Leibniz-Institut für Katalyse e.V.

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Studies Towards Radical and Metalhydride Mediated Carbonylation Reactions

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„Ich muss Sie leider verhaften. Wollen Sie Ihren Sherry noch austrinken?“

- Columbo

“All life is problem solving”

- Karl Popper

Acknowledgement

I am fortunate to have had the privilege of doing my graduate work in three different research groups at three different universities. There is no better way to gain insight into how other people work. I am grateful to my teachers Jens, Manuel, and now Xiao-Feng, for giving me a chance. A constant in my path as a chemist has been my unparalleled parents. They have supported me in every endeavor I have undertaken from the beginning and made this work possible in the first place. I have always been interested in nature and all things scientific, so my parents bought me "Was ist was”-books, other booklets and tapes about dinosaurs, and other fitting literature. Now I am an adult, or at least the age of an adult, and I am writing my doctoral thesis at an institute. So, the books have paid off!

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Abstract

Studies Towards Radical and Metalhydride Mediated Carbonylation Reactions

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In this dissertation, we mainly demonstrate the reactivity of various carbon and nitrogen centered radicals. First, a new method on Mn-catalyzed ring-opening carbonylation of cyclobutanols is introduced. Precious long-chain 1,5-keto esters, which are difficult to access by other methods, could be synthesized. Subsequently, we endeavored to generate chalcones photocatalytically by a carbonylation reaction. However, only the direct coupling reaction of alkenylboronic acids and arenediazonium tetrafluoroborate salts to stilbenes was successful. This was likewise a hitherto unknown method. The reaction procedure is very green (metal- and base-free, with very small amounts of organic dye as catalyst in a mixture of water and ethanol). Hereafter, we report the first Pd-catalyzed oxidative carbonylation in which the oxidant could be completely replaced by visible light. Oxalamides were obtained from the respective amines. Our new approach used a Pd-BINAP complex that could be partially recycled despite homogeneous reaction performance. Control experiments demonstrated the Pd(I), nitrogen radical, the intermediate acyl radical and the formation of hydrogen. Finally, we describe the direct one-step synthesis of valuable ethylene glycol from paraformaldehydes. In the corresponding literature, the reaction conditions were very harsh with pressures above 400 bar and high temperatures. However, under milder conditions, the selectivity was on the side of glycol aldehyde (GA) and the hydrogenation product methanol. In the presence of our Rh-Pincer catalyzed system, we succeeded in direct one-pot synthesis of EG from paraformaldehyde (PFA) at remarkably mild conditions (70 bar, 100 °C) with yields of up to 40%.

Studien zu radikal- und metallhydridvermittelten Carbonylierungsreaktionen

Tim Meyer

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In dieser Dissertation zeigen wir hauptsächlich die Reaktivität verschiedener kohlenstoff- und stickstoffzentrierter Radikale. Zunächst wird eine neue Methode zu Mn-katalysierte ringöffnenden Carbonylierung von Cyclobutanolen eingeführt. Es konnten wertvolle und auf anderem Wege schwer zugängliche langkettige 1,5-Ketoestern synthetisiert werden. Anschließend bemühten wir uns in einer Carbonylierungsreaktion photokatalytisch Chalcone zu generieren. Es gelang jedoch nur die direkte Kupplungsreaktion von Alkenylboronsäuren und Arenediazonium-Tetrafluoroboratsalzen zu Stilbenen. Eine ebenfalls bis dahin unbekannte Methode. Die Reaktionsführung ist äußerst grün (metall- und

basenfrei, mit sehr geringen Mengen organischem Farbstoff als Katalysator in einer Mischung aus Wasser und Ethanol). Hierauf berichten wir über die erste Pd-katalysierte oxidative Carbonylierung, bei der das Oxidationsmittel vollständig durch sichtbares Licht ersetzt werden konnte. Es wurden Oxalamide aus den jeweiligen Aminen gewonnen. Unser neuer Ansatz verwendet einen Pd-BINAP-Komplex der trotz homogener Reaktionsführung teilweise recycelt werden konnte. Kontrollexperimente wiesen die Pd(I), Stickstoffradikal, das intermediäre Acylradikal und die Bildung von Wasserstoff nach. Zum Schluss beschreiben wir die direkte einstufige Synthese von wertvollem Ethylene Glykol aus Paraformaldehyde. In der einschlägigen Literatur waren die Reaktionsbedingungen sehr harsch mit Drücken über 400 bar und hohen Temperaturen. Unter milderen Bedingungen lag die Selektivität jedoch auf der Seite des Glykolaldehyds (GA) und des Hydrierungsprodukts Methanol. In Gegenwart unseres Rh-Pincer-katalysiertem Systems gelang die direkte Eintopfsynthese von EG aus Paraformaldehyd (PFA) bei bemerkenswert milden Bedingungen (70 bar, 100 °C) und mit Ausbeuten von bis zu 40 %.

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List of Abbreviations

1,5 HAT	1,5-hydrogen atom transfer
acac	Acetylacetone
^{t}AmOH	2-Methylbutan-2-ol
Ar	Aryl
B_2pin_2	Bis(pinacolato)diboron
Bu	Butyl
Bn	Benzyl
bpy	2,2'-bipyridine
BHT	Butylated hydroxytoluene
Boc	Butyloxycarbonyl
BQ	1,4-Benzoquinone
cat.	Catalyst
CO	Carbon monoxide
cod	Cycloocta-1,5-diene
$C_6O_6 \cdot 8H_2O$	Hexaketocyclohexane octahydrate
CN	Nitrile
Cy	Cyclohexyl
DCE	1,2-Dichloroethane
DEAD	Diethyl azodicarboxylate
DIAD	Diisopropyl azodicarboxylate
DMAc	Dimethylacetamide
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
dppp	1,3-Bis(diphenylphosphino)propane
DTBP	Di-*tert*-butyl peroxide
E^+	Electrophile
eosin Y	2',4',5',7'-Tetrabromofluorescein
EG	Ethyle glycol
Et	Ethyl
equiv.	Equivalent
GC-FID	Gas chromatograph with flame ionizer
GC-MS	Gas chromatograph with mass spectroscopy
h	Hour
HFIP	Hexafluoroisopropanol
iso or ***i***	Sum of branched products
KIE	Kinetic isotope effect
Me	Methyl
MeCN	Acetonitrile
MeOH	Methanol
mmol	Millimole
NMR	Nuclear Magnetic Resonance
Nu^-	Nucleophile

OA	Oxidative addition
Oct	Octyl
OAc	Acetate
Ph	Phenyl
Pr	Propyl
RE	Reductive elimination
RT	Room temperature
SelectFluor	1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)
SET	Single electron transfer
TEMPO	2,2,6,6-Tetramethyl-1-piperidinyloxy, free radical
TFA	Trifluoroacetic acid
TFE	2,2,2-Trifluoroethanol
TFT	α,α,α-Trifluorotoluene
THF	Tetrahydrofuran
TM	Transition metal
UV	ultraviolet
vis	visible
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

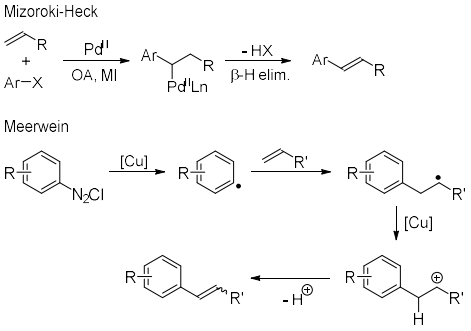
List of Schemes

1. Introduction

For the chemical industry and in everyday laboratory work, the application and development of clean environmentally friendly synthesis methods should be a top priority. In 1998, Anastas and Warner disclosed how best to follow such a guideline in their 12 principles of green chemistry.[1] The fact that carbon monoxide (CO) is a readily available gas and the incorporation of this C1 building block makes it particularly interesting from an atom economy point of view (principle 2). Among the C1 building blocks used, CO is extremely versatile and cost-effective. It can be produced directly from natural gas, coal, and biomass.[2] However, its use in daily laboratory work requires special safety measures and specialization. Therefore, examples of non-industrial application are still relatively rare.

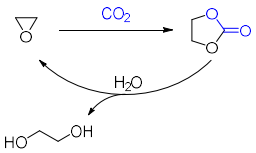
Another aspect is the input of energy necessary for a chemical reaction. The use of a macroscopic element like a heating plate is well established. Particularly attractive and in the focus of science is the inexhaustible, clean, and direct solar energy. Visible light is environmentally friendly and non-hazardous. An overwhelming number of papers have been published describing methods for harvesting visible light for chemical reactions.[3] The present thesis aims to deal with these two areas of research, which are important for the future our planet and to tries ultimately to establish a bridge between them. Thematically, photocarbonylation fits into the topic of radical chemistry since irradiation is a more direct way to generate radicals. Over the last 30 years, radical chemistry has undergone enormous development. A radical reaction often proceeds under comparably mild conditions, has high compatibility with functional groups and protective groups can often be omitted.[4]

The classical Pd-catalyzed Mizoroki-Heck reaction, along with other cross-coupling reactions (such as Negishi and Suzuki), is of outstanding importance to the daily routine of many chemists worldwide. This was confirmed not least by the Nobel Prize in 2010.[5] As early as 1939, Meerwein introduced a method for the arylation of olefins, which could not stand up to these supreme TM-catalyzed C-C couplings (Scheme 1).[6] However, he demonstrated the Cu-catalyzed arylation of olefins with aryl diazonium salts. New discoveries in the field of photocatalysis which mechanistically often proceeds via SET, allowed a revival of this design as there are new possibilities for the activation of aryldiazonium salts.[7] In this thesis, a novel protocol for photocatalytic $C(sp^2)$-$C(sp^2)$ coupling is presented.



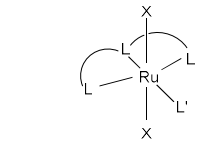
Scheme 1. Mizori-Heck coupling and Meerwein arylation.

Ethylene glycol (EG) is the simplest diol and an exceptionally important compound used in a variety of industrial applications (polyester fibers, antifreeze, and heat-transfer agent).[8] Therefore, the catalytic synthesis of EG from bulk chemicals is of particular interest. The state-of-the-art technology since its development has been the Omega process. In this process, ethylene oxide (EO) is reacted with CO_2 to form ethylene carbonate, followed by selective hydrolysis to EG (Scheme 2). Due to the industrial importance and established status of this process, many efforts have been made to further improve the synthesis method.[9] The EO is commercially produced from ethylene, which was originally derived from fossil fuels. In terms of sustainability and green chemistry, a method from other bulk chemicals or directly from syngas would be very interesting.[9b]



Scheme 2. OMEGA process by Shell company.

