Leibniz-Institut für Katalyse e.V.

an der Universität Rostock

Transition Metal-Catalyzed Carbonylation of Nitrogen-Containing Heterocycles via C-H Activation

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The road ahead will be long and our climb will be steep.

路漫漫其修远兮，吾将上下而求索。--- 屈原

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Abstract

Transition metal-catalyzed carbonylation of nitrogen-containing heterocycles via C-H activation

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The dissertation is mainly concerned with the development of transition metal-catalyzed carbonylation of nitrogen-containing compounds via C-H activation, which includes different catalysts, various nitrogen-containing substrates, safe CO surrogates, and the applications of novel carbonylative methods. We have described a palladium-catalyzed carbonylation of aromatic C-H bonds with alcohols using $Mo(CO)_6$ as the CO Source. Then we have synthesized 3-methyleneisoindolin-1-ones and 2-phenylisoindolin-1-ones via C-H carbonylation using $Mo(CO)_6$ as well. In addition, a convenient procedure for the synthesis of 3-acylindoles from simple indoles and aryl iodides has been established via C-H carbonylation. Furthermore, we have described a copper-catalyzed double carbonylation reaction of indoles with alcohols using $C_6O_6{\cdot}8H_2O$ as the CO Source. Besides, we have described many control experiments to understand the transition metal-catalyzed carbonylation mechanisms such as the palladium, the ruthenium, and the copper catalytic cycle.

Übergangsmetall-katalysierte Carbonylierung von stickstoffhaltigen Heterocyclen über CH-Aktivierung

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Die vorliegende Dissertation beschäftigt sich hauptsächlich mit der Entwicklung der Übergangsmetall-katalysierten Carbonylierung von stickstoffhaltigen Heterocyclen über CH-Aktivierung, der verschiedenen Katalysatoren, der verschiedenen stickstoffhaltige Substrate, sicheren CO-Surrogaten und der Anwendung neuartiger carbonylierender Methoden. Wir haben eine Palladium-katalysierte Carbonylierung von aromatischen CH-Bindungen mit Alkoholen beschrieben, wobei $Mo(CO)_6$ als CO-Quelle verwendet wurde. Weiterhin wurden 3-Methylenisoindolin-1-one und 2-Phenylisoindolin-1-one über CH-Carbonylierung mit $Mo(CO)_6$ synthetisiert. Darüber hinaus wurde ein effizientes Verfahren zur Synthese von 3-Acylindolen aus einfachen Indolen und Aryliodiden über die C-H-Carbonylierung entwickelt. Anschließend wird eine kupferkatalysierte Doppelcarbonylierung von Indolen mit Alkoholen mit C_6O_6 $8H_2O$ als CO-Quelle beschrieben. Schließlich wird auf diverse Kontrollexperimente eingegangen, die zum Verständnis der Übergangsmetall-katalysierten Carbonylierungsmechanismen im Falle des Katalysezyklus von Palladium, Ruthenium und Kupfer beitragen.

List of Abbreviations

acac	Acetylacetone
^{t}AmOH	2-Methylbutan-2-ol
Ar	Aryl
b	Branch
Bu	Butyl
Bn	Benzyl
BHT	Butylated hydroxytoluene
Boc	Butyloxycarbonyl
BQ	1,4-Benzoquinone
cat.	Catalyst
CO	Carbon monoxide
cod	Cycloocta-1,5-diene
$C_6O_6 \cdot 8H_2O$	Hexaketocyclohexane octahydrate
CN	Nitrile
Cy	Cyclohexyl
DCE	1,2-Dichloroethane
DEAD	Diethyl azodicarboxylate
DFT	Density functional theory
DIAD	Diisopropyl azodicarboxylate
DMA	Dimethylacetamide
DMF	Dimethylformamide
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
dppp	1,3-Bis(diphenylphosphino)propane
DTBP	Di-*tert*-butyl peroxide
Et	Ethyl
equiv.	Equivalent
h	Hour
HFIP	Hexafluoroisopropanol
iso or ***i***	Sum of branched products
KIE	Kinetic isotope effect
MeCN	Acetonitrile
MeOH	Methanol
mmol	Millimole
n	Amount of linear product

NMR	Nuclear Magnetic Resonance
NuH	Nucleophile
Oct	Octyl
OAc	Acetate
Ph	Phenyl
pK_a	Acid dissociation constant
PPh_3	Triphenylphosphine
PivOH	Pivalic acid
Pr	Propyl
$TBAPF_6$	Tetrabutylammonium hexafluorophosphate
TBS	*tert*-Butyldimethylsilyl
TEMPO	2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl
TFA	Trifluoroacetic acid
TFBen	Benzene-1,3,5-triyl triformate
TFE	2,2,2-Trifluoroethanol
THAB	Tetrahexylammonium benzoate
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
Ts	Tosyl
X	Leaving group, (pseudo)halide
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

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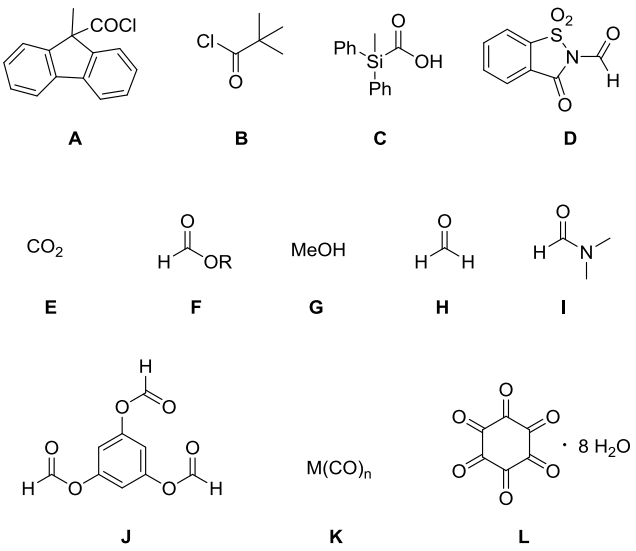
List of Schemes

1. Introduction

Transition metal-catalyzed carbonylation reactions have already become one of the most powerful reactions in the toolbox of modern organic chemists.[1] Since the pioneering work by Heck in 1974 with palladium catalyst,[2] it became one of the most preferred ways of introducing a carbonyl group in organic molecules with various nucleophiles. During last decades, many achievements have been made in this area. However, the interests have been mainly focused on the utility of aryl halides as the starting materials for the formation of carbon-metal bond via the oxidative addition of metal catalyst to the C-X bond.[3] However, the pre-functionalization of arene is required to synthesize the aromatic halides, which causes the waste of halogens. At this point, the straightforward taking advantage of hydrocarbon itself will enhance the efficiency. The inert C-H bond activation has also experienced impressive improvements as it can avoid the pre-functionalization step, which is environmentally benign and green.[4] As compared with the non-carbonylative C-H functionalization reactions, the reports on C-H carbonylation reactions are fewer, indicating that this research area still faces many challenges: (i) The research of catalyst in C-H activation cabonylation is mainly on palladium catalyst. (ii) Carbon monoxide is utilized as the CO source in most research.[5]

Carbon monoxide is the mainly applied carbonyl source. With carbon monoxide as a carbonyl source, valuable carbonyl-containing organic molecules can be easily prepared. Although CO as one of the cheapest carbonyl sources, holding advantages in industrial scale applications, its special characters (eg., high toxicity, smell-less, flammable, and etc.) limit its usage in laboratories. Notably, the CO pressure is usually high in carbonylations. Hence, the developing of synthetic procedures based on CO surrogates will be meaningful for the synthetic community.[6] The typical known CO surrogates are listed in Scheme 1.1. 'CO gen' (**A**),[7] pivaloyl chloride (**B**),[7] and silacarboxylic acids (**C**)[8] are sufficient to promote carbonylative transformations. *N*-formylsaccharin (**D**) is known as a CO source for the transition metal-catalyzed carbonylation of aryl halides to access aryl aldehydes as well.[9] However, the atom efficiency and waste generation for CO alternatives **A**-**D** still remain to be concerned. CO_2 (**E**) becomes an ideal C1 building block in organic synthesis because of its abundance, nontoxicity, and recyclability. Notably, the catalytic in situ generation of CO from CO_2 reduction and its incorporation in the following carbonylation reactions has been realized.[10] It is a promising process using CO_2 instead of CO as a carbonyl resource. However, the substrate scope is limited by the required reductants. It is well known that CO can be released from formic acid (**F**; R=H) by dehydration in sulfuric acid (Morgan reaction).[11] Methanol (**G**) is an abundant and potentially renewable chemical and can be a carbonyl source as well.[12] In addition, formaldehyde (**H**) is also an atom economic CO surrogate for carbonylation reactions with suitable reactivity.[13] Formamides (**I**) have already been used for the carbonylation.[14] Recently, our group developed benzene-1,3,5-triyl triformate (TFBen, **J**) as a kind of convenient and efficient CO source for the first time.[15] The character of TFBen as a potent

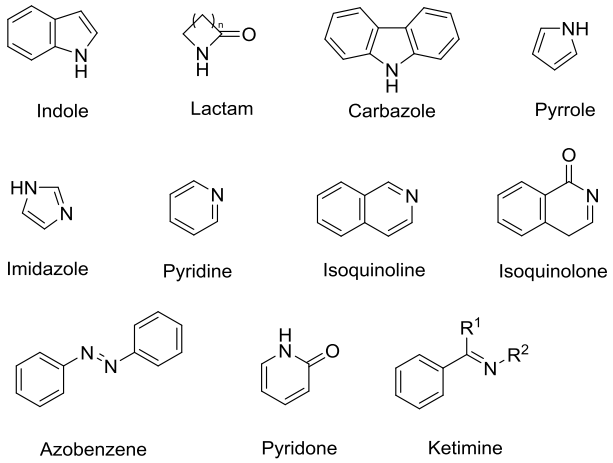
and non-reacting CO source has been proven by the numerous synthetic applications in carbonylation reactions. 1,3,5-trihydroxybenzene, the starting material for TFBen synthesis, is an abundant and naturally occurring substance which is recovered during the product purification process. Moreover, transition metal carbonyls are useful in organic synthesis, which can release CO gas. A variety of transition metal carbonyls have been reported in carbonylation reactions such as $Cr(CO)_6$,[16] $Mo(CO)_6$,[17] $W(CO)_6$,[18] and $Co_2(CO)_8$.[19] A potential drawback of them is the presence of stoichiometric amounts of additional transition metals in the reaction mixture. It is a major problem on an industrial scale. However, the preparative ease of this system far outweighs this disadvantage for small applications in research laboratories. When one compares classical carbonylations with those carried out with solid CO surrogates, the ease with which many syntheses can be conducted quickly and safely, results in an overall reduction in the cost per compound. Besides, hexaketocyclohexane octahydrate ($C_6O_6 \cdot 8H_2O$, **L**) as a non-toxic solid is an attractive CO source, which was formed by oligomerization of carbon monoxide through the formation of molybdenum carbonyls.[20] Among all the candidates, $Mo(CO)_6$ and $C_6O_6 \cdot 8H_2O$ were studied in my research.



Scheme 1.1 Typical CO surrogates.

Nitrogen-containing compounds (Scheme 1.2), such as indoles, lactams, carbazoles, pyrroles, imidazoles, pyridines, isoquinolines, isoquinolones, azobenzenes, pyridones, and ketimines, have been found to be important in natural products, synthetic intermediates, pharmaceutical agents, wide range of potential biological activities, and therapeutically useful materials.[21] For this reason, more and more synthetic chemists are interested in the construction and functionalization of heterocyclic cores. On the other hand, carbonylations have already been applied in the C-H activation of nitrogen-containing compounds in past years. Therefore, it is important to broaden the area of C-H

carbonylation using nitrogen-containing compounds. In my experiments, pyridines, ketimines, azobenzenes and indoles are discussed as the nitrogen-containing substrates.



Scheme 1.2 Nitrogen-containing compounds.

Above all mentioned, this dissertation mainly focuses on developing new methods of transition metal-catalyzed C-H carbonylation of nitrogen-containing compounds using different CO surrogates.

1.1 Palladium-catalyzed carbonylation of nitrogen-containing compounds via C-H activation

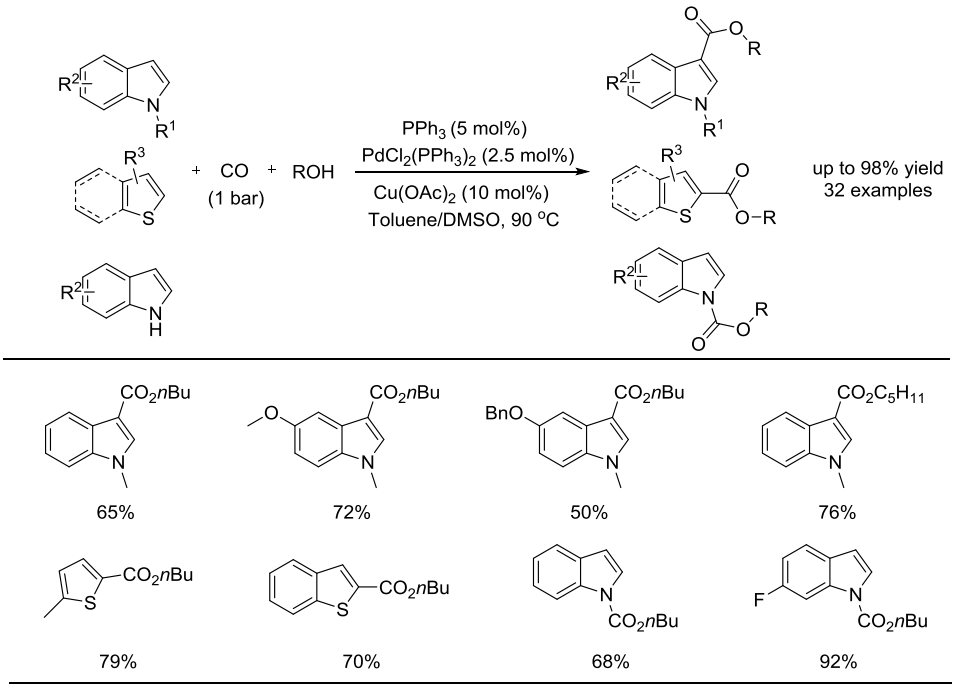
1.1.1 C-H carbonylation without directing group

In 2011, Lei and co-workers reported a protocol for a palladium-catalyzed C-H carbonylation of heteroarenes using alcohols as the nucleophiles (Scheme 1.3).[22] Aliphatic alcohols and aromatic alcohols worked well under the conditions. Both electron-donating and electron-withdrawing substituents on indole ring were well tolerated in this reaction. Thiophene and benzo[*b*]thiophene were also investigated and C-H activation predominantly occurred at C2 position in this oxidative carbonylation. In addition, when *NH* indoles were employed in this oxidative carbonylation, the regioselectivity of the oxidative process was switched in favor of reaction at *NH* site. This reaction with primary and secondary alcohols could afford the corresponding carbamates. Various indoles with both electron-donating and electron-withdrawing groups were tested and the *N*-carbonylation products were formed in good to excellent yields. Halogen substituents were well tolerated in this carbonylation as well.

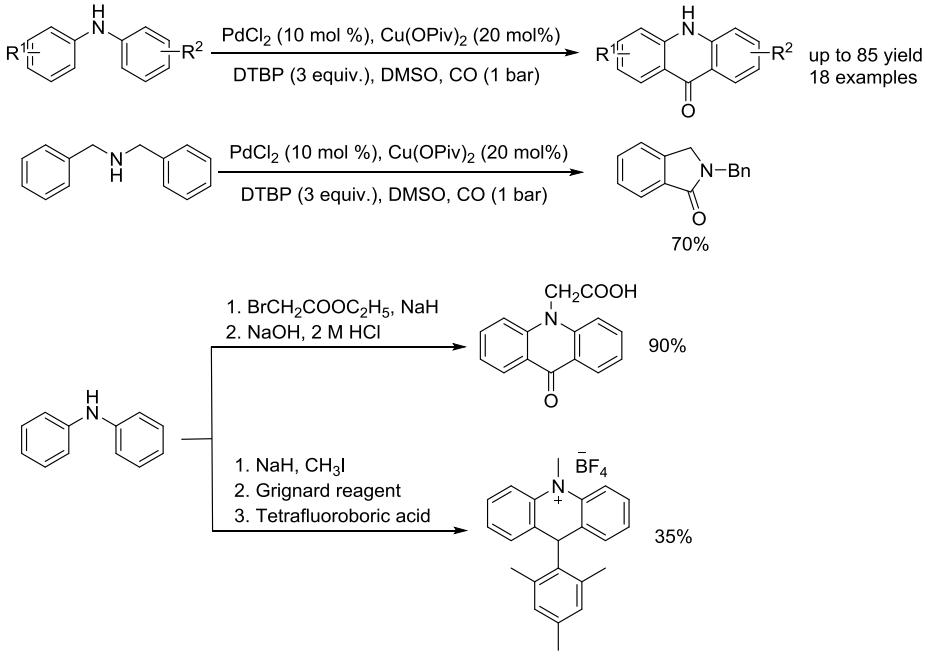
Later on, they developed a palladium/copper co-catalyzed oxidative double C-H carbonylation of diphenylamines with DTBP as the oxidant under 1 bar of CO (Scheme 1.4).[23] This reaction delivered an efficient and atom economic way to access synthetically useful acridones. Various acridones were synthesized in good to high yields. Diphenylamines with electron-donating substituents, such as OMe,

OEt, and *t*-Bu, gave in high yields of products. The electron-withdrawing group on the aromatic ring could also furnish the desired products. However, the yield was slightly lower. In addition, substitution on the *ortho*- or *meta*-position of the diphenylamines could lead to the desired products in good yield. It was worth noting that 2-benzylisoindolin-1-one was obtained in 70% yield under the standard conditions when they used dibenzylamine as the substrate. They also demonstrated the post synthetic transformations of nitrogen-containing acridones.

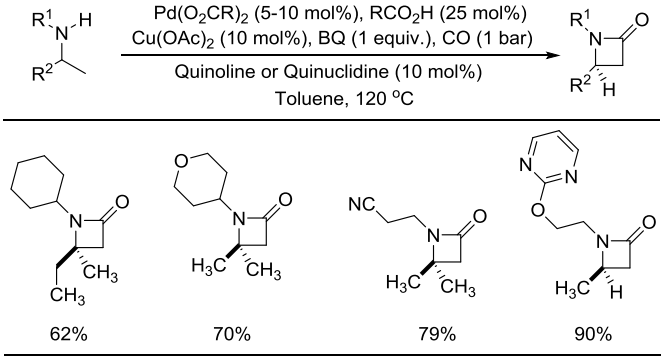
Gaunt and co-workers developed a general process for the palladium-catalyzed carbonylation of methylene C-H bonds at the *β*-position to an unprotected aliphatic amine (Scheme 1.5).[24] The operationally straightforward palladium-catalyzed process exploited a distinct reaction pathway, wherein a sterically hindered carboxylate ligand orchestrated an amine attack on a palladium anhydride to transform aliphatic amines into *β*-lactams. The reaction was well worked with a wide range of amines. Branching at the *α*- and *β*-carbon atoms on the non-reacting side of the amine was well tolerated to provide the *β*-lactams in good yields. A variety of functional groups, such as alkene, ester, arene, and oxetane moieties, could be accommodated by the reaction, which afforded the corresponding *β*-lactams in good yields. Among these, they noted that: i) A thioether motif neither deactivated the catalyst nor succumbed to oxidation; ii) The free *NH β*-lactam can be obtained through photochemical cleavage of an *N*-benzyl derivative; iii) The reaction could be performed on gram scale.



Scheme 1.3 Pd-catalyzed C-H carbonylation of heteroarenes.



Scheme 1.4 Pd/Cu co-catalyzed oxidative double C-H carbonylation.

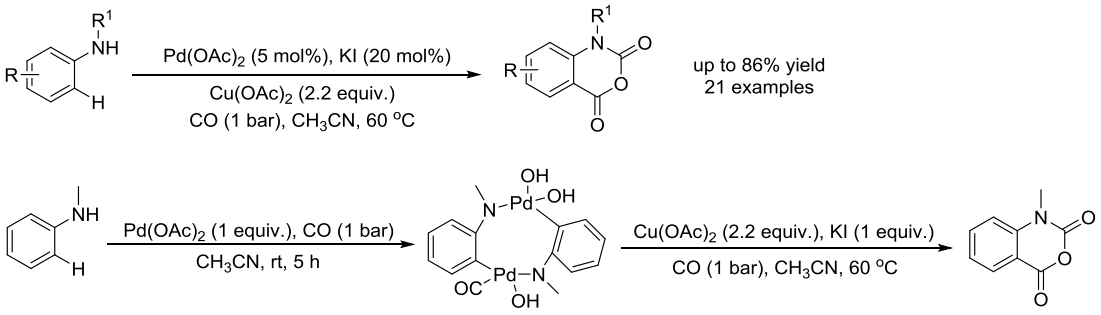


Scheme 1.5 Pd-catalyzed carbonylation of methylene C-H bonds.

1.1.2 C-H carbonylation with directing group

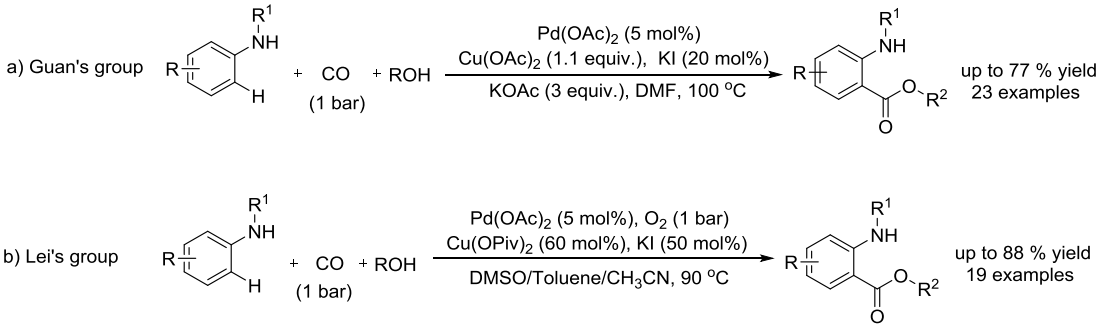
In 2012, Guan and co-workers developed a palladium-catalyzed C-H bond carbonylation of *N*-alkyl anilines for the synthesis of isatoic anhydrides (Scheme 1.6).[25] A key intermediate was isolated and characterized through the mechanism experiment. This reaction tolerated a wide range of functional groups, such as methyl, methoxyl, fluoro, chloro, bromo, formyl aldehyde nitro, acetyl, and ester groups, which gave the corresponding substituted isatoic anhydrides in good to high yields. Generally, the electron-rich substrates showed more reactivity, which was consistent with an electrophilic palladation mechanism. *Ortho*-substituted anilines gave low yields of the corresponding isatoic anhydrides. The steric effect was observed in the transformation, which improved the regioselectivity

of the carbonylation of *meta*-substituted anilines. Only less sterically hindered products were obtained. Different alkyl substituents on the anilines were also investigated. *N*-ethyl, propyl, or cyclohexyl substituted anilines could be used and provided the corresponding carbonylation products in moderate to good yields. The mechanism was investigated. A stoichiometric reaction of $Pd(OAc)_2$ with *N*-methylaniline was conducted under a CO atmosphere in the absence of $Cu(OAc)_2$, which delivered a palladium complex.



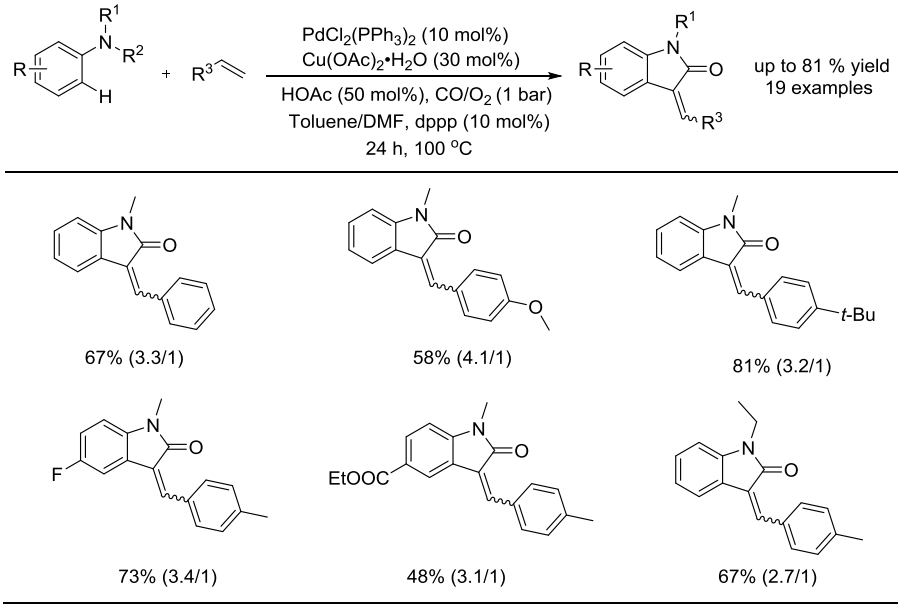
Scheme 1.6 Pd-catalyzed carbonylation of *N*-methyl anilines for the synthesis of isatoic anhydrides.

Subsequently, Guan's group and Lei's group reported palladium-catalyzed oxidative C-H carbonylations of *N*-alkylanilines with alcohols for the synthesis of *o*-aminobenzoates under mild balloon pressure of CO (Scheme 1.7).[26] Various aliphatic alcohols and phenol were tolerated in the reaction to afford the *o*-aminobenzoates in good yields. This reaction was sensitive to electronic features of the *N*-methylanilines. Both electron-donating and electron-withdrawing groups such as methyl, methoxyl, chloro, and bromo groups on phenyl rings were worked smoothly. However, *N*-methylanilines with electron-rich substrates were more reactive because of their slightly stronger nucleophilicity. However, the strong electron-donating methoxy group on the phenyl ring decreased the yield of the reactions because of the formation of an isatoic anhydride byproduct.



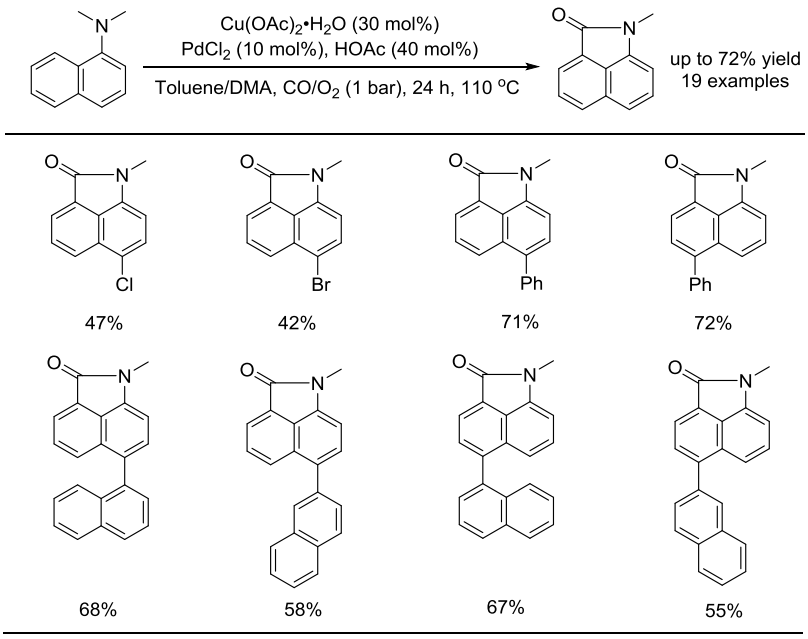
Scheme 1.7 Pd-catalyzed carbonylation of *N*-methyl anilines and alcohols.

In 2013, Lei and co-workers developed a straightforward approach for the synthesis of 3-methyleneindolin-2-one derivatives by using commercial and simple tertiary anilines, olefins, and CO gas. (Scheme 1.8).[27] Both electron-donating and electron-withdrawing substituents on the aryl ring of substituted styrenes were well tolerated under the conditions. The position of substituent on aryl ring had little influence. *N,N*-dimethylanilines bearing halogens and electron-withdrawing substituents afforded the corresponding 3-methyleneindolin-2-ones in moderate to good yields. Several experiments were carried out to study the reaction mechanism, indicating that the C-H cleavage might be involved in the rate-determining step.



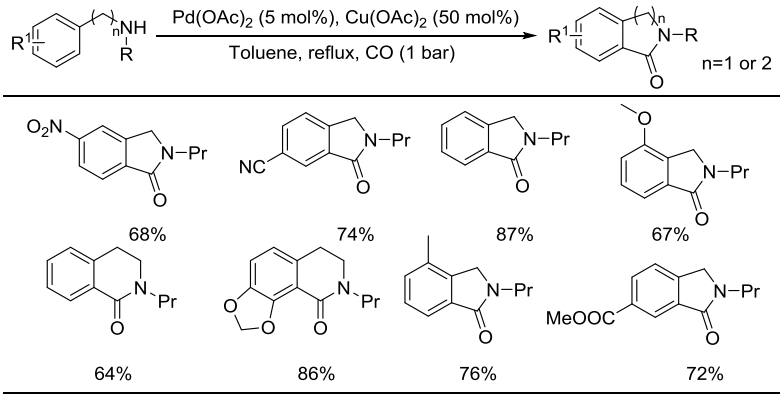
Scheme 1.8 Pd/Cu-catalyzed C-H carbonylation of tertiary anilines.

Recently, they reported a palladium-catalyzed intramolecular aerobic oxidative amine directed C-H carbonylation reaction of tertiary naphthalen-1-amines, which provided an efficient protocol towards the synthesis of biologically and synthetically useful heterocycles (Scheme 1.9).[28] Substrates substituted with halogens including Cl and Br furnished the corresponding carbonylation products in moderate to good yields. However, substrates substituted with NO_2, COOMe and other electron-withdrawing groups gave low yields of products in this protocol. Both electron-donating and electron-withdrawing substituents on the benzene ring of 4-phenylnaphthalen-1-amine derivatives were well tolerated under the conditions. Besides, this protocol could also be applied to *N,N*-dialkylnaphthalen-1-amines with different *N*-alkyl substituents such as Et, Bu, and Oct. The intermolecular KIE experiments were carried out, suggesting that C-H bond cleavage might be involved in the rate-determining step.



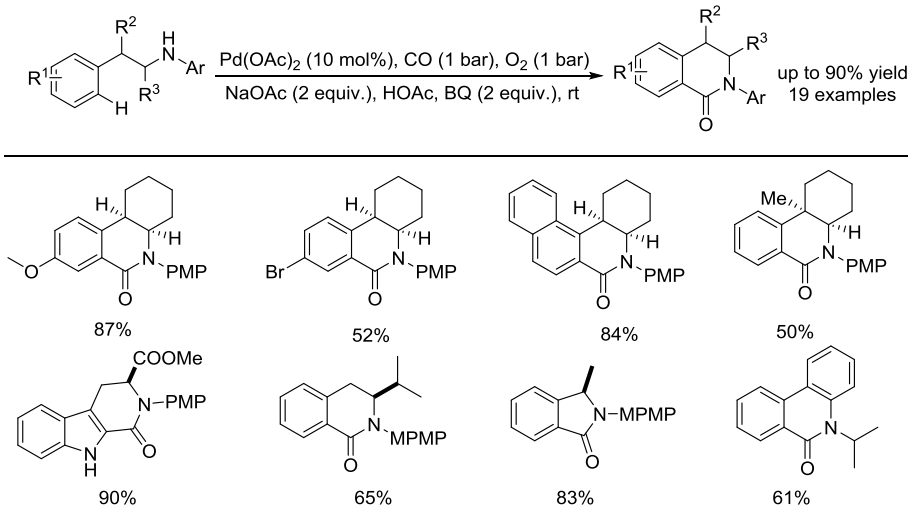
Scheme 1.9 Pd-catalyzed intramolecular aerobic oxidative amine directed C-H carbonylation.

Orito and co-workers developed a palladium-catalyzed carbonylation of secondary *ω*-phenylalkylamines that afforded a variety of five- or six-membered benzolactams (Scheme 1.10).[29] This reaction was carried out in a phosphine-free catalytic system using $Pd(OAc)_2$, $Cu(OAc)_2$ in an atmosphere of CO gas containing air. From the results, they also found that benzylic amines underwent carbonylation at a rate much faster than that of the corresponding phenethylamines. In addition, the rate of the five-membered ring formation was 11 times greater than that of the six-membered ring formation. Benzylic amines with electron-withdrawing groups or electron-donating groups could also undergo smoothly.



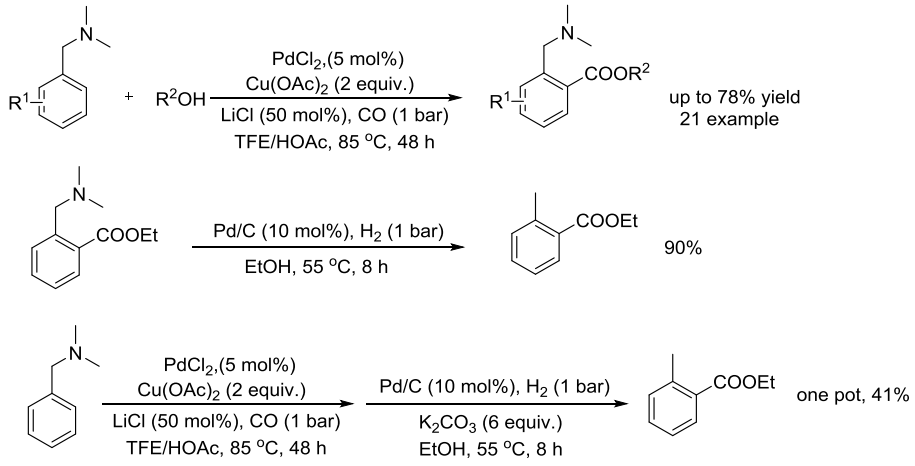
Scheme 1.10 Pd-catalyzed carbonylation of amines.

In 2010, Gaunt demonstrated amine directed palladium-catalyzed C-H carbonylations, which proceeded at room temperature and tolerated various functional groups (Scheme 1.11).[30] The nature of the arene could also be varied with naphthalene, pyrrole and indole derived heteroarenes affording carbonylation products in good yields. Interestingly, straight chain amines required to use a more sterically hindered aryl group to suppress addition of the amine to BQ. This reaction could not work with arenes displaying strongly electron withdrawing groups. To further understand the mechanism, they prepared amine with the 4-methoxyphenyl group. They found that carbopalladation proceeded at room temperature providing a dimeric complex. When the palladacycle was subjected to a CO atmosphere in the presence of BQ, it underwent carbonylation to a synthetically versatile intermediate dihydro-2-quinolone.



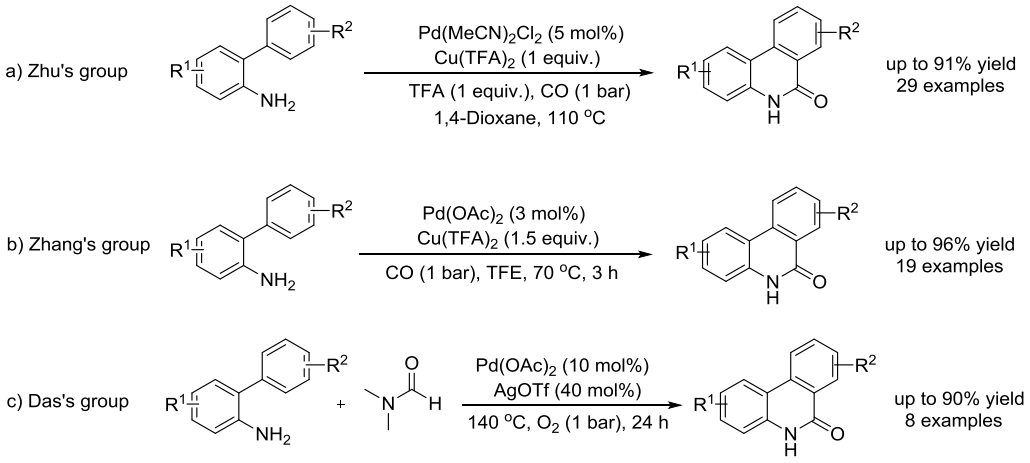
Scheme 1.11 Amine directed Pd-catalyzed C-H bond carbonylation.

Shi and co-workers developed a palladium catalyzed *ortho*-olefination of *N,N*-dimethylbenzylamines (Scheme 1.12).[31] Notably, LiCl was found to promote this carbonylation reaction. Methanol, ethanol, and other long chain aliphatic alcohols were suitable in this reaction. However, steric hindered alcohols performed low efficiency. Other nucleophiles, such as phenol and amines, completely failed under the conditions. They also used different substituents on the phenyl ring of *N,N*-dimethylbenzylamines. Both electron-donating groups and electron-withdrawing groups were tolerated in this reaction. Further transformation to afford *ortho*-functionalization of substituted toluene in one pot was explored. Under reductive hydrogen atmosphere with Pd/C as catalyst, the *N,N*-dimethylaminomethyl group could be converted into a methyl group. Further studies to combine *ortho*-carbonylation and hydrogenation into one pot were conducted.



Scheme 1.12 Pd-catalyzed *ortho*-carbonylation of *N,N*-dimethylbenzylamines.

