see Supporting Information). The following compounds have already been reported in the literature: butyl esters (Table 2, entries 4,[12c] 7,[12c] 8[15]), methyl and ethyl esters (Table 3, entries 1,[18] 2[18]) and amides (Table 3, entries 4,[19] 5[20]).

General Procedure for the 6-fold Parallel Autoclave

A 50 mL Schlenk flask was charged with $Pd(OAc)_2$ (22.5 mg, 0.5 mol%), cata*CX*ium® A (108 mg, 1.5 mol%) and *n* butanol (20 mL). Subsequently, hexadecane (1.17 mL, internal GC standard) and TMEDA (*N,N,N′,N′* tetramethyl ethylenediamine) (2.25 mL, 15 mmol) were added. 2.34 mL of this clear yellow stock solution were transferred to the 6

vials (4 mL reaction volume) equipped with a septum, a small cannula, a stirring bar and 2 mmol of the correspond ing aryl bromide. The vials were placed in an alloy plate, which was transferred to 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 and the reaction was performed for 16 h at 115 °C. Before and after the reaction an aliquot of the reaction mixture was subject ed to GC analysis for determination of yield and conver sion.

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4.3 Catalytic and stoichiometric synthesis of novel 3-amino-carbonyl-, 3-alkoxycarbonyl-, and 3-amino-4-indolylmaleimides

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Contributions

In this paper, I planned, performed and analyzed all experiments. I wrote the manuscript, compiled the supporting information and was involved in discussions. My contribution as co-author of this paper is approximately 85%.

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Catalytic and Stoichiometric Synthesis of Novel 3-Aminocarbonyl-, 3-Alkoxycarbonyl-, and 3-Amino-4-indolylmaleimides

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Keywords: Carbonylation / Palladium / Amination / Homogeneous catalysis / Protein kinase C inhibitors / Nitrogen heterocycles

Novel nonsymmetrically substituted 4-indolylmaleimides have been synthesized via palladium-catalyzed alkoxy- and aminocarbonylation of 3-bromo-1-methyl-4-(2-methyl-3-indolyl)maleimide (**1**) with alcohols and amines in the presence of carbon monoxide. The resulting carboxamide derivatives represent a new class of potentially bioactive compounds. In addition, the direct amination reaction of **1** proceeded smoothly in the absence of catalyst and gave the desired 3-amino-4-indolylmaleimides in good yields.

Introduction

Protein kinase C (PKC) represents an important family of serine/threonine kinases, which have been associated with numerous diseases such as cardiovascular illnesses, cancer, central nervous system disorders, Alzheimer, inflammation and autoimmune diseases, e.g. diabetes. Since PKCs are involved in signal transduction, gene expression, cell growth and cell differentiation,[1] they have been important targets for the development of new therapeutic agents. Hence, over the past few years there have been significant research activities towards selective inhibitors for PKC.[2]

In this respect, maleimides, especially symmetrical and nonsymmetrical (macrocyclic) 3,4-bis-indolylmaleimides have been found to be potent inhibitors of different protein kinases, especially PKC.[3] Among these products, naturally occurring arcyriarubins[4] and analogues thereof are useful intermediates in the synthesis of bioactive indolocarbazole alkaloids (Figure 1).[4,5]

Structurally related derivatives, in which one indole substituent is replaced by other (hetero)arenes, have been identified as strong kinase inhibitors as well.[3g,6] Notably, such 3-indolyl-4-(heteroaryl)maleimides show a wide spectra of further biological activities.[7]

Herein, we describe the synthesis of novel 3-alkoxycarbonyl- and 3-aminocarbonyl-4-indolylmaleimides through palladium-catalyzed alkoxy- and aminocarbonylation reactions of 3-bromo-1-methyl-4-(2-methyl-3-indolyl)maleimide. To the best of our knowledge, such carbonylation reactions have not been studied, and the corresponding carboxamide derivatives are only mentioned in the patent literature.[8] Without the palladium catalyst, the corresponding 3-amino-4-indolylmaleimides are formed in good yield.

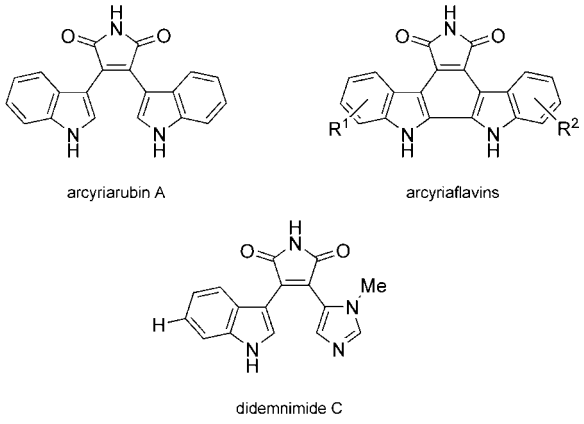

Figure 1. Biologically active compounds with an indolylmaleimide subunit.

Results and Discussion

For some time, we have been engaged in transition-metal-catalyzed syntheses of indoles.[9] In addition, we are interested in the development of practical palladium catalysts and their application in different cross-coupling reactions of heteroaryl halides.[10,11] Recently, by combining these two areas, we presented an improved Pd-catalyzed synthesis of 3-aryl-4-indolylmaleimides[12] through the Suzuki coupling of 3-bromo-1-methyl-4-(2-methyl-3-indolyl)maleimide.[13] The coupling of both aryl- and heteroaryl boronic acids proceeded smoothly with good to excellent yields by employing simple $Pd(OAc)_2/PPh_3$ or $Pd(OAc)_2$/di-1-ada-

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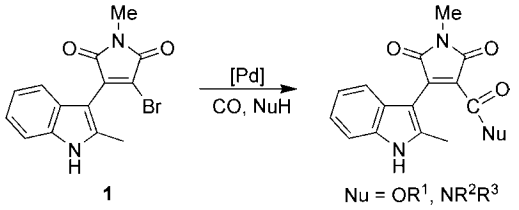
mantyl-*n*-butylphosphane (cata*CX*ium® A) as catalyst systems. Encouraged by these results and on the basis of our experiences in carbonylation chemistry,[14] we decided to investigate the carbonylation reactions of 3-bromo-4-indolylmaleimides.

Initially, we prepared 3-bromo-1-methyl-4-(2-methyl-3-indolyl)maleimide (**1**) from commercially available 3,4-dibromomaleimide and 2-methylindole by applying lithium hexamethyldisilazane as base.[12] The desired compound **1** was obtained in excellent selectivity and yield (95%). Typically, all carbonylation experiments of **1** with different nucleophiles (Scheme 1) were carried out in a modified sixfold parallel autoclave with a reaction volume of 4 mL.

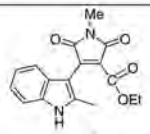
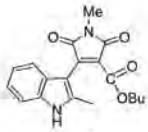
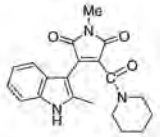
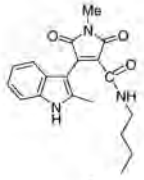
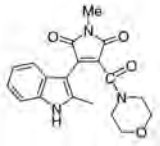
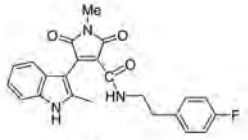
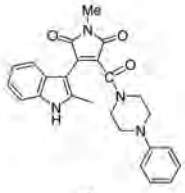


Scheme 1. Palladium-catalyzed carbonylation of **1** with alcohols or amines.

First, the alkoxycarbonylation of **1** in the presence of ethanol and *n*-butanol was investigated. More specifically, **1** reacted at 5 bar of carbon monoxide in the corresponding alcohol as solvent. By employing 0.5 mol-% $Pd(OAc)_2$ and a threefold excess of di-1-adamantyl-*n*-butylphosphane, the desired ethyl ester[15] **2** and butyl ester **3** were obtained in 25–29% isolated yields (Table 1, Entries 1 and 2).[16] Although the reaction proceeded with 100% conversion, 3-dimethylamino-1-methyl-4-(2-methyl-3-indolyl)maleimide and 1-methyl-3-(2-methyl-3-indolyl)maleimide were identified as main side products. Apparently, the primary side product was formed by nucleophilic exchange of the bromine atom as a result of the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) during the reaction. The latter by-product simply resulted from a reductive dehalogenation reaction of compound **1**, which also took place under these conditions. We then focused on the aminocarbonylation of **1**. This type of carbonylation reaction should be of wider interest because the resulting carboxamides offer an additional hydrogen-bonding motif.

All aminocarbonylation reactions were performed at two different carbon monoxide pressures (5 and 15 bar CO) and with different amine concentrations. The results for the optimized reaction conditions are shown in Table 1. Reaction of 3-bromo-1-methyl-4-(2-methyl-3-indolyl)-maleimide with 1 equiv. piperidine gave the best result at 15 bar of carbon monoxide [48% isolated yield of 1-methyl-4-(2-methyl-3-indolyl)maleimide-3-(piperidine)carboxamide **4**; Table 1, Entry 3]. NMR spectroscopy revealed a dynamic behaviour of the amide bond and the piperidine chair conformation. Again, we observed 100% conversion; however, the main side product was 1-methyl-4-(2-methyl-3-indolyl)-3-(1-piperidinyl)maleimide. Notably, this by-product was detected by gas chromatography even before carbonylation pro-

Table 1. Pd-catalyzed alkoxycarbonylation/aminocarbonylation of 3-bromo-1-methyl-4-(2-methyl-3-indolyl)maleimide.[a]

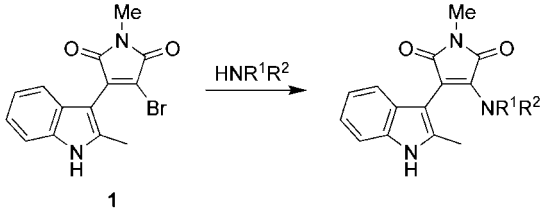
Entry	Product	p_{CO} [bar]	T [°C]	Isolated yield [%]
1[b]	 **2**	5	90	25
2[b]	 **3**	5	115	29
3[c,d]	 **4**	15	115	48
4[e,g]	 **5**	5	115	32
5[c]	 **6**	15	100	32
6[c]	 **7**	15	100	60
7[c]	 **8**	15	100	70

[a] Reaction conditions: 3-Bromo-1-methyl-4-(2-methyl-3-indolyl)-maleimide (0.25 mmol), $Pd(OAc)_2$ (0.5 mol-%), di-1-adamantyl-*n*-butylphosphane (1.5 mol-%), solvent (2 mL), base, 16 h. [b] Reaction performed in the corresponding alcohol, TMEDA (0.75 equiv.) as base. [c] Toluene as solvent, TMEDA (0.75 equiv.) as base. [d] Addition of piperidine (1 equiv.). [e] Addition of *n*-butylamine (4 equiv.). [f] *N*,1-Dibutyl-4-(2-methyl-3-indolyl)maleimide-3-carboxamide was obtained as a side product (10% yield). [g] Addition of the corresponding amine (2 equiv.), dioxane as solvent, NEt_3 (0.75 equiv.) as base.

ceeded. Clearly, catalytic aminocarbonylation competed with nucleophilic substitution by the corresponding amine under these reaction conditions.

By applying *n*-butylamine, the catalytic carbonylation proceeded best at lower CO pressures (5 bar). After column chromatography, *N*-butyl-1-methyl-4-(2-methyl-3-indolyl)-maleimide-3-carboxamide (**5**) was obtained in 32% yield (Table 1, Entry 4). Surprisingly, we also isolated the corresponding *N*,1-dibutyl-4-(2-methyl-3-indolyl)maleimide-3-carboxamide in 10% yield. In addition, a significant amount of 3-butylamino-1-methyl-4-(2-methyl-3-indolyl)-maleimide was formed, which resulted from the noncatalytic amination reaction. Carbonylation of **1** at 15 bar CO in the presence of morpholine, 4-fluorophenylethylamine and *N*-phenylpiperazine occurred with high conversion (>95%) and gave the respective amides **6**–**8** in 32%, 60% and 70% yield, respectively (Table 1, Entries 5–7). In each case, minor amounts (<10%) of the corresponding amination products were formed as well.

Because of the competing amination, we decided to investigate this reaction for the selective synthesis of 3-amino-4-indolylmaleimides in more detail (Scheme 2). Sergheraert et al. reported that PKC selectivity is promoted by the addition of amine substituents on the maleimide ring.[17] Thus, various polyamine–linked-,[17,18] alkylamino-,[19] arylalkylamino-,[20] anilinoindolylmaleimides,[21] indolylimidazolylmaleimides[6a,22] (e.g. didemnimides) and indolopyrrolemaleimides[7a,7d,7f,23] have been synthesized. Moreover, transformation of 3-bromo-4-indolylmaleimides to the corresponding amines have been described.[15a,17–19,20b] Interestingly, there is one known example of a Pd-catalyzed cross-coupling of an analogue bromide with aniline.[24]



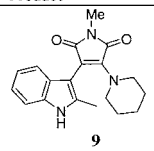
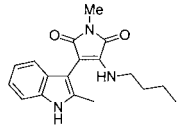
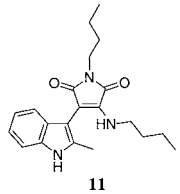
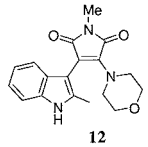
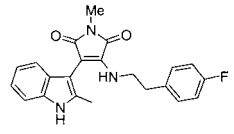
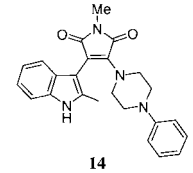
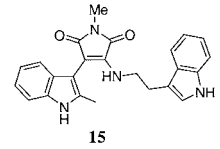
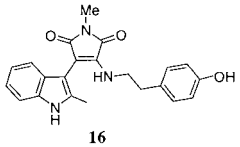
1

Scheme 2. Amination of the model substrate **1**.

In Table 2, the results for the direct amination are summarized. Reaction of **1** with 1 equiv. piperidine in the absence of carbon monoxide took place already at room temperature and yielded 50% of 1-methyl-4-(2-methyl-3-indolyl)-3-(1-piperidinyl)maleimide (**9**).[25] Noteworthy, the reaction proceeded similarly without any palladium catalyst. Thus, all following amination experiments were carried out in the absence of any catalyst.

By using twice the amount of TMEDA (1.5 equiv.) and piperidine as solvent, the yield of amine **9** increased to 91% (Table 2, Entry 1). When *n*-butylamine was employed as solvent, we obtained 79% of 1-butyl-3-butylamino-4-(2-methyl-3-indolyl)maleimide (**11**) as the main product (Table 2, Entry 3) and 17% of 3-butylamino-1-methyl-4-(2-methyl-3-indolyl)maleimide (**10**). However, in dioxane as solvent (4 equiv. *n*-butylamine), product **10** was isolated in

Table 2. Amination of 3-bromo-1-methyl-4-(2-methyl-3-indolyl)-maleimide.[a]

Entry	Product	Isolated yield [%]
1[b]	 **9**	91
2[c]	 **10**	71
3[b]	 **11**	79
4[d]	 **12**	88
5[e]	 **13**	69
6[e]	 **14**	75
7[f]	 **15**	70
8[f]	 **16**	89

[a] Reaction conditions: 3-Bromo-1-methyl-4-(2-methyl-3-indolyl)-maleimide (1 mmol). [b] Corresponding amine (10 mL), TMEDA (1.5 equiv.), room temperature, overnight. [c] *n*-Butylamine (4 equiv.), dioxane (10 mL), TMEDA (0.75 equiv.), 50 °C, overnight. [d] Morpholine (4 equiv.), dioxane (10 mL), TMEDA (1.5 equiv.), 100 °C, overnight. [e] Corresponding amine (4 equiv.), dioxane (10 mL), NEt_3 (1 equiv.), 100 °C, overnight. [f] Corresponding amine (4 equiv.), dioxane (10 mL), NEt_3 (2 equiv.), 100 °C, overnight.

good selectivity and yield (71%, Table 2, Entry 2). By increasing the temperature, 1-methyl-4-(2-methyl-3-indolyl)-3-(4-morpholinyl)maleimide (**12**) was maintained in high yield (88%, Table 2, Entry 4). Similarly, 3-amino-4-indolylmaleimides **13** and **14** were isolated in 69% and 75% yield, when NEt_3 was applied as base (Table 2, Entries 5 and 6). Finally, 3-bromo-1-methyl-4-(2-methyl-3-indolyl)maleimide was treated with tryptamine and tyramine in the presence of 2 equiv. NEt_3 to give the corresponding 3-amino-4-indolylmaleimides **15** and **16** in 70% and 89% yield, respectively (Table 2, Entries 7 and 8). All isolated products are bright-coloured crystalline compounds.

Conclusions

In summary, we have demonstrated that 3-bromo-1-methyl-4-(2-methyl-3-indolyl)maleimide can successfully be carbonylated with alcohols or amines in the presence of $Pd(OAc)_2$/di-1-adamantyl-*n*-butylphosphane (cata*CX*ium® A). The resulting 3-alkoxycarbonyl-4-indolylmaleimides and 3-aminocarbonyl-4-indolylmaleimides were obtained in 25–70% yields. Stoichiometric amination of 3-bromo-1-methyl-4-(2-methyl-3-indolyl)maleimide was carried out to synthesize several novel 3-amino-4-indolylmaleimides in good yields. Biological tests of the isolated compounds are currently in progress.