Shaw's pioneering work in 1976 introduced a powerful tool to activate inert bonds via a hydrogenation reaction using tridentate Pincer ligands.[10] In the context of this thesis, an attempt was made to develop a direct synthesis of EG from the C1 building block formaldehyde using this new but thoroughly studied tool. Pincer ligands are highly modifiable in structural and electronic terms. This allows the selective activation of bonds. Pincer ligands and precursors are now often commercially available, which facilitates their use in the laboratory.[11] A schematic representation for established Ru pincer complexes is shown below (Scheme 3).

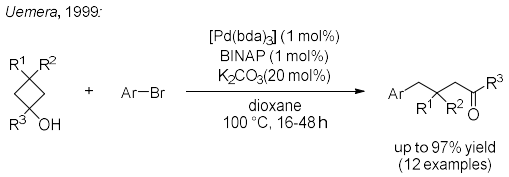


L (neutral) = PR_2, NR_2, OR, :C (NHC), e.g.
X (anionic) = H, Cl, Br, NR_2 e.g.

Scheme 3. Typical Ru pincer complexes.

1.1 Ring-Opening Functionalization of Cyclobutanols

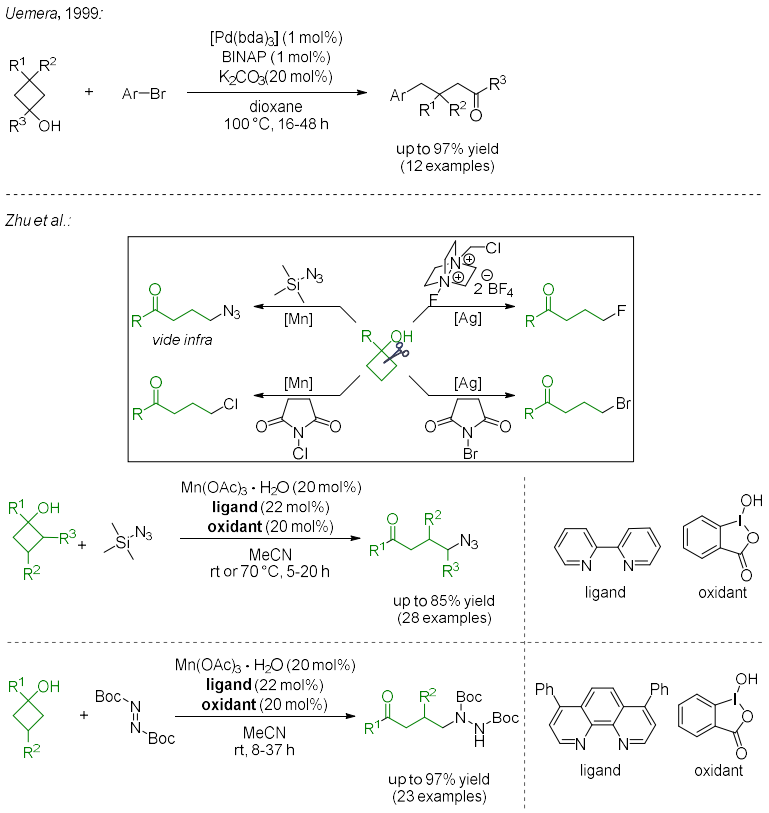
Radical reactions are now a popular method for forming C-C and C-heteroatom bonds. Sterically overloaded quaternary centers are also accessible to them. Under mild reaction conditions, extra introduction of protecting groups is rarely necessary.[12] Our group has a strong background in the field of C centered radicals. The first objective of this PhD thesis was the investigation of C-centered radicals and their application in carbonylation reactions. Cyclopropane rings are prone to ring-opening reactions.[13] The ring tension of cyclopropanes is only slightly higher than the one of cyclobutane with 1 kcal mol^{-1} difference in strain energy and about 10 kcal mol^{-1} for the C-C bond tension.[14] Consequently, efforts were made to develop ring-opening reactions of cyclobutanes. More than 30 years ago, the Uemura group succeeded in the Pd-catalyzed oxidative ring cleavage of *tert*-cyclobutanols in an oxygen atmosphere (Scheme 4).[15]



Scheme 4. Pd-catalyzed ring-opening of cyclobutanols by Uemura group.

More recently reported methods often proceed via a radical mechanism. In this context, the versatile ring-opening functionalization to γ-substituted ketones was achieved by Ren and Zhu. Fluorination proceeded smoothly in the presence of catalytic amounts of $AgBF_4$ and stoichiometric amounts of SelectFluor.[16] Bromination proceeded Ag-catalyzed using *N*-bromosuccinimide (NBS). Similarly, chlorination and azidation are carried out under a protocol using cheap and abundant 3d metal catalyst

Mn.[16-17] The obtained alkyl azides deserve special mention here, as they are a precursor for significant powerful organic transformations.[18] Moreover, the ring-opening hydrazination to alkyl hydrazines was achieved. These products were readily turned into pyridazines by treatment with hot acetic acid.[19] The individual reaction pathways are shown in Scheme 5.

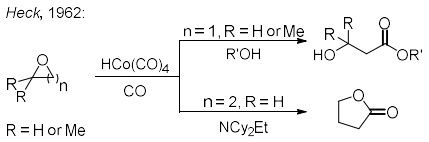


Scheme 5. Summary of radical ring-opening functionalization of cyclobutanols.

1.1.1 Ring-Opening and Ring-Expanding Carbonylations

The previous chapter explained that small ring systems (three- and four-membered rings) are a privileged substrate for C-C bond cleavage since the released ring strain energy can be used to cleave the bond. Heck was the first to come up with the idea of using this property in carbonylation in 1962.[20] His Co-carbonyl anion promoted protocol was a milestone in carbonylation chemistry and has inspired many working groups. As shown in Scheme 6, the Co-carbonyl anion was able to form a Co-acyl intermediate in the presence of the epoxides (n = 1) and oxetanes (n = 2) used, under ring opening.

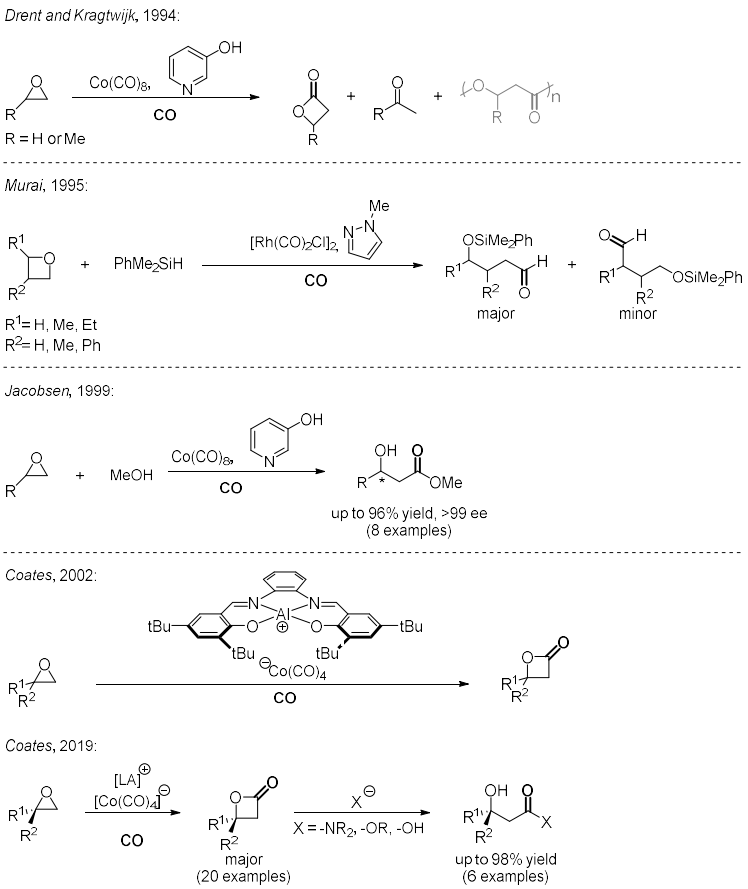
Moreover, he already provided considerable evidence on the mechanism of the reaction. Depending on n and the reagents used, either β-hydroxy esters or γ-lactones were formed. In addition to polymerization, which is not discussed here, there is ring-opening carbonylation and carbonylative ring expansion.



Scheme 6. Pioneering work on the carbonylation of three- and four-membered ring.

30 years later, Drent and Kragtwijk reported on the catalytic synthesis of β-lactones.[21] $Co(CO)_8$ was the catalyst and in the presence of catalytic amounts of 3-hydroxypyridine (3-HP), β -lactones, and with different reaction parameters (longer reaction time, higher temperatures) polymers could be obtained (Scheme 7). One year later Murai and co-workers demonstrated the activity of Rh-amine catalysts in the silylformylation of four-membered ring oxetanes. *N*-methylpyrazole was used as a co-catalyst to obtain γ-siloxy aldehydes. The protocol was compelling for its regioselectivity (95%) for the insertion of CO. Up to 83% Yields for the shown major product was obtained.[22]

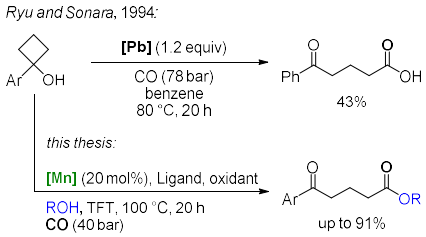
In 1999, the Jacobsen group succeeded in adapting the Drent system to the carbomethoxylation of enantiomerically pure terminal epoxides.[23] The reaction was highly selective (> 99% ee) for the linear hydroxy ester. The yields were also particularly good in nearly all cases (> 90%). The absolute configuration was preserved. Three years later, Coates group showed that a self-designed LA (Lewis acid) co-catalyst, enabled carbonylation with superior reactivity and selectivity for β-lactones to nearly quantitative yields.[24] There are constantly new efforts in this area of research. Thus, most recently, the same group reported on the carbonylation of 2,2-disubstituted epoxides. Regioselectively, β,β-disubstituted β-lactones were obtained.[25] They established a new route to ketone-aldol products and displayed that enantiomerically pure epoxides undergo the carbonylation/ring opening process while retaining stereochemistry, giving enantiomerically pure β-hydroxy esters.



Scheme 7. Historical context (selected examples) for the carbonylation of three- and four-membered rings.

In summary, the synthetic toolbox for the ring opening of three- (and four-) membered rings has broadened in recent decades. More recently comprehensive work on radical ring openings was published by the Zhu group. In the field of carbonylation, Heck's original reaction, the anion-catalyzed ring opening of epoxides and oxetanes, is the starting point. Our interest was to bring the novel insights on cheap and earth-abundant Mn-catalyzed radical ring opening into the research field of carbonylation.

