Palladium-Catalyzed Heterocycles Synthesis *via* Carbonylative Activation of Ar-X and Ar-H Bonds

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Universität Rostock

Abstract

Palladium-Catalyzed Heterocycles Synthesis *via* Carbonylative Activation of Ar-X and Ar-H Bonds

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This thesis composed of two major parts. The first part mainly contains the carbonylation of aryl halides towards heteroaromatic ring synthesis catalysed by homogeneous palladium systems. The second part includes the investigation of carbonlytive C-H functionalization for the preparation of heterocycle also. The resulted heterocycles such as quinazolinone, isoquinolin-1(2*H*)-one, phthalimides (thalidomide, caprolactam and butyrolactam derived phthalimides), isoindoloquinazoliones, 2-quinazolines and *N*-(2-pyridyl)indoles constitute an important class of life science molecules which are frequently encountered in the medicinal and biological chemistry. Despite established procedures for the synthesis of these heterocycles, still there is a need for the practical methodologies for the production of all kinds of heterocycles. Specifically, we show heterogeneous Pd/CeO_2 system is efficient for the synthesis of indole derivatives *via* sustainble C-H activation processes. In all the synthetic reactions the systematic catalyst optimization studies and the scope of the protocols are presented.

Diese Arbeit besteht aus zwei Teilen, im Ersten Teil werden Carbonylierung von Arylhalogeniden an heteroaromatischen Ringsystemen in Gegenwart von homogenen Palladiumkatalysatoren behandelt. Im Zweiten Teil dieser Arbeit werden cabonyliernde C-H Aktivierungen an Heterocyclischen Verbindungen beschrieben. Mit diesen Reaktionen konnten verschiedene Substanzklassen synthetisiert werden unter anden Quinazolinone, Isoquinolin-1(2*H*)-one, Phthalimide wie Thalidomid, Caprolactam und Butyrolactam, Isoindoloquinazolione, 2-Quinazolin und *N*-(2-pyridyl)Indole. Die Intention für die Synthese der aufgeführten Substanzen ist ihre wichtige Bedeutung als Leitstruktur in der medizinischen und biologisch Chemie. Desweiteren kann mit dieser Arbeit erstmals eine C-H Aktivierung an Indolen mittels heterogenen Katalysatoren durchgeführt werden. Dabei hat sich Pd/CeO_2 als besonders aktiver Katalysator erwiesen. Für alle Teilgebiete dieser Arbeit wurden systematische Katalysatoroptimierungen durchgeführt und die Ergebnisse konnten in internationalen Journalen veröffentlicht werden.

Table of Contents

List of Abbreviations

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

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

1 Introduction

Carbonylation reactions have gained numerous attentions during the past several decades as they serve as a powerful synthesis toolkit for the chemists. Since the pioneering work by Heck in 1974 with palladium catalyst,[1] many achievements have been made in the last 40 years. Carbonylation reaction is the most potent methodology to produce carbonyl compounds and increases the carbon number at the meantime. For most of the cases, the interests have been mainly focused on the utility of aryl halide or pseudo halides (ArX) as the starting material for the formation of carbon-metal bond via the oxidative addition of metal catalyst to the C-X bond.[2] However, the pre-functionalization of arene was required to synthesize the required aromatic halides. Thus caused the waste of energy and time. 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.[3] In this regard, the oxidative carbonylation with naturally abundant arene and its hydrocarbon complex as the starting material has been exploited recently.[4] Compared to well-defined carbonylation reaction of aryl halides, the carbonylative C-H bond functionalization have faces many challenges: (i) the reduction of Pd (II) to Pd (0) is more easily underwent under the CO atmosphere which has excellent reducing ability; (ii) strong binding ability of CO might inhibit the electronic attach of Pd (II) toward the aromatic C-H bonds because of occupying the active sites; (iii) CO as an excellent π-acid behaving the unique π-back bonding might also decrease the electron density on Pd center. The efforts and the solutions to solve these challenges are partially provided by the following publications in this chapter.

Heterocyclic molecules are important class of compounds which are frequently encountered in the medicinal and biological chemistry. Based on the importance of these life science molecules, in recent years number of efforts have been made to synthesize the core heterocycles [2b, 5]. However, there were not many reports on the carbonylation reaction for the synthesis of heterocycles[2b]. Therefore, here we discuss the main progress in the carbonylative C-H bond functionalization for the heterocyclic synthesis.

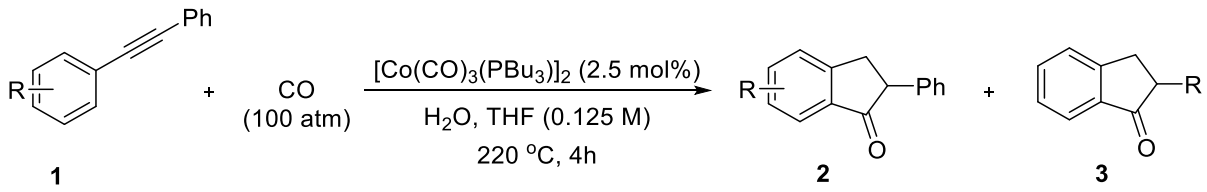
The present thesis highlights the recent achievements in carbonylative heteroaromatic rings synthesis via C-H activation process. It is also presented as a cumulative collection of publications which have been already published and submitted in international journals as well as in patent applications.

1.1 Cobalt-Catalyzed Heterocycles Synthesis *via* Carbonylative C-H Activation.

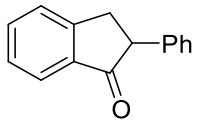
1.1.1 Five-membered ring synthesis

Takahashi *et al* reported that acetylene could be transformed into indan-1-one under water gas shift condition with cobalt as the catalysis in 1990.[6] However, the reaction proceeds at harsh conditions (100 atm of CO and 220 ^{o}C) and 8 examples have been given in acceptable to good yields (Table 1).

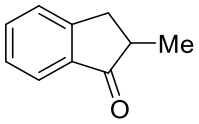
Table 1. Scope of the cyclocarbonylation of acetylene.[a]



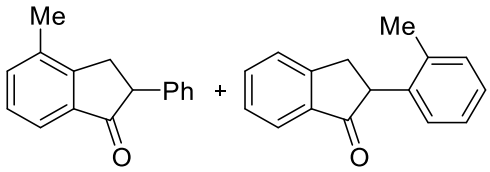
1 **2** **3**



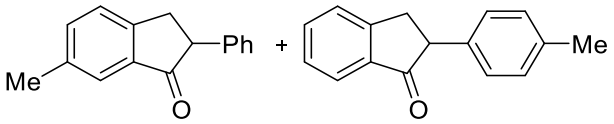
2a 77%



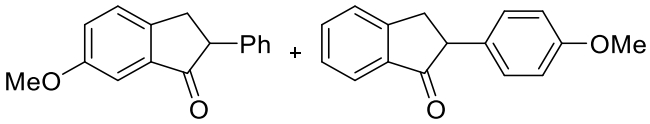
2b 17%[b]



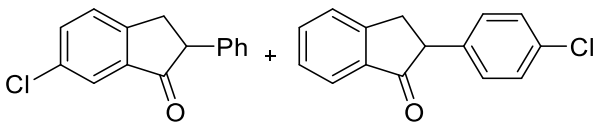
2c/**3c** (50/50) 65%[c]



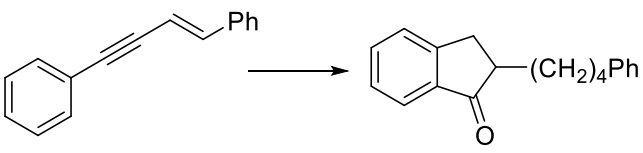
2d/**3d** (52/48) 74%[c]



2e/**3e** 86%



2f/**3f** (41/59) 63%[c]

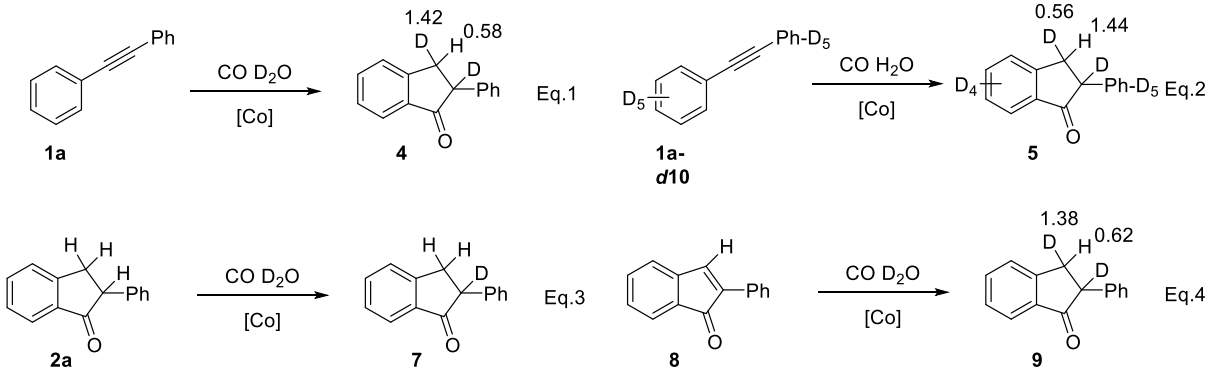


1g **3g** 41%

Reaction conditions: [a] **1** alkyne (5 mmol), $[Co(CO)_3(PBu_3)]_2$ (2,5 mol%), H_2O (11 equiv), THF (40 mL), CO (100 atm), 220 ^{o}C, 4h, isolated yields. [b] Determined by GLC. [c] Determined by ^{1}H NMR spectroscopy.

In order to obtain some details about this transformation, a series of deuterium-isotope-labeled experiments were conducted. By treating **1a** with D_2O instead of H_2O, the deuterated indanone **4** was obtained indicating that hydrogen comes from water [Eq. 1]. The ratio of the H/D was in good agreement with the results of the reaction of decadeuteriodiphenylacetylene **1a**-*d*10 with water [Eq. 2]. These data suggested that the hydrogen of aromatic C-H bond migrated to the acetylenic carbon of the diphenylacetlyene during this cyclocarbonylation. Using molecular hydrogen as the hydrogen source, no desired **2a** was obtained, whereas only dibenzyl was formed in good yield. This indicates that the water-gas condition is essential for this transformation. When **2a** was treated under the standard condition in the presence of D_2O, hydrogen in the methyne group of indanone **7** was almost changed to the deuterium while the methylene group was intact [Eq. 3]. Indenone **8** also gave the deuterated indanone **9** by the same treatment. The ^1H NMR spectrums show that the H/D ratio in **9** was 0.62/1.38 and the methine group was entirely exchanged by deuterium [Eq. 4].

Scheme 1. Deuterium labeling experiments.

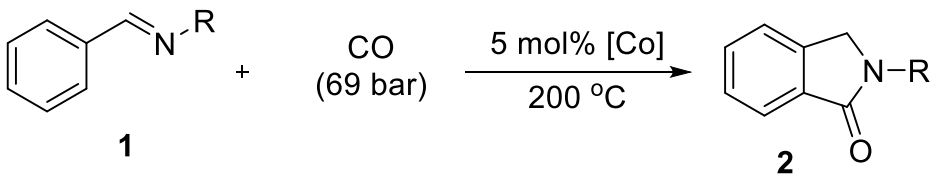


A plausible mechanism was outlined by the authors. The coordination of diphenylacetylene (**1a**) to the cobalt complex could induce an electronic attack of the central cobalt metal on the aromatic ring and migration of the aromatic hydrogen to the acetylenic carbon initialing the C-H metalation step. Insertion of CO into the cobaltocycle complex give the indenone **8**. The resultant indenone could be hydrogenated by the [Co]-H species formed under water gas shift reaction conditions to furnish the indanone formation as discuss above.

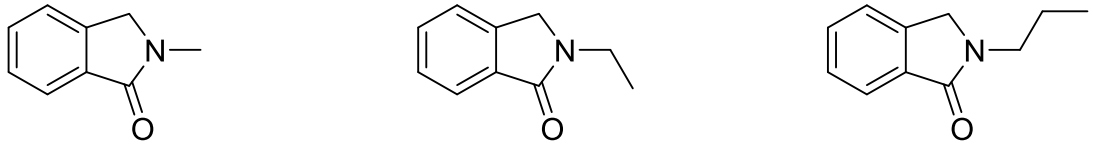
The formation of *N*-alkyl isoindolin-1-one through carbonylative C-H activation of *N*-alkyl benzaldimines with a cobalt as the catalyst was achieved by Sen and co-workers in 2006 (Table 2).[7] The author wants to exploit the formation of polypeptides from aldimines with CO, after the analysis of the products with GCMS, NMR and X-ray, it turns out to be the isoindolin-1-one scaffolds. Reactions run under high temperature and pressure (100 ^oC and 69 bar of CO) and deuterium experiments indicates that the [Co]-H species was generated

by the C-H metalation step of the aromatic ring, followed by insertion to the C=N bond of the benzaldimine affording the final products.

Table 2. Scope of carbonylation of aldimides.[a]



1 **2**

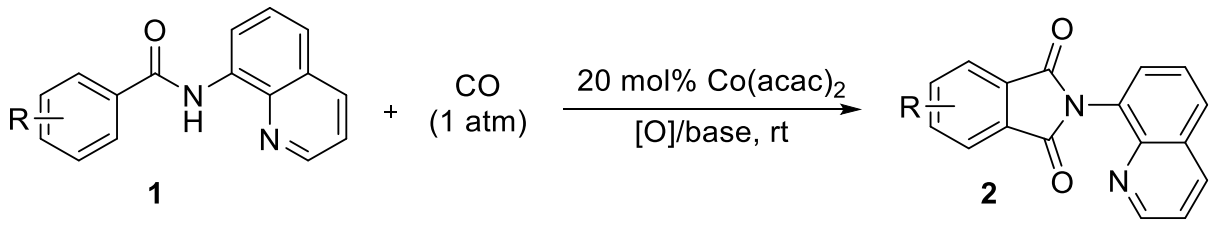


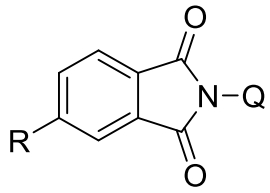
2a 71% 48h **2b** 71% 48h (92%[b]) **2c** 62% 24h

Reaction conditions: [a] **1** *N*-alkylbenzaldimine (0,4 mmol), [Co(^{13}MeCO(CO)$_3$(P(*o*-tol)$_3$)] (5mol%), (D_8)-1,4-dioxane (2 mL), CO (69 bar), 200 °C, noted time, yields were determined by ^{1}H NMR spectroscopy with 1,3,5-trioxane as an external standard in $CDCl_3$. [b] **1b** (1,2 mmol), $Co_2(CO)_8$ 5 mol%, in C_6D_6 (2 mL), 6h.

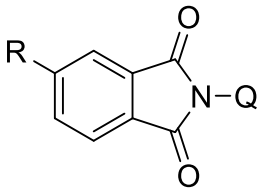
In 2014, the cobalt-catalyzed carbonylative synthesis of phthalimide motifs from benzamides was demonstrated by Daugulis and co-worker.[8] Here they used the 8-aminoquinoline as the *N*,*N* -bidentate directing system. Reactions run even at room temperature under 1 atm of CO in trifluoroethanol solvent, use oxygen from air as an oxidant, and require $Mn(OAc)_3 \cdot H_2O$ as an additive (Table 3). A wide range of functional groups including methyl, methoxy, cyano, ester, trifluoromethyl and trifluoromethoxyl can be compatible well in good yield (**2a**-**h**). Notably, the nitro group which was easily reduced under CO conditions was incorporated into the products without any problem (**2j**). Interestingly, the substrates bearing halogen group such as bromo and iodo gave the corresponding products in 80% and 84% yield, respectively(**2c**, **i**). Control experiments indicates that oxygen from air serve as the oxidant (without air, only 20% yield of **2d** was obtained). The author inferred that $Mn(OAc)_3 \cdot H_2O$ play the role of cocatalyst.

Table 3. Scope of carbonylation of amides.[a]

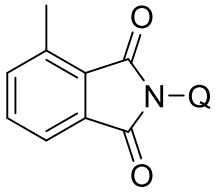




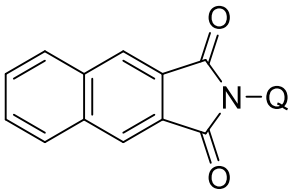
R=H **2a** 81%
R=CF_3 **2b** 83%
R=Br **2c** 80%
R=Me **2d** 84%
R=OMe **2e** 94% 30h
R=OCF_3 **2f** 66% 40h
R=CN **2g** 75% 30h
R=CO_2Et **2h** 60% 40h



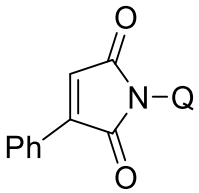
R=I **2i** 84%
R=NO_2 **2j** 69% 32h



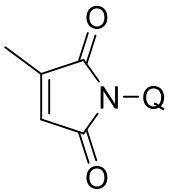
2k 72% 24h



2l 77% 30h



2m 60% 24h



2n 33% 40h

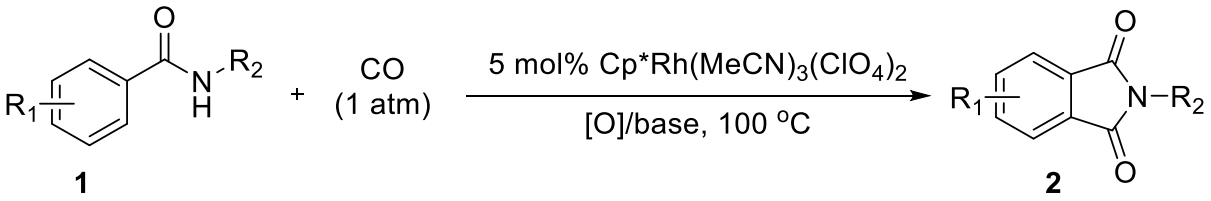
Reaction conditions: [a] **1** amide (0,5 mmol), $Co(acac)_2$ (20 mol%), $Mn(OAc)_3{\cdot}H_2O$ (1,0 equiv), NaOPiv (2,0 equiv), TFEtOH (5 mL), CO (1 atm, balloon), air, rt, 16h unless otherwise noted, Q = 8-quinolinyl.

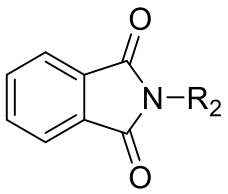
1.2 Rhodium-Catalyzed Heterocycles Synthesis via Carbonylative C-H Activation

1.2.1 Five-membered ring synthesis

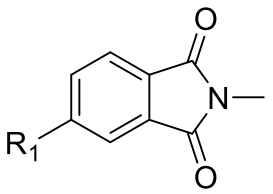
In 2011, an efficient approach for the formation of phthalimides through oxidative carbonylation of aromatic amides have been developed by Rovis and co-workers in the present of rhodium catalyst.[9] In this report, 16 examples were synthesized (Table 4). Especially, different kinds of *N*-protecting groups such as alkyl (methyl, *n*-butyl, *n*-hexyl and isopropyl), benzyl, phenyl ethyl and CH_2CO_2Me can be utilized with moderate to good efficiency (**2a**-**d**, **2j**). Substrates bearing *para* or *meta* electron-donating groups with the example of methyl, methoxy and phenyl on aromatic ring provide the phthalimide products in high yields (**2e-f**, **2h-i**). Notably, the bromo functionality was successfully untouched under this condition and yields 33% desired product (**2g**). Interestingly, heteroaryl amide works well in this system giving the corresponding phthalimide in moderate yield (**2k**). Reactions show a preference for the electro-rich aromatic amides in the C-H activation step and the deuterium experiments suggest that C-H metalation step is largely irreversible.

Table 4. Represent examples of carbonylation of amides toward phthalimides.[a]

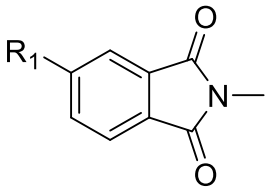




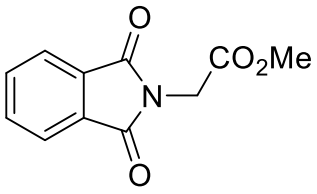
R_2=Me **2a** 94%
R_2=Et **2b** 87%
R_2=*n*Bu **2c** 92%
R_2=Bn **2d** 86%



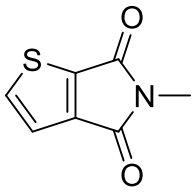
R_1=OMe **2e** 82%
R_1=Ph **2f** 87%
R_1=Br **2g** 33%



R_1=Me **2h** 80%
R_1=OMe **2i** 95%



2j 43%



2k 42%

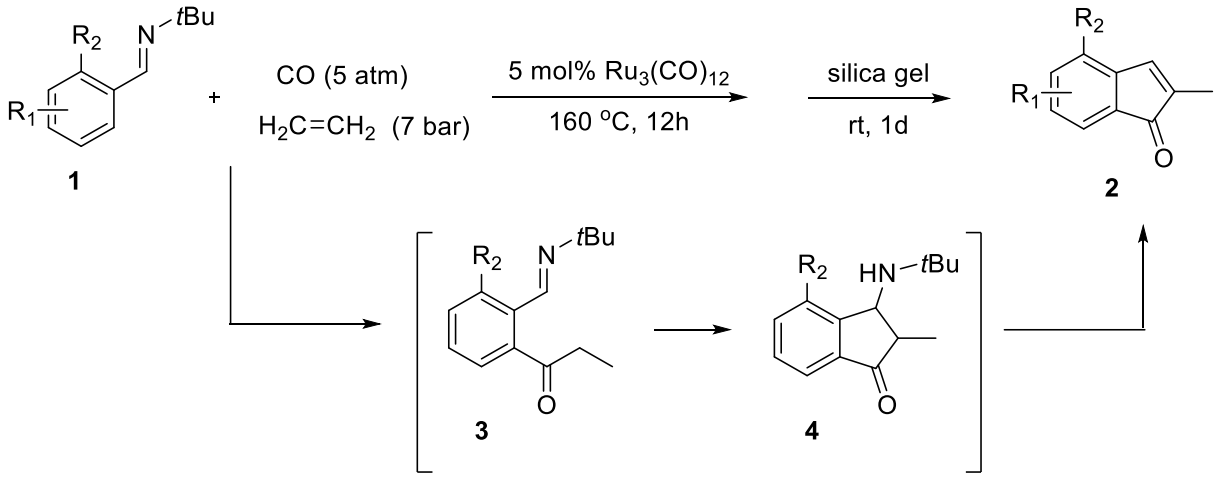
Reaction conditions: [a] **1** aromatic amide (0,2 mmol), $Cp^*Rh(MeCN)_3(ClO_4)_2$ (5 mol%), Ag_2CO_3 (2,0 equiv), KH_2PO_4 (2,0 equiv), *t*-AmOH (0,37 mL), CO (1 atm, balloon), 100 °C 24h.