Supporting Information (see footnote on the first page of this article): Experimental procedure and detailed spectroscopic data for all new compounds are presented.

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4.4 A general synthesis of diarylketones by means of a three-component cross-coupling of aryl and heteroaryl bromides, carbon monoxide, and boronic acids

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Contributions

In this paper, I performed initial experiments on the Pd-catalyzed hydroxycarbonylation (Scheme 2). I was involved in the interpretation of the experimental data, the preparation of the manuscript, the compilation of the supporting information and I contributed to discussions. My contribution as co-author of this paper is approximately 35%.

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A General Synthesis of Diarylketones by Means of a Three-Component Cross-Coupling of Aryl and Heteroaryl Bromides, Carbon Monoxide, and Boronic acids

Helfried Neumann, Anne Brennführer, and Matthias Beller*[a]

Dedicated to Professor Wolfgang A. Herrmann on the occasion of his 60th birthday

Abstract: $Pd(OAc)_2$/di 1 adamantyl *n* butylphosphine (cata*CX*ium A) is highly active in the three component Suzuki carbonylation and represents the most gen eral catalyst system reported up to now. A broad range of aryl/heteroaryl bromides and aryl boronic acids can be coupled to the corresponding diarylketones at low catalyst loadings.

Keywords: carbon monoxide · diarylketones · homogeneous catalysis · palladium · three component reactions

Introduction

Diarylketones constitute an interesting and versatile struc tural motif[1] which is frequently present in natural products (e.g. Cotoin, Papaveraldine), in non steroidal anti inflamma tory drugs (e.g. Suprofen, Ketoprofen), and occurs in UV screens (e.g. Sulisobenzone, Oxybenzone). Typically, diaryl ketones are prepared by Friedel Crafts acylation of *ortho*/*para* directing arenes with acyl halides.[2] Unfortunately, this reaction requires overstoichiometric amounts of Lewis acid and the regioselectivity is often limited to the *para* position. Other synthetic strategies use cross coupling reactions of benzoic halides with organotin compounds,[3] palladium cat alyzed coupling of boronic acids with carboxylic anhydride,[4] or nickel catalyzed coupling reactions of aryl iodides with aromatic aldehydes.[5] An especially versatile approach for the synthesis of diarylketones[6] is the transition metal cata lyzed three component cross coupling of Aryl X (X = Br, I, OTf, N_2^+) derivatives, carbon monoxide, and arylmetal re agents. However, the coupling reaction of organoalumin ium,[7] organosilane,[8] or organotin[9] compounds with elec tron poor aryl halides is severely limited due to the forma tion of biaryl side products. Here, electron withdrawing groups on the aryl ring accelerate the rate of transmetalla tion to form the Ar Pd Ar intermediate and hinder the in sertion of carbon monoxide into the Ar Pd X species. In 1993, Suzuki et al. introduced the coupling of aryl boronic acids with aryl iodides in the synthesis of diarylketones (Suzuki carbonylation).[10] In principle, these reactions pro vide a versatile tool for organic synthesis as boronic acids are generally nontoxic and thermally, air, and moisture stable. However, the selectivity of the coupling reaction drops when aryl bromides are used. Although Suzuki et al. later improved the cross coupling for aryl triflates and aryl bromides by using $PdCl_2$ and 1,1′ bis(diphenylphosphino) ferrocene as a catalyst, still three equivalents of NaI or KI were required as an additive.[11]

Until now, relatively few palladium mediated catalyst sys tems have been applied to the carbonylative Suzuki reac tion, and limitations of the protocols still remain. Castanet et al.[12] introduced a catalyst system ($[PdCl_2(PCy_3)_2]$) which is applicable for carbonylative cross coupling of pyridyl halides with phenyl boronic acid in the presence of carbon monoxide. Pd/thiourea catalysts with a phosphine free ligand[13] only promote the Suzuki carbonylation of aryl iodides. More recently, $[Pd(PPh_3)_4]$ has been applied to aryl triflates, but again additional halide salts are needed.[14] To the best of our knowledge, there is no general method for the synthesis of diaryl and aryl heteroaryl ketones by means of a Suzuki type carbonylative cross coupling reaction.

Some years ago, we introduced Pd/diadamantylalkyl phosphine catalysts for coupling reactions. The most power ful system is based on Pd/diadamantyl *n* butylphosphine (cata*CX*ium A), which is active in Heck,[15] Suzuki,[16] and Sonogashira coupling reactions,[17] amination of aryl chlor ides,[18] as well as α arylation of ketones with chloro

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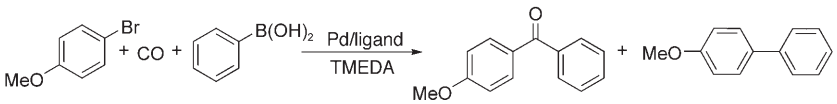
arenes.[19] More recently, we successfully employed this catalyst system in reductive carbonylations[20] and alkoxycarbonylations[21] of aryl and heteroaryl bromides. Encouraged by these results and in order to overcome the limitations of known procedures, we started to look at the palladium catalyzed Suzuki carbonylation. Herein, we describe our investigations which led to a convenient and general method to synthesize all kinds of symmetrical and unsymmetrical diarylketones.

Results and Discussion

As a starting point the reaction of 4-bromoanisole with phenyl boronic acid (1.5 equiv) in the presence of carbon monoxide was investigated (Scheme 1). The experiments on the model system were carried out in a modified six-fold parallel autoclave (reaction volume 4 mL) under 5 bar CO at 100 °C. Comparably low catalyst loading (0.5 mol % $Pd(OAc)_2$) and a three-fold excess of ligand (P/Pd 3:1) were used. Initially, we tested the activity of 12 different phosphine and carbene ligands. The results of the ligand screening are shown in Table 1.

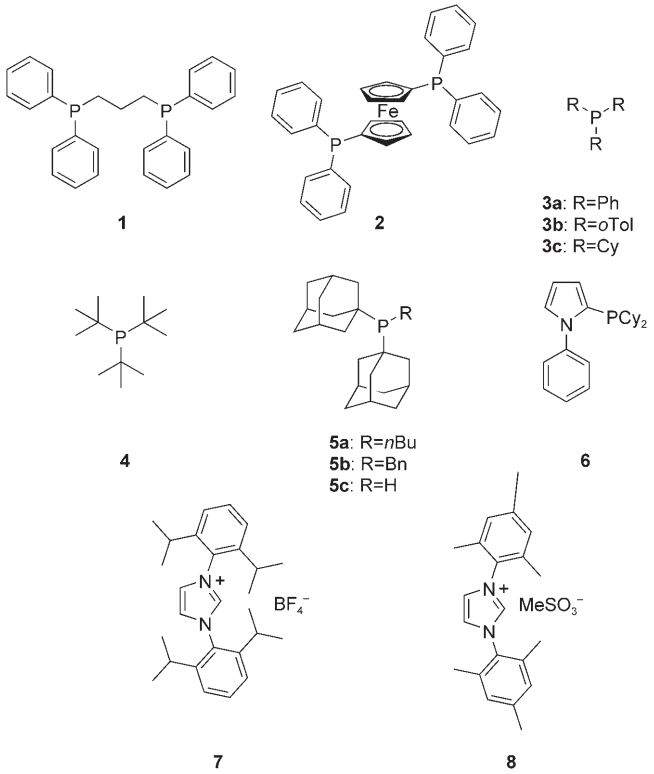


Scheme 1. Carbonylative Suzuki reaction of the model substrate.

Table 1. Screening of various ligands for the model reaction.

Entry	Ligand	Ligand [mol %]	Conversion [%][a]	Diaryl ketone [%][a]	Biaryl [%][a]	Selectivity [%][a]
1	**1**	0.75	20	2	0	12
2	**2**	0.75	12	10	0	87
3	**3a**	1.5	6	6	0	92
4	**3b**	1.5	1	0	0	0
5	**3c**	1.5	12	11	0	90
6	**4**	1.5	87	13	1	15
7	**5a**	**1.5**	**99**	**51**	**5**	**54**
8	**5b**	1.5	92	41	13	44
9	**5c**	1.5	21	18	0	86
10	**6**	1.5	26	7	0	27
11	**7**	1.5	1.5	0	0	0
12	**8**	1.5	1.5	0	0	0

Reaction conditions: 4-bromoanisole (2 mmol), $PhB(OH)_2$ (3 mmol), $Pd(OAc)_2$ (0.5 mol %), TMEDA (1 equiv), toluene (2 mL), hexadecane (0.2 equiv), 5 bar CO, 100 °C, 24 h. [a] Determined by gas chromatography.

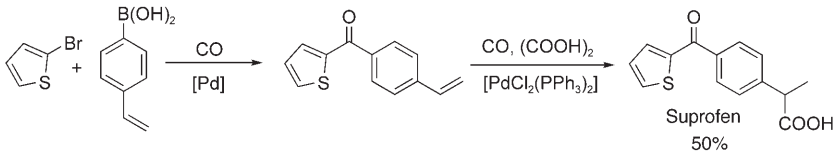


Chelating ligands 1,3-bis(diphenylphosphino)propane (dppp, **1**) and 1,1′-bis(diphenylphosphino)ferrocene (dppf, **2**), which are used in alkoxycarbonylation of aryl halides,[22] gave only a low conversion (12–20 %) and yield (2–10 %) of the desired product (Table 1, entries 1–2). Also a number of standard monodentate phosphines (**3a–c**) yielded 4-methoxybenzophenone in low amounts (0–11 %, Table 1, entries 3–5). In contrast, adamantylphosphines **5a** (cata*CX*ium A), and **5b** afforded the target compound in 41–54 % yield and the undesired biaryl side product was obtained in only 5–13 % yield, respectively (Table 1, entries 7–8). Interestingly, when we used the sterically and electronically comparable tri-*tert*-butylphosphine **4**, we observed high conversion (87 %), but only low selectivity (13 % yield) (Table 1, entry 6). Dialkyl heteroaryl phosphines were significantly less active or nearly inactive for the desired reaction (Table 1, entries 10–12).

Based on the promising results, we studied the influence of pressure and base in the model carbonylation in the presence of **5a** more carefully. As shown in Table 2, carbonylative cross coupling in the presence of solid bases, for example, K_2CO_3, K_3PO_4, or NaOEt, gave low selectivity and yields of the desired product (3–20 %, entries 1–3). Applying trialkylamines showed that a proper choice of the CO pressure is crucial for yield and chemoselectivity. Interestingly, $EtN(iPr)_2$ and NEt_3 provided an increased product yield at higher CO pressure than at low pressure (5 bar, 55–88 % versus 2.5 bar, 23–66 %, Table 2, entries 4–7). In contrast, the unwanted Suzuki coupling product is formed predominantly at low CO pressure (5 bar, 2–7 % versus 2.5 bar, 34–35 %). This behavior is not surprising as transmetallation of the Ar-Pd-X intermediate is suppressed by a higher CO pressure. Therefore, the yield of the desired diarylketone is increased. In contrast, TMEDA (TMEDA: *N,N,N′,N′*-tetramethylethylenediamine) yielded more product at 2.5 bar CO

(60%) than at 5 bar CO (51%) while the amount of by product is low (6 7%) in each case (Table 2, entries 8 9).

Next, we explored the gen erality of our catalyst system (Pd/cata*CX*ium A) by reacting different aryl and heteroaryl bromides with aryl boronic acids in the presence of CO. Table 3 shows that both electron rich and poor aryl



Scheme 2. Synthesis of Suprofen.

Table 2. Influence of different bases on the yield of 4 methoxybenzo phenone.

Entry	Base	*p* [bar]	Conversion [%][a]	Diaryl ketone [%][a]	Biaryl [%][a]	Selectivity [%][a]
1	K_2CO_3	5.0	52	20	33	38
2	K_3PO_4	5.0	61	19	43	31
3	NaOEt	5.0	94	3	65	4
4	NEt_3	5.0	94	88	2	94
5		2.5	99	66	35	67
6	$EtN(iPr)_2$	5.0	92	55	7	60
7		2.5	69	23	34	33
8	TMEDA	5.0	98	51	6	60
9		2.5	93	60	7	76
10	pyridine	5.0	7	0	0	0
11		2.5	9	1	0	11

Reaction conditions: 4 bromoanisole (2 mmol), $PhB(OH)_2$ (3 mmol), $Pd(OAc)_2$ (0.5 mol%), cata*CX*ium A (1.5 mol%), base (2 equiv), toluene (2 mL), hexadecane (0.2 equiv), 2.5 5.0 bar CO, 100°C, 24 h. [a] Deter mined by gas chromatography.

bromides and aryl boronic acids were successfully converted by means of a carbonylative cross coupling reaction. Nota bly, for aryl bromides with electron withdrawing substitu ents, which are known to support direct coupling to give biaryls, an increased CO pressure of 5 bar often led to better results. As an example, reaction of 4 bromobenzotri fluoride with different boronic acids gave selectively (>99%) the diarylketones as a single product (Table 3, en tries 3 5). Experiments using 4 chlorobromobenzene, 3 bro mopyridine, and 2 and 4 bromobenzonitrile provided the diarylketone/biaryl in 70/7, 64/4, 60/39, and 89/10% yields, respectively (Table 3, entries 21, 25 27). When electron rich and electron neutral aryl bromides were employed, the cou pling reaction proceeded with good yields and in almost every case no biaryl side products were observed (Table 3, entries 1, 2, 6, 9, 22 24, and 28). From a synthetic viewpoint, it is important to note that various combinations of hetero aryl bromides with heteroaryl boronic acids can be coupled efficiently by our catalyst system. Hence, a carbonylative Suzuki reaction of 3 bromobenzothiophene, 3 bromothio phene, and 3 bromopyridine[23] with 3 thiophene boronic acid resulted in diarylketone/biaryl in 81/11, 59/0, and 60/ 25% yields, respectively (Table 3, entries 13, 17, and 20).

When NEt_3 was used as the base, in general the Suzuki carbonylation occurred with lower selectivity with the ex ception that the symmetrical bis(3 thienyl) ketone was ob tained in 67% yield (Table 3, entry 18). Remarkable exam ples for the high selectivity of the catalyst are the cross coupling reactions of 4 vinylphenylboronic acid. Despite the possibility of a competitive Heck , Suzuki , and carbonyla tive Heck reaction, these couplings proceeded with excellent selectivity. Thus, 4 bromobenzotrifluoride, 4 bromoanisole, and 2 and 3 bromothiophene reacted with 4 vinylphenyl boronic acid in the presence of CO to give exclusively the desired diarylketones in 80, 73, 63, and 65% yields, respec tively (Table 3, entries 8 9 and 11 12). The resulting diaryl ketones are interesting substrates for further refinement to wards pharmaceuticals. Hence, 4 vinylphenyl 2 thienyl ketone (Table 3, entry 12) is easily hydroxycarbonylated[24] in one step to Suprofen, a commercial nonsteroidal anti in flammatory drug (Scheme 2).

Conclusion

We have developed a general and efficient synthesis of diaryl , diheteroaryl , and aryl heteroaryl ketones by a three component cross coupling reaction of aryl/heteroaryl bromides, aryl boronic acids, and carbon monoxide. This re action offers efficient access to various biologically active compounds as shown by the two step preparation of Suprofen. Remarkable features of our catalyst are the high selectivity and the improved productivity. Furthermore the system is easily handled (air stable).

Experimental Section

General information: Toluene was destilled from sodium and benzo phenone. All reactions were performed by using standard Schlenk tech niques (argon). ^1H and ^{13}C NMR spectra were recorded on a Bruker AV 300/AV 400 spectrometer at 25°C. Chemical shifts (δ) are given in ppm and refer to the residual undeuterated solvent as the internal standard ($[D_6]DMSO$: $\delta = 2.50/39.7$ ppm). Gas chromatography was performed on a Hewlett Packard HP 6890 chromatograph with a HP5 column. Chemi cals were purchased from Fluka, Aldrich, Strem and used as received. The cata*CX*ium A ligand is available from Strem or directly from Evonik Degussa.

General procedure for the 6-fold parallel autoclave: A 50 mL Schlenk flask was charged with $Pd(OAc)_2$ (22.5 mg, 0.5 mol%), cata*CX*ium A (108 mg, 1.5 mol%) and toluene (20 mL). Subsequently, hexadecane (1.17 mL, internal GC standard) and TMEDA (2.25 mL, 15 mmol) were added. This clear yellow stock solution (2.34 mL) was transferred to six vials (4 mL reaction volume) equipped with a septum, a small cannula, a stirring bar, 2 mmol of the corresponding aryl bromide, and 3 mmol of the corresponding boronic acid. The vials were placed in an alloy plate, which was transferred to a 300 mL autoclave of the 4560 series from Parr Instruments under an argon atmosphere. After flushing the autoclave

Table 3. Scope and limitations of the carbonylative Suzuki reaction.