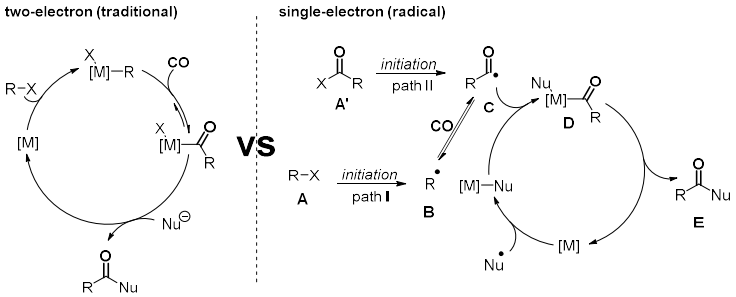
In the framework of this thesis, we have achieved this goal with the Mn-catalyzed ring-opening carbonylation of cyclobutanol derivatives.[26] To the best of our knowledge, the only comparable protocol was published by Ryu and Sonada. Here the carbonylation could only be realized using superstoichiometric $Pb(OAc)_4$ (LTA, 1.2 equiv) as single electron oxidation system and catalyst in benzene.[27] LTA is a toxic chemical as well as benzene and they should be avoided from a green chemistry point of view. Moreover, only low selectivity and yields were achieved. Our new Mn-catalyzed method for the preparation of 1,5-ketoesters could overcome the mentioned drawbacks (Scheme 8).



Scheme 8. Summary of radical ring-opening functionalization of cyclobutanols.

1.2 Radical Carbonylation Reactions

Our established method (Scheme 8) is part of 3d metal-catalyzed radical carbonylation reactions. Although examples for these metals have been reported,[28] noble metals are typically used in carbonylation reactions. Here, the established Pd-catalyzed carbonylative C-C coupling (adapted Heck-, Suzuki-, Sonogashira-) as well as the formation of esters and amides via C-X coupling of organohalides with nucleophilic alcohols/amines (Pd, Ir, Rh) should be mentioned.[29] As well as the mainly Rh-catalyzed hydroformylation. Mechanistically, these methods have two-electron processes in common. A typical catalytic cycle is shown below (Scheme 9, left), it always includes an OA and RE step. There is a preference for coupling partners with C(sp^2)-hybridized C atoms. However, activation of C(sp^3)-hybridized coupling partners is slower via OA. Moreover, there is β-hydrogen elimination as an undesired competitive reaction which is accelerated by open coordination sites on the catalyst.[30]



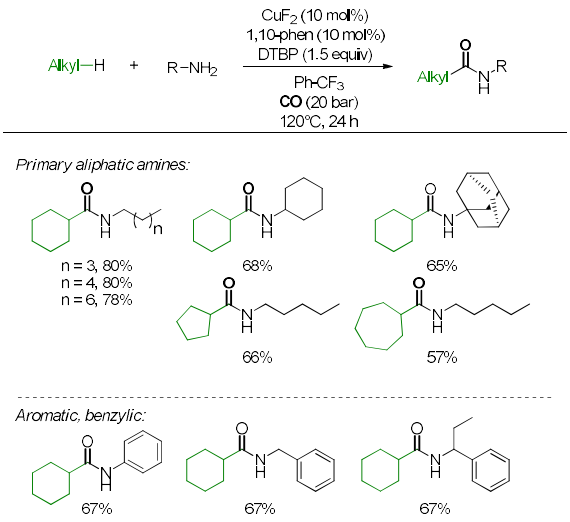
Scheme 9. Typical two-electron carbonylative coupling vs radical SET coupling.

Radical carbonylations can be catalyst-induced, oxidant-induced, or photo-induced.[31] 3d-Metals have the tendency to form polycarbonyls under CO atmosphere,[28a] thus the development of radical

methods based on a SET is difficult and the field of research is rather limited. In the above shown Scheme 9 (right side) a typical catalytic cycle is shown. An alkyl radical **B** is generated via metal-mediated SET, hydrogen/halogen atom abstraction, radical chain reaction, or light-induced (noted as initiation) from substrate **A**. In the presence of CO, the acyl radical is reversibly formed. Alternative pathways are also known (path ii). Acyl radical **C** attaches to the metal and generates a highly valent metal-acyl intermediate **D**, which reacts via RE to form the product **E** under regeneration of the catalyst. The involved metal-alkyl intermediate prevents side reactions (as β-hydride elimination) and the SET sequence allows cleavage of previously unexploited bonds. The extensive theoretical and experimental work supporting the proposed catalytic cycle was mainly provided by the Ryu group.[32]

1.2.1 Oxidant Initiated Radical Carbonylations

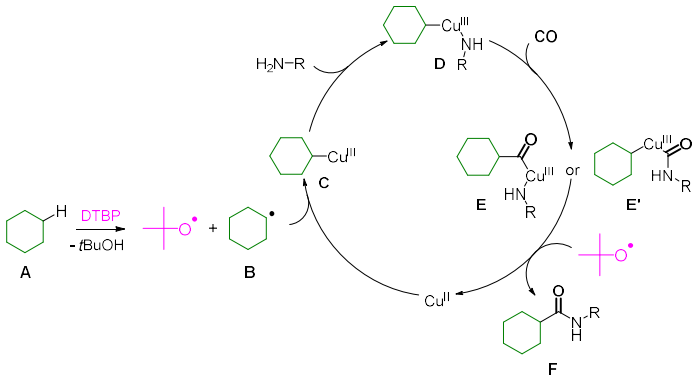
In 2016, our group succeeded in the Cu-catalyzed direct synthesis of aliphatic amides from alkanes and amines. This added a fundamental tool to the field of non-noble catalyzed alkoxycarbonylation of C(sp^3)-H bonds. Stoichiometric amounts of DTBP were necessary for the performance of the reaction.[33] Two years later, a similar protocol with alcohols as nucleophiles was also realized.[34]



Scheme 10. Cu-catalyzed radical carbonylation of alkanes with primary amines.

Mechanistically, a homolytic cleavage of DTBP takes place, then a hydrogen atom is abstracted from substrate **A** to the alkyl radical **B**. This adds to the Cu-(II) catalyst. This would form the Cu(III) complex **C**,

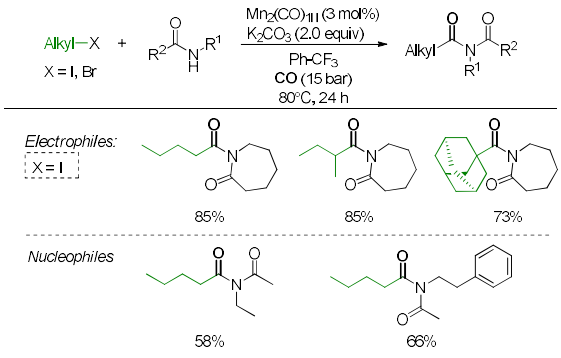
which undergoes X ligand exchange with nucleophilic amines to give **E** or **E'**. Subsequent RE releases carbonylated amide product **F**, the Cu(I) intermediate will immediately be oxidized to Cu(II) by the oxygen radical.



Scheme 11. Mechanism of Cu-catalyzed radical carbonylation of alkanes with primary amines.

1.2.2 Metal Initiated Radical Carbonylations

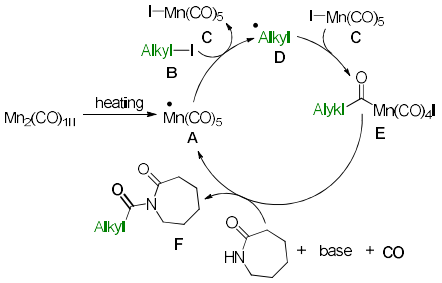
Recently, our group reported a protocol for the Mn-catalyzed carbonylation of alkyl iodides and bromides with amides.[35] The reaction proceeded in the absence of costly ligands and additives.



Scheme 12. Mn-catalyzed radical carbonylative coupling of alkyl iodides with amides.

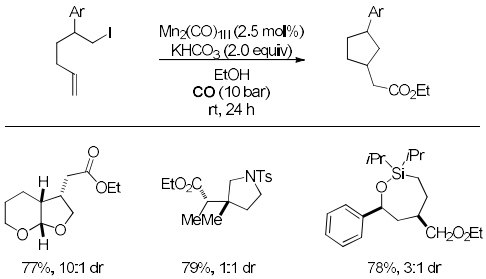
Mechanistically, it has been proposed that there is a thermally induced cleavage of the Mn-Mn bond of $Mn_2(CO)_{10}$. This would produce two radicals **A**. The alkyl iodide **B** abstracts an iodine radical to

generate an alkyl-centered radical **D**. In this step, I-Mn(CO)$_5$ (**C**) is formed, which undergoes a carbonylation to form acyl-Mn intermediate **E**. In the presence of an amide, **E** could now react further to form the desired product **F**.



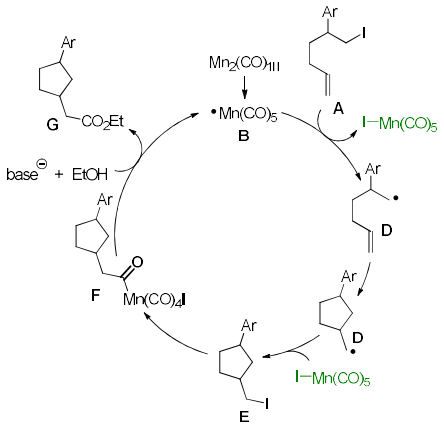
Scheme 13. Mechanism of Mn-catalyzed radical carbonylative coupling of alkyl iodides with amides.

Pioneers in this area were Heck and Breslow, who described the polycarbonyl anion catalyzed carboyxalkylation of alkyl iodides by Co and Mn as early as 1963.[36] More recently, Alexanian *et al.* succeeded in the Mn-catalyzed carboacylation of alkenes with alkyl iodides and CO to cyclic esters. Under mild conditions primary and secondary alkyl iodides could be used and five-, six- and seven-membered ring compounds could be synthesized.[37]



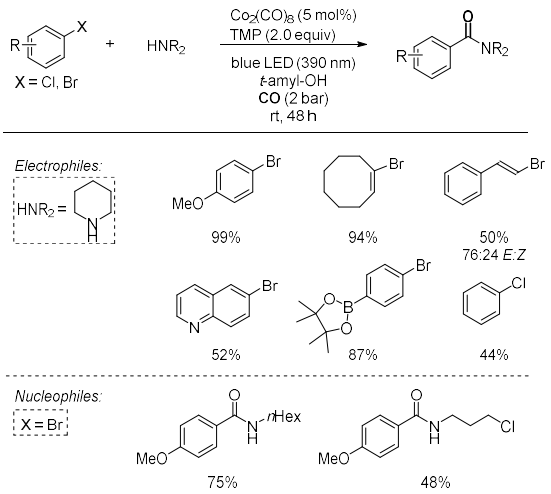
Scheme 14. Radical Mn-catalyzed carboacylations of alkenes with alkyl iodides.