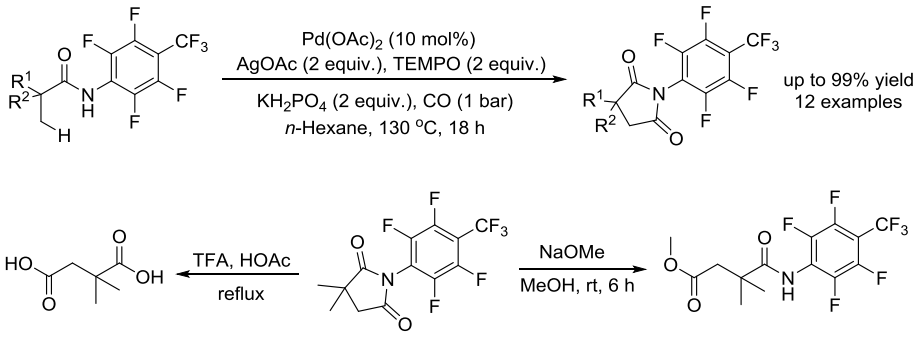
Recently, Zhu, Zhang, and Das reported palladium-catalyzed C-H carbonylations of biaryl-2-amine to form phenanthridinones, respectively (Scheme 1.13).[32] In this reaction, unprotected aniline-nitrogen was used as a directing group to prepare free *NH*-lactams. The major challenge of using free aniline as a directing group in C-H aminocarbonylation reaction was its incompatibility with the oxidative reaction conditions and urea byproduct formation. The reaction conditions of Zhu's group and Zhang's group were similar. They both used palladium salt as the catalyst and $Cu(TFA)_2$ as the oxidant under CO atmosphere. However, Das's group used DMF as the CO source and O_2 as the oxidant.



Scheme 1.13 Pd-catalyzed C-H aminocarbonylation of unprotected anilines.

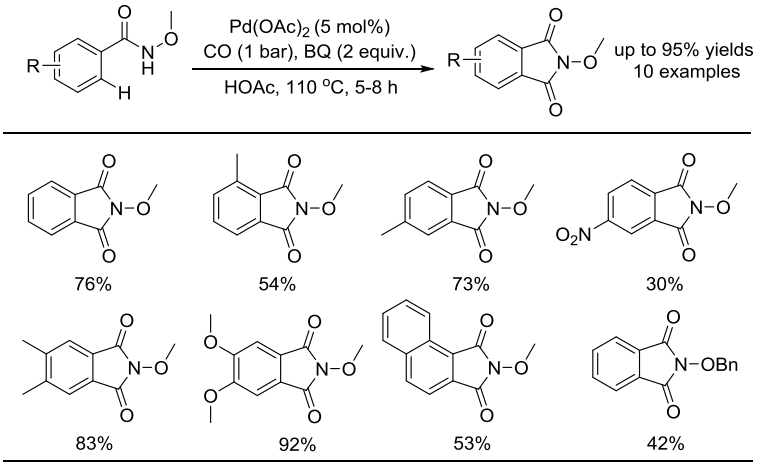
In 2010, Yu and co-workers developed a palladium-catalyzed amide directed C-H carbonylation of *N*-arylamides under CO atmosphere (Scheme 1.14).[33] Substrates with a quaternary *α*-carbon atom gave good to excellent yields of the succinimide products. Products containing ether groups could also be obtained in good yields. The benzyl moiety proved to be a better protecting group than the TIPS

group for *β*-hydroxyl substrates, while TBS-protected substrates gave none of the desired product. Notably, this method was also effective for the carbonylation of methylene C-H bonds in cyclopropane substrates. To demonstrate the synthetic utility of this reaction, succinimide product was subjected to two different ring-opening conditions to obtain either 1,4-dicarboxylic acid or 1,4-dicarbonyl molecule.



Scheme 1.14 Pd-catalyzed C-H carbonylation of *N*-arylamides.

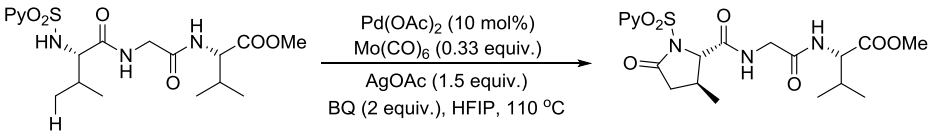
Lloyd-Jones and Booker-Milburn reported a palladium-catalyzed C-H carbonylation of *N*-methoxybenzamides under 1 bar of CO, which provided a direct route to substituted phthalimides (Scheme 1.15).[34] The reaction proved to be very sensitive to the solution phase CO concentration, increasing the CO pressure (2-4 bar) or diluting with N_2 (1:1) resulted in reduced yields. Surprisingly, they found that the "reduced volume" Radleys tubes were found to be optimal, whereas reactions in a standard round-bottom flask under identical conditions resulted in consistently poor yields.



Scheme 1.15 Pd-catalyzed C-H carbonylation of *N*-methoxybenzamides.

In 2016, Carretero and co-workers developed a palladium-catalyzed C-H carbonylative cyclization of *N*-(2-pyridyl)sulphonyl (*N*-SO_2Py)-protected amines by using palladium catalyst and $Mo(CO)_6$ as a CO

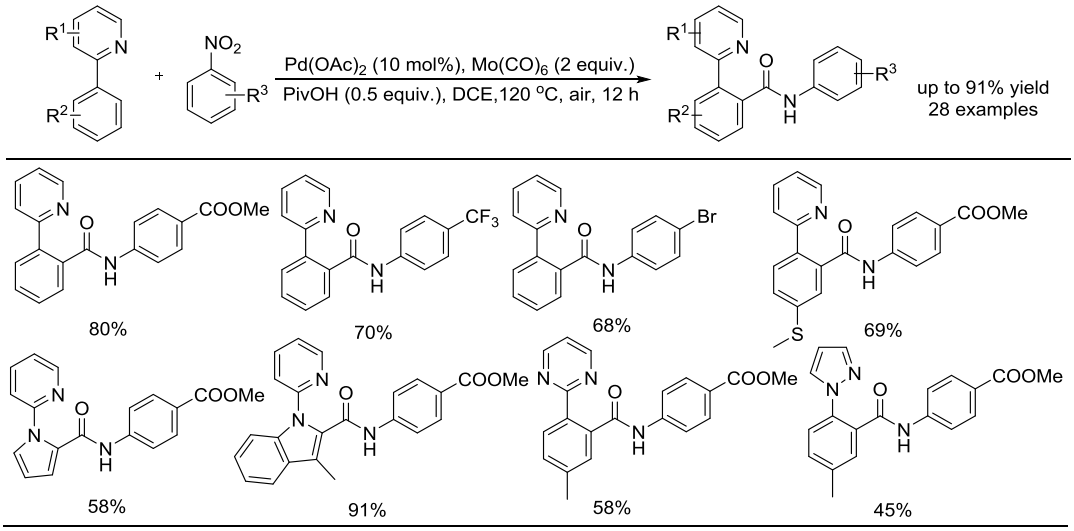
source (Scheme 1.16).[35] This carbonylation protocol relied on the directing group *N*-SO_2Py, which proved to be easily removed. This procedure also allowed late-stage modifications of more-complex, functional compounds such as dipeptides or tripeptides, thereby illustrating the capacity of the bidentate *N*-SO_2Py directing group to override other inherent substrate coordinating elements, as well as broad functional group tolerance. In addition to providing an attractive solution to the difficulties in handling hazardous CO gas, the use of $Mo(CO)_6$ as a solid CO source in substoichiometric amount (0.33 equiv.) ensured the palladium-catalytic activity. Indeed, significantly lower efficiency was observed when the reactions were carried out under 1 bar of CO, or in the presence of increased the amount of $Mo(CO)_6$. A series of experimental and DFT mechanistic studies were carried out to further study the mechanism.



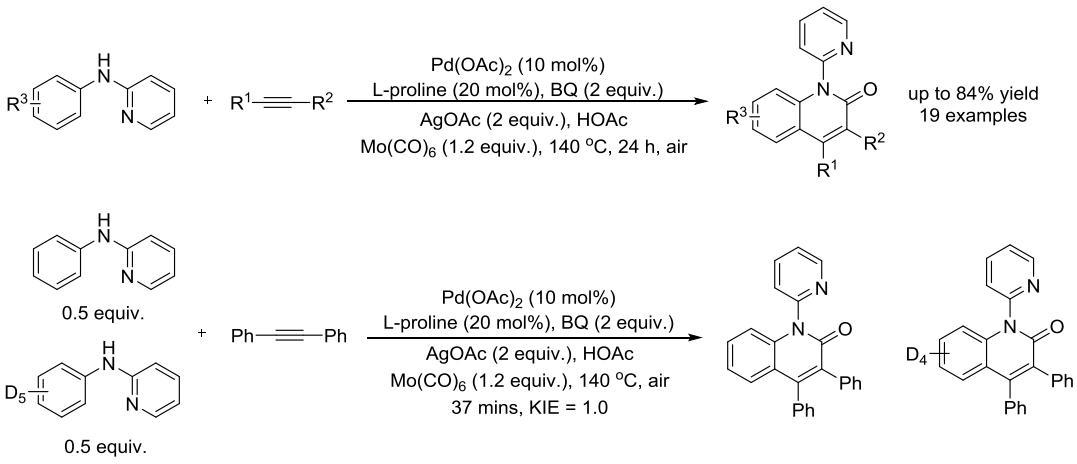
Scheme 1.16 Pd-catalyzed carbonylative cyclization of amines.

As shown in Scheme 1.17, Driver and co-workers reported a palladium-catalyzed aminocarbonylation of aryl C-H bonds using nitroarenes as the nitrogen source and $Mo(CO)_6$ as the CO source.[36] This intermolecular C-H bond functionalization did not require any ligand. The electronic nature of the nitroarene impacted the success of the reaction with the highest yields when electron-deficient substituents were present on the nitroarene. However, increasing the steric environment around the nitro group had a detrimental effect on the reaction. Additionally, the mechanism experiments indicated that the palladacycle catalyst served to reduce the nitroarene to a nitrosoarene and activated the C-H bond. Besides, the C-H bond activation step was both the product-determining and the turnover-limiting step.

In 2014, our group described a palladium-catalyzed carbonylative [3+2+1] annulation of *N*-aryl-pyridine-2-amines with internal alkynes by C-H activation (Scheme 1.18).[37] $Mo(CO)_6$ was applied as a solid CO source and the reaction proceeded in an atom economic manner. Different kinds of internal alkynes were tested in our system. Alkynes substituted with electron-donating groups such as *n*-butyl or electron-withdrawing groups such as fluoro, bromo, acetyl, and trifluoromethyl were tolerated in our procedure with good yields. The substitutes on the *N*-arylpyrine-2-amine were detected as well. The *N*-aryl-pyridine-2-amines bearing electron-donating groups, such as methyl and methoxyl, worked well with synthetically useful yields as well as electron-deficient substrates. To gain some detail of the mechanism, the KIE experiment was conducted. The KIE was 1.0, indicating that the C-H activation step was reversible and might not be the rate-determining step for this procedure.



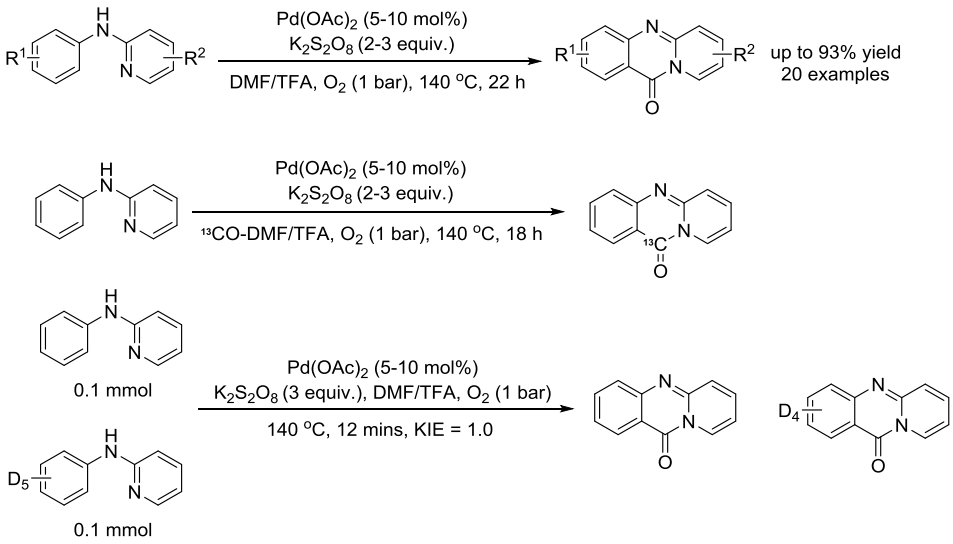
Scheme 1.17 Pd-catalyzed aryl C-H bond aminocarbonylation.



Scheme 1.18 Pd-catalyzed carbonylative [3+2+1] annulation of *N*-aryl-pyridine-2-amines.

Recently, our group reported a palladium-catalyzed carbonylative cyclization of *N*-arylpyridin-2-amines via C-H activation using DMF as the CO surrogate (Scheme 1.19).[38] In this reaction, both electron-donating and electron-withdrawing substituted *N*-arylpyridin-2-amines were transformed into carbonylation products in moderate to good yields. Benzene rings bearing halide, phenyl and benzyloxy groups at *para*-positions were well tolerated to give the corresponding products in good yields. The ^{13}CO-labelling DMF experiment and other control experiments proved that the carbonyl group of DMF was the CO source in this methodology. Moreover, the KIE experiment

suggested that C-H activation step might not be involved in the rate-determining step under our conditions.

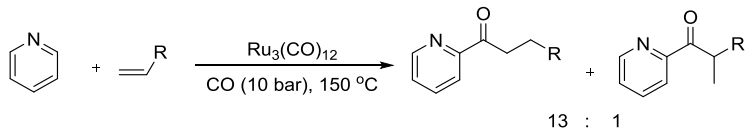


Scheme 1.19 Pd-catalyzed carbonylative cyclization of arenes by C-H Activation.

1.2 Ruthenium-catalyzed carbonylation of nitrogen-containing compounds via C-H activation

1.2.1 C-H carbonylation without directing group

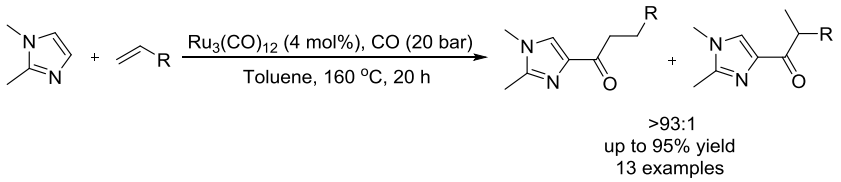
In 1992, Murai and co-workers reported $Ru_3(CO)_{12}$-catalyzed C-H carbonylation of pyridine (Scheme 1.20).[39] In this reaction, pyridine was also employed as a solvent and the reaction was conducted at 150 °C under 10 bar of CO. Conversion of 1-hexene to the pyridyl ketone mixture was 65% after 16 hours. Only *ortho*-substituted products were observed, making the reaction highly regioselective. The kinetics of the acylation reaction was examined in some detail. The reaction exhibited first-order rate kinetics with respect to pyridine and $Ru_3(CO)_{12}$ and was zero-order in CO pressure (3-10 bar) and olefin concentration.



Scheme 1.20 Ru-catalyzed C-H carbonylation of pyridines.

In 1996, Murai and co-workers demonstrated $Ru_3(CO)_{12}$-catalyzed C-H carbonylation of imidazoles (Scheme 1.21).[40] The reaction of 1,2-dimethylimidazole with 1-hexene under 20 bar of CO in toluene at 160 °C for 20 hours in the presence of $Ru_3(CO)_{12}$ gave the carbonylative products with a linear to branched ratio of 94:6. The coupling occurred highly regioselectively at the 4-position. No

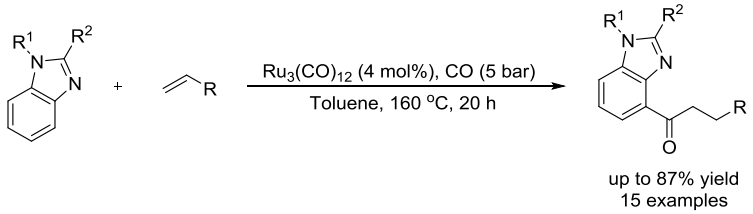
5-heptanoylation isomer was detected. Different olefins such as alkyl, aryl, and trialkylsilyl substituted alkenes were utilized in this reaction. Surprisingly, they found that the linear to branched ratio was affected by the steric factor and that the reaction of electron deficient olefins such as acrylonitrile and ethyl acrylate did not proceed.



Scheme 1.21 Ru-catalyzed C-H carbonylation of imidazoles.

Later on, they extended this $Ru_3(CO)_{12}$-catalyzed C-H carbonylation reaction.[41] A wide range of olefins with various functional groups were utilized in the carbonylation reaction. Other five-membered *N*-heteroaromatic compounds, such as pyrazoles, oxazoles, and thiazoles, could also work well. The reactivity of the five-membered heterocycles corresponded to the pK_a of the conjugate acid of these heterocycles. High pK_a of the substrate gave the high reactivity. It indicated that the pK_a values were related to the ability of the nitrogen atom in the substrates to coordinate to a ruthenium center. The coordination of the substrates to the ruthenium center in the catalyst complex was a necessary prerequisite for the carbonylation to proceed.

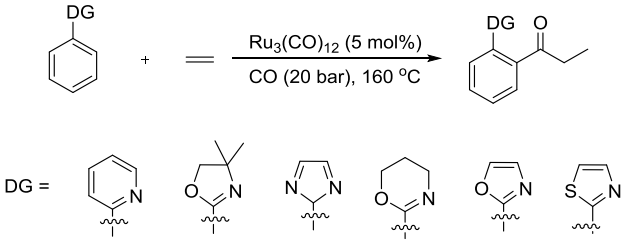
In 1998, they described $Ru_3(CO)_{12}$-catalyzed siteselective carbonylation at a C-H bond *β* to the nitrogen (Scheme 1.22).[42] Imidazoles were used as the substrates with olefins under 5 bar of CO in toluene at 160 °C for 20 hours. Interestingly, the carbonylation occurred highly siteselectively at the 4-position. Higher CO pressure suppressed the coordination of substrates to the ruthenium center, which was essential for the metal to cleave the C-H bond. The effects of substituents (R^1 and R^2) on the reaction were examined. The bulkiness of R^1 appeared to be an important factor.



Scheme 1.22 Ru-catalyzed siteselective carbonylation of imidazoles.

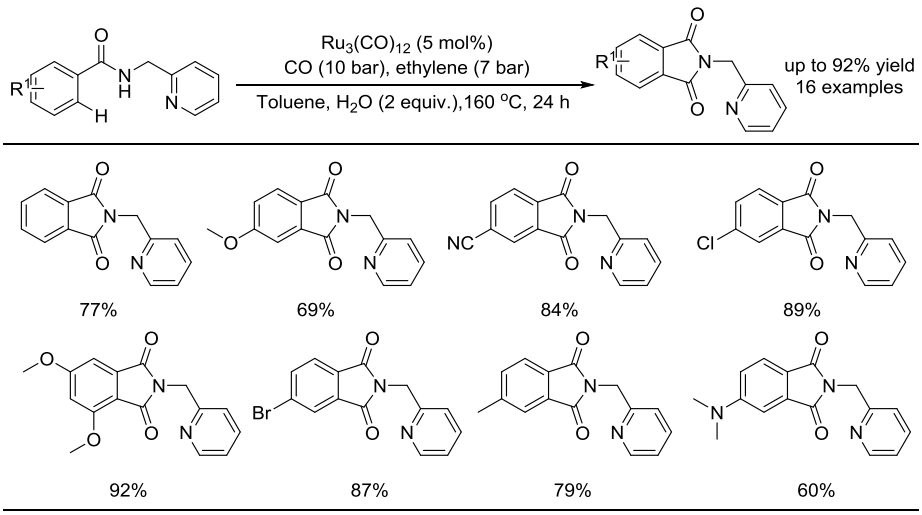
1.2.2 C-H carbonylation with directing group

Murai and Chatani developed ruthenium-catalyzed carbonylations at a C-H bond in a phenyl ring under CO (20 bar) and ethylene at 160 °C (Scheme 1.23).[43] Carbonylation took place selectively at the *ortho* C-H bond in the phenyl ring using directing groups such as pyridine, oxazoline, oxazine, oxazole, pyrazole, and thiazoline. It was found that the siteselectivity was determined by steric factors. Olefins such as propene and trimethylvinylsilane in place of ethylene could be used in the carbonylation reaction, while other olefins, such as 1-hexene, *tert*-butylethylene, vinylcyclohexane, isoprene, 1,5-hexadiene, cyclohexene, 1,5-cyclooctadiene, styrene, methyl acrylate, vinyl acetate, allyltrimethylsilane, and triethoxyvinylsilane did not afford the carbonylation products. The results of deuterium labelling experiments suggested that the catalysis involved reversible C-H bonds cleavage and that the rate-determining step was not the cleavage of the C-H bond. The results of kinetic study of the effects of CO pressure showed that the reaction rate accelerated with decreasing CO pressure.



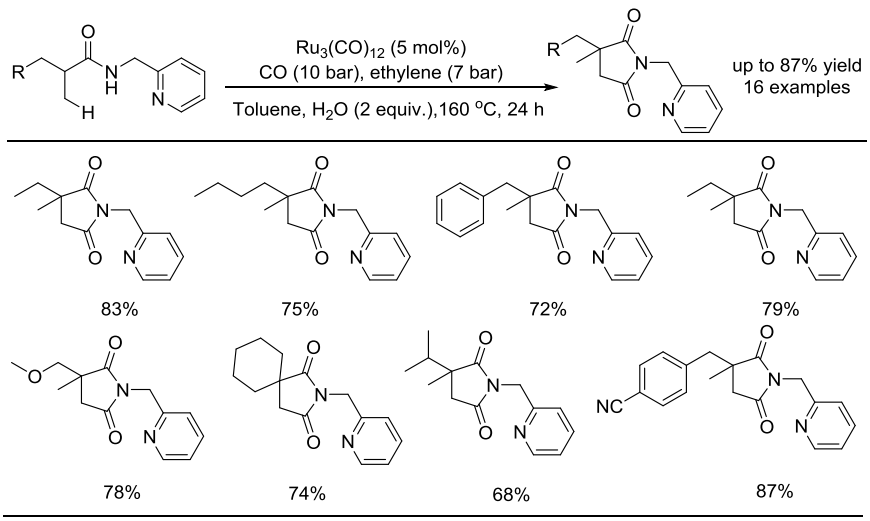
Scheme 1.23 Ru-catalyzed siteselective carbonylation of heterocycles.

In 2009, Chatani and co-workers described that aromatic amides having a pyridin-2-ylmethylamine moiety underwent *ortho* carbonylation of C-H bonds, leading to phthalimides using $Ru_3(CO)_{12}$ as the catalyst (Scheme 1.24).[44] In this reaction, a wide variety of functional groups, including methoxy, amino, ester, ketone, cyano, chloro, bromo groups, could be substituted for aromatic amides in high yields. After they examined the regioselectivity of the carbonylation using *meta*-substituted aromatic amides, they found that electronic effects were not dominant factors. However, the steric nature of the substituents was a significant effect on the regioselectivity of the reaction. To further understand the reaction mechanism, ^1H NMR experiments on a stoichiometric reaction were performed. A new ruthenium complex was formed as a single organometallic product. Unfortunately, no reaction occurred for the reaction in the presence of ruthenium complex as a catalyst under the standard reaction conditions without H_2O, which indicated that the presence of H_2O was required for the conversion of ruthenium complex into an active catalytic species. Thus, they suggested that ruthenium complex was not included in the main catalytic cycle. However, an active catalytic species was probably generated from ruthenium complex by reduction under water-gas-shift reaction conditions.



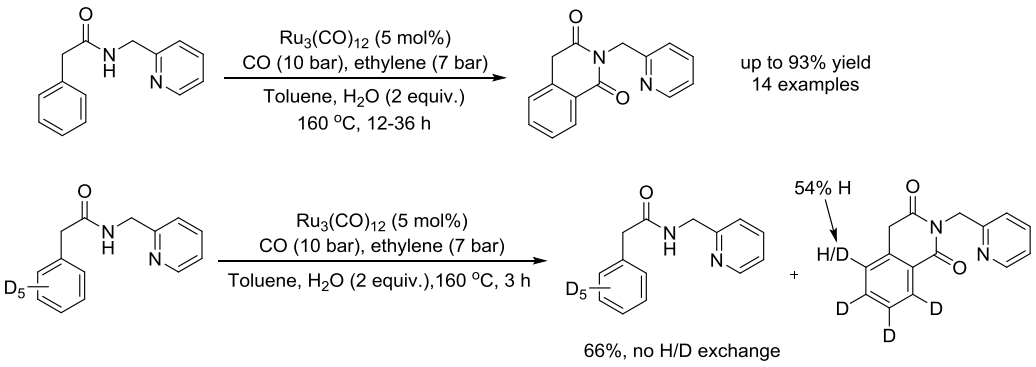
Scheme 1.24 Ru-catalyzed siteselective carbonylation at *ortho* C-H bonds in aromatic amides.

Subsequently, they reported a highly regioselective carbonylation reaction of unactivated C(sp^3)-H bonds by $Ru_3(CO)_{12}$ (Scheme 1.25).[45] In this reaction, the presence of the 2-pyridinylmethylamine moiety in the amide was crucial. The reaction showed a preference for C-H bonds of methyl groups as opposed to methylene C-H bonds. Five-membered-ring closure occurred preferentially over six-membered-ring formation in substrates containing multiple methyl substituents. The reaction tolerated a variety of functional groups such as OMe, Cl, CF_3, CN, and Br under the conditions. An intramolecular competition experiment was carried out to further understand the mechanism, which indicated that the cleavage of the C-H bond was the rate-determining step. The stoichiometric reaction of an amide with $Ru_3(CO)_{12}$ gave a dinuclear ruthenium complex in which the 2-pyridinylmethylamino moiety was coordinated to the ruthenium center in an *N,N* manner.



Scheme 1.25 Ru-catalyzed cyclocarbonylation of aliphatic amides.

Based on their previous reports, they described a ruthenium-catalyzed carbonylation of *ortho* C-H bonds in arylacetamides, which delivered six-membered-ring products (Scheme 1.26).[46] They examined the effect of directing groups on the progress of the carbonylation of the C-H bond of phenylacetic amides. Directing groups amides with shorter and longer carbon chains did not give the corresponding carbonylation products. The results proved that coordination was a key step for the reaction to proceed. Moreover, this reaction tolerated a variety of functional groups such as OMe, Cl, CF_3, CN, and Br. It was also applicable to the carbonylation of heteroaromatic rings, such as thiophene and indole. To gain insight into the reaction mechanism, a deuterium labelling experiment was carried out. No H/D exchange at *ortho*-position was detected in the recovered starting amide, indicating that the cleavage of the C-H bond was irreversible. Curiously, unexpected and significant amount of H/D exchange took place at 5-position of the product.

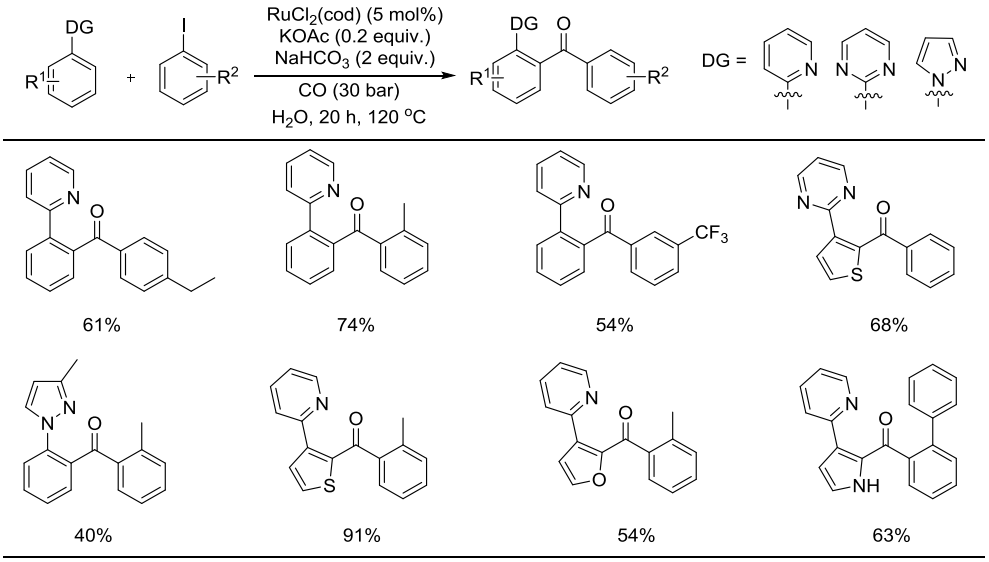


Scheme 1.26 Ru-catalyzed cyclocarbonylation of arylacetamides.

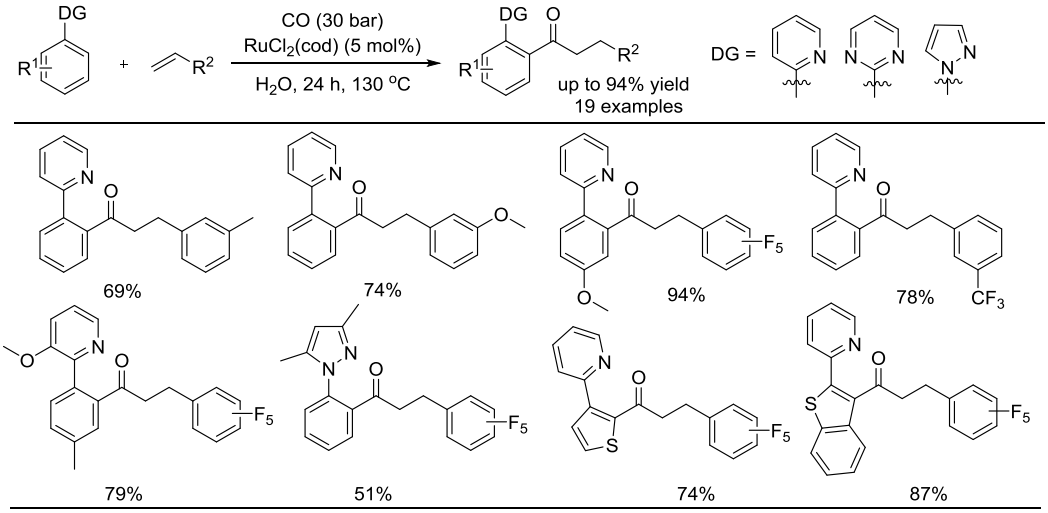
Our group developed a general and selective ruthenium-catalyzed carbonylation with heteroarene bearing *ortho*-directing groups (Scheme 1.27).[47] The carbonylation of 2-arylpyridines and related derivatives proceeded highly selective with water as the solvent. Using aryl iodides with either electron-donating or electron-withdrawing groups led to the formation of the corresponding benzophenone derivatives in moderate to good yields. However, aryl iodides with electron-withdrawing groups were less reactive than the ones with electron-donating groups. Aryl iodides substituted with alkyl groups in *ortho*-, *meta*-, or *para*-position were all effective. Directing groups such as pyrazole and pyrimidine could make this reaction work as well. Remarkably, stoichiometric amounts of organometallic reagents were avoided in this reaction.

A ruthenium-catalyzed carbonylation reaction of alkenes via C-H activation was reported by our group (Scheme 1.28).[48] Styrenes bearing either electron-donating or electron-withdrawing groups gave the corresponding ketone derivatives in moderate to good yields. No general trend was observed if the styrene was substituted in *ortho*-, *meta*-, or *para*-position. Besides, we found that the use of an excess amount of the styrene derivative in some cases also led to olefin dimerization, especially for

styrenes substituted with electron-withdrawing groups. Next, we turned our attention to the variation of the heteroarene and the directing group. Heteroarene substituted with a strong donating group delivered the best result. This reaction could also bear directing groups such as pyrazole and pyrimidine. H/D exchange experiments were performed. The results confirmed the reversibility of the metalation step.



Scheme 1.27 Ru-catalyzed carbonylative C-C coupling in water by directed C-H activation.

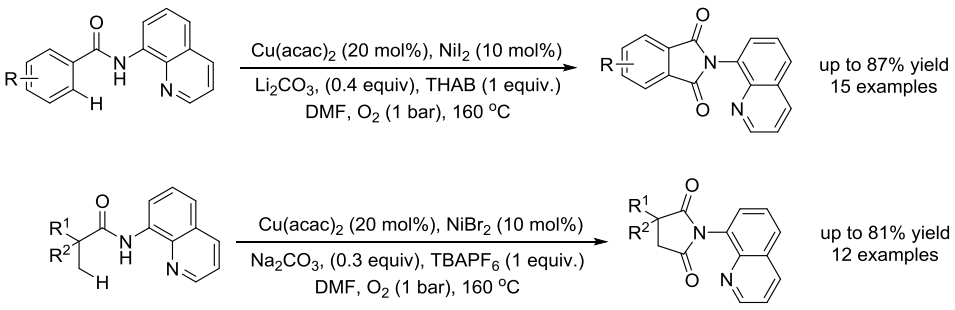


Scheme 1.28 Ru-catalyzed carbonylation of alkenes.

1.3 Copper-catalyzed carbonylation of nitrogen-containing compounds via C-H activation

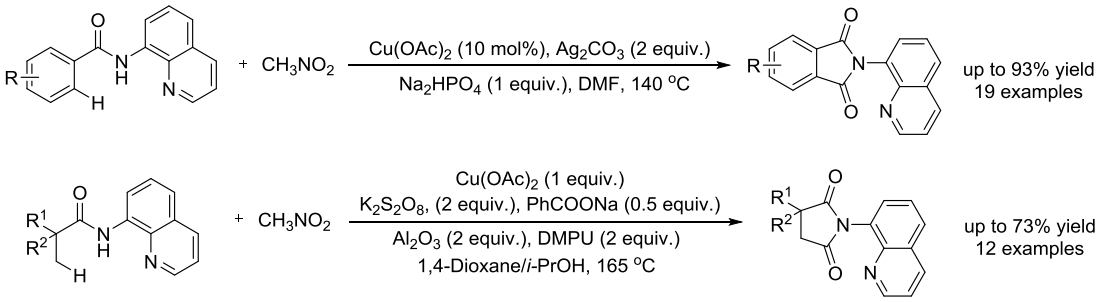
1.3.1 C-H carbonylation with directing group

In 2015, Ge and co-workers developed a carbonylation of C(sp^2)-H and C(sp^3)-H bonds through nickel/copper synergistic catalysis under O_2 with the assistance of a bidentate directing group. (Scheme 1.29).[49] The C(sp^2)-H activation was featured with high regioselectivity and good compatibility with a broad range of functional groups such as methoxyl, methyl, halogen (F, Cl, and Br), cyano, trifluoromethyl, and nitro groups. Additionally, substrates with electron-withdrawing groups on the phenyl ring gave lower yields compared with those with electron-donating groups. Unfortunately, heteroaromatic substrates failed to provide any desired products. The C(sp^3)-H activation showed a predominant preference for the *α*-methyl groups over the *α*- methylene and *β*- or *γ*-methyl groups. Good yields were obtained with 2,2-disubstituted propanamides bearing either the linear or cyclic chains. Mechanistic studies suggested that this reaction was performed through nickel/copper synergistic catalysis with the nickel species initiating the C-H activation of an amide to generate a nucleophile and DMF providing an electrophile by the copper species. Interestingly, it was found that C-H bond cleavage of aromatic amides was a reversible step, while C-H bond cleavage of aliphatic amides was the rate-limiting step, indicating that C-H activation on sp^3 carbons was a more challenging process compared with sp^2 carbons. Remarkably, DMF was used as the CO source.



Scheme 1.29 Carbonylation of C(sp^2)-H and C(sp^3)-H bonds via Cu/Ni synergistic catalysis.

Recently, they reported a copper-promoted siteselective carbonylation of C(sp^2)-H and C(sp^3)-H bonds using nitromethane as the CO source with the assistance of an 8-aminoquinolyl auxiliary (Scheme 1.30).[50] The C(sp^2)-H carbonylation featured high regioselectivity. A wide range of functional electron-donating groups and electron-withdrawing groups were well tolerated. The C(sp^3)-H carbonylation showed high siteselectivity as well. KIE studies indicated that the C(sp^3)-H bond breaking step was reversible, whereas the C(sp^2)-H bond cleavage was an irreversible but not the rate-determining step. Control experiments suggested that the substrate underwent a dehydrogenative coupling reaction with nitromethane, followed by a Nef reaction to form the carbonylation product.