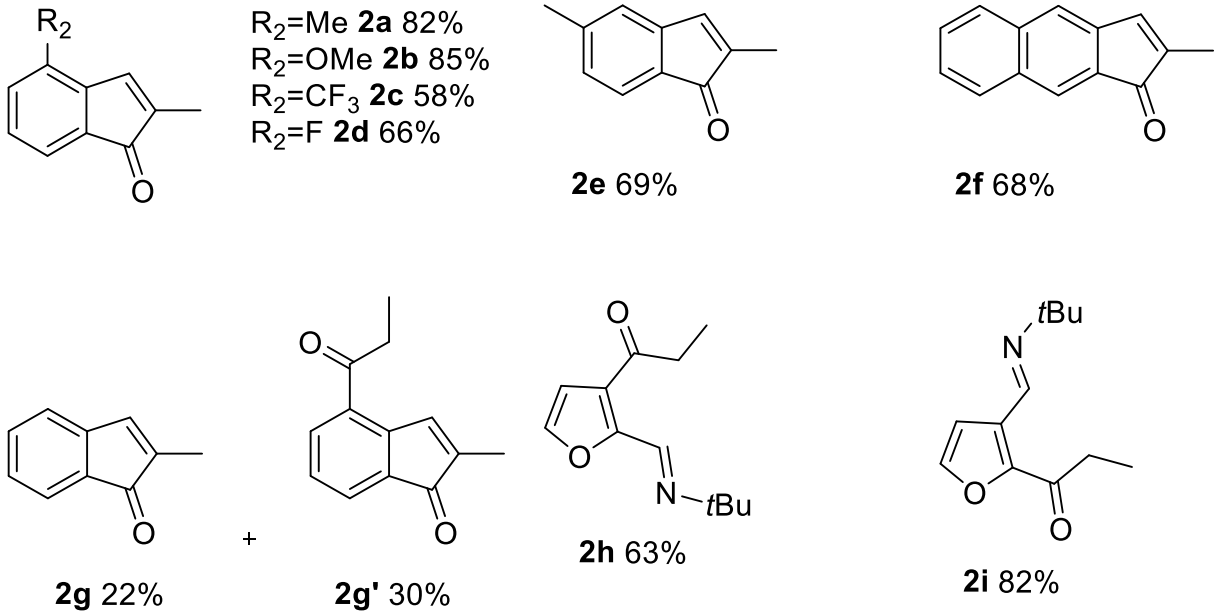
1.3 Ruthenium-Catalyzed Heterocycles Synthesis via Carbonylative C-H Activation

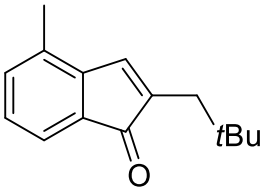
1.3.1 Five-membered ring synthesis

Mural *et al* in 1997 developed the carbonylation of aromatic imines for the preparation of indenones in the presence of $Ru_3(CO)_{12}$.[10] This process runs under 7 bar of ethylene and 5 atm of CO at 160 ^oC (Table 5). Controled experiments demonstrated the one-pot two steps reaction is involved: first, the carbonylation of aromatic imines with CO and ethylene giving the keto imine **3**, then intramolecular aldol-type condensation of keto imine **3** would readily undergo to generate **4** *in situ*. Treatment of the crude reaction mixture with silica gel rueslted in the elimination of *tert*-butylamine from **4** delivering final product **2**.

Table 5. Selective examples for the preparation of indenones from aromatic imines.[a]

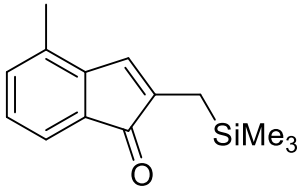






$H_2C{=}CHtBu$ (4 equiv)

2j 41% 40h



$H_2C{=}CHSiMe_3$ (4 equiv)

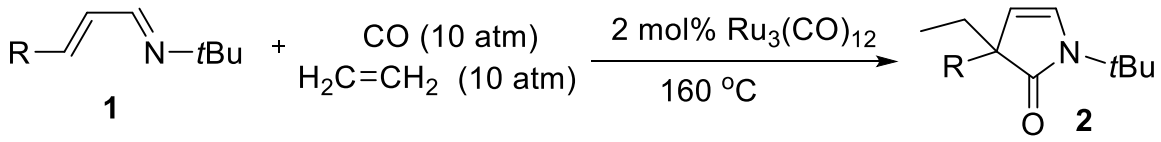
2k 64%[b] 20h

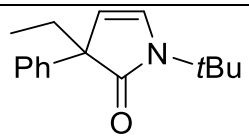
Reaction conditions: [a] **1** aromatic imines (2 mmol), $Ru_3(CO)_{12}$ (5 mol%), toluene (6,0 mL), CO (5 atm), ethylene (7 bar), 160 ^oC, 12-40h. [b] with 14% of **2a** was formed.

The *ortho*-substituted group can be varied with electron-donating group such as methoxy (**2b**) or with electron-withdrawal group such as trifluoromethyl and fluoro (**2c, d**) in good yields. The reaction of *N*-benzylidene-*tert*-butylamine **1g** afforded two products among which the second acylation took place giving **2g'** in 30% yield. The heteroaromatic compound only generates the corresponding acylated ketone, no further aldol type condensation took place under this standard conditions perhaps because the keto and imino group are located too far from one to another (**2h**, **i**). Olefins such as the 1-hexene, styrene and methyl acrylate failed whereas the *tert*-butylethylene (**2j**) and trimethylvinylsilane (**2k**) underwent smoothly to produce the final products in 41% and 64% yields, respectively.

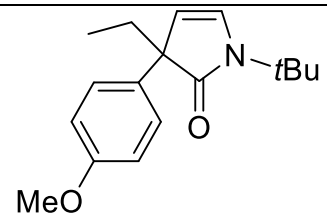
Mural and Chatani extend the method from aromatic imines to α, β-unsaturated imines in 2002. Very interestingly, no formation of the anticipated cyclopentadienones was detected yet β,γ-unsaturated γ-butyrolactams was formed (Table 6).[11]

Table 6. Selective products for the carbonylation of α, β-unsaturated imines.[a]

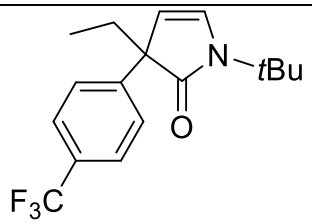




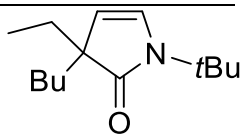
2a 73%



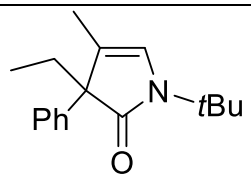
2b 68%



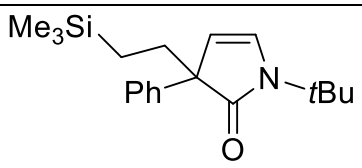
2c 27%



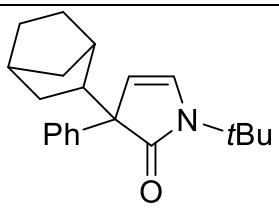
2d 35%



2e 75%



2f 72%[b]



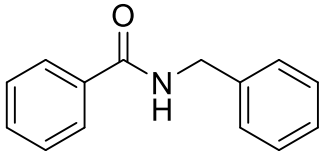
2g 44%[b]

Reaction conditions: [a] **1** imines (1 mmol), $Ru_3(CO)_{12}$ (2 mol%), toluene (2,0 mL), CO (10 atm), ethylene (10 atm), 160 ^{o}C, 20h. [b] with 14% of **2a** was formed.

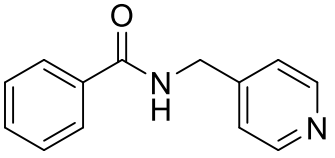
The reaction proceeds via a two-step sequence involving the initial carbonylation at the β-olefinic C-H bond of α,β-unsaturated imines forming the ketone derivatives, followed by the intramolecular nucleophilic attack of the imine nitrogen on the ketonic carbon to generate a tetrahydral intermediate, which then undergo a 1,2-alkyl migration. Compared to the electron-donating group, the trifluoromethyl as an example of electron-withdrawing group resulted in the lower yield (**2b** *vs* **2c**). Notably, imines containing an alkyl group at the β-position can also be applied to this condition albeit in low yield (**2d**). Terminal alkene such as the 1-hexene failed while the vinylsilane and norbornene as the alkene partners run smoothly forming the lactam products in 72% and 44% yields, respectively. In this case, direct carbonylation at the olefinic C-H bonds is the key step. The author proposed a mechanism in which 1, 2-hydride shifts and 1, 2-alkyl migration are involved for this transformation.

Chatani *et al* exploded a bidentate-chelation system in 2009 in the presence of ruthenium catalyst, in which carbonylation took place at the *ortho* C-H bonds in aromatic amides leading to phthalimides (Table 7).[12] Intriguingly, no acylation was observed although the condition is very similar to their previous work. It should be noted that compared to the normal monodentate system, ethylene server as H_2 acceptor and *N*, *N*-bidentate are key features for the successful cyclocarbonylation as utilizing compound (**4**-**8**) as the starting material no any carbonylation occurred (Scheme 2).

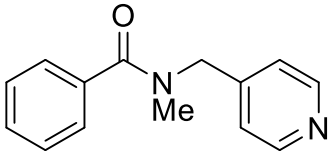
Scheme 2. Other amides compare to the *N*, *N*-bidentate system.



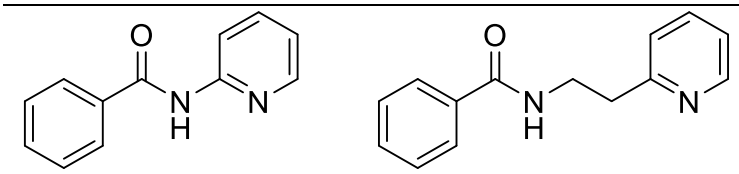
4



5



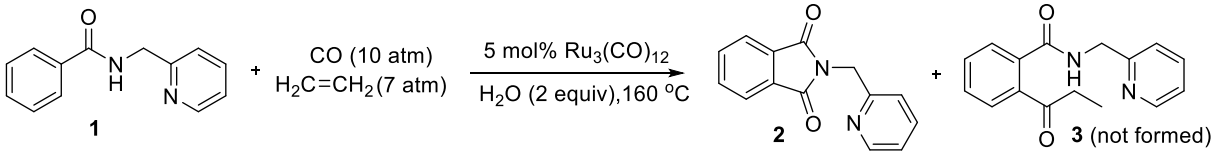
6

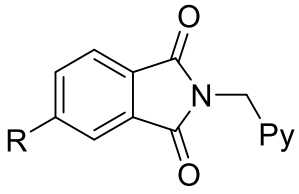


7 **8**

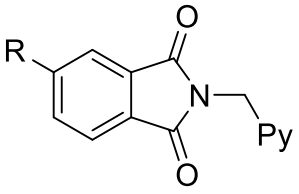
A wide variety of functional groups, including methoxy, amino, ester, cyano even bromo can be incorporated into the products (**2a**-**f**). Next *meta*-substituted amides were used to test the regioselectivity. Except the methyl, other functional groups such as the OCF_3, NMe_2 and ketone substituted analogs favor the less sterically hindered position which indicates that the electron effect is not a dominant factor (**2g**-**j**). Investigations demonstrate that the true active species is a dinuclear Ru (I) confirmed by X-ray crystallography. It should be kept in mind that the water is necessary in this procedure as the yield would be drop sharply without water.

Table 7. Bidentate system for the carbonylation of amides.[a]





R=H **2a** 77%
R=OMe **2b** 69%
R=NMe_2 **2c** 60%
R=COOMe **2d** 82%
R=CN **2e** 84%
R=Br **2f** 87%



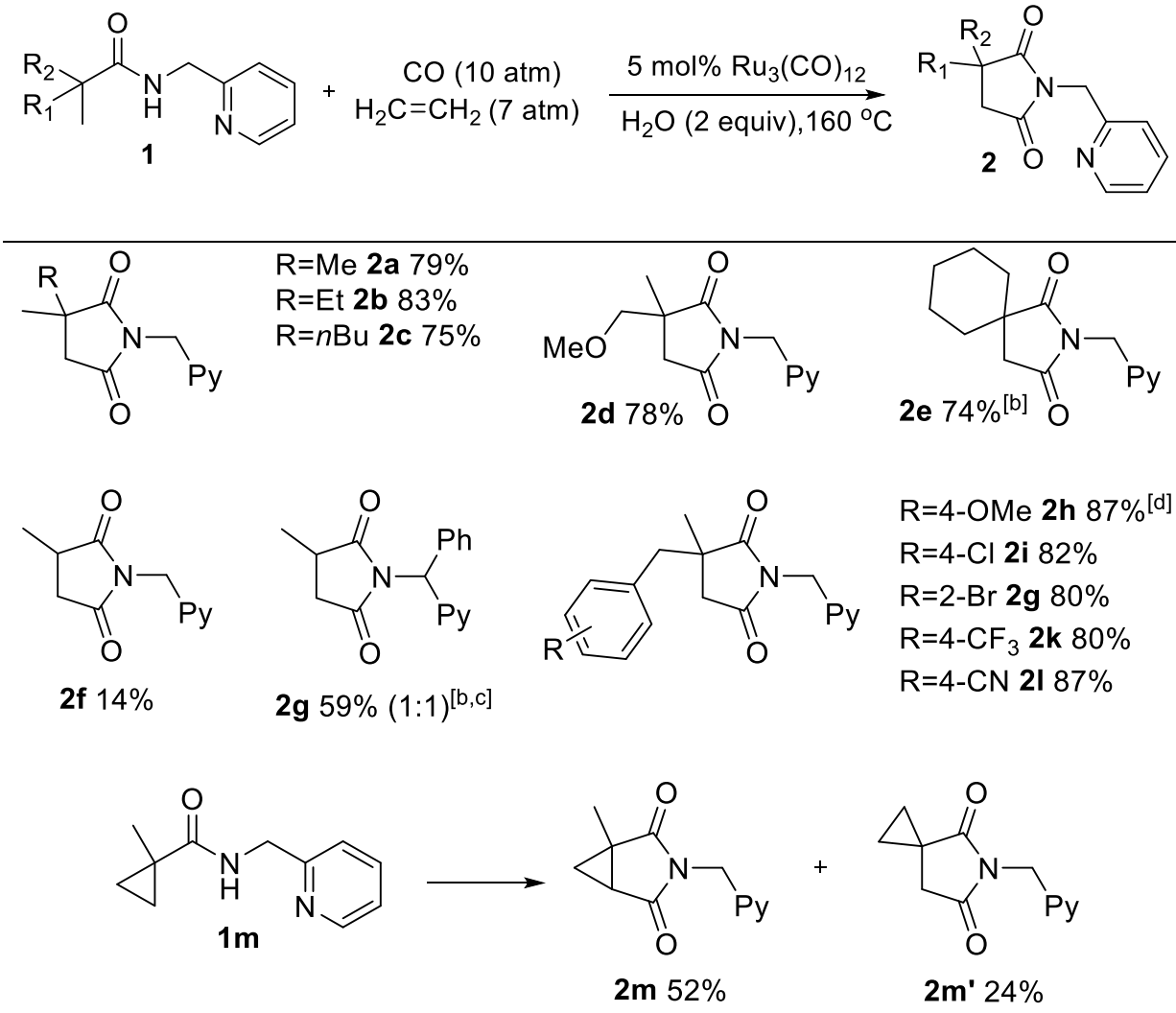
R=Me **2g** 68% (1:1)[b]
R=OCF_3 **2h** 80% (9:1)[b]
R=NMe_2 **2i** 86% (>20:1)[b]
R=C(O)Me **2j** 82% (20:1)[b]

Reaction conditions: [a] **1** amides (1 mmol), $Ru_3(CO)_{12}$ (5 mol%), H_2O (2,0 equiv), toluene (3,0 mL), CO (10 atm), ethylene (7 atm), 160 ^oC, 24h. [b] Major products were given.

In 2011, the group of Chatani extend the bidentate-chelation system to the inactivated C(sp^3)-H bonds in the presence of ruthenium carbonyl compounds leading to the corresponding imides (Table 8).[13] Reactions proceed under similar conditions[12] and show a preference for C-H bonds of methyl groups as opposed to methylene C-H bonds. A series of aliphatic amides can be transformed into the imides (**2a**-**g**). Compared to the ethyl, butyl, methoxylmethyl and cyclohexyl, the methyl group was selectively carbonylated to give the products in high yields (**2a**-**e**). The steric effective was a predominant factor as exemplified by **2f** and hydrolysis of the starting material **1f** is a contaminated result. To avoid hydrolysis, a more sterically bulky directing group **1g** was design. As expected, the CO was successfully

incorporated into imide **2g**. Interestingly, different kinds of benzyl group were still intact under this system (**2h**-**l**). The cyclopropyl show higher activity than the methyl group (**1m**). Stoichiometric reaction of an amide with $Ru_3(CO)_{12}$ genarated a dinuclear ruthenium complex which was confirmed by the X-ray crystallography. Inter-and intramolecular kinetic isotope effect (KIE) values suggest that the cleavage of C-H bond involve in the rate-determining step.

Table 8. Represent products for the C (sp^3)-H carbonylation.[a]



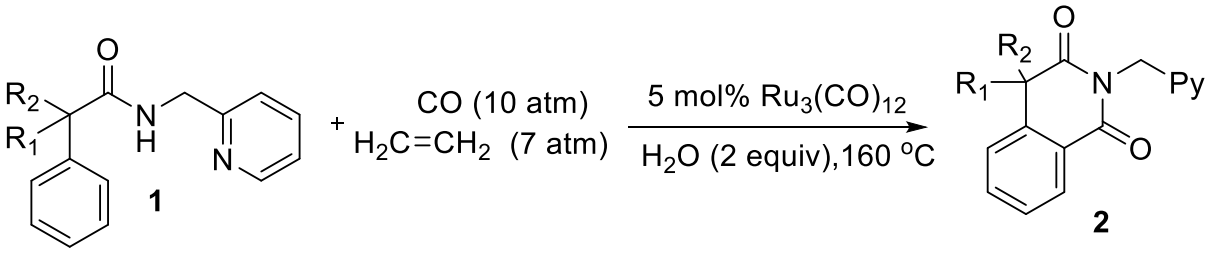
Reaction conditions: [a] **1** amides (1 mmol), $Ru_3(CO)_{12}$ (5 mol%), H_2O (2.0 equiv), toluene (3.0 mL), CO (10 atm), ethylene (7 atm), 160 °C, 5d. [b] $Ru_3(CO)_{12}$ (10 mol%) [c] Diastereomeric ratio [d] Toluene (4.0 mL).

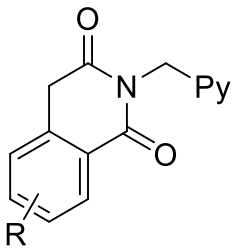
1.3.2 Six-membered ring synthesis

After gaining some acknowledge on the bidentate-chelating system, Chatani *et al* in 2012 simply change the starting material to the arylacetamides, as expected, the isoquinoline-1,3(2*H*,4*H*)-diones could be obtained in good yield (Table 9).[14] Compare to inactivated

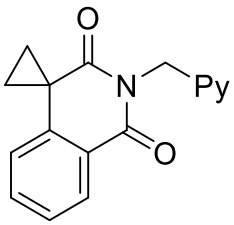
C(sp^3)-H, the C(sp^2)-H bonds of the aromatic ring is more easy to participate in this reaction which is understandable as the bond energy of C(sp^2)-H is far more low than the C(sp^3)-H one. In this context, except ethylene, the methyl acrylate can also serve as the hydrogen acceptor producing **2g** in 83% yield. Also stoichiometric reaction of an arylacetamide with $Ru_3(CO)_{12}$ gave one dinuclear ruthenium complex which was also confirmed by the X-ray crystallography. Instead of $Ru_3(CO)_{12}$, this dinuclear ruthenium complex could be used as the catalyst in presence of water as the additive.

Table 9. Selective examples for the carbonylative isoquinoline-1,3(2*H*,4*H*)-diones preparation.[a]

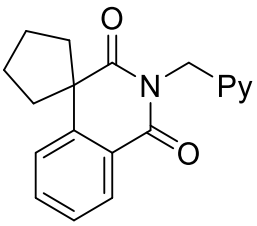




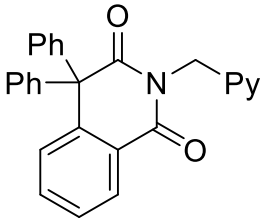
R=H **2a** 93%
R=4-OMe **2b** 83%
R=4-Br **2c** 72%[b] 12h
R=3-CF_3 **2d** 82%
R=2-F **2e** 81%



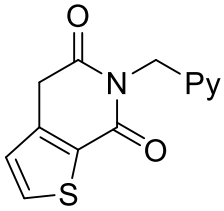
2f 84% 36h



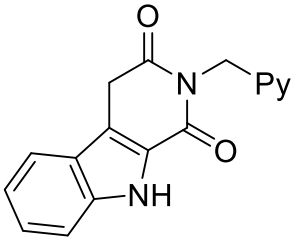
2g 83%



2h 89%



2i 41% 36h



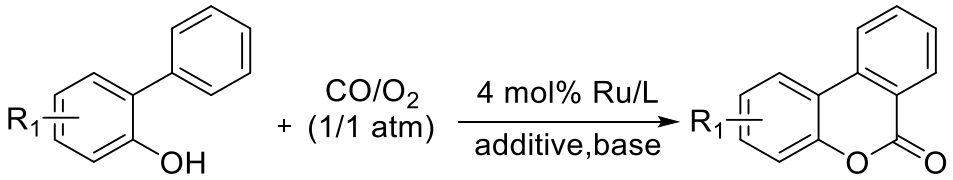
2g 69%[b]

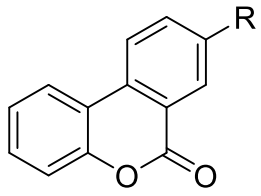
Reaction conditions: [a] **1** amides (1 mmol), $Ru_3(CO)_{12}$ (5 mol%), H_2O (2,0 equiv), toluene (3,0 mL), CO (10 atm), ethylene (7 atm), 160 °C, 1d. [b] Dioxane as solvent.

In 2013, Kondo and inamoto reported carbonylative C-H cyclization of 2-arylphenol with ruthenium complex as the catalyst and *N*-heterocyclic carbene (*NHC*) as the ligand.[15] This approach works under atmospheric pressure of CO with O_2 (balloon also) producing 6*H*-dibenzo[*b*,*d*]pyran-6-ones in acceptable to good yields (Table 10). The electron-donation or withdrawing substituents on the *ortho*-phenyl rings do not show explicit difference (**2a**-**h**). For

the phenol ring part, substituents on the *ortho* position impeded the reaction (**2i**) while the *meta* or *para* substituted analogues provided the product without any problem (**2j**, **2k**). An intermolecular competition experiment indicates that electro-rich materials show more reactivity and kinetic isotope effect (KIE) results exemplify the C-H metalation step is reversible.