In the mechanism provided, homolysis of $Mn_2(CO)_{10}$ to the radical starter $[Mn(CO)_5]^{\cdot}$ also occurs as the initial step. By abstracting the iodine atom from substrate **A**, a carbon-centered radical **B** is then formed. This cyclizes to an intermediate **D**. Transfer of the iodine atom followed by carbonylation would generate intermediate **F**. In the presence of a base and ethanol, product **G** is formed.



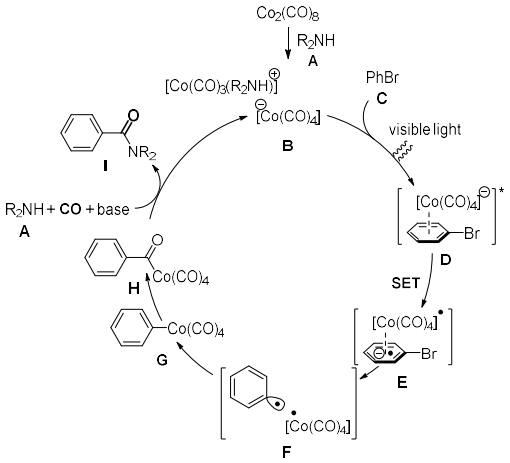
Scheme 15. Mechanism of Radical Mn-catalyzed carboacylations of alkenes with alkyl iodides.

Very recently, the same group developed an adapted protocol for the cobalt-catalyzed aminocarbonylation of aryl halides (sp^2 electrophiles) to amides.[38] The radical nature of the reaction allows it to be promoted by visible light (390 nm), which significantly increase the efficiency (<2% yield instead of 99% for the model reaction in the absence of light after 48 h). The mechanistic details of this new reaction have not yet been elucidated. A photochemical charge transfer of the donor-acceptor complex is thought to take place, involving the sp^2 electrophile and $Co(CO)_4^-$. UV-vis spectroscopic measurements revealed that the Co anion in the presence of bromobenzene shows a new absorption peak at λ=275 nm. This also supports a light-promoted activation. This work represents a crossover between the classification in metal initiated radical carbonylation by cobalt and photocatalysis.



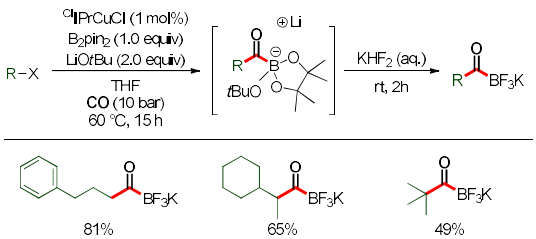
Scheme 16. Co-catalyzed aminocarbonylation of aryl halides mediated by visible light.

It was proposed that the reaction undergoes a light-promoted intermolecular charge transfer involving a donor-acceptor complex of substrate and cobaltate in the key activation step. $Co_2(CO)_8$ would disproportionate to the cobaltate anion **B** by addition of the amine **A**. It adds to the electrophile **C** followed by a reversible light-promoted charge transfer of the donor-acceptor complex shown (**D**, **E**). Loss of bromine in an $S_{RN}1$ mechanism gives radical couple **F**. Recombination leads to intermediate **G**. Subsequent CO migration insertion would generate an acyl-Co species **H**, which is then substituted by an amine to give the product **I** to.



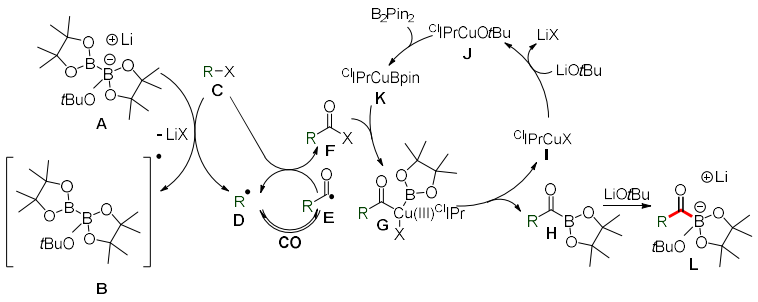
Scheme 17. Mechanism of Co-catalyzed aminocarbonylation of aryl halides mediated by visible light.

Very recently, Mankad group achieved a breakthrough in generating the highly elusive acylboron compounds if generated by carbonylation.[39] The acylborons were made *via* Cu-catalysis from alkyl halides. Radical atom transfer carbonylation (ATC) mechanism was a key step of this reaction.



Scheme 18. Acylboron compounds via Cu-catalyzed carbonylative borylation of alkyl halides.

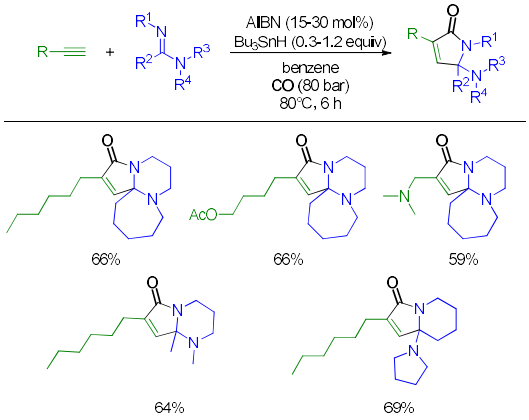
Mechanistically, LiO*t*Bu with B_2pin_2 would generate the tetra-alkoxy diboron compound **A**. This can reduce the alkyl halide **C** in a SET. The free alkyl radical **D** is known to further react with CO to form the acyl radical **E**. The resulting acyl halide **F** can continue the radical chain. Subsequently, in an OA, with the boryl-Cu complex **K**. Then, the oxidative addition of acyl halide **F** to the boryl copper **K** forms the Cu(III) complex **G**. RE gives the acyl borone **H**, which further combines with a LiO*t*Bu to give the much more stable and isolable tetracoordinated boron complex **L**.



Scheme 19. Mechanism to the acylboron compounds via Cu-catalyzed carbonylative borylation of alkyl halides.

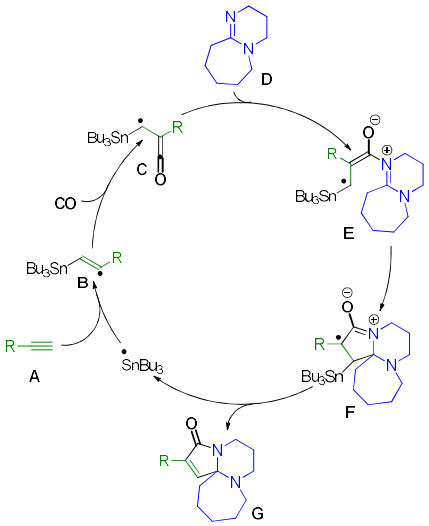
1.2.3 Radical Chain Initiated Carbonylations

In 2013, the Ryu group reported radical-mediated [2 + 2 + 1]-cycloaddition reaction of acetylenes with amidines in the presence of CO. In a radical chain reaction, α,β-unsaturated lactams were obtained.[40]



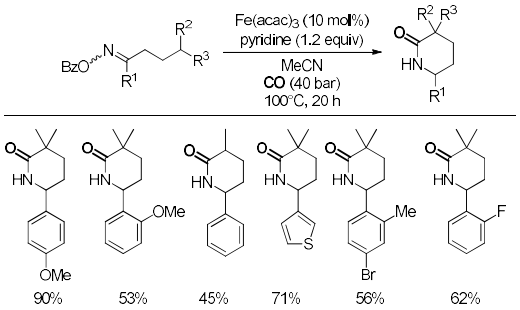
Scheme 20. Radical [2 + 2 + 1] cycloaddition of acetylenes, amidines, and CO to generate α,β-unsaturated lactams.

According to their suggested reaction mechanism, alkyne **A** would generate a,β-stannylated vinyl radical **B**. Subsequent carbonylation. generates α-ketenyl radical **C**. The intermolecular scavenging of which with amidine **D**, provides intermediate **E**. Subsequent 5-endo-cyclization of gives intermediate **F**, which after a β-cleavage gives lactam product **G**.



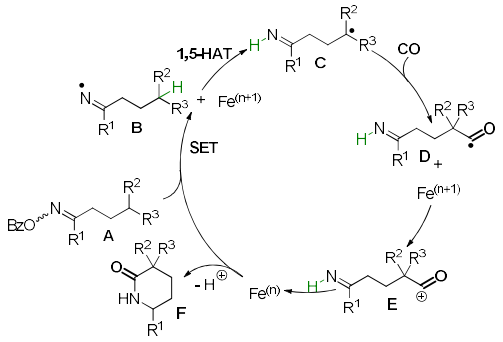
Scheme 21. Mechanism of the Radical [2 + 2 + 1] cycloaddition of acetylenes, amidines, and CO to generate α,β-unsaturated lactams.

Our group recently succeeded in the Fe-catalyzed carbonylation of tertiary carbon radicals: synthesis of lactams.[41]



Scheme 22. Carbonylation of tertiary carbon radicals for the synthesis of lactams.

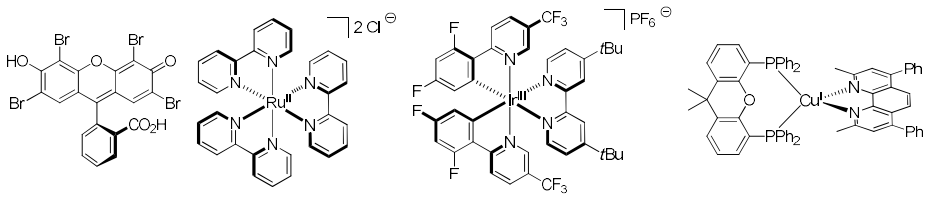
Mechanistically, the o-benzyloxime substrate **A** is converted to the iminyl radical **B** by a low valent Fe species in a SET. **B** undergoes a 1,5-HAT to form a new carbon-centered radical **C**. After CO addition to **C**, the Fe(n+1) is reduced back to Fe(n) and carbocation **E** is formed. An intramolecular ring closure and isomerization of the double bond gives the lactam **F**.



Scheme 23. Mechanism for the carbonylation of tertiary carbon radicals for the synthesis of lactams.