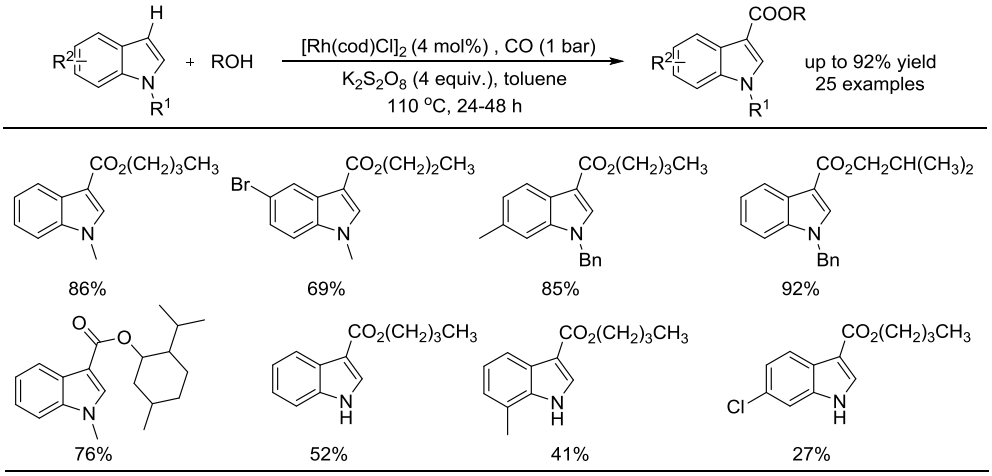


Scheme 1.30 Cu-promoted siteselective carbonylation of C(sp^2)-H and C(sp^3)-H bonds.

1.4 Rhodium-catalyzed carbonylation of nitrogen-containing compounds via C-H activation

1.4.1 C-H carbonylation without directing group

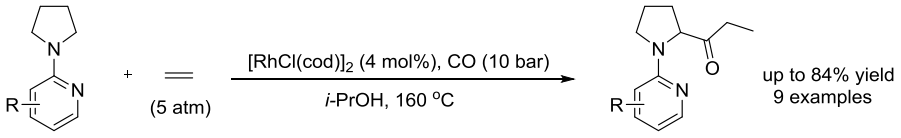
In 2011, Li and co-workers demonstrated a rhodium-catalyzed C-H carbonylation of indoles under 1 bar of CO (Scheme 1.31).[51] Various substituted indoles with linear or cyclic alcohols could afford the carbonylation products. Significant electronic effects of the substituents on the benzene ring of *N*-methyl indole toward reactivity were observed. Electron-deficient indoles gave better yields under the reaction conditions. Interestingly, substituents at the *N*-position of indole also significantly influenced the efficiency of the direct C-H carbonylation. The *N*-benzyl indole and its derivatives further substituted by electron-donating methyl groups at the 5-position or 6-position worked efficiently. However, only a trace amount of products could be observed when indole was *N*-substituted by strong electron-withdrawing groups such as Ts and Boc, indicating that the presence of Ts or Boc rendered the indole ring highly electron-deficient and retarded electrophilic metalation. Replacing indole with *N*-substituted pyrrole proceeded smoothly. Surprisingly, *NH*-free indole could also be regioselectively carboxylated at the C3 position instead of the *NH* position.



Scheme 1.31 Rh-catalyzed direct carbonylation of indoles.

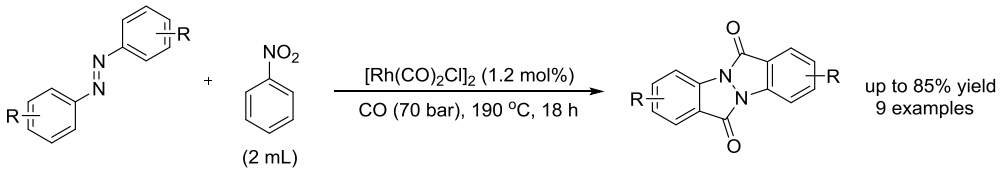
1.4.2 C-H carbonylation with directing group

In 2000, Murai and co-workers reported a rhodium-catalyzed C(sp^3)-H carbonylation reaction (Scheme 1.32).[52] They used cyclic amines as the substrates in conjunction with a rhodium complex and 2-propanol providing saturated ketones. No other regioisomeric products were observed. It was noteworthy that the nature of the substituents on the pyridine ring had a significant effect on the yields of products. Steric hindrance around the pyridine nitrogen and electron-deficient pyridine dramatically decreased the product yields.



Scheme 1.32 Rh-catalyzed C(sp^3)-H carbonylation of heterocycles.

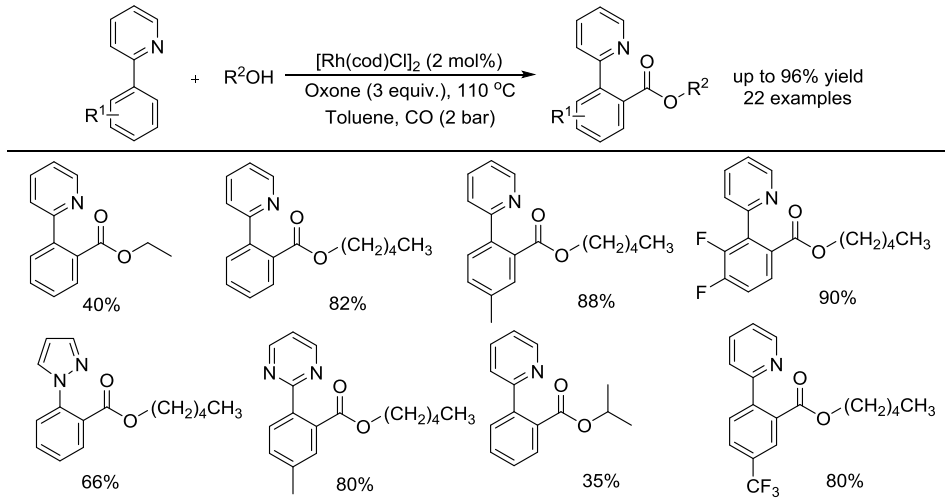
In 2004, Takahashi described a rhodium-catalyzed C-H carbonylation of azobenzenes (Scheme 1.33).[53] This reaction was in the presence of nitrobenzene as a hydrogen acceptor and gave four-ring heterocyclic products in good yields. They examined the reactivity of azobenzene derivatives bearing electron-donating and electron-withdrawing groups at *meta*-position or *para*-position relative to the azo group. The results indicated that the substituents gave a little electronic influence on the reactivity of azobenzene towards the carbonylation. However, decreasing the electron density on the phenyl ring would depress the C-H activation at *ortho*-position. In addition, the steric factor gave a strong effect on the carbonylation.



Scheme 1.33 Rh-catalyzed cyclocarbonylation of azobenzenes.

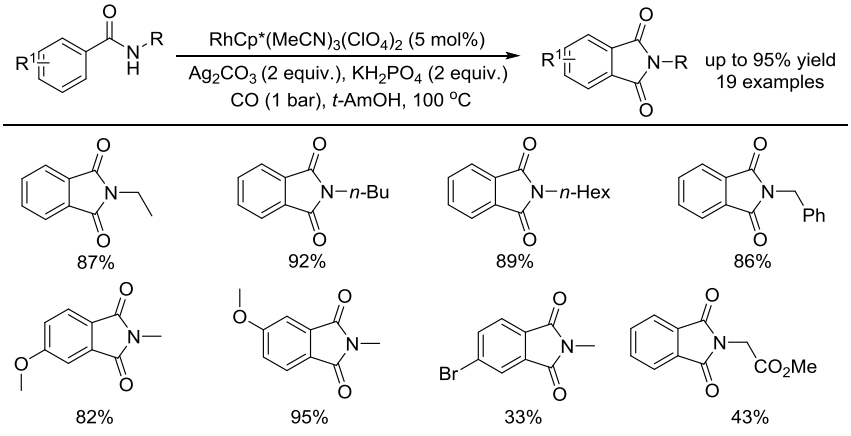
Guan and co-workers reported a rhodium-catalyzed oxidative carbonylation of arenes and heteroarenes with carbon monoxide and alcohols (Scheme 1.34).[54] Oxone was utilized as an inexpensive oxidant in this reaction. This reaction showed high regioselectivity and tolerated many good functional groups such as ester, trifluoromethyl, halogen and ether groups. Up to 96% yield of *ortho*-substituted aryl or heteroaryl carboxylic esters were obtained. They also found that electron-rich arenes showed more reactivity and gave slightly higher yields than electron-deficient arenes. Different directing groups, such as pyrazole, pyrimidine, and quinoline, could also work well under the conditions and generate the carbonylation products in moderate to good yields. Various

alcohols were tested and worked well in this carbonylation reaction. Notably, both steric hindrance and boiling point of alcohols played important roles in the transformation.



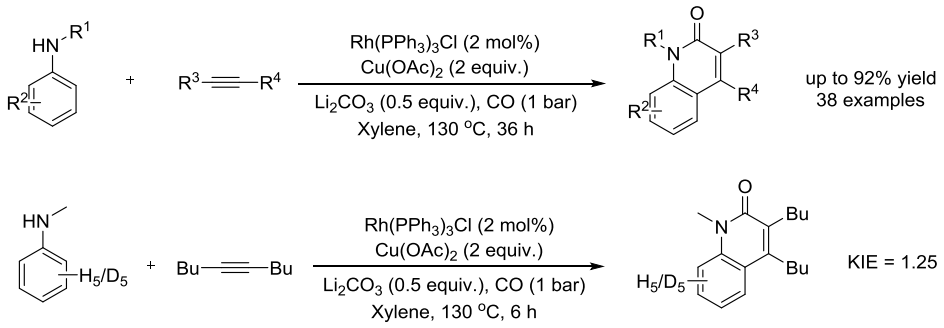
Scheme 1.34 Rh-catalyzed carbonylation of heteroarenes.

In 2011, Rovis and co-workers reported a rhodium-catalyzed oxidative carbonylation of benzamides with carbon monoxide (Scheme 1.35).[55] Various amides bearing alkyl groups at the nitrogen atom proceeded smoothly to deliver phthalimides in excellent yields. Substrates bearing *p*-methoxy and *p*-phenyl substituents were efficient. Amides with electron-withdrawing groups provided phthalimides in low yields. Substitution at the *meta*-position led to 3-substituted phthalimides as single regioisomers. Amides with *ortho*-substituted groups such as methoxy, methyl, phenyl and fluoro afforded phthalimides in minimal yields.



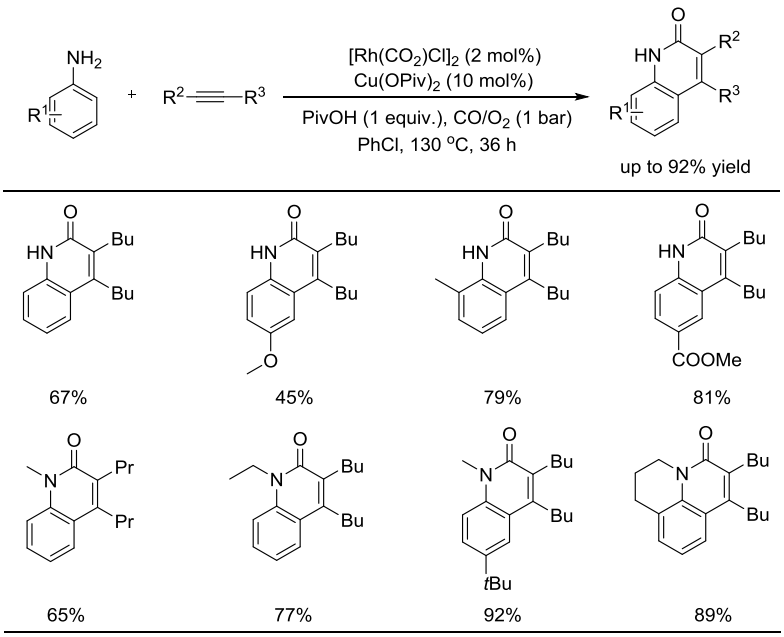
Scheme 1.35 Rh-catalyzed C-H carbonylation of benzamides.

Jiao and co-workers developed a rhodium-catalyzed carbonylation of simple anilines with carbon monoxide and alkynes (Scheme 1.36).[56] A variety of *N*-methylanilines bearing electron-donating groups, such as OMe, NHAc, Me, *t*-Bu, proceeded well under the conditions. *N*-methylanilines with weak electron-withdrawing groups such as Ph and Cl could also perform well. However, strong electron-withdrawing groups, such as F, COOMe, CN, and NO_2, were relatively sluggish and provided moderate yields. It was noteworthy that tetrahydroquinoline, tetrahydro-1H-benzo[*b*]azepine, and dihydrodibenzooxazepines performed smoothly to give moderate to good yields. Moreover, many aliphatic and aromatic internal alkynes were employed in this procedure as well, which gave the corresponding products in moderate to good yields. Besides, several isotope-labelling experiments were conducted. An intermolecular KIE of K_H/K_D = 1.25 was determined for the annulation reaction, which suggested that C-H bond cleavage was not involved in the rate-determining step of the catalytic cycle.



Scheme 1.36 Rh-catalyzed C-H carbonylation of anilines.

Recently, they reported an efficient rhodium-catalyzed C-H cyclization of simple anilines, alkynes, and carbon monoxide (Scheme 1.37).[57] Compared to their previous paper, there were three advantages in this procedure: i) A wide range of anilines were employed in this carbonylation protocol; ii) O_2 was utilized as the environmentally friendly oxidant for this reaction; iii) This reaction provided a three component cyclization approach to *N*-heterocycles with CO, which was used as a prominent C1 synthon in organic synthesis. In general, both electron-donating and electron-withdrawing substituents of anilines were well tolerated under the conditions. Primary anilines and secondary anilines containing electron-donating or electron-withdrawing groups reacted smoothly. Control experiments showed that no desired product was observed in the absence or presence of CO, which indicated that the formation of formylated aniline was not involved in this process. In addition, they conducted a DFT investigation, suggesting that Cu catalyst played a pivotal role in the transformation. CO insertion and alkyne insertion in the Rh(III) species were the key processes in this reaction.

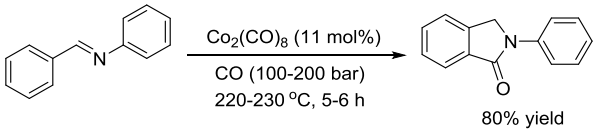


Scheme 1.37 Rh-catalyzed cyclization of anilines.

1.5 Cobalt-catalyzed carbonylation of nitrogen-containing compounds via C-H activation

1.5.1 C-H carbonylation with directing group

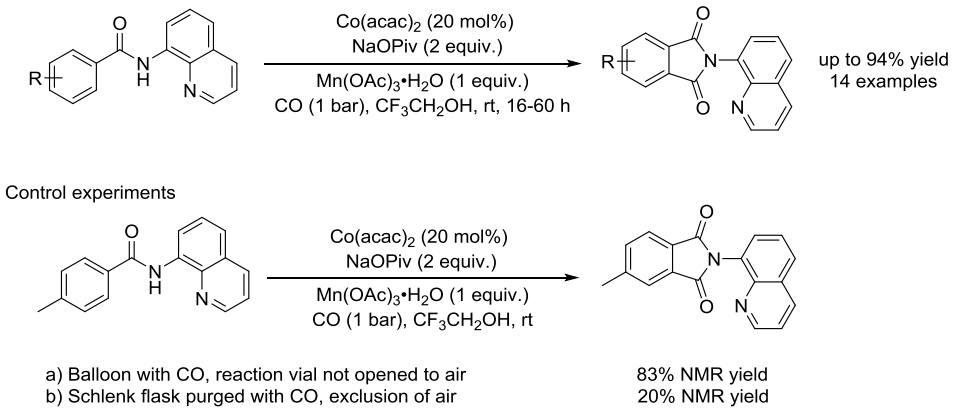
In 1955, Murahashi reported a cobalt carbonylation to synthesize phthalimidines (Scheme 1.38).[58] In this reaction, diphenylmethanimine was the substrate, using dicobalt octacarbonyl as the catalyst under 100-200 bar of CO at 220-230 °C for 5-6 hours, affording 2-phenylphthalimidine in 80% yield.



Scheme 1.38 Co-catalyzed carbonylation to synthesize phthalimidines.

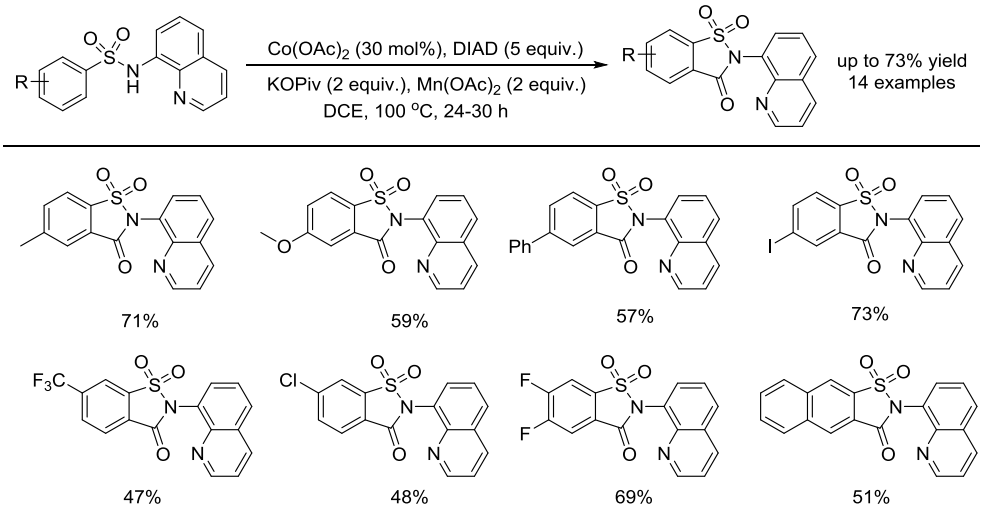
In 2014, Daugulis and co-workers demonstrated a cobalt-catalyzed C-H carbonylation of aminoquinoline benzamides (Scheme 1.39).[59] Reactions proceeded at room temperature in trifluoroethanol solvent, using oxygen from air as an oxidant. Halogen, nitro, ether, cyano, and ester functional groups were tolerated well. Carbonylation of aminoquinoline *p*-toluoylamide could also be carried out on 5 mmol scale, giving carbonylation product in 91% yield. It indicated that scale-up of the reaction was feasible. The directing group could be removed by treatment with ammonia, affording a high yield of a phthalimide derivative. Two control experiments were performed to determine the source of the oxidant. First, *p*-toluoylamide of aminoquinoline was carbonylated without opening of the reaction vial to air. CO was delivered from a balloon equipped with a needle.

The NMR yield of product was 83%. Second, the reaction was carried out in a CO-filled Schlenk flask with exclusion of oxygen. The NMR yield of the product was 20%. This result indicated that oxygen was delivered to the reaction via slow diffusion of air through the surface of the balloon.



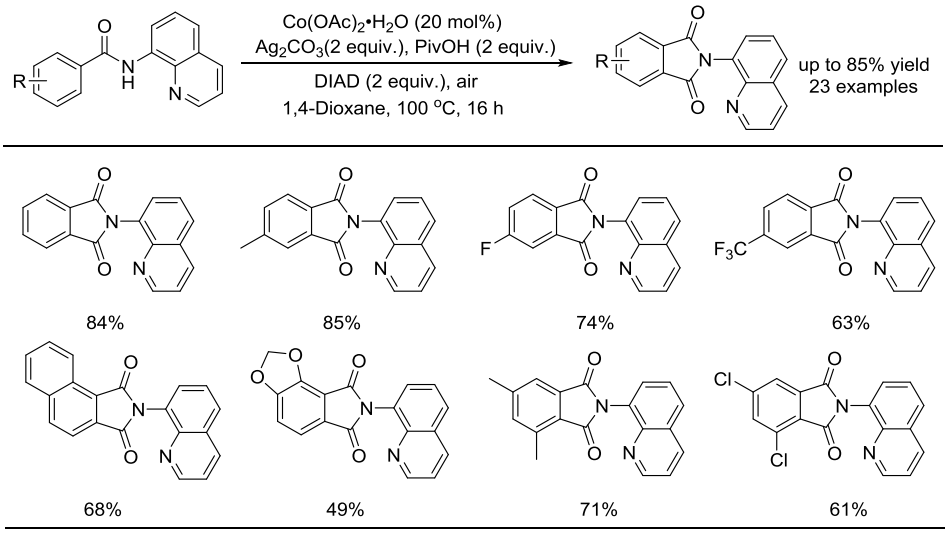
Scheme 1.39 Co-catalyzed carbonylation of aminoquinoline benzamides.

Recently, they developed a method for cobalt-catalyzed, aminoquinoline directed C(sp^2)-H bond carbonylation of sulphonamides (Scheme 1.40).[60] The reaction proceeded in a dichloroethane solvent, diisopropyl azodicarboxylate as a CO source, $Mn(OAc)_2$ as a co-oxidant and potassium pivalate as a base. Both electron-rich and electron-poor substrates afforded corresponding products in moderate to good yields. The reaction tolerated many functional groups such as alkoxy, iodo, bromo, trifluoromethoxy, trifluoromethyl, chloro, fluoro, naphthyl, unsaturated ester, and amide groups. Nitro-substituted sulphonamides did not give any carbonylation product.



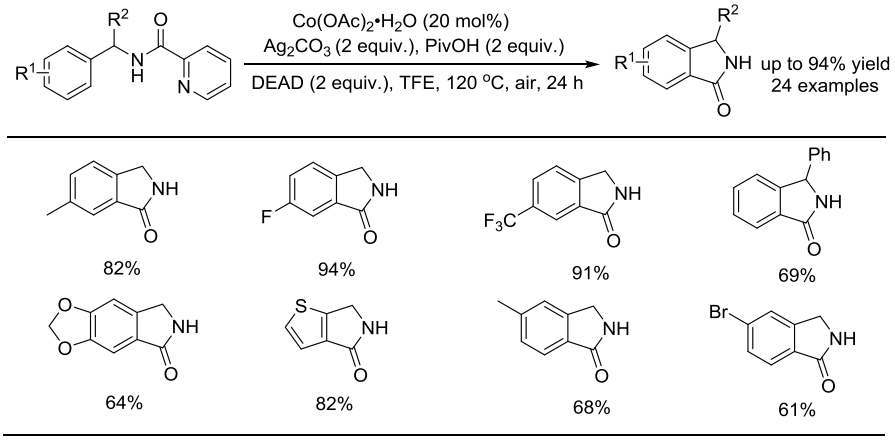
Scheme 1.40 Co-catalyzed carbonylation of aryl sulphonamides.

In 2016, Zhang and co-workers developed an approach for the C-H bond carbonylation of benzamides (Scheme 1.41).[61] They used $Co(OAc)_2 \cdot 4H_2O$ as a catalyst and diisopropyl azodicarboxylate as a nontoxic carbonyl source. Aromatic amides with electron-donating (Me, OMe, *t*-Bu) or electron-withdrawing (acetyl, halide) groups at *para*-position showed good compatibility. For *meta*-substituted benzamides, it was found that the reactions occurred at both *ortho*-positions, but the less hindered *ortho*-position was favored. The K_H/K_D value of 1.39 suggested that C-H bond cleavage probably occurred in the rate-determining step. In addition, they found that radical scavengers, such as TEMPO and BHT, significantly suppressed the reaction, which indicated that a single electron transfer process might be involved in the reaction.



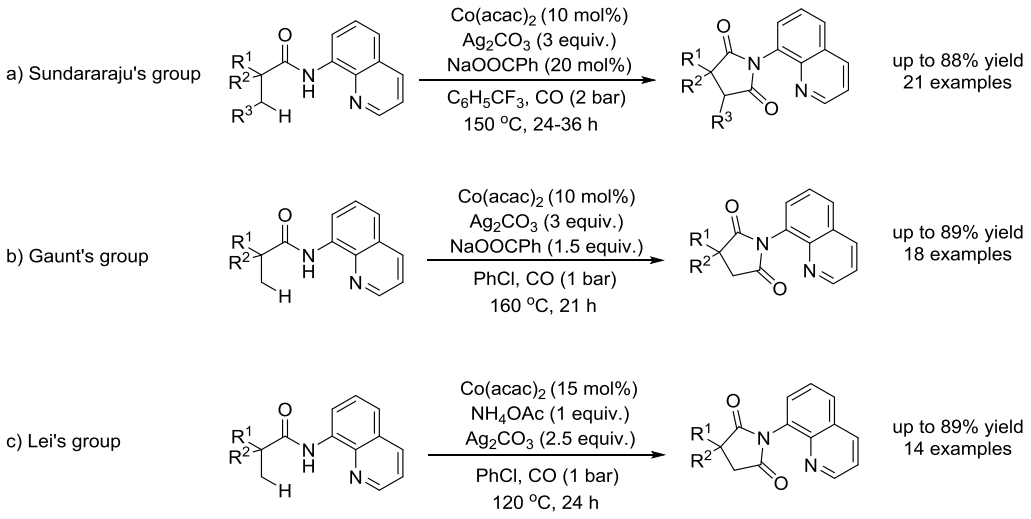
Scheme 1.41 Co-catalyzed carbonylation of benzamides with DIAD.

Zhong and co-workers described a cobalt-catalyzed *ortho* C-H carbonylation of benzylamines with diethyl azodicarboxylate via C-H activation (Scheme 1.42).[62] They used picolinamide as a traceless directing group, which accessed a variety of *N*-unprotected isoindolinones with excellent regioselectivity. Benzylamines containing electron-withdrawing groups proceeded in better yields than those with electron-donating counterparts. In addition, the substitution patterns of aryl moieties had a slight effect on this reaction. It was note of that this process exhibited excellent selectivity for *meta*-substituted substrates at 6-position. Additionally, this carbonylation strategy was also compatible with various aromatic or heteroaromatic substituted amines. Remarkably, diethyl azodicarboxylate was utilized as the environmentally benign carbonyl source.



Scheme 1.42 Co-catalyzed carbonylation of benzamides with DEAD.

Recently, Sundararaju, Gaunt, and Lei reported cobalt-catalyzed C-H carbonylative cyclizations of aliphatic amides, respectively (Scheme 1.43).[63] Central to the success of this procedure was the stabilizing effect of the quinolinamide directing group. Notably, Ag salt was crucial to this reaction. Various substituted propanamides were selectively transformed into corresponding succinimides in good to high yields.



Scheme 1.43 Co-catalyzed C-H carbonylative cyclization of aliphatic amides.

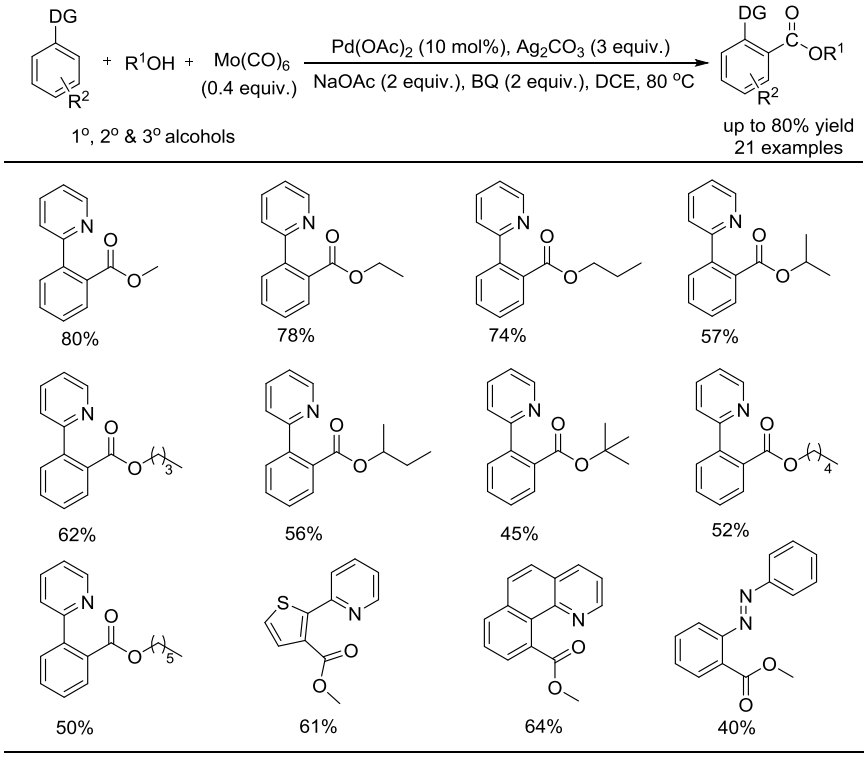
2. Objectives of this work

As described in the introduction, transition metal-catalyzed carbonylation reactions have attracted numerous attentions during the past several decades as they serve as a powerful synthesis toolkit for the chemists. Although many studies have been accomplished in this field, there are still so many parts to be discussed. The objectives of this work focus on different catalysts, various nitrogen-containing substrates, safe CO surrogates, and the applications of novel carbonylative methods. As we all know, palladium-catalyzed carbonylation reactions via C-H activation have been reported widely. However, other transition metal catalysts such as copper and ruthenium are very limited. Herein, palladium, ruthenium, and copper are selected as the catalysts which are highly efficient to construct various carbonyl compounds. In addition, nitrogen-containing compounds such as 2-substituted pyridines, ketimines, azoarenes, and indoles are used as the substrates which are important skeletons in natural products and pharmaceutical molecules. Series of nucleophiles such as alcohols and amines are discussed in this dissertation as well. In order to overcome the limitations of gaseous carbon monoxide in synthetic application, the development of CO surrogates to access safer and more operator friendly carbonylation reactions has been desirable. Molybdenum hexacarbonyl and hexaketocyclohexane are utilized as the solid CO sources which are cheap and easily handling in laboratory. Moreover, we have described many control experiments to further understand the transition metal-catalyzed carbonylation mechanisms such as the palladium, the ruthenium, and the copper catalytic cycle.

3. Summary of works

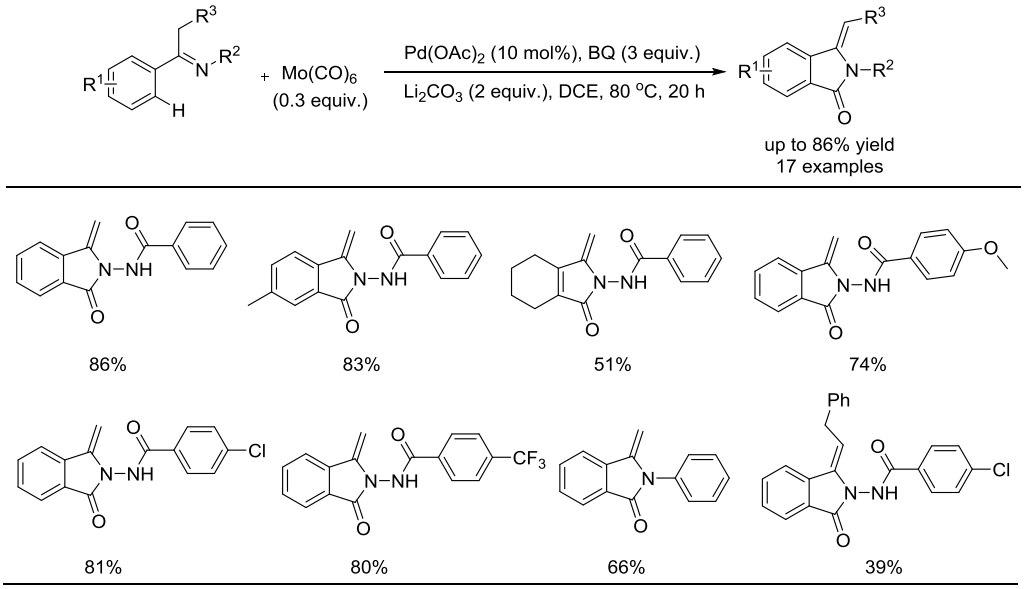
Following the objectives in this dissertation and based on the understanding of fundamental organometallic chemistry and transition metal-catalyzed carbonylations, the development of different transition metal-catalyzed carbonylations of nitrogen-containing compounds via C-H activation is described in this dissertation.

Palladium-catalyzed oxidative carbonylation of aromatic C-H bonds with alcohols using molybdenum hexacarbonyl as the carbon monoxide source (*Adv. Synth. Catal.* **2016**, *358*, 2855-2859). In this paper, a mild and general procedure for palladium-catalyzed alkoxycarbonylation of arenes with $Mo(CO)_6$ as the CO source was developed (Scheme 3.1). A variety of primary, secondary and tertiary alcohols could be applied as substrates under our reaction conditions and gave the corresponding esters in moderate to good yields. High regioselectivity as well as good functional group tolerance could be demonstrated. The desired carbonylation products were isolated in moderate to good yields. Nitrogen heterocycles, such as pyrazole and pyrimidine, served as efficient directing groups and generated the carbonylation products in good yields under the optimal conditions. Additionally, only 0.4 equivalent of $Mo(CO)_6$ as a solid and safe CO source was required for this new procedure.



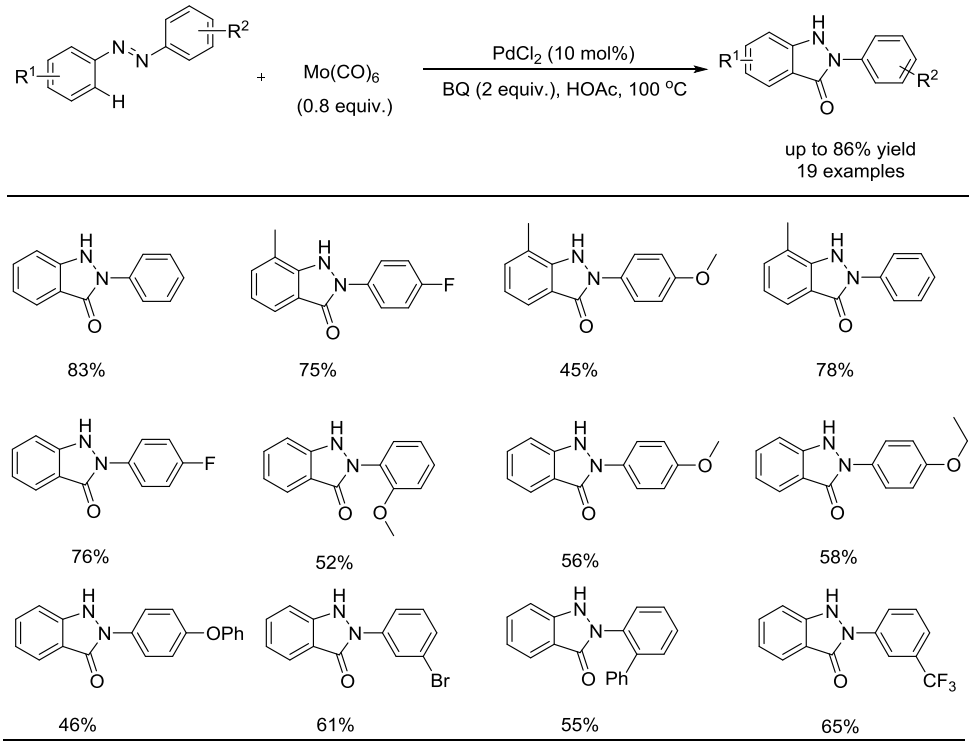
Scheme 3.1 Pd-catalyzed carbonylation of C-H bonds with alcohols.

Palladium-catalyzed carbonylative synthesis of 3-methyleneisoindolin-1-ones from ketimines with hexacarbonylmolybdenum as the carbon monoxide source (*ChemCatChem* **2017**, *9*, 94-98). In this paper, we also used $Mo(CO)_6$ instead of carbon monoxide as the CO source to synthesize 3-methyleneisoindolin-1-ones (Scheme 3.2). Among the heterocyclic scaffolds, the 3-methyleneisoindolin-1-one skeleton was one of the most important structures in nature products and pharmaceutical molecules. Traditionally, 3-methyleneisoindolin-1-ones were prepared from phthalimides. In this case, a new palladium-catalyzed carbonylative intramolecular cyclization of ketimines via C-H bond activation was developed. In the presence of a palladium catalyst and $Mo(CO)_6$ (0.3 equiv.), the desired substituted 3-methyleneisoindolin-1-ones were isolated in moderate to good yields.



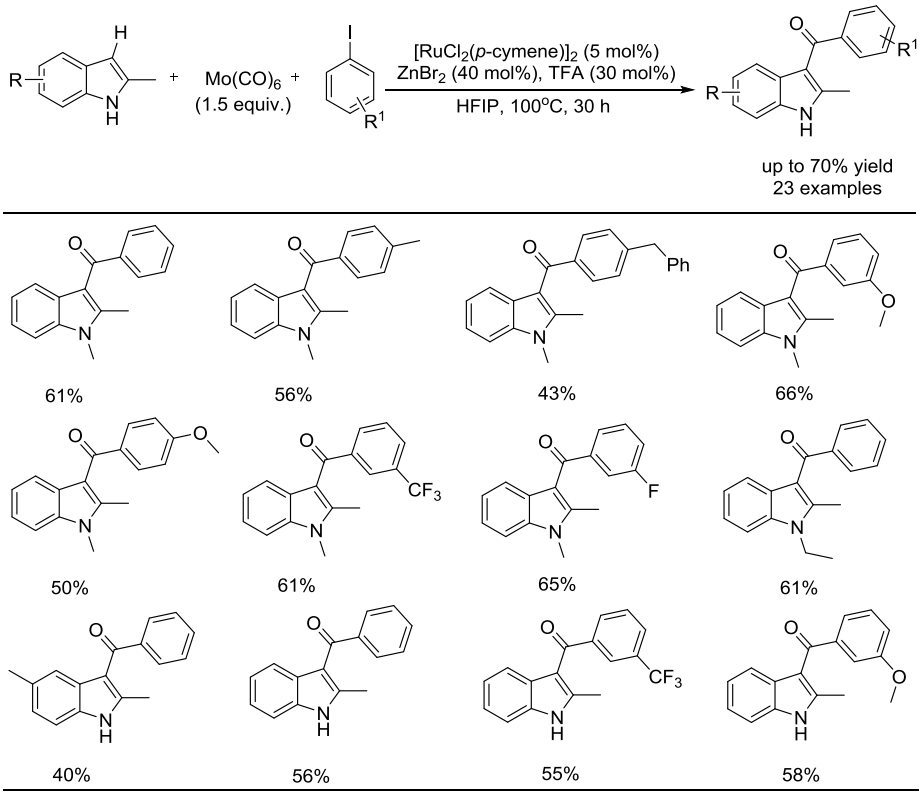
Scheme 3.2 Pd-catalyzed carbonylative synthesis of 3-methyleneisoindolin-1-ones.