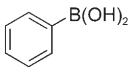
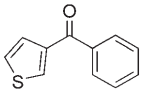
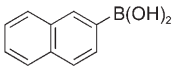
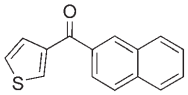
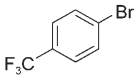
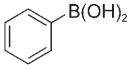
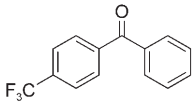
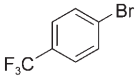
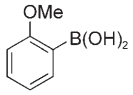
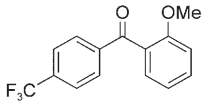
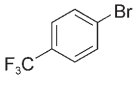
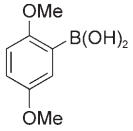
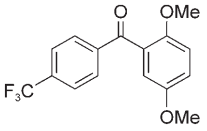
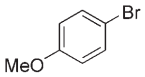
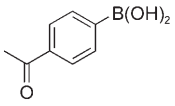
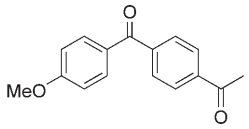
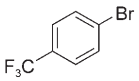
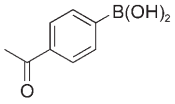
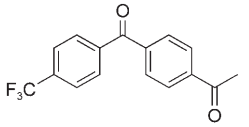
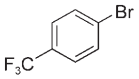
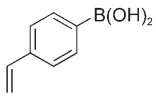
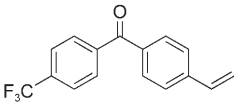
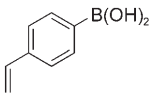
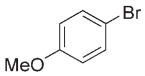
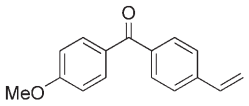
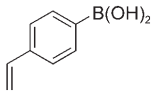
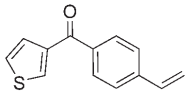
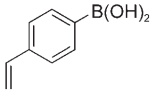
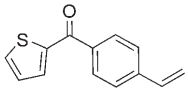
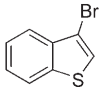
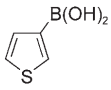
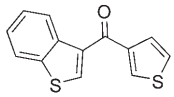
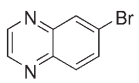
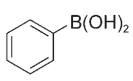
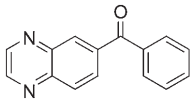
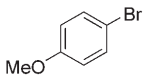
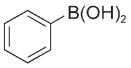
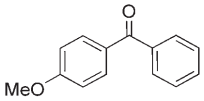
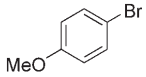
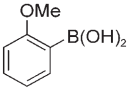
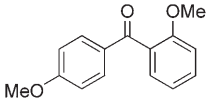
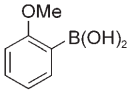
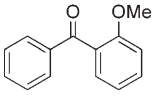
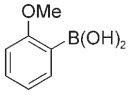
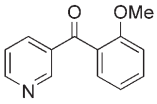
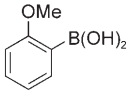
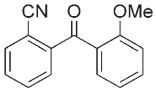
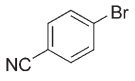
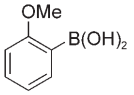
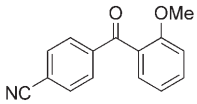
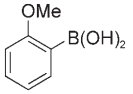
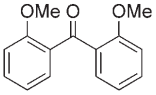
Entry	Aryl bromide	Boronic acid	T [°C]	CO [bar]	Ketone	Yield [%]	Biaryl [%]
1			100	5.0		70	0
2			100	5.0		63	0
3			100	5.0		79	0
4			100	5.0		73	0
5			100	5.0		81	0
6[a]			100	2.5		65	0
7[a]			80	2.5		65	3
8[a]			80	2.5		80	0
9[a]			100	2.5		73	0
10[a],[b]			100	5.0		43	35
11[a]			100	2.5		63	0
12[a]			80	2.5		65	0
13[a]			80	2.5		81	11
14[a],[b]			100	5.0		26	84
15[a]			80	2.5		75	10
16[a],[b]			100	5.0		28	62
17[a]			100	2.5		59	0
18[a],[b]			110	5.0		67	0
19[a]			100	5.0		45	30
20[a]			120	10		60	25
21			100	5.0		70	7

Table 3. (Continued)

Entry	Aryl bromide	Boronic acid	T [°C]	CO [bar]	Ketone	Yield [%]	Biaryl [%]
22[a]			100	2.5		60	0
23			100	5.0		74	0
24			100	5.0		73	0
25			100	5.0		64	4
26[a]			100	5.0		60	39
27[a]			100	5.0		89	10
28[a]			100	5.0		64	0

Reaction conditions: aryl bromide (2 mmol), aryl boronic acid (3 mmol), $Pd(OAc)_2$ (0.5 mol%), cata*CX*ium A (1.5 mol%), TMEDA (1 equiv), toluene (2 mL), hexadecane (0.2 equiv), 2.5 5.0 bar CO, 80°C–120°C, 24 h. [a] Yield determined by gas chromatography. [b] NEt_3 (2 equiv) is used as the base.

three times with carbon monoxide a pressure of 2.5 to 5 bar, the carbon monoxide was adjusted at ambient temperature and the reaction was per formed for 24 h at 80 100°C. Before and after the reaction, an aliquot of the reaction mixture was subjected to GC analysis for determination of yield and conversion.

Phenyl thiophen-3-yl methanone: Colorless oil; yield 70%; R_f=0.11 (EtOAc/heptane 0.25:10); ^{1}H NMR (300 MHz; [D$_6$]DMSO): δ=8.22 (dd, J=2.8, 1.3 Hz, 1H), 7.82 7.79 (m, 2H), 7.72 (dd, J=4.9, 2.8 Hz, 1H), 7.70 7.64 (m, 1H), 7.59 7.52 ppm (m, 3H); ^{13}C NMR (75 MHz; [D$_6$]DMSO): δ=189.3 (C=O), 140.6, 138.3, 135.5 (CH), 132.6 (CH), 129.2 (CH), 128.8 (CH), 128.2 (CH), 127.8 ppm (CH); IR (KBr): $\tilde{\nu}$=3106 (m), 2927 (w), 1650 (vs, C=O), 1598 (s), 1577 (m), 1510 (vs), 1446 (s), 1410 (vs), 1388 (s), 1307 (m), 1277 (vs), 1178 (m), 1138 (m), 1075 (m), 1028 (w), 1001 (w), 969 (m), 859 (vs), 821 (s), 781 (s), 718 (vs), 672 cm^{-1} (s); MS (70 eV): m/z (%): 188 (100) [M^+], 160 (6), 111 (93), 105 (31), 83 (14), 77 (40), 51 (21); elemental analysis calcd (%) for $C_{11}H_8OS$: C 70.18, H 4.28, S 17.03; found: C 70.20, H 4.39, S 16.87.

Naphthalen-2-yl thiophen-3-yl methanone: Yield 63%; m.p. 109 110°C; R_f=0.14 (EtOAc/heptane 1:20); ^{1}H NMR (400 MHz; [D$_6$]DMSO): δ= 8.44 (brs, 1H), 8.33 (dd, J=2.7, 1.2 Hz, 1H), 8.14 (d, J=8.1 Hz, 1H), 8.08 (d, J=8.5 Hz, 1H), 8.03 (d, J=8.3 Hz, 1H), 7.88 (dd, J=8.5, 1.9 Hz, 1H), 7.75 (dd, J=5.0, 2.7 Hz, 1H), 7.70 7.62 (m, 2H), 7.60 ppm (dd, J= 5.0, 1.2 Hz, 1H); ^{13}C NMR (75 MHz; [D$_6$]DMSO): δ=189.3 (C=O), 140.7, 135.6 (CH), 135.5, 134.9, 132.1, 130.8 (CH), 129.7 (CH), 128.6 (CH), 128.5 (CH), 128.3 (CH), 127.8 (CH), 127.8 (CH), 127.1 (CH), 125.2 ppm (CH); IR (KBr): $\tilde{\nu}$=3120 (s), 3103 (s), 3090 (s), 3058 (m), 1636 (vs, C=O), 1574 (m), 1510 (vs), 1467 (s), 1411 (vs), 1391 (vs), 1349 (m), 1283 (vs), 1271 (vs), 1237 (vs), 1206 (m), 1184 (vs), 1139 (vs), 1114 (s), 1073 (s), 1019 (w), 980 (m), 960 (m), 918 (s), 887 (vs), 872 (vs), 836 (vs), 830 (vs), 812 (s), 792 (vs), 771 (vs), 732 (vs), 718 (s), 629 (m), 597 (s), 488 cm^{-1} (vs); MS (70 eV): m/z (%): 238 (100) [M^+], 210 (9), 155 (49), 127 (54), 111 (57), 83 (11), 77 (9); HRMS (EI): m/z: calcd for $C_{15}H_{10}OS$: 238.04469; found: 238.04424 [M^+].

4-Trifluoromethylbenzophenone: Yield 79%; m.p. 109°C; R_f=0.25 (EtOAc/heptane 0.25:10); ^{1}H NMR (300 MHz; [D$_6$]DMSO): δ=7.96 7.90 (brs, 4H), 7.79 7.76 (m, 2H), 7.75 7.70 (m, 1H), 7.61 7.56 ppm (m, 2H); ^{13}C NMR (75 MHz; [D$_6$]DMSO): δ=195.1 (C=O), 140.9, 136.4, 133.5 (CH), 132.1 (q, ^2J(C,F)=32 Hz), 130.4 (CH), 130.0 (CH), 128.9 (CH), 125.7 (q, ^3J(C,F)=3.9 Hz, CH), 124.0 ppm (q, ^1J(C,F)=272 Hz); IR (KBr): $\tilde{\nu}$=3063 (w), 1652 (vs, C=O), 1598 (m), 1577 (m), 1508 (m), 1448 (m), 1409 (s), 1330 (vs), 1282 (vs), 1169 (vs), 1122 (vs), 1066 (vs), 1017 (s), 943 (s), 925 (s), 858 (vs), 797 (m), 751 (s), 716 (s), 699 (vs), 656 (m), 468 cm^{-1} (m); MS (70 eV): m/z (%): 250 (67) [M^+], 231 (12), 181 (9), 173 (42), 145 (54), 125 (9), 105 (100), 95 (11), 77 (50), 51 (21); HRMS (EI): m/z: calcd for $C_{14}H_9F_3O$: 250.06000; found: 250.05946 [M^+].

2-Methoxyphenyl 4-trifluoromethylphenyl methanone: Yield 73%; m.p. 78°C; R_f=0.15 (EtOAc/heptane 0.5:10); ^{1}H NMR (400 MHz; [D$_6$]DMSO): δ=7.90 7.85 (m, 4H), 7.59 (quasi td, J=7.9, 1.3 Hz, 1H), 7.41 (dd, J=7.5, 1.3 Hz, 1H), 7.22 (d, J=8.3 Hz, 1H), 7.12 (t, J=7.5 Hz, 1H), 3.66 ppm (s, 3H; OCH_3); ^{13}C NMR (75 MHz; [D$_6$]DMSO): δ= 195.1 (C=O), 157.1, 140.7, 133.1 (CH), 132.6 (q, ^2J(C,F)=31 Hz), 129.9 (CH), 129.5 (CH), 127.6, 125.8 (q, ^3J(C,F)=3.7 Hz, CH), 124.0 (q, ^1J (C,F)=274 Hz), 121.0 (CH), 112.4 (CH), 55.8 ppm (OCH_3); IR (KBr): $\tilde{\nu}$=3069 (m), 3013 (w), 2941 (w), 2840 (m), 1677 (vs, C=O), 1601 (vs), 1585 (s), 1510 (m), 1488 (vs), 1468 (vs), 1433 (vs), 1411 (vs), 1327 (vs), 1315 (vs), 1295 (vs), 1265 (vs), 1248 (vs), 1161 (vs), 1139 (vs), 1111 (vs), 1065 (vs), 1048 (s), 1018 (s), 943 (vs), 926 (vs), 864 (vs), 773 (s), 756 (vs), 703 (s), 648 cm^{-1} (s); MS (70 eV): m/z (%): 280 (40) [M^+], 263 (22), 211 (12), 173 (17), 145 (39), 135 (100), 121 (10), 92 (16), 77 (27); elemental analysis calcd (%) for $C_{15}H_{11}F_3O_2$: C 64.29, H 3.96; found: C 64.34, H 3.72.

2,5-Dimethoxyphenyl 4-trifluoromethylphenyl methanone: Yield 81%; m.p. 85 86°C; R_f=0.08 (EtOAc/heptane 0.5:10); ^{1}H NMR (400 MHz;

[D$_6$]DMSO): δ = 7.88 (brs, 4H), 7.15 (brs, 2H), 6.98 (brs, 1H), 3.75 (s, 3H, OCH_3), 3.59 ppm (s, 3H, OCH_3); ^{13}C NMR (75 MHz; [D$_6$]DMSO): δ = 194.7 (C=O), 153.4, 151.1, 140.6, 132.3 (q, ^2J(C,F) = 33 Hz), 130.0 (CH), 128.2, 125.8 (q, ^3J(C,F) = 4.0 Hz, CH), 123.9 (q, ^1J(C,F) = 276 Hz), 118.1 (CH), 114.2 (CH), 113.8 (CH), 56.2 (OCH_3), 55.8 ppm (OCH_3); IR (KBr): $\tilde{\nu}$ = 3067 (w), 2963 (w), 2836 (m), 1954 (w), 1677 (vs, C=O), 1588 (m), 1495 (vs), 1473 (s), 1445 (s), 1425 (vs), 1410 (s), 1325 (vs), 1313 (vs), 1290 (vs), 1263 (s), 1236 (vs), 1219 (vs), 1171 (vs), 1139 (vs), 1112 (s), 1064 (vs), 1048 (vs), 1023 (vs), 967 (vs), 867 (vs), 850 (s), 810 (vs), 777 (s), 726 (s), 705 cm^{-1} (s); MS (70 eV): *m*/*z* (%): 310 (100) [M^+], 293 (23), 252 (17), 173 (25), 165 (57), 151 (34), 145 (55), 122 (8), 107 (13), 95 (8), 77 (10); elemental analysis calcd (%) for $C_{16}H_{13}F_3O_3$: C 61.94, H 4.22; found: C 61.99, H 4.02.

1-[4-(4-Methoxybenzoyl)phenyl]-ethanone: Yield 57%; m.p. 105 106°C; R_f = 0.17 (EtOAc/heptane 1:5); ^{1}H NMR (400 MHz; [D$_6$]DMSO): δ = 8.09 (quasi d, *J* = 8.5 Hz, 2H), 7.78 (quasi d, *J* = 8.5 Hz, 2H), 7.76 (quasi d, *J* = 9.0 Hz, 2H), 7.10 (quasi d, *J* = 9.0 Hz, 2H), 3.87 (s, 3H; OCH_3), 2.65 ppm (s, 3H; COCH_3); ^{13}C NMR (75 MHz; [D$_6$]DMSO): δ = 197.7 (C=O), 193.9 (C=O), 163.3, 141.5, 138.9, 132.3 (CH), 129.3 (CH), 128.9, 128.2 (CH), 114.0 (CH), 55.6 (OCH_3), 27.0 ppm (COCH_3); IR (KBr): $\tilde{\nu}$ = 2967 (m), 2938 (m), 2843 (m), 1685 (vs, C=O), 1642 (vs, C=O), 1603 (vs), 1576 (m), 1509 (m), 1497 (m), 1417 (m), 1403 (m), 1358 (m), 1307 (vs), 1291 (vs), 1258 (vs), 1175 (s), 1149 (s), 1119 (m), 1028 (s), 963 (w), 932 (s), 862 (s), 850 (s), 837 (s), 766 (vs), 684 (s), 652 cm^{-1} (m); MS (70 eV): *m*/*z* (%): 254 (58) [M^+], 239 (28), 211 (8), 147 (6), 136 (9), 135 (100), 107 (6), 92 (16), 77 (16); elemental analysis calcd (%) for $C_{16}H_{14}O_3$: C 75.57, H 5.55; found: C 75.35, H 5.31.

1-{4-[4-(trifluoromethyl)benzoyl]phenyl}-ethanone: Yield 56%; m.p. 124 125°C; R_f = 0.16 (EtOAc/heptane 1:7); ^{1}H NMR (400 MHz; [D$_6$]DMSO): δ = 8.12 (quasi d, *J* = 8.6 Hz, 2H), 7.95 (brs, 4H), 7.88 (quasi d, *J* = 8.6 Hz, 2H), 2.66 ppm (s, 3H; COCH_3); ^{13}C NMR (75 MHz; [D$_6$]DMSO): δ = 197.9 (C=O), 194.8 (C=O), 140.3, 139.9, 139.9, 132.5 (q, ^2J(C,F) = 32 Hz), 130.6 (CH), 130.2 (CH), 128.6 (CH), 125.9 (q, ^3J(C,F) = 3.7 Hz; CH), 124.0 (q, ^1J(C,F) = 274 Hz), 27.3 ppm (COCH_3); IR (KBr): $\tilde{\nu}$ = 2925 (w), 2850 (w), 1687 (vs, C=O), 1650 (vs, C=O), 1406 (s), 1362 (m), 1330 (vs), 1313 (vs), 1283 (s), 1266 (s), 1173 (s), 1135 (vs), 1068 (vs), 1017 (s), 964 (w), 932 (s), 865 (s), 837 (m), 771 (s), 754 (m), 697 (m), 679 (s), 617 (w), 604 (w), 590 cm^{-1} (m); MS (70 eV): *m*/*z* (%): 292 (16) [M^+], 277 (100), 201 (10), 180 (6), 173 (24), 145 (26), 76 (7); elemental analysis calcd (%) for $C_{16}H_{11}F_3O_2$: C 65.76, H 3.79; found: C 65.86, H 3.75.