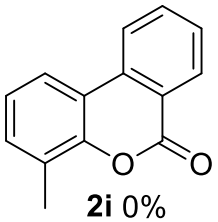
Table 10. Represent examples for carbonylation of *ortho*-phenyl phenol.[a]



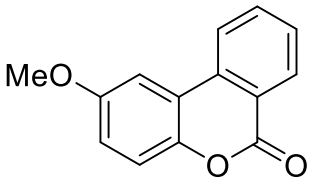


2a R=Me 94%
2b R=OMe 89%
2c R=F 56%[b]
2d R=Br 77%

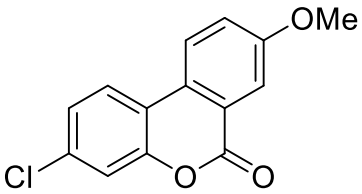
2e R=Ac 81%
2f R=CF_3 83%
2g R=CO_2Me 79%[b]
2h R=CN 28%[b]



2i 0%



2j 65%



2k 55%

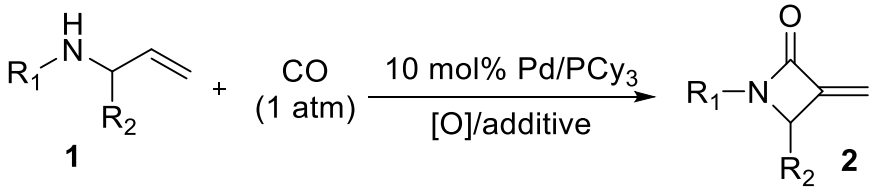
Reaction conditions: [a] *ortho*-aryl phenol, $[RuCl_2(p\text{-cymene})]_2$ (4 mol%), IPr-HCl (12 mol%), PivOH (10 mol%), Cs_2CO_3 (3,0 equiv), mesitylene, CO (1 atm, balloon), O_2 (1 atm, balloon), 100 ^oC, 24h. [b] $[RuCl_2(p\text{-cymene})]_2$ (8 mol%), IPr-HCl (24 mol%).

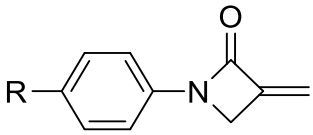
1.4 Palladium-Catalyzed Heterocycles Synthesis via Carbonylative C-H Activation

1.4.1 Four-membered ring synthesis

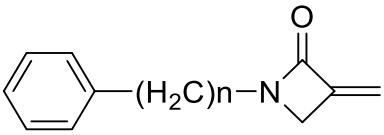
In 2014, Lei and You demonstrated the β-lactam scaffold synthesis though oxidative carbonylation of *N*-allylamines in the presence of palladium catalyst, thus a series of (19 examples) α-methylene-β-lactams was produced smoothly (Table 11)[16]. DFT calculations indicated that a four-membered-ring transition state is favorable. As we can see, *N*-allylanilines bearing electron-withdrawal or -donating groups on the aniline rings process well under this condition provides the lactam in acceptable to good yield (**2a**-**i**). Remarkably, the *N*-alkyl substituted allylic amines also can be applied to this carbonylation process (**2g** - **j**). Notably, no loss of enantioselectivity was observed when enantioenriched *N*-allylamine was used as the starting material (**2l**). This approach presence of remarkable progress for the carbonylation and has the potential to be used in organic and medicinal chemistry.

Table 11. Selective products of α-methylene-β-lactams formation though carbonylation of *N*-allylamines.[a]

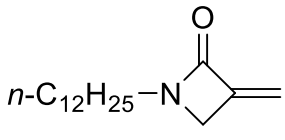




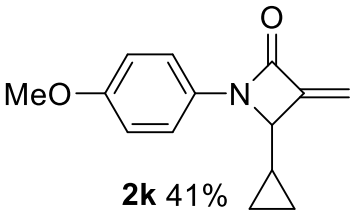
2a R=H 64%
2b R=Me 74%
2c R=OMe 82%
2d R=F 53%
2e R=Br 51%
2f R=CF_3 27%



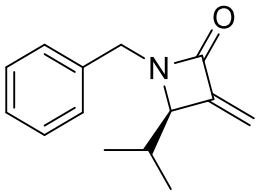
2g n=1 98%
2h n=2 53%
2i n=3 77%



2j 62%



2k 41%



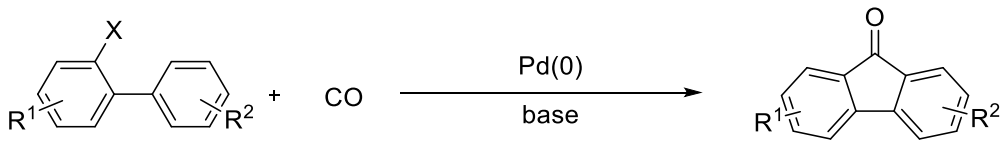
2l 60%, 98%ee

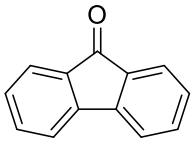
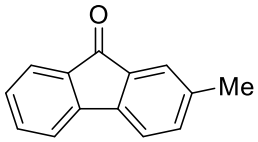
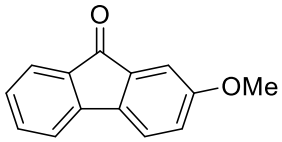
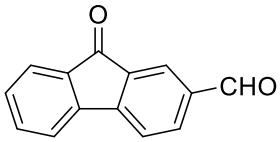
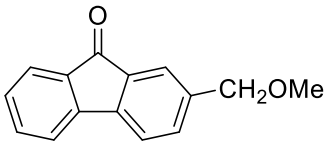
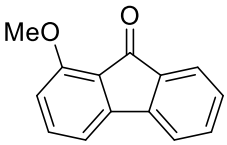
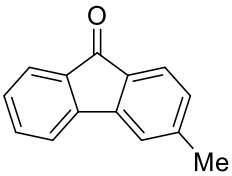
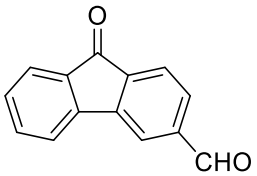
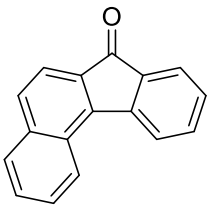
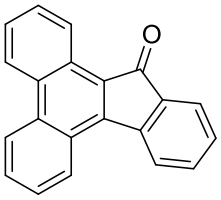
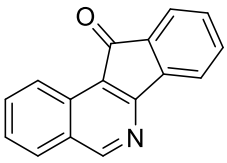
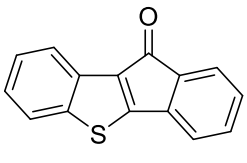
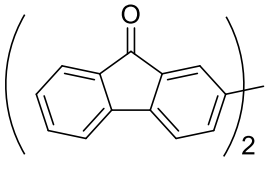
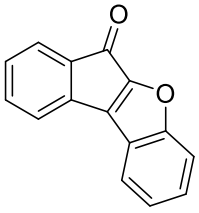
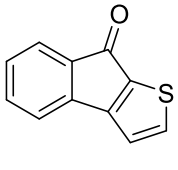
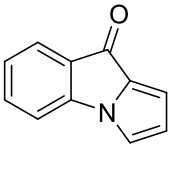
Reaction conditions: [a] *N*-allyl amines (0,2 mmol), $PdCl_2$ (10 mol%), PCy_3 (20 mol%), $Cu(OPiv)_2$ (2,0 equiv), PivOH (2,0 equiv), DMF (2,0 mL), CO (1 atm), 100 ^oC, 1-24h.

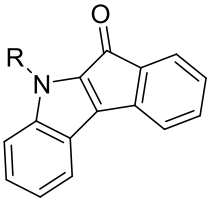
1.4.2 Five-membered ring synthesis

Larock *et al* in 2000 developed the fluoren-9-ones synthesis by the cyclocarbonylation of *ortho*-halobiarys with a commercially available $Pd(PCy_3)$ catalyst[17] This procedure was initiated by the palladium (0) and could be utilized to the synthesis of polycyclic and heterocyclic fluorenones containing the fused isoquinoline, indole, pyrrole, thiophene, benzothiophene, and benzofuran rings (Table 12).

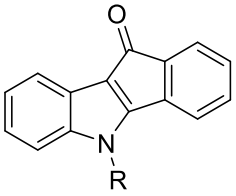
Table 12. Scope for the fluoren-9-ones synthesis via carbonylation of *ortho*-halobiarys.[a]



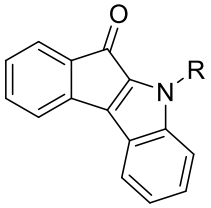
			
X=Br 100% X=I 100%	X=I 97%	X=I 100%	X=I 100%
			
X=I 100%	X=I 100%	X=I 90%[b]	X=I 94%, (9:1)[c]
			
X=Br 96%	X=I 98%	X=I 95%	X=I 67%
			
X=Br 87%[d]	X=I 81%	X=Br 86%[e]	X=I 96%



X=I R=H 0%
R=Me 49%



X=I R=H 0%
R=H 45%[f]
R=Me 21%

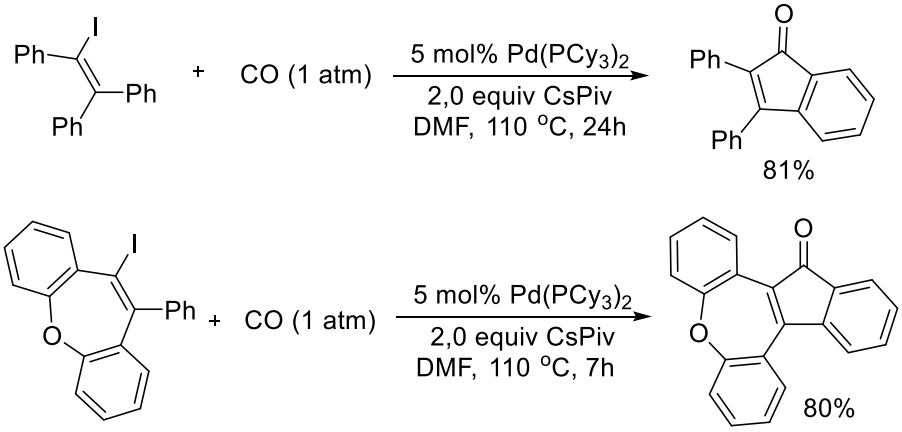


X=Br R=H 55%[g]

Reaction conditions: [a] ArX (0,25 mmol), $Pd(PCy_3)_2$ (5 mol%), CsPiv (2,0 equiv), CO (1 atm), DMF (6 mL), 110 ^oC, 7h. [b] With 10% isomer formed. [c] Main products, the ratio was determined by ^1H NMR spectroscopic analysis. [d] 0,125 mmol, 14h. [e] 14h. [f] For the starting material R=Ts. [g] For the starting material R=Ts. and 42% of starting material was recovered.

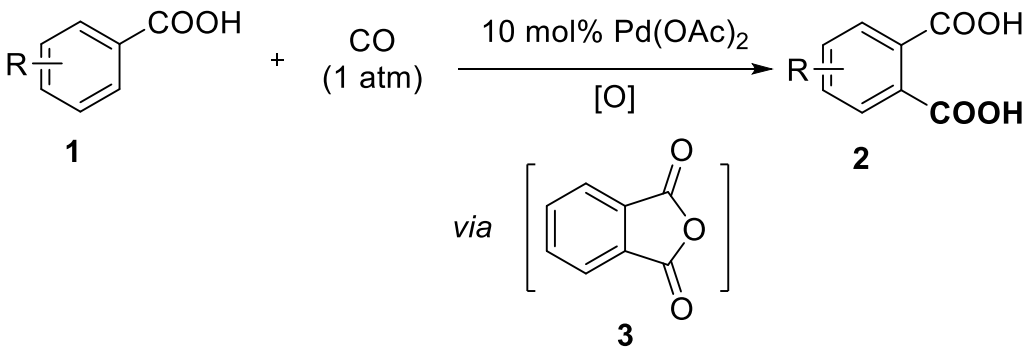
It should be noted that this protocol could be applied to the vinylic halides and the corresponding products were isolated in high yields (Scheme 3). The author proposed an Pd(0)/Pd(II) catalytic cycle.

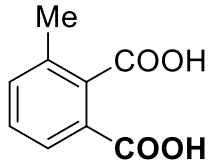
Scheme 3. Carbonylation of vinylic halides.



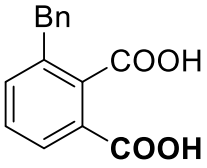
Yu *et al* in 2008 pioneered the palladium(II)-catalyzed carbonylation of aromatic or vinyl acid for the preparation of 1,2- and 1,3-dicarboxylic acid under 1 atm of CO (Table 13).[18] Treatment of sodium carboxylate with $Pd(OAc)_2$ in CH_2Cl_2 or dioxane at 100 ^oC formed an C-H insertion intermediate complex. A suspension of this palladacycle in solvent could react stoichiometrically with CO under room temperature producing the anhydride acid quantitatively which was finally hydrolyzed to dicarboxylic acid *in situ* under the base and trace amount of water. 24 examples were isolated through this protocol.

Table 13. Selected examples of carbonylation of aromatic acid.[a]

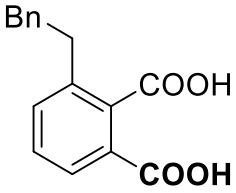




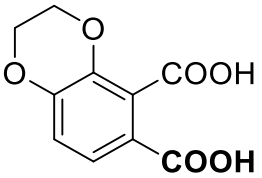
2a 80%



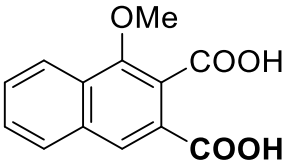
2b 91%



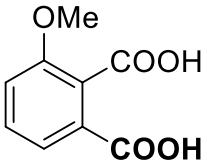
2c 93%



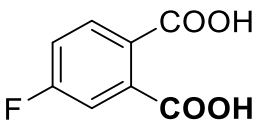
2d 45%[b] 30h



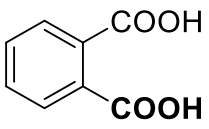
2e 90% 30h



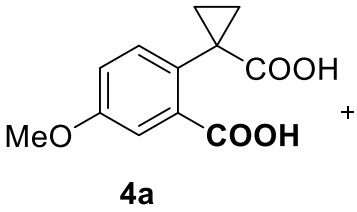
2f 45%,150 °C, 30h



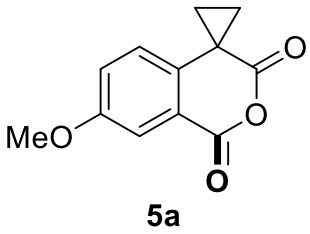
2g 40%, 150 °C, 48h



2h 41%, 150 °C, 48h

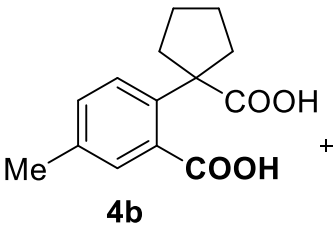


4a

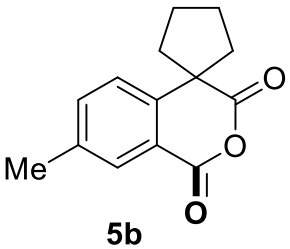


5a

88%, **4a:5a**=5:2

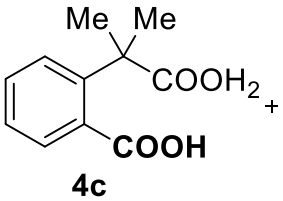


4b

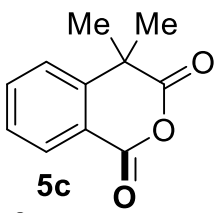


5b

81%, **4b:5b**=2:1

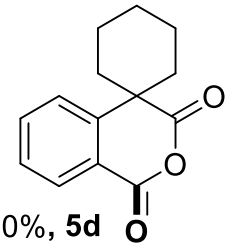


4c

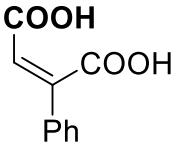


5c

75%, **4c:5c**=3:2



50%, **5d**

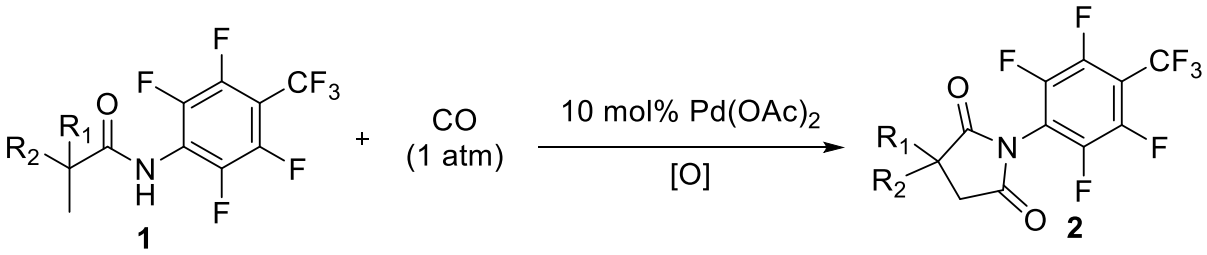


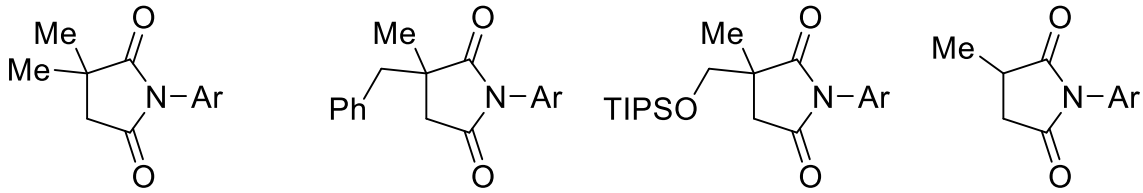
68%, **6a**

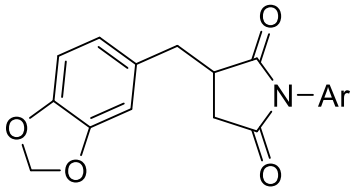
Reaction conditions: [a] Using $Pd(OAc)_2$ (10 mol%), Ag_2CO_3 (2,0 equiv), NaOAc (2,0 equiv), CO (1 atm), dioxane (2 mL), 130 °C, 18h. [b] K_2HPO_4 in place of NaOAc.

Later the same group extend this methodology to the inactivated C(sp^3)-H bonds leading to the corresponding succinimides.[19] The major obstacles for this transformation is that the excess CO inhibits the activation of the inert C(sp^3)-H by competitively occupying coordination sites on palladium(II) center, thereby preventing the requisite C-H agnostic interaction. Compared to the *N*-toluene-sulfonyl amide, the analogous acidic amides which used as the directing group gave the corresponding succinimides in better yields. Interestingly, screening the additive reveals that a TEMPO serve as the co-oxidant with AgOAc gave the full conversion. Even the precise role of TEMPO remains to be elucidated, one plausible explanation is that oxoammnium salts (the oxidize from TEMPO) reoxidized Pd(0) to Pd(II) more efficiently than solely AgOAc. Starting material (Table 14) bearing quaternary α-atom provides the desired products in good to excellent yields (**2a-c**, **2f**, **2h**). Reactions took place favorably at the methyl C (sp^3)-H bonds instead of the benzylic C (sp^3)-H bond (**2b**, **2e**). The benzyl motif proved to be a better protecting group for the β-hydroxy substrates (**2b** *vs* **2c**) while TBS protected substrates failed under this condition. Notably, this protocol was effective for the methylene C (sp^3)-H bonds of cyclopropyl substrates (**2f-h**). Intriguingly, cyclopropyl C(sp^3)-H bonds could be selectively carbonylated over a methyl C(sp^3)-H bond (in **2f**) and an *ortho*-aryl C(sp^2)-H bond (in **2h**). 16 examples have been prepared with this methodology.

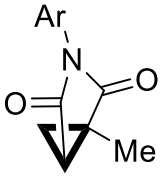
Table 14. Represent substrates for the carbonylation of C (sp^3)-H bonds.[a]



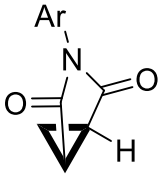




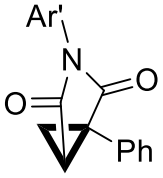
2e 52%



2f 86%



2g 65%

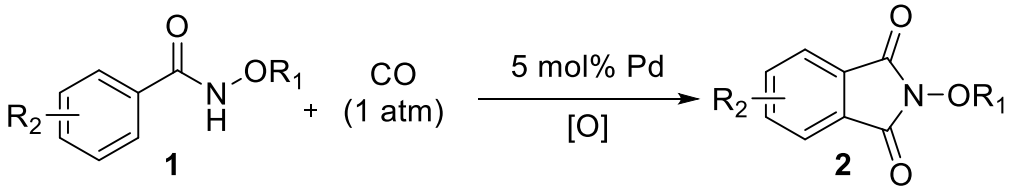


2h 65%

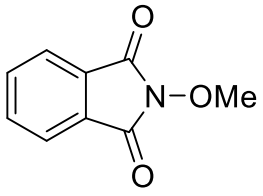
Reaction conditions: [a] Amides substrate (0,1 mmol), $Pd(OAc)_2$ (10 mol%), AgOAc (2,0 equiv), TEMPO (2,0 equiv), K_2HPO_4 (2,0 equiv), CO (1 atm), *n*-hexane (1 mL), 130 ^oC, 18h. [b] K_2HPO_4 in place of NaOAc.

Booker-Milburn and Lloyd-Jones in 2011 developed a procedure for the substituted phthalimides synthesis via Pd(II)-catalyzed carbonylative C-H functionalization of *N*-alkoxybenzamides under 1 atm of CO.[20] A series of *N*-alkylphthalimides (10 examples) were achieved in moderate to excellent yield (Table 15). Notably, the nitro group was still intact albeit with low yield (**2b**, 30% yield). *Ortho*-substituted substrates underwent favorably the less steric site giving the corresponding products with high selectivity (**2e**, **2f**).

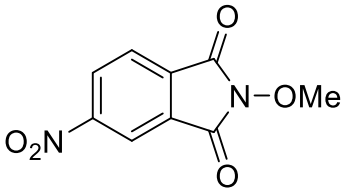
Table 15. Phthalimides synthesis via Pd(II)-catalyzed carbonylative C-H functionalization of *N*-alkoxybenzamides.[a]



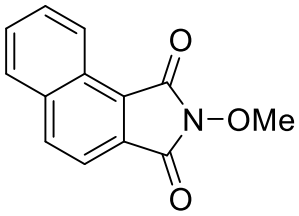
1 **2**



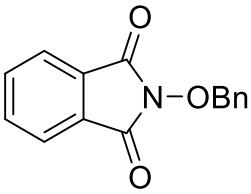
2a 76%



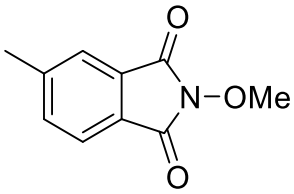
2b 30%



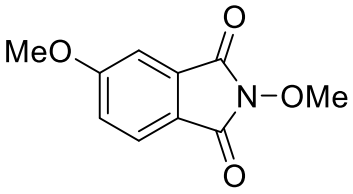
2c 53%



2d 42%



2e 95%, (11:1)

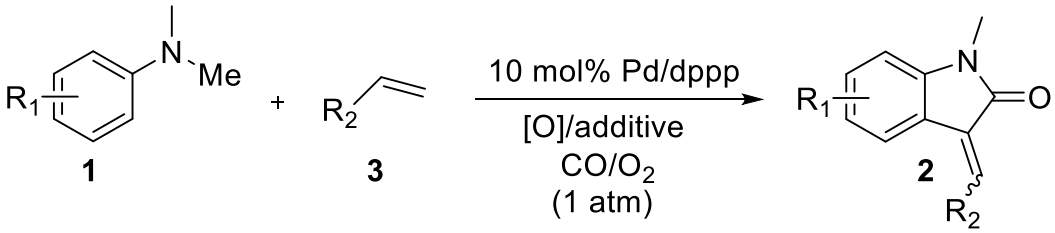


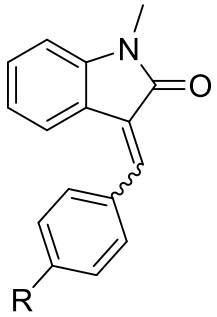
2f 90%, (13:2)

Reaction conditons: [a] *N*-methoxybenzamides (0,5 mmol), $Pd(OAc)_2$ (5 mol%), BQ (2,0 equiv), HOAc (4,0 mL), CO (1 atm), 110 ^oC, 5-18h.