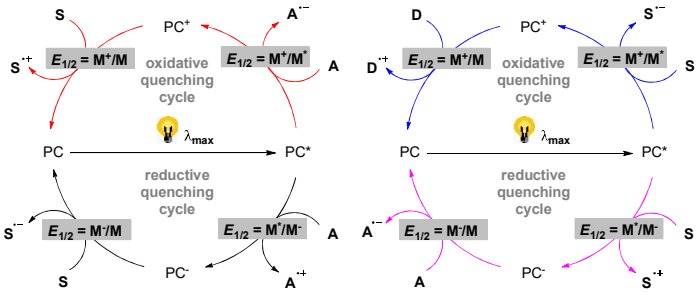
1.3 Photocatalysis

Ciamician's article from 1912 started with the words "Modern civilization is the daughter of coal, ..." followed by discussions on how to harness the sheer endless solar energy.[42] The topic is red-hot, nowadays politics still deals with the change to renewable energies. While nature has already perfected photosynthesis and provides energy for life on earth, there are still huge development potentials for chemical reactions in the laboratory and in industry. However, significant advances in photocatalysis have already been made.[3b, 3d, 43] The general goal of this research area is to develop new activation modes for small molecules. Historically, attempts have been made to directly excite target molecules. Required for an absorption in the visible spectrum is the chromaticity of the reacting compounds. Most organic molecules absorb only UV radiation (250-300 nm) and therefore photocatalysts (PC) are needed.[3b] PC are metal complexes or organic dyes which mechanistically undergo single electron transfer (SET) with the organic substrate after photoexcitation. Highly prominent are eosin Y and polypyridine complex of Ru(II), Ir(III), or Cu(I) complexes (Scheme 24, from left to right). The redox potentials must be matched to the substrate to cause reduction or oxidation.



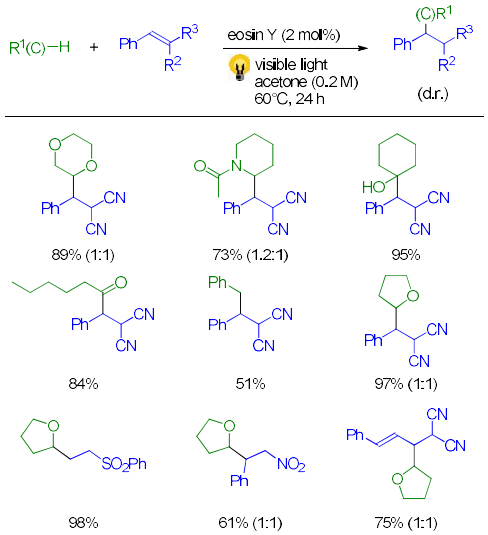
Scheme 24. Examples of photocatalysts.

In a photoredox catalyzed transformation of a substrate S, there are two possible pathways for the transition from PC to excited PC* after irradiation with wavelength of maximum absorption λ_{max}. If a sacrificial electron donor is present, then it is acting as a reductive quencher of PC* (Scheme 25, black path), PC^- is generated. In a reductive quenching cycle, the reduced PC can then transfer an electron to S. This results in the anion radical $S^{\bullet-}$, which is available for subsequent transformations. If the PC can react with a sacrificial electron acceptor, then in an oxidative quenching cycle, is oxidized to PC^+ and then reduced by S under regeneration of the catalytic cycle and a radical cation $S^{\bullet+}$ is released, this can react with a radical trap (red path). On the right side of the scheme, the second case is shown. Here S, as quenching reductant, can transfer an electron to the PC* so that PC^- is formed. The oxidized $S^{\bullet+}$ can then participate in radical transformations. Regeneration occurs with a sacrificial electron acceptor A (pink path). If PC transfers an electron to S, then it is oxidized to PC^+. In the presence of a sacrificial electron donor D, the reduced $S^{\bullet-}$ can undergo radical transformations and PC can be regenerated (blue path). Not shown here, it is also possible to perform photocatalysis without sacrificial electron acceptors or donors. A back electron transfer of the electron from a formed intermediate to the catalyst takes place.[3d, 44]



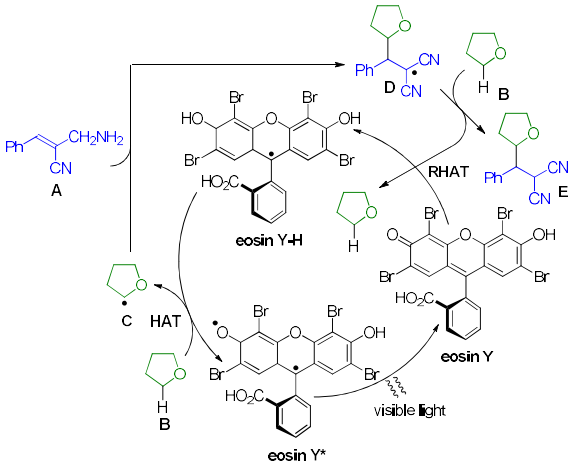
Scheme 25. Photocatalysis: oxidative and reductive quenching cycle.

Eosin Y is an organic dye and a well-known cost-effective alternative to metal catalysts in visible light.[45] Recently, Wu group described its properties as a direct hydrogen atom transfer catalyst for C-H activation. This opens up many new possibilities for the functionalization of native C-H bonds and makes the scope for eosin Y photocatalysis even broader.[46]



Scheme 26. Photocatalysis: eosin Y as HAT Photocatalyst for the functionalization of C–H bonds.

Mechanistic reasoning is shown below explaining the RHAT.



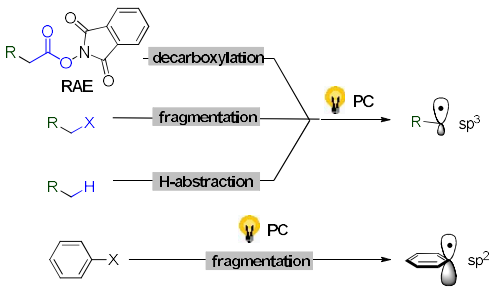
Scheme 27. Mechanism for eosinY as HAT Photocatalyst for the functionalization of C–H bonds.

In this dissertation, an attempt was made to establish a protocol for the three-component coupling reaction between an aryl radical, which is readily accessible via photocatalysis with eosin Y (starting from aryldiazonium salt), an alkene as nucleophile, and CO. However, direct C-C coupling was preferred under all reaction conditions. Fortunately, the photocatalytic cross-coupling of alkenyl boronic acids and arenediazonium tetrafluoroborates was yet unknown.[47] Our protocol fits into the range of Meerwein arylations which is known to proceed Cu, Fe (II), and iodine catalyzed. However, yields were low and byproducts were formed. These drawbacks led to the neglect of Meerwein arylation in organic synthesis.

In recent years, the König group has made significant progress in the photocatalytic version of the Meerwein reaction.[48]

1.3.1 Formation of C-Centered Radicals

Interesting with respect to their efficiency of addition to unsaturated systems, such as olefins and arenes, are the sp^3 hybrid carbon radicals, which are particularly efficient. In general, the substituent on the alkyl radical determines hereby the reactivity in these transformations. It can react as a nucleophile (Nu^-) or an electrophile (E^+).[49] In recent years, many publications have focused on the generation of C(sp^3) radicals starting from so-called redox active esters (RAE). Under the right reaction conditions, these can easily decarboxylate and release the radical (Scheme 28).[50] Likewise, reductive or oxidative fragmentation (of dihydropyridines (DHPs), silicates, BF_4 salts e.g.), the hydrogen atom transfer (HAT) are known to be fundamental strategies to generate this class of radicals.[51] Arylation reactions are of outstanding importance in synthesis. But the generation of C(sp^2) radicals has been known for a long time. Their reactivity has been investigated since the introduction of the Sandmeyer (1884) and Meerwein reaction (1939).[6, 52] They can be generated from aryl diazonium salts, haloarenes, e.g. and react smoothly with arenes, alkenes, or alkynes.[53]

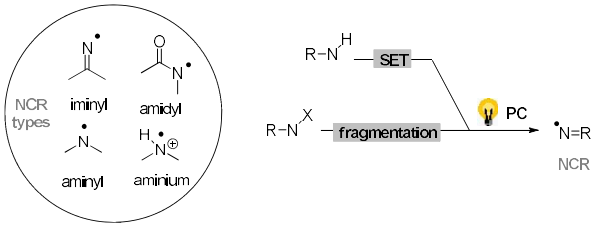


Scheme 28. Photocatalysis: synthetic strategies towards carbon based radicals.

1.3.2 Formation of N-Centered Radicals (NCRs)

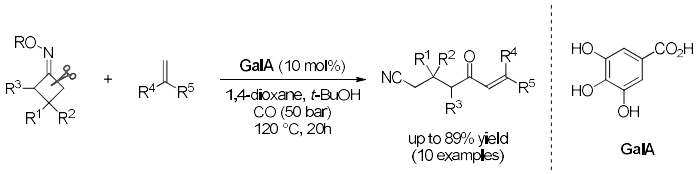
Many natural compounds contain the C-N bond. Therefore, NCRs are particularly useful synthetic intermediates. This is reflected in the abundance of scientific literature on their reactivity.[4, 54] Generation takes place via reductive cleavage of weak N-X bonds (X = halogen, S, O). This is particularly

mild under photocatalytic conditions. NCRs can be categorized into four different classes according to hybridization of the N atom and substitution (see Scheme 29) and smoothly add to unsaturated systems.[55]



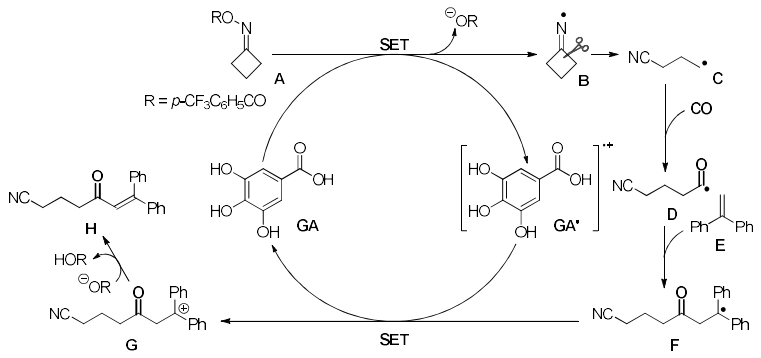
Scheme 29. Photocatalysis: generation of NCRs.

In CO chemistry, the number of publications is rather limited. For the functionalization of sp^2 hybridized N, our group has recently had some successful results in a non-photocatalytical approach. With the help of gallic acid (GalA), the carbonative catalyzed conversion of cyclobutone oximes in the presence of a suitable alkene was achieved (Scheme 30).[56]



Scheme 30. Gallic Acid-catalyzed SET Process for cyclobutanone oximes activation.