4-Trifluoromethylphenyl 4-vinylphenyl methanone: Yield 30%; m.p. 132 133°C; R_f = 0.47 (EtOAc/heptane 1:10); ^{1}H NMR (400 MHz; [D$_6$]DMSO): δ = 7.95 7.90 (m, 4H), 7.76 (d, *J* = 8.4 Hz, 2H), 7.67 (d, *J* = 8.4 Hz, 2H), 6.86 (dd, *J* = 17.7, 10.9 Hz, 1H), 6.04 (d, *J* = 17.7 Hz, 1H), 5.47 ppm (d, *J* = 10.9 Hz, 1H); ^{13}C NMR (75 MHz; [D$_6$]DMSO): δ = 194.6 (C=O), 142.0, 141.1, 135.9 (CH), 135.5, 132.1 (q, ^2J(C,F) = 32 Hz), 130.6 (CH), 130.3 (CH), 126.6 (CH), 125.7 (q, ^3J(C,F) = 3.7 Hz, CH), 124.0 (q, ^1J(C,F) = 273 Hz), 117.9 ppm (*C*H$_2$); IR (KBr): $\tilde{\nu}$ = 3069 (w), 2855 (w), 1940 (w), 1650 (vs, C=O), 1603 (vs), 1579 (w), 1554 (w), 1509 (w), 1408 (vs), 1329 (vs), 1314 (vs), 1287 (vs), 1171 (vs), 1130 (vs), 1110 (vs), 1068 (vs), 1017 (vs), 991 (s), 974 (w), 933 (vs), 865 (vs), 847 (s), 779 (vs), 772 (m), 704 (s), 688 (vs), 600 cm^{-1} (w); MS (70 eV): *m*/*z* (%): 276 (70) [M^+], 257 (8), 173 (15), 145 (32), 131 (100), 103 (20), 95 (7), 77 (25); elemental analysis calcd (%) for $C_{16}H_{11}F_3O$: C 69.56, H 4.01; found: C 69.34, H 4.30.

4-Methoxyphenyl 4-vinylphenyl methanone: Yield 53%; m.p. 90 91°C; R_f = 0.35 (EtOAc/heptane 1:10); ^{1}H NMR (400 MHz; [D$_6$]DMSO): δ = 7.75 (quasi d, *J* = 9.0 Hz, 2H), 7.68 (quasi d, *J* = 8.6 Hz, 2H), 7.64 (quasi d, *J* = 8.6 Hz, 2H), 7.09 (quasi d, *J* = 9.0 Hz, 2H), 6.84 (dd, *J* = 17.8, 11.0 Hz, 1H), 6.01 (d, *J* = 17.8 Hz, 1H), 5.43 (d, *J* = 11.0 Hz, 1H), 3.86 ppm (s, 3H; OCH_3); ^{13}C NMR (75 MHz; [D$_6$]DMSO): δ = 193.9 (C=O), 162.9, 140.7, 136.9, 135.9 (CH), 132.1 (CH), 129.8 (CH), 129.5, 126.1 (CH), 117.0 (*C*H$_2$), 113.9 (CH), 55.6 ppm (OCH_3); IR (KBr): $\tilde{\nu}$ = 3003 (w), 2964 (m), 2839 (m), 1642 (vs, C=O), 1604 (vs), 1577 (s), 1554 (m), 1504 (s), 1465 (w), 1442 (w), 1416 (m), 1401 (m), 1308 (vs), 1292 (vs), 1251 (vs), 1175 (vs), 1148 (s), 1120 (m), 1032 (s), 996 (m), 968 (w), 932 (s), 859 (vs), 839 (vs), 776 (vs), 739 (m), 693 cm^{-1} (vs); MS (70 eV): *m*/*z* (%): 238 (91) [M^+], 207 (11), 195 (6), 165 (6), 135 (100), 103 (12), 92 (16), 77 (30), 63 (7); elemental analysis calcd (%) for $C_{16}H_{14}O_2$: C 80.65, H 5.92; found: C 80.66, H 5.80.

Thiophen-3-yl 4-vinylphenyl methanone: Yield 63%; m.p. 45 46°C; R_f = 0.26 (EtOAc/heptane 1:20); ^{1}H NMR (400 MHz; [D$_6$]DMSO): δ = 8.24 (dd, *J* = 2.8, 1.4 Hz, 1H), 7.79 (quasi d, *J* = 8.3 Hz, 2H), 7.72 (dd, *J* = 5.1, 2.8 Hz, 1H), 7.65 (quasi d, *J* = 8.3 Hz, 2H), 7.53 (dd, *J* = 5.1, 1.4 Hz, 1H), 6.85 (dd, *J* = 17.7, 10.9 Hz, 1H), 6.02 (d, *J* = 17.7 Hz, 1H), 5.44 ppm (d, *J* = 10.9 Hz, 1H); ^{13}C NMR (75 MHz; [D$_6$]DMSO): δ = 188.7 (C=O), 141.2, 140.6, 137.4, 136.0 (CH), 135.2 (CH), 129.8 (CH), 128.2 (CH), 127.8 (CH), 126.4 (CH), 117.3 ppm (*C*H$_2$); IR (KBr): $\tilde{\nu}$ = 3102 (m), 3082 (s), 2925 (w), 1635 (vs, C=O), 1603 (vs), 1558 (m), 1511 (s), 1411 (vs), 1387 (s), 1308 (m), 1281 (vs), 1232 (m), 1202 (w), 1180 (m), 1138 (s), 1118 (m), 1077 (w), 995 (s), 972 (s), 914 (s), 880 (m), 864 (vs), 855 (vs), 813 (s), 766 (vs), 717 (vs), 701 cm^{-1} (vs); MS (70 eV): *m*/*z* (%): 214 (100) [M^+], 186 (9), 152 (3); elemental analysis calcd (%) for $C_{13}H_{10}OS$: C 72.87, H 4.70, S 14.96; found: C 72.52, H 4.96, S 14.56.

Thiophen-2-yl 4-vinylphenyl methanone: Yield 60%; m.p. 47 48°C; R_f = 0.22 (EtOAc/heptane 1:20); ^{1}H NMR (400 MHz; [D$_6$]DMSO): δ = 8.12 (dd, *J* = 4.9, 1.1 Hz, 1H), 7.83 (quasi d, *J* = 8.3 Hz, 2H), 7.74 (dd, *J* = 3.8, 1.1 Hz, 1H), 7.67 (quasi d, *J* = 8.3 Hz, 2H), 7.29 (dd, *J* = 4.9, 3.8 Hz, 1H), 6.85 (dd, *J* = 17.7, 10.9 Hz, 1H), 6.02 (d, *J* = 17.7 Hz, 1H), 5.45 ppm (d, *J* = 10.9 Hz, 1H); ^{13}C NMR (75 MHz; [D$_6$]DMSO): δ = 186.7 (C=O), 142.8, 141.0, 136.6, 135.8 (CH), 135.6 (CH), 135.3 (CH), 129.4 (CH), 128.8 (CH), 126.3 (CH), 117.2 ppm (*C*H$_2$); IR (KBr): $\tilde{\nu}$ = 3084 (m), 1623 (vs, C=O), 1602 (s), 1510 (m), 1411 (s), 1355 (s), 1294 (s), 1233 (w), 1183 (w), 1056 (w), 1003 (w), 928 (m), 884 (m), 860 (s), 780 (m), 740 (s), 714 cm^{-1} (s); MS (70 eV): *m*/*z* (%): 214 (100) [M^+], 197 (9) 187 (11), 152 (2); elemental analysis calcd (%) for $C_{13}H_{10}OS$: C 72.87, H 4.70, S 14.96; found: C 73.06, H 4.63, S 14.61.

Benzo[*b*]thiophen-3-yl thiophen-3-yl methanone: Yield 40%; m.p. 86 87°C; R_f = 0.21 (EtOAc/heptane 1:20); ^{1}H NMR (300 MHz; [D$_6$]DMSO): δ = 8.62 (brs, 1H), 8.41 8.40 (m, 1H), 8.36 (dd, *J* = 2.8, 1.4 Hz, 1H), 8.14 8.11 (m, 1H), 7.74 (dd, *J* = 5.1, 2.8 Hz, 1H), 7.60 (dd, *J* = 5.1, 1.4 Hz, 1H), 7.56 7.46 ppm (m, 2H); ^{13}C NMR (75 MHz; [D$_6$]DMSO): δ = 183.7 (C=O), 142.0, 139.8, 139.1 (CH), 137.1, 134.6 (CH), 134.4, 128.0 (CH), 127.8 (CH), 125.7 (CH), 124.4 (CH), 123.1 ppm (CH); IR (KBr): $\tilde{\nu}$ = 3104 (s), 2925 (w), 1635 (vs, C=O), 1591 (s), 1557 (m), 1507 (vs), 1494 (vs), 1459 (vs), 1425 (vs), 1351 (s), 1261 (vs), 1243 (vs), 1202 (s), 1180 (vs), 1152 (m), 1134 (m), 1090 (s), 1051 (s), 1019 (m), 938 (w), 864 (s), 834 (vs), 789 (vs), 767 (vs), 737 (vs), 719 (vs), 706 (vs), 636 (m), 568 cm^{-1} (m); MS (70 eV): *m*/*z* (%): 244 (100) [M^+], 227 (7), 211 (29), 171 (13), 161 (43); HRMS (EI): calcd for $C_{13}H_8OS_2$: 244.00111; found: 244.00110 [M^+].

3-Thiophen-3-yl-benzo[*b*]thiophene: Colorless oil: yield 45%; R_f = 0.25 (EtOAc/heptane 0.5:10); ^{1}H NMR (300 MHz; [D$_6$]DMSO): δ = 8.07 8.03 (m, 2H), 7.88 (brs, 1H), 7.86 (dd, *J* = 2.9, 1.3 Hz, 1H), 7.72 (dd, *J* = 4.9, 2.9 Hz, 1H), 7.50 (dd, *J* = 4.9, 1.3 Hz, 1H), 7.47 7.40 ppm (m, 2H); ^{13}C NMR (75 MHz; [D$_6$]DMSO): δ = 140.1, 137.3, 135.7, 132.0, 128.1 (CH), 126.9 (CH), 124.9 (CH), 124.8 (CH), 124.4 (CH), 123.4 (CH), 122.9 (CH), 122.5 ppm (CH); IR (KBr): $\tilde{\nu}$ = 3100 (m), 3064 (w), 1559 (m), 1457 (m), 1428 (vs), 1404 (m), 1322 (w), 1259 (m), 1216 (m), 1178 (m), 1082 (s), 1060 (vs), 1022 (m), 883 (w), 837 (s), 791 (s), 773 (vs), 759 (vs), 732 (vs), 648 (vs), 617 cm^{-1} (w); MS (70 eV): *m*/*z* (%): 216 (100) [M^+], 184 (8), 171 (30); elemental analysis calcd (%) for $C_{12}H_8S_2$: C 66.63, H 3.73, S 29.65; found: C 66.85, H 3.61, S 30.00.

Phenyl-quinoxalin-6-yl methanone: Yield 65%; m.p. 117°C; R_f = 0.11 (EtOAc/heptane 1:5); ^{1}H NMR (300 MHz; [D$_6$]DMSO): δ = 9.07 (dd, *J* = 4.7, 1.9 Hz, 2H), 8.32 (d, *J* = 1.9 Hz, 1H), 8.26 (d, *J* = 8.5 Hz, 1H), 8.17 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.86 7.83 (m, 2H), 7.77 7.71 (m, 1H), 7.63 7.58 ppm (m, 2H); ^{13}C NMR (75 MHz; [D$_6$]DMSO): δ = 195.2 (C=O), 147.8 (CH), 147.2 (CH), 144.0, 141.5, 138.2, 136.7, 133.4 (CH), 131.7 (CH), 130.1 (CH), 130.0 (CH), 129.7 (CH), 128.9 ppm (CH); IR (KBr): $\tilde{\nu}$ = 3061 (m), 1654 (vs, C=O), 1609 (m), 1597 (s), 1576 (m), 1444 (s), 1421 (m), 1370 (s), 1352 (vs), 1298 (vs), 1279 (vs), 1247 (s), 1207 (w), 1176 (s), 1133 (s), 1113 (vs), 1024 (s), 964 (s), 931 (m), 910 (s), 872 (vs), 843 (m), 784 (m), 729 (vs), 703 (vs), 685 (m), 619 cm^{-1} (s); MS (70 eV): *m*/*z* (%): 234 (61) [M^+], 205 (45), 157 (66), 129 (36), 105 (100), 102 (31), 77 (77), 51 (29); HRMS (EI): *m*/*z*: calcd for $C_{15}H_{10}N_2O$: 234.07876; found: 234.07815 [M^+].

6-Phenyl-quinoxaline: Yield 26%; m.p. 89 91°C; R_f=0.19 (EtOAc/heptane 1:5); ^{1}H NMR (300 MHz; [D$_6$]DMSO): δ=8.96 (dd, J=10.6, 1.9 Hz, 2H), 8.34 (d, J=1.9 Hz, 1H), 8.21 (quasi dd, J=8.7, 1.9 Hz, 1H), 8.17 (quasi dd, J=8.7, 0.8 Hz, 1H), 7.91 7.87 (m, 2H), 7.58 7.52 (m, 2H), 7.49 7.44 ppm (m, 1H); ^{13}C NMR (75 MHz; [D$_6$]DMSO): δ=146.4 (CH), 145.8 (CH), 142.7, 141.9, 141.8, 138.8, 129.9 (CH), 129.6 (CH), 129.4 (CH), 128.6 (CH), 127.5 (CH), 126.3 ppm (CH); IR (KBr): $\tilde{\nu}$=3066 (w), 3024 (w), 2924 (s), 2853 (m), 1935 (w), 1616 (s), 1578 (m), 1484 (vs), 1454 (s), 1431 (s), 1370 (s), 1348 (m), 1317 (w), 1305 (m), 1245 (w), 1168 (m), 1134 (s), 1078 (m), 1023 (vs), 1013 (vs), 951 (vs), 897 (vs), 885 (m), 866 (vs), 839 (s), 775 (vs), 766 (vs), 698 (vs), 665 (m), 608 (w), 560 (w), 496 (m), 409 cm^{-1} (s); MS (70 eV): m/z (%): 206 (100) [M^+], 179 (4), 152 (34), 102 (28), 76 (10), 63 (5); HRMS (EI): m/z: calcd for $C_{14}H_{10}N_2$: 206.08385; found: 206.08402 [M^+].

Di[3]thienyl ketone: Yield 43%; m.p. 71°C; R_f=0.22 (EtOAc/heptane 1:10); ^{1}H NMR (300 MHz; [D$_6$]DMSO): δ=8.36 (quasi dd, J=2.4, 1.2 Hz, 2H), 7.71 (quasi dd, J=4.9, 2.4 Hz, 2H), 7.55 ppm (quasi dd, J=4.9, 1.2 Hz, 2H); ^{13}C NMR (75 MHz; [D$_6$]DMSO): δ=182.6 (C=O), 141.3, 134.3 (CH), 128.0 (CH), 127.7 ppm (CH); IR (KBr): $\tilde{\nu}$=3106 (s), 1629 (vs, C=O), 1513 (vs), 1427 (vs), 1394 (w), 1271 (s), 1219 (w), 1178 (w), 1136 (vs), 1078 (m), 984 (w), 916 (w), 883 (s), 850 (vs), 826 (vs), 776 (s), 741 (vs), 697 (vs), 624 cm^{-1} (w); MS (70 eV): m/z (%): 194 (78) [M^+], 166 (6), 111 (100), 83 (18), 57 (7); HRMS (EI): m/z: calcd for $C_9H_6OS_2$: 193.98546; found: 193.98529 [M^+].

Pyridin-3-ylthiophen-3-yl methanone: Yield 45%; m.p. 68°C; R_f=0.16 (EtOAc/heptane 1:2); ^{1}H NMR (300 MHz; [D$_6$]DMSO): δ=8.94 (d, J=1.4 Hz, 1H), 8.83 (dd, J=4.9, 1.4 Hz, 1H), 8.34 (dd, J=2.8, 1.4 Hz, 1H), 8.17 (dt, J=7.9, 2.0 Hz, 1H), 7.75 (dd, J=4.9, 2.8 Hz, 1H), 7.62 7.59 (m, 1H), 7.57 ppm (dd, J=4.9, 1.4 Hz, 1H); ^{13}C NMR (75 MHz; [D$_6$]DMSO): δ=187.9 (C=O), 152.9 (CH), 149.6 (CH), 140.3, 136.7 (CH), 136.6 (CH), 134.0, 128.2 (CH), 127.9 (CH), 123.9 ppm (CH); IR (KBr): $\tilde{\nu}$=3062 (s), 1650 (vs, C=O), 1586 (vs), 1512 (s), 1478 (m), 1419 (vs), 1389 (s), 1336 (w), 1284 (vs), 1197 (m), 1155 (m), 1025 (m), 977 (w), 967 (w), 885 (w), 859 (s), 845 (s), 825 (m), 746 (s), 713 (vs), 694 (s), 623 cm^{-1} (w); MS (70 eV): m/z (%): 189 (97) [M^+], 161 (10), 111 (100), 106 (7), 83 (18), 78 (21), 51 (25); HRMS (EI): m/z: calcd for $C_{10}H_7NOS$: 189.02429; found: 189.02382 [M^+].