Palladium-catalyzed carbonylative cyclization of azoarenes (*ChemCatChem* **2017**, *9*, 3637-3640). In this paper, a palladium-catalyzed carbonylative synthesis of substituted 2-arylindazolones from symmetrical and unsymmetrical azoarenes was developed (Scheme 3.3). With $Mo(CO)_6$ (0.8 equiv.) as a solid CO source, moderate to good yields of the desired products were obtained with high regioselectivity through C-H bond activation. Readily available aniline could also be applied, and a good yield of the target product was obtained. Notably, the reaction tolerated a variety of functional groups, including fluoro, bromo, methoxy, phenoxy, and trifluoromethyl groups.



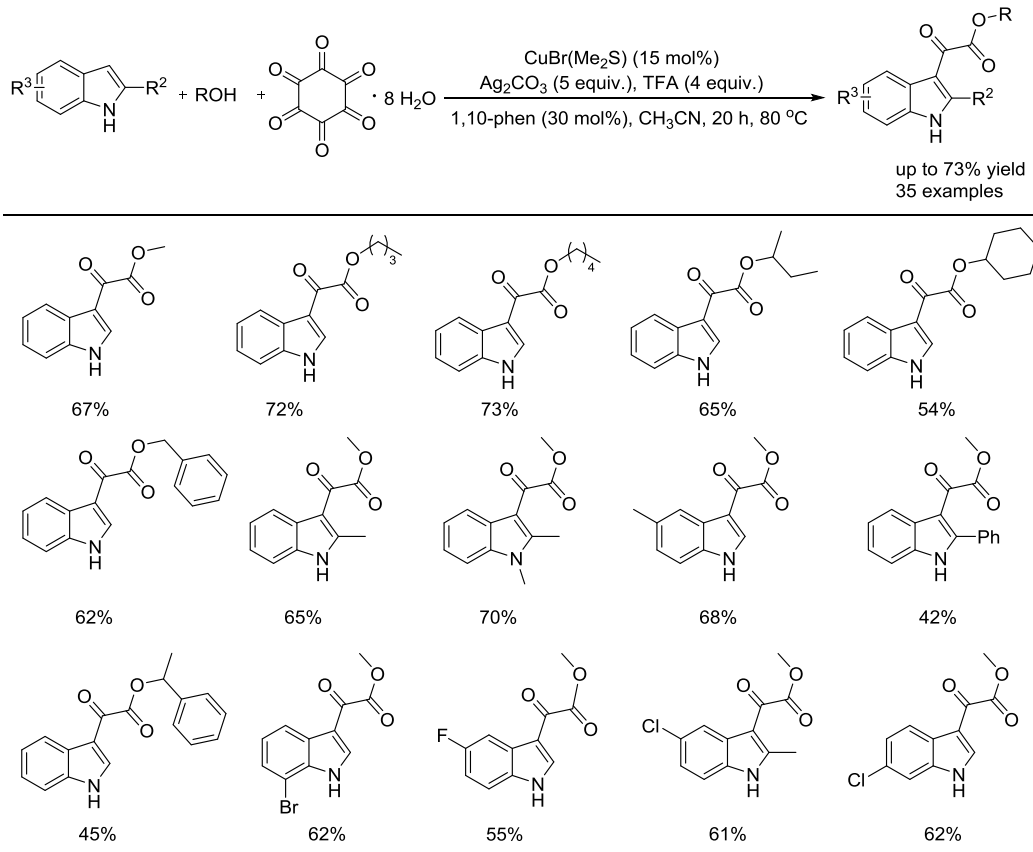
Scheme 3.3 Pd-catalyzed carbonylative cyclization of azoarenes.

3-Acylindoles synthesis: ruthenium-catalyzed carbonylative coupling of indoles and aryl iodides (*Org. Lett.* **2017**, *19*, 4680-4683). In this paper, we used ruthenium as the catalyst which was attractive due to their relative low cost and high reaction selectivity. We developed an interesting procedure for the synthesis of 3-acylindoles (Scheme 3.4). Through ruthenium-catalyzed carbonylative C-H functionalization with $Mo(CO)_6$ as the solid CO source, moderate to good yields of the desired products could be prepared with good functional group tolerance. Using iodoarenes with either electron-donating or electron-withdrawing groups led to the formation of the corresponding carbonylation products in moderate to good yields. Substrates tolerated various functional groups such as Bn, OMe, CF_3, Cl, F, and COOMe. Iodoarenes substituted with functional groups at *meta*-position could give higher yields than that at *para*-position. *N*-Substituted indoles could be readily carbonylated with iodoarenes to provide moderate to good yields of the corresponding carbonylation products. The methyl group at 2-position of indoles played a crucial role in the carbonylative C-H activation reaction.



Scheme 3.4 Ru-catalyzed carbonylative coupling of indoles and aryl iodides.

Copper-catalyzed double carbonylation of indoles using hexaketocyclohexane as the carbon monoxide source (*Chem. Commun.* **2018**, *54*, 4798-4801). In this paper, copper was used as the catalyst. The CO source used in this reaction was $C_6O_6{\cdot}8H_2O$ which was formed by oligomerization of carbon monoxide through the formation of molybdenum carbonyls. The use of $C_6O_6{\cdot}8H_2O$ as an inexpensive and environmental friendly CO source made this reaction attractive in organic synthesis. We developed a new copper-catalyzed double carbonylation of indoles and alcohols with $C_6O_6{\cdot}8H_2O$ as a solid and safe CO source (Scheme 3.5). In the presence of 1 equivalent of $C_6O_6{\cdot}8H_2O$, various alcohols were carbonylated in moderate to good yields. Primary and secondary alcohols worked well under our reaction conditions and gave the double carbonylation products in moderate to good yields. Both aliphatic alcohols and aromatic alcohols were applicable as reaction partners. A series of functional groups, such as OMe, Ph, CF_3, Cl, and Br were compatible under our conditions, which gave the desired double carbonylation products in good isolated yields. However, no product was detected when COOMe group substituted at 2-position of indole.



Scheme 3.5 Cu-catalyzed double carbonylation of indoles.

4. References

[1] a) J. Alvarez-Builla, J. J. Vaquero, J. Barluenga, *Modern Heterocyclic Chemistry*, Wiley-VCH, **2011**; b) J. A. Joule, K. Mills, *Heterocyclic Chemistry*, Wiley-Blackwell, Oxford, **2010**; c) L. D. Quin, J. Tyrell, *Fundamentals of Heterocyclic Chemistry*, Wiley-Blackwell, Oxford, **2010**; d) A. R. Katritzky, C. A. Ramsden, J. A. Joule, V. V. Zhdankin, *Handbook of Heterocyclic Chemistry*, Elsevier, Amsterdam, **2010**; e) R. K. Bansal, *Heterocyclic Chemistry*, Anshan, Tunbridge Wells, **2008**; f) T. Eicher, S. Hauptmann, *The Chemistry of Heterocycles*, Wiley-VCH, **2003**; g) J. Dinges, C. Lamberth, *Bioactive Heterocyclic Compound Classes: Pharmaceuticals*, Wiley-VCH, **2012**.

[2] a) A. Schoenberg, R. F. Heck*, J. Am. Chem. Soc.* **1974**, *96*, 7761-7764; b) A. Schoenberg, R. F. Heck, *J. Org. Chem*. **1974**, *39*, 3327-3331; c) A. Schoenberg, I. Bartoletti, R. F. Heck, *J. Org. Chem.* **1974**, *39*, 3318-3326.

[3] a) X. F. Wu, H. Neumann, M. Beller, *Chem. Soc. Rev.* **2011**, *40*, 4986-5009; b) X. F. Wu, H. Neumann, M. Beller, *Chem. Rev.* **2013**, *113*, 1-35.

[4] a) X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2009**, *48*, 5094-5115; b) R.-Y. Tang, G. Li, J.-Q. Yu, *Nature* **2014**, *507*, 215-220; c) J. He, S. Li, Y. Deng, H. Fu, B. N. Laforteza, J. E. Spangler, A. Homs, J.-Q. Yu, *Science* **2014**, *343*, 1216-1220; d) L. Chu, K.-J. Xiao, J.-Q. Yu, *Science* **2014**, *346*, 451-455; e) Y.-J. Liu, H. Xu, W.-J. Kong, M. Shang, H.-X. Dai, J.-Q. Yu, *Nature* **2014**, *515*, 389-393; f) C.-L. Sun, Z.-J. Shi, *Chem. Rev.* **2014**, *114*, 9219-9280; g) C.-L. Sun, B.-J. Li, Z.-J. Shi, *Chem. Rev.* **2010**, *111*, 1293-1314; h) L. Ackermann, R. Vicente, A. R. Kapdi, *Angew. Chem. Int. Ed.* **2009**, *48*, 9792-9826; i) C. S. Yeung, V. M. Dong, *Chem. Rev.* **2011**, *111*, 1215-1292; j) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147-1169.

[5] a) S. Ohashi, S. Sakaguchi, Y. Ishii, *Chem. Commun.* **2005**, *4*, 486-488; b) W. Y. Yu, W. N. Sit, K. M. Lai, Z. Zhou, A. S. C. Chan*, J. Am. Chem. Soc.* **2008**, *130*, 3304-3306; c) B. Liu, F. Hu, B. F. Shi, *ACS Catal.* **2015**, *5*, 1863-1881.

[6] a) T. Morimoto, K. Kakiuchi, *Angew. Chem. Int. Ed.* **2004**, *43*, 5580-5588; b) P. Gautam, B. M. Bhanage, *Catal. Sci. Technol.* **2015**, *5*, 4663-4702; c) S. D. Friis, A. T. Lindhardt, T. Skrydstrup, *Acc. Chem. Res*. **2016**, *49*, 594-605.

[7] P. Hermange, A. T. Lindhardt, R. H. Taaning, K. Bjerglund, D. Lupp, T. Skrydstrup, *J. Am. Chem. Soc.* **2011**, *133*, 6061-6071.

[8] S. D. Friis, R. H. Taaning, A. T. Lindhardt, T. Skrydstrup, *J. Am. Chem. Soc.* **2011**, *133*, 18114-18117.

[9] T. Ueda, H. Konishi, K. Manabe, *Angew. Chem. Int. Ed.* **2013**, *52*, 8611-8615.

[10] a) K.-I. Tominaga, Y. Sasaki, *Catal. Commun.* **2000**, *1*, 1-3; b) K.-I. Tominaga, Y. Sasaki, *J. Mol. Catal. A* **2004**, *220*, 159-165; c) T. G. Ostapowicz, M. Schmitz, M. Krystof, J. Klankermayer, W. Leitner, *Angew. Chem. Int. Ed.* **2013**, *52*, 12119-12123; d) L. Wu, Q. Liu, I. Fleischer, R. Jackstell, M. Beller, *Nat. Commun.* **2014**, *5*, 3091-3096; e) Q. Liu, L. Wu, I. Fleischer, D. Selent, R. Franke, R. Jackstell, M. Beller, *Chem. Eur. J.* **2014**, *20*, 6888-6894.

[11] C. Brancour, T. Fukuyama, Y. Mukai, T. Skrydstrup, I. Ryu, *Org. Lett.* **2013**, *15*, 2794-2797.

[12] Q. Liu, K. Yuan, P. -B. Arockiam, R. Franke, H. Doucet, R. Jackstell, M. Beller, *Angew. Chem. Int. Ed.* **2015**, *54*, 4493-4497.

[13] a) K. Fuji, T. Morimoto, K. Tsutsumi, K. Kakiuchi, *Angew. Chem. Int. Ed.* **2003**, *42*, 2409-2411; b) K. Fuji, T. Morimoto, K. Tsutsumi, K. Kakiuchi, *Tetrahedron Lett.* **2004**, *45*, 9163-9166; c) K. Fuji, T. Morimoto, K. Tsutsumi, K. Kakiuchi, *Chem. Commun.* **2005**, *26*, 3295-3297; d) T. Morimoto,

K. Yamasaki, A. Hirano, K. Tsutsumi, N. Kagawa, K. Kakiuchi, Y. Harada, Y. Fukumoto, N. Chatani, T. Nishioka, *Org. Lett.* **2009**, *11*, 1777-1780; e) G. Makado, T. Morimoto, Y. Sugimoto, K. Tsutsumi, N. Kagawa, K. Kakiuchi, *Adv. Synth. Catal.* **2010**, *352*, 299-304; f) A. Köpfer, B. Sam, B. Breit, M. J. Krische, *Chem. Sci.* **2013**, *4*, 1876-1880; g) K. Natte, A. Dumrath, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.* **2014**, *53*, 10090-10094; h) Q. Liu, L. Wu, R. Jackstell, M. Beller, *ChemCatChem* **2014**, *6*, 2805-2809.

[14] a) Y. Wan, M. Alterman, M. Larhed, A. Hallberg, *J. Org. Chem.* **2002**, *67*,6232-6235; b) X. Wu, Y. Zhao, H. Ge, *J. Am. Chem. Soc.* **2015**, *137*, 4924-4927.

[15] L. -B. Jiang, X. Qi, X. -F. Wu, *Tetrahedron Lett.* **2016**, *57*, 3368-3370.

[16] P. Caldirola, R. Chowdhury, A. M. Johansson, U. Hacksell, *Organometallics* **1995**, *14*, 3897-3900.

[17] J. Georgsson, A. Hallberg, M. Larhed, *J. Comb. Chem.* **2003**, *5*, 350-352.

[18] J. E. McCusker, A. D. Main, K. S. Johnson, C. A. Grasso, L. McElwee-White, *J. Org. Chem.* **2000**, *65*, 5216-5222.

[19] S. Murahashi, *J. Am. Chem. Soc.* **1955**, *77*, 6403-6404.

[20] R. B. Wyrwas, C. C. Jarrold, *J. Am. Chem. Soc.* **2006**, *128*, 13688-13689.

[21] A. Ricci, *Amino Group Chemistry: From Synthesis to the Life Sciences*, Wiley-VCH: Weinheim, **2008**.

[22] H. Zhang, D. Liu, C. Chen, C. Liu, A. Lei, *Chem. Eur. J.* **2011**, *17*, 9581-9585.

[23] J. Wen, S. Tang, F. Zhang, R. Shi, A. Lei, *Org. Lett.* **2017**, *19*, 94-97.

[24] a) D. Willcox, B. G. N. Chappell, K. F. Hogg, J. Calleja, A. P. Smalley, M. J. Gaunt, *Science* **2016**, 354, 851-857; b) J. R. Cabrera-Pardo, A. Trowbridge, M. Nappi, K. Ozaki, M. J. Gaunt, *Angew. Chem. Int. Ed.* **2017**, *56*, 11958-11962.

[25] Z. -H. Guan, M. Chen, Z. -H. Ren, *J. Am. Chem. Soc.* **2012**, *134*, 17490-17493.

[26] a) M. Chen, Z. -H. Ren, Y. -Y. Wang, Z. -H. Guan, *J. Org. Chem.* **2015**, *80*, 1258-1263; b) W. Li, Z. Duan, R. Jiang, A. Lei, *Org. Lett.* **2015**, *17*, 1397-1400.

[27] R. Shi, L. Lu, H. Zhang, B. Chen, Y. Sha, C. Liu, A. Lei, *Angew. Chem. Int. Ed.* **2013**, *52*, 10582-10585.

[28] R. Shi, L. Lu, H. Xie, J. Yan, T. Xu, H. Zhang, X. Qi, Y. Lan, A. Lei, *Chem. Commun.* **2016**, *52*, 13307-13310.

[29] a) K. Orito, A. Horibata, T. Nakamura, H. Ushito, H. Nagasaki, M. Yuguchi, S.i Yamashita, M. Tokuda, *J. Am. Chem. Soc.* **2004**, *126*, 14342-14343; b) K. Orito, M. Miyazawa, T. Nakamura, A. Horibata, H. Ushito, H. Nagasaki, M. Yuguchi, S. Yamashita, T. Yamazaki, M. Tokuda, *J. Org. Chem.* **2006**, *71*, 5951-5958.

[30] B. Haffemayer, M. Gulias, M. J. Gaunt, *Chem. Sci.* **2011**, *2*, 312-315.

[31] H. Li, G. -X. Caia, Z. -J. Shi, *Dalton Trans.* **2010**, *39*, 10442-10446.

[32] a) D. Liang, Z. Hu, J. Peng, J. Huang, Q. Zhu, *Chem. Commun.* **2013**, *49*, 173-175; b) Z. Liang, J. Zhang, Z. Liu, K. Wang, Y. Zhang, *Tetrahedron* **2013**, *69*, 6519-6526; c) D. N. Rao, Sk. Rasheed, P. Das, *Org. Lett.* **2016**, *18*, 3142-3145.

[33] E. J. Yoo, M. Wasa, J. -Q. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 17378-17380.

[34] J. W. Wrigglesworth, B. Cox, G. C. Lloyd-Jones, K. I. Booker-Milburn, *Org. Lett.* **2011**, *13*, 5326-5329.

[35] E. Hernando, J. Villalva, Á. M. Martínez, I. Alonso, N. Rodríguez, R. G. Arrayás, J. C. Carretero, *ACS Catal.* **2016**, *6*, 6868-6882.

[36] F. Zhou, D. -S. Wang, X. Guan, T. G. Driver, *Angew. Chem. Int. Ed.* **2017**, *56*, 4530-4534.

[37] J. Chen, K. Natte, A. Spannenberg, H. Neumann, M. Beller, X. -F. Wu, *Chem. Eur. J.* **2014**, *20*, 14189-14193.

[38] J. Chen, J. -B. Feng, K. Natte, X. -F. Wu, *Chem. Eur. J.* **2015**, *21*, 16370-16373.

[39] E. J. Moore, W. R. Pretzer, T. J. O'Connell, J. Harris, L. LaBounty, L. Chou, S. S. Grimmer, *J. Am. Chem. Soc.* **1992**, *114*, 5888-5890.

[40] N. Chatani, T. Fukuyama, F. Kakiuchi, S. Murai, *J. Am. Chem. Soc.* **1996**, *118*, 493-494.

[41] N. Chatani, T. Fukuyama, H. Tatamidani, F. Kakiuchi, S. Murai, *J. Org. Chem.* **2000**, *65*, 4039-4047.

[42] T. Fukuyama, N. Chatani, J. Tatsumi, F. Kakiuchi, S. Murai, *J. Am. Chem. Soc.* **1998**, *120*, 11522-11523.

[43] a) N. Chatani, Y. Ie, F. Kakiuchi, S. Murai, *J. Org. Chem.* **1997**, *62*, 2604-2610; b) Y. Ie, N. Chatani, T. Ogo, D. R. Marshall, T. Fukuyama, F. Kakiuchi, S. Murai, *J. Org. Chem.* **2000**, *65*, 1475-1488; c) N. Chatani, S. Yorimitsu, T. Asaumi, F. Kakiuchi, S. Murai, *J. Org. Chem.* **2002**, *67*, 7557-7560; d) T. Asaumi, N. Chatani, T. Matsuo, F. Kakiuchi, S. Murai, *J. Org. Chem.* **2003**, *68*, 7538-7540.

[44] S. Inoue, H. Shiota, Y. Fukumoto, N. Chatani, *J. Am. Chem. Soc.* **2009**, *131*, 6898-6899.

[45] N. Hasegawa, V. Charra, S. Inoue, Y. Fukumoto, N. Chatani, *J. Am. Chem. Soc.* **2011**, *133*, 8070-8073.

[46] K. Shibata, N. Hasegawa, Y. Fukumoto, N. Chatani, *ChemCatChem* **2012**, *4*, 1733-1736.

[47] a) A. Tlili, J. Schranck, J. Pospech, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.* **2013**, *52*, 6293-6297; b) J. Pospech, A. Tlili, A. Spannenberg, H. Neumann, M. Beller, *Chem. Eur. J.* **2014**, *20*, 3135-3141.

[48] A. Tlili, J. Schranck, J. Pospech, H. Neumann, M. Beller, *ChemCatChem* **2014**, *6*, 1562-1566.

[49] X. Wu, Y. Zhao, H. Ge, *J. Am. Chem. Soc.* **2015**, *137*, 4924-4927.

[50] X. Wu, J. Miao, Y. Li, G. Li, H. Ge, *Chem. Sci.* **2016**, *7*, 5260-5264.

[51] R. Lang, J. Wu, L. Shi, C. Xia, F. Li, *Chem. Commun.* **2011**, *47*, 12553-12555.

[52] N. Chatani, T. Asaumi, T. Ikeda, S. Yorimitsu, Y. Ishii, F. Kakiuchi, S. Murai, *J. Am. Chem. Soc.* **2000**, *122*, 12882-12883.

[53] D. -Y. Zhou, T. Koike, S. Suetsugu, K. Onitsuka, S. Takahashi, *Inorganica. Chimica. Acta.* **2004**, *357*, 3057-3063.

[54] Z. -H. Guan, Z. -H. Ren, S. M. Spinella, S. Yu, Y. -M. Liang, X. Zhang, *J. Am. Chem. Soc.* **2009**, *131*, 729-733.

[55] Y. Du, T. K. Hyster, T. Rovis, *Chem. Commun.* **2011**, *47*, 12074-12076.

[56] X. Li, X. Li, N. Jiao, *J. Am. Chem. Soc.* **2015**, *137*, 9246-9249.

[57] X. Li, J. Pan, H. Wua, N. Jiao, *Chem. Sci.* **2017**, *8*, 6266-6273.

[58] S. Murahashi, *J. Am. Chem. Soc.* **1955**, *77*, 6403-6404.

[59] L. Grigorjeva, O. Daugulis, *Org. Lett.* **2014**, *16*, 4688-4690.

[60] T. T. Nguyen, L. Grigorjeva, O. Daugulis, *Chem. Commun.* **2017**, *53*, 5136-5138.

[61] J. Ni, J. Li, Z. Fan, A. Zhang, *Org. Lett.* **2016**, *18*, 5960-5963.

[62] F. Ling, C. Ai, Y. Lv, W. Zhong, *Adv. Synth. Catal.* **2017**, *359*, 3707-3712.

[63] a) N. Barsu, S. K. Bolli, B. Sundararaju, *Chem. Sci.* **2017**, *8*, 2431-2435; b) P. Williamson, A. Galván, M. J. Gaunt, *Chem. Sci.* **2017**, *8*, 2588-2591; c) L. Zeng, S. Tang, D. Wang, Y. Deng, J. -L. Chen, J. -F. Lee, A. Lei, *Org. Lett.* **2017**, *19*, 2170-2173.

5. Publications

5.1 Palladium-Catalyzed Oxidative Carbonylation of Aromatic C-H Bonds with Alcohols using Molybdenum Hexacarbonyl as the Carbon Monoxide Source

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Author contributions:

In this paper, I finished the optimization of reaction conditions, investigation of substrate scope and writing the manuscript. My contribution as the first author of this paper is approximately 80%.

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Palladium-Catalyzed Oxidative Carbonylation of Aromatic C–H Bonds with Alcohols using Molybdenum Hexacarbonyl as the Carbon Monoxide Source

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Abstract: With molybdenum hexacarbonyl as the carbon monoxide source, a general palladium-catalyzed carbonylative transformation of the C–H bond on aromatic rings to produce esters has been developed. Good yields of the corresponding products have been obtained with wide functional group tolerance and excellent regioselectivity. A variety of aliphatic alcohols are suitable reactants here.

Keywords: carbonylation; C–H activation; molybdenum hexacarbonyl; palladium catalyst; 2-phenylpyridines

Carboxylic esters are important chemicals with wide applications in fine chemicals, natural products, and polymers.[1] Traditionally, esters are mainly prepared from the corresponding carboxylic acids or their derivatives and alcohols. Alternatively, direct oxidative esterifications of aldehydes, alcohols and arenes with alcohols have been investigated as well.[2]

On the other hand, transition metal-catalyzed carbonylation reactions have already become a powerful tool in modern organic synthesis.[3] By incorporating carbon monoxide as an inexpensive and abundant C_1 source, numerous carbonyl-containing compounds can be easily prepared. Depending on the nucleophiles, esters can be effectively produced when alcohols are added (called alkoxycarbonylation). However, most of the known alkoxycarbonylation procedures need aryl halides or analogues as the starting materials which require pre-activation steps.

Based on the achievements in transition metal-catalyzed C–H activation reactions,[4] the merging of carbonylation and C–H bond activation in ester synthesis will be attractive. Indeed, some interesting transformations have been achieved recently. In 2009, a general rhodium-catalyzed carbonylation of arenes to produce esters was reported.[5] By using Oxone as the oxidant under a carbon monoxide (2 bar) atmosphere, the desired esters were formed in good to excellent yields with primary alcohols. Compared with expensive rhodium catalysts, palladium catalysts were explored in this topic as well. In 2010, Z. J. Shi and co-workers reported a novel palladium-catalyzed *ortho*-carbonylation of *N,N*-dimethylbenzylamines to produce the corresponding *ortho*-methyl benzoates.[6] With $Cu(OAc)_2$ as the oxidant, moderate to good yields of the desired products were isolated. LiCl was found to play an important role here. In 2013, B. F. Shi and co-workers reported an interesting palladium-catalyzed alkoxycarbonylation procedure for the synthesis of aryl carboxylic esters *via* C–H activation under an atmospheric pressure of carbon monoxide.[7] With oxygen as the co-oxidant, good yields of the desired products can be achieved with 2-arylpyridines and primary alcohols as the reactants. More recently, Lei[8] and Guan[9] reported their achievements on palladium-catalyzed carbonylative syntheses of *o*-aminobenzoates from *N*-alkylanilines *via* C–>H activation. With a copper(II) salt, KI and oxygen as the oxidation system, good yields of *o*-aminobenzoates can be isolated in both cases.

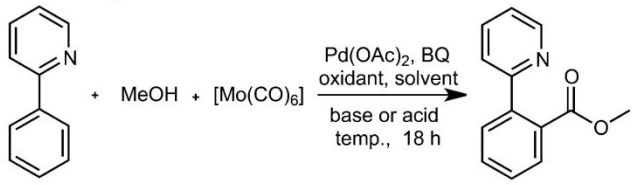
However, the above discussed procedures all require carbon monoxide gas as the CO source and primary or secondary alcohols as the reaction partner. Although carbon monoxide, as one of the cheapest C_1 sources, does hold a non-replaceable position in industrial scale applications, its high toxicity and odourless character limit its usage in laboratories. Hence, the development of new procedure based on CO surrogates will be interesting for the synthetic community.[10] Among all the candidates, $Mo(CO)_6$ as a non-toxic solid is an attractive CO source.[11] Against this background, we wish to report herein a general palladium-catalyzed oxidative carbonylation of aromatic C–H bonds with $Mo(CO)_6$ as the CO source. In the presence of only 0.4 equivalent of $Mo(CO)_6$, various

kinds of alcohols were carbonylated in moderate to good yields. In addition to 2-arylpyridine derivatives, 1,2-diphenyldiazene, 1-phenyl-1*H*-pyrazole and 2-phenylpyrimidine are all suitable substrates here. Not only primary alcohols, but also secondary and tertiary alcohols are applicable as reaction partners.

Our initial investigation was started with 2-phenylpyridine (**1a**, 1 equiv.) and methanol (**2a**, 15 equiv.), $Pd(OAc)_2$,(10 mol%), $[Mo(CO)_6]$ (1 equiv.), BQ (benzoquinone, 2 equiv.), NaOAc (2 equiv.) and Ag_2CO_3 (3 equiv.) in chlorobenzene and, to our delight, a 45% yield of the desired carbonylation product **3a** was formed after 18 h at 130 °C (Table 1, entry 1). In our further optimization studies, we found that the use of BQ was essential for the formation of the carbonylation products **3**. Presumably, BQ can facilitate the reductive elimination step.[12] The yield of product **3a** was decreased when we changed the amounts of NaOAc or Ag_2CO_3 used (Table 1, entries 2–5). Various other oxidants such as Ag_2O, $AgNO_3$, $Cu(OAc)_2$, $CuCl_2$, CuO, $K_2S_2O_8$, and Oxone were tested in this reaction as well (Table 1, entries 6–12). However, none of them could give improved results.

Then the effects of other bases and acids were investigated (Table 1, entries 13–19). NaOAc was found to be the best base here, whereas Na_2CO_3, $NaHCO_3$,

Table 1. Optimization of the reaction conditions.[a]



1a **2a** **3a**

Entry	Temp. [°C]	Base or Acid	Oxidant	Solvent	Yield [%][b]
1	130	NaOAc	Ag_2CO_3	PhCl	45
2	130	NaOAc	Ag_2CO_3 (2 equiv.)	PhCl	40
3	130	NaOAc	-	PhCl	23
4	130	-	Ag_2CO_3	PhCl	36
5	130	NaOAc (4 equiv.)	Ag_2CO_3	PhCl	41
6	130	NaOAc	Ag_2O	PhCl	trace
7	130	NaOAc	$AgNO_3$	PhCl	34
8	130	NaOAc	$Cu(OAc)_2$	PhCl	trace
9	130	NaOAc	$CuCl_2$	PhCl	trace
10	130	NaOAc	CuO	PhCl	20
11	130	NaOAc	$K_2S_2O_8$	PhCl	trace
12	130	NaOAc	oxone	PhCl	29
13	130	Na_2CO_3	Ag_2CO_3	PhCl	10
14	130	$NaHCO_3$	Ag_2CO_3	PhCl	12
15	130	KOAc	Ag_2CO_3	PhCl	8
16	130	K_2CO_3	Ag_2CO_3	PhCl	20
17	130	Cs_2CO_3	Ag_2CO_3	PhCl	trace
18	130	Li_2CO_3	Ag_2CO_3	PhCl	trace
19	130	DBU	Ag_2CO_3	PhCl	0
20	130	HOAc	Ag_2CO_3	PhCl	0
21	100	NaOAc	Ag_2CO_3	MeOH	43
22	100	NaOAc	Ag_2CO_3	DCE	81
23	130	NaOAc	Ag_2CO_3	DMSO	0
24	130	NaOAc	Ag_2CO_3	HOAc	0
25	80	NaOAc	Ag_2CO_3	DCE	56[c]
26	80	NaOAc	Ag_2CO_3	DCE	57[d]
27	**80**	**NaOAc**	**Ag_2CO_3**	**DCE**	**85 (80)[e]**
28	80	NaOAc	Ag_2CO_3	DCE	82[f]

[a] *Reaction conditions:* **1a** (0.5 mmol, 1 equiv.), **2a** (7.5 mmol, 15 equiv.), $[Mo(CO)_6]$ (0.5 mmol, 1 equiv.), $Pd(OAc)_2$ (0.05 mmol, 10 mol%), BQ (1 mmol, 2 equiv.), base or acid (1 mmol, 2 equiv.) and oxidant (1.5 mmol, 3 equiv.), solvent (2 mL) for 18 h in a sealed tube.

[b] Yields were determined by GC-MS. Isolated yield is given in parenthesis.

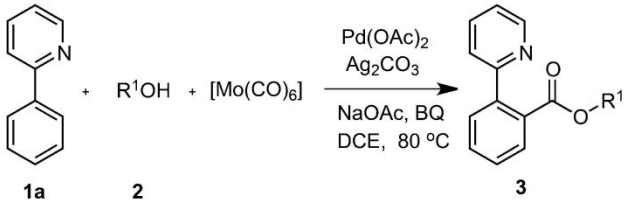
[c] $[Mo(CO)_6]$ (0.1 mmol, 0.2 equiv.).

[d] $[Mo(CO)_6]$ (0.15 mmol, 0.3 equiv.).

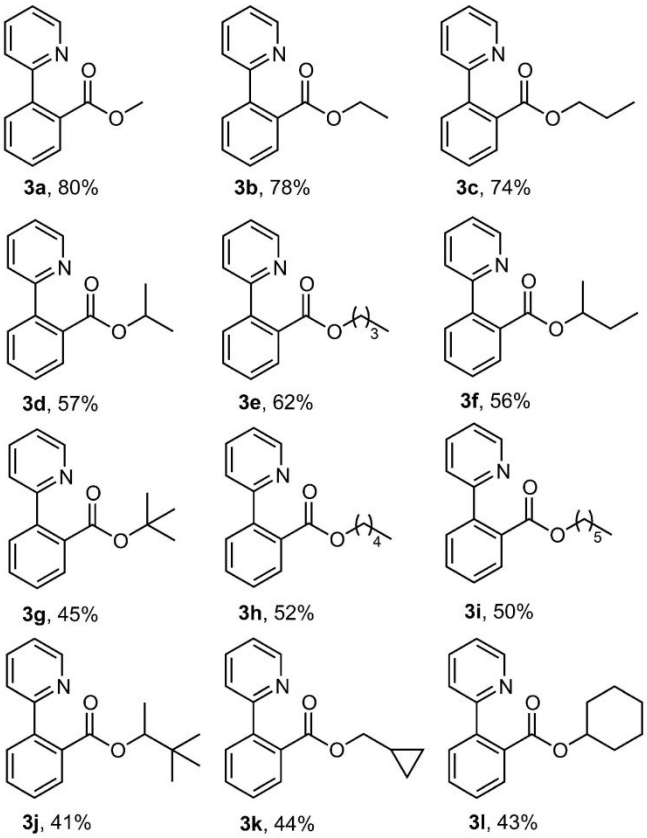
[e] $[Mo(CO)_6]$ (0.2 mmol, 0.4 equiv.).

[f] $[Mo(CO)_6]$ (0.25 mmol, 0.5 equiv.).

Table 2. Carbonylation of 2-phenylpyridine with different alcohols.[a]



1a **2** **3**



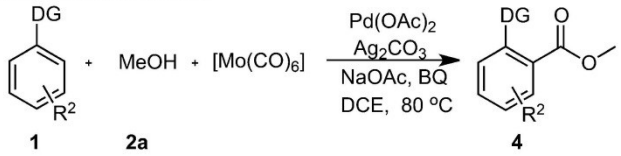
[a] 2-Phenylpyridine **1a** (0.5 mmol), alcohol **2** (7.5 mmol), $[Mo(CO)_6]$ (0.2 mmol), $Pd(OAc)_2$ (0.05 mmol), BQ (1 mmol), NaOAc (1 mmol) and Ag_2CO_3 (1.5 mmol) in DCE (2 mL) at 80 °C for 18 h, isolated yields.

KOAc, K_2CO_3, Cs_2CO_3, and Li_2CO_3 were all found to be inferior. DBU inhibited the reaction completely (Table 1, entry 19). No carbonylation product could be detected when AcOH was added (Table 1, entry 20). The solvent was found to function critically in this reaction. The yield decreased to 43% when MeOH was applied as the solvent (Table 1, entry 21) and no desired product can be observed when DMSO (dimethyl sulfoxide) or AcOH was used (Table 1, entries 23 and 24). However, 81% of the desired product **3a** can be formed when DCE (1,2-dichloroethane) was applied as the reaction medium (Table 1, entry 22). To our surprise, the yield can even be further improved by using 0.4 equiv. of $Mo(CO)_6$ (Table 1, entry 27).

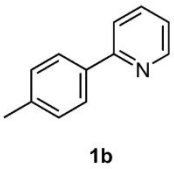
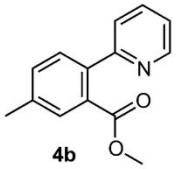
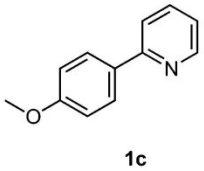
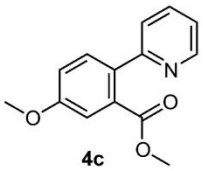
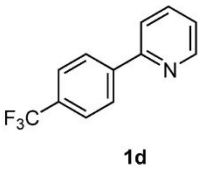
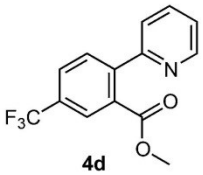
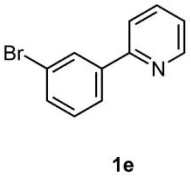
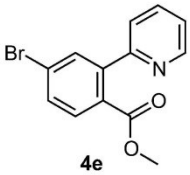
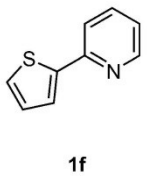
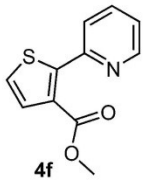
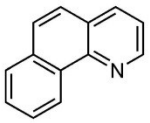
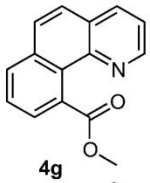
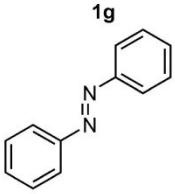
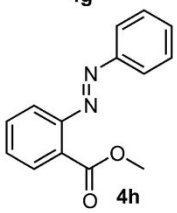
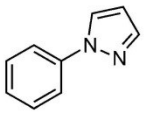
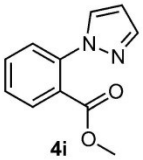
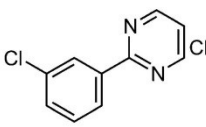
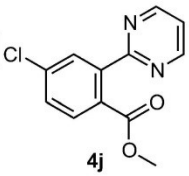
With the optimized conditions in hand (Table 1, entry 27), a screening of different alcohols was performed subsequently. As shown in Table 2, various primary, secondary and tertiary alcohols worked well under our reaction conditions and gave the corresponding esters in moderate to good yields. Nevertheless, no desired product could be detected when phenol, benzyl alcohol or amines was applied instead of aliphatic alcohols.