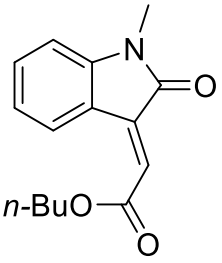
Lei *et al* in 2013 developed the palladium/copper-catalyzed oxidative C-H alkenylation/*N*-dealkylative carbonylation of tertiary anilines towards the synthesis of 3-methyleneindolin-2-ones derivatives (Table 16).[21] For the olefins partner, electron-rich and electron-poor substrates worked well under this condition (**2a**-**g**) giving the products in moderate to good yields. Anilines with electron-withdraw or donating substituents also run smoothly providing the desired products in good yield without any problem (**2h**-**n**). Notably, the bromo group was still (**2f**, **2k**) untouched under this system, thus providing the reaction site for further manipulations. Interestingly, *N*-ethyl-*N*-methyl aniline generates two types of products **2n** and **2n'** in 13% and 48% yields respectively, suggesting that the C-N bond cleavage favored the less sterically hindered alkyl group (Scheme 4). Control experiments show that the dealkylation step took place through copper/oxygen-mediated C-N bond cleavage of tertiary amines. Intermolecular or intramolecular KIE experiments and *in situ* IR spectroscopy reaction rates of *N, N*-dimethylaniline with $[D]_5$-*N,N*-dimethylaniline indicated that the C-H cleavage might be involved in the rate-determining step.

Table 16. The palladium/copper-catalyzed oxidative C-H alkenylation/*N*-dealkylative carbonylation of tertiary anilines.[a]

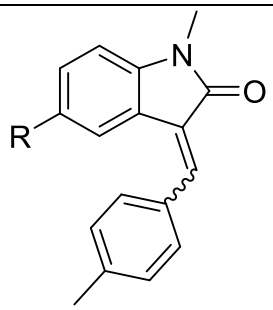




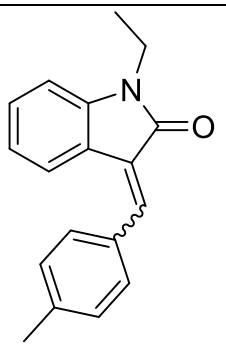
2a R=H 67% (3,3:1)
2b R=Me 66% (4,1:1)
2c R=OMe 58% (4,1:1)
2d R=F 64% (3,3:1)
2e R=Cl 66% (4,9:1)
2f R=Br 61% (5,8:1)



2g 35% (E only)



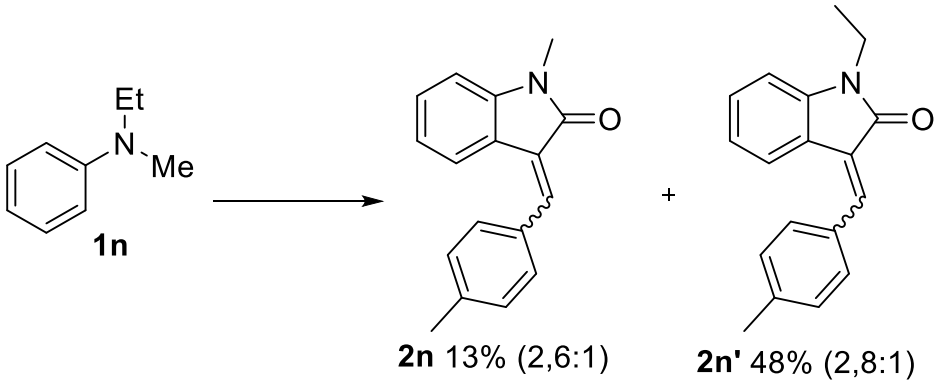
2h R=Me 75% (3,5:1)
2i R=F 73% (3,4:1)
2j R=Cl 65% (2,8:1)
2k R=Br 45% (3,4:1)
2l R=CF_3 54% (2,8:1)



2m 63%[b] (2,7:1)

Reaction conditions: [a] *N,N*-dialkyl anilines (2,0 equiv), olefins (0,2 mmol), $Pd(PPh_3)_2Cl_2$ (10 mol%), dppp (10 mol%), $Cu(OAc)_2{\cdot}H_2O$ (30 mol%), HOAc (50 mol%), Toluene:DMF (3,0:0,3 mL), CO/O_2 (1 atm, 7:1), 100 ^oC, 24h. The ratio of E/Z was determined by ^1H NMR spectroscopy. [b] Using *N*,*N*-diethylaniline **1m** as starting material.

Scheme 4. *N*-ethyl-*N*-methyl aniline for the C-N cleavage.



1n

2n 13% (2,6:1)

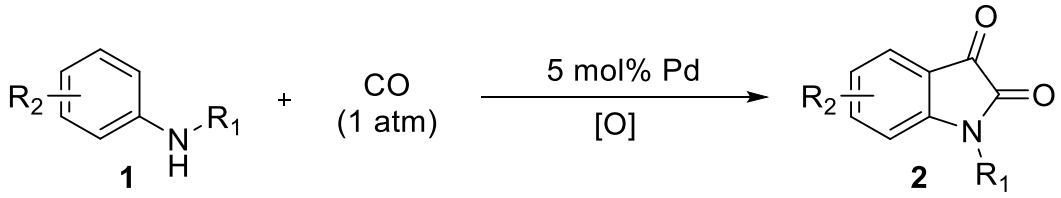
2n' 48% (2,8:1)

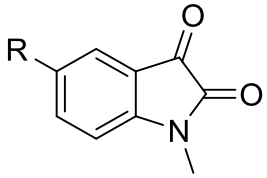
Xu *et al* in 2013 exploited the synthesis of tetrasubstituted furan carboxylates using a tandem cycloisomerization/carbonylation sequence of cyclopropenes.[22] In the presence of palladium and copper, this tandem metal relay catalysis (TMRC) pathway accounted for the high efficiency of this transformation. The key step is the ring-opening reaction of the cyclopropene in the presence of copper catalyst and subsequent transmetalation to palladium generating the key C-Pd bonds, which underwent the carbonylative steps providing the desired products.

Lei *et al* in 2014 pioneered the isatin synthesis from readily available anilines *via* a palladium-catalyzed double carbonylation of C-H bonds.[23] Here, reactions proceed under atmospheric pressure of CO without any additives and 24 examples have been shown (Table 17). Interestingly, number of *N*-methyl anilines proceed smoothly under this oxidative condition affording the respective isatins in moderate to good yields (**2a**-**d**). Also *N*-substituted allyl and cyclic tetrahydroquinoline gave the corresponding isatins products in 56% and 38% respectively. Intriguingly, no benzolactam[24] (in sharp contrast to Orito's work) was detected under this system for the *N*-benzyl anilines and selectively underwent the double

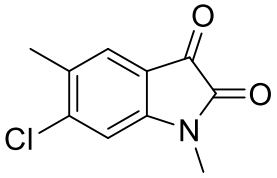
carbonylation reactions affording the corresponding isatin products in moderate yields (**2g**-**k**). This is the first examples to exploit the C-H oxidative double carbonylation for the various heterocyclic compound synthesis.

Table 17. The palladium-catalyzed double carbonylation of aniline C-H bonds to prepare isatin.[a]

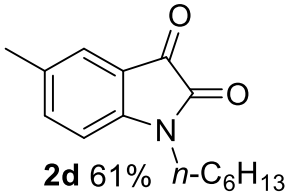




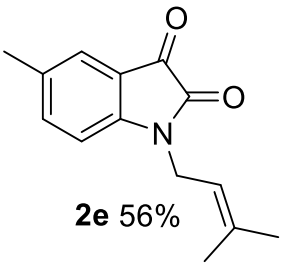
2a R=*t*Bu 82%
2b R=Ph 60%



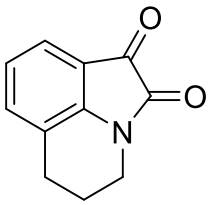
2c 43%



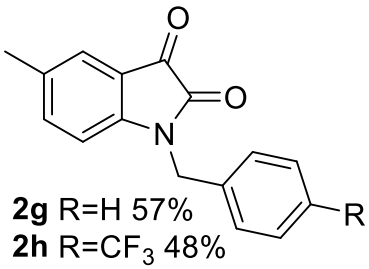
2d 61% *n*-C_6H_{13}



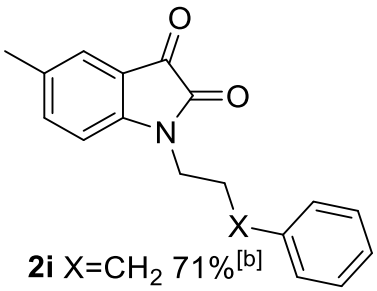
2e 56%



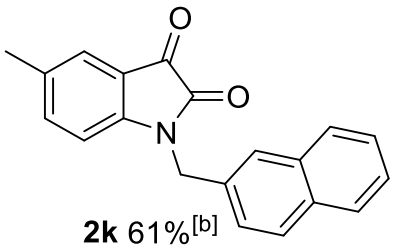
2f 38%



2g R=H 57%
2h R=CF_3 48%



2i X=CH_2 71%[b]
2j X=O 55%[b]



2k 61%[b]

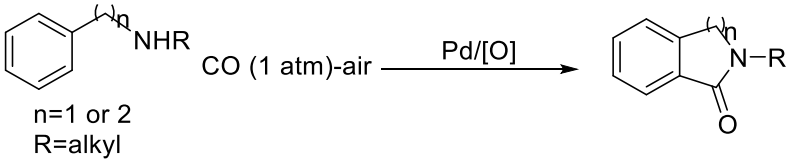
Reaction conditons: [a] *N*-alkyl anilines (0,2 mmol), $Pd(PPh_3)_2Cl_2$ (5 mol%), $Cu(OPiv)_2$ (2,0 equiv), Toluene:DMSO (0,5:0,5 mL), CO (1 atm), 100 ^oC, 24h. [b] With pivalic acid (2.0 equiv).

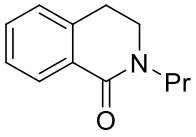
1.4.3 Six-membered ring synthesis

Orito *et al* in 2004 pioneered the carbonylation of secondary amines leading to benzolactams in the presence of $Pd(OAc)_2$ and $Cu(OAc)_2$ under 1 atm of CO containing

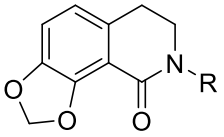
air.[24-25] 30 examples have been tested giving moderate to good yield with good functional tolerance (Table 18). Generally speaking, the benzylic amines underwent carbonylation at a rate much faster than that of corresponding phenethylamines. Rate of the five-membered ring formation was 11 times greater than that of six-membered ring formation (**2j**).

Table 18. Selective benzolactams synthesis from carbonylation of secondary amines.[a]

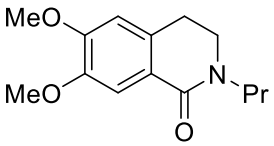




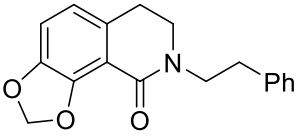
2a 64%, 24h



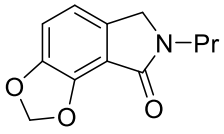
R=Me **2b** 42%, 2h
R=Pr **2c** 86%, 2h
R=nonyl **2d** 63%, 2h



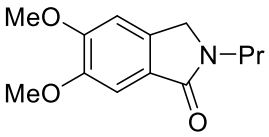
2e 24%, 24h



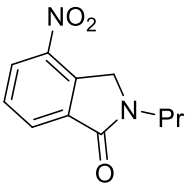
2f 86% (10:1), 24h[b]



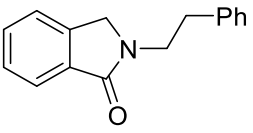
2g 86% (4:1), 2h[b]



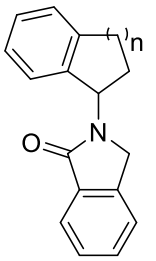
2h 88% (3:1), 2h[b]



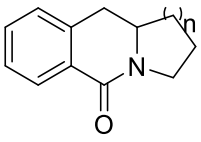
2i 69%, 2h



2j 84% (11:1), 24h[b]



n=1, **2k** 87%
n=2, **2l** 66%
n=1, **2m** 74%, 24h



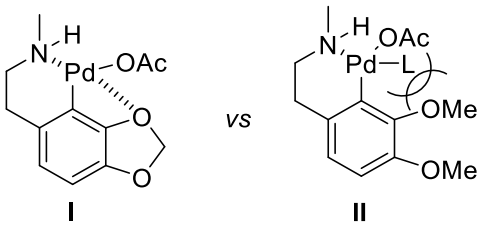
n=1, **2n** 83%
n=2, **2o** 17%
n=1, **2p** 7%, 24h

Reaction conditions: [a] *N*-alkyl-ω-arylalkylamines (0,25 mmol), $Pd(OAc)_2$ (5 mol%), $Cu(OAc)_2$ (0,5 equiv), CO (1 atm) containing air (0,5 molar equiv of O_2), Toluene (0,1 M), 120 ^oC, 2 or 24h. [b] Main products, the ratio were determined by ^1H NMR spectroscopic analysis.

The huge difference between **2c** and **2e** could be explained by the Scheme 5, in which the intermediate **II** is more steric hindrance. Control experiments suggested that $Cu(OAc)_2$ served as not only an oxidant but also as ligand. Only *N,N'*-dialkylureas were generated when the primary amine was applied as the starting material. In 2007 and 2009, Orito applied this methodology to the preparation of *N*-protected staurosporinones or benzolactams such

as phenanthro[9,10-*b*]indolizidin-9-ones and phenanthro[9,10-*b*]quinolizidin-9-ons, respectively.[26]

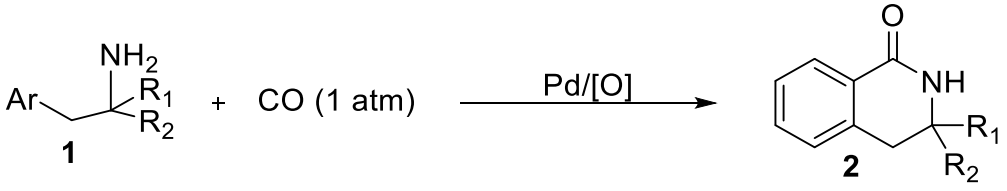
Scheme 5. Explanation of intermediates.



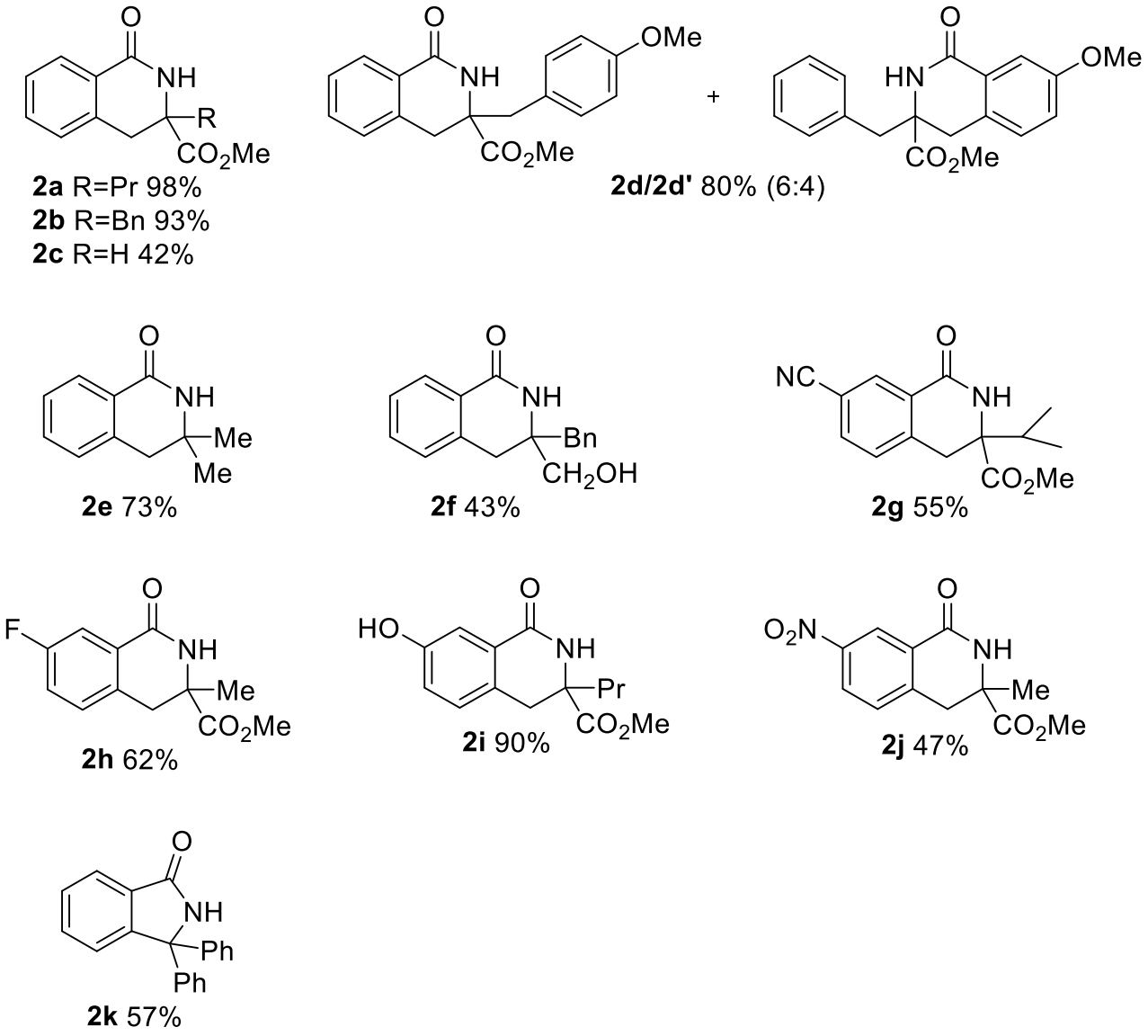
I **II**

Vicente and Saura-Llamas *et al* in 2007 reported the *ortho*-palladation of L-phenylalanine methyl ester and then carbonylation of this cyclopalladated complex under 1 atm of CO delivering the corresponding lactams.[27] It should be keep in mind that it's a stoichiometric amount of palladium has been used for the carbonylation of phenylalanine methyl ester. So Granell and Garcia *et al* in 2011 developed a catalytic process for the same substrates, *N*-unprotected arylethylamines, with $Pd(OAc)_2$ as the catalyst and benzoquinone (BQ) as the oxidant under 1 atm of CO in refluxing HOAc (Table 19).[28] Thus a series of quaternary α-amino acid esters could be transformed into the corresponding benzolactams and about 16 products have been isolated in moderate to good yields. Interestingly, secondary amine also be used as the substrate (**2c**) and dimethylphenethylamine produced lactam in 73% yields (**2e**). The hydroxymethyl still be intact under this oxidative condition (**2f**). The substituted group on the aromatic ring such as hydroxyl and nitro group could be tolerant in moderate to excellent yield (**2i**, **2j**). Unfortunately, only one example for the five-membered benzolactam was achieved with triphenylamine as the starting material (**2k**). Compared to Orito's procedure[24], with $Cu(OAc)_2$ as the co-oxidant, in which the five-membered ring analogues were clearly favored for the carbonylation of secondary amines, this protocol with BQ as the oxidant more favor the six-membered benzolactam.

Table 19. Carbonylation of quaternary α-amino acid esters toward benzolactam synthesis.[a]



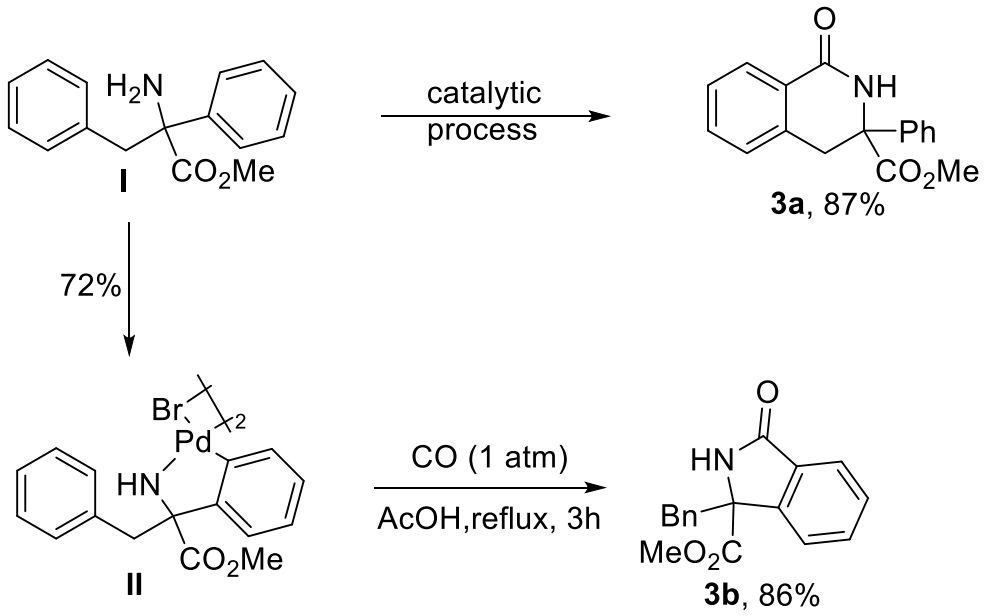
1 **2**



Reaction conditions: [a] Arylethylamines, $Pd(OAc)_2$ (5 mol%), BQ (2,0 equiv), CO (1 atm), HOAc as solvent, reflux, 6h.