3-Thiophen-3-yl-pyridine: Yield 30%; m.p. 70 71°C; R_f=0.24 (EtOAc/heptane 1:2); ^{1}H NMR (300 MHz; [D$_6$]DMSO): δ=8.98 (d, J=1.5 Hz, 1H), 8.49 (dd, J=4.9, 1.2 Hz, 1H), 8.11 (quasi dt, J=8.0, 1.2 Hz, 1H), 8.04 (dd, J=2.9, 1.5 Hz, 1H), 7.70 (quasi dd, J=4.9, 2.9 Hz, 1H), 7.65 (dd, J=4.9, 1.5 Hz, 1H), 7.43 ppm (quasi dd, J=8.0, 4.9 Hz, 1H); ^{13}C NMR (75 MHz; [D$_6$]DMSO): δ=148.2 (CH), 147.4 (CH), 138.4, 133.4 (CH), 130.9, 127.8 (CH), 126.2 (CH), 124.1 (CH), 122.4 ppm (CH); IR (KBr): $\tilde{\nu}$=3100 (s), 3077 (s), 3030 (s), 2924 (s), 1574 (s), 1527 (w), 1473 (s), 1431 (s), 1366 (m), 1322 (s), 1260 (m), 1223 (s), 1207 (m), 1182 (s), 1128 (w), 1080 (w), 1020 (s), 983 (w), 949 (m), 895 (m), 862 (vs), 822 (m), 797 (vs), 706 (vs), 641 cm^{-1} (s); MS (70 eV): m/z (%): 161 (100) [M^+], 134 (12), 117 (31), 108 (9), 89 (13), 63 (12); HRMS (EI): m/z: calcd for C_9H_7NS: 161.02937; found: 161.02929 [M^+].

4-Chlorophenyl 2-methoxyphenyl methanone: Yield 70%; m.p. 78°C; R_f=0.2 (EtOAc/heptane 1:10); ^{1}H NMR (400 MHz; [D$_6$]DMSO): δ=7.70 7.67 (m, 2H), 7.59 7.54 (m, 3H), 7.35 (dd, J=7.5, 1.8 Hz, 1H), 7.19 (d, J=8.2 Hz, 1H), 7.09 (td, J=7.5, 1.0 Hz, 1H), 3.67 ppm (s, 3H; OCH_3); ^{13}C NMR (75 MHz; [D$_6$]DMSO): δ=194.6 (C=O), 156.7, 138.1, 135.8, 132.3 (CH), 131.0 (CH), 128.9 (CH), 128.8 (CH), 127.8, 120.7 (CH), 112.0 (CH), 55.5 ppm (OCH_3); IR (KBr): $\tilde{\nu}$=3310 (w), 3086 (w), 3056 (m), 3018 (w), 2939 (m), 2838 (m), 1662 (vs, C=O), 1601 (vs), 1585 (vs), 1489 (vs), 1466 (vs), 1453 (s), 1432 (vs), 1399 (s), 1365 (w), 1304 (vs), 1296 (vs), 1266 (vs), 1244 (vs), 1178 (m), 1152 (s), 1111 (s), 1086 (vs), 1047 (s), 1024 (vs), 1013 (s), 972 (w), 941 (vs), 924 (vs), 848 (vs), 767 (s), 753 (vs), 742 (vs), 684 (m), 655 (s), 562 (m), 536 (m), 506 (s), 486 cm^{-1} (m); MS (70 eV): m/z (%): 246 (100) [M^+], 229 (60), 211 (75), 201 (17), 193 (23), 181 (17), 168 (27), 152 (19); HRMS (EI): m/z: calcd for $C_{14}H_{11}ClO_2$: 246.04421; found: 246.04437 [M^+]; elemental analysis calcd (%) for $C_{14}H_{11}ClO_2$: C 68.16, H 4.49; found: C 68.32, H 4.70.

4′-Chloro-2-methoxybiphenyl: Pale yellow oil; yield 31%; R_f=0.46 (EtOAc/heptane 0.5:20); ^{1}H NMR (300 MHz; [D$_6$]DMSO): δ=7.51 7.43 (m, 4H), 7.39 7.33 (m, 1H), 7.29 (dd, J=7.5, 1.7 Hz, 1H), 7.12 (d, J=8.3 Hz, 1H), 7.03 (td, J=7.5, 1.2 Hz, 1H), 3.76 ppm (s, 3H; OCH_3); ^{13}C NMR (75 MHz; [D$_6$]DMSO): δ=156.2, 137.1, 131.8, 131.2 (CH), 130.4 (CH), 129.5 (CH), 128.6, 128.2 (CH), 121.0 (CH), 112.0 (CH), 55.7 ppm (OCH_3); IR (KBr): $\tilde{\nu}$=3067 (w), 2936 (m), 2835 (m), 1502 (m), 1479 (vs), 1463 (s), 1436 (s), 1397 (m), 1256 (s), 1236 (s), 1180 (m), 1162 (m), 1123 (s), 1090 (vs), 1056 (m), 1028 (s), 1004 (s), 829 (m), 801 (w), 747 cm^{-1} (vs); MS (70 eV): m/z (%): 218 (89) [M^+], 203 (11), 183 (7), 168 (100), 152 (9), 149 (9), 139 (39); elemental analysis calcd (%) for $C_{13}H_{11}ClO$: C 71.40, H 5.07, Cl 16.21; found: C 71.55, H 4.82, Cl 15.9.

4-Methoxybenzophenone: Yield 75%; m.p. 52°C; R_f=0.2 (EtOAc/heptane 1:10); ^{1}H NMR (300 MHz; [D$_6$]DMSO): δ=7.76 (quasi d, J=9.0 Hz, 2H), 7.70 7.62 (m, 3H), 7.57 7.52 (m, 2H), 7.09 (quasi d, J=9.0 Hz, 2H), 3.86 ppm (s, 3H; OCH_3); ^{13}C NMR (75 MHz; [D$_6$]DMSO): δ=194.5 (C=O), 163.0, 137.8, 132.2 (CH), 132.1 (CH), 129.4, 129.3 (CH), 128.5 (CH), 113.9 (CH), 55.6 ppm (OCH_3); IR (KBr): $\tilde{\nu}$=3060 (w), 2934 (m), 2840 (m) 1653 (vs, C=O), 1600 (vs), 1577 (vs), 1508 (vs), 1446 (vs), 1420 (s), 1318 (vs), 1282 (vs), 1258 (vs), 1172 (vs), 1149 (m), 1112 (m), 1074 (w), 1029 (vs), 938 (s), 923 (vs), 844 (s), 793 (m), 740 (s), 702 (s), 678 (m), 600 cm^{-1} (s); MS (70 eV): m/z (%): 212 (42) [M^+], 135 (100), 105 (8), 92 (10), 77 (21); elemental analysis calcd (%) for $C_{14}H_{12}O_2$: C 79.22, H 5.70; found: C 78.92, H 5.77.

2,4′-Dimethoxybenzophenone: Colorless oil; yield 4%; R_f=0.17 (EtOAc/heptane 1:5); ^{1}H NMR (300 MHz; [D$_6$]DMSO): δ=7.66 (quasi d, J=9.0 Hz, 2H), 7.54 7.48 (m, 1H), 7.26 (dd, J=7.4, 1.9 Hz, 1H), 7.17 (d, J=8.1 Hz, 1H), 7.07 (dd, J=7.4, 0.9 Hz, 1H), 7.03 (quasi d, J=9.0 Hz, 2H), 3.83 (s, 3H; OCH_3), 3.68 ppm (s, 3H; OCH_3); ^{13}C NMR (75 MHz; [D$_6$]DMSO): δ=194.3 (C=O), 163.5, 156.5, 131.9 (CH), 131.7 (CH), 130.1, 129.1, 128.6 (CH), 120.7 (CH), 114.1 (CH), 112.0 (CH), 55.7 (OCH_3), 55.7 ppm (OCH_3); IR (KBr): $\tilde{\nu}$=3006 (m), 2964 (m), 2938 (m), 2845 (m), 2055 (w), 1918 (w), 1727 (m), 1654 (vs, C=O), 1600 (vs), 1576 (vs), 1509 (vs), 1486 (vs), 1465 (vs), 1450 (vs), 1422 (vs), 1306 (vs), 1296 (vs), 1257 (vs), 1195 (s), 1180 (vs), 1148 (vs), 1109 (s), 1046 (s), 1032 (vs), 942 (s), 925 (vs), 851 (vs), 789 (m), 771 (s), 756 (vs), 698 (m), 635 (m), 610 (vs), 586 (m), 561 (m), 513 cm^{-1} (m); MS (70 eV): m/z (%): 242 (40) [M^+], 225 (43), 211 (19), 197 (10), 135 (100), 121 (25), 107 (11), 92 (28), 77 (36), 64 (11); elemental analysis calcd (%) for $C_{15}H_{14}O_3$: C 74.36, H 5.82; found: C 74.38, H 5.82.

2-Methoxybenzophenone: Pale yellow oil; yield 73%; R_f=0.16 (EtOAc/heptane 1:10); ^{1}H NMR (300 MHz; [D$_6$]DMSO): δ=7.71 7.61 (m, 3H), 7.57 7.48 (m, 3H), 7.32 (dd, J=7.5, 1.9 Hz, 1H), 7.19 (d, J=7.9 Hz, 1H), 7.08 (td, J=7.5, 0.9 Hz, 1H), 3.67 ppm (s, 3H; OCH_3); ^{13}C NMR (75 MHz; [D$_6$]DMSO): δ=195.9 (C=O), 156.8, 137.3, 133.5 (CH), 132.2 (CH), 129.4 (CH), 128.9 (CH), 128.8 (CH), 128.6, 120.8 (CH), 112.2 (CH), 55.7 ppm (OCH_3); IR (KBr): $\tilde{\nu}$=3061 (m), 2942 (m), 2838 (m), 1667 (vs, C=O), 1599 (vs), 1581 (s), 1487 (vs), 1463 (vs), 1449 (vs), 1436 (vs), 1316 (vs), 1295 (vs), 1245 (vs), 1181 (m), 1163 (m), 1151 (m), 1110 (m), 1073 (w), 1048 (s), 1024 (s), 926 (vs), 807 (m), 756 (s), 703 (s), 636 cm^{-1} (s); MS (70 eV): m/z (%): 212 (48) [M^+], 195 (26), 181 (7), 167 (9), 152 (7), 135 (100), 121 (20), 105 (33), 92 (21), 77 (72), 63 (8), 51 (19); elemental analysis calcd (%) for $C_{14}H_{12}O_2$: C 79.22, H 5.70; found: C 79.11, H 5.37.

3-(2-Methoxybenzoyl)pyridine: Yellow oil; yield 64%; R_f=0.1 (EtOAc/heptane 1:3); ^{1}H NMR (300 MHz; [D$_6$]DMSO): δ=8.79 8.77 (m, 2H), 8.03 (quasi dt, J=3.4, 1.7 Hz, 1H), 7.63 7.53 (m, 2H), 7.42 (dd, J=7.5, 1.7 Hz, 1H), 7.21 (d, J=8.2 Hz, 1H), 7.12 (td, J=7.5, 0.9 Hz, 1H), 3.67 ppm (s, 3H, OCH_3); ^{13}C NMR (75 MHz; [D$_6$]DMSO): δ=194.9 (C=O), 157.1, 153.5 (CH), 150.2 (CH), 136.6 (CH), 133.2 (CH), 132.9, 129.6 (CH), 127.4, 124.0 (CH), 121.0 (CH), 112.4 (CH), 55.8 ppm (OCH_3); IR (KBr): $\tilde{\nu}$=3048 (m), 2964 (m), 2944 (m), 2839 (m), 1666 (vs, C=O), 1599 (vs), 1585 (vs), 1487 (vs), 1464 (s), 1437 (s), 1418 (s), 1329 (m), 1302 (vs), 1263 (vs), 1247 (vs), 1195 (w), 1182 (w), 1163 (m), 1112 (m), 1049 (m), 1024 (s), 928 (vs), 757 (vs), 714 (s), 648 cm^{-1} (s); MS (70 eV): m/z (%): 213 (32) [M^+], 196 (16), 184 (10), 168 (6), 135 (100), 106 (8), 92 (22), 77 (33), 63 (8), 51 (18); HRMS (EI): m/z: calcd for $C_{13}H_{11}NO_2$: 213.07843; found: 213.07781 [M^+].

3-(2-Methoxyphenyl)pyridine: Pale yellow oil; yield 4%; R_f=0.18 (EtOAc/heptane 1:3); ^{1}H NMR (300 MHz; $CDCl_3$): δ=8.78 (br s, 1H),

8.56 (d, J=3.8 Hz, 1H), 7.87 (dt, J=3.4, 1.8 Hz, 1H), 7.41 7.31 (m, 3H), 7.07 (td, J=7.5, 1.0 Hz, 1H), 7.02 (quasi d, J=8.2 Hz, 1H), 3.83 ppm (s, 3H; OCH_3); ^{13}C NMR (75 MHz; $CDCl_3$): δ=156.7, 150.5 (CH), 148.1 (CH), 137.0 (CH), 134.4, 130.8 (CH), 129.7 (CH), 127.2, 123.1 (CH), 121.2 (CH), 111.4 (CH), 55.7 ppm (OCH_3); IR (KBr): $\tilde{\nu}$=2937 (w), 2836 (w), 1731 (w), 1599 (m), 1583 (w), 1497 (s), 1463 (s), 1436 (s), 1406 (vs), 1266 (vs), 1237 (vs), 1180 (s), 1122 (vs), 1060 (m), 1049 (m), 1025 (vs), 999 (s), 801 (s), 752 (vs), 711 cm^{-1} (vs); MS (70 eV): m/z (%): 185 (100) [M^+], 170 (58), 141 (6), 115 (30), 89 (8), 63 (8); HRMS (EI): calcd for $C_{12}H_{11}NO$: 185.08352; found: 185.08319 [M^+].

2-(2-Methoxybenzoyl)benzonitrile: Yield 66%; m.p. 89 90°C; R_f=0.07 (EtOAc/heptane 1:5); ^{1}H NMR (300 MHz; [D$_6$]DMSO): δ=8.03 8.00 (m, 1H), 7.78 (quasi dd, J=5.4, 3.6 Hz, 2H), 7.66 7.60 (m, 1H), 7.58 7.55 (m, 1H), 7.52 (dd, J=7.6, 1.7 Hz, 1H), 7.19 (d, J=8.3 Hz, 1H), 7.13 (td, J=7.6, 1.0 Hz, 1H), 3.60 ppm (s, 3H; OCH_3); ^{13}C NMR (75 MHz; [D$_6$]DMSO): δ=193.8 (C=O), 158.1, 141.5, 134.8 (CH), 134.4 (CH), 133.2 (CH), 132.6 (CH), 130.6 (CH), 130.4 (CH), 126.7, 121.1 (CH), 117.7, 112.7 (CH), 109.7, 55.9 ppm (OCH_3); IR (KBr): $\tilde{\nu}$=3076 (w), 2959 (m), 2929 (m), 2837 (m), 2227 (s, CN), 1729 (m), 1661 (vs, C=O), 1601 (vs), 1571 (s), 1487 (vs), 1473 (s), 1456 (s), 1437 (s), 1381 (w), 1305 (vs), 1259 (vs), 1190 (m), 1161 (m), 1120 (s), 1098 (w), 1073 (w), 1023 (s), 947 (m), 931 (vs), 811 (m), 774 (vs), 751 (vs), 691 (m), 642 (vs), 558 (w), 493 cm^{-1} (w); MS (70 eV): m/z (%): 237 (72) [M^+], 220 (22), 208 (16), 181 (37), 135 (100), 130 (17), 102 (31), 92 (31), 77 (45), 63 (13), 51 (12); elemental analysis calcd (%) for $C_{15}H_{11}NO_2$: C 75.94, H 4.67, N 5.90; found: C 76.02, H 4.46, N 5.73.

2′-Methoxybiphenyl-2-carbonitrile: Colorless oil; yield 33%; R_f=0.27 (EtOAc/heptane 1:5); ^{1}H NMR (300 MHz; [D$_6$]DMSO): δ=7.88 (dd, J=7.7, 1.0 Hz, 1H), 7.75 (td, J=7.7, 1.3 Hz, 1H), 7.55 (dd, J=7.7, 1.0 Hz, 1H), 7.52 7.43 (m, 2H), 7.26 (dd, J=7.5, 1.7 Hz, 1H), 7.18 (d, J=8.2 Hz, 1H), 7.08 (td, J=7.5, 1.0 Hz, 1H), 3.77 ppm (s, 3H, OCH_3); ^{13}C NMR (75 MHz; [D$_6$]DMSO): δ=156.1, 141.9, 133.0 (CH), 132.7 (CH), 130.9 (CH), 130.6 (CH), 130.4 (CH), 127.9 (CH), 126.8, 120.6 (CH), 118.4, 112.4, 111.7 (CH), 55.4 ppm (OCH_3); IR (KBr): $\tilde{\nu}$=3066 (w), 2935 (m), 2837 (m, OCH$_3$), 2227 (s, CN), 1602 (s), 1583 (m), 1500 (vs), 1479 (vs), 1463 (vs), 1433 (vs), 1281 (vs), 1255 (vs), 1237 (vs), 1181 (m), 1163 (m), 1126 (s), 1100 (m), 1054 (s), 1026 (vs), 1004 (m), 808 (w), 755 (vs), 621 (w), 550 cm^{-1} (m); MS (70 eV): m/z (%): 209 (100) [M^+], 194 (11), 181 (51), 166 (18), 152 (10), 140 (35), 113 (7), 63 (7); elemental analysis calcd (%) for $C_{14}H_{11}NO$: C 80.40, H 5.30, N 6.69; found: C 77.16, H 5.23, N 6.17.