Successively, various directed arenes (**1b–j**) were screened with methanol (Table 3). Delightfully, a series of functional groups, such as Me, OMe, CF_3 and Br were compatible under our conditions, and gave the desired carbonylation products **4** in moderate to good isolated yields (Table 3, entries 1–4). In

Table 3. Carbonylation of arenes with methanol.[a]



1 2a 4

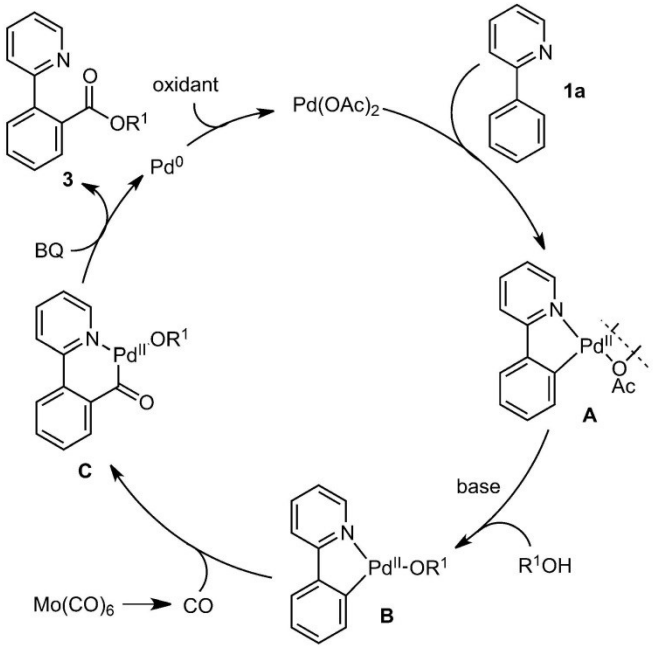
Entry	Substrate	Product	Yield[b]
1	 1b	 4b	78%
2	 1c	 4c	76%
3	 1d	 4d	55%
4	 1e	 4e	48%
5	 1f	 4f	61%
6	 1g	 4g	64%
7	 1h	 4h	40%
8	 1i	 4i	61%
9	 1j	 4j	63%

[a] *Reaction conditions:* **1** (0.5 mmol), methanol **2a** (7.5 mmol), BQ (1 mmol), $[Mo(CO)_6]$ (0.2 mmol), $Pd(OAc)_2$ (0.05 mmol), NaOAc (1 mmol) and Ag_2CO_3 (1.5 mmol) in DCE (2 mL) at 80 °C for 18 h.
[b] Isolated yields.

the case of the analogues **1f** and **1g**, the reaction worked efficiently and gave the corresponding carbonylation product **4f** and **4g** in 61% and 64% yields, respectively. Interestingly, 1,2-diphenyldiazene, 1-phenyl-1*H*-pyrazole and 2-phenylpyrimidine as examples of substrates with easily removable directing groups were found to be suitable substrates here as well (Table 3, entries 7–9).[13] Nitrogen heterocycles, such as pyrazole and pyrimidine, served as efficient directing groups and generated the carbonylation products in good yields under the optimal conditions (Table 3, entries 7 and 8). Good yields of the desired products were isolated (**4i**–**4j**; 40–63%). It's important to mention that 2-ethylpyridine, aniline, acetanilide, *N,N*-dimethylbenzylamine, and *N,N*-dimethylbenzamide were all tested under our standard conditions, but no carbonylation products could be observed.

A plausible reaction pathway is proposed on the basis of the above results and previous studies (Scheme 1).[14] The reaction started with C–H bond activation of 2-phenylpyridine **1a** which generates dimeric palladium intermediate **A**, that undergoes ligand exchange to provide intermediate **B**. Subsequently, a six-membered cyclic intermediate **C** is generated through the coordination and insertion of CO into the Pd–C bond. The final product will be eliminated after reductive elimination of intermediate **C** promoted by BQ which could also acts as a co-oxidant. The meanwhile formed Pd(0) will be re-oxidized to Pd(II) to complete the catalytic cycle.

In conclusion, we have developed a mild and general procedure for palladium-catalyzed alkoxycarbonylation of arenes with $Mo(CO)_6$ as the CO source. A variety of primary, secondary and tertiary alcohols can be applied as substrates here. Additionally, only 0.4 equivalent of $Mo(CO)_6$ as a solid and safe CO source is required for this new procedure. High regioselectivity and good functional group tolerance can be demonstrated, the desired carbonylation products were isolated in moderate to good yields.



Scheme 1. Proposed mechanism.

Experimental Section

General Procedure for Palladium-Catalyzed Oxidative Carbonylation

In a 25-mL sealed tube, a mixture of 2-substituted pyridine **1** (0.5 mmol, 1.0 equiv.), alcohol **2** (7.5 mmol, 15 equiv.), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol, 10 mol%), Ag_2CO_3 (414 mg, 1.5 mmol, 3.0 equiv.), $Mo(CO)_6$ (52.8 mg, 0.2 mmol, 0.4 equiv.), BQ (108 mg, 1.0 mmol, 2 equiv.) and NaOAc (82 mg, 1.0 mmol, 2 equiv.) in DCE (2.0 mL) was stirred at 80 °C under air. After 18 h, the mixture was cooled to room temperature. The residue was diluted with H_2O (10 mL) and extracted with EtOAc (3×10 mL). The organic solvent was then evaporated under vacuum. The crude products were purified by using column chromatography on silica gel (pentane/ethyl acetate) to give the pure products.

Acknowledgements

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References

[1] *Esterification: methods, reactions, and applications*, (Ed.: J. Otera), Wiley-VCH, Weinheim, **2010**.
[2] a) K. Ekoue-Kovi, C. Wolf, *Chem. Eur. J.* **2008**, *14*, 6302–6315; b) D. Milstein, *Top. Catal.* **2010**, *53*, 915–923; c) S. Tang, J. Yuan, C. Liu, A. Lei, *Dalton Trans.* **2014**, *43*, 13460–13470; d) H. Miyamura, S. Kobayashi, *Acc. Chem. Res.* **2014**, *47*, 1054–1066; e) B. Liu, F. Hu, B. F. Shi, *ACS Catal.* **2015**, *5*, 1863–1881.
[3] a) C. F. J. Barnard, *Organometallics* **2008**, *27*, 5402–5422; b) A. Brennführer, H. Neumann, M. Beller, *Angew. Chem.* **2009**, *121*, 4176–4196; *Angew. Chem. Int. Ed.* **2009**, *48*, 4114–4133; c) X. F. Wu, H. Neumann, M. Beller, *Chem. Soc. Rev.* **2011**, *40*, 4986–5009; d) X. F. Wu, H. Neumann, M. Beller, *Chem. Rev.* **2013**, *113*, 1–35; e) X.-F. Wu, H. Neumann, *ChemCatChem* **2012**, *4*, 447–458; f) X.-F. Wu, H. Neumann, M. Beller, *ChemSusChem* **2013**, *6*, 229–241; g) L. Wu, X. Fang, Q. Liu, R. Jackstell, M. Beller, X.-F. Wu, *ACS Catal.* **2014**, *4*, 2977–2989; h) X.-F. Wu, X. Fang, L. Wu, R. Jackstell, H. Neumann, M. Beller, *Acc. Chem. Res.* **2014**, *47*,

1041–1053; i) X. F. Wu, *Chem. Eur. J.* **2015**, *21*, 12252–12265.

[4] For selected reviews on C–H activation, see: a) X. Chen, K. M. Engle, D. H. Wang, J. Q. Yu, *Angew. Chem.* **2009**, *121*, 5196–5217; *Angew. Chem. Int. Ed.* **2009**, *48*, 5094–5115; b) L. Ackermann, R. Vicente, A. R. Kapdi, *Angew. Chem.* **2009**, *121*, 9976–10011; *Angew. Chem. Int. Ed.* **2009**, *48*, 9792–9826; c) I. A. I. Mkhalid, J. H. Barnard, T. B. Marder, J. M. Murphy, J. F. Hartwig, *Chem. Rev.* **2010**, *110*, 890–931; d) S. H. Cho, J. Y. Kim, J. Kwak, S. Chang, *Chem. Soc. Rev.* **2011**, *40*, 5068–5083; e) K. M. Engle, T. Mei, M. Wasa, J. Q. Yu, *Acc. Chem. Res.* **2012**, *45*, 788–802; f) S. D. Sarkar, W. Liu, S. I. Kozhushkov, L. Ackermann, *Adv. Synth. Catal.* **2014**, *356*, 1461–1479; g) V. S. Thirunavukkarasu, S. I. Kozhushkov, L. Ackermann, *Chem. Commun.* **2014**, *50*, 29–39; h) J. Q. Yu, Z. Shi, *Top. Curr. Chem.* **2010**, *292*, 1–378; i) O. Daugulis, H.-Q. Do, D. Shabashov, *Acc. Chem. Res.* **2009**, *42*, 1074–1086; j) D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 624–655; k) J. Wencel-Delord, T. Drçge, F. Liu, F. Glorius, *Chem. Soc. Rev.* **2011**, *40*, 4740–4761; l) F. Zhang, D. R. Spring, *Chem. Soc. Rev.* **2014**, *43*, 6906–6919; m) Z. Chen, B. Wang, J. Zhang, W. Yu, Z. Liu, Y. Zhang, *Org. Chem. Front.* **2015**, *2*, 1107–1295; n) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147–1169.

[5] Z. H. Guan, Z. H. Ren, S. M. Spinella, S. Yu, Y. M. Liang, X. Zhang, *J. Am. Chem. Soc.* **2009**, *131*, 729–733.

[6] H. Li, G. X. Cai, Z. J. Shi, *Dalton Trans.* **2010**, *39*, 10442–10446.

[7] a) B. Liu, B.-F. Shi, *Synlett* **2013**, 2274–2278; b) B. Liu, H.-Z. Jiang, B.-F. Shi, *Org. Biomol. Chem.* **2014**, *12*, 2538–2542.

[8] W. Li, Z. Duan, R. Jiang, A. Lei, *Org. Lett.* **2015**, *17*, 1397–1400.

[9] M. Chen, Z. H. Ren, Y. Y. Wang, Z. H. Guan, *J. Org. Chem.* **2015**, *80*, 1258–1263.

[10] a) T. Morimoto, K. Kakiuchi, *Angew. Chem.* **2004**, *116*, 5698–5706; *Angew. Chem. Int. Ed.* **2004**, *43*, 5580–5588; b) P. Gautam, B. M. Bhanage, *Catal. Sci. Technol.* **2015**, *5*, 4663–4702.

[11] L. R. Odell, F. Russo, M. Larhed, *Synlett* **2012**, 685–698.

[12] a) X. Chen, J. J. Li,, X. S. Hao, C. E. Goodhue, J. Q. Yu, *J. Am. Chem. Soc.* **2006**, *128*, 78–79; b) X. Chen, C. E. Goodhue, J. Q. Yu, *J. Am. Chem. Soc.* **2006**, *128*, 12634–12635.

[13] a) G. Rousseau, B. Breit, *Angew. Chem.* **2011**, *123*, 2498–2543; *Angew. Chem. Int. Ed.* **2011**, *50*, 2450–2494; b) C. Wang, Y. Huang, *Synlett* **2013**, 145–149; c) B. Liu, B. F. Shi, *Chem. Commun.* **2015**, *51*, 5093–5096; d) L. Zhang, H. Li, Z. Shi, *ChemCatChem* **2014**, *6*, 3069–3074.

[14] J. H. Chu, P. S. Lin, M. J. Wu, *Organometallics* **2010**, *29*, 4058–4065.

5.2 Palladium-Catalyzed Carbonylative Synthesis of 3-Methyleneisoindolin-1-ones from Ketimines with Hexacarbonylmolybdenum(0) as the Carbon Monoxide Source

Zechao Wang, Fengxiang Zhu, Yahui Li, and Xiao-Feng Wu*

ChemCatChem **2017**, *9*, 94-98.

Author contributions:

In this paper, I finished the optimization of reaction conditions, investigation of substrate scope and writing the manuscript. My contribution as the first author of this paper is approximately 80%.

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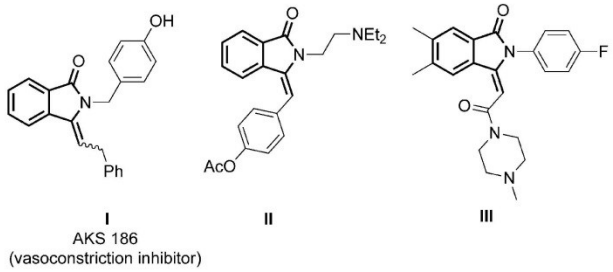
Palladium-Catalyzed Carbonylative Synthesis of 3-Methyleneisoindolin-1-ones from Ketimines with Hexacarbonylmolybdenum(0) as the Carbon Monoxide Source

Zechao Wang, Fengxiang Zhu, Yahui Li, and Xiao-Feng Wu*[a]

An interesting procedure for the palladium-catalyzed carbonylative synthesis of 3-methyleneisoindolin-1-ones from ketimines was established. By using $Mo(CO)_6$ (0.3 equiv.) as the solid CO source and through $C(sp^2)$–H bond activation, the desired 3-methyleneisoindolin-1-ones were isolated in moderate to good yields.

The presence of the heterocyclic motif dominates in biologically active molecules.[1] Among the heterocyclic scaffolds, the 3-methyleneisoindolin-1-one skeleton is one of the most important structures present in nature products and various pharmaceutical molecules (Scheme 1).[2] For example, AKS 186 (**I**) is a known vasoconstriction inhibitor,[2b] compound **II** has been reported to have anesthetic activity,[2c] and compound **III** exhibits sedative activity (Scheme 1).[2d] Additionally, 3-methyleneisoindolin-1-ones also serve as key intermediates in organic synthesis.[3]



I
AKS 186
(vasoconstriction inhibitor)

II

III

Scheme 1. Representative pharmaceutical molecules.

As a result of the proven importance of 3-methyleneisoindolin-1-ones, considerable attention has been devoted to developing new procedures for their preparation. Traditionally, 3-methyleneisoindolin-1-ones are prepared from phthalimides, either by the Wittig reaction or by the addition of organometallic reagents followed by a dehydration sequence.[4] Alternative procedures have also been established. Most of the reported methods involve the use of *o*-(1-alkynyl)benzamides as the substrates or intermediates through heteroannulation to give the final target products.[5] Recently, procedures based on C–H activation have also been developed. In 2013, Li, Zhou, and co-workers reported a novel rhodium-catalyzed annulation of aryl ketone *O*-methyl oximes with isocyanates for the synthesis of 3-methyleneisoindolin-1-ones.[6] Good yields of the desired products could be obtained by C–H bond activation. In 2014, ruthenium-catalyzed C–H bond activation was applied in the synthesis of 3-methyleneisoindolin-1-ones. By cyclization of benzimidates or aromatic nitriles with alkenes through C–H bond activation, moderate to good yields of the desired products were obtained.[7,8] More recently, a palladium-catalyzed cyclization of readily available carboxamides with carboxylic acids or anhydrides to produce isoindolinones was reported.[9] A broad range of substrates could be applied to give the desired products in good yields with good functional group tolerance.

On the other hand, transition-metal-catalyzed carbonylation reactions have already become one of the most powerful reactions in the toolbox of modern organic chemists.[10] With carbon monoxide (CO) as the C_1 source, valuable carbonyl-containing organic molecules can be easily prepared. Hence, the development of new carbonylative transformations is meaningful. Additionally, given the abovementioned importance of heterocycles, the application of carbonylation in the synthesis of heterocycles is even more attractive.[11] Indeed, carbonylation procedures for the synthesis of 3-methyleneisoindolin-1-ones have been developed. A procedure involving a palladium-catalyzed Sonogashira coupling/carbonylation/hydroamination sequence in phosphonium salt based ionic liquids was reported in 2008 by Alper and co-workers.[5f] Good yields of the desired products were produced from 2-haloiodobenzenes. Recently, Gabriele, Mancuso, and co-workers developed an interesting PdI_2-catalyzed cyclization of 2-alkynylbenzamides with secondary amines under oxidative carbonylation conditions. Good yields of 3-[(dialkylcarbamoyl)methylene]isoindolin-1-ones were obtained.[12] Jiang's group reported an attractive method for the palladium-catalyzed carbonylation of aromatic oximes for the preparation of 3-methyleneisoindolin-1-ones through C–H bond activation.[13] With oximes as the substrates under an atmosphere of carbon monoxide, good yields of the desired heterocycles were isolated. More recently, Huang and co-workers developed a novel procedure for the rhodium-catalyzed oxidative carbonylation of ketimines.[14] Good yields of 3-

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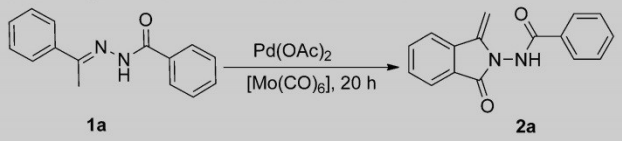
methyleneisoindolin-1-ones were obtained under a CO atmosphere (3.0 MPa) by C–H activation. Although carbon monoxide as one of the cheapest C_1 sources has advantages in terms of industrial-scale applications, its special properties (e.g., high toxicity, odorless nature, flammability, and etc.) limit its use in laboratories. Hence, the development of synthetic procedures based on CO surrogates will be interesting for our synthetic community.[15] Among all the candidates, $Mo(CO)_6$ as a nontoxic solid is an attractive CO source.[16] With this background, we wish to report here a new palladium-catalyzed carbonylative intramolecular cyclization of ketimines through C–H bond activation with $[Mo(CO)_6]$ as the solid and safe CO source. In the presence of a palladium catalyst and $Mo(CO)_6$ (0.3 equiv.), the desired substituted 3-methyleneisoindolin-1-ones were isolated in moderate to good yields.

Our initial investigation started with the reaction of 1-phenyl-2-(1-phenylethylidene)hydrazine (**1a**) in the presence of $Pd(OAc)_2$ (10 mol%), $[Mo(CO)_6]$ (1 equiv.), and $Cu(OAc)_2$ (2 equiv.) in 1,2-dichloroethane (DCE) at 80 °C; to our delight, desired *N*-(1-methylene-3-oxoisoindolin-2-yl)benzamide (**2a**) was formed in 33% yield after 20 h (Table 1, entry 1). On the basis of this initial finding, various oxidants were subsequently tested. The yield of product **2a** decreased to 18% upon using AgOAc as the oxidant (Table 1, entry 2). No product could be detected with $PhI(OAc)_2$ or $K_2S_2O_8$ as the oxidant (Table 1, entries 3 and 4). Improved results were obtained upon using BQ (1,4-benzoquinone) as the oxidant (Table 1, entry 5). To improve the outcome further, the effects of the base were investigated (Table 1, entries 6–11). Positive effects were observed with NaOAc, CsF, and Li_2CO_3, and a 56% yield was achieved with Li_2CO_3 (Table 1, entry 10). However, only a trace amount of the desired product was detected in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (Table 1, entry 11). Upon varying the loading of BQ, 3 equivalents of BQ gave the best results (Table 1, entry 12). Screening of the solvents revealed that toluene, DMSO (dimethyl sulfoxide), 1,4-dioxane, and DMF (*N*,*N*-Dimethylformamide) were all inferior to DCE (Table 1, entries 14–17). Interestingly, upon adding 0.3 equivalents of $Mo(CO)_6$, the targeted 3-methyleneisoindolin-1-one was isolated in an improved 86% yield (Table 1, entry 18).

Table 1. Optimization of the reaction conditions.[a]



Entry	Oxidant	Base	Solvent	Yield[b] [%]
1	$Cu(OAc)_2$	–	DCE	33
2	AgOAc	–	DCE	18
3	$PhI(OAc)_2$	–	DCE	0
4	$K_2S_2O_8$	–	DCE	0
5	BQ	–	DCE	46
6	BQ	NaOAc	DCE	51
7	BQ	K_2CO_3	DCE	40
8	BQ	Cs_2CO_3	DCE	43
9	BQ	CsF	DCE	49
10	BQ	Li_2CO_3	DCE	56
11	BQ	DBU	DCE	trace
12	BQ (3 equiv.)	Li_2CO_3	DCE	74
13	BQ (4 equiv.)	Li_2CO_3	DCE	55
14	BQ (3 equiv.)	Li_2CO_3	toluene	54
15	BQ (3 equiv.)	Li_2CO_3	DMSO	28
16	BQ (3 equiv.)	Li_2CO_3	1,4-dioxane	15
17	BQ (3 equiv.)	Li_2CO_3	DMF	trace
18[c]	BQ (3 equiv.)	Li_2CO_3	DCE	84 (86)
19[d]	BQ (3 equiv.)	Li_2CO_3	DCE	58

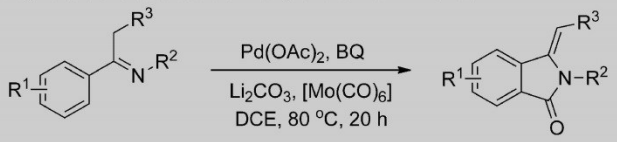
[a] Reaction conditions: 1-phenyl-2-(1-phenylethylidene)hydrazine (**1a**; 0.5 mmol, 1 equiv.), $[Mo(CO)_6]$ (0.5 mmol, 1 equiv.), $Pd(OAc)_2$ (0.05 mmol, 10 mol%), oxidant (1 mmol, 2 equiv.), base (1 mmol, 2 equiv.), and solvent (2 mL) for 20 h at 80 °C in a sealed tube. [b] Yield was determined by GC–MS. Yield of isolated product is given in parentheses. [c] $[Mo(CO)_6]$ (0.5 mmol, 0.3 equiv.). [d] $[Mo(CO)_6]$ (0.5 mmol, 0.2 equiv.).

With the optimized conditions, we focused our attention on the scope of the substrates. Overall, all the substrates studied were conveniently converted into the corresponding carbonylated products in moderate to good yields (Table 2, see products **2a**–**q**). Substrates with methyl or methoxy groups on the benzene ring were explored and afforded the corresponding products in moderate to good yields (Table 2, see products **2b**, **2d**, **2h**, **2i**, **2j**). If the methoxy group was substituted at the *meta* position of the substrate, only a trace amount of desired product **2r** was detected by GC–MS. Interestingly, (*E*)-*N*′-[1-(cyclohex-1-en-1-yl)ethylidene]benzohydrazide could also be applied as a starting material, and it gave corresponding product **2c** in 51% yield without further optimization. In addition to benzohydrazide, other related derivatives could also be applied. 4-Chlorobenzohydrazide, 4-(trifluoromethyl)benzohydrazide, and 4-methoxybenzohydrazide were all shown to be proper substrates here and gave the desired products in 43–81% yield (Table 2, see products **2e**–**m**). (*E*)-*N*-[1-Oxo-3-(2-phenylethylidene)isoindolin-2-yl]benzamide derivatives were also produced in moderate yields (Table 2, see products **2k**–**m**). The use of aniline as a directing group was tested, and 3-methylene-2-phenylisoindolin-1-one **2n** was produced in 66% yield under the standard conditions. *O*-Methylhydroxylamine and acetohydrazide were also viable directing groups, and they gave corresponding products **2o** and **2p**–**q** in moderate yields. However, no product was detected with phenylhydrazine as the directing group under our conditions (see compound **2s**). To our delight, 2,4-diphenylphthalazin-1(2*H*)-one (**4a**) was produced in 31% yield from 1-(diphenylmethylene)-2-phenylhydrazine (**3a**) with high selectivity by using phenylhydrazine as the reaction partner (Scheme 2).

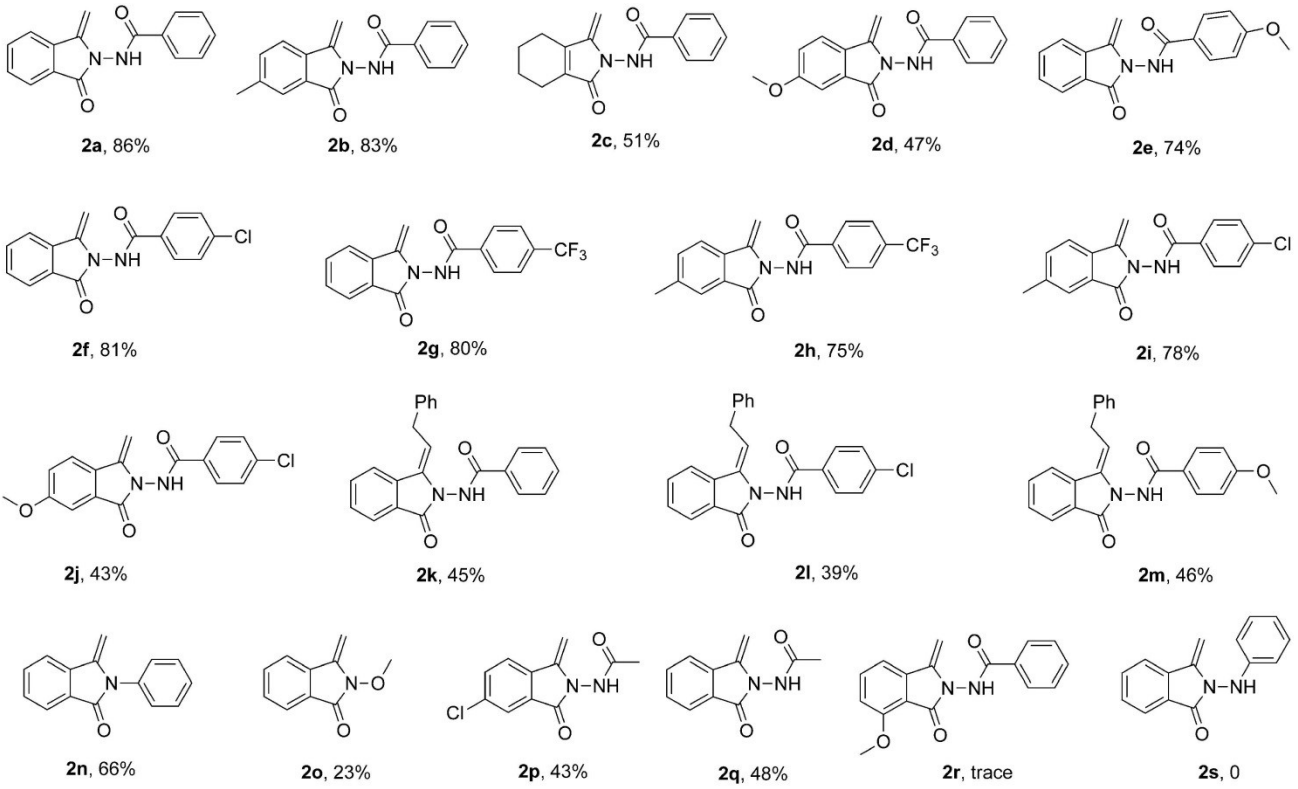
To prove the applicability of this procedure, a one-pot synthesis was performed (Scheme 3). Acetophenone was treated with benzohydrazide in DCE for 10 h, and this was followed by the addition of our catalyst system; *N*-(1-methylene-3-oxoisoindolin-2-yl)benzamide was isolated in 45% yield.

On the basis of these results, a plausible reaction mechanism is proposed (Scheme 4). First, palladium acetate reacts with imine **1** to give *ortho*-activated palladium complex **A**. Under the assistance of base, complex **B** is generated by isomerization of the imine and ligand exchange by the coordination of CO. Moreover, CO is released from $Mo(CO)_6$ by coordination of BQ. Acylpalladium **C** as the key intermediate is formed after

Table 2. Palladium-catalyzed carbonylative synthesis of substituted 3-methyleneisoindolin-1-ones.[a]



1a **2a**



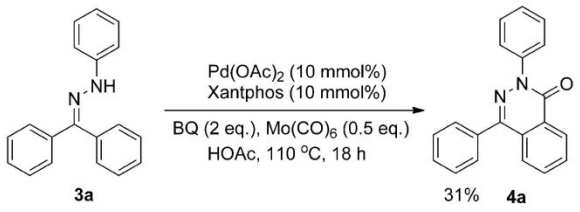
2a, 86% **2b**, 83% **2c**, 51% **2d**, 47% **2e**, 74%

2f, 81% **2g**, 80% **2h**, 75% **2i**, 78%

2j, 43% **2k**, 45% **2l**, 39% **2m**, 46%

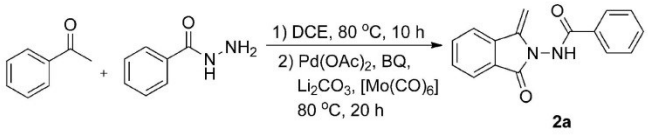
2n, 66% **2o**, 23% **2p**, 43% **2q**, 48% **2r**, trace **2s**, 0

[a] Reaction conditions: substrate **1** (0.5 mmol, 1.0 equiv.), $Pd(OAc)_2$ (0.05 mmol, 10 mol%), $[Mo(CO)_6]$ (0.15 mmol, 0.3 equiv.), BQ (1.5 mmol, 3 equiv.), Li_2CO_3 (1.0 mmol, 2 equiv.), DCE (2.0 mL), 80 °C, 20 h, air; yields of isolated products are given.



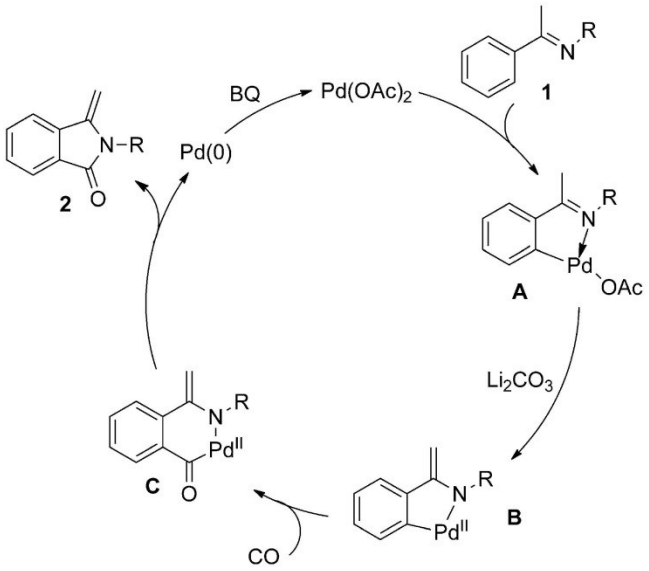
3a 31% **4a**

Scheme 2. Carbonylative synthesis of 2,4-diphenylphthalazin-1(2*H*)-one. Xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene.



2a

Scheme 3. One-pot synthesis from acetophenone.



Scheme 4. Proposed reaction mechanism.

the reaction of CO with complex **B**. The final product is then eliminated after reductive elimination of intermediate **C**, and the formed Pd^0 species is reoxidized to Pd^{II} to complete the catalytic cycle. However, a Pd^{II}/Pd^{IV} cycle cannot be excluded here.

In summary, an interesting palladium-catalyzed carbonylative synthesis of substituted 3-methyleneisoindolin-1-ones from ketimines was developed. With the use of $Mo(CO)_6$ (0.3 equiv.) as the solid CO source, moderate to good yields of the desired products were obtained by C–H bond activation.

Experimental Section

General procedure for the synthesis of ketohydrazones 1a–s: Benzonylhydrazine (408 mg, 3 mmol, 1.5 equiv.) was added to a stirred solution of acetophenone (240 mg, 2 mmol, 1 equiv.) in ethanol (15 mL) at 80 °C. After heating the mixture for 10 h, the solvent was evaporated under vacuum. The crude product was purified by recrystallization from pentane to afford hydrazine **1a** as a white solid.

General procedure for the palladium-catalyzed cyclocarbonylation reaction to give 2a–s: In a 25 mL sealed tube, a mixture of ketohydrazone **1** (0.5 mmol, 1.0 equiv.), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol, 10 mol%), $[Mo(CO)_6]$ (39.6 mg, 0.15 mmol, 0.3 equiv.), BQ (162 mg, 1.5 mmol, 3 equiv.), and Li_2CO_3 (74 mg, 1.0 mmol, 2 equiv.) in DCE (2.0 mL) was stirred at 80 °C in air. After 20 h, the mixture was cooled to room temperature. The residue was diluted with H_2O (10 mL) and extracted with EtOAc (3×10 mL). The solvent was then evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, pentane/ethyl acetate) to give pure product **2**.

General procedure for the one-pot synthesis of cyclocarbonylation product 2a: In a 25 mL sealed tube, benzonylhydrazine (136 mg, 1 mmol, 1 equiv.) was added to a stirred solution of acetophenone (120 mg, 1 mmol, 1 equiv.) in DCE (5 mL) at 80 °C. The mixture was heated for 10 h, and then $Pd(OAc)_2$ (22.4 mg, 0.1 mmol, 10 mol%), $[Mo(CO)_6]$ (79.2 mg, 0.3 mmol, 0.3 equiv.), BQ (324 mg, 3.0 mmol, 3 equiv.), and Li_2CO_3 (148 mg, 2.0 mmol, 2 equiv.) were added into the sealed tube. Then, the mixture was stirred at 80 °C in air for 20 h. The residue was diluted with H_2O (10 mL) and extracted with EtOAc (3×10 mL). The solvent was then evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, pentane/ethyl acetate = 4:1) to give pure product **2a** as a yellow oil.

General procedure for the palladium-catalyzed cyclocarbonylation reaction to give 4a: In a 25 mL sealed tube, a mixture of 1-(diphenylmethylene)-2-phenylhydrazine (**3a**; 0.5 mmol, 1.0 equiv.), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol, 10 mol%), Xantphos (25.9 mg, 0.05 mmol, 10 mmol%), $[Mo(CO)_6]$ (66 mg, 0.25 mmol, 0.5 equiv.), and BQ (162 mg, 1.0 mmol, 2 equiv.) in HOAc (2.0 mL) was stirred at 110 °C in air. After 18 h, the mixture was cooled to room temperature. The residue was diluted with H_2O (10 mL) and extracted with EtOAc (3×10 mL). The solvent was then evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, pentane/ethyl acetate) to give pure product **4a**.

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Keywords: carbonylation · domino reactions · heterocycles · molybdenum · palladium

[1] a) J. Alvarez-Builla, J. J. Vaquero, J. Barluenga, *Modern Heterocyclic Chemistry*, Wiley-VCH, **2011**; b) J. A. Joule, K. Mills, *Heterocyclic Chemistry*, Wiley-Blackwell, Oxford, **2010**; c) L. D. Quin, J. Tyrell, *Fundamentals of Heterocyclic Chemistry*, Wiley-Blackwell, Oxford, **2010**; d) A. R. Katritzky, C. A. Ramsden, J. A. Joule, V. V. Zhdankin, *Handbook of Heterocyclic Chemistry*, Elsevier, Amsterdam, **2010**; e) R. K. Bansal, *Heterocyclic Chemistry*, Anshan, Tunbridge Wells, **2008**; f) T. Eicher, S. Hauptmann, *The Chemistry of Heterocycles*, Wiley-VCH, **2003**; g) J. Dinges, C. Lamberth, *Bioactive Heterocyclic Compound Classes: Pharmaceuticals*, Wiley-VCH, **2012**.

[2] a) G. Blaskó, D. J. Gula, M. Shamma, *J. Nat. Prod.* **1982**, *45*, 105–122; b) N. Kanamitsu, T. Osaki, Y. Itsuji, M. Yoshimura, H. Tsujimoto, M. Soga, *Chem. Pharm. Bull.* **2007**, *55*, 1682–1688; c) H. M. Botero Cid, C. Trankle, K. Baumann, R. Pick, E. Mies-Klomfass, E. Kostenis, K. Mohr, U. Holzgrabe, *J. Med. Chem.* **2000**, *43*, 2155–2164; d) Y. Kato, M. Takemoto, K. Achiwa, *Chem. Pharm. Bull.* **1993**, *41*, 2003–2006.

[3] a) V. Rys, A. Couture, E. Deniau, P. Grandclaudon, *Tetrahedron* **2003**, *59*, 6615–6619; b) S. Couty, C. Meyer, J. Cossy, *Tetrahedron Lett.* **2006**, *47*, 767–769; c) A. Moreau, A. Couture, E. Deniau, P. Grandclaudon, *J. Org. Chem.* **2004**, *69*, 4527–4530; d) A. Couture, E. Deniau, P. Grandclaudon, H. R. Rosen, S. Léonce, B. Pfeiffer, P. Renard, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3557–3559; e) R. Bergmann, R. Gericke, *J. Med. Chem.* **1990**, *33*, 492–504; f) E. De Clercq, *J. Med. Chem.* **1995**, *38*, 2491–2517; g) M. H. Norman, D. J. Minick, G. C. Rigdon, *J. Med. Chem.* **1996**, *39*, 149–157; h) Z.-P. Zhuang, M.-P. Kung, M. Mu, H. F. Kung, *J. Med. Chem.* **1998**, *41*, 157–166.