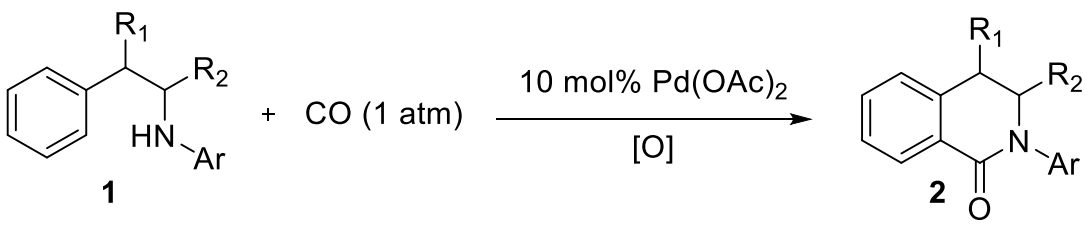
A further experiment was especially significant (Scheme 6). Treatment of **I** with the standard conditions gave only six-membered ring lactam **3a**. In contrast, first cyclometallation of **I** gave the favored five-membered palladacycle **II** which was applied to the carbonylation with CO in the absence of benzoquinone (BQ) affording the five-member lactam **3b** in 86% yield as well as a minor amount (6%) of the isomer. The steric hindrance around the amino group is pivotal for the success of this transformation because the full substitution of the carbon in α position of the amino esters play an important role in their cyclopalladation step.

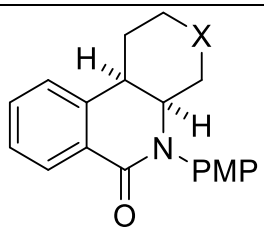
Scheme 6. Catalytic process *vs* stepwise pathway.



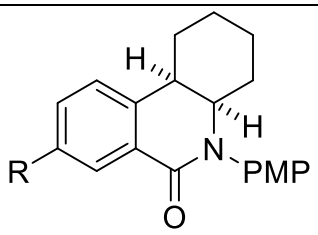
Gaunt *et al* in 2011 demonstrated the carbonylation of secondary amine with *N*-bearing aryl group in the presence of $Pd(OAc)_2$ under 1 atm of CO and O_2 *at room temperature* providing the corresponding lactams (Table 20).[28a] Reactions are tolerant of delicate stereogenic centers (**2a-f**) and functionality. The aryl group on the nitrogen atom as the protecting group is necessary and 15 examples have been prepared in moderate to good yields. Tetrahydropyrane (**2b**) and piperidine (**2c**) ring system run smoothly, and piperidine **2c** in particular represent an attractive scaffold for the medicine chemistry purpose. The nature of arene could be varied with naphthalene, pyrrole (**2h**) and indole (**2i**) derived heteroarenes. The tryptophan derived **2i** could be obtained without erosion of enantiomeric purity highlighting its potential in complex molecular architectures application. More steric bulk *N*-aryl substituent was required when the chain amines were used as the substrates (**2g, j**) to suppress the addition of amine to benzoquinone. It should be noted that carbopalladation proceed at room temperature generating a dimeric complex 1a·Pd and O_2, BQ and *t*-BuO_2Ac in all playing the role of oxidant. The solvent HOAc appears could be to suppress the CO mediated reduction of the Pd(II) to palladium black.

Table 20. Selected examples for the carbonylation of secondary amine.[a]

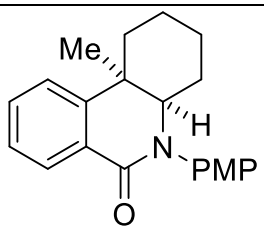




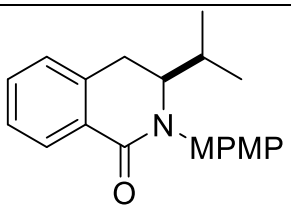
X=CH_2 **2a** 85%
X=O **2b** 55%
X=N-Ts **2c** 54%



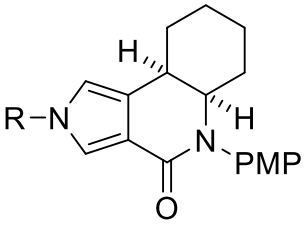
R=OMe **2d** 87%
R=Br **2e** 52%



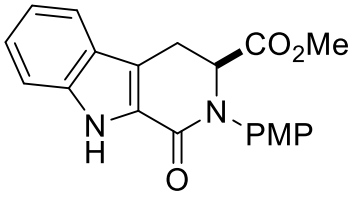
2f 50%



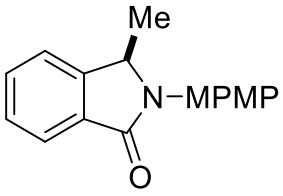
2g 65%



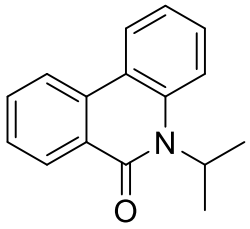
R=TIPS, **2h** 75%



2i 90%, 97% ee



2j 83%

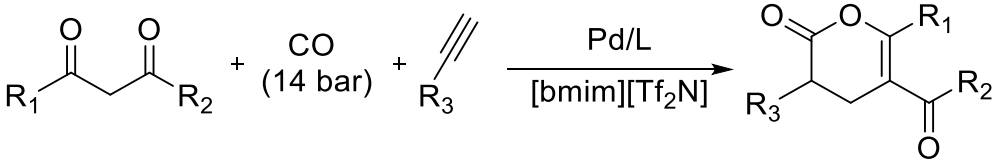


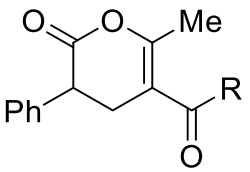
2k 61%

Reaction conditions: [a] *N*-arylethylamines (0,2 mmol), $Pd(OAc)_2$ (10 mol%), BQ (2,0 equiv), t-BuO_2Ac (2,0 equiv), NaOAc (6,0 equiv), CO (1 atm) containing O_2, HOAc (2 mL) as solvent, room temperature. PMP = *para*-methoxyphenyl; MPMP = 4-methoxy-2-methylphenyl.

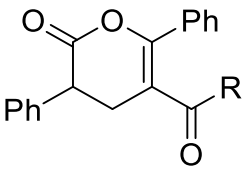
Alper and Yu in 2007 developed the palladium-catalyzed highly substituted endocyclic enol lactones synthesis via the carbonylation of terminal alkyne and 1,3-diketones in an ionic liquid system (Table 21).[29] 13 examples have been isolated under this process. It should be noted that this catalyst system can be recycled five times with only modest loss of its catalytic activity.

Table 21. Carbonylation for the highly substituted endocyclic enol lactones synthesis.[a]

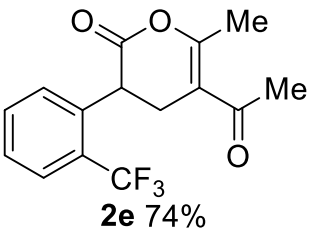




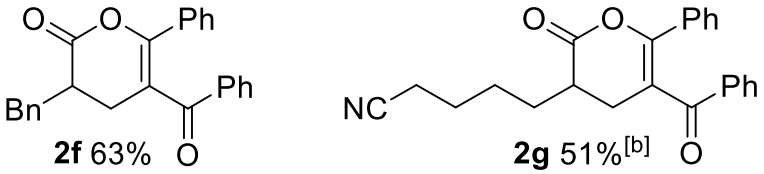
R=Me **2a** 63%
R=Ph **2b** 60%[b]



R=Ph **2c** 61%
R=OEt **2d** 50%



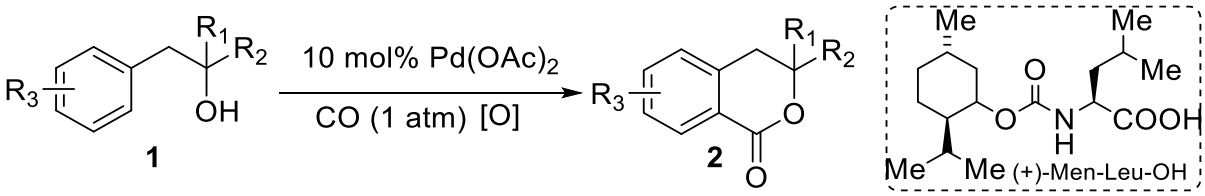
2e 74%

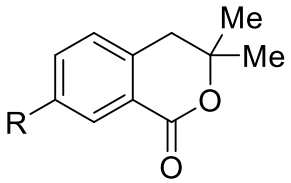


Reaction conditions: [a] Alkyne (2 equiv), 1,3-dicarbony compound (1 mmol), $Pd(PPh)_3Cl_2$ (3 mol%), dppp (6 mol%), CO (14 bar), [bmim][Tf_2N]HOAc (2 g) as solvent, 110 ^oC, 24h. [b] (±)-BINAP instead of dppp.

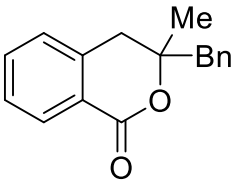
Yu *et al* in 2011 revealed an approach to 1-isochromanones via hydroxyl-directed carbonylative C-H bond of tertiary alcohol enabled by mono-*N*-protected amino acid ligand.[30] The author tested several *N*-Boc-protected amino acid as the ligand, among them Boc-Leu-OH·H_2O increased the yield to 66% and (+)-menthyl(O_2C)-Leu-OH also gave the similar efficacy. Perhaps this kind of amino acid ligands can reduce the reduction rate of Pd(II) to palladium black under CO atmosphere. About 20 examples have been synthesized use this method (Table 22). In general, substrates bearing electron-rich aryl group performed better than the analogous with electron-poor aryl group. It should be noted that this approach can tolerance the halide groups such as the Br (**2d**). The substituent effects on the alkyl chain adjacent to the hydroxyl group were also tested by the author. Different level of steric bulk did not show detriment to the system (**2e-h**). Most importantly, this protocol potential application was highlight by the synthesis of a biologically active molecule histamine release inhibitor **2i**.

Table 22. Carbonylation of tertiary alcohol.[a]

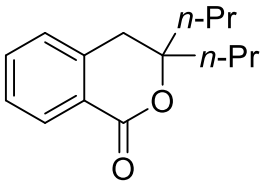




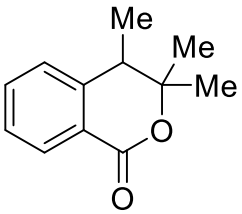
2a R=Me, 94%
2b R=OMe 82%, 80^oC
2c R=F, 74%
2d R=Br, 60%



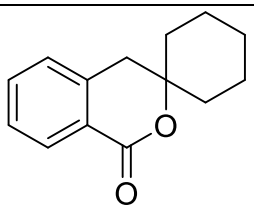
2e 61%, 80^oC



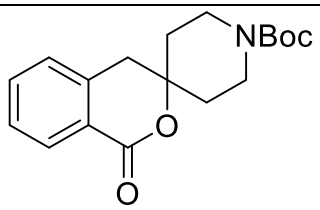
2f 86%, 80^oC



2g 89%



2h 88%

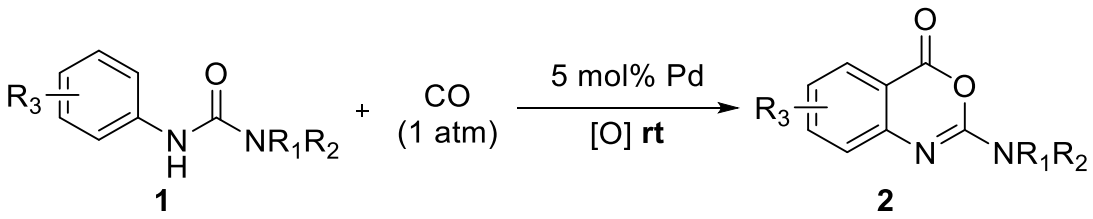


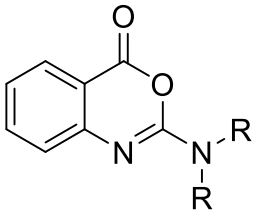
2i 62%

Reaction conditions: [a] Phenethyl alcohol (1,0 equiv), $Pd(OAc)_2$ (10 mol%), (+)-menthyl(O_2C)-Leu-OH (20 mol%), AgOAc (3,0 equiv), Li_2CO_3 (1,0 equiv), CO (1 atm), DCM, 110 ^oC, 48h.

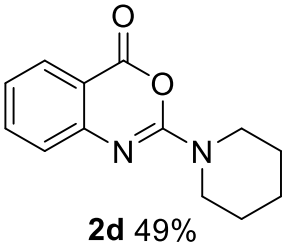
Booker-Milburn and Lloyd-Jones in 2009 discovered that cationic palladium-catalyzed carbonylation of aryl urea derivatives *at room temperature* under 1 atm of CO forming the cyclic imidates.[31] Key features of this procedure is the utilize of the $Pd(OTs)_2(MeCN)_2$ as the catalyst precursor and the powerful activating effect of the aniline-urea moiety in contrast with acetanilide (0% yield). For the *N*,*N*-disubstituted substrates (Table 23) the yields was dropping with the steric bulk increasing (**2a-c**) whereas for the *N*-mono substituted analogues trend was opposite (**2e-h**). Prolonged reaction time resulted in low yields which can be rationalized by the reflection that the imidate products were sensitive to the added acid.

Table 23. Represented products for the carbonylation of aryl urea derivatives.[a]

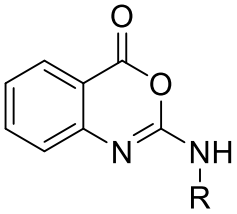




2a R=Me, 67%
2b R=Et, 50%
2c R=*i*Pr, 40%



2d 49%



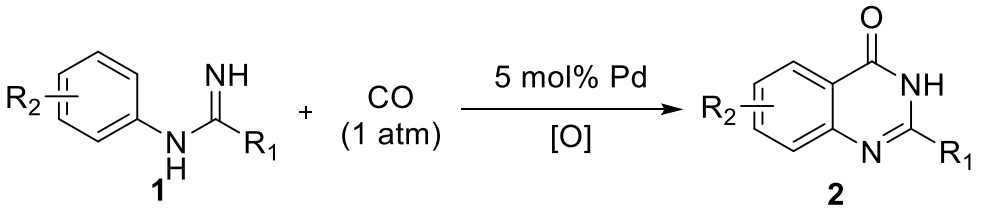
2e R=Me, 34%
2f R=Et, 40%
2g R=*i*Pr, 66%
2h R=*t*Bu, 85%

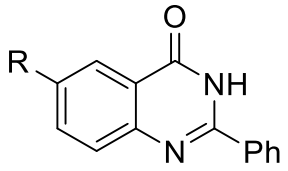
Reaction conditions: [a] Aryl urea derivatives (1,0 mmol), $[(MeCN)_2Pd(OTs)_2]$ (5 mol%), BQ (2,0 equiv), TsOH (1,0 equiv), CO (1 atm), DCM, ambient temperature, 3-5h.

A synthetic route to the quinazolin-4(3*H*)-ones *via* Pd(II)-catalyzed intramolecular aminocarbonylation of *N*-arylamidines has been disclosed by Zhu *et al* in 2011.[32] Reactions precede in refluxing HOAc under 1 atm of CO with CuO as the oxidant and about 16

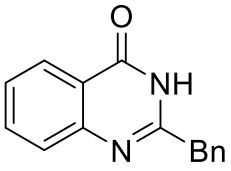
examples have been given in moderate to good yields (Table 24). Deuterium experiments indicated that C-H bond metalation step was reversible and deuterium-hydrogen scrambling occurred during the reaction.

Table 24. Selected examples for the carbonylative synthesis of quinazolin-4(3*H*)-ones.[a]

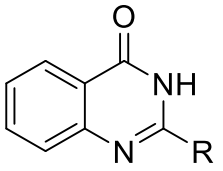




2a R=Me, 68%
2b R=OMe, 54%



2c 60%

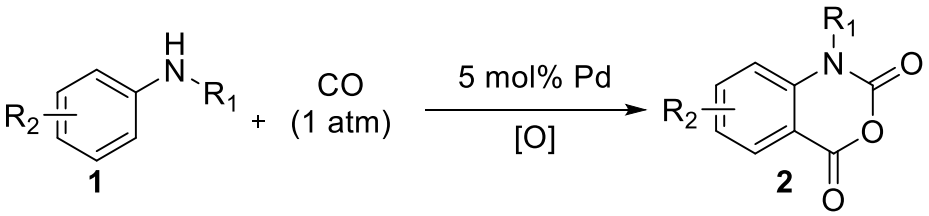


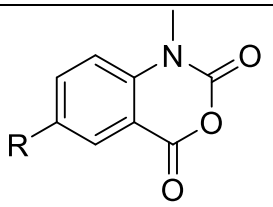
2d R=*i*Pr, 80%
2e R=*t*Bu, 60%
2f R=Me, 81%

Reaction conditions: [a] *N*-arylamidines (0,2 mmol), $Pd(OAc)_2$ (10 mol%), CuO (1,0 equiv), HOAc (1,5 mL), CO (1 atm, balloon), 110 ^{o}C, 23h.

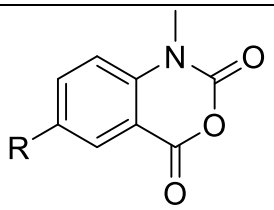
Guan *et al* in 2012 pioneered the directed carbonylation of the simplest *N*-alkyl anilines in the presence of palladium catalyst under 1-2 atm of CO.[33] In this case, no external directing group is needed and thus the elaboration of readily available *N*-alkyl anilines resulted a series of isatoic anhydrides in good yield with good functional group tolerance under mild reaction conditions (Table 25). Electron-rich anilines could run smoothly even *at ambient temperature* (**2c**), while additive such as pivalic acid and oxygen were necessary for the electron-poor analogues to obtain good yields (**2d**-**g**). Especially, the *meta*-nitroanilines worked well under the system (**2g**). Although the indoline **1h** was almost inert to the transformation, tetrahydroquinoline **1i** was carbonylated into the tricyclic corresponding products in 75% yield. It should be noted that the substituents on the nitrogen atom can be varied with other alkyl group or benzyl group (**2i**-**m**). Interestingly, the key intermediate for this transformation has been isolated and characterized by X-ray.

Table 25. Carbonylation of *N*-alkyl anilines toward to isatoic anhydrides.[a]

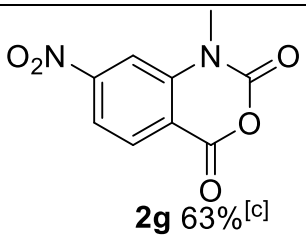




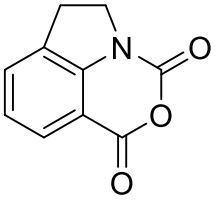
2a R=H 85%
2b R=Me 76%
2c R=OMe 70%[b].



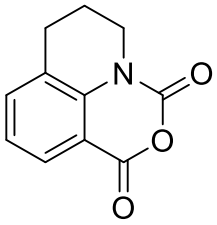
2d R=F 66%[c]
2e R=Br 86%[c]
2f R=CHO 77%[c]



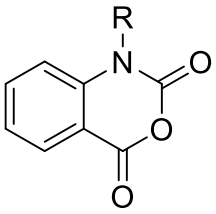
2g 63%[c]



2h <5%



2i 75%

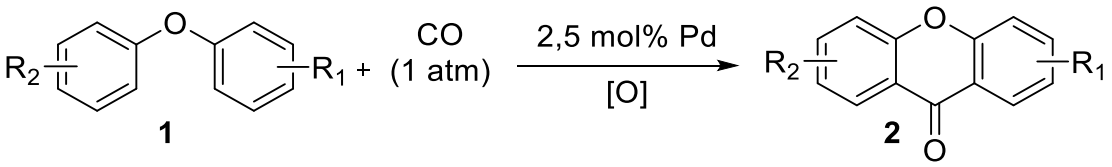


2j R=Et 84%
2k R=Pr 63%
2l R=Cy 51%
2m R=Bn 72%

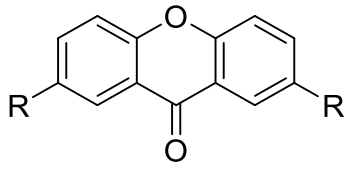
Reaction conditions: [a] anilines (0,2 mmol), $Pd(OAc)_2$ (5 mol%), $Cu(OAc)_2$ (2,2 equiv), KI (0,2 equiv), MeCN (2,0 mL), CO (1 atm), 60 ^oC, 5-18h. [b] at rt. [c] Pivalic acid (1,0 equiv) was added, CO/O_2 (2:1) (3 atm).

An interesting route for the synthesis of xanthone derivatives was pioneered by Lei *et al* in 2012, which provided an atom-economical approach to form biologically active compounds using diaryl ether as starting material.[34] This process runs under 1 atm of CO and in trifluoroacetic acid (TFA) at 50 ^oC (Table 26). Symmetrically, the diaryl ethers worked well forming the xanthone products in moderate to excellent yields (**2a**-**d**) as well as the asymmetrically analogues does (**2e**-**f**). It should be noted that the bromo was untouched under this conditions which was impossible for the Pd(0)-catalyzed chemistry (**2d**, **2h**). Intriguingly, the biphenyl ether only generates the xanthone products in 27% yields. IR spectroscopy experiments show that zero-order kinetics for the carbonylation of different substrates were observed, thus indicating that the first C-H functionalization of diaryl ether step with Pd(II) was not the rate-determining step. The kinetic profiles of different CO pressure suggest that the insertion of CO was not the rate-determining step under the experimental the conditions.

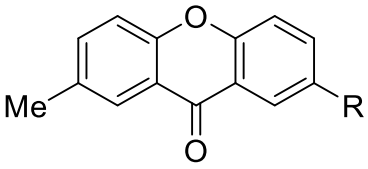
Table 26. Double C-H carbonylative activation of diary ether for the synthesis of xanthones.[a]



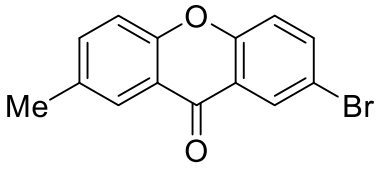
1 **2**



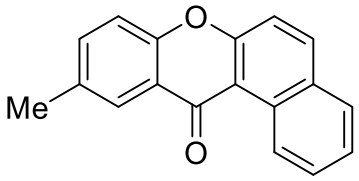
2a R=Me 96%
2b R=*t*Bu 92%
2c R=OMe 50%
2d R=Br 95%



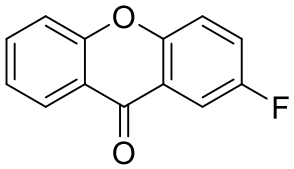
2e R=CF_3 56%
2f R=CO2Et 51%
2g R=COMe 58%



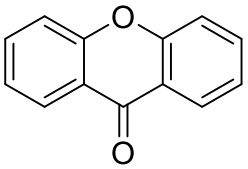
2h 70%



2i 70%



2j 34%



2k 27%

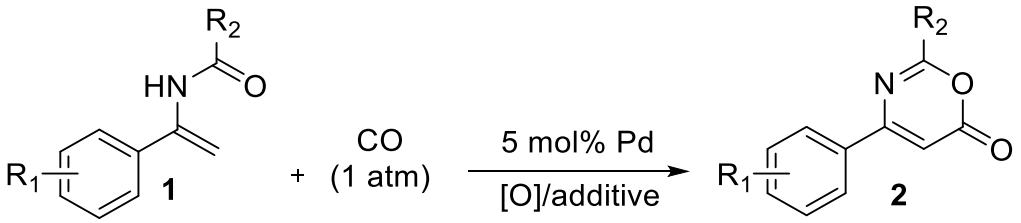
Reaction conditions: [a] diaryl ethers (0,2 mmol), $Pd(OAc)_2$ (2,5 mol%), $K_2S_2O_8$ (2,0 equiv), TFA (1,0 mL), CO (1 atm), 50 ^oC, 2-6h.