2,2′-Dimethoxybenzophenone: Yield 52%; m.p. 90 91°C; R_f=0.15 (EtOAc/heptane 1:5); ^{1}H NMR (300 MHz; [D$_6$]DMSO): δ=7.53 7.47 (m, 2H), 7.39 (dd, J=7.5, 1.9 Hz, 2H), 7.08 (d, J=8.3 Hz, 2H), 7.01 (td, J=7.5, 0.8 Hz, 2H), 3.58 ppm (s, 6H; 2OCH_3); ^{13}C NMR (75 MHz; [D$_6$]DMSO): δ=194.5 (C=O), 158.0, 133.1 (CH), 129.9, 129.7 (CH), 120.4 (CH), 112.2 (CH), 55.8 ppm (OCH_3); IR (KBr): $\tilde{\nu}$=3103 (m), 3074 (m), 2969 (s), 2944 (s), 2842 (m), 1728 (w), 1629 (vs), 1596 (vs), 1486 (vs), 1461 (vs), 1435 (vs), 1313 (vs), 1282 (vs), 1249 (vs), 1180 (vs), 1161 (vs), 1115 (s), 1049 (s), 1018 (vs), 945 (m), 930 (vs), 793 (m), 759 (vs), 690 (m), 635 (vs), 532 (m), 419 cm^{-1} (s); MS (70 eV): m/z (%): 242 (27) [M^+], 225 (15), 211 (17), 181 (11), 135 (100), 121 (23), 92 (26), 77 (37), 63 (11), 51 (8); elemental analysis calcd (%) for $C_{15}H_{14}O_3$: C 74.36, H 5.82; found: C 74.39, H 5.86.

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4.5 An efficient and practical sequential one-pot-synthesis of suprofen, ketoprofen and other 2-arylpropionic acids

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Contributions

In this paper, I contributed to the writing process of the manuscript and was involved in discussions. My contribution as co-author of this paper is approximately 15%.

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An Efficient and Practical Sequential One-Pot Synthesis of Suprofen, Ketoprofen and Other 2-Arylpropionic Acids

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Abstract: A novel sequential double carbonylation to synthesize anti-inflammatory drugs such as Ketoprofen and Suprofen has been developed. Starting from easily available aryl halides and arylboronic acids a one-pot carbonylative Suzuki and hydroxycarbonylation reaction sequence proceeds in good selectivity and high yield in the presence of the palladium/cata*CX*ium® A catalyst system. Applying optimized conditions different 2-arylpropionic acids were synthesized in good yields.

Keywords: homogeneous catalysis; hydroxycarbonylation; palladium; profenes; Suzuki carbonylation

Introduction

2-Arylpropionic acids constitute an important class of non-steroidal anti-inflammatory drugs (NSAID) and analgesic agents.[1] Ibuprofen, the prototype of the 2-arylpropionic acid family, was developed already in 1965 by Stuarts. Since then, a number of structurally related drugs such as Naproxen, Ketoprofen, and Suprofen have been established and are used for the treatment of diverse diseases.

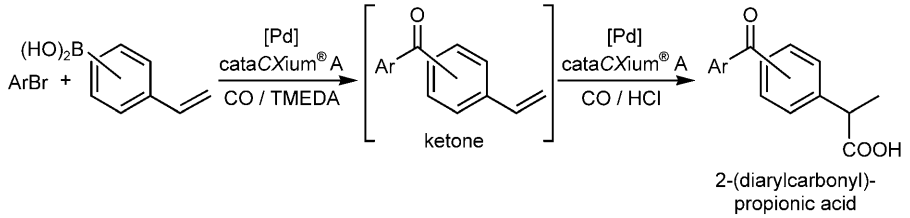
Among the various methods developed for the synthesis of 2-arylpropionic acids,[2] the acid-mediated and palladium-catalyzed hydroxycarbonylation of vinylarenes constitutes a straightforward and general approach towards profenes. Due to the commercial and pharmaceutical importance of these drugs, several papers and patents have been published on this subject. The range of known catalyst systems varies from simple $Pd(OAc)_2$-LiCl-TsOH[3], [Pd]-$CuCl_2$-H^+ in the presence of O_2[4] and phosphine ligands[5], $Pd(OAc)_2$ in the presence of mono- or diphosphines and oxalic acid,[6] to water-soluble Pd complexes containing trisulfonated triphenylphosphine.[7]

Recently, we developed a novel synthetic protocol for the preparation of diaryl ketones *via* carbonylative Suzuki coupling in the presence of $Pd(OAc)_2$/cata*CX*ium® A.[8] More specifically, we demonstrated that, at a low pressure of carbon monoxide, even vinyl-substituted diaryl ketones are formed in high yield starting from vinyl-substituted arylboronic acids and aryl bromides. Based on this methodology, we had the idea to combine carbonylative Suzuki reactions with a palladium-catalyzed hydroxycarbonylation (Scheme 1).

Such a one-pot protocol would circumvent the laborious industrial multi-step procedure for Ketoprofen[9] and Suprofen[10]. Here, we describe an efficient process for palladium-catalyzed sequential carbonylations towards various aryl propionic acids, e.g., Ketoprofen and Suprofen. We believe our protocol constitutes the shortest route to this type of profenes.

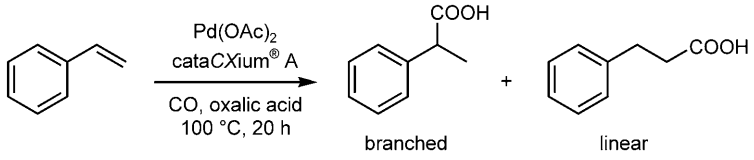
Results and Discussion

Initially, the palladium-catalyzed hydroxycarbonylation of styrene was studied as a model system. Since palladium/cata*CX*ium® A has been proven to be optimal for the carbonylative Suzuki reaction, we started



Scheme 1. A novel approach towards arylpropionic acids.

Table 1. Hydroxycarbonylation of styrene: Screening of reaction parameters.[a]



Entry	$Pd(OAc)_2$ [mol%]	Cata*CX*ium® A [mol%]	Solvent	CO [bar]	Conversion[b] [%]	Branched[c] [%]	Linear[c] [%]
1	0.75	4.5	DME	30	49	24	3
2	0.75	4.5	DME	5	31	3	0
3	0.75	4.5	dioxane	30	76	68	1
4	0.75	4.5	dioxane	10	57	40	2
5	0.75	4.5	dioxane	40	87	78	0
6	0.75	4.5	dioxane	50	83	76	0
7	0.50	1.5	dioxane	40	50	42	0
8	0.50	2.0	dioxane	40	64	56	0
9	0.50	3.0	dioxane	40	76	69	0
10[d]	0.75	4.5	dioxane	40	98	67	0
11[e]	0.75	4.5	dioxane	40	80	74	0

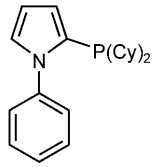
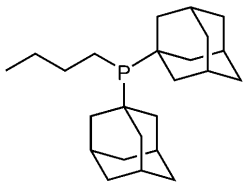
[a] *Reaction conditions:* 1 mmol styrene, 1 equiv. of oxalic acid, 0.5 0.75 mol% $Pd(OAc)_2$, 1.5 4.5 mol% cata*CX*ium® A, 2 mL solvent, 0.2 equiv. of hexadecane (internal standard), 5 50 bar CO, 100 °C, 20 h.
[b] Reaction mixture was used to determine the conversion by GC.
[c] A sample was esterified with MeOH and trimethylsilyldiazomethane to determine the yield by GC.
[d] Addition of 2 equiv. of H_2O.
[e] Addition of 2 equiv. of MeOH gave only 9% yield without esterification with trimethylsilyldiazomethane.

investigating this catalyst system.[11] Based on the results of Alper et al. and van Leeuwen et al.[6], we decided to examine the carbonylation reaction in the presence of oxalic acid (Table 1). Applying 0.75 mol% $Pd(OAc)_2$/4.5 mol% cata*CX*ium® A and one equiv. of oxalic acid, we obtained 24% of the desired branched 2-arylpropionic acid and 3% of the linear regioisomer in DME at 30 bar CO and 100 °C (Table 1, entry 1). When the CO pressure was reduced to 5 bar, the yield dropped to 3% (Table 1, entry 2). Advantageously, the yield was significantly improved by using dioxane as solvent. Thus, we obtained 68% of the desired product with >98% regioselectivity at 30 bar CO and 100 °C (Table 1, entry 3). Addition of two equiv. of H_2O did not change the yield (Table 1, entry 10). However, adding two equiv. of MeOH slightly increased the yield up to 74% (Table 1, entry 11). The optimum of yield was found at 40–50 bar CO (76–78%, Table 1, entries 5 and 6). Even in the presence of 0.5 mol% $Pd(OAc)_2$ 69% of the desired product was obtained (Table 1, entry 9). Next, we tested the influence of different ligands and acids in our optimized hydroxycarbonylation reaction (Table 2). Monodendate ligands such as cata*CX*ium PCy_2, PPh_3 and PCy_3 showed high regioselectivity, but the yield decreased to 30–58% (Table 2, entries 1, 3, and 5). In accordance with the results of van Leeuwen, we observed for the bidendate ligands DPPP and DPPF a shift towards the linear product, although the yield was low under these conditions (13-.24%, Table 2, entries 7 and 9). In contrast to the reactions with oxalic acid, the use of 37% HCl resulted in higher yield and full conversion since chloride ions are known to promote the hydroxycarbonylation.[5b] In the case of cata*CX*ium PCy_2 and PPh_3 the product was observed in 77% and 54%, respectively (Table 2, entries 2 and 4). Cata*CX*ium® A even furnished 94% of the branched acid (Table 2, entry 11)! On the other hand, only low yield (0–5%) was achieved in the presence of PCy_3 and the chelating ligands DPPP and DPPF (Table 2, entries 6, 8 and 10). Using either *p*-TSA or formic acid in the presence of cata*CX*ium® A caused lower conversion (32–37%) and yield (7–10%, Table 2, entries 12 and 13).

Applying the optimized conditions, Suprofen and Ketoprofen were synthesized in good to excellent yield (80 and 99%) from thiophen-2-yl 4-vinylphenyl ketone and phenyl 3-vinylphenyl ketone, respectively (Scheme 2). The starting material is obtained by Suzuki carbonylation of the corresponding aryl bromide and vinylboronic acids according to our previous protocol.[8] Since both single carbonylation reactions proceeded with high yield and selectivity in the presence of the same type of catalyst, we studied the possibility to run both reactions without any isolation of intermediates in one pot.

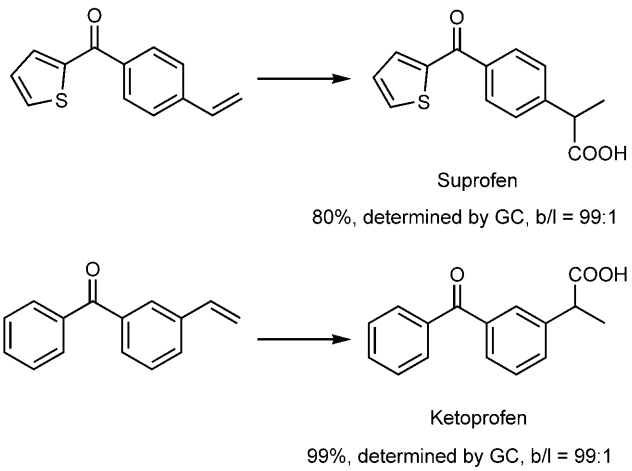
The conditions for the first step were adopted from the synthetic protocol for the Suzuki carbonylation. Instead of one equiv. of TMEDA, 0.75 equiv. of base were used. This reduced amount of TMEDA did not

Table 2. Hydroxycarbonylation of styrene: different ligands and acids.[a]

Entry	Ligand	Acid	Conversion[b] [%]	Branched[c] [%]	Linear[c] [%]
1		oxalic acid	36	30	0
2		37% HCl	100	77	0
	cataCXium PCy_2				
3	PPh_3	oxalic acid	37	30	0
4		37% HCl	100	54	2
5	PCy_3	oxalic acid	59	58	1
6		37% HCl	100	0	0
7	dppp	oxalic acid	56	2	13
8		37% HCl	100	4	0
9	dppf	oxalic acid	48	11	24
10		37% HCl	100	5	0
11		37% HCl	100	94	0
12		*p* TSA	37	10	1
13		98% formic acid	32	7	1
	cataCXium® A				

[a] *Reaction conditions:* 1 mmol styrene, 1 mmol acid, 0.75 mol% $Pd(OAc)_2$, 4.5 mol% of monodendate or 2.25 mol% of bi dendate ligand, 2 mL of dioxane, 0.2 mmol hexadecane (internal standard), 40 bar CO, 100 °C, 20 h.
[b] Reaction mixture was used to determine the conversion by GC.
[c] A sample was esterified with MeOH and trimethylsilyldiazomethane.

decrease the yield and should avoid an inhibition of the hydroxycarbonylation, which proceeds under acid conditions. After Suzuki carbonylation, one equiv. of 37% HCl in dioxane was added to the reaction mixture, which started the hydroxycarbonylation process. The results of the sequential double carbonylation process are summarized in Table 3. To our delight, the hydroxycarbonylation was not hampered and provided Suprofen (72%) and Ketoprofen (93%) with excellent selectivity (Table 3, entries 1 and 2). Our novel double carbonylation protocol was further successfully extended to other aryl bromides containing both electron-donating and electron-withdrawing substituents. Starting from 4-bromoanisole, 71% of the desired product was observed in the hydroxycarbonylation step and 45% over-all yield is achieved after esterification (Table 3, entry 3). 4-Trifluorobromobenzene provided 95% of product in the hydroxycarbonylation step and 70% isolated over-all yield after esterification (Table 3, entry 4). Finally, to demonstrate the feasibility of our approach on a larger scale we synthesized Ketoprofen on a 51-g scale with an over-all yield of 74%.



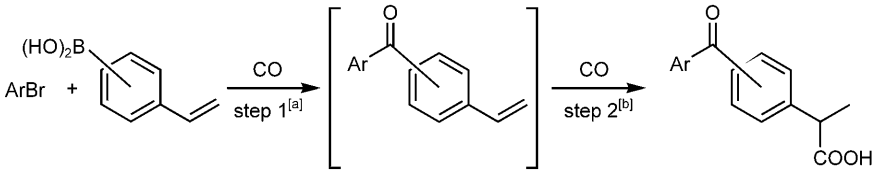
Reaction conditions: 1 mmol vinyl aryl ketone, 1 mmol 37% HCl, 0.75 mol% $Pd(OAc)_2$, 4.5 mol% cataCXium® A, 2 mL dioxane, 0.4 mmol hexadecane (internal standard), 40 bar CO, 100 °C, 20 h.

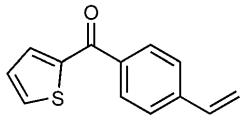
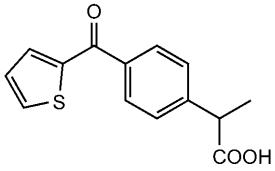
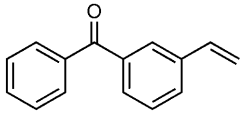
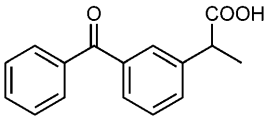
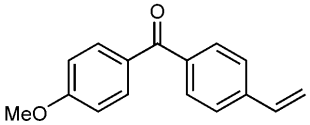
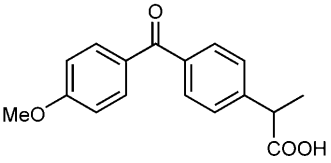
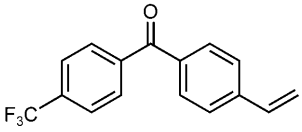
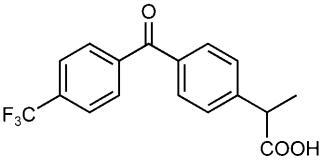
Scheme 2. Synthesis of Suprofen and Ketoprofen.

Conclusions

In conclusion, we have developed a novel synthetic protocol for pharmaceutically important profenes,

Table 3. One pot Suzuki carbonylation hydroxycarbonylation sequence.



Entry	Ketone[a]	Con version [%]	Yield [%]	2 (Diarylcarbonyl) propionic acid[b]	Con version[c] [%]	Branched[d] [%]	Linear[d] [%]	Yield[e] [%]
1		100	97		98	72	2	68
2		81	70		100	93	2	60
3		100	68		100	71	8	45
4		100	78		95	95	2	70

[a] *Reaction conditions:* 10 mmol ArBr, 15 mmol vinyl boronic acid, 7.5 mmol TMEDA, 0.75 mol% $Pd(OAc)_2$, 4.5 mol% cata*CX*ium® A, 10 mL toluene, 2 mmol hexadecane (internal standard), 2.5 bar CO, 80 °C, 24 h; in the case of 4 bromo anisole a temperature of 100 °C was required.
[b] *Reaction conditions:* 15 mL dioxane, 10 mmol 37% HCl, 40 bar CO, 100 °C, 20 h.
[c] Reaction mixture was used to determine the conversion.
[d] A sample was esterified with MeOH and trimethylsilyldiazomethane to determine the yield by GC.
[e] Isolated over all yield of branched methyl ester.

which includes two different catalytic carbonylation reactions. Both the Suzuki carbonylation and the hydroxycarbonylation are catalyzed by the same catalyst system [$Pd(OAc)_2$/cata*CX*ium® A] and can be carried out efficiently in one pot.