[4] a) W. Flitsch, H. Peters, *Tetrahedron Lett.* **1969**, *10*, 1161–1162; b) A. G. Griesbeck, K.-D. Warzecha, J.-M. Neudorfl, H. Gorner, *Synlett* **2004**, 2347–2350; c) T. Bousquet, J.-F. Fleury, A. Daich, P. Netchitailo, *Tetrahedron* **2006**, *62*, 706–715; d) X. Chen, F.-F Ge, T. Lu, Q.-F. Zhou, *J. Org. Chem.* **2015**, *80*, 3295–3301.

[5] a) W.-D. Lu, C.-F. Lin, C.-J. Wang, S.-J. Wang, M.-J. Wu, *Tetrahedron* **2002**, *58*, 7315–7319; b) C. Koradin, W. Dohle, A. L. Rodriguez, B. Schmid, P. Knochel, *Tetrahedron* **2003**, *59*, 1571–1587; c) T. Yao, R. C. Larock, *J. Org. Chem.* **2005**, *70*, 1432–1437; d) C. Sun, B. Xu, *J. Org. Chem.* **2008**, *73*, 7361–7364; e) L. Li, M. Wang, X. Zhang, Y. Jiang, D. Ma, *Org. Lett.* **2009**, *11*, 1309–1312; f) H. Cao, L. McNamee, H. Alper, *Org. Lett.* **2008**, *10*, 5281–5284; g) S. B. Munoz, A. N. Aloia, A. K. Moore, A. Papp, T. Mathew, S. Fustero, G. A. Olah, G. K. S. Prakash, *Org. Biomol. Chem.* **2016**, *14*, 85–92.

[6] a) B. Zhou, W. Hou, Y. Yang, Y. Li, *Chem. Eur. J.* **2013**, *19*, 4701–4706; b) W. Hou, B. Zhou, Y. Yang, H. Feng, Y. Li, *Org. Lett.* **2013**, *15*, 1814–1817.

[7] a) X. G. Li, M. Sun, K. Liu, P. N. Liu, *Adv. Synth. Catal.* **2015**, *357*, 395–399; b) M. C. Reddy, M. Jeganmohan, *Org. Lett.* **2014**, *16*, 4866–4869.

[8] a) B. Li, P. H. Dixneuf, *Chem. Soc. Rev.* **2013**, *42*, 5744–5767; b) P. B. Arockiam, C. Bruneau, P. H. Dixneuf, *Chem. Rev.* **2012**, *112*, 5879–5918; c) S. Ruiz, P. Villuendas, E. P. Urriolabeitia, *Tetrahedron Lett.* **2016**, *57*, 3413–3432.

[9] H.-W. Liang, W. Ding, K. Jiang, L. Shuai, Y. Yuan, Y. Wei, Y.-C. Chen, *Org. Lett.* **2015**, *17*, 2764–2767.

[10] a) L. Kollár, *Modern Carbonylation Methods*, Wiley-VCH, **2008**; b) X.-F. Wu, H. Neumann, *ChemCatChem* **2012**, *4*, 447–458; c) X.-F. Wu, H. Neumann, M. Beller, *ChemSusChem* **2013**, *6*, 229–241; d) X.-F. Wu, H. X. Fang, L. Wu, R. Jackstell Neumann, M. Beller, *Acc. Chem. Res.* **2014**, *47*, 1041–1053; e) R. Skoda-Foldes, L. Kollör, *Curr. Org. Chem.* **2002**, *6*, 1097–1119;

f) B. Gabriele, R. Mancuso, G. Salerno, *Eur. J. Org. Chem.* **2012**, 6825 – 6839; g) X.-F. Wu, *RSC Adv.* **2016**, *6*, 83831 – 83837.
[11] X.-F. Wu, H. Neumann, M. Beller, *Chem. Rev.* **2013**, *113*, 1 – 35.
[12] R. Mancuso, I. Ziccarelli, D. Armentano, N. Marino, S. V. Giofrè, B. Gabriele, *J. Org. Chem.* **2014**, *79*, 3506 – 3518.
[13] Y. Xu, W. Hu, X. Tang, J. Zhao, W. Wu, H. Jiang, *Chem. Commun.* **2015**, *51*, 6843 – 6846.
[14] B. Gao, S. Liu, Y. Lan, H. Huang, *Organometallics* **2016**, *35*, 1480 – 1487.
[15] a) T. Morimoto, K. Kakiuchi, *Angew. Chem. Int. Ed.* **2004**, *43*, 5580 – 5588; *Angew. Chem.* **2004**, *116*, 5698 – 5706; b) P. Gautam, B. M. Bhanage, *Catal. Sci. Technol.* **2015**, *5*, 4663 – 4702; c) S. D. Friis, A. T. Lindhardt, T. Skrydstrup, *Acc. Chem. Res.* **2016**, *49*, 594 – 605.
[16] L. R. Odell, F. Russo, M. Larhed, *Synlett* **2012**, 685 – 698.

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5.3 Palladium-Catalyzed Carbonylative Cyclization of Azoarenes

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ChemCatChem **2017**, *9*, 3637-3640.

Author contributions:

In this paper, I finished the optimization of reaction conditions, investigation of substrate scope and writing the manuscript. My contribution as the first author of this paper is approximately 80%.

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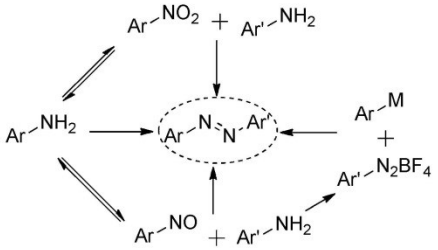
CHEMCATCHEM Communications

Palladium-Catalyzed Carbonylative Cyclization of Azoarenes

Zechao Wang,[a] Zhiping Yin,[a] Fengxiang Zhu,[a] Yahui Li,[a] and Xiao-Feng Wu*[a, b]

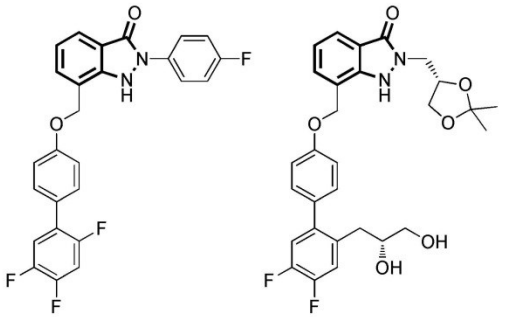
In this communication, we established an interesting palladium-catalyzed carbonylation protocol for the intramolecular cyclization of azoarenes. With $Mo(CO)_6$ as the solid CO source and through $C(sp^2)$–H bond activation, a series of azoarenes were transformed into the corresponding 2-arylindazolones in moderate to good yields. Notably, not only symmetrical azoarenes, but also unsymmetrical substrates underwent the reaction with excellent regioselectivity.

Among the core interests of organic chemistry is the use of easily available substrates for the preparation of valuable compounds. The abundance and diversity of starting materials can promise accessibility and variability of the related products, which can then be used in subsequent applications. From commercially accessible chemicals, thousands of anilines and nitrobenzenes are already in storage. They are usually used as parent molecules for the synthesis of azoarenes through various well-established methods (Scheme 1).[1–3] Azoarenes themselves are recognized as a highly important class of compounds owing to their applications as dyes, indicators, food additives, pigments, nonlinear optics, photochemical switches, and pharmaceuticals.[4] Generally, azoarenes are readily accessible through the dimerization of anilines,[1] condensation of anilines with nitrosoarenes (Mills reaction),[2] reaction of nitroarenes with aromatic amines,[3] or electrophilic reactions of diazonium salts with organometallic reagents.



Scheme 1. Procedures for the preparation of azoarenes.

Owing to the easy availability of azoarenes, many synthetic procedures have been developed for their transformations. Among them, 2-arylindazolones, a class of biological molecules, have also been reported to be preparable from azoarenes (Scheme 2).[5] However, drawbacks including harsh reaction conditions (15.0 MPa and 190 °C), multiple steps, very limited substrate scope, and low efficiency still exist. On the other hand, transition-metal-catalyzed carbonylative transformations have already been accepted as powerful methods in modern organic chemistry.[6] Although carbon monoxide gas is cheap and abundant, small-scale carbonylation reactions, which are correlated with the synthesis of fine chemicals, would be more desirable if they could be performed with CO surrogates.[7] With this background, a method for the carbonylative synthesis of 2-arylindazolones from azobenzenes under CO-gas-free conditions is very attractive.



Scheme 2. Selected examples of biologically active 2-arylindazolones.

Our initial investigation started with the reaction of azobenzene (**1a**) in the presence of $PdCl_2$ (10 mol%), $Mo(CO)_6$ (1 equiv.), and *p*-benzoquinone (BQ, 2 equiv.) in hexafluoroisopropanol (HFIP) at 100 °C. To our delight, desired 2-phenyl-1,2-dihydro-3*H*-indazol-3-one (**2a**) was formed in 13% yield after 24 h (Table 1, entry 1). On the basis of this initial finding, various solvents were then tested. Product **2a** was obtained in 10% yield upon using 2,2,2-trifluorethanol (TFE) as the solvent (Table 1, entry 2). Only a trace amount of product **2a** was detected with 1,2-dichloroethane (DCE), 1,4-dioxane, and H_2O as the reaction media (Table 1, entries 3–5). Delightfully, upon using acetic acid (HOAc) as the solvent, product **2a** was obtained in 73% yield (Table 1, entry 6). Acetic acid is widely used in the chemical industry as a polar protic solvent, and approximately 20% of acetic acid (1 million tonnes per year) is used for the production of terephthalic acid.[8] To improve the yield further, the effect of the oxidant was also investigated

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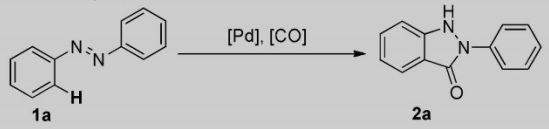
Table 1. Concept establishment.[a]



Entry	Catalyst	Oxidant	Solvent	Yield [%][b]
1	$PdCl_2$	BQ	HFIP	13
2	$PdCl_2$	BQ	TFE	10
3	$PdCl_2$	BQ	DCE	trace
4	$PdCl_2$	BQ	dioxane	trace
5	$PdCl_2$	BQ	H_2O	trace
6	$PdCl_2$	BQ	HOAc	73
7	$PdCl_2$	Ag_2CO_3	HOAc	18
8	$PdCl_2$	$K_2S_2O_8$	HOAc	12
9	$PdCl_2$	$Ce(SO_4)_2$	HOAc	33
10	$PdCl_2$	BQ (1 equiv.)	HOAc	39
11	$PdCl_2$	BQ (2.5 equiv.)	HOAc	61
12	$PdCl_2$	BQ (3 equiv.)	HOAc	50
13	$PdCl_2$	BQ (4 equiv.)	HOAc	32
14	$Pd(MeCN)_2Cl_2$	BQ	HOAc	44
15	$Pd(cod)Cl_2$	BQ	HOAc	41
16	$[Pd(cinnamyl)Cl]_2$	BQ	HOAc	52
17	$Pd(OAc)_2$	BQ	HOAc	28
18[c]	$PdCl_2$	BQ	HOAc	54
19[d]	$PdCl_2$	BQ	HOAc	81 (83)

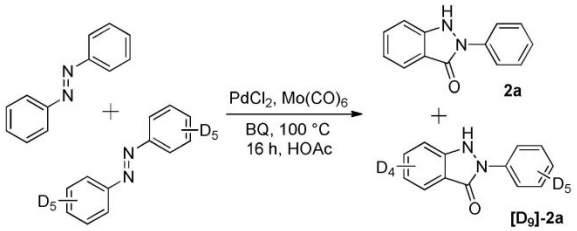
[a] Reaction conditions: azobenzene (**1a**; 0.3 mmol, 1 equiv.), $Mo(CO)_6$ (0.3 mmol, 1 equiv.), [Pd] (0.03 mmol, 10 mol%), oxidant (0.6 mmol, 2 equiv.), and solvent (2 mL) at 100 °C for 24 h in a sealed tube. [b] Yield was determined by GC by using *n*-hexadecane as the internal standard. Yield of isolated product is given in parentheses. [c] $Mo(CO)_6$ (0.18 mmol, 0.6 equiv.). [d] $Mo(CO)_6$ (0.24 mmol, 0.8 equiv.).

(Table 1, entries 7–13). However, Ag_2CO_3, $K_2S_2O_8$, and $Ce(SO_4)_2$ all displayed inferior reactivities (Table 1, entries 7–9). By varying the loading of BQ, we discovered that 2 equivalents of BQ was the optimal amount (Table 1, entries 6, 10–13). $Pd(MeCN)_2Cl_2$, $Pd(cod)Cl_2$ (cod = cyclooctadiene), $[Pd(cinnamyl)Cl]_2$, and $Pd(OAc)_2$ as commonly applied palladium precursors were tested as well, but they did not give better results (Table 1, entries 14–17). Interestingly, upon adding $Mo(CO)_6$ (0.8 equiv.), the yield of desired 2-phenyl-1,2-dihydro-3*H*-indazol-3-one (**2a**) was improved further to 83% yield (Table 1, entry 19). Notably, the model reaction was also performed with other CO sources [e.g., formic acid, benzene-1,3,5-triyl triformate, CO (0.1 MPa), CO (0.1 MPa) + $Mo(CO)_6$ (10 mol%)], but none of them gave a detectable amount of the product. These results implied that $Mo(CO)_6$ might play several roles in this transformation. Additionally, in the failed reactions, azobenzene decomposed and produced *N*-acetylaniline.

With the optimized conditions in hand, we focused our attention on the substrate scope of this transformation (Table 2). Overall, all of the substrates studies were conveniently converted into corresponding carbonylated products **2a–q** in moderate to good yields. Symmetrical azoarenes were explored and afforded corresponding products **2a–c** in good yields. A range of unsymmetrical azoarenes smoothly underwent carbonylation to produce 2-arylindazolones **2d–q** in moderate to good yields. No regioselectivity problems occurred in this catalytic system. Notably, the reaction tolerated a variety of functional groups, including fluoro, bromo, methoxy, phenoxy, and trifluoromethyl groups. Interestingly, the C–H activation carbonylative reaction also took place for substrates containing a methyl group in the *ortho* position of the phenyl ring to give products **2d–i**. The reaction of an azoarene with a fluoro substituent proceeded to give **2d** in 75% yield. We also investigated the effects of various substituents on the regioselectivity of the reaction and found that the carbonylative reaction took place mainly on the aromatic ring that was not substituted (Table 2, see products **2h–q**). Substrates with a bromo or trifluoromethyl group performed better than those with a methoxy or phenoxy group. However, no product was detected if the azobenzene contained a heterocyclic ring under our conditions (Table 2, see products **2r** and **2s**).

To obtain further insight into the reaction, an experiment with deuterium azobenzene was also performed (Scheme 3). Under our standard reaction conditions, the kinetic isotopic effect (KIE), K_H/K_D, was determined to be 2, which indicated that the C–H activation process might have been the rate-determining step for this transformation.[9] Additionally, no N-H deuterated product (i.e., N-D) was detected.

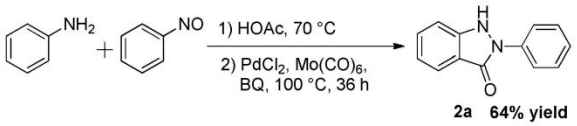
To prove the applicability of this procedure, a one-pot synthesis was also performed (Scheme 4). Aniline and nitrosobenzene were applied as the substrates in HOAc for 18 h. Then



Scheme 3. Deuterium experiment.

our catalyst system was introduced, and the mixture was stirred for 36 h. 2-Phenyl-1,2-dihydro-3*H*-indazol-3-one (**2a**) was isolated in 64% yield as the desired product.

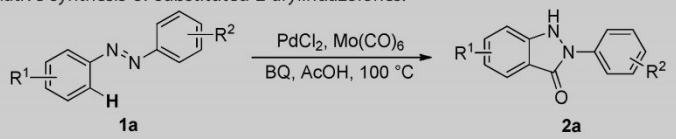
On the basis of our observations, a most possible reaction mechanism is proposed (Scheme 5). Palladium acetate first reacts with azobenzene (**1a**) to give *ortho*-activated palladium



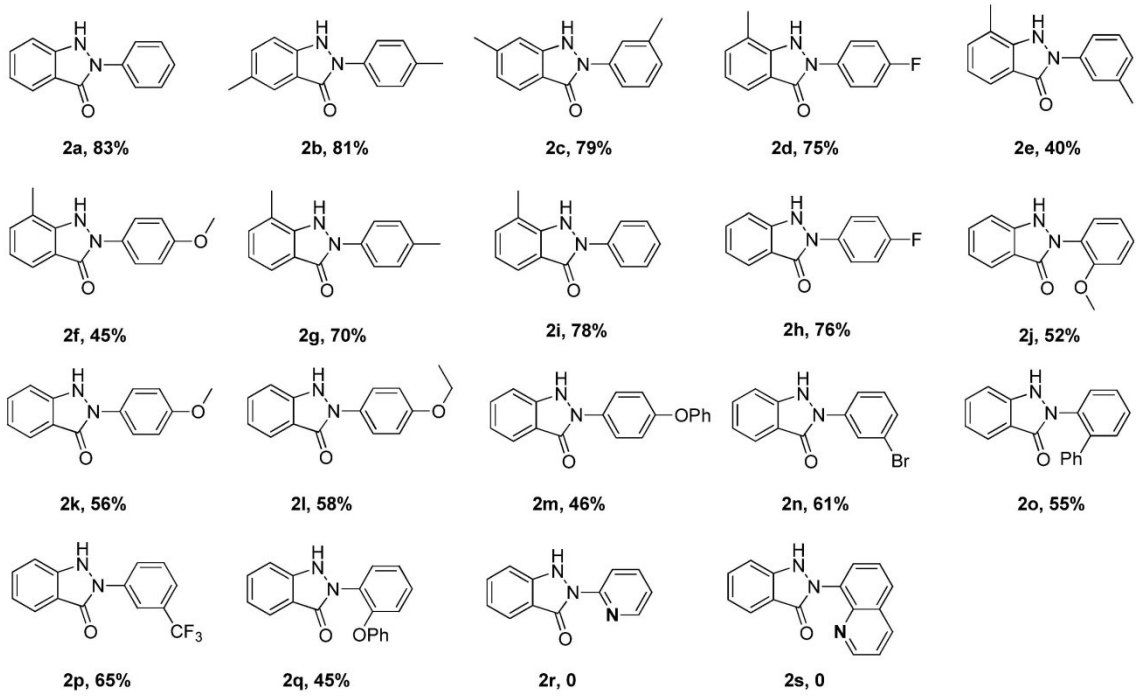
Scheme 4. One-pot procedure from aniline.

complex **A**. Subsequently, six-membered cyclic intermediate **B** is generated through coordination and insertion of CO into the Pd–C bond. Intermediate **C** as the key intermediate can be formed by insertion of the palladium catalyst. Final product **2a** is then eliminated after acidolysis of intermediate **C** with acetic acid. Moreover, regenerated free Pd^{II} is ready for the next cata-

Table 2. Palladium-catalyzed carbonylative synthesis of substituted 2-arylindazolones.[a]



1a 2a



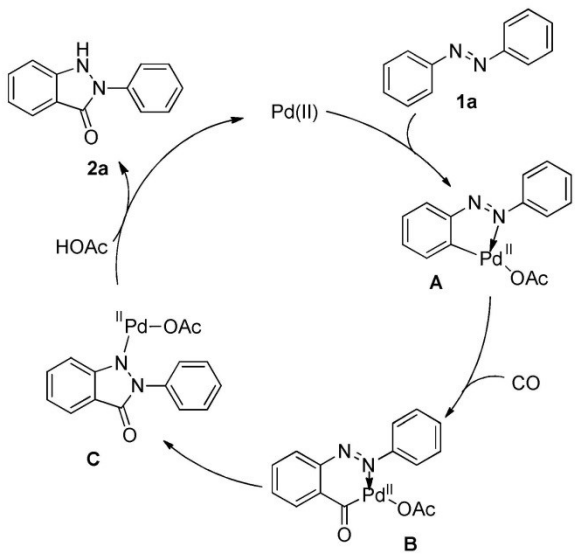
2a, 83% 2b, 81% 2c, 79% 2d, 75% 2e, 40%

2f, 45% 2g, 70% 2i, 78% 2h, 76% 2j, 52%

2k, 56% 2l, 58% 2m, 46% 2n, 61% 2o, 55%

2p, 65% 2q, 45% 2r, 0 2s, 0

[a] Reaction conditions: substrate **1** (0.3 mmol, 1.0 equiv.), $PdCl_2$ (0.03 mmol, 10 mol%), $Mo(CO)_6$ (0.24 mmol, 0.8 equiv.), BQ (0.6 mmol, 2 equiv.), HOAc (2.0 mL), 100 °C, 24 h, air; yields of isolated products are given.



Scheme 5. Proposed reaction pathway.

lytic cycle. In this process, the role of BQ is to stabilize Pd^{II} to avoid the generation of palladium black, and it might also assist in the release of CO from $Mo(CO)_6$. However, a $Pd^{II}/Pd^{0}/Pd^{II}$ or $Pd^{II}/Pd^{IV}/Pd^{II}$ cycle cannot be excluded here.

In summary, an interesting palladium-catalyzed carbonylative synthesis of substituted 2-arylindazolones from symmetrical and unsymmetrical azoarenes was developed. With $Mo(CO)_6$ (0.8 equiv.) as the solid CO source, moderate to good yields of the desired products were obtained with high regioselectivity through C–H bond activation. Readily available aniline could also be applied, and a good yield of the target product was obtained.

Experimental Section

General procedure for the synthesis of azobenzenes 1 a–s

Method A (**1 a–g**): A mixture containing the aniline derivatives (10 mmol), CuBr (0.6 mmol), pyridine (1.8 mmol), and toluene (10 mL) was stirred at 60 °C in air for 24 h. After cooling to room temperature and concentrating under vacuum, the residue was purified by flash chromatography (pentane) to give product **1 a–g**. The spectroscopic and analytical data of substrates **1 a–c** and **1 e–g** were known.

Method B (**1 h–s**): A mixture of nitrosobenzene (2 mmol), aniline (2.6 mmol), and acetic acid (5 mL) was stirred at 70 °C in air for 20 h. After cooling to room temperature and concentrating under vacuum, the residue was purified by flash chromatography (pentane) to give product **1 h–s**. The spectroscopic and analytical data of substrates **1 h–l**, **1 n–p**, and **1 s** were known.

General procedure for the palladium-catalyzed cyclocarbonylation

In a 25 mL sealed tube, a mixture of azoarene **1** (0.3 mmol, 1.0 equiv.), $PdCl_2$ (5.3 mg, 0.03 mmol, 10 mol%), $Mo(CO)_6$ (63.4 mg, 0.24 mmol, 0.8 equiv.), and BQ (0.6 mmol, 2 equiv.) in HOAc (2 mL) was stirred at 100 °C in air. After 24 h, the mixture was cooled to room temperature. The residue was diluted with H_2O (10 mL) and extracted with EtOAc (3×10 mL). The solvent was then evaporated under vacuum. The crude product was purified by column chromatography (silica gel, pentane/ethyl acetate) to give pure product **2**.

General procedure for the KIE experiment

In a 25 mL sealed tube, a mixture of azobenzene (**1a**; 27.3 mg, 0.15 mmol), [D_{10}]-azobenzene ([**D_{10}**]-**1a**; 28.8 mg, 0.15 mmol), $PdCl_2$ (5.3 mg, 0.03 mmol, 10 mol%), $Mo(CO)_6$ (63.4 mg, 0.24 mmol, 0.8 equiv.), and BQ (0.6 mmol, 2 equiv.) in HOAc (2 mL) was stirred at 100 °C in air. After 16 h, the mixture was cooled to room temperature. The residue was diluted with H_2O (10 mL) and extracted with EtOAc (3×10 mL). The solvent was then evaporated under vacuum. The crude product was purified by column chromatography (silica gel, pentane/ethyl acetate = 6:1) to give pure products **2a** and [**D_9**]-**2a**.

One-pot synthesis of cyclocarbonylation products 2a

In a 25 mL sealed tube, aniline (60.5 mg, 0.65 mmol, 1.3 equiv.) was added to a stirred solution of nitrosobenzene (53.5 mg, 0.5 mmol, 1 equiv.) in HOAc (5 mL) at 70 °C. The mixture was heated for 18 h, and then $PdCl_2$ (8.8 mg, 0.05 mmol, 10 mol%), $Mo(CO)_6$ (105.6 mg, 0.4 mmol, 0.8 equiv.), and BQ (1 mmol, 2 equiv.) were added into the sealed tube. Then, the mixture was stirred at 100 °C in air for 36 h. The residue was diluted with H_2O (10 mL) and extracted with EtOAc (3×10 mL). The solvent was then evaporated under vacuum. The crude product was purified by column chromatography (silica gel, pentane/ethyl acetate = 6:1) to give pure product **2a** as a white solid.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: azoarenes · carbonylation · domino reactions · palladium · synthetic methods

[1] a) M. Hedayatullah, J. P. Dechatre, L. Denivelle, *Tetrahedron Lett.* **1975**, *16*, 2039; b) M. Hirano, S. Yakabe, H. Chikamori, J. H. Clark, T. Morimoto, *J. Chem. Soc.* **1998**, 770; c) A. Shaabani, D. G. Lee, *Tetrahedron Lett.* **2001**, *42*, 5833; d) Y. Saiki, H. Sugiura, K. Nakamura, M. Yamaguchi, T. Hoshi, J. I. Anzai, *J. Am. Chem. Soc.* **2003**, *125*, 9268; e) A. K. Flatt, S. M. Dirk, J. C. Henderson, D. E. Shen, J. Su, M. A. Reed, J. M. Tour, *Tetrahedron* **2003**, *59*, 8555; f) H. Naeimi, J. Safari, A. Heidarnezhad, *Dyes Pigm.* **2007**, *73*, 251; g) C. Zhang, N. Jiao, *Angew. Chem. Int. Ed.* **2010**, *49*, 6174; *Angew. Chem.* **2010**, *122*, 6310.

[2] a) W. H. Nutting, R. A. Jewell, H. Rapoport, *J. Org. Chem.* **1970**, *35*, 505; b) K. Krageloh, G. H. Anderson, P. J. Stang, *J. Am. Chem. Soc.* **1984**, *106*, 6015; c) Z. Liu, M. Jiang, *J. Mater. Chem.* **2007**, *17*, 4249; d) F. Hamon, F. Djedaini-Pilard, F. Barbot, C. Len, *Tetrahedron* **2009**, *65*, 10105; e) E. Merino, *Chem. Soc. Rev.* **2011**, *40*, 3835; f) H. A. Dabbagh, A. Teimouri, A. N. Chermahini, *Dyes Pigm.* **2007**, *73*, 239; g) M. Barbero, S. Cadamuro, S. Dughera, C. Giaveno, *Eur. J. Org. Chem.* **2006**, 4884.

[3] a) G. V. Teplyakov, L. I. Blyakhman, A. M. Yakubson, *J. Appl. Chem.* **1982**, *55*, 1431; b) R. Zhao, C. Tan, Y. Xie, C. Gao, H. Liu, Y. Jiang, *Tetrahedron Lett.* **2011**, *52*, 3805.

[4] a) R. G. Anderson, G. Nickless, *Analyst* **1967**, *92*, 207; b) R. D. Athey, Jr., *Eur. Coat. J.* **1998**, *3*, 146; c) D. M. Burland, R. D. Miller, C. A. Walsh, *Chem. Rev.* **1994**, *94*, 31; d) A. J. Harvey, A. D. Abell, *Tetrahedron* **2000**, *56*, 9763; e) W. J. Sandborn, *Am. J. Gastroenterol.* **2002**, *97*, 2939; f) K. Hunger, *Industrial Dyes. Chemistry, Properties, Applications*, Wiley-VCH, Weinheim, **2003**; g) E. Ishow, C. Bellaiche, L. Bouteiller, K. Nakatani, J. A. Delaire, *J. Am. Chem. Soc.* **2003**, *125*, 15744; h) A. Bafana, S. S. Devi, T. Chakrabarti, *Environ. Rev.* **2011**, *19*, 350; i) I. Papagiannouli, K. Iliopoulos, D. Gindre, B. Sahraoui, O. Krupka, V. Smokal, A. Kolendo, S. Couris, *Chem. Phys. Lett.* **2012**, *554*, 107.

[5] a) Y. Qian, D. Bolina, K. Conde-Knapeb, P. Gillespie, S. Hayden, K. Huang, A. R. Olivier, T. Sato, Q. Xiang, W. Yun, X. Zhang, *Bioorg. Med. Chem. Lett.* **2013**, *23*, 2936; b) S. J. Foster, P. Bruneau, E. R. Walker, R. M. McMiillan, *Br. J. Pharmacol.* **1990**, *99*, 113; c) E. Pontiki, D. Hadjipavlou-Litina, *Med. Res. Rev.* **2008**, *28*, 39; d) C. W. Bird, J. C. W. Chng, N. H. Rama, A. Saeed, *Synth. Commun.* **1991**, *21*, 545; e) M. V. Peters, R. S. Stoll, R. Goddard, G. Buth, S. Hecht, *J. Org. Chem.* **2006**, *71*, 7840; f) W. Wang, J. Chen, Z. Chen, Y. Zeng, X. Zhang, M. Yan, A. S. C. Chan, *Synthesis* **2016**, *48*, 3551; g) S. Murahashi, S. Horiie, *J. Am. Chem. Soc.* **1956**, *78*, 4816.

[6] a) L. Kollár, *Modern Carbonylation Methods*, Wiley-VCH, **2008**; b) X.-F. Wu, H. Neumann, *ChemCatChem* **2012**, *4*, 447; c) X.-F. Wu, H. Neumann, M. Beller, *ChemSusChem* **2013**, *6*, 229; d) X.-F. Wu, *RSC Adv.* **2016**, *6*, 83831; e) R. Skoda-Foldes, L. Kollör, *Curr. Org. Chem.* **2002**, *6*, 1097; f) B. Gabriele, R. Mancuso, G. Salerno, *Eur. J. Org. Chem.* **2012**, 6825; g) S. Sumino, A. Fusano, T. Fukuyama, I. Ryu, *Acc. Chem. Res.* **2014**, *47*, 1563.

[7] a) L. R. Odell, F. Russo, M. Larhed, *Synlett* **2012**, 685; b) T. Morimoto, K. Kakiuchi, *Angew. Chem. Int. Ed.* **2004**, *43*, 5580; *Angew. Chem.* **2004**, *116*, 5698; c) L. Wu, Q. Liu, R. Jackstell, M. Beller, *Angew. Chem. Int. Ed.* **2014**, *53*, 6310; *Angew. Chem.* **2014**, *126*, 6426; d) P. Gautam, B. M. Bhanage, *Catal. Sci. Technol.* **2015**, *5*, 4663; e) B. Sam, B. Breit, M. J. Krische, *Angew. Chem. Int. Ed.* **2015**, *54*, 3267; *Angew. Chem.* **2015**, *127*, 3317; f) S. D. Friis, A. T. Lindhardt, T. Skrydstrup, *Acc. Chem. Res.* **2016**, *49*, 594.

[8] *Chemicals Economic Handbook*, IHS Markit, **2016**.

[9] E. M. Simmons, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2012**, *51*, 3066; *Angew. Chem.* **2012**, *124*, 3120.

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5.4 3-Acylindoles Synthesis: Ruthenium-Catalyzed Carbonylative Coupling of Indoles and Aryl Iodides

Zechao Wang, Zhiping Yin, and Xiao-Feng Wu*

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Author contributions:

In this paper, I finished the optimization of reaction conditions, investigation of substrate scope and writing the manuscript. My contribution as the first author of this paper is approximately 80%.

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3-Acylindoles Synthesis: Ruthenium-Catalyzed Carbonylative Coupling of Indoles and Aryl Iodides

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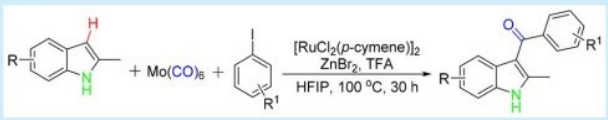
Supporting Information

ABSTRACT: A novel and convenient procedure for the synthesis of 3-acylindoles from simple indoles and aryl iodides has been established. Through ruthenium-catalyzed carbonylative C−H functionalization of indoles, with $Mo(CO)_6$ as the solid CO source, the desired indol-3-yl aryl ketones were isolated in moderate to good yields. Not only *N*-alkylindoles but also *N*-H indoles can be applied here.



During the past years, transition-metal catalysts have been extensively explored as a topic of new C−C bond formation through direct C−H activation.[1] Among the various noble metal catalysts, ruthenium catalysts are attractive due to their relative low cost and high reaction selectivity.[2,3] Several challenging transformations have been realized with ruthenium complex as the catalyst, such as C−H alkenylation,[4] arylation,[5] and alkyne annulations.[6] However, the reports on ruthenium-catalyzed carbonylation reactions are still very limited. In 1992, Moore's group reported a $Ru_3(CO)_{12}$-catalyzed sp^2 C−H carbonylation of aromatic heterocycles with olefins.[7] This reaction exhibited high regioselectivity and high catalyst turnover frequencies. Subsequently, Murai's group studied the $Ru_3(CO)_{12}$-catalyzed carbonylative coupling reaction of imidazoles with olefins, which has good yields, impressive catalytic efficiency, and wide functional group compatibility.[8] Then Chatani and co-workers demonstrated $Ru_3(CO)_{12}$-catalyzed carbonylative transformation of sp^2 C−H and sp^3 C−H with pyridine as the directing group.[9] The desired carbonylation products were formed in moderate to good yields. More recently, Beller's group reported a $[Ru(cod)Cl_2]_n$-catalyzed directing group assisted carbonylative C−H activation of arenes.[10] The reactions were carried out in water and aryl iodides and styrenes were used as the coupling partners. Indoles have been studied as well, but the presence of the directing group was essential.