Mechanistically, the reaction should occur via SET reduction of cyclobutanone oxime A to the N-centered iminyl radical **B**. The gallic acid undergoes its own SET cycle to the galloyl radical GA'. In the course of a ring opening, cyanoalkyl radical **C** is formed, which rapidly reacts further with CO to form the acyl radical **D**. The acyl radical **D** is Addition of the alkene **E** gives intermediate **F**. A SET under regeneration of the catalyst GA gives cation **G**, which reacts further under protonation to the product **H**.

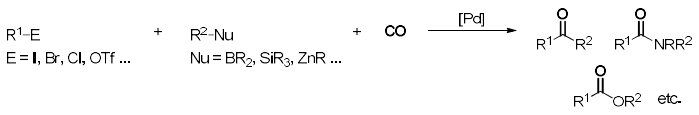


Scheme 31. Mechanism for Gallic Acid-catalyzed SET Process for cyclobutanone oximes activation.

1.4 Pd in Oxidative Dehydrogenative Carbonylations

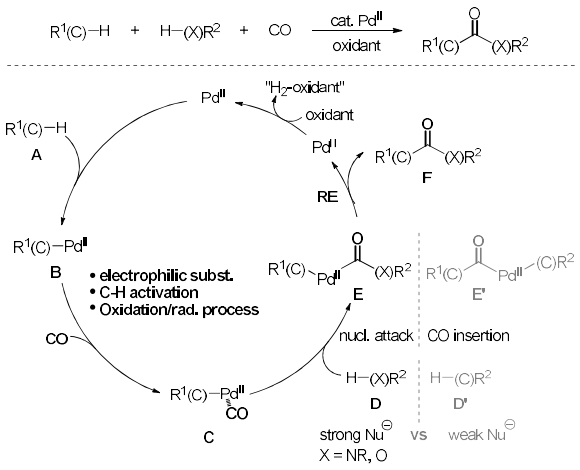
The next intermediate goal of this work was to develop a green system of photomediated synthesis of oxalamides. Oxalamides are of outstanding importance for the hydrogenation to EG,[57] which is one of the target molecules of this thesis. Ultimately, the transfer to an immobilized catalytic system for the generation of oxalamides from amines in continues flow would be desireable. This would thus provide the starting material for subsequent Ru- or Fe catalyzed hydrogenation to the bulk chemical ethylene glycol (EG). In this chapter, the necessary background of the known literature Pd catalyzed oxidative dehydrogenative carbonylations will be discussed.

Pd is very frequently used in oxidative carbonylation reactions, as it can participate in many organometallic reaction steps. Among them are OA, RE, migratory insertion (MI), β-elimination, and nucleophilic attack on coordinated ligands. Some examples of cross-coupling reactions under CO atmosphere of electrophiles and nucleophiles are given below. Often the reaction conditions differ significantly from the straightforward cross-coupling reaction in the absence of CO gas. Sufficiently optimized, they represent a valuable tool to produce carbonyl-containing compounds.[58]



Scheme 32. Overview of Pd-catalyzed carbonylation reactions.

An obvious drawback is the required pre-functionalization of the substrates (see various electrophiles (E+) and nucleophiles (Nu-) in Scheme 32). Desirable would be methods that allow carbonylation coupling reactions without this step. With the oxidative dehydrogenative variant, there is a direct approach for the construction of carbonyl-containing compounds using only X-H bonds (with X = C, N, O). The by-product of the reaction is "H_2 -oxidant" which is often water. From the point of view of green chemistry, synthesis steps can be saved and a very high level of atom economy is achieved. Mechanistically, depending on the interaction between substrates and catalyst (electrophilic substitution, C-H activation (with and without DG) or oxidation via radical processes), intermediate **B** is generated from substrate **A**. Coordination of a CO to palladium leads to the intermediate **C**. From here on, the mechanism proceeds differently depending on the nature of the Nu was used. A strong Nu **D** can start a nucleophilic attack on the CO group. This results in intermediate **E**. A weak Nu **D'**, on the other hand, leads to CO insertion and intermediate **E'**. Subsequently, RE occurs in both cases, resulting in Product **F** and a Pd(0) species. The latter is reoxidized with an oxidant to active Pd(II) and the catalytic cycle starts again.[58b]



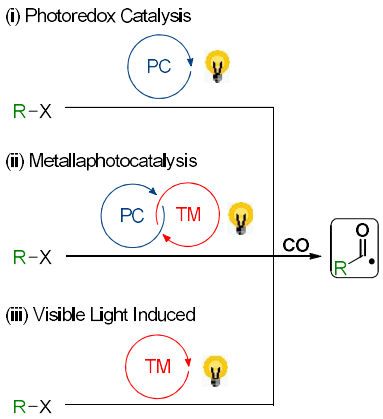
Scheme 33. Mechanistic background of Pd-catalyzed oxidative dehydrogenative carbonylations.

1.5 Pd Catalyzed Carbonylations in Photochemistry

In principle, photocatalyzed chemical reactions can be divided into three categories.[59] If a photoinduced interspherical SET between substrate and catalyst is involved, this is referred to as

photoredox catalysis (an example for a carbonylation reaction is shown in Scheme 34, path *i*). There is an outer sphere electron transfer or energy transfer to be triggered. In this case, the PC is not directly involved in bond formation or bond breaking. The second category is the so-called metallaphotocatalysis.[60] It has one additional catalytic cycle (path *ii*). An exogenous PC harvested the light and transfers electrons or energy to the TM catalyst, which is directly involved in the bond formation or bond breaking process. The third category is particularly interesting. Many TM complexes are themselves colored and can therefore absorb visible light. This is excited by light and is directly involved in bond formation (path *iii*).[32b] The Catalyst-free reaction control will be not described here.

In the context of carbonylation reactions, the acyl radical is the key intermediate. Products featuring a CO building block like ketones, esters, amides and as in our case oxalamides, have great importance for the chemical industry. Radical carbonylation reactions without the use of light are very well studied. They now exist with almost any TM catalyst in the presence of external initiators.

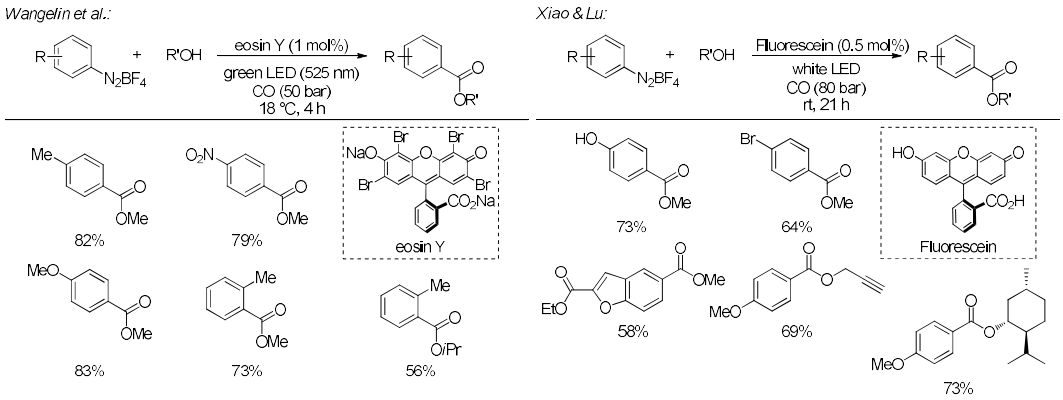


Scheme 34. Photocatalysis: Schematic classification of photocatalytic reactions using PC, PC and TM, or only TM. TM = Pd e.g..

1.5.1 Photoredox Catalysis in CO Chemistry

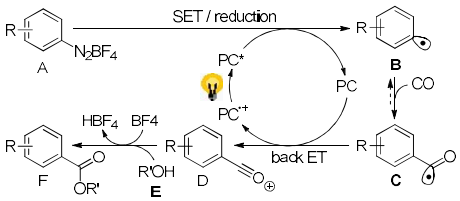
The use of light opened the possibility of generating radicals directly without the use of additional additives, a greener atom-economical option. Unfortunately, the use of high energy UV light was often

accompanied by low selectivity and efficiency. Wavelengths in this range unselectively excite many FGs and make broad scopes impossible.[3b] The renaissance of photocatalysis, which has been witnessed over the last 15 years, has also made inroads into the fields of carbonylation reactions. In particular, the efforts of Wangelin group as well as Xiao group should be mentioned here, who independently succeeded in converting alcohols to esters (Scheme 35) using their metal free protocol.[61] High CO pressures (>50 bar) was necessary for efficient reaction control and low loadings of the organic dye eosin Y or Fluorescein. Both works have their justification. The work of Wangelin and their detailed mechanistic studies and transfer to industrial application for the preparation of 2-ethylhexyl benzoate, in which the starting material 2-ethylhexanol is accessible via hydroformylation. In a further step, the dye could be separated from the reaction mixture by simple filtration through alumina. Xiao and Lu showed an impressive scope (31 ester products) and tolerance of EDG, EWG, and heteroaryl rest on the diazonium salt. Notably, terminal alkynes, which are good radical acceptors, remained untouched, contrary to intuition. Natural isolated products such as (–)-Menthol could also be used.



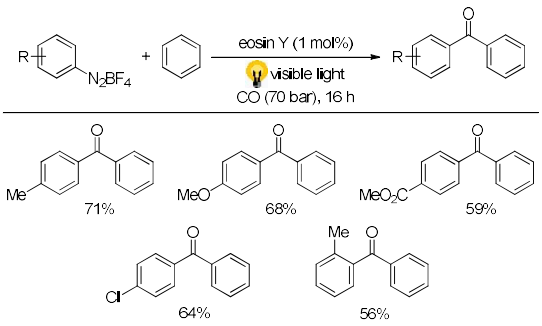
Scheme 35. Photocatalysis: Comparison of the radical alkoxycarbonylation of aryldiazonium salts with alcohols by Wangelin and Lu.

Mechanistically, it has been proposed that irradiation of the PC with visible light provides excitation to the longer-lived excited PC*in the photo redox catalytic cycle (Scheme 2). A SET on the diazonium salt **A** takes place and causes reduction to the aryl radical **B**. This is molecule quickly captured by a CO and the key species acyl radical **C** is formed. With $PC^{\bullet+}$, oxidation to the benzylidyneoxonium **D** is possible in a further SET with regeneration of PC. In the final step, the ester **F** is formed in a reaction of **D** and alcohol **E**.



Scheme 36. Mechanism for the visible light promoted photo redox carbonylation of diazonium salts with alcohols.