Experimental Section

All reactions were carried out under an argon atmosphere using Schlenk techniques. DME and dioxane were distilled from calcium hydride under argon. Toluene was distilled from sodium and benzophenone ketyl. Chemicals were purchased from Aldrich, Fluka and Strem and were used without further purification. Cata*CX*ium® A was provided by Evonik Industries. *m* Vinylbenzeneboronic acid[12] was synthesized from *m* bromostyrene[13] which was obtained from commercially available 3 bromo α methylbenzyl alcohol. Column chromatography was performed on Silica gel 60 (230 400 mesh). Gas chromatography was done on a Hewlett Packard HP 6890 chromatograph with a HP5 column. NMR data were obtained from a Bruker ARX 300. ^1H and ^{13}C NMR spectra are referenced to the residual solvent signals. IR spectra of compounds were recorded using ATR method on a Nicolet Magna 550. Mass spectroscopy was performed on a 5973 Network Mass Selective Detector from Agilent Technologies. Elemental analyses were determined uisng a TruSpec® micro analysator from Leco.

Experimental Procedure for the Ligand and Acid Screening

The reaction was carried out in a 300 mL autoclave from the 4560 series of Parr Instruments®. The autoclave contained an alloy plate to hold six 4 mL glass vials. The vials

were charged with 4.5×10^{-2} mmol (4.5 mol%) monodentate ligand or with 2.25×10^{-2} mmol (2.25 mol%) bidentate ligand and a magnetic stirring bar. The vials were closed *via* septums containing an inlet needle and were flushed with argon. When solid acids were used, 1 mmol *p* TSA or 1 mmol oxalic acid were added to the vials. 2.17 mL of stock solution containing styrene (1.15 mL, 10 mmol), $Pd(OAc)_2$ (16.8 mg, 0.075 mmol), hexadecane (590 μL, 2 mmol) and 20 mL of dioxane were added to each vial by syringe. Subse quently, in the case of liquid acids 1 mmol of 37% HCl or 1 mmol of 98% formic acid was added to the solution. Then, the alloy plate was transferred into the autoclave. The sealed autoclave was purged with CO several times and pressurized with 5 50 bar CO at room temperature. After wards, it was heated to 100 °C and the reaction was run for 20 h at this temperature. In order to determine the yield by GC, a sample of 100 μL of each reaction solution was esteri fied with trimethylsilyldiazomethane in the presence of 100 μL MeOH. Since trimethylsilyldiazomethane reacts sometimes with vinylarenes, a sample of the reaction solu tion with one aliquot of MeOH was taken without addition of trimethylsilyldiazomethane to determine the conversion by GC.

Experimental Procedure for the Sequential Double Carbonylation in One Pot

A 100 mL Schlenk flask was charged with $Pd(OAc)_2$ (16.8 mg, 0.075 mmol), cata*CX*ium® A (161.3 mg, 0.45 mmol) and a stirring bar. The flask was evacuated, filled with argon three times and 10 mL toluene were added. The yellow solution was stirred for 10 min. Then, hexade cane (590 μL, 2 mmol), aryl bromide (10 mmol), and TMEDA (1.12 mL, 7.5 mmol) were added. Meanwhile, a 100 mL autoclave was charged with vinylboronic acid (15 mmol, 2.22 g), evacuated and filled with argon three times. Subsequently, the yellow solution was transferred to the autoclave *via* syringe. After the autoclave had been purged with CO several times, the reaction was run at 2.5 bar CO and at 80 100 °C. After 24 h the reaction was fin ished. The autoclave was cooled to ambient temperature and a sample was taken to determine the yield of the first step by GC. Without opening the autoclave, a solution of di oxane (15 mL) and 37% HCl (832 μL, 10 mmol) was trans ferred by syringe into the autoclave. The second reaction was carried out at 40 bar CO and 100 °C for 20 h. After cooling to room temperature, the reaction solution was transferred to a 250 mL round bottom flask containing 50 mL MeOH. From this solution, 200 μL were reacted with trimethylsilyldiazomethane to give the corresponding ester. Subsequently, the reaction solution was filtered, 98% H_2SO_4 (110 μL) was added and the solution was refluxed for 5 h. Finally, the solvent was evaporated and the formed ester was further purified by chromatography or crystallization.

Experimental Procedure for the 51-g Scale Synthesis of Ketoprofen

According to our synthetic protocol for 2 (diarylcarbonyl) methyl propionate, we charged a 2 L autoclave with bromo benzene (21.02 mL, 200 mmol). We obtained 39.8 g (74%) of the methyl ester of Ketoprofen. To isolate the free acid, we added 50 mL of 20% NaOH solution and 50 mL of MeOH. The mixture was refluxed for 1 h and MeOH was removed under vacuum. The solution was acidified to pH 2 by 2 N HCl, extracted with diethyl ether three times and washed with brine. After drying with $NaSO_4$, the solvent was removed and 37.4 g (73.5%) of a viscous yellow product was obtained.

Methyl Ester of Ketoprofen: Yield: 60%; light yellow oil; R_f (EE/heptane = 1:10): 0.17; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.82 7.80 (m, 2H, 2CH), 7.75 (dd, J = 1.6 Hz, 1H, CH), 7.68 (dpt, J = 7.5, 1.6 Hz, 1H, CH), 7.63 7.56 (m, 1H, CH), 7.54 (dpt, J = 7.7, 1.6 Hz, 1H, CH), 7.51 7.40 (m, 3H, 3CH), 3.81 (q, J = 7.3 Hz, 1H, C*H*CH_3), 3.68 (s, 3H, OCH_3), 1.54 (d, J = 7.3 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.9 and 175.0 (2CO), 141.3, 138.4 and 137.9 (3C), 132.9, 131.9, 130.0, 130.0, 129.2, 129.0, 128.5, 128.3, 128.3 (9CH), 52.1 and 45.2 (*C*HCH_3, OCH_3), 18.5 (CH_3); MS (70 eV): m/z (%) = 268 (42) [M^+], 209 (100), 191 (23), 105 (51), 77 (36); IR (ATR): ν_{max} = 2950 (w), 1734 (s), 1657 (s), 1597 (w), 1580 (w), 1447 (m), 1434 (m), 1317 (m), 1281 (s), 1207 (s), 1165 (s), 1075 (m), 1024 (w), 999 (w), 978 (w), 950 (m), 859 (w), 820 (w), 788 cm^{-1} (w); anal. calcd. for $C_{17}H_{16}O_3$: C 76.10, H 6.01; found: C 76.07, H 6.22.

Methyl Ester of Suprofen: Yield: 68%; light yellow solid, mp 53 °C; R_f (EE/heptane = 1:5): 0.19; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.84 (d, J = 8.5 Hz, 2H, CH), 7.42 (d, J = 8.5 Hz, 2H, CH), 7.72 (dd, J = 4.9, 1.2 Hz, 1H, CH), 7.65 (dd, J = 3.8, 1.2 Hz, 1H, CH), 7.16 (dd, J = 4.9, 3.8 Hz, 1H, CH), 3.82 (q, J = 7.2 Hz, 1H, C*H*CH_3), 3.69 (s, 3H, OCH_3), 1.55 (d, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 187.7 and 174.3 (2CO), 144.9, 143.6 and 137.0 (3C), 134.8, 134.2, 129.7, 129.7, 128.0, 127.7, 127.7 (7CH), 52.3 and 45.5 (*C*HCH_3, OCH_3), 18.5 (CH_3); MS (70 eV): m/z (%) = 274 (56) [M^+], 215 (100), 111 (53), 103 (10); IR (ATR): ν_{max} = 3099 (w), 2947 (w), 1727 (s), 1630 (s), 1604 (m), 1514 (w), 1431 (w), 1414 (s), 1326 (w), 1284 (s), 1261 (s), 1232 (m), 1203 (s), 1161 (s), 1128 (w), 1085 (w), 1060 (m), 1012 (w), 964 (w), 886 (w), 866 (m), 845 (m), 807 (w), 774 (w), 737 (s), 695 cm^{-1} (w); anal. calcd. for $C_{15}H_{14}O_3S$: C 65.67, H 5.14, S 11.69; found: C 65.89, H 5.11, S 11.73.

Methyl 2-[4-(4-methoxybenzoyl)phenyl]propionate: Yield: 45%; light yellow oil; R_f (EE/heptane = 1:10): 0.15; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.82 (d, J = 8.9 Hz, 2H, Ph), 7.72 (d, J = 8.4 Hz, 2H, Ph), 7.40 (d, J = 8.4 Hz, 2H, Ph), 6.96 (d, J = 8.9 Hz, 2H, Ph), 3.88 (s, 1H, OCH_3), 3.81 (q, J = 7.2 Hz, 1H, C*H*CH_3), 3.69 (s, 1H, OCH_3), 1.54 (d, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 195.1 and 174.5 (2CO), 163.3, 144.6, 137.2 and 130.1 (4C), 132.6, 130.2, 127.4 and 113.6 (4CH), 55.5, 52.3 and 45.5 (2 OCH_3, *C*HCH_3), 18.5 (CH_3); MS (70 eV): m/z (%) = 298 (95) [M^+], 239 (81), 211 (32), 191 (17), 135 (100), 103 (10), 77 (16); IR (ATR): ν_{max} = 2979 (w), 2951 (w), 1734 (s), 1649 (m), 1598 (s), 1508 (w), 1456 (w), 1416 (w), 1305 (m), 1281 (m), 1252 (s), 1208 (m), 1169 (s), 1147 (s), 1116 (w), 1068 (w), 1026 (m), 965 (w), 928 (s), 840 (m), 773 (m), 753 (m), 687 cm^{-1} (m); anal. calcd. for $C_{18}H_{18}O_4$: C 72.47, H 6.08; found: C 72.66, H 6.01.

Methyl 2-[4-(4-trifluoromethylbenzoyl)phenyl]propionate: Yield: 70%; light yellow oil; R_f (EE/heptane = 1:10): 0.10; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.89 (d, J = 8.3 Hz, 2H, Ph), 7.80 7.72 (m, 4H, Ph), 7.44 (d, J = 8.3 Hz, 2H, Ph), 3.83 (q, J = 7.2 Hz, 1H, C*H*CH_3), 3.69 (s, 1H, OCH_3), 1.55 (d, J =

7.2 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 195.0$ and 174.2 (2CO), 145.9, 140.7, 135.6 (3C), 133.7 (q, $^2J(C,F) = 32$ Hz, C), 130.5, 130.1 and 127.8 (3CH), 125.3 (q, $^3J(C,F) = 3.9$ Hz, CH), 120.1 (q, $^1J(C,F) = 174$ Hz, CF_3), 52.2 and 45.4 (OCH_3, $CHCH_3$), 18.4 (CH_3); MS (70 eV): *m/z* (%) = 336 (34) [M^+], 277 (100), 191 (15), 173 (45), 145 (28); IR (ATR): $\nu_{max} = 2984$ (w), 2953 (w), 1736 (m), 1663 (m), 1606 (s), 1408 (w), 1323 (s), 1311 (s), 1277 (s), 1209 (m), 1164 (s), 1125 (s), 1109 (s), 1064 (s), 1017 (m), 930 (s), 860 (m), 773 (m), 757 (m), 690 cm^{-1} (m); anal. calcd. for $C_{18}H_{15}F_3O_3$: C 64.28, H 4.50; found: C 64.49, H 4.65.

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4.6 Palladium-catalyzed reductive carbonylation of aryl triflates with synthesis gas

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Contributions

In this paper, I planned, performed and analyzed all experiments. I wrote the manuscript and was involved in discussions. My contribution as co-author of this paper is approximately 85%.

Palladium-Catalyzed Reductive Carbonylation of Aryl Triflates with Synthesis Gas

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Abstract: A general palladium-catalyzed reductive carbonylation of aryl triflates in the presence of synthesis gas (CO/H_2) has been developed. The reaction with this most simple and environmentally benign formylation source proceeds under mild conditions and various aromatic aldehydes have been prepared in good to high yield.

Key words: carbonylation, palladium, aryl triflates, aldehydes, homogenous catalysis

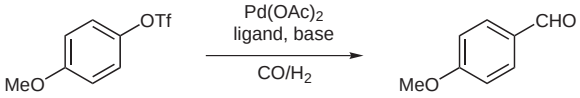
Vinyl and aryl trifluoromethanesulfonates (triflates) offer a highly reactive leaving group and therefore are often used as versatile intermediates in modern organic synthesis, particularly in the preparation of biologically active compounds.[1] In general, palladium-catalyzed coupling reactions of aryl triflates allow for various functionalizations of the corresponding arene. Among the different known coupling reactions of aryl triflates, the palladium-catalyzed carbonylation provides in principle an elegant and simple route to aromatic aldehydes, carboxylic acids,[2] and the corresponding esters[3] or amides.[4]

Today, a variety of catalysts are available for the alkoxy- and aminocarbonylation of aryl triflates, but there are only few general protocols concerning the synthetically more interesting formylation of these substrates.

The first catalytic formylation reaction of enol triflates was reported by Baillargeon and Stille in 1986 using tin hydride and carbon monoxide.[5] Under relatively mild conditions (50 °C, 1–3 atm of CO, and 2.5–3.5 h reaction time) few α,β-unsaturated aldehydes were prepared in good yields. Later on, the original work of Stille has been improved by employing organosilanes instead of tin hydride as hydrogen donor.[6]

Only little work has been done using synthesis gas (CO/H_2), which represents the most simple and cheap formylation source. To the best of our knowledge, only Holzapfel et al. reported a reductive carbonylation of (hetero)aryl triflates with CO/H_2.[7] However, the main drawback of this protocol is the limited scope explored.

For some years, we have been interested in the development of practical Pd catalysts and their use in different coupling reactions.[8] As examples we developed novel biarylphosphines and adamantylphosphines.[9] Palladium/di-adamantyl-*n*-butylphosphine (cata*CX*ium® A), especially, is a powerful catalyst system that is active in Heck,[10] Suzuki coupling reactions,[11] amination,[12] and cyanation[13] of aryl chlorides, as well as α-arylation of ketones with chloroarenes.[14] More recently, we successfully employed this catalyst system in reductive carbonylations,[15] as well as in alkoxycarbonylations[16] of aryl and heteroaryl bromides. Encouraged by these results and in order to overcome the limitations of known procedures, we became interested in the formylation of aryl triflates. Herein, we describe our investigations which led to a convenient novel reductive carbonylation procedure of aryl triflates.[17,18]



Scheme 1 Reductive carbonylation of the model substrate

Initially, the formylation of 4-methoxyphenyl trifluoromethanesulfonate to give 4-methoxybenzaldehyde was investigated as model system in the presence of eight different phosphine ligands (Scheme 1). Typically, all experiments were carried out in a modified sixfold parallel autoclave (reaction volume of 4 mL), which allows fast testing of catalysts and variation of reaction conditions. Selected results of the ligand screening are shown in Table 1. In contrast to aryl halides[19] only the bidentate ligands 1,2-bis(diphenylphosphino)ethane (dppe) and 1,3-bis(diphenylphosphino)propane yielded the desired 4-methoxybenzaldehyde (23–31% yield, Table 1, entries 1 and 2). Further extension of the alkyl chain of this ligand scaffold did not improve conversion and yield. Bulky monodentate (cata*CX*ium® A) and bidentate (BINAP) phosphine ligands did not lead to significant conversion and aldehyde formation (Table 1, entries 14 and 15).

After having found a suitable ligand for the model system, we investigated the influence of base more carefully (Table 1, entries 2–9). Among the different amines tested, pyridine gave the best results (57% yield; 79% selectivity) (Table 1, entry 4). In general, inorganic bases, for example K_2CO_3, gave full conversion, but only low selectivity for the aldehyde. Here, the carboxylic acid is produced as major side product.

Figure 1 demonstrates the influence of the synthesis gas pressure and the substrate concentration on the yield of the model system. At lower CO/H_2 pressure (5 bar)

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Table 1 Palladium-Catalyzed Formylation of 4-Methoxyphenyl Trifluoromethanesulfonate[a]

Entry	Ligand	Base	Conversion (%)[b]	Yield (%)[b]	Selectivity (%)[b]
1	dppe	Et_3N	79	23	29
2	dppp	Et_3N	94	31	33
3	dppp	TMEDA	100	36	36
4	dppp	Pyridine	73	57	79
5	dppp	Bn_3N	46	36	78
6	dppp	DABCO	85	8	10
7	dppp	K_2CO_3	100	9	9
8	dppp	Cs_2CO_3	100	6	6
9	dppp	NaOAc	100	10	10
10[c]	dppb	Et_3N	16	0	0
11	dpppentane	Et_3N	20	0	0
12	dpphexane	Et_3N	8	0	0
13	dppf	Et_3N	49	0	0
14	BINAP	Et_3N	18	0	0
15[d]	cata*CX*ium® A	Et_3N	1	0	0

[a] Reaction conditions: 4-methoxyphenyl trifluoromethanesulfonate (0.5 mmol), $Pd(OAc)_2$ (1.5 mol%), ligand (2.25 mol%), base (1.5 equiv), 2-butoxyethyl ether (0.7 equiv; internal standard), DMF (2 mL), CO/H_2 (5 bar, 1:1), 100 °C, 16 h.
[b] Determined by gas chromatography.
[c] Toluene as solvent.
[d] 4.5 mol% cata*CX*ium® A.