On the other hand, 3-acylindoles are common structural motifs in many biologically active compounds, natural products,[11] and pharmaceutical compounds,[12] such as indiacen A, indiacen B, and MK-0533. Additionally, 3-acylindoles have been applied as key intermediates for synthesis of some other value-added compounds as well.[13g] Because of the versatile values and applications, their preparation attracts much interest. Traditional procedures include Friedel−Crafts acylations,[13] Vilsmeier−Haack-type reactions,[14] and indole Grignard reactions.[15] The most frequently used Friedel−Crafts reaction requires troublesome *N*-protection, especially for indoles bearing an electron-donating group with a stoichiometric Lewis acid promoter and strict exclusion of moisture. Hence, alternative methods for 3-acylindole preparation are highly desired. Carbonylative 3-acylation of indoles is one of the most straightforward procedures. In 2015, Arndtsen's group demonstrated a palladium-catalyzed carbonylative coupling of heterocycles with aryl iodides via C−H functionalization.[16] 3-Acylindoles can be effectively produced under CO pressure. Meanwhile, Guan and co-workers described a novel palladium-catalyzed carbonylative coupling of indoles with aromatic boronic acids.[17] With the addition of I_2 and KOH, via in situ generation of 3-iodoindole intermediates,[18] good yields of 3-acylindoles can be prepared with a wide range of functional groups tolerance. More recently, the application of visible light in carbonylative synthesis of 3-acylindoles has been realized by the groups of Gu[19] and Li and Liang[20] as well. With the assistance of photoredox catalysts under high CO pressure (70−80 bar), 3-acylindoles were formed at room temperature. In this paper, we report here a new procedure for the synthesis of 3-acylindoles. With ruthenium as the catalyst using simple indoles and readily available aryl iodides as the substrates, the desired 3-acylindoles can be produced even from *N*-H indoles. Notably, $Mo(CO)_6$ has been applied as the solid and safe CO source here.[21]

Our initial investigation began with 1,2-dimethyl-1*H*-indole (**1a**, 1 equiv) and iodobenzene (**2a**, 2 equiv), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), and $[Mo(CO)_6]$ (1 equiv) in HFIP (hexafluoroisopropanol). To our delight, 20% yield of the desired carbonylation product **3a** was formed after 30 h at 100 °C (Table 1, entry 1). Subsequently, various ruthenium catalysts such as $CpRuCl(PPh_3)_2$, $[RuCl_2(cod)]_n$, and $RuCl_2(PPh_3)_3$ were tested (Table 1, entries 2−4). Unfortunately, none of them could give improved results. Then the effects of bases and acids were investigated (Table 1, entries 5−14). TFA was found to be the best in this reaction, whereas K_2HPO_4, Li_2CO_3, LiBr, LiCl, KH_2PO_4, and $MesCO_2H$ (2, 4, 6-trimethylbenzoic acid) were all found to be inferior. Et_3N and DBU inhibited the reaction completely, and no conversion of **1a** was observed (Table 1, entries 5 and 6). Only a trace of

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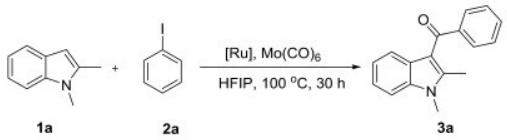
Table 1. Optimization of Reaction Conditions[a]



1a 2a 3a

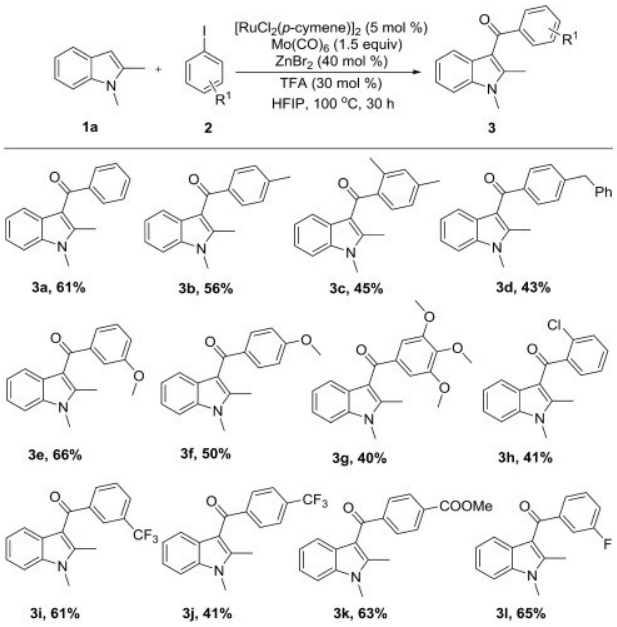
entry	catalyst	base/acid	additive	yield[b] (%)
1	$[RuCl_2(p\text{-cymene})]_2$			22 (20)
2	$CpRuCl(PPh_3)_2$			0
3	$[RuCl_2(cod)]_n$			<5
4	$RuCl_2(PPh_3)_3$			0
5	$[RuCl_2(p\text{-cymene})]_2$	Et_3N		0
6	$[RuCl_2(p\text{-cymene})]_2$	DBU		0
7	$[RuCl_2(p\text{-cymene})]_2$	K_2HPO_4		15
8	$[RuCl_2(p\text{-cymene})]_2$	Li_2CO_3		32
9	$[RuCl_2(p\text{-cymene})]_2$	LiBr		40
10	$[RuCl_2(p\text{-cymene})]_2$	LiCl		35
11	$[RuCl_2(p\text{-cymene})]_2$	KH_2PO_4		42 (40)
12	$[RuCl_2(p\text{-cymene})]_2$	CH_3SO_3H		<5
13	$[RuCl_2(p\text{-cymene})]_2$	$MesCO_2H$		28
14	$[RuCl_2(p\text{-cymene})]_2$	TFA		45
15[c]	$[RuCl_2(p\text{-cymene})]_2$	TFA		48
16[c]	$[RuCl_2(p\text{-cymene})]_2$	TFA	$FeCl_3$	44
17[c]	$[RuCl_2(p\text{-cymene})]_2$	TFA	$MgCl_2$	46
18[c]	$[RuCl_2(p\text{-cymene})]_2$	TFA	$ZnCl_2$	50
19[c]	$[RuCl_2(p\text{-cymene})]_2$	TFA	$ZnBr_2$	55
20[c,d]	$[RuCl_2(p\text{-cymene})]_2$	TFA	$ZnBr_2$	35
21[c,e]	**$[RuCl_2(p\text{-cymene})]_2$**	**TFA**	**$ZnBr_2$**	**62 (61)**
22[c,f]	$[RuCl_2(p\text{-cymene})]_2$	TFA	$ZnBr_2$	57

[a]Conditions: **1a** (0.2 mmol, 1 equiv), **2a** (0.4 mmol, 2 equiv), catalyst (0.01 mmol, 5 mol %), $Mo(CO)_6$ (0.2 mmol, 1 equiv), base/acid (0.2 mmol, 1 equiv), additive (0.08 mmol, 40 mol %), HFIP (1 mL), stirring at 100 °C for 30 h under air. [b]Yields were determined by GC using *n*-hexadecane as the internal standard. Isolated yield is in parentheses. [c]TFA (0.06 mmol, 30 mol %). [d]$Mo(CO)_6$ (0.1 mmol, 0.5 equiv). [e]$Mo(CO)_6$ (0.3 mmol, 1.5 equiv). [f]$Mo(CO)_6$ (0.4 mmol, 2 equiv).

carbonylation product **3a** could be detected when CH_3SO_3H was added (Table 1, entry 12). Further study showed that a lower amount of TFA led to higher yield (48%; Table 1, entry 15). To further improve the outcome, different additives were used in this reaction (Table 1, entries 16−19). Surprisingly, we found that $ZnBr_2$ can give the carbonylation product in 55% yield (Table 1, entry 19). Replacement of $ZnBr_2$ with $FeCl_3$, $MgCl_2$, or $ZnCl_2$ proved detrimental to the efficiency of the process, with product **3a** being formed in diminished 44%, 46%, and 50% yield, respectively (Table 1, entries 16−18). Notably, the amount of $Mo(CO)_6$ played a crucial role for the outcome of this reaction (Table 1, entries 20 and 21). The yield could be improved by increasing the amount of $Mo(CO)_6$ to 1.5 equiv, and we could obtain the carbonylation product **3a** in 61% yield (Table 1, entry 21). In addition, the model reaction was also performed with other CO sources such as formic acid, CO, $Cr(CO)_6$, $Co_2(CO)_8$, and $Fe_2(CO)_9$. However, none of them gave better results (see the Supporting Information). These results imply that $Mo(CO)_6$ might play several roles in this transformation. In the case of temperature testing, we found that less than 5% of the desired product was formed at 80 °C and the yield decreased as well at higher temperature (120 °C; 28% yield). Importantly, no product could be detected in the absence of ruthenium catalyst. Additionally, less than 10% of the desired product could be detected when the reaction was performed under pure O_2 (1 bar) pressure or argon atmosphere. These results suggest that the oxygen in air joined in the reaction, but pure oxygen destroyed the catalyst activity.

With the optimized conditions in hand (Table 1, entry 21), we began to investigate the scope of iodoarenes subsequently. As shown in Scheme 1, carbonylation of 1,2-dimethyl-1*H*-indole with iodoarenes proceeded smoothly under our standard reaction conditions. Using iodoarenes with either electron-donating or electron-withdrawing groups led to the formation of the corresponding carbonylation products in moderate to good yields. Substrates can tolerate various functional groups such as Bn, OCH_3, CF_3, Cl, F, and COOMe. However, iodoarenes substituted with OH or NO_2 could not give the desired carbonylation product. No carbonylation products could be obtained with 3-iodopyridine as the substrate. Importantly, the position of substituent R^1 had a critical effect on this carbonylation reaction. Iodoarenes substituted with functional groups in the *meta* position could give higher yields than that in the *para* position (**3e** vs **3f**, **3i** vs **3j**).

Scheme 1. 3-Acylindole Synthesis: Variation of Aryl Iodides[a]



[a]Reaction conditions: 1,2-dimethyl-1*H*-indole **1a** (0.2 mmol, 1 equiv), iodoarenes **2** (0.4 mmol, 2 equiv), $[RuCl_2(p\text{-cymene})]_2$ (0.01 mmol, 5 mol %), $Mo(CO)_6$ (0.2 mmol, 1 equiv), TFA (0.06 mmol, 30 mol %), $ZnBr_2$ (0.08 mmol, 40 mol %), HFIP (1 mL), 100 °C, 30 h, air, isolated yield.

Next, various indoles were investigated for further extending the substrates scope (Scheme 2). *N*-Substituted indoles can be readily carbonylated with iodoarenes to provide moderate to good yields of the corresponding carbonylation products (**4a**−**d**). A yield of 70% can be achieved with −COOMe-decorated aryl iodide. Remarkably, free *NH*-indoles can be successfully applied as well (**4e**−**i**) and gave good yields of the desired products with total chemoselectivity. Here, the obtained N-H free 3-acylindole products (**4e**−**i**) are ready for further C−N coupling reactions. However, we could not detect the products **4j** or **4k** when indole or 3-methyl-1*H*-indole was used as the substrate. These results revealed that the methyl group on the

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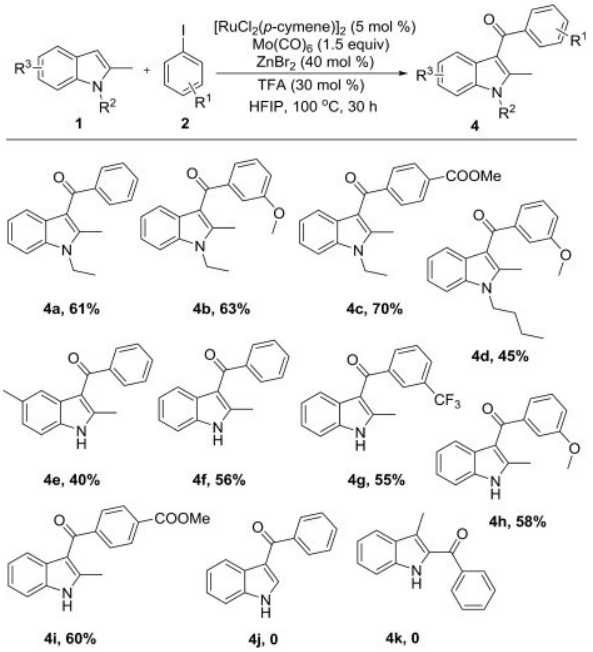
Scheme 2. 3-Acylindole Synthesis: Variation of Indoles[a]

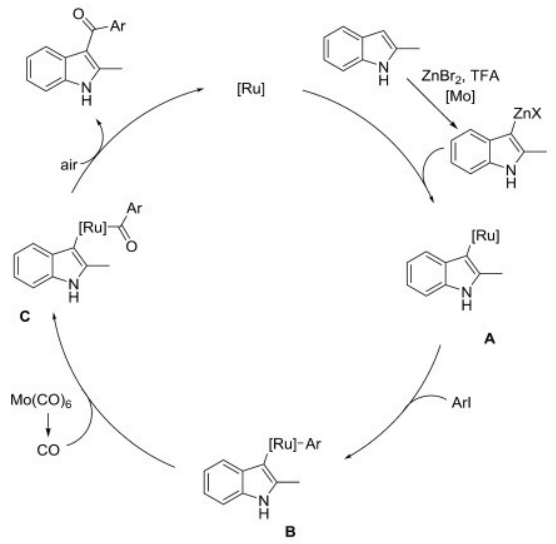


[a]Reaction conditions: indoles **1a** (0.2 mmol, 1 equiv), iodoarenes **2** (0.4 mmol, 2 equiv), $[RuCl_2(p\text{-cymene})]_2$ (0.01 mmol, 5 mol %), $Mo(CO)_6$ (0.2 mmol, 1 equiv), TFA (0.06 mmol, 30 mol %), $ZnBr_2$ (0.08 mmol, 40 mol %), HFIP (1 mL), 100 °C, 30 h, air, isolated yield.

2-position of indoles played a crucial role in the carbonylative C−H activation reaction. Additionally, heterocycles such as benzothiazole, benzothiophene, and pyrrole were also tested in the reaction conditions, but none of them could give the desired carbonylation products.

On the basis of the above results and literature, we postulated a possible reaction mechanism for the ruthenium-catalyzed carbonylation of indoles (Scheme 3). First, indoles were activated and transformed into the corresponding organometallic reagents in the presence of $ZnBr_2$, TFA, and molybdenum slat. The in situ generated zinc reagent then moved to transmetalation with ruthenium catalyst to produce the ruthenium intermediate **A**. Following this, the ruthenium species **A** underwent oxidative addition upon formation of intermediate **B**. Subsequently, intermediate **C** was generated through the coordination and insertion of CO into the Ru−C bond. Finally, the terminal product could be eliminated through reductive elimination, and the active ruthenium catalyst for the next catalytic cycle was regenerated under the presence of air.

Scheme 3. Proposed Reaction Mechanism



In summary, we have developed an interesting procedure for the synthesis of 3-acylindoles. Through ruthenium-catalyzed carbonylative C−H functionalization with $Mo(CO)_6$ as the solid CO source, moderate to good yields of the desired products can be prepared with good functional group tolerance.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02320.

Experimental procedures and NMR spectra for obtained compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For general reviews on C−H bond functionalization: (a) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147−1169. (b) Sehnal, P.; Taylor, R. J. K.; Fairlamb, I. J. S. *Chem. Rev.* **2010**, *110*, 824−889. (c) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094−5115. (d) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169−196. (e) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633−639. (f) McGlacken, G. P.; Bateman, L. M. *Chem. Soc. Rev.* **2009**, *38*, 2447−2464. (g) Gunay, A.; Theopold, K. H. *Chem. Rev.* **2010**, *110*, 1060−1081. (h) Wendlandt, A. E.; Suess, A. M.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 11062−11087. (i) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Rev.* **2011**, *111*, 1293−1314.

(2) For reviews on C−H bond activation with Ru catalysts: (a) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792−9826. (b) Ackermann, L.; Vicente, R. *Top. Curr. Chem.* **2009**, *292*, 211−229. (c) Ackermann, L. *Chem. Commun.* **2010**, *46*, 4866−4877. (d) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315−1345. (e) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879−5918.

(3) (a) Ferrer-Flegeau, E.; Bruneau, C.; Dixneuf, P. H.; Jutand, A. *J. Am. Chem. Soc.* **2011**, *133*, 10161−10170. (b) Ackermann, L.; Vicente, R.; Althammer, A. *Org. Lett.* **2008**, *10*, 2299−2302. (c) Pozgan, F.; Dixneuf, P. H. *Adv. Synth. Catal.* **2009**, *351*, 1737−1743.

DOI: 10.1021/acs.orglett.7b02320
Org. Lett. 2017, 19, 4680−4683

(d) Ackermann, L.; Pospech, J.; Potukuchi, H. K. *Org. Lett.* **2012**, *14*, 2146−2149. (e) Arockiam, P.; Poirier, V.; Fischmeister, C.; Bruneau, C.; Dixneuf, P. H. *Green Chem.* **2009**, *11*, 1871−1875. (f) Li, W. B.; Arockiam, P. B.; Fischmeister, C.; Bruneau, C.; Dixneuf, P. H. *Green Chem.* **2011**, *13*, 2315−2319. (g) Onodera, G.; Imajima, H.; Yamanashi, M.; Nishibayashi, Y.; Hidai, M.; Uemura, S. *Organometallics* **2004**, *23*, 5841−5848. (h) Inamoto, K.; Kadokawa, J.; Kondo, Y. *Org. Lett.* **2013**, *15*, 3962−3965.

(4) (a) Kozhushkov, S. I.; Ackermann, L. *Chem. Sci.* **2013**, *4*, 886−896. (b) Kozhushkov, S. I.; Potukuchi, H. K.; Ackermann, L. *Catal. Sci. Technol.* **2013**, *3*, 562−571.

(5) (a) Oi, S.; Ogino, Y.; Fukita, S.; Inoue, Y. *Org. Lett.* **2002**, *4*, 1783−1785. (b) Oi, S.; Sakai, K.; Inoue, Y. *Org. Lett.* **2005**, *7*, 4009−4011. (c) Ackermann, L.; Novàk, P. *Org. Lett.* **2009**, *11*, 4966−4969. (d) Ackermann, L.; Novàk, P.; Vicente, R.; Hofmann, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 6045−6048. (e) Ackermann, L.; Pospech, J.; Potukuchi, H. K. *Org. Lett.* **2012**, *14*, 2146−2149. (f) Arockiam, P. B.; Fischmeister, C.; Bruneau, C.; Dixneuf, P. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 6629−6632. (g) Özdemir, I.; Demir, S.; Cetinkaya, B.; Gourlaouen, C.; Maseras, F.; Bruneau, C.; Dixneuf, P. H. *J. Am. Chem. Soc.* **2008**, *130*, 1156−1157. (h) Ackermann, L. *Synlett* **2007**, *2007*, 2833−2836. (i) Ackermann, L. *Org. Lett.* **2005**, *7*, 3123−3125.

(6) Ackermann, L. *Acc. Chem. Res.* **2014**, *47*, 281−295.

(7) Moore, E. J.; Pretzer, W. R.; O'Connell, T. J.; Harris, J.; Labounty, L.; Chou, L.; Grimmer, S. S. *J. Am. Chem. Soc.* **1992**, *114*, 5888−5890.

(8) (a) Chatani, N.; Fukuyama, T.; Kakiuchi, F.; Murai, S. J. *J. Am. Chem. Soc.* **1996**, *118*, 493−494. (b) Fukuyama, T.; Chatani, N.; Tatsumi, J.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **1998**, *120*, 11522−11523. (c) Chatani, N.; Fukuyama, T.; Tatamidani, H.; Kakiuchi, F.; Murai, S. *J. Org. Chem.* **2000**, *65*, 4039−4047. (d) Chatani, N.; Ie, Y.; Kakiuchi, F.; Murai, S. *J. Org. Chem.* **1997**, *62*, 2604−2610. (e) Chatani, N.; Ishii, Y.; Ie, Y.; Kakiuchi, F.; Murai, S. *J. Org. Chem.* **1998**, *63*, 5129−5136. (f) Ie, Y.; Chatani, N.; Ogo, T.; Marshall, D. R.; Fukuyama, T.; Kakiuchi, F.; Murai, S. *J. Org. Chem.* **2000**, *65*, 1475−1488. (g) Chatani, N.; Yorimitsu, S.; Asaumi, T.; Kakiuchi, F.; Murai, S. *J. Org. Chem.* **2002**, *67*, 7557−7560. (h) Asaumi, T.; Chatani, N.; Matsuo, T.; Kakiuchi, F.; Murai, S. *J. Org. Chem.* **2003**, *68*, 7538−7540.

(9) (a) Inoue, S.; Shiota, H.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2009**, *131*, 6898−6899. (b) Hasegawa, N.; Charra, V.; Inoue, S.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 8070−8073. (c) Shibata, K.; Hasegawa, N.; Fukumoto, Y.; Chatani, N. *ChemCatChem* **2012**, *4*, 1733−1736.

(10) (a) Tlili, A.; Schranck, J.; Pospech, J.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 6293−6297. (b) Pospech, J.; Tlili, A.; Spannenberg, A.; Neumann, H.; Beller, M. *Chem. - Eur. J.* **2014**, *20*, 3135−3141. (c) Tlili, A.; Schranck, J.; Pospech, J.; Neumann, H.; Beller, M. *ChemCatChem* **2014**, *6*, 1562−1566.

(11) Nicolaou, K. C.; Snyder, S. A. *Classics in Total Synthesis II*; Wiley-VCH: Weinheim, 2003.

(12) (a) Pais, G. C. G.; Zhang, X.; Marchand, C.; Neamati, N.; Cowansage, K.; Svarovskaia, E. S.; Pathak, V. K.; Tang, Y.; Nicklaus, M.; Pommier, Y.; Burke, T. R. *J. Med. Chem.* **2002**, *45*, 3184−3194. (b) Barreca, M. L.; Ferro, S.; Rao, A.; De Luca, L.; Zappala, M.; Monforte, A.-M.; Debyser, Z.; Witvrouw, M.; Chimirri, A. *J. Med. Chem.* **2005**, *48*, 7084−7088. (c) Wu, Y.-S.; Coumar, M. S.; Chang, J.-Y.; Sun, H.-Y.; Kuo, F.-M.; Kuo, C.-C.; Chen, Y.-J.; Chang, C.-Y.; Hsiao, C.-L.; Liou, J.-P.; Chen, C.-P.; Yao, H.-T.; Chiang, Y.-K.; Tan, U.-K.; Chen, C.-T.; Chu, C.-Y.; Wu, S.-Y.; Yeh, T.-K.; Lin, C.-Y.; Hsieh, H.-P. *J. Med. Chem.* **2009**, *52*, 4941−4945.

(13) (a) Ketcha, D. M.; Gribble, G. W. *J. Org. Chem.* **1985**, *50*, 5451−5457. (b) Okauchi, T.; Itonaga, M.; Minami, T.; Owa, T.; Kitoh, K.; Yoshino, H. *Org. Lett.* **2000**, *2*, 1485−1487. (c) Ottoni, O.; Neder, A. de V. F.; Dias, A. K. B.; Cruz, R. P. A.; Aquino, L. B. *Org. Lett.* **2001**, *3*, 1005−1007. (d) Katritzky, A. R.; Suzuki, K.; Singh, S. K.; He, H.-Y. *J. Org. Chem.* **2003**, *68*, 5720−5723. (e) Wynne, J. H.; Lloyd, C. T.; Jensen, S. D.; Boson, S.; Stalick, W. M. *Synthesis* **2004**, *2004*, 2277−2282. (f) Guchhait, S. K.; Kashyap, M.; Kamble, H. *J. Org. Chem.* **2011**, *76*, 4753−4758. (g) Yao, S.-J.; Ren, Z.-H.; Guan, Z.-H. *Tetrahedron Lett.* **2016**, *57*, 3892−3901.

(14) Sundberg, R. J. *The Chemistry of Indoles*; Academic Press: New York, 1970.

(15) Bergman, J.; Venemalm, L. *Tetrahedron Lett.* **1987**, *28*, 3741−3744.

(16) Tjutrins, J.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2015**, *137*, 12050−12054.

(17) Zhao, M.-A.; Ran, L.; Chen, M.; Ren, Z.-H.; Wang, Y.-Y.; Guan, Z.-H. *ACS Catal.* **2015**, *5*, 1210−1213.

(18) (a) Lang, R.; Shi, L.; Li, D.; Xia, C.; Li, F. *Org. Lett.* **2012**, *14*, 4130−4133. (b) Li, D.; Shan, S.; Shi, L.; Lang, R.; Xia, C.; Li, F. *Chin. J. Catal.* **2013**, *34*, 185−192.

(19) Gu, L.; Jin, C.; Liu, J. *Green Chem.* **2015**, *17*, 3733−3736.

(20) Li, X.; Liang, D.; Huang, W.; Zhou, H.; Li, Z.; Wang, B.; Ma, Y.; Wang, H. *Tetrahedron* **2016**, *72*, 8442−8448.

(21) For a review and one example on $Mo(CO)_6$, see: Odell, L. R.; Russo, F.; Larhed, M. *Synlett* **2012**, *23*, 685−698. (b) Motwani, H. V.; Larhed, M. *Eur. J. Org. Chem.* **2013**, *2013*, 4729−4733.

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5.5 Pd/C-Catalyzed Aminocarbonylation of Aryl Iodides with Anthranils in Water Using $Mo(CO)_6$ as the CO Source

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Author contributions:

In this paper, I finished the optimization of reaction conditions, investigation of substrate scope and writing the manuscript. My contribution as the first author of this paper is approximately 80%.

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Cross-Coupling

Pd/C-Catalyzed Aminocarbonylation of Aryl Iodides with Anthranils in Water Using $Mo(CO)_6$ as the CO Source

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Abstract: A convenient procedure for the synthesis of *N*-(2-carbonylaryl)benzamides has been developed. Through Pd/C-catalyzed aminocarbonylation of anthranils with various hindered and functionalized aryl iodides, the desired amides were afforded in moderate to good yields. The protocol is advantageous due to the recyclable Pd/C catalyst, safe $Mo(CO)_6$ as the solid CO source, and environmentally benign water as solvent. No inert atmosphere protection is needed.

Transition-metal-catalyzed aminocarbonylation is an interesting and important chemical transformation method for the direct synthesis of aromatic amides through coupling of aryl, heteroaryl, or alkynyl halides with amines, which are important building blocks for various natural products and designed pharmaceutical molecules.[1] Some heterocyclic amides are reported as the potential CNS (central nervous system)-active compounds.[2] Therefore, a large number of methods toward amides synthesize have been developed. Since the first report on palladium-catalyzed aminocarbonylation of aryl halides with carbon monoxide from Heck and Schoenberg in 1974,[3] this transformation has been studied by different groups with various homogeneous palladium catalysts,[4–8] such as $PdX_2(PPh_3)_2$,[3] $Pd(dppp)Cl_2$,[5] $Pd(OAc)_2$/DCPP [DCPP = 1,3-bis(dicyclohexylphosphino)propane],[6] $Pd(OAc)_2$/xantphos,[7] and $Pd(OAc)_2/PPh_3$.[8] Concerning the nitrogen partners applied in aminocarbonylation reactions, mostly amines,[9] but also amides,[10] and even organic nitro compounds[11] have all been studied.

Anthranil, a class of benzo-fused heterocycle that contains a N–O bond in the ring, has been applied as a reagent in nickel-catalyzed cross-coupling with organozinc reagents and ring expansion reactions with aryldiazoacetates.[12] More recently, anthranils have been used as a nitrogen source by many research groups.[13–16] Hashmi and co-workers studied the C–H annulation of anthranil derivatives with alkynes to produce unprotected 7-acylindoles with gold as the catalyst.[13] Meanwhile, Li's group[14] and Jiao's group[15] have studied the application of anthranils as N-source in various C–H activation reactions; various amides were produced in good yields. Tiwari and co-workers developed a novel copper-catalyzed synthesis of functionalized quinolines from ketones and anthranils with aza-Michael addition as the key step.[16] Inspired by these interesting achievements, and also based on our continuing interests in carbonylation chemistry, we became interested in using anthranil as a nitrogen source in aminocarbonylation. Herein, we wish to report our new results on aminocarbonylation of aryl iodides with anthranils for the synthesis of *N*-(2-carbonylaryl)-benzamides. With Pd/C as a recyclable catalyst, using $Mo(CO)_6$[17] as the solid and safe CO source, and water as the green solvent, the desired amides were formed in good yields. Additionally, the reactions were carried out under air; no inert atmosphere protection is needed.

Our initial investigation was started with anthranil (**1a**, 1 equivalent), iodobenzene (**2a**, 2.5 equivalents), Pd/C (10 mol%), [$Mo(CO)_6$] (1 equivalent), and Cs_2CO_3 (2 equivalent) in distilled water. To our delight, 16% yield of the desired carbonylation product **3a** was formed after 18 hours at 80 °C (Table 1, entry 1). Subsequently, various bases were tested (Table 1, entries 2–5). Et_3N (triethylamine) was found to be the best in this reaction, whereas DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), DABCO (1,4-diazabicyclo[2.2.2]octane), and DiPEA (*N*,*N*-diisopropyl-ethylamine) were all found to be inferior. To further improve the outcome, different additives were used in this reaction (Table 1, entries 6–8). Surprisingly, we found that the desired product **3a** can be formed in 62% yield with TBAB (tetrabutylammonium bromide) as the additive (Table 1, entry 6). Replacement of TBAB with TBAC (tetrabutylammonium chloride) or TBAHS (tetrabutylammonium hydrogen sulfate) proved to be detrimental to the efficiency of the process, with product **3a** being formed in 56% and 49% yields, respectively (Table 1, entries 7 and 8). Next, we increased the amount of TBAB to 5 mol% and 10 mol% in the reaction conditions (Table 1, entries 9–10); however, the yield of product **3a** decreased. Different loadings of Et_3N affected the reaction yields, and we obtained 73% yield of product **3a** with 3 equivalents of Et_3N (Table 1, entries 11 and 12). Notably, the amount of $Mo(CO)_6$ played a crucial role for the outcome of this reaction (Table 1, entries 13–15). The yield of the desired product could be improved to 83% by adding 0.5 equivalent of $Mo(CO)_6$ (Table 1, entry 14). Additionally, the yield decreased with 1.5 equivalents of iodobenzene, and only 32% of the desired

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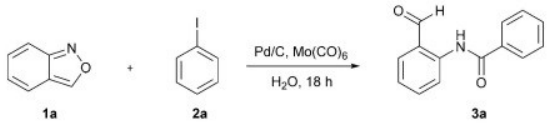
Table 1. Optimization of the reaction conditions.[a]



1a 2a 3a

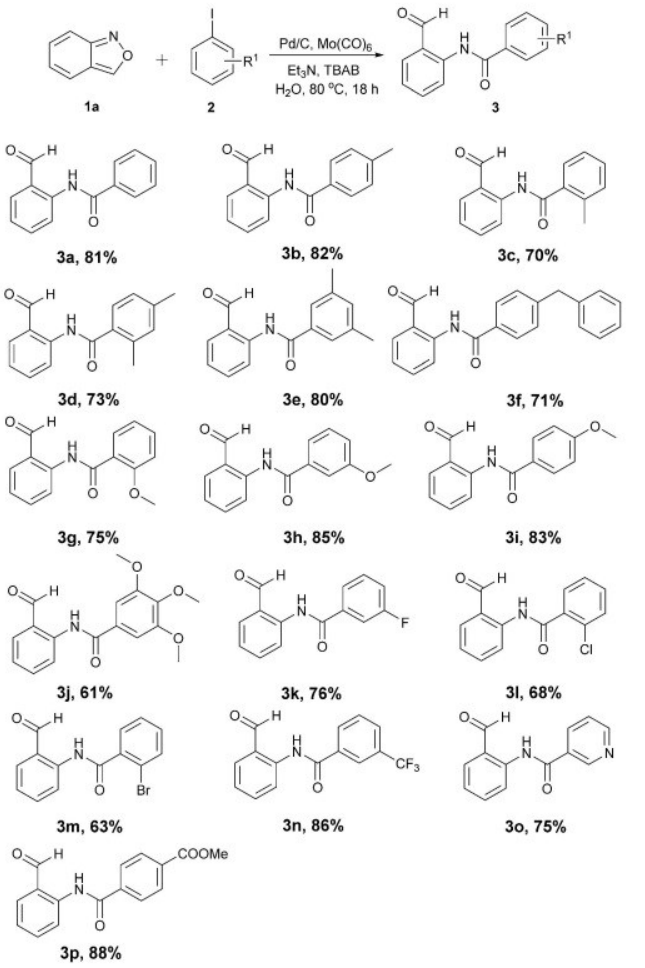
Entry	Base	Additive	Yield[%][b]
1	Cs_2CO_3	–	16
2	Et_3N	–	42
3	DBU	–	trace
4	DABCO	–	trace
5	DIPEA	–	37
6	Et_3N	TBAB	62
7	Et_3N	TBAC	56
8	Et_3N	TBAHS	49
9	Et_3N	TBAB (5 mol%)	58
10	Et_3N	TBAB (10 mol%)	51
11	Et_3N (1 equiv)	TBAB	33
12	Et_3N (3 equiv)	TBAB	73
13[c]	Et_3N (3 equiv)	TBAB	44
14[d]	**Et_3N (3 equiv)**	**TBAB**	**83 (81)**
15[e]	Et_3N (3 equiv)	TBAB	76

[a] Reaction conditions: **1a** (0.3 mmol, 1 equiv), **2a** (0.75 mmol, 2.5 equiv), Pd/C (3.2 mg, 10 mol%), $Mo(CO)_6$ (0.3 mmol, 1 equiv), base (0.6 mmol, 2 equiv), and additive (3 mol%) in distilled H_2O (2 mL) was stirred at 80 °C for 18 h under air. [b] Yields were determined by GC using *n*-hexadecane as the internal standard. [c] $Mo(CO)_6$ (0.09 mmol, 0.3 equiv). [d] $Mo(CO)_6$ (0.15 mmol, 0.5 equiv). [e] $Mo(CO)_6$ (0.24 mmol, 0.8 equiv).

product could be detected with one equivalent of iodobenzene. The same yield can be obtained if the reaction was performed under argon, which proves that this system is tolerant to aerobic conditions.

With the optimized conditions in hand (Table 1, entry 14), a series of aryl iodides were subsequently tested. As shown in Scheme 1, various aryl iodides with either electron-donating or electron-withdrawing groups worked well under our reaction conditions and gave the corresponding amides in moderate to good yields. Substrates can tolerate various functional groups such as CH_3, Benzyl, OCH_3, CF_3, Br, Cl, F, and COOMe. However, aryl iodides substituted with OH, NH_2 or NO_2 could not give the desired carbonylation products. The system permitted the reaction of sterically hindered aryl iodides such as 2-iodotoluene, 2-iodoanisole, 1-chloro-2-iodobenzene and 2-bromoiodo-benzene with anthranils providing 70%, 75%, 68%, and 63% yield, respectively (**3c**, **3g**, **3l**, **3m**). The reaction of the heterocyclic iodide 3-iodopyridine with anthranil proceeded smoothly under these reaction conditions, and provided 75% yield of the desired product **3o**. Interestingly, methyl 4-iodobenzoate reacted with anthranil and provided the highest yield of the corresponding product **3p** of 88%.

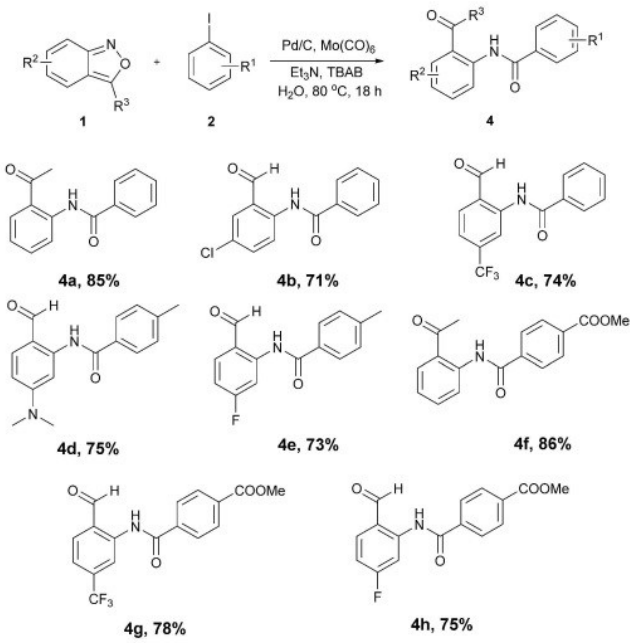
Then, various anthranils were investigated to further extend the substrates scope (Scheme 2). Several substituted anthranils performed well and delivered the corresponding amides in moderate to good yields. Owing to the mild reaction conditions, different functional groups, such as F, Cl, CF_3, and NMe_2, can be contained in the substrates. In addition, introduction of a substituted methyl group into the 3-position of the anthranil ring was fully tolerated, giving the desired amides in 85% and



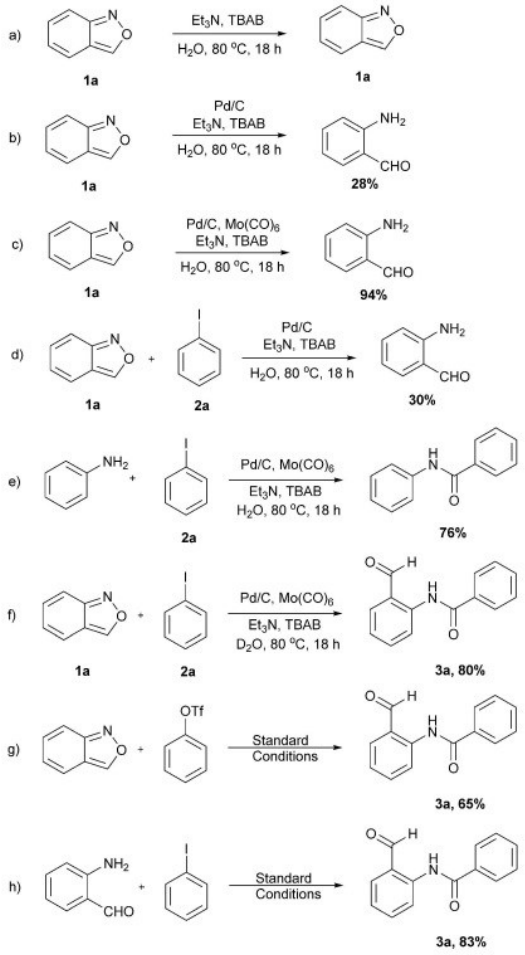
Scheme 1. Amide synthesis; variation of aryl iodides. Reaction conditions: Anthranil **1a** (0.3 mmol, 1 equiv), aryl iodides **2** (0.75 mmol, 2.5 equiv), Pd/C (3.2 mg, 10 mol%), $Mo(CO)_6$ (0.15 mmol, 0.5 equiv), Et_3N (0.9 mmol, 3 equiv), TBAB (0.009 mmol, 3 mol%), H_2O (2 mL), 80 °C, 18 h, air, isolated yield.

86% yields (**4a** and **4f**). Additionally, as one advantage of using a heterogeneous catalyst, catalyst recycling experiments were performed as well. In our model system, the catalyst could be reused several times (see Supporting Information), and 54% yield could still be achieved on the third run. 4-Bromoisoxazole was tested with iodobenzene as well, but no desired product could be detected.