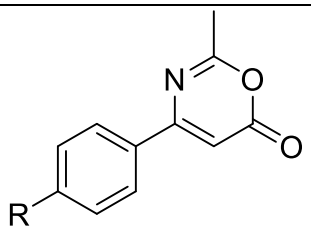
Du and Zhang in 2014 reported another protocol for the xanthone synthesis via palladium(0)-catalyzed carbonylation of *ortho*-diazonium salts of diaryl ether.[35] Compared to Lei's work, this transformation was initiated by Pd(0) with catalytic amount tetrabutyl ammonium bromide as the additive. In this context, 23 examples have been prepared in accepted to good yields.

Guan *et al* in 2013 described the synthesis of 1,3-oxazin-6-ones via the palladium-catalyzed carbonylation of alkenyl C-H bonds in the enamides.[36] Until now, most of the palladium-catalyzed carbonylation of C-H bonds preferentially proceeds under the acidic conditions which may favor in generating the cationic Pd(II) species and which inhibits the possible reduction of Pd(II) to Pd(0) by CO. But this procedure runs under basic conditions (in DMF with basic DABCO and KI as the additive, Table 27). Many kinds of substituents on the aromatic ring of enamides were tolerated and especially the bromo and nitro groups still intact under this system (**2d**, **2g**). The *tert*-butoxycarbonyl protected amino also runs well under this conditions (**2e**). Furthermore, the *N*-propionyl and *N*-benzoyl enamide analogues were also explored this carbonylation protocol scope giving the corresponding the 2-substituteated 1, 3-oxazin-6-ones in good yields (**2h**-**j**). However, the β-substituted enamides were unable to generate the products (**2k**). The key intermediates, six-membered

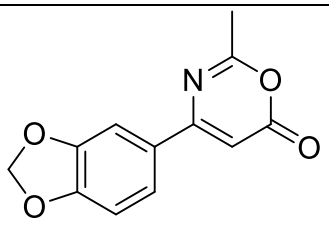
vinylpalladium complex, was synthesized and treated with CO providing the final products smoothly.

Table 27. Carbonylative synthesis 1, 3-oxazin-6-ones from palladium-catalyzed alkenyl C-H bonds activation in the enamides.[a]

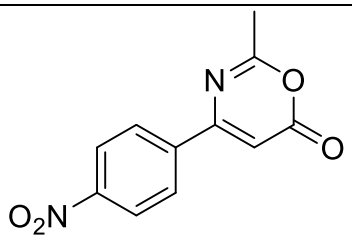




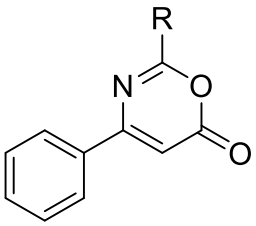
2a R=Me 86%
2b R=OMe 89%
2c R=Cl 79%
2d R=Br 70%
2e R=BocNH 74%



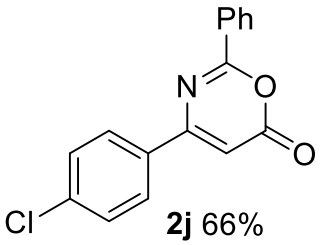
2f 81%



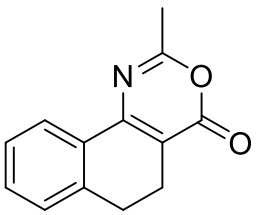
2g 40%



2h R=Et 61%
2i R=Ph 83%



2j 66%



2k <5%

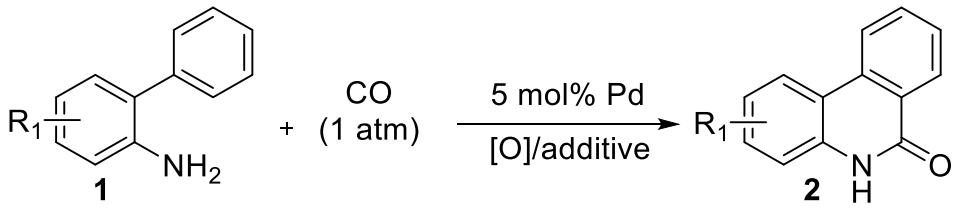
Reaction conditions: [a] enamides (0,2 mmol), $Pd(OAc)_2$ (5 mol%), $Cu(OAc)_2$ (2,0 equiv),KI (1,0 equiv), Ac_2O (3,0 equiv), DABCO (1,0 equiv), DMF (2,0 mL), CO (1 atm, balloon), 80 ^oC, 2-6h.

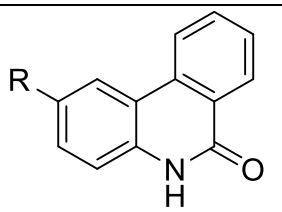
Elman in 2013 reported the synthesis of naphthalic anhydride (NAn) via the $Pd(OAc)_2$-catalyzed oxidative carbonylation of aromatics with $K_2S_2O_8$ as the oxidant under 2 atm of CO *at room temperature*.[37] The subsequent alkaline hydrolysis of naphthalic anhydride and isomerization of the obtained 1,8-naphthalenedicarboxylic acid salt is known to generate the NDA.

Zhu and Zhang groups described the synthesis of phenanthridinone *via* the palladium-catalyzed aminocarbonylation of unprotected *ortho*-aryl anilines in 2013, independently.[38] A series of substituents can be tolerated under this procedure (Table 28). Notably, the free

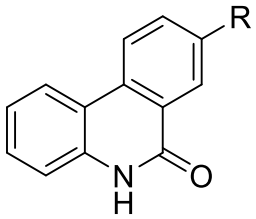
hydroxyl group is not detrimental to this procedure forming the products in good yields (**2g**, **2j**). It should be reminding that the heteroaryl aniline substrates also worked well providing the products **2n**-**p** in good yields. Importantly, the palladacyclic intermediate was isolated and further treated with CO providing the carbonylated products smoothly in 70% yield.

Table 28. Carbonylation of *ortho*-amino biaryl.[a]

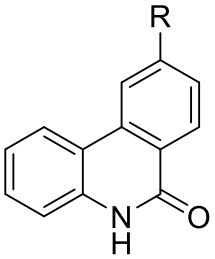




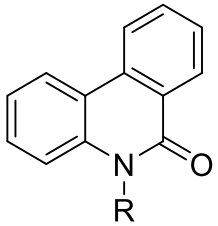
2a R=Me 84% 32h
2b R=F 73% 51h
2c R=Cl 80% 25h
2d R=CF_3 57% 24h
2e R=CO_2Me 61% 40h



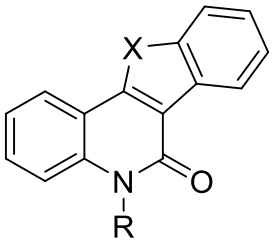
2g R=OH 74% 26h
2h R=Cl 53% 50h
2i R=CF_3 38% 65h



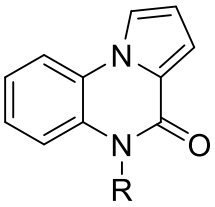
2j R=CH2OH 60% 28h
2k R=Cl 54% 60h



2l R=Me 86% 12h
2m R=Bn 65% 24h



2n X=NH 77% 7h
2o X=O 60% 31h

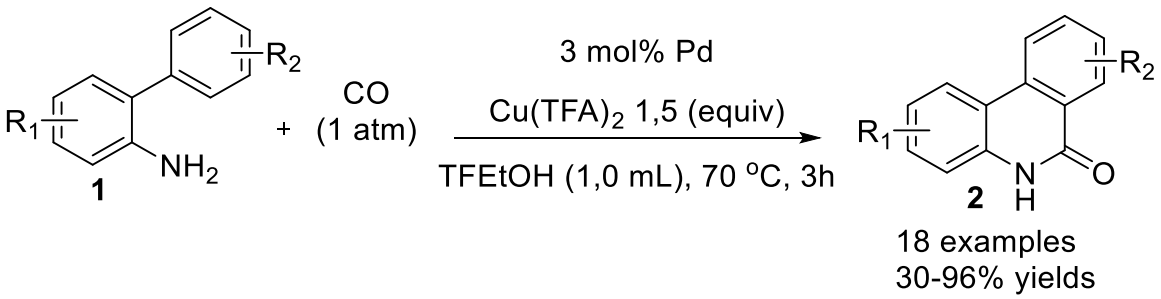


2p 76% 22h 90 ^{o}C

Reaction conditions: [a] *ortho*-aryl anilines (0,2 mmol), $Pd(MeCN)_2Cl_2$ (5 mol%), $Cu(TFA)_2$ (1,0 equiv), TFA (1,0 equiv), 1,4-dioxane (1,0 mL), CO (1 atm, balloon), 110 ^{o}C.

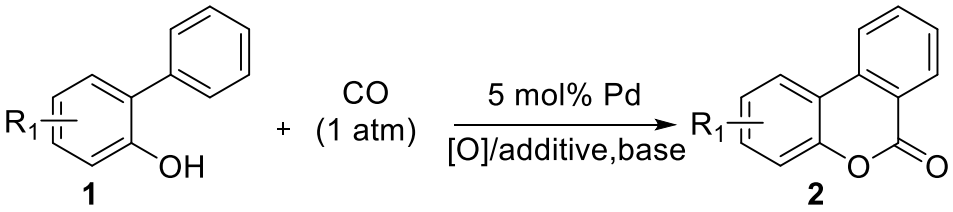
The acidic additive or solvent is necessary for those transformations. While Zhang's process utilize the trifluoroethanol (TFEOH) as the solvent with $Cu(TFA)_2$ as the oxidant in the presence of the $Pd(OAc)_2$ under atm pressure of CO at 70 ^{o}C and 19 examples have been prepared (Scheme 7).

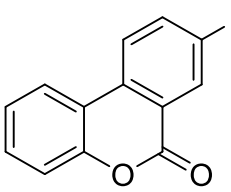
Scheme 7. Zhang's procedure for the synthesis of phenanthridinones.



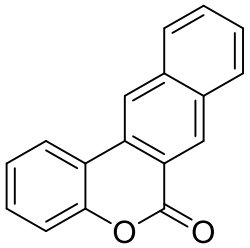
Similarly, the group of Shi and group of Chuang and Cheng in 2013 revealed the palladium-catalyzed carbonylation of *ortho*-arylphenols leading to dibenzopyranones independently.[39] For the substrate scope (Table 29), a numerous of functionality can be tolerated (**2a**-**o**) and about 30 examples were isolated, among which especially for the nitro group (**2g**) was intact albeit in low yields (31%). Remarkably, reactions proceed under basic conditions in mesitylene in the presence of sodium carbonate (2 equivalents) as the base and pivlic acid as the additive. Deuterium experiments indicate that the C-H metalation step might go through a S_EAr mechanism rather than the concerted metalation deprotonation (CMD) pathway.

Table 29. Carbonylation of *ortho*-hydroxy biaryl.[a]

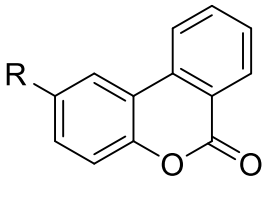




2a R=H 89%
2b R=Me 83%
2c R=OMe 60%
2d R=F 66%
2e R=Cl 68%
2f R=CO_2Me 64%
2g R=NO_2 31%



2h 79%

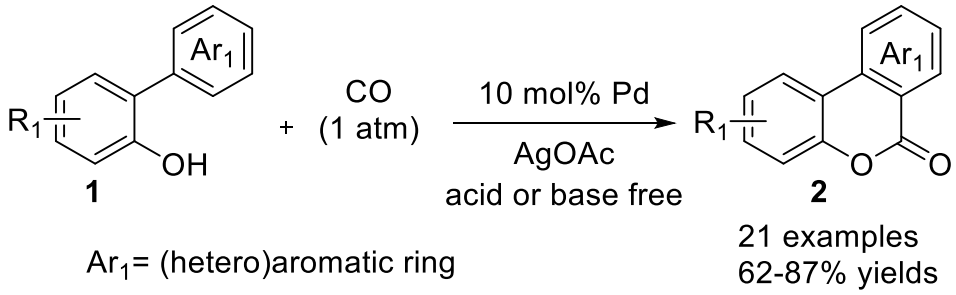


2i R=Me 69%
2j R=Ph 72%
2k R=F 41%
2l R=OMe 25%
2m R=OPh 25%
2o R=CO_2Me 60%

Reaction conditions: [a] *ortho*-aryl phenol (0,2 mmol), $Pd(OAc)_2$ (5 mol%), $Cu(OAc)_2$ (10 mol%), Na_2CO_3 (2,0 equiv), PivOH (0,5 equiv), mesitylene (2,0 mL), CO (1 atm), air,120 °C, 6h.

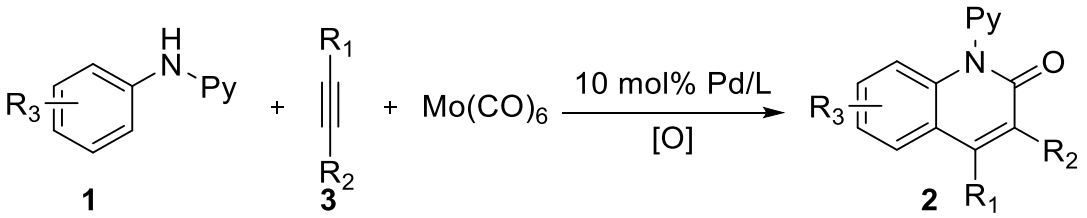
Interestingly, in contrast to Shi's procedure, Chuang and Cheng's system apply the Ag (I) as oxidant without extra acid or base and high yield was obtained with broad substrates scope (Scheme 8).

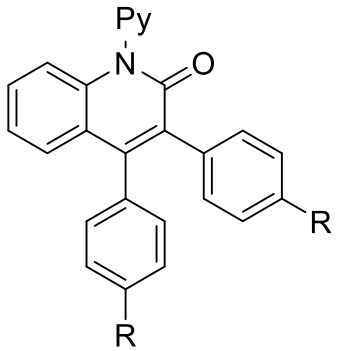
Scheme 8. Acid or base free procedure.



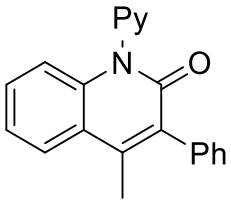
Notably, in 2014 we developed the first cabonylative [3+2+1] annulation of *N*-pyridyl anilines with internal alkynes and $Mo(CO)_6$ towards facile synthesis of 2-quinolinones and 19 examples were synthesized.[40] Here, the solid CO source $Mo(CO)_6$ was used instead of the CO gas which is highly toxic (Table 30). A series of symmetric and asymmetric internal alkynes could be used as the coupling partners giving the quinolinones in moderate to good yields (**2a**-**g**) and the regioselectivity was high (**2f**, **2g**). Substrates bearing electron-withdrawal or donating groups on the aniline ring run smoothly delivering the products in moderate to good yields (**2h**-**n**). KIE experiments (K_H/K_D = 1.0) show that the C-H bonds metalation step might be not involved in the rate-determining step.

Table 30. 2-Quinolinones synthesis from cabonylative [3+2+1] annulation of *N*-pyridyl anilines with internal alkynes and $Mo(CO)_6$.[a]

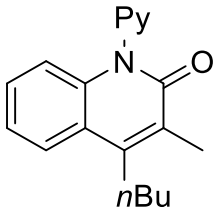




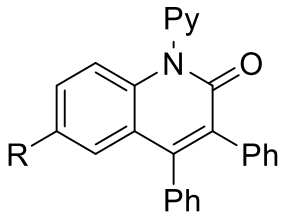
2a R=H 80%
2b R=*n*Bu 60%
2c R=F 65%
2d R=Br 30%
2e R=Ac 70%



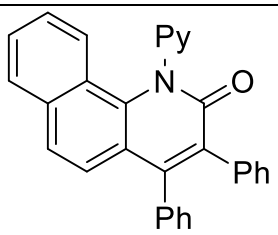
2f 77% (7:1)[b]



2g 26%



2h R=Me 73%
2i R=OMe 57%
2j R=F 64%
2k R=Cl 84%
2l R=CO_2Me 40%
2m R=OCF_3 26%
2n R=SMe 63%

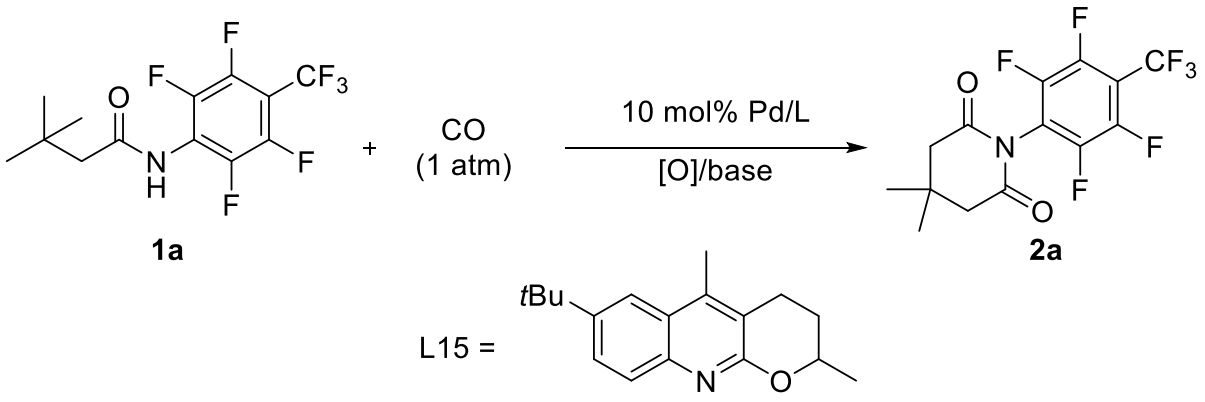


2o 32%

Reaction conditions: [a] *N*-pyridyl anilines (1,2 equiv), alkyne (0,2 mmol), $Pd(OAc)_2$ (10 mol%), L-proline (20 mol%), BQ (2,0 equiv), AgOAc (2,0 equiv), HAOc (2 mL), $Mo(CO)_6$ (1,2 equiv), air, 140 ^oC, 24h. [b] Major prodructs were given.

In 2014 , Yu *et al* accomplished the γ-C-H functionalization of aliphatic acid utilizing a combination of a quinoline-base ligand and a weakly coordinating directing group.[41] The corresponding lactam derivatives could be obtained in good yields which provides a new route for constructing richly functionalized all-carbon quaternary carbon centers at the β-position of aliphatic acids (Table 31). Only one example has been given in this context. The large scale experiment highlighted the potential application as reaction was performed successfully in 1g scale generating **2a** in 61% isolated yield.

Table 31. Carbonylative γ-C-H functionalization of aliphatic acid[a]

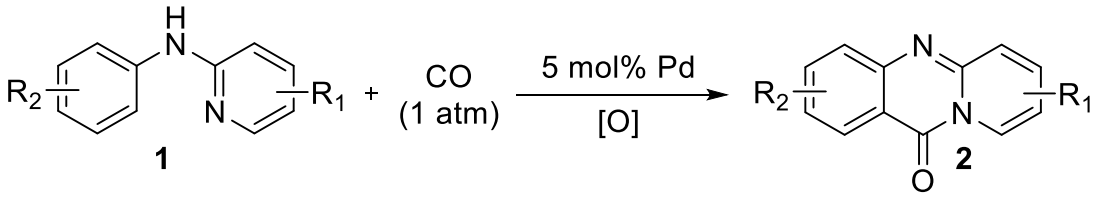


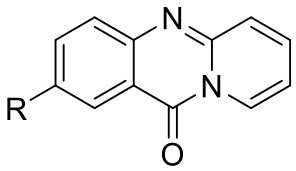
Reaction conditions: [a] aliphatic amides (0,1 mmol), $Pd(OAc)_2$ (10 mol%), Ligand (20 mol%), AgOAc (2,0 equiv), $^tBuOOBu^t$ (2,0 equiv), KH_2PO_4 (2,0 equiv), hexane (2 mL), CO (1 atm), 150 ^oC, 20h.

In 2014, Zhu *et al* reported the palladium-catalyzed pyridocarbonylation of *N*-pyridyl anilines forming 11*H*-pyrido[2,1-*b*]-quinazolin-11-one.[42] This process runs in the trifluoroacetic acid (TFA) as the solvent with $K_2S_2O_8$ as oxidant under atmospheric pressure of CO and 19 examples were listed (Table 32). Electron-donating or withdrawing groups on the aromatic or the pyridine rings worked well giving the quinazolinone scaffold in good yields (**2a**-**l**). For the *meta*-substituted group on the anilines, reactions favored the less sterically hindered position (**2g**-**i**). Notably, the *N*-pyrimidyl aniline can provide the product **2m** in 40%

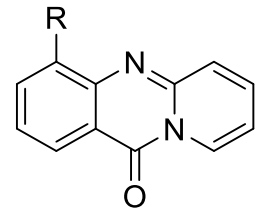
yield. Here, the pyridyl group not only serves as the directing group but also as the nucleophile for intramolecular transformation.

Table 32. Selected examples for pyridocarbonylation of *N*-pyridyl anilines to form 11*H*-pyrido[2,1-*b*]-quinazolin-11-one.[a]

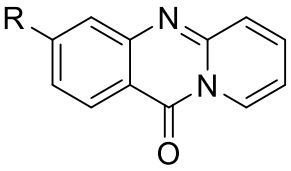




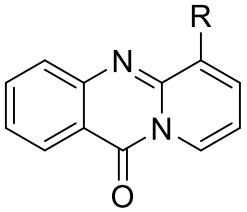
2a R=*t*Bu 77% 6,5h
2b R=F 70% 6h
2c R=Cl 77% 3h[b]



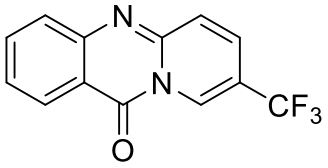
2d R=Me 81% 4,5h
2e R=OMe 66% 3h
2f R=F 77% 6h[b]



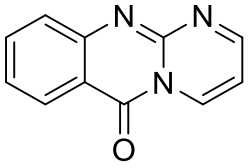
2g R=Me 59% 7h
2h R=Ph 75% 4,5h
2i R=Cl 70% 7h[b] (10:6)[c]



2j R=Me 86% 4h
2k R=Cl 67% 7h[b]



2l 76% 1,5h[b]



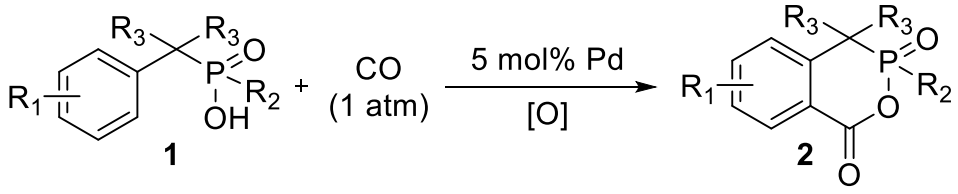
2m 40% 4h

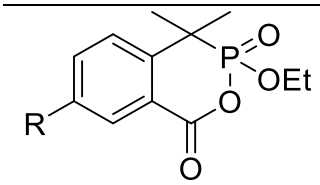
Reaction conditions: [a] *N*-pyridyl anilines (0,2 mmol), $Pd(OAc)_2$ (5 mol%), $K_2S_2O_8$ (3,0 equiv), TFA (1,0 mL), CO (1 atm; balloon), 70 °C, 24h. [b] $K_2S_2O_8$ (5,0 equiv). [c] Major product was given.