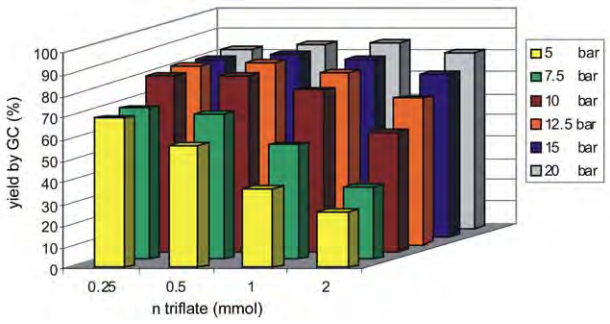

Figure 1 Influence of synthesis gas pressure and substrate concentration on the yield of 4-methoxybenzaldehyde

decreasing the substrate concentration significantly improved the yield of 4-methoxybenzaldehyde.

Further investigations showed that this effect is minimized when a higher synthesis gas pressure (>10 bar) is used.

Next, we studied the scope and limitations of the catalyst system (Table 2). In general, product yields in between 50–92% are obtained. In addition to the model substrate, aryl triflates with different functional groups in the *para* position are formylated successfully. In general, electron-rich substituents (e.g., *p*-tolyl triflate, 3,5-di-*tert*-butylphenyl triflate) decrease the reactivity compared to electron-deficient substrates (e.g., *p*-trifluoromethylphenyl triflate, *p*-chlorophenyl triflate). The protocol works well also for 1-naphthyl triflate, 2-naphthyl triflate, and 3-trifluoromethyl-sulfonyloxyestra-1,3,5(10)-trien-17-one (Table 2, entries 11, 12, 16). The presence of *ortho* substituents led to a decreased yield of the corresponding aldehyde since these triflates are less reactive towards formylation than the corresponding *para* isomers. Nevertheless, prolonging the reaction time from 24 hours to 60 hours, *o*-tolualdehyde is obtained in 85% yield (Table 2, entry 3). Unfortunately, a change in reaction time and synthesis gas mixture did not improve the yield of *o*-formylbenzonitrile (Table 2, entry 14).

From a synthetic perspective it is noteworthy that the reductive carbonylation of 4-methoxyphenyl trifluoromethanesulfonate can be carried out in situ as well.

Without optimization the one-pot sulfonylation–carbonylation sequence furnished 4-methoxybenzaldehyde in 44% yield (Scheme 2; Table 2, entry 1). This constitutes, to the best of our knowledge, the first one-pot carbonylation of a phenol derivative.

In conclusion, we have demonstrated that aryl triflates are successfully carbonylated with available and environmentally benign synthesis gas in the presence of Pd/dppp. The shown palladium-catalyzed reductive carbonylation represents a useful method for the synthesis of aromatic aldehydes from readily available phenols.

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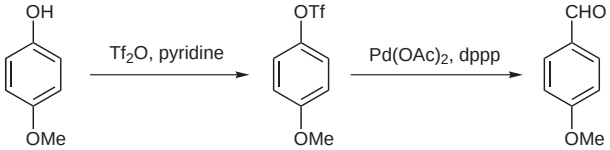
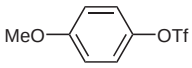
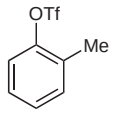
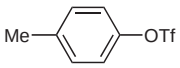
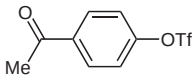
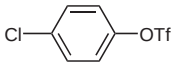
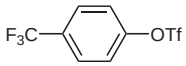
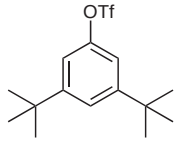
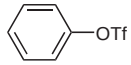
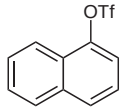
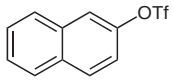
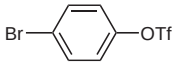
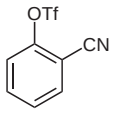
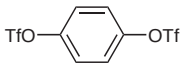
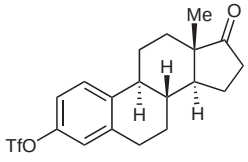


Scheme 2 In situ synthesis of 4-methoxybenzaldehyde[18]

Table 2 Scope and Limitations of the Catalyst System[a]

Entry	Aryl triflate	Temp (°C)	Conversion (%)[b]	Yield (%)[b]	Selectivity (%)[b]
1[c]		100	85	44	52
2		100	98	80	81
3[d]		80	85	85	99
4		100	100	45	45
5		100	99	76	77
6[c]		80	100	92	92
7		80	97	91	93
8[d]		80	100	87	87
9		100	68	53	79
10		100	100	65	65
11		80	100	50	50
12		80	100	69	69
13[d]		80	48	41	86
14[d,e]		80	100	16	16
15[d]		80	96	67	70
16[f]		100	90	49	55

[a] Reaction conditions: aryl triflate (1 mmol), $Pd(OAc)_2$ (1.5 mol%), dppp (2.25 mol%), pyridine (1.5 equiv), 2-butoxyethyl ether (0.7 equiv; internal standard), DMF (2 mL), CO/H_2 (20 bar, 1:1), 24 h.
[b] Determined by gas chromatography.
[c] In situ synthesis of 4-methoxybenzaldehyde.
[d] Reaction time 60 h.
[e] CO/H_2 (3:1): 20 bar.
[f] Isolated yield.

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(17) Aryl triflates were prepared from the corresponding phenols by a well-established method: Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 5478.

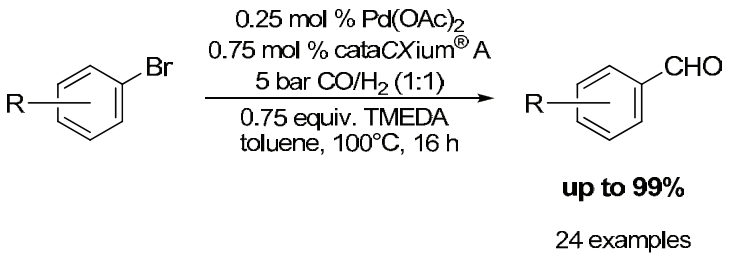
(18) A 50 mL round-bottom flask was charged with 4-methoxyphenol (1.86 g, 15 mmol) and sealed with a septum. Subsequently, pyridine (15 mL) was added. The clear solution was cooled to 0 °C and trifluoromethanesulfonic anhydride (2.8 mL, 17 mmol) was added dropwise. The resulting orange solution was stirred over night at r.t. Another 10 mL Schlenk flask was charged with $Pd(OAc)_2$ (50.5 mg, 1.5 mol%), 1,3-bis(diphenylphosphino)propane (139.2 mg, 2.25 mol%), DMF (5 mL), and 2-butoxyethyl ether (2.61 mL, internal GC standard). Both solutions were combined and transferred to a 100 mL autoclave of the 4560 series from Parr Instruments® under argon atmosphere. After flushing the autoclave three times with CO/H_2 (1:1), 20 bar of synthesis gas were adjusted at ambient temperature and the reaction was performed for 24 h at 100 °C. Before and after the reductive carbonylation an aliquot of the reaction mixture was subjected to GC analysis for determination of yield and conversion.

(19) For previous work on palladium-catalyzed carbonylations of aryl halides applying CO, see for example: (a) Ashfield, L.; Barnard, C. F. J. *Org. Process Res. Dev.* **2007**, *11*, 39. (b) Cai, M.-Z.; Zhao, H.; Zhou, J.; Song, C.-S. *Synth. Commun.* **2002**, *32*, 923. (c) Schnyder, A.; Beller, M.; Mehltretter, G.; Nsenda, T.; Studer, M.; Indolese, A. F. *J. Org. Chem.* **2001**, *66*, 4311. (d) Bates, R. W.; Gabel, C. J.; Ji, J.; Rama-Devi, T. *Tetrahedron* **1995**, *51*, 8199. (e) Hartman, G. D.; Halczenko, W. *Synth. Commun.* **1991**, *21*, 2103. (f) Mutin, R.; Lucas, C.; Thivolle-Cazat, J.; Dufaud, V.; Dany, F.; Basset, J. M. *J. Chem. Soc., Chem. Commun.* **1988**, 896. (g) See ref. 5. (h) Pri-Bar, I.; Buchman, O. *J. Org. Chem.* **1984**, *49*, 4009. (i) Baillargeon, V. P.; Stille, J. K. *J. Am. Chem. Soc.* **1983**, *105*, 7175. (j) Schoenberg, A.; Heck, R. F. *J. Am. Chem. Soc.* **1974**, *96*, 7761.

5 Summary

In conclusion, we have successfully established the catalyst system palladium acetate/di-1-adamantyl-*n*-butylphosphine (cata*CX*ium® A) in diverse palladium-catalyzed carbonylation reactions such as reductive carbonylations, alkoxycarbonylations and carbonylative coupling reactions. Advantageously, carbon monoxide could be used as simple and environmentally benign building block. Our catalyst system is highly active and easy to handle since the commercially available ligand is stable towards air and moisture.

In ″Tetrahedron″ (Publication 4.1, **2007**), the general and efficient palladium-catalyzed reductive carbonylation of aryl halides employing the most simple and environmentally benign formylation source, synthesis gas, is described in detail. The formylation of aryl and heteroaryl bromides proceeded smoothly in the presence of $Pd(OAc)_2$/cata*CX*ium® A under comparatively low pressure of CO/H_2 (5 bar) to afford a variety of aromatic and heteroaromatic aldehydes in good yields and excellent selectivity (Scheme 45). Remarkably, only low catalyst loadings (0.25 mol % Pd or below) were required. In addition, the synthetic protocol was successfully applied to vinyl halides which led to the formation of α,β-unsaturated aldehydes in 41-98% yield. Thus, our investigations resulted in the most general, active, and productive palladium catalyst known to date for the reductive carbonylation of aryl and vinyl halides.

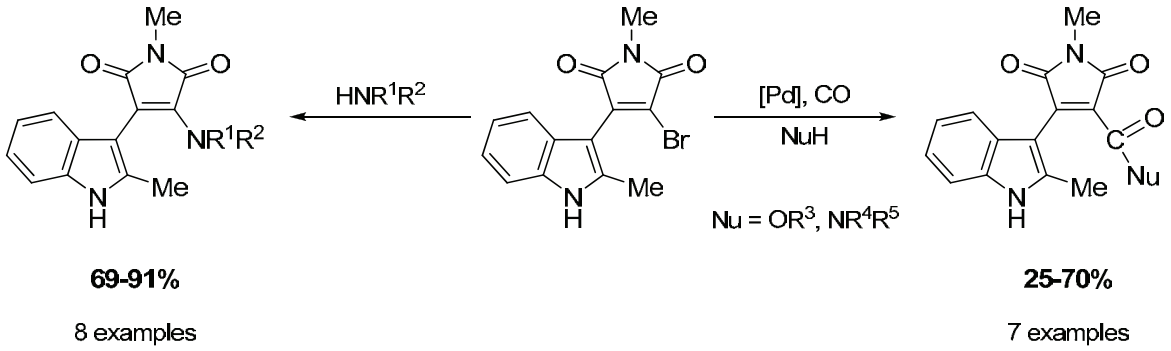


Scheme 45. Reductive carbonylation of (hetero)aryl bromides in the presence of cata*CX*ium® A.[83a,86]

Encouraged by these results, we focused on the palladium-catalyzed alkoxycarbonylation of (hetero)aryl halides. An initial catalyst screening for the butoxycarbonylation of three model substrates revealed once again the advantages of cata*CX*ium® A compared to other ligands. Due to its superior performance, the catalyst system was used to synthesize various

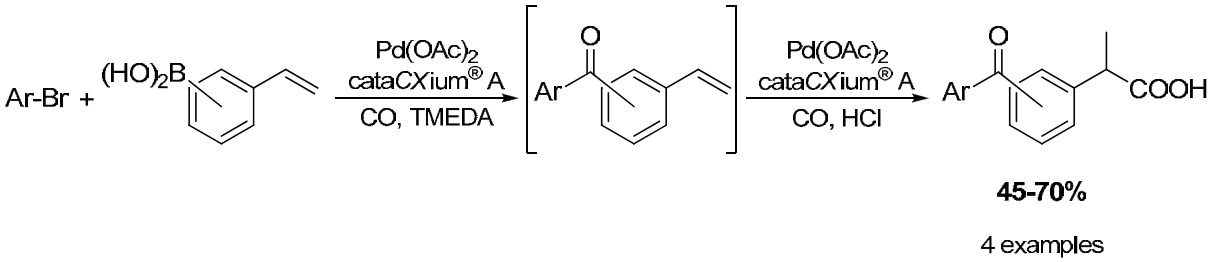
aromatic and heteroaromatic esters, amides, and acids from the corresponding bromides under mild reaction conditions (Publication 4.2, *Adv. Synth. Catal.* **2006**). For example, high conversion (>95%) and excellent selectivity (>98%) were observed for the butoxycarbonylation of several mono-substituted bromoarenes.

Based on our experiences in carbonylation chemistry and transition metal-catalyzed syntheses of indoles, we decided to investigate functionalization reactions of indolylmaleimides (Publication 4.3, *Eur. J. Org. Chem.* **2008**, and Scheme 46). Thus, novel potentially bioactive 3-alkoxycarbonyl- and 3-aminocarbonyl-4-indolylmaleimides have been prepared by Pd-catalyzed carbonylation of 3-bromo-1-methyl-4-(2-methyl-3-indolyl)-maleimide with alcohols and amines in the presence of cata*CX*ium® A and carbon monoxide. Furthermore, it was shown that there was no need for a palladium catalyst to produce novel 3-amino-4-indolylmaleimides in good yields (69-91%).



Scheme 46. Catalytic and stoichiometric synthesis of novel indolylmaleimides.[34]

In addition, we presented a novel synthetic protocol for the preparation of diaryl-, diheteroaryl-, and aryl heteroaryl ketones via carbonylative Suzuki coupling in the presence of $Pd(OAc)_2$/cata*CX*ium® A (Publication 4.4, *Chem. Eur. J.* **2008**). Remarkable features of our catalyst were its high selectivity and improved productivity. At a low pressure of carbon monoxide, even vinyl-substituted diarylketones were formed in high yields starting from vinyl-substituted arylboronic acids and aryl bromides. Based on this work, we developed an efficient and practical sequential one-pot synthesis of pharmaceutically important suprofen, ketoprofen and other 2-arylpropionic acids by combining the carbonylative Suzuki reaction with a palladium-catalyzed hydroxycarbonylation (Publication 4.5, *Adv. Synth. Catal.* **2008**, Scheme 47). We believe our protocol constitutes the shortest route to this type of profenes.



Scheme 47. Sequential one-pot synthesis of 2-arylpropionic acids.[104]

Finally, we reported a convenient novel reductive carbonylation of aryl triflates with synthesis gas (Publication 4.6, *Synlett* **2007**). Under mild conditions, various aromatic aldehydes were obtained in good to high yields by employing palladium acetate and 1,3-bis-(diphenylphosphino)propane (dppp). From a synthetic perspective it is noteworthy that the formylation was also carried out in situ starting from readily available phenols.

Selbstständigkeitserklärung

Ich versichere hiermit an Eides statt, dass ich die vorliegende Arbeit selbstständig angefertigt und ohne fremde Hilfe verfasst habe, keine außer den von mir angegebenen Hilfsmitteln und Quellen dazu verwendet habe und die den benutzten Werken inhaltlich und wörtlich entnommenen Stellen als solche kenntlich gemacht habe.

Rostock, den 28.11.2008

Anne Brennführer

Curriculum Vitae

PERSONAL DETAILS

Name:	Anne Brennführer
Date of birth:	16.08.1981 in Rostock
Marital status:	Unwed

QUALIFICATION

10/2005 – 04/2009	**Doctorate** Leibniz Institute for Catalysis at the University of Rostock Supervisor: Prof. Dr. M. Beller Dissertation: *Palladium/di-1-adamantyl-n-butylphosphine catalyzed carbonylation reactions* Oral examination subjects: Organic chemistry, toxicology
10/2004 – 09/2005	**Master thesis** Leibniz Institute for Catalysis at the University of Rostock Supervisor: Prof. Dr. M. Beller Topic: *Studies of the biomimetic oxidative phenolic coupling of arylalkylamines for the synthesis of Amaryllidacae alkaloids* Degree: Diplom-Chemikerin (Master of Science)
10/2000 – 09/2004	**Basic and advanced studies in chemistry** University of Rostock Specialization: Catalysis
06/2000	**Abitur** (university entrance qualification) Ernst-Barlach-Gymnasium Rostock Advanced courses: Chemistry, English

WORKING EXPERIENCE

04/2003 – 08/2003	**Student research assistant** University of Rostock, Department of Chemistry Laboratory assistant in the sub-department “Inorganic Chemistry”
10/2002 – 03/2003	**Student research assistant** University of Rostock, Department of Chemistry Tutor for: “Inorganic chemistry for biologists” (laboratory)
07/2000	**Internship** Micromod Partikeltechnologie GmbH, Rostock Analytical determination of the zeta potential of particles

Rostock, 10.04.2009