To understand the mechanism, some control experiments were performed. From Scheme 3a and 3b, we found that the cleavage of N–O bond would take place in the presence of Pd/C and the presence of $Mo(CO)_6$ improves the yield (Scheme 3c). In the absence of $Mo(CO)_6$, no direct crosscoupling product 2-(phenylamino)benzaldehyde could be detected but only 2-aminobenzaldehyde was formed in 30% yield (Scheme 3d). These results show the importance of Pd/C and the dual roles of $Mo(CO)_6$ (to promote the generation of 2-aminobenzaldehyde, and act as a CO source). We could produce *N*-phenylbenzamide in 76% yield when aniline was used instead of anthranil under our standard conditions (Scheme 3e). Then, D_2O was used as the solvent in Scheme 3f. We could only produce **3a** in 80% yield, and no deuterated product was



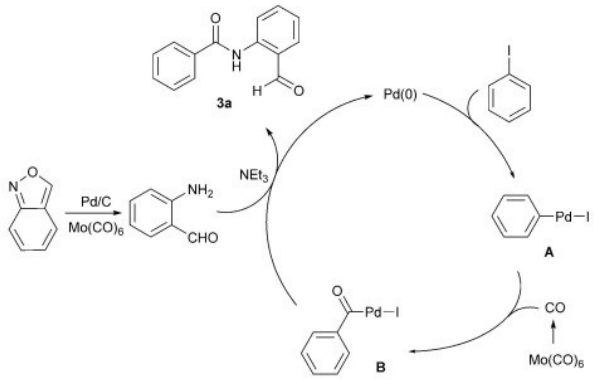
Scheme 2. Amide synthesis; variation of anthranils. Reaction conditions: Anthranils **1** (0.3 mmol, 1 equiv), aryl iodides **2** (0.75 mmol, 2.5 equiv), Pd/C (3.2 mg, 10 mol%), $Mo(CO)_6$ (0.15 mmol, 0.5 equiv), Et_3N (0.9 mmol, 3 equiv), TBAB (0.009 mmol, 3 mol%), H_2O (2 mL), 80 °C, 18 h, air, isolated yield.



Scheme 3. Control experiments, isolated yield.

detected, which could be due to the instability of the N–D bond. Notably, PhOTf can be applied as the substrate as well, thereby providing the desired product in 65% yield without any further optimization (Scheme 3g). 2-aminobenzaldehyde was also tested, giving 83% of the corresponding product under our standard conditions (Scheme 3h).

According to the control experiments, we postulated a possible reaction mechanism for this palladium-catalyzed aminocarbonylation (Scheme 4). Firstly, the iodobenzene reacted



Scheme 4. Proposed mechanism.

with palladium to give the aryl palladium complex **A**. Then, carbon monoxide, which was produced from $Mo(CO)_6$, coordinated and inserted into palladium complex **A** to generate the acyl palladium complex **B**. This acyl palladium complex **B** reacted with 2-aminobenzaldehyde to give the final product and regenerate the palladium catalyst for the next catalytic cycle.

In conclusion, we have developed a convenient procedure for the synthesis of *N*-(2-carbonylaryl)benzamides. Moderate to good yields of the desired amides could be prepared with good functional group tolerance. Additionally, this procedure also features advantages such as a recyclable Pd/C catalyst, safe $Mo(CO)_6$ as the solid CO source, water as an environmentally benign solvent, and no inert gas requirement.

Experimental Section

General procedure: In a 25 mL sealed tube, a mixture of anthranils 1 (0.3 mmol, 1 equiv), aryl iodides 2 (0.75 mmol, 2.5 equiv), Pd/C (3.2 mg, 10 mol%), $Mo(CO)_6$ (0.15 mmol, 0.5 equiv), Et_3N (0.9 mmol, 3 equiv), and TBAB (0.009 mmol, 3 mol%) in distilled water (2 mL) was stirred at 80 °C under air. After 18 h, the mixture was cooled to room temperature. The residue was diluted with H_2O solution (10 mL) and extracted with EtOAc (3×10 mL). The solvent was then evaporated under vacuum. The crude products were purified by using column chromatography on silica gel (pentane/ethyl acetate 4:1–2:1) to give the pure products.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: anthranils · carbonylation · domino reaction · green chemistry · palladium

[1] a) M. V. Khedkar, T. Sasaki, B. M. Bhanage, *ACS Catal.* **2013**, *3*, 287–293; b) V. R. Pattabiraman, J. W. Bode, *Nature* **2011**, *480*, 471–479; c) T. Cupido, J. Tulla-Puche, J. Spengler, F. Albericio, *Curr. Opin. Drug Discovery Dev.* **2007**, *10*, 768–783; d) C. Locatelli, F. B. Filippin-Monteiro, T. B. Creczynski-Pasa, *Eur. J. Med. Chem.* **2013**, *60*, 233–239; e) A. C. Fonseca, M. H. Gil, P. N. Simoes, *Prog. Polym. Sci.* **2014**, *39*, 1291–1311.

[2] K. Kumar, A. Zapf, D. Michalik, A. Tillack, T. Heinrich, H. Bottcher, M. Arlt, M. Beller, *Org. Lett.* **2004**, *6*, 7–10.

[3] A. Schoenberg, R. F. Heck, *J. Org. Chem.* **1974**, *39*, 3327–3331.

[4] For selected examples, see: a) W. Fang, Q. Deng, M. Xu, T. Tu, *Org. Lett.* **2013**, *15*, 3678–3681; b) E. Mizushima, T. Hayashi, M. Tanaka, *Green Chem.* **2001**, *3*, 76–79; c) T. T. Dang, Y. Zhu, J. S. Y. Ngiam, S. C. Ghosh, A. Chen, A. M. Seayad, *ACS Catal.* **2013**, *3*, 1406–1410; d) Z. S. Qureshi, S. A. Revankar, M. V. Khedkar, B. M. Bhanage, *Catal. Today* **2012**, *198*, 148–153; e) A. Siva Prasad, B. Satyanarayana, *J. Mol. Catal. A* **2013**, *370*, 205–209; f) R. H. Munday, J. R. Martinelli, S. L. Buchwald, *J. Am. Chem. Soc.* **2008**, *130*, 2754–2755.

[5] P. W. Miller, N. J. Long, A. J. Mello, R. Vilar, J. Passchier, A. Gee, *Chem. Commun.* **2006**, *5*, 546–548.

[6] J. R. Martinelli, T. P. Clark, D. A. Watson, R. H. Munday, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2007**, *46*, 8460–8463; *Angew. Chem.* **2007**, *119*, 8612–8615.

[7] J. R. Martinelli, D. A. Watson, D. M. M. Freckmann, T. E. Barder, S. L. Buchwald, *J. Org. Chem.* **2008**, *73*, 7102–7107.

[8] R. Skoda-Földes, E. Takacs, J. Horvath, Z. Tuba, L. Kollar, *Green Chem.* **2003**, *5*, 643–645.

[9] a) P. J. Tambade, Y. P. Patil, M. J. Bhanushali, B. M. Bhanage, *Synthesis* **2008**, *15*, 2347–2352; b) R. S. Mane, T. Sasakib, B. M. Bhanage, *RSC Adv.* **2015**, *5*, 94776–94785; c) N. Iranpoor, H. Firouzabadi, E. Etemadi-Davan, A. Nematollahi, H. R. Firouzi, *New J. Chem.* **2015**, *39*, 6445–6452; d) A.-R. Hajipour, Z. Tavangar-Rizia, N. Iranpoorc, *RSC Adv.* **2016**, *6*, 78468–78476.

[10] a) L. Ran, Z.-H. Ren, Y.-Y. Wang, Z.-H. Guan, *Chem. Asian J.* **2014**, *9*, 577–583; b) A. Schnyder, A. F. Indolese, *J. Org. Chem.* **2002**, *67*, 594–597; c) H. Li, K. Dong, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.* **2015**, *54*, 10239–10243; *Angew. Chem.* **2015**, *127*, 10377–10381; d) Y. Li, K. Dong, F. Zhu, Z. Wang, X.-F. Wu, *Angew. Chem. Int. Ed.* **2016**, *55*, 7227–7230; *Angew. Chem.* **2016**, *128*, 7343–7346.

[11] a) T. Mise, P. Hong, H. Yamazaki, *Chem. Lett.* **1980**, *9*, 439–440; b) L. He, M. Sharif, H. Neumann, M. Beller, X.-F. Wu, *Green Chem.* **2014**, *16*, 3763–3767.

[12] a) J. S. Baum, M. E. Condon, D. A. Shook, *J. Org. Chem.* **1987**, *52*, 2983–2988; b) J. R. Manning, H. M. Davies, *Tetrahedron* **2008**, *64*, 6901–6908.

[13] H. Jin, L. Huang, J. Xie, M. Rudolph, F. Rominger, A. S. K. Hashmi, *Angew. Chem. Int. Ed.* **2016**, *55*, 794–797; *Angew. Chem.* **2016**, *128*, 804–808.

[14] a) S. Yu, G. Tang, Y. Li, X. Zhou, Y. Lan, X. Li, *Angew. Chem. Int. Ed.* **2016**, *55*, 8696–8700; *Angew. Chem.* **2016**, *128*, 8838–8842; b) L. Li, H. Wang, S. Yu, X. Yang, X. Li, *Org. Lett.* **2016**, *18*, 3662–3665; c) S. Yu, Y. Li, X. Zhou, H. Wang, L. Kong, X. Li, *Org. Lett.* **2016**, *18*, 2812–2815.

[15] a) C. Tang, M. Zou, J. Liu, X. Wen, X. Sun, Y. Zhang, N. Jiao, *Chem. Eur. J.* **2016**, *22*, 11165–11169; b) M. Zou, J. Liu, C. Tang, N. Jiao, *Org. Lett.* **2016**, *18*, 3030–3033.

[16] D. K. Tiwari, M. Phanindrudu, S. B. Wakade, J. B. Nanuboluc, D. K. Tiwari, *Chem. Commun.* **2017**, *53*, 5302–5305.

[17] For an excellent review and examples on $Mo(CO)_6$, see: a) L. R. Odell, F. Russo, M. Larhed, *Synlett* **2012**, *23*, 685–698; b) N.-F. K. Kaiser, A. Hallberg, M. Larhed, *J. Comb. Chem.* **2002**, *4*, 109–111; c) J. Wannberg, M. Larhed, *J. Org. Chem.* **2003**, *68*, 5750–5753.

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5.6 Copper-Catalyzed Double Carbonylation of Indoles using Hexaketocyclohexane as the Carbon Monoxide Source

Zechao Wang, Zhiping Yin, and Xiao-Feng Wu*

Chem. Commun. **2018**, *54*, 4798-4801.

Author contributions:

In this paper, I finished the optimization of reaction conditions, investigation of substrate scope and writing the manuscript. My contribution as the first author of this paper is approximately 80%.

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Copper-catalyzed carbonylative transformations of indoles with hexaketocyclohexane†

Zechao Wang, Zhiping Yin and Xiao-Feng Wu *

With hexaketocyclohexane octahydrate as the carbon monoxide source, a novel procedure for copper-catalyzed direct double carbonylation of indoles has been established. Using alcohols as reaction partners, moderate to good yields of the desired double carbonylation products have been obtained. Wide functional group tolerance and substrate scope can be observed.

Transition-metal-catalyzed carbonylation reactions have already become one of the most powerful tools in modern organic chemistry.[1] To date, most of the efforts have been focused on monocarbonylation processes, while double carbonylation with the introduction of two adjacent carbonyl groups into organic molecules has been less explored.[2] The challenge comes from the high reactivity of the acyl-metal intermediate, which is more trend to go reductive elimination, decarbonylation or nucleophilic attract. Hence, in the reported achievements, besides the need for palladium as a catalyst, usually high CO pressure (>50 bar) is necessary together with aryl iodides as substrates.[3]

Additionally, although carbon monoxide is considered as one of the cheapest C1 sources and possesses non-replaceable advantages in industrial scale applications, its special characteristics (*e.g.*, being highly toxic, odor-less, flammable, *etc.*) limited its usage in laboratories. These properties also make special equipment (CO detector, autoclave, *etc.*) obligatory. Hence, the development of CO surrogates and exploration of their synthetic applications have become a new topic in chemistry research.[4] The known CO surrogates have common drawbacks including low efficiency, low stability and/or high activation energy, *etc.* In our effort to perform research on CO sources,[5] hexaketocyclohexane octahydrate comes to our mind.[6] Hexaketocyclohexane octahydrate ($C_6O_6{\cdot}8H_2O$) is a kind of non-toxic stable solid.[7] It was originally produced by oligomerization of carbon monoxide, and can be considered to be six-fold of carbon monoxide ($C_6O_6^{\bullet} \approx 6 \times CO$) with 100% atom efficiency and as the CO source. Because the ring of hexaketocyclohexane is highly strained, it can potentially decompose to CO in the reaction solution.[8] In this case, the CO concentration in the real solution can be significantly increased without affecting the catalyst center. And new reactivities can potentially be observed which are difficult in the case of pressurized carbon monoxide gas.

Our initial investigation started with the reaction of indole (**1a**) with methanol (**2a**), in the presence of $C_6O_6{\cdot}8H_2O$ (1 equiv.), 15 mol% of $Cu(OAc)_2$ and Ag_2CO_3 (1 equiv.) in CH_3CN at 80 °C. To our delight, the double carbonylation product **3a** was formed in 23% yield after 20 hours (Table 1, entry 1). Based on this initial finding, various oxidants such as $K_2S_2O_8$, BQ (1,4-benzoquinone), O_2, AgOAc, AgOTf, and AgTFA were tested subsequently. Unfortunately, none of them could give improved results (Table 1, entries 2–7). Then the amount of Ag_2CO_3 was varied (Table 1, entries 8–11). Surprisingly, 5 equivalents of Ag_2CO_3 gave the best result (Table 1, entry 10). In order to further improve the reaction outcome, the effects of acids were investigated as well (Table 1, entries 12–16). TFA can improve the yield of the double carbonylation product to 40% (Table 1, entry 16), whereas HOAc, PivOH, PhCOOH, and CH_3SO_3H were all found to be inferior. In the loading variation of TFA, 4 equivalents of TFA can give **3a** in the highest yield (Table 1, entries 17–19). In addition, a series of copper catalysts and palladium catalysts were tested as well (Table 1, entries 21–28). When using $CuBr(Me_2S)$ as the catalyst and 1,10-phen as the ligand (see the ESI†), we can obtain **3a in** the highest yield (69%; Table 1, entry 24). Subsequently, various commonly applied solvents were tested as well, such as HFIP (hexafluoroisopropanol), H_2O, HOAc, DMSO (dimethyl sulfoxide), toluene, DCE (1,2-dichloroethane), DMF (*N*,*N*-dimethylmethanamide), 1,4-dioxane, and THF (tetrahydrofuran), and no better results could be obtained (see the ESI†). Then the amounts of the catalyst, methanol and $C_6O_6{\cdot}8H_2O$ were varied as well, the yields of the target product decreased (see the ESI†). Interestingly, $Mo(CO)_6$ and CO (1 bar) were applied instead of $C_6O_6{\cdot}8H_2O$ in the model reaction, but only a trace amount of the desired product could be detected.

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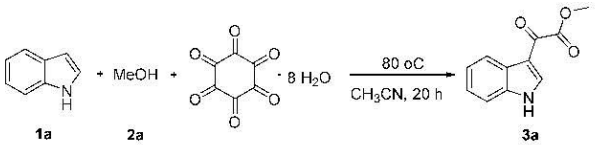
† Electronic supplementary information (ESI) available: General procedures, analytical data and NMR spectra (PDF). See DOI: 10.1039/c8cc01784k

Table 1 Optimization of the reaction conditions[a]

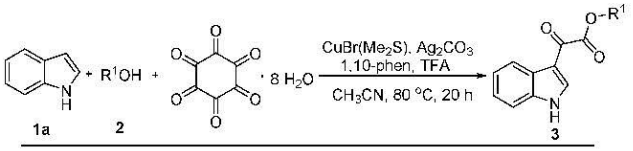


1a 2a 3a

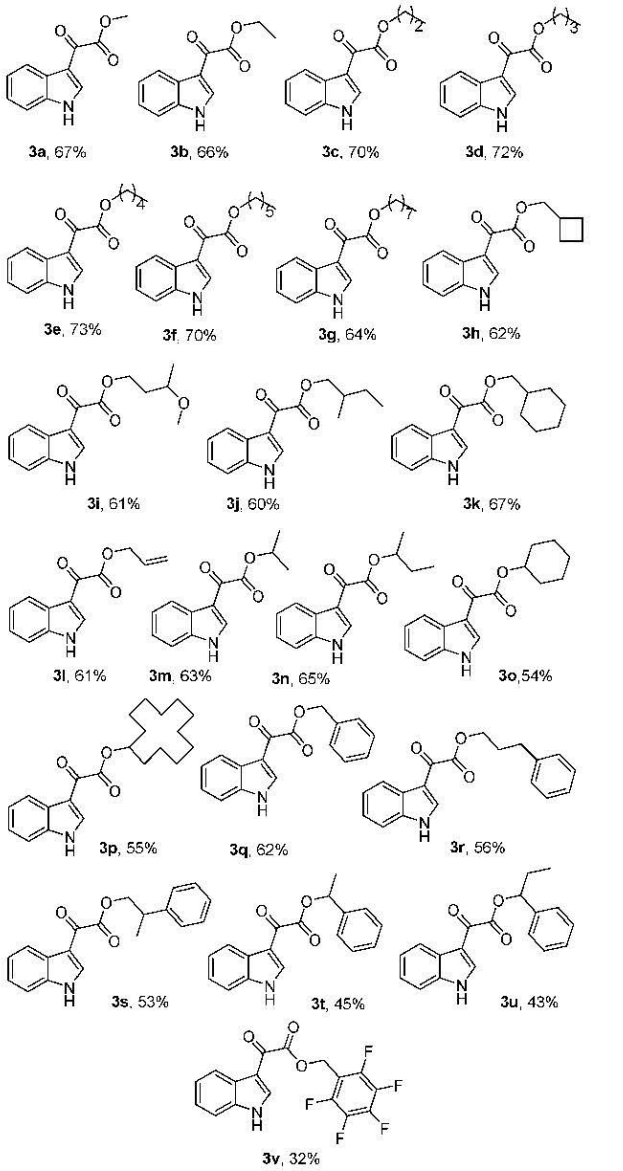
Entry	Oxidant	Acid	Catalyst	Yield[b] (%)
1	Ag_2CO_3	—	$Cu(OAc)_2$	23
2	$K_2S_2O_8$	—	$Cu(OAc)_2$	0
3	BQ	—	$Cu(OAc)_2$	0
4	O_2	—	$Cu(OAc)_2$	0
5	AgOAc	—	$Cu(OAc)_2$	Trace
6	AgOTf	—	$Cu(OAc)_2$	Trace
7	AgTFA	—	$Cu(OAc)_2$	Trace
8	Ag_2CO_3 (3 eq.)	—	$Cu(OAc)_2$	25
9	Ag_2CO_3 (4 eq.)	—	$Cu(OAc)_2$	30
10	Ag_2CO_3 (5 eq.)	—	$Cu(OAc)_2$	36
11	Ag_2CO_3 (6 eq.)	—	$Cu(OAc)_2$	35
12[c]	Ag_2CO_3	HOAc	$Cu(OAc)_2$	26
13[c]	Ag_2CO_3	PivOH	$Cu(OAc)_2$	30
14[c]	Ag_2CO_3	PhCOOH	$Cu(OAc)_2$	36
15[c]	Ag_2CO_3	CH_3SO_3H	$Cu(OAc)_2$	27
16[c]	Ag_2CO_3	TFA	$Cu(OAc)_2$	40
17[c]	Ag_2CO_3	TFA (3 eq.)	$Cu(OAc)_2$	41
18[c]	Ag_2CO_3	TFA (4 eq.)	$Cu(OAc)_2$	46
19[c]	Ag_2CO_3	TFA (5 eq.)	$Cu(OAc)_2$	40
20[d]	Ag_2CO_3	TFA	$Cu(OAc)_2$	55
21[d]	Ag_2CO_3	TFA	$CuBr_2$	52
22[d]	Ag_2CO_3	TFA	$CuCl_2$	54
23[d]	Ag_2CO_3	TFA	CuI	58(57)
24[d]	Ag_2CO_3	TFA	$CuBr(Me_2S)$	69(67)
25[d]	Ag_2CO_3	TFA	$Cu(acac)_2$	48
26[d]	Ag_2CO_3	TFA	$Pd(OAc)_2$	58
27[d]	Ag_2CO_3	TFA	$PdCl_2$	58
28[d]	Ag_2CO_3	TFA	$Pd(TFA)_2$	56

[a] Reaction conditions: indole **1a** (0.2 mmol, 1 equiv.), methanol **2a** (6 mmol, 30 equiv.), $C_6O_6{\cdot}8H_2O$ (0.2 mmol, 1 equiv.), oxidant (0.2 mmol, 1 equiv.), acid (0.2 mmol, 1 equiv.), and catalyst (0.03 mmol, 15 mol%) in CH_3CN (1 mL) for 20 h at 80 °C in sealed tubes in air. [b] Yields were determined by GC using *n*-hexadecane as the internal standard. Isolated yields are in parentheses. [c] Ag_2CO_3 (1 mmol, 5 equiv.). [d] Ag_2CO_3 (1 mmol, 5 equiv.), TFA (0.8 mmol, 4 equiv.), and 1,10-phen (0.06 mmol, 30 mol%).

Table 2 Double carbonylation of indoles with alcohols[a]



1a 2 3



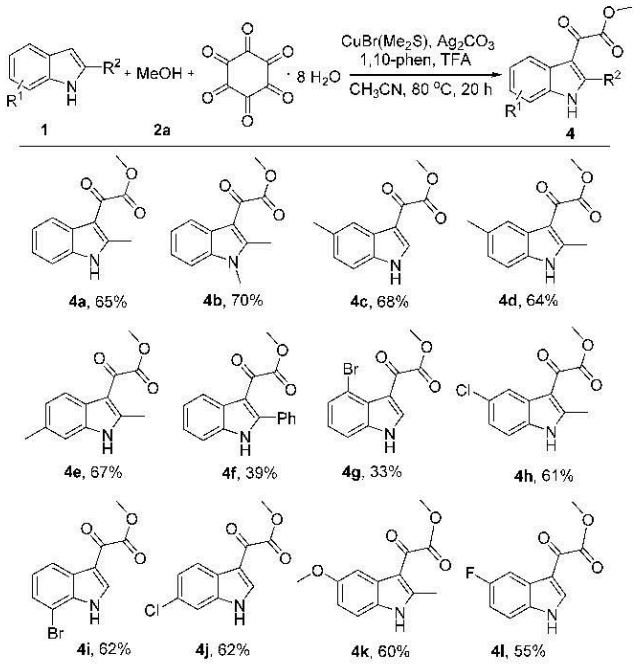
[a] Reaction conditions: indole **1a** (0.2 mmol, 1 equiv.), alcohols **2** (6 mmol, 30 equiv.), $C_6O_6{\cdot}8H_2O$ (0.2 mmol, 1 equiv.), $CuBr(Me_2S)$ (0.03 mmol, 15 mol%), 1,10-phen (0.06 mmol, 30 mol%), Ag_2CO_3 (1 mmol, 5 equiv.), TFA (0.8 mmol, 4 equiv.), CH_3CN (1 mL), 20 h, 80 °C, air, isolated yield.

With the optimized conditions in hand (Table 1, entry 24), screening of different alcohols was performed subsequently. As shown in Table 2, various primary and secondary alcohols worked well under our reaction conditions and gave the corresponding double carbonylation products in moderate to good yields. However, tertiary alcohols such as *tert*-butanol and *tert*-amyl alcohol give only trace amounts of the desired double carbonylation products. To our delight, benzylic alcohols can be applied under our reaction conditions as well to give the corresponding products in moderate yields without any further optimization.

Successively, various indoles were investigated for further extending the substrate scope (Table 3). To our delight, a series of functional groups, such as OMe, Ph, CF_3, Cl, and Br, were compatible under our conditions, which gave the desired double carbonylation products **4** in moderate to good isolated yields. 2-Phenyl substituted indole can be transformed as well, and the desired methyl 2-oxo-2-(2-phenyl-1*H*-indol-3-yl)acetate (**4f**) was isolated in 42% yield. Unfortunately, no target product could be detected when the COOMe group was substituted at the 2-position of indole. Comparing **4g** with **4i**, we found that the yield of the double carbonylation product decreased when there is a substitution at the 4-position of the indole applied, which can be explained by the steric hindrance effects. Not only *N*-H free indoles, but also *N*-Me substituted indoles can be applied.

In order to get some insight into the reaction pathway, control experiments were carried out. We found hexaketocyclohexane

Table 3 Double carbonylation of indoles with methanol[a]

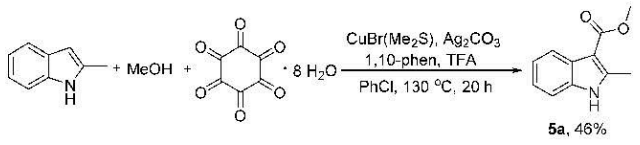


[a] Reaction conditions: indoles **1** (0.2 mmol, 1 equiv.), methanol **2a** (6 mmol, 30 equiv.), $C_6O_6{\cdot}8H_2O$ (0.2 mmol, 1 equiv.), $CuBr(Me_2S)$ (0.03 mmol, 15 mol%), 1,10-phen (0.06 mmol, 30 mol%), Ag_2CO_3 (1 mmol, 5 equiv.), TFA (0.8 mmol, 4 equiv.), CH_3CN (1 mL), 20 h, 80 °C, air, isolated yield.

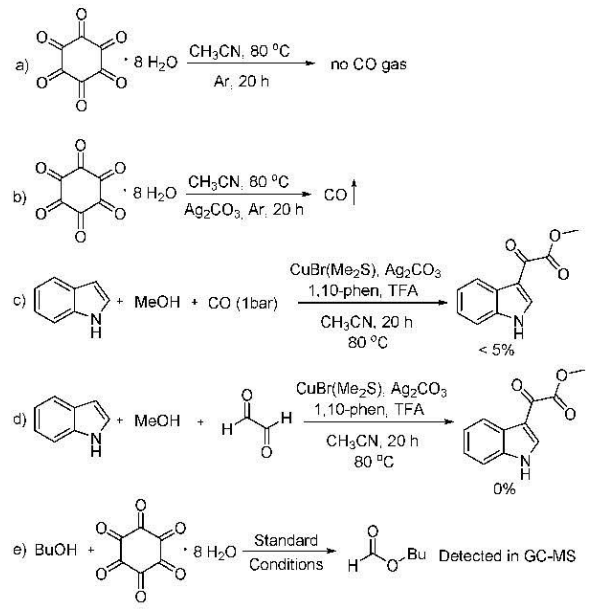
octahydrate to be stable at 80 °C in MeCN in the absence of a catalyst (Scheme 2, eqn (a)). Carbon monoxide gas can be detected after the addition of Ag_2CO_3 (Scheme 2, eqn (b)). However, by performing the model reaction system under CO gas (1 bar) with standard conditions, only a trace amount of methyl 2-(1*H*-indol-3-yl)-2-oxoacetate could be detected (Scheme 2, eqn (c)).

Here, it is also important to mention that a monocarbonylation product can be detected in some cases during the optimization process. In order to extend the use of hexaketocyclohexane octahydrate as the CO source, we performed further studies to increase the yield of the monocarbonylation product. To our delight, the monocarbonylation product **5a** can be obtained in 46% yield by using chlorobenzene as the solvent at 130 °C for 20 hours (Scheme 1).

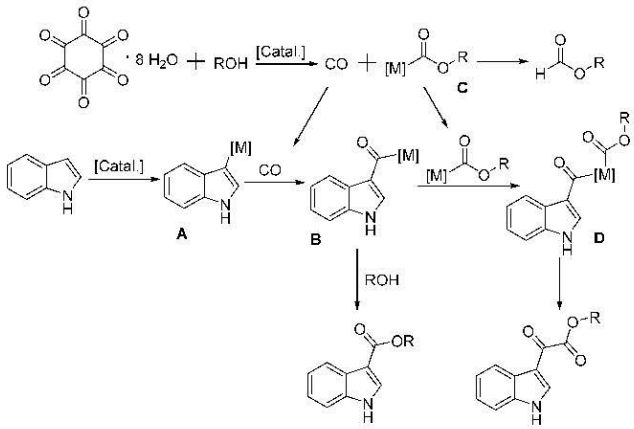
The possibility that involves glyoxal as the intermediate can be excluded during the experiment as shown in Scheme 2, eqn (d). In the absence of indole, under standard conditions, butyl formate can be detected in GC-MS (Scheme 2, eqn (e)). Based on our results, a possible reaction pathway is proposed (Scheme 3). In the presence of a catalyst and alcohol, hexaketocyclohexane octahydrate was



Scheme 1 Cu-catalyzed monocarbonylation of indole.



Scheme 2 Control experiments.



Scheme 3 Proposed reaction pathway.

transformed into CO and the corresponding alkyl formate *via* a carboalkoxy complex **C**. The presence of TFA can promote the formation of intermediate **A**.[9] Then complex **A** reacted with CO to give the acyl intermediate **B**. After transmetalation with carboalkoxy complex **C**, the key intermediate **D** was formed,[10] which can produce the final double carbonylation product after reductive elimination. As alkyl formate and the carboalkoxy complex **C** further decomposed into CO and alcohol at high temperature, only the monocarbonylation product was produced by the reaction between complex **B** and alcohol.

In summary, a novel procedure for copper-catalyzed double carbonylation of indoles with alcohols *via* C–H bond functionalization has been developed. With hexaketocyclohexane octahydrate as the CO source, the desired products were produced in moderate to good yields. And monocarbonylation can be realized as well. $C_6O_6{\cdot}8H_2O$ has been explored as an efficient CO source for the first time.

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Conflicts of interest

The authors declare no competing financial interest.

References

1 (*a*) J. Alvarez-Builla, J. J. Vaquero and J. Barluenga, *Modern Heterocyclic Chemistry*, Wiley-VCH, 2011; (*b*) X.-F. Wu, *RSC Adv.*, 2016, **6**, 83831–83837; (*c*) M. Beller, *Catalytic carbonylation reactions*, Springer, Berlin, New York, 2006; (*d*) L. Kollár, *Modern Carbonylation Methods*, Wiley-VCH, Weinheim, 2008; (*e*) X.-F. Wu and H. Neumann, *ChemCatChem*, 2012, **4**, 447–458; (*f*) X.-F. Wu, H. Neumann and M. Beller, *ChemSusChem*, 2013, **6**, 229–241; (*g*) X.-F. Wu, X. Fang, L. Wu, R. Jackstell, H. Neumann and M. Beller, *Acc. Chem. Res.*, 2014, **47**, 1041–1053; (*h*) R. Skoda-Foldes and L. Kollör, *Curr. Org. Chem.*, 2002, **6**, 1097–1119; (*i*) B. Gabriele, R. Mancuso and G. Salerno, *Eur. J. Org. Chem.*, 2012, 6825–6839.

2 (*a*) Y.-S. Lin and A. Yamamoto, *Handbook of Organopalladium Chemistry for Organic Synthesis*, John Wiley & Sons, Inc., 2003, pp. 2399–2423; (*b*) H. Abbayes and J.-Y. Salaun, *Dalton Trans.*, 2003, 1041–1052.

3 (*a*) Y. Uozumi, T. Arii and T. Watanabe, *J. Org. Chem.*, 2001, **66**, 5272–5274; (*b*) D. U. Nielsen, K. Neumann, R. H. Taaning, A. T. Lindhardt, A. Modvig and T. Skrydstrup, *J. Org. Chem.*, 2012, 77, 6155–6165; (*c*) W. Li, Z. Duan, X. Zhang, H. Zhang, M. Wang, R. Jiang, H. Zeng, C. Liu and A. Lei, *Angew. Chem., Int. Ed.*, 2015, **54**, 1893–1896; (*d*) Q. Xing, L. Shi, R. Lang, C. Xia and F. Li, *Chem. Commun.*, 2012, **48**, 11023–11025; (*e*) F. Ozawa and A. Yamamoto, *Chem. Lett.*, 1982, 865–868; (*f*) C. De. Risi, G. P. Pollini and V. Zanirato, *Chem. Rev.*, 2016, **116**, 3241–3305; (*g*) P. Hermange, A. T. Lindhardt, R. H. Taaning, K. Bjerglund, D. Lupp and T. Skrydstrup, *J. Am. Chem. Soc.*, 2011, **133**, 6061–6071; (*h*) S. D. Friis, R. H. Taaning, A. T. Lindhardt and T. Skrydstrup, *J. Am. Chem. Soc.*, 2011, **133**, 18114–18117; (*i*) V. de la. Fuente, C. Godard, E. Zangrando, C. Claver and S. Castillón, *Chem. Commun.*, 2012, **48**, 1695–1697; (*j*) S. Zheng, Y. Wang, C. Zhang, J. Liu and C. Xia, *Appl. Organomet. Chem.*, 2014, **28**, 48–53; (*k*) C. Zhang, J. Liu and C. Xia, *Org. Biomol. Chem.*, 2014, **12**, 9702–9706; (*l*) V. M. Fernández-Alvarez, V. De la. Fuente, C. Godard, S. Castillón, C. Claver, F. Maseras and J. J. Carbó, *Chem. – Eur. J.*, 2014, **20**, 10982–10989; (*m*) H. Du, Q. Ruan, M. Qi and W. Han, *J. Org. Chem.*, 2015, **80**, 7816–7823; (*n*) N. Saito, T. Taniguchi, N. Hoshiya, S. Shuto, M. Arisawa and Y. Sato, *Green Chem.*, 2015, **17**, 2358–2361; (*o*) Z. Wang, C. Liu, Y. Huang, Y. Hu and B. Zhang, *Chem. Commun.*, 2016, **52**, 2960–2963.

4 (*a*) T. Morimoto and K. Kakiuchi, *Angew. Chem., Int. Ed.*, 2004, **43**, 5580–5588; (*b*) S. D. Friis, A. T. Lindhardt and T. Skrydstrup, *Acc. Chem. Res.*, 2016, **49**, 594–605.

5 (*a*) J.-B. Peng, X. Qi and X.-F. Wu, *Synlett*, 2016, 175–194; (*b*) L.-B. Jiang, X. Qi and X.-F. Wu, *Tetrahedron Lett.*, 2016, **57**, 3368–3370.

6 Hexaketocyclohexane octahydrate, CAS Number: 527-31-1.

7 (*a*) G. Seitz and P. Imming, *Chem. Rev.*, 1992, **92**, 1227–1260; (*b*) R. B. Wyrwas and C. C. Jarrold, *J. Am. Chem. Soc.*, 2006, **128**, 13688–13689.

8 (*a*) D. Schröder, H. Schwarz, S. Dua, S. J. Blanksby and J. H. Bowie, *Int. J. Mass Spectrom.*, 1999, **188**, 17–25; (*b*) X. Bao, X. Zhou, C. F. Lovitt, A. Venkatraman, D. A. Hrovat, R. Gleiter, R. Hoffmann and W. T. Borden, *J. Am. Chem. Soc.*, 2012, **134**, 10259–10270.

9 Z. Wang, Z. Yin and X.-F. Wu, *Org. Lett.*, 2017, **19**, 4680–4683.

10 (*a*) P. L. Burk, D. Van Engen and K. S. Campo, *Organometallics*, 1984, **3**, 493–495; (*b*) E. Amadio, Z. Freixa, P. W. N. M. van Leeuwen and L. Toniolo, *Catal. Sci. Technol.*, 2015, **5**, 2856–2864.

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2. **Zechao Wang**, Fengxiang Zhu, Yahui Li, Xiao-Feng Wu*, *ChemCatChem* **2017**, *9*, 94-98.

3. **Zechao Wang**, Zhiping Yin, Fengxiang Zhu, Yahui Li, Xiao-Feng Wu*, *ChemCatChem* **2017**, *9*, 3637-3640.
4. **Zechao Wang**, Zhiping Yin, Xiao-Feng Wu*, *Org. Lett.* **2017**, *19*, 4680-4683.
5. **Zechao Wang**, Zhiping Yin, Xiao-Feng Wu*, *Chem. Eur. J.* **2017**, *23*, 15026-15029.
6. **Zechao Wang**, Zhiping Yin, Xiao-Feng Wu*, *Chem. Commun.* **2018**, *54*, 4798-4801.
7. Zhiping Yin, **Zechao Wang**, Xiao-Feng Wu*, Org. Biomol. Chem. **2018**, *16*, 3707-3710. (co-first author)
8. Zhiping Yin, **Zechao Wang**, Wanfang Li, Xiao-Feng Wu*, *Eur. J. Org. Chem.* **2017**, *2017*, 1769-1772.
9. Zhiping Yin, **Zechao Wang**, Xiao-Feng Wu*, *Org. Lett.* **2017**, *19*, 6232-6235.
10. Zhiping Yin, **Zechao Wang**, Xiao-Feng Wu*, *ChemistrySelect* **2017**, *2*, 6689-6692.
11. Zhiping Yin, **Zechao Wang**, Xiao-Feng Wu*, *Eur. J. Org. Chem.* **2017**, *2017*, 3992-3995.
12. Fengxiang Zhu, **Zechao Wang**, Yahui Li, Xiao-Feng Wu*, *Chem. Eur. J.* **2017**, *23*, 3276-3279.
13. Yahui Li, **Zechao Wang**, Xiao-Feng Wu*, *ACS Catal.* **2018**, *8*, 738-741.
14. Fengxiang Zhu, Yahui Li, **Zechao Wang**, Romano V. Orru, Bert U. W. Maes, Xiao-Feng Wu*, *Chem. Eur. J.* **2016**, 22, 7743-7746.
15. Zhiping Yin, Dennis J. Power, **Zechao Wang**, Scott G. Stewart*, Xiao-Feng Wu*, Synthesis, DOI: 10.1055/s-0037-1609481.

7. Selbstständigkeitserklärung

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

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Ich habe eine Dissertation zum Thema

Transition Metal-Catalyzed Carbonylation of Nitrogen-Containing Compounds via C-H Activation

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

Prof. Dr. Matthias Beller

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