Lee *et al* in 2014 exploited the phosphonic and phosphinic acid as the directing group for the carbonylative phosphaannulation in the presence of palladium catalyst, thus a series of oxaphosphorinanone oxides were obtained (Table 33).[43] Effect of substituents at the α-position of the ethyl hydrogen benzylphosphonate indicates that introduction of two substituents at the α-position is essential for successful carbonylation. A series of electron-donating and -withdrawing groups can be tolerated (**2a**-**d, 2h-k**) and especially for the example of bromo show further manipulation opportunity (**2d**). Not only the phosphonic acid but also the phosphinic acid proceeded well affording the corresponding products in 67% yields (**2e**). Substrates bearing five- and six- membered spiro type ring at the α-position are also excellent starting material for this C-H carbonylation delivering the desired

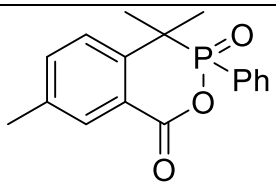
oxaphosphorinanone oxides in good yield (**2f**-**g**). KIE experiments (K_H/K_D = 3.76) indicated that C-H metalation at the *ortho*-position of benzylphosphonic acid is most likely to be involved in the rate-determining step.

Table 33. Pd(II)-catalyzed carbonylative phosphaannulation of phosphonic and phosphinic acid to prepare oxaphosphorinanone oxides.[a]

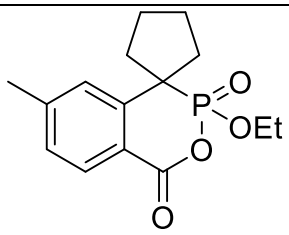




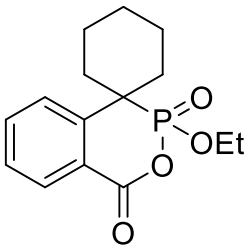
2a R=Me 81%
2b R=*t*Bu 67%
2c R=OMe 74%
2d R=Br 56%



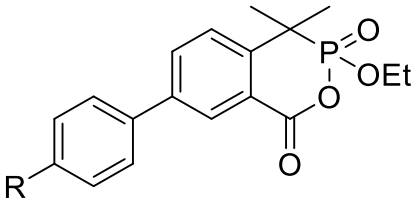
2e R=Me 67%[b]



2f 82%



2g 60%



2h R=H 76%
2i R=*t*Bu 80%
2j R=OMe 65%[b]
2k R=Cl 76%[b]

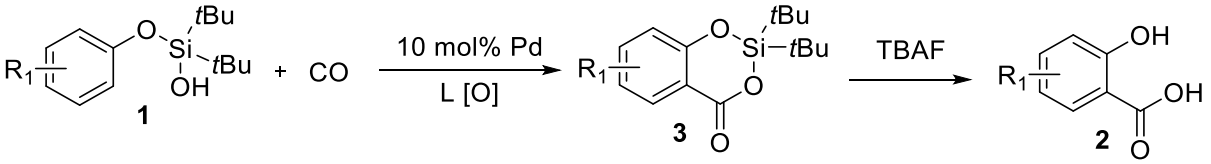
Reaction conditions: [a] ethyl hydrogen benzylphosphonates (0,2 mmol), $Pd(OAc)_2$ (5 mol%), $PhI(OAc)_2$ (1,5 equiv), AgOAc (1,5 equiv), DCE (2,0 mL), CO (1 atm), 60 ^oC, 20h. [b] 36h, $PhI(OAc)_2$ (2,0 equiv) was used.

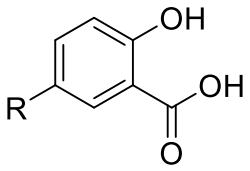
The synthesis of frutinone A and its derivatives was developed by Hong and Lee in 2014 *via* the palladium-catalyzed carbonylation of 2-phenolchromones.[44] Remarkably, several products were applied to test the inhibitory activities of the CYP1A2 enzyme in the nanomolar range and exerted potent efficiency.

Recently, Gevorgyan *et al* disclosed the palladium-catalyzed silanol-directed carbonylation of phenol affording the 4*H*-benzo[*d*][1,3,2]dioxasilin-4-one which was then followed by desilylation giving the final salicylic acid.[45] Here, silanol serve as a powerful traceless directing group, thus producing a useful method for the preparation of salicyclic acid from accessible phenol. Substrates containing electron-donating or –withdrawing groups on the *ortho*, *meta* and *para* position of phenol are compatible well (Table 34). Notably, α or β

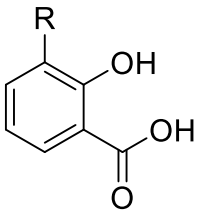
naphthalenol generate the corresponding salicyclic acid in 66% and 85% yields, respectively (**2j**, **k**). Interestingly, a special ether group can also work well in this system (**2o**) and the heterocyclic aromatic phenol gave the product in 64% yields (**2p**). The α,β-unsaturated ketonyl group at the *meta* position run smoothly (**2q**) in 66% yield.

Table 34. Selected products for silanol-directed carbonylation toward salicylic acid synthesis.[a]

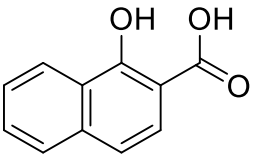




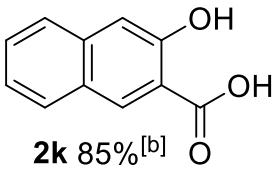
R=H **2a** 76%
R=*t*Bu **2b** 91%
R=Ph **2c** 65%
R=OMe **2d** 80%
R=OAc **2e** 71%
R=Cl **2f** 49%



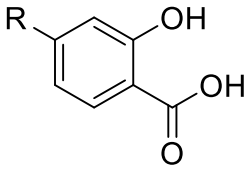
R=Me **2g** 89%
R=Ph **2h** 63%
R=Cl **2i** 45%



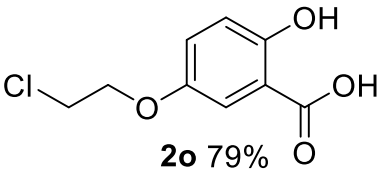
2j 66%



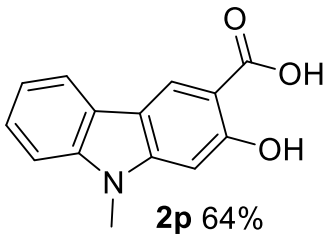
2k 85%[b]



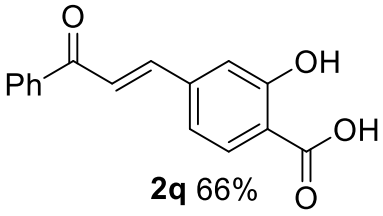
R=Me **2l** 92%
R=OMe **2m** 57%
R=OAc **2n** 69%



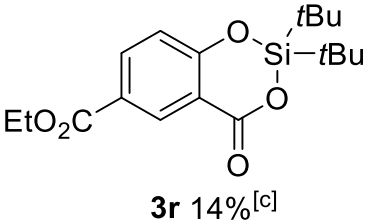
2o 79%



2p 64%



2q 66%

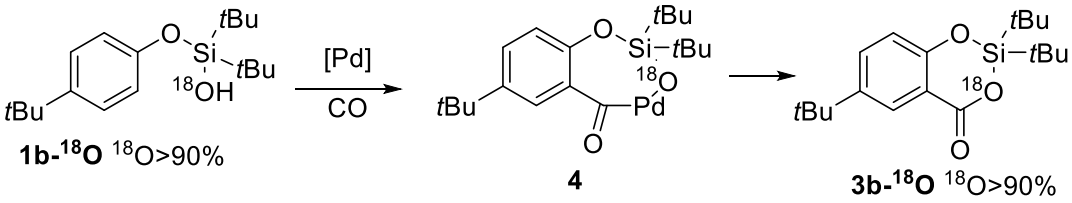


3r 14%[c]

Reaction conditions: [a] **1** (0,2 mmol), $Pd(OAc)_2$ (10 mol%), Boc-Leu-OH (20 mol%), AgOAc (3,0 equiv), CF_3CH_2OH (3,0 equiv), DCE (0,8 mL), CO/Ar (1:8, balloon), 95 ^oC, 18h. [b] A 2:1 ratio of regioisomers were formed, main product was shown. [c] Yield of the silacycle after the first step, as determined by NMR spectroscopy.

Interestingly, when ^{18}O-labeled **1b-^{18}O** was subjected to the standard conditions, the results revealed that complete retention of the ^{18}O labeled in the silacyclic compound **3b-^{18}O**. Thus, the intermediate **4** should be formed in the catalytic cycles (Scheme 9).

Scheme 9. ^{18}O-labeling experiments.



1b-^{18}O ^{18}O>90% **4** **3b-^{18}O** ^{18}O>90%

1.5 Summary and outlook

The transition metal catalyzed carbonyaltive C-H functionalization toward heterocycles synthesis was summarized. The cobalt, ruthenium, rhodium and palladium based catalyst systems were explored for the synthesis of important five- or six- membered heterocycles. Among these catalytic reactions, palladium-based system attracted more attention and the systematic studies have been made. The main challenges in the Pd-catalyzed carbonylation is the excellent reducing ability of CO introducing the rapidly reductant of Pd(II) to Pd(0). Solutions to handle this problem include: (i) utilizing of unique ligand[30, 41] such as special α-amino acid; (ii) employment of cationic Pd (II) precursor[31, 46] which could enhance the nucleophilic attack of the C-H bond toward the palladium center; (iii) using acid as solvent or the additive which also favor the generation of cationic palladium center.[34, 40, 46-47] In the coming days, efforts should be focused on the following topics: (i) the development of mild reaction conditions such as room temperature, employment of molecular oxygen as a 'green' oxidant and acid-free conditions; (ii) exploiting no directing group substrates; (iii) the application of double carbonylation to C-H heterocycles preparation; (v) taking advantages of CO gas free environmentally benign carbonyl source.

1.6 References

[1] 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.

[2] For the resently selectecd reviews please see: 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.

[3] For the resently selectecd reviews and examples please see: 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.

[4] For the resently selectecd reviews please see: a) X. F. Wu, H. Neumann, M. Beller, *ChemSusChem* **2013**, *6*, 229-241; b) Q. Liu, H. Zhang, A. Lei, *Angew. Chem. Int. Ed*. **2011**, *50*, 10788-10799.

[5] For the resently selectecd reviews and examples please see: a) X.-X. Guo, D.-W. Gu, Z. Wu, W. Zhang, *Chem. Rev.* **2015**, *115*, 1622-1651; b) A. V. Gulevich, A. S. Dudnik, N. Chernyak, V. Gevorgyan, *Chem. Rev.* **2013**, *113*, 3084-3213.

[6] T. Joh, K. Doyama, K. Fujiwara, K. Maeshima, S. Takahashi, *Organometallics* **1991**, *10*, 508-513.

[7] J. K. Funk, H. Yennawar, A. Sen, *Helv. Chim. Acta* **2006**, *89*, 1687-1695.

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

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

[10] T. Fukuyama, N. Chatani, F. Kakiuchi, S. Murai, *J. Org. Chem*. **1997**, *62*, 5647-5650.

[11] N. Chatani, A. Kamitani, S. Murai, *J. Org. Chem.* **2002**, *67*, 7014-7018.

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

[13] a) N. Hasegawa, V. Charra, S. Inoue, Y. Fukumoto, N. Chatani, *J. Am. Chem. Soc.* **2011**, *133*, 8070-8073; b) N. Hasegawa, K. Shibata, V. Charra, S. Inoue, Y. Fukumoto, N. Chatani, *Tetrahedron* **2013**, *69*, 4466-4472.

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

[15] K. Inamoto, J. Kadokawa, Y. Kondo, *Org. Lett.* **2013**, *15*, 3962-3965.

[16] W. Li, C. Liu, H. Zhang, K. Ye, G. Zhang, W. Zhang, Z. Duan, S. You, A. Lei, *Angew. Chem. Int. Ed.* **2014**, *53*, 2443-2446.

[17] a) M. A. Campo, R. C. Larock, *Org. Lett.* **2000**, *2*, 3675-3677; b) M. A. Campo, R. C. Larock, *J. Org. Chem*. **2002**, *67*, 5616-5620.

[18] R. Giri, J.-Q. Yu, *J. Am. Chem. Soc.* **2008**, *130*, 14082.

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

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

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

[22] C. Song, S. Dong, L. Feng, X. Peng, M. Wang, J. Wang, Z. Xu, *Org. Biomol. Chem.* **2013**, *11*, 6258-6262.

[23] W. Li, Z. Duan, X. Zhang, H. Zhang, M. Wang, R. Jiang, H. Zeng, C. Liu, A. Lei, *Angew. Chem. Int. Ed.* **2015**, *54*, 1893-1896.

[24] K. Orito, A. Horibata, T. Nakamura, H. Ushito, H. Nagasaki, M. Yuguchi, S. Yamashita, M. Tokuda, *J. Am. Chem. Soc.* **2004**, *126*, 14342-14343.

[25] 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.

[26] a) Yasuhiro Wada, Hideo Nagasaki, Masao Tokuda, K. Orito, *J. Org. Chem.* **2007**, *72*, 2008-2014; b) S. Yamashita, N. Kurono, H. Senboku, M. Tokuda, K. Orito, *Eur. J. Org. Chem.* **2009**, 1173-1180.

[27] a) Jose Vicente, Isabel Saura-Llamas, Jose Antonio Garcıa-Lopez, B. Calmuschi-Cula, *Organometallics* **2007**, *26*, 2768-2776; b) Jose Grupo, I. Saura-Llamas, Jose-Antonio, Garcıa-Lopez, *Organometallics* **2009**, *28*, 448-464.

[28] a) B. Haffemayer, M. Gulias, M. J. Gaunt, *Chem. Sci.* **2011**, *2*, 312; b) J. Albert, X. Ariza, T. Calvet, M. Font-Bardia, J. Garcia, J. Granell, A. Lamela, B. López, M. Martinez, L. Ortega, A. Rodriguez, D. Santos, *Organometallics* **2013**, *32*, 649-659.

[29] Y. Li, Z. Yu, H. Alper, *Org. Lett.* **2007**, *9*, 1647-1649.

[30] Y. Lu, D. Leow, X. Wang, K. M. Engle, J.-Q. Yu, *Chem. Sci.* **2011**, *2*, 967-971.

[31] C. E. Houlden, M. Hutchby, C. D. Bailey, J. G. Ford, S. N. Tyler, M. R. Gagne, G. C. Lloyd-Jones, K. I. Booker-Milburn, *Angew. Chem. Int. Ed.* **2009**, *48*, 1830-1833.

[32] B. Ma, Y. Wang, J. Peng, Q. Zhu, *J. Org. Chem.* **2011**, *76*, 6362-6366.

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

[34] H. Zhang, R. Shi, P. Gan, C. Liu, A. Ding, Q. Wang, A. Lei, *Angew. Chem. Int. Ed.* **2012**, *51*, 5204-5207.

[35] Y. Xu, J. Zhou, C. Zhang, K. Chen, T. Zhang, Z. Du, *Tetrahedron Lett.* **2014**. *55*, 6432-6434

[36] M. Chen, Z.-H. Ren, Y.-Y. Wang, Z.-H. Guan, *Angew. Chem. Int. Ed.* **2013**, *52*, 14196-14199.

[37] A. R. Elman, *Tetrahedron Lett.* **2013**, *54*, 5527-5531.

[38] a) Z. Liang, J. Zhang, Z. Liu, K. Wang, Y. Zhang, *Tetrahedron* **2013**, *69*, 6519-6526; b) D. Liang, Z. Hu, J. Peng, J. Huang, Q. Zhu, *Chem Commun* **2013**, *49*, 173-175.

[39] a) T.-H. Lee, J. Jayakumar, C.-H. Cheng, S.-C. Chuang, *Chem. Commun.* **2013**, *49*, 11797-11799; b) S. Luo, F. X. Luo, X. S. Zhang, Z. J. Shi, *Angew. Chem. Int. Ed.* **2013**, *52*, 10598-10601.

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

[41] S. Li, G. Chen, C.-G. Feng, W. Gong, J.-Q. Yu, *J. Am. Chem. Soc.* **2014**, *136*, 5267-5270.

[42] D. Liang, Y. He, Q. Zhu, *Org. Lett.* **2014**, *16*, 2748-2751.

[43] S. Shin, Y. Jeong, W. H. Jeon, P. H. Lee, *Org. Lett.* **2014**, *16*, 2930-2933.

[44] Y. Shin, C. Yoo, Y. Moon, Y. Lee, S. Hong, *Chem. - Asian J.* **2015**, *10*, 878-881.

2. Objectives of this work

As described in the introduction, carbonylation is an important process for the construction of many C-C bonds and valuble molecules. This process attracted the attaention of the chemists since decades as an important and convenient method for the selective preparation of important fine and bulk chemicals. Heterocyclic molecules are important class of compounds which are frequently encountered in the medical and pharmaceutical chemistry. Although research has been accomplished in this field utilizing ArX (X=Br, I; OTf, N_2BF_4), still there exists significant academic and industrial interests for the synthesis of heterocycles *via* carbonylation through the development of new catalyst systems.

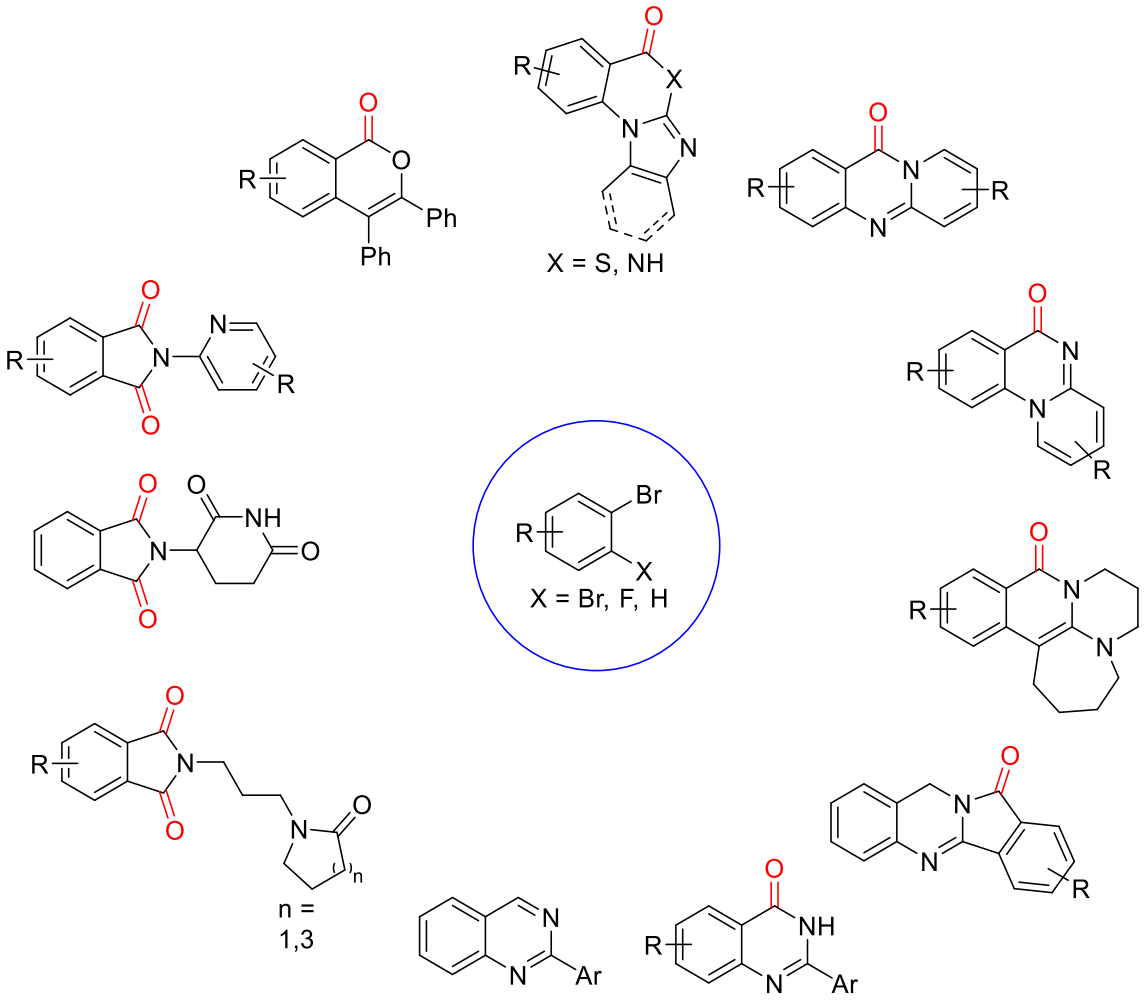


Figure 1: Carbonylation of aryl halides towards heterocycles synthesis.

Compared to the synthesis of heterocycles starting from aryl halides, the direct activation of the C-H bond is more sustainable, atomic and step economic because this process avoids the pre-functionalization step. Surprisingly very limited research has been done in carbonylative C-H functionalization. Interestingly there exists notable advantages and challenges in this C-H activation chemistry: (i) the reduction of Pd (II) to Pd (0) is more easily

undergoing in the CO atmosphere which has excellent reducing ability; (ii) strong binding ability of CO might inhibit the electronic attach of Pd (II) toward the aromatic C-H bonds because of occupying the active sites; (iii) CO as an excellent π-acid behaving the unique π-back bonding might also decrease the electron density on Pd center.

Therefore, the major aim of this work is the development of novel catalyst systems for the preparation of heteroaromatic rings, especially the biologically active compounds *via* carbonylation of aryl halides. (Figure 1). Next aim is the exploitation of carbonylative C-H activation applying novel processes to fine or bulk chemicals (Figure 2). These processes are of particular interest in terms of atom-efficiency, selectivity and applicability.