The key intermediate to these new conversions was the benzylidyneoxonium, and only a short time later Gu group succeeded in transforming it together with (hetero)arenes into the corresponding arylketones.[62] Activating the chemical inert C(sp^2)-H bond of arenes. Broad tolerance to FG was observed (Scheme 37). Electron donating groups in *para* position of the phenyl ring (-Me, -OMe) of the diazonium salt were superior to those substituted in *ortho* and *meta* position which is in accordance with expectations. With electron withdrawing rests (-Cl, -CO_2Me) slightly lower yields were obtained. The efficiency of the protocol could be mainly influenced by steric and less by electronic effects.



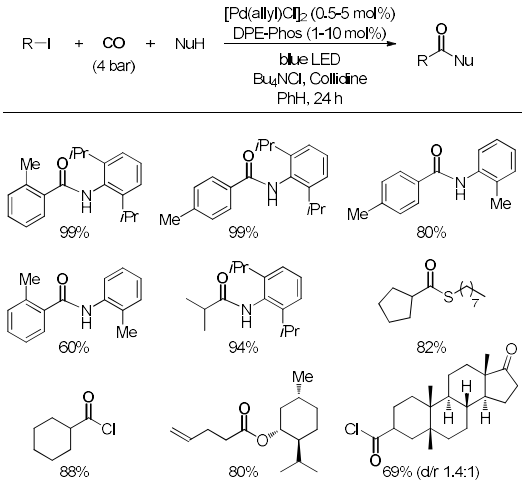
Scheme 37. Mechanism of the visible light promoted photo redox carbonylation of diazonium salts and (hetero) arenes.

1.5.2 Metallaphotocatalysis in CO Chemistry

Metallaphotocatalysis is a new tool that has already found many applications in photochemistry.[3d, 60] In carbonylation chemistry the examples are rarer. It is the dual catalysis of the photocatalysis and

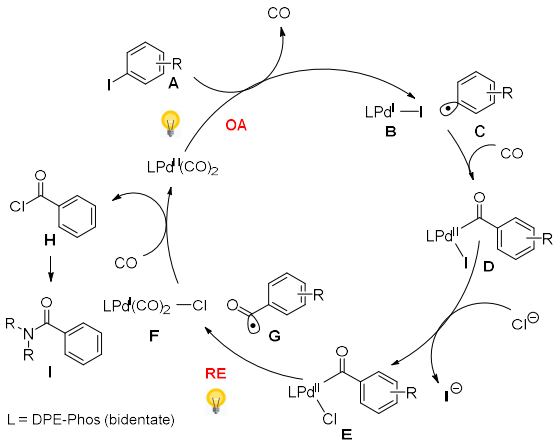
TM catalyst. An exogenous PC that harvests light and transfers a single electron (SET) or energy to the TM catalyst, is necessary. Only the latter is directly involved in the formation or breaking of a chemical bond.

Recently, Arndtsen group achieved a breakthrough in this research area with carbonylative coupling of alkyl and aryl halides with challenging nucleophiles.[63]



Scheme 38. Photocatalysis: Carbonylative coupling of aryl and alkyl halides with challenging nucleophiles.

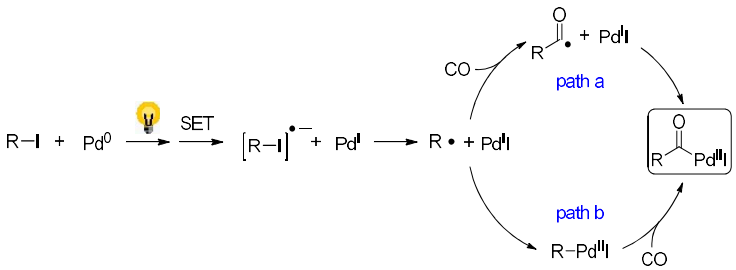
Mechanistic studies showed that the parallel excitation of palladium(0) and palladium(II) species is responsible for this extraordinary activity. Cholesterol-lowering drug fenofibrate was shown as an example of application. An unprecedented phenomenon was observed: Light was able to excite both intermediates responsible for the crucial steps of OA and RE. A Pd(I) species and the respective organoradical was detected, which in a coupling step with low pressure CO, complete the OA. This is succeeded by a ligand exchange with chloride. The new intermediate can undergo a previously unknown radical-induced RE in the presence of visible light. In an OA step the substrate **A** reacts with Pd(0) carbonyl catalyst. The aryl **C** is released, which immediately becomes an acyl radical in the presence of CO. From this transition state Pd(II) species **D** is generated. Subsequent ligand exchange gives species **E**. Mechanistically unprecedented, the radical induced RE is accelerated by light to drive the formation of acid chloride **H** from pd(I) species **F** and acyl radical **G**.



Scheme 39. Mechanism of the carbonylative coupling of aryl and alkyl halides.

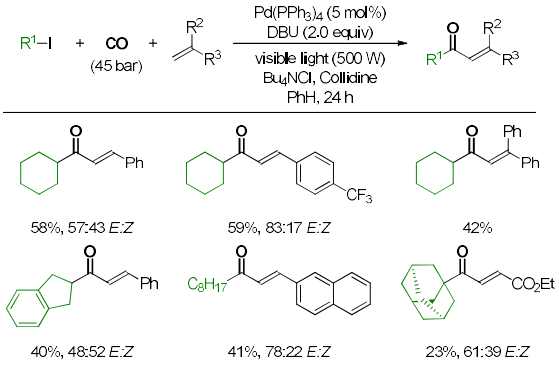
1.5.3 Visible Light-Induced Reactions in CO Chemistry

Although the advantages of reaction control without exogenous PC are obvious, this is an underdeveloped field of research.[64] Pioneering work in the field of photoinduced metal-catalyzed carbonylations of alkyl iodides was done by the Ryu group. The photoinduced variants were found to be a mild and well applicable alternative, often even with extension of the substrate scope and FG tolerance.[32b] The two possible pathways towards the acyl-Pd species are shown in Scheme 40.



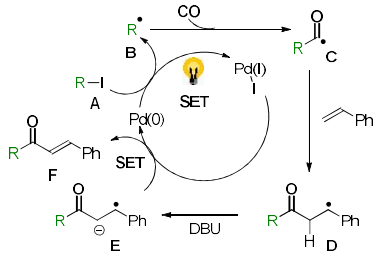
Scheme 40. Pathways of acylpalladium formation

In 2015, the same group achieved the Carbonylative Mizoroki-Heck reaction.[65] A simple Pd catalyst was used in the presence of DBU and light to obtain very valuable α,β-unsaturated ketones (Scheme 41).



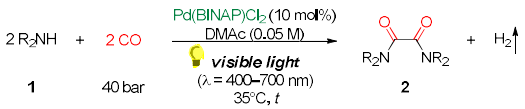
Scheme 41. Photocatalysis: Carbonylative Mizoroki-Heck.

In their mechanistic reasoning, they propose that in a SET between halogen alkyl **A** and Pd(0) under the action of light, the Pd(I) species and alkyl radical **B** are formed. Under CO atmosphere, the acyl radical **C** is rapidly formed, which together with an alkene forms the βketo radical **D**. A further SET leads to the product **F**.



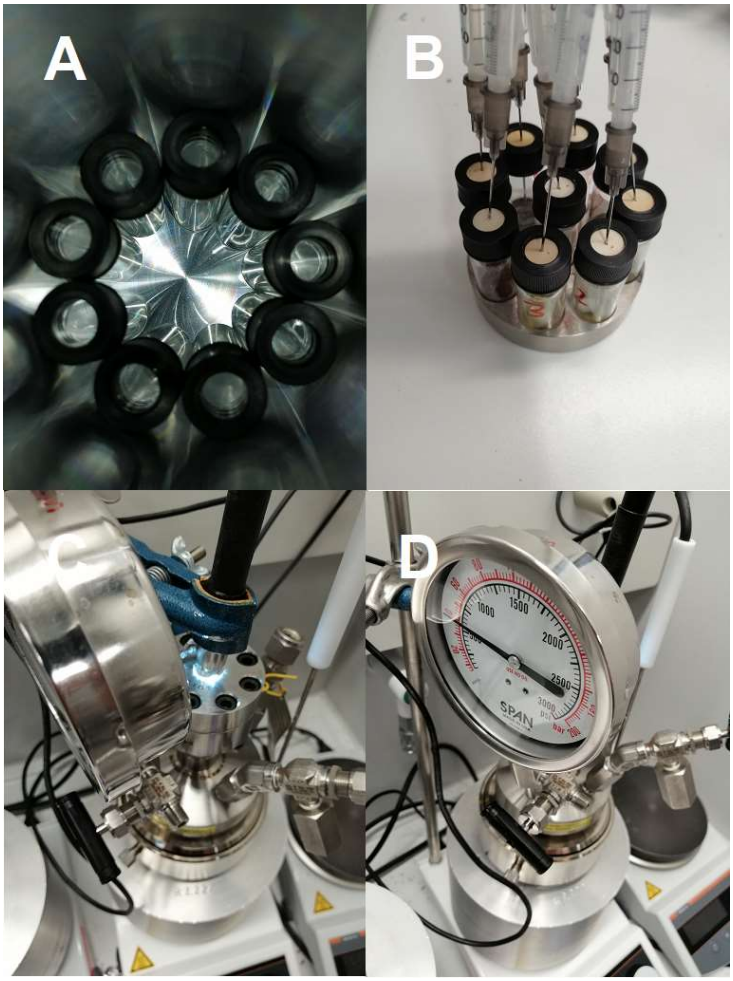
Scheme 42. Mechanism of the CarbonylativeCarbonylative Mizoroki-Heck.

Fortunately, we were able to expand this area of research in this dissertation with the visible Light-induced Pd-catalyzed dehydrogenative carbonylation of amines to valuable oxalamides (Scheme 43). The oxalamides obtained in this way have a particular importance for the potential extraction of EG, as will be outlined in the following chapter.



Scheme 43. Photocatalysis: visible light induced Pd-catalyzed dehydrogenative carbonylation of amines to oxalamides (*see publications*).

In the case of light-promoted carbonylation with high-pressure CO in particular, a well-designed reactor system was used. In our case a stainless steel autoclave with a quartz glass window at the top was used, which allows for an even light irradiation of our samples. Like this, up to 9 reactions can be carried out simultaneously. Irradiation is partly indirect by reflection of the autoclave bottom: Scheme 44 shows a typical Screening procedure. A: Typical setup for the irradiation of nine samples (the vials were placed in a revolver-like manner without an alloy plate). Arrangement of the reaction vials inside the photoautoclave for even distribution of light. B: Charging procedure under argon counterflow. C: Irradiation via SUPERLITE S04 (150 W lamp). At the top of the autoclave is a window made of quartz glass, which allows irradiation to the center. The clean autoclave bottom allows for consistent reflection. D: Usually no more than 40 bar of CO pressure used. The close-fitting aluminum block allows passive cooling. A straight measurement of the temperature of the samples after completion of the reaction showed that no more than 35 °C was reached.