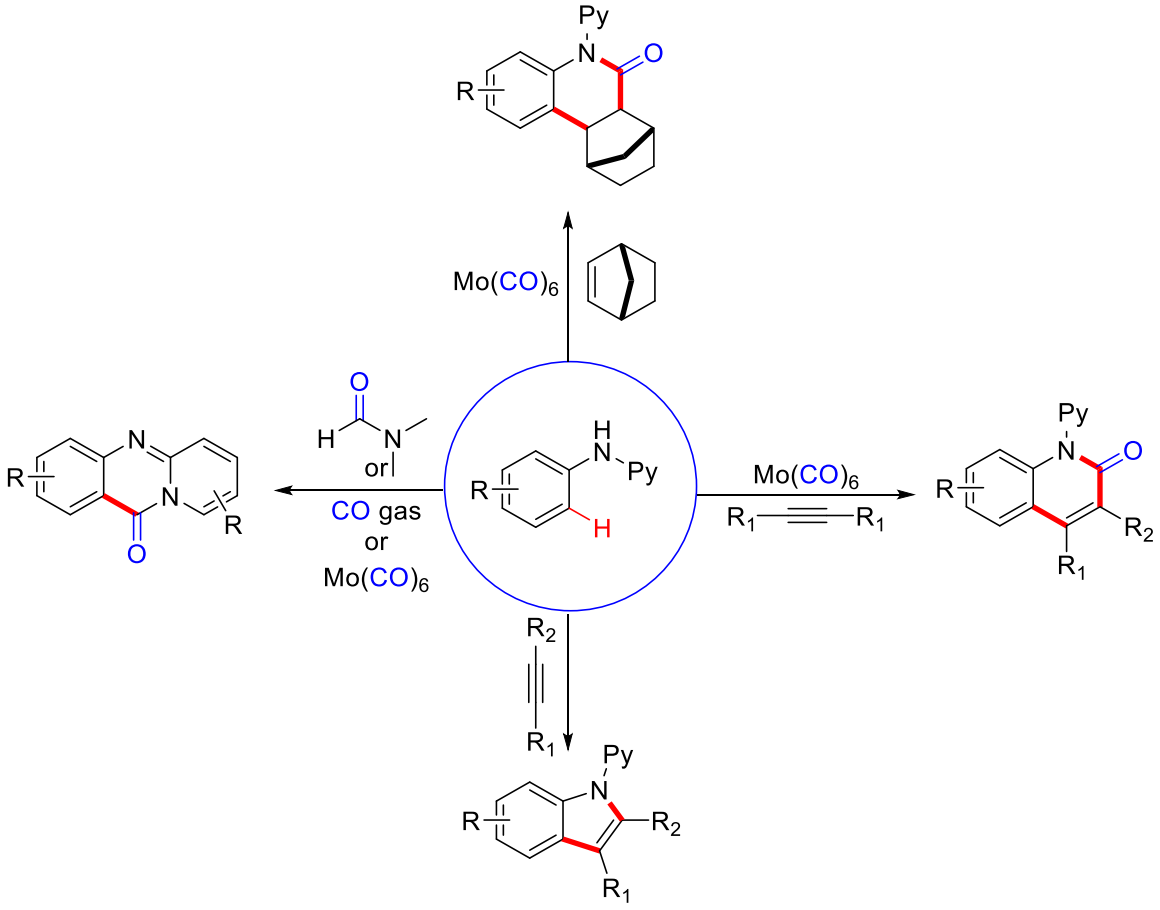


Figure 2: Heteroaromatic ring synthesis *via* carbonylative C-H activation.

3. Summary and publications

3.1 Base-Controlled Selectivity toward Linear and Angular Fused Quinazolinones via Palladium-Catalyzed Carbonylation/Nucleophilic Aromatic Substitution Sequence

Jianbin Chen, Kishore Natte, Anke Spannenberg, Helfried Neumann, Peter Langer, Matthias Beller* and Xiao-Feng Wu*

Angewandte Chemie **2014**, *126*, 7709–7713; *Angewandte Chemie International Edition* **2014**, *53*, 7579-7583.

Summary: A new approach for the facile synthesis of fused quinazolinone scaffolds through a palladium-catalyzed carbonylative coupling followed by intramolecular nucleophilic aromatic substitution process is described.The base serves as the key modulator: Whereas DUB gives rise to the linear isomers, Et_3N promotes the preferential formation of angular products. Interestingly, light induced 4+4 reaction of the product was also observed.

Contributions

In this paper, I planned, performed and analyzed most experiments for this manuscript. I have done the major part of writing of the manuscript. My contribution as co-author of this paper is approximately 85%.

3.2 Palladium-Catalyzed Carbonylative Reactions of 1-Bromo-2-fluorobenzenes with Various Nucleophiles: Effective Combination of Carbonylation and Nucleophilic Substitution

Jianbin Chen, Kishore Natte, Helfried Neumann, and Xiao-Feng Wu*

Chemistry - A European Journal **2014,** *20*, 16107 – 16110.

Summary: A systematic study on the carbonylative transformation of 1-bromo-2-fluorobenzenes with various nucleophiles has been performed. Different types of double nucleophiles, such as N-N, N-C, O-C, and N-S, can be effectively applied as coupling partners. The corresponding six-membered heterocycles were isolated in moderate to good yields.

Contributions

In this paper, I planned, performed and analyzed most experiments for this manuscript. I have done the major part of writing of the manuscript. My contribution as co-author of this paper is approximately 85%.

3.3 Efficient palladium-catalyzed double carbonylation of o-dibromobenzenes: synthesis of thalidomide

Jianbin Chen, Kishore Natte, Anke Spannenberg, Helfried Neumann, Matthias Beller and Xiao-Feng Wu*

Organic & Biomolecular Chemistry **2014**, *12*, 5578-5581.

Summary: We describe here a convenient and mild procedure for double carbonylation of o-dibromobenzenes with various 2-amino pyridines and naturally occurring amines, thus providing in good to excellent yields N-substituted phthalimides by using this palladium-catalyzed carbonylation procedure. Furthermore, for the first time we have applied the developed synthetic protocol for the synthesis of biologically active molecule thalidomide via a single step carbonylative cyclization reaction in excellent yield.

Contributions

In this paper, I planned, performed and analyzed most experiments for this manuscript. I have done the major part of writing of the manuscript. My contribution as co-author of this paper is approximately 65%.

3.4 Palladium-catalyzed synthesis of isoindoloquinazolinones *via* dicarbonylation dicarbonylation of 1,2-dibromoarenes

Jianbin Chen, Helfried Neumann, Matthias Beller and Xiao-Feng Wu*

Organic & Biomolecular Chemistry **2014**, *12*, 5835-5838.

Summary: A convenient procedure for the carbonylative synthesis of isoindolo quinazolinones has been developed. Using 1,2-dibromobenzenes and 2-aminobenzyl amine as substrates and palladium as the catalyst, the desired products were isolated in moderate to good yields with the installation of two molecules of carbon monoxide. Notably, this is the first example of carbonylative synthesis of batracylin analogues.

Contributions

In this paper, I planned, performed and analyzed most experiments for this manuscript. I have done the major part of writing of the manuscript. My contribution as co-author of this paper is approximately 90%.

3.5 A convenient palladium-catalyzed carbonylative synthesis of quinazolines from 2-aminobenzylamine and aryl bromides

Jianbin Chen, Kishore Natte, Helfried Neumann and Xiao-Feng Wu*

RSC Advances **2014**, *4*, 56502-56505.

Summary: A novel and practical strategy towards quinazoline scaffolds synthesis has been achieved. Through palladium-catalyzed carbonylative coupling of 2-aminobenzylamine with aryl bromides, the desired quinazolines were produced in moderate to good yields for the first time. The reactions followed an aminocarbonylation–condensation–oxidation sequence in a one-pot one-step manner. Preliminary investigation showed DMSO serves both as solvent and oxidant in this procedure.

Contributions

In this paper, I planned, performed and analyzed most experiments for this manuscript. I have done the major part of writing of the manuscript. My contribution as co-author of this paper is approximately 65%.

3.6 Convenient palladium-catalyzed carbonylative synthesis of caprolactam and butyrolactam derived phthalimides and amides by using DBU and DBN as the nitrogen source

Jianbin Chen, Kishore Natte, and Xiao-Feng Wu*

Tetrahedron Letters **2015**, 56, 342-345.

Summary: A novel and convenient strategy toward caprolactam and butyrolactam derived phthalimide and amide scaffolds has been fulfilled through the palladium-catalyzed carbonylative coupling in a one-pot one step manner. The nucleophilicity of DBU and DBN was applied to the carbonylation reaction for the first time and followed by hydrolysis leading to the ring opening reaction of DBU and DBN. It should be noted that the chlorobenzene worked successfully under this approach.

Contributions

In this paper, I planned, performed and analyzed most experiments for this manuscript. I have done the major part of writing of the manuscript. My contribution as co-author of this paper is approximately 90%.

3.7 Convenient copper-mediated Chan–Lam coupling of 2-aminopyridine: facile synthesis of *N*-arylpyridin-2-amines

Jianbin Chena, Kishore Natte a, Nikki Y. T. Manb, Scott G. Stewart b, Xiao-Feng Wu*

Tetrahedron Letters **2015**, 56, 4843-4847.

Summary: A new and practical process for the synthesis of N-arylpyridin-2-amine derivatives has been developed. Under the assistance of copper, the desired products were produced from commercially available 2-aminopyridine and aryl boronic acids in moderate to good yields with good functional group tolerance.

Contributions

In this paper, I planned, performed and analyzed most experiments for this manuscript. I have done the major part of writing of the manuscript. My contribution as co-author of this paper is approximately 80%.

3.8 Palladium-Catalyzed Carbonylative [3+2+1] Annulation of *N*-Aryl-Pyridine-2-Amines with Internal Alkynes by C-H Activation: Facile Synthesis of 2-Quinolinones

Jianbin Chen, Kishore Natte, Anke Spannenberg, Helfried Neumann, Matthias Beller, and Xiao-Feng Wu*

Chemistry - A European Journal **2014,** *20*, 14189-14193.

Summary: We describe here a novel procedure for the synthesis of highly substituted 2-quinolinones. By this newly developed approach, 2-quinolinone derivatives were prepared in moderate to good yields by carbonylative cyclization of N-aryl-pyridine-2-amines and internal alkynes by C-H activation. Remarkably, [$Mo(CO)_6$] was applied asa solid CO source and the reaction proceeded in an atom economic manner.

Contributions

In this paper, I planned, performed and analyzed most experiments for this manuscript. I have done the major part of writing of the manuscript. My contribution as co-author of this paper is approximately 85%.

3.9 Palladium@Cerium(IV) Oxide-Catalyzed Oxidative Synthesis of *N*-(2-Pyridyl)indoles via C-H Activation Reaction

Jianbin Chen, Lin He, Kishore Natte, Helfried Neumann, Matthias Beller, and Xiao-Feng Wu*

Advanced Synthesis & Catalysis **2014,** *356*, 2955-2959.

Summary: An interesting protocol for the synthesis of *N*-(2-pyridyl)indoles based on a palladium@cerium(IV) oxide-catalyzed oxidative C-H activation reaction has been developed. By using alkynes and *N*-phenylpyridin-2-amines as substrates, the corresponding indoles were isolated in moderate to excellent yields. Notably, palladium@cerium(IV) oxide showed better activity compared with other tested commercially available heterogeneous catalysts and only catalytic amounts of copper(II) salt and air as co-oxidant were required here.

Contributions

In this paper, I planned, performed and analyzed most experiments for this manuscript. I have done the major part of writing of the manuscript. My contribution as co-author of this paper is approximately 80%.

3.10 Palladium- Catalyzed Carbonylative Cyclization of Arenes via C-H Bond Activation with DMF as the Carbonyl Source

Jianbin Chen, Jian-Bo Feng, Kishore Natte, Helfried Neumann, Matthias Beller, and Xiao-Feng Wu*

Chemistry - A European Journal **2015**, *21*, 1 – 5.

Summary: A novel palladium-catalyzed CO-gas and autoclave free protocol for the synthesis of 11H-pyrido[2,1-*b*]quinazolin-11-ones has been developed. With DMF as the CO surrogates via C-H bond activation and annulation, quinazolinones can be prepared in good yields which is an omnipresent motif found in many pharmaceuticals, agrochemicals. ^{13}C-labelled DMF and control experiments demonstrate CO gas was released from the carbonyl of DMF with the acid as the promotor. KIE value indicates that C-H activation step may was not involved in the rate-determining-step. This methodology shows broad substrate scope with good to excellent yields and as well operational simple.

Summary: **Contributions**

In this paper, I planned, performed and analyzed most experiments for this manuscript. I have done the major part of writing of the manuscript. My contribution as co-author of this paper is approximately 65%.

3.11 Palladium- Catalyzed Carbonylative C-H Activation of Arenes with Norbornene as the Coupling Partner

Jianbin Chen, Kishore Natte, and Xiao-Feng Wu*

Submitted, **2015**

Summary: An interesting transformation on palladium-catalyzed carbonylative C-H activation of arenes with norbornene as the coupling partner has been developed. By applying molybdenum hexacarbonyl ($Mo(CO)_6$) or paraformaldehyde as the solid CO sources, various 5-(pyridin-2-yl)-hexahydro-7,10-methanophenanthridin-6(5*H*)-ones were produced in moderate yields in the presence of palladium. Interestingly, when DDQ was applied the oxidant, the product was over oxidized to the corresponding 5-(pyridin-2-yl)-tetrahydro-7,10-methanophenanthridin-6(5*H*)-one.

Contributions

In this paper, I planned, performed and analyzed most experiments for this manuscript. I have done the major part of writing of the manuscript. My contribution as co-author of this paper is approximately 90%.

Jianbin Chen

Curriculum Vitae

Personal details

Name	Jianbin
Surname	Chen
Place and Date of Birth	Shandong, P. R. China, 08/11/1986

Education

10/2013 – 11/2015 **Research Doctorate**

Leibniz-Institute for Catalysis at the University of Rostock

Topic: *Palladium-Catalyzed Heterocycles Synthesis via Carbonylative Activation of Ar-X and Ar-H Bonds*

Supervisor: Prof. Dr. Matthias Beller

09/2010 – 07/2013 **Master of College of Chemistry & Materials Engineering, Wenzhou University**, Wenzhou, P. R. China.

Topic: *Transition metal-catalyzed desulfitative cyanation and formylation reaction*

Supervisor: Prof. Dr.Jiang Cheng

09/2006 – 07/2010 **Bachelor of Dept. of Chemistry, Xinzhou Normal University**, Xinzhou, P. R. China

Award

2013	Leibniz Scholarship in Leibniz Institute for Catalysis
2012	University Students' Scientific Innovation Foundation of Zhejiang Province
2011	Second Prize of Wenzhou University Scholarship
2010	Excellent Graduation Thesis, Xinzhou Normal University
2008	Excellent Leader of the Communist Youth League of China in Xinzhou
2008	Excellent pacesetter who volunteer to be a teacher in the mountain villages
2007	National Encouragement Scholarship, Xinzhou Normal University
2007	Silver Medal in Men's 800 Meters, Xinzhou Normal University
2006	First Prize of Xinzhou Normal University Scholarship

Working experience

01/2008-07/2008 Teacher of Daifang Primary School Class 4, Xinzhou

Research experiences

10/2013-11/2015 **Doctoral research experiences**

1 Development of the carbonylative reactions towards heterocycles synthesis

2 Design and synthesis of biologically relevant heterocyclic compounds (Quinazolinones, Quinolines, Indoles, Pthalimides, Isoindolones, etc.)

3 Exploring of new C-H carbonylation reactions

4 Development of new CO surrogates

5 Development of the carbonylative annulation reactions

6 Experience with transition-metal-catalyzed C-H Activations

7 Synthesis of fine chemicals *via* ruthenium-catalyzed hydrogen-borrowing reactions

09/2010-07/2013 **Master research experiences**

8 Development of tertiary amine with water as the formylation sources

9 Development of desulfitative cynation

10 Design and Development of tertiary amine and ammonium as the safety CN sources

Relevant skills

Experimental: Proficient with the construction and operation of Schlenk system as well as high pressure equipment (i.e. different scale of autoclaves), experience in handling air and water-sensitive chemicals and purification of organic materials
Technical: Skilled in operation and analysis of some analytical instruments, for example NMR, GC-MS, IR, and HPLC
IT: Excellent ability with MS Office, Origin, experienced in the use of SciFinder, Reaxys database, NMR Topspin, Chemdraw etc and various graphic application tools

List of Publications

[1] **Jianbin Chen**, Kishore Natte, Anke Spannenberg, Helfried Neumann, Peter Langer, Matthias Beller, and Xiao-Feng Wu Base-Controlled Selectivity in the Synthesis of Linear and Angular Fused Quinazolinones by a Palladium-Catalyzed Carbonylation/Nucleophilic Aromatic Substitution Sequence A*ngew. Chem. Int. Ed.* **2014**, *53*, 7579-7583. ***'Highlighted in synfacts 2014, 10(8), 0802'***

[2] **Jianbin Chen**, Kishore Natte, Anke Spannenberg, Helfried Neumann, Matthias Beller, and Xiao-Feng Wu Palladium-Catalyzed Carbonylative [3+2+1] Annulation of N-Aryl-pyridine-2-amines with Internal Alkynes via C-H Activation: Facile Synthesis of 2-Quinolinones *Chem. Eur. J.* **2014**, *20*, 14189-14193. ***Most accessed article in October 2014****.*

[3] **Jianbin Chen**, Kishore Natte, Helfried Neumann, and Xiao-Feng Wu Palladium-Catalyzed Carbonylative Reactions of 1-Bromo-2-fluorobenzenes with Various Nucleophiles: Effective Combination of Carbonylation and Nucleophilic Substitution *Chem. Eur. J.* **2014**, *20*, 16107-16110.

[4] **Jianbin Chen**, Lin He, Kishore Natte, Helfried Neumann, Matthias Beller and Xiao-Feng Wu Palladium@Cerium(IV) oxide-Catalyzed Oxidative Synthesis of *N*-(2-Pyridyl)Indoles via C-H Activation Reaction *Adv. Synth. Catal.* **2014**, *356*, 2955-2959. *'**Highlighted in synfacts 2015, 11(2), 0217'***

[5] **Jianbin Chen**, Kishore Natte, Anke Spannenberg, Helfried Neumann, Matthias Beller and Xiao-Feng Wu Efficient palladium-catalyzed double carbonylation of *o*-dibromobenzenes: synthesis of thalidomide *Org. Biomol. Chem.* **2014**, *12*, 5578-5581. ***'Selected as inside cover picture'***

[6] **Jianbin Chen**, Helfried Neumann, Matthias Beller and Xiao-Feng Wu Palladium-catalyzed synthesis of isoindoloquinazolinones via dicarbonylation of 1,2-dibromoarenes *Org. Biomol. Chem.* **2014**, *12*, 5835-5838.

[7] **Jianbin Chen**, Kishore Natte, Helfried Neumann and Xiao-Feng Wu A convenient palladium-catalyzed carbonylative synthesis of quinazolines from 2-aminobenzylamine and aryl bromides *RSC Adv.,***2014**, *4*, 56502-56505.

[8] **Jianbin Chen**, Kishore Natte, Xiao-Feng Wu Convenient palladium-catalyzed carbonylative synthesis of caprolactam and butyrolactam derived phthalimides and amides by using DBU and DBN as the nitrogen source *Tetrahedron Lett.* **2015**, *56*, 342-345.

[9] **Jianbin Chen**, Kishore Natte, Nikki Y. T. Man, Scott G. Stewart, Helfried Neumann, and Xiao-Feng Wu Convenient copper-mediated Chan-Lam coupling of 2-aminopyridine: facile synthesis of *N*-arylpyridin-2-amines, *Tetrahedron Lett.* **2015**, *56*, 4843-4847.

[10] **Jianbin Chen**, Jian-Bo Feng, Kishore Natte, Helfried Neumann, Matthias Beller and Xiao-Feng Wu Palladium-Catalyzed Carbonylative Cyclization of Arenes *via* C-H Bond Activation with DMF as the Carbonyl Source, *Chem. Eur. J.* **2015**, *21*,1–5.

[11] **Jianbin Chen**, Kishore Natte, and Xiao-Feng Wu Pd/C-catalyzed carbonylative C–H activation with DMF as the CO source, *Tetrahedron Lett.* **2015**, *56*, 6413-6416.

[12] **Jianbin Chen**, Kishore Natte, and Xiao-Feng Wu Palladium-Catalyzed Carbonylative C-H Activation of Arenes with Norbornene as the Coupling Partner **2015,** *Submitted*

[13] **Jianbin Chen**, Helfried Neumann, Matthias Beller, and Xiao-Feng Wu Tansition-Metal-Catalyzed Heterocyclic Synthesis *via* Carbonylative C-H Activation Book chapter, **2015** *Submitted*

[14] Kishore Natte, **Jianbin Chen**, Haoquan Li, Helfried Neumann, Matthias Beller, and Xiao-Feng Wu Palladium-Catalyzed Carbonylation of 2-Bromoanilines with 2-Formylbenzoic Acid and 2-Halobenzaldehydes: Efficient Synthesis of Functionalized Isoindolinones *Chem. Eur. J.* **2014**, *20*, 14184-14188. ***'Hot paper'***

[15] Kishore Natte, **Jianbin Chen**, Helfried Neumann, Matthias Beller and Xiao-Feng Wu Palladium-catalyzed oxidative carbonylative coupling of arylboronic acids with terminal alkynes to alkynones *Org. Biomol. Chem.* **2014**, *12*, 5590-5593.

[16] Muhammad Sharif, **Jianbin Chen**, Peter Langer, Matthias Beller and Xiao-Feng Wu TBAI-catalyzed oxidative synthesis of benzamides from acetophenones and carbinols *Org. Biomol. Chem*.,**2014**, *12*, 6359-6362.

[17] Lin He, Haoquan Li, **Jianbin Chen** and Xiao-Feng Wu Recent advances in 4(3*H*)-quinazolinone syntheses *RSC Adv.*, **2014**, *4*, 12065-12077.

Master Degree:

[18] **Jianbin Chen**, Yang Sun, Bin Liu, Dongfang Liu and Jiang Cheng. The palladium-catalyzed desulfitative cyanation of arenesulfonyl chlorides and sodium sulfinates. *Chem. Commun.*, **2012**, *48*, 449-451.

[19] **Jianbin Chen**, Bin Liu, Dongfang Liu and Jiang Cheng. The copper-catalyzed C3-

formylation of indole C-H bonds using tertiary amines and molecular oxygen. *Adv. Synth. Catal.*, **2012**, *13*, 2438-2442.

[20] Xinyi Ren, **Jianbin Chen,** Fan Chen and Jiang Cheng. The palladium-catalyzed cyanation of indole C-H bonds with the combination of NH_4HCO_3 and DMSO as a safe cyanide source. *Chem. Commun.*, **2011**, *47*, 6725-6727.

[21] Guoying Zhang, Xinyi Ren, **Jianbin Chen,** Maolin Hu and Jiang Cheng. Copper-mediated cyanation of aryl halide with the combined cyanide source. *Org. Lett.* **2011**, *13*, 5004-5007.

[22] Bo Zhang, Bin Liu, **Jianbin Chen**, Jiehui Wang, Miaochang Liu I_2-mediated C3-formylation of indoles by tertiary amine and H_2O *Tetrahedron Lett.* **2014**, *55*, 5618-5621.

[23] Bin Liu, Jiehui Wang, Bo Zhang, Yang Sun, Lei Wang, **Jianbin Chen** and Jiang Cheng. Copper-mediated C3-cyanation of indoles by the combination of amine and ammonium. *Chem. Commun.* **2014**, *50*, 2315-2317.

Conference participations

[1] **Poster** 'Palladium-Catalyzed Annulations of *N*-Aryl-pyridine-2-amines *via* C-H Activation'

Jianbin Chen, Helfried Neumann, Matthias Beller, and Xiao-Feng Wu

at 2nd International Symposium on C-H Activation, June 30-July 3, **2014**, Rennes, France.