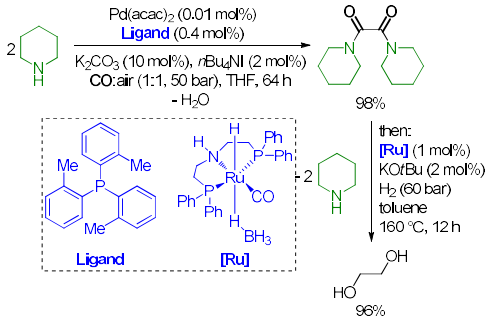


Scheme 44. Typical reaction set up for the visible light induced Pd-catalyzed dehydrogenative

carbonylation of amines to oxalamides (*see publications*)..

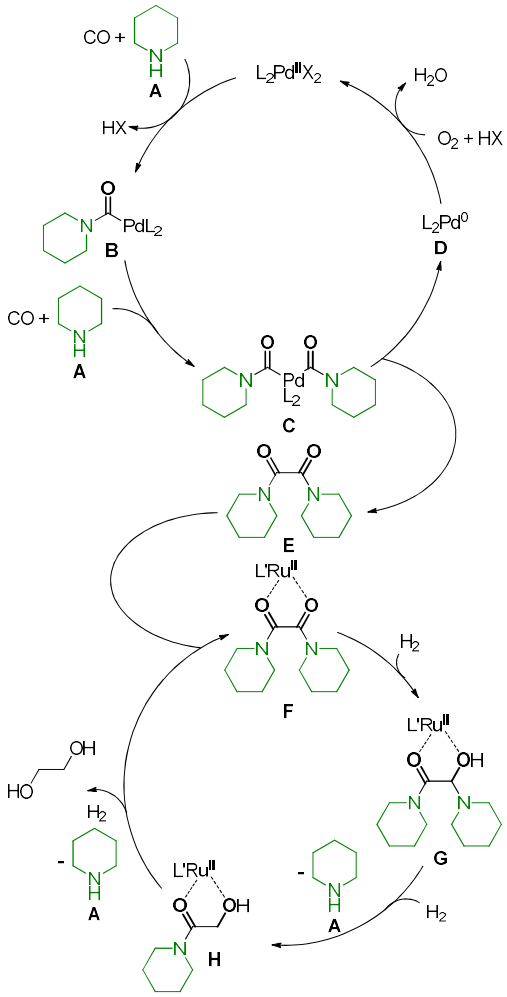
1.6 Synthesis of EG from CO

In 2016, the Beller group described a selective two-step process for EG from CO.[57a] Their strategy consisted of an initial oxidative coupling and a reduction in the second step. The Pd-catalyzed oxycarbonylation of amines to oxalamides was followed by a Ru- (or Fe-) catalyzed hydrogenation to EG. Their optimized conditions are shown below.



Scheme 45. Optimized conditions for the piperidine-mediated production of EG from CO in two steps.

This publication is thematically close to this work. They were able to produce the oxalamides generated *via* oxidative carbonylation using photo mediated carbonylation under oxygen-free conditions. Mechanistically, two cycles of catalysis were proposed. In the first one the amine (here cyclohexylamine as a model) reacts under CO atmosphere to form the Pd (II) intermediate **B** another **A** can coordinate to the Pd to generate bis(carbamoyl)palladium intermediate **C**. In a RE, the oxalamide **E** is generated exclusively (no urea detected). The oxygen is now able to regenerate the catalyst. This cycle is followed by hydrogenation. An outer-sphere bifunctional activation mode was proposed. The direct hydrogenolysis of the amide bond in **G** takes place. A further hydrogenation step gives the desired EG and amine **A**, which can be used for a new cycle.



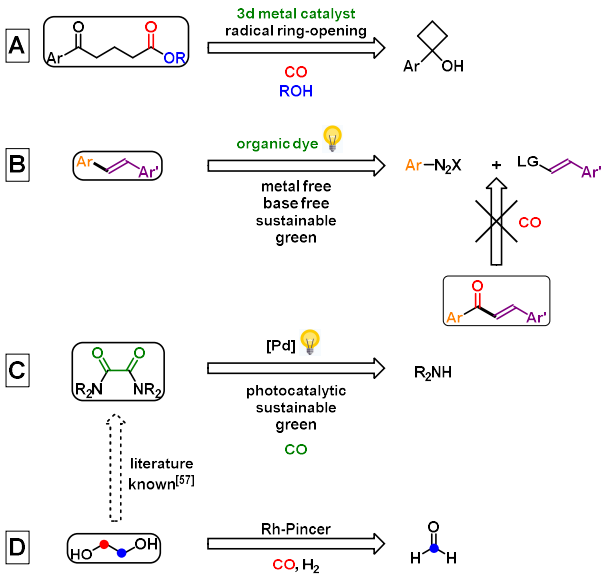
Scheme 46. Mechanism for the piperidine-mediated production of EG from CO in two steps.

The obvious disadvantage of this otherwise very sophisticated method of obtaining EC is that two steps are required. As in the introduction described, our intellectual interest was to overcome this drawback and produce EG in a one-pot synthesis from the important bulk chemical formaldehyde. We have succeeded in doing so in the framework this dissertation.[66]

2. Objectives of This Work

As described in the introduction, this dissertation has several small objectives. Across all the work, the goal is to generate C-centered (or N-centered) radicals. Initially, the research field of carbonylated ring opening reactions was extended to catalysis with cheap and earth-abundant Mn. An application area of C(sp^3) centered radicals (A). The second project dealt with C(sp^2) centered radicals. They were generated starting from aryl diazonium salt and a styrene derivative. In the presence of CO we tried to obtain chalcones. Unfortunately, the direct C-C coupling to stilbenes was preferred. However, this reaction is particularly green and was previously unknown. It represents a highly selective alternative to the known Heck coupling and Meerwein arylation (B).

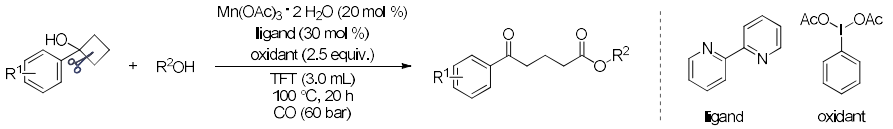
The third and fourth projects worked toward the same goal: the synthesis of EG. First, oxalamides were obtained from amines in a photomediated dehydrogenative carbonylation. The reaction was completely oxidant free and the catalyst could be partially recovered. The oxalamides obtained are suitable starting material for the synthesis of EG. The fourth project describes the successful attempt to facilitate the one-pot synthesis of EG from bulk chemical formaldehyde under mild conditions using a pincer ligand.



Scheme 47. Summary of research topics.

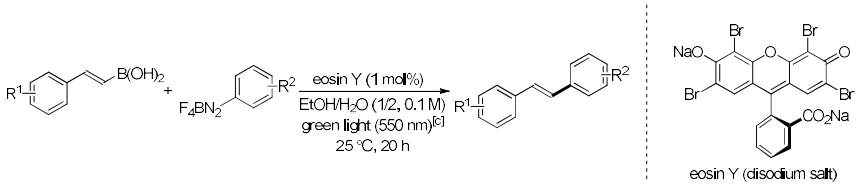
3. Summary of Publications

(1) Manganese-catalyzed ring-opening carbonylation of cyclobutanol derivatives (*Tetrahedron Lett.* **2019**, *60*, 864; DOI: 10.1016/j.tetlet.2019.02.028). In this work, we reported on the manganese-catalyzed ring-opening carbonylation of cyclobutanol derivatives through cyclic C-C bond cleavage. The reaction occurs through a radical-mediated pathway to selectively generate 1,5-ketoesters. A selection of substrates with substituents on the aromatic ring reacted with linear alcohols of different chain lengths. Obtained aliphatic esters are usually difficult to access and therefore attractive.



Scheme 48. Mn-catalyzed ring-opening carbonylation of cyclobutanol derivatives.

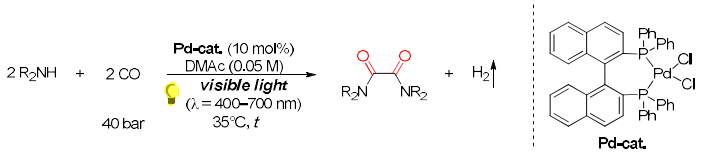
(2) Photocatalytic Synthesis of Stilbenes via Cross-Coupling of Alkenyl Boronic Acids and Arenediazonium Tetrafluoroborate Salts (*ChemPhotoChem.* **2020**, *4*, 713; DOI: 10.1002/cptc.202000061). In this paper, we described the development of a novel method for the photocatalytic selective synthesis of (*E*)-stilbenes by the coupling of alkenyl boronic acids and aryldiazonium salts. In a metal-free system, visible light is used as an energy source and a "green" mixture of water and ethanol is used as solvent. A mechanistic proposal is presented which is supported by several control experiments (including EPR). The reaction proceeds via a radical pathway, which are formed from both diazonium salt and boronic acid in the presence of visible light.



Scheme 49. Photocatalytic synthesis of stilbenes via cross-coupling of alkenyl boronic acids and arenediazonium tetrafluoroborate salts.

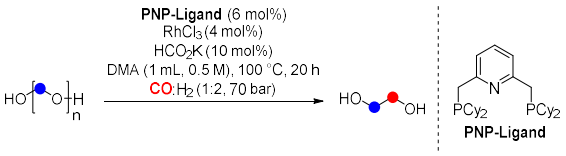
(3) Visible Light Induced Palladium-Catalyzed Dehydrogenative Carbonylation of Amines to Oxalamides (DOI: 10.1002/chem.202100009). In this work, we described the first palladium-catalyzed oxidative carbonylation in which the oxidant was fully replaced by visible light. Our new approach uses a simple robust Pd-BINAP complex, which can be partially recycled. Control

experiments and EPR studies were conducted. It showed that Pd(I) was formed and Pd(0) was the active species. Both nitrogen- and the intermediate acyl radical could be detected. Moreover, the formation of hydrogen was confirmed by gas GC. With the help of these data, a plausible reaction mechanism could be provided.



Scheme 50. Visible light Induced Pd-catalyzed dehydrogenative carbonylation of amines to oxalamides.

(4) Pincer Ligand Enhanced Rhodium-Catalyzed Carbonylation of Formaldehyde: Direct Ethylene Glycol Production (*Asian J. Org. Chem.* **2020**, *9*, 1; DOI: 10.1002/ajoc.202000573). In the systems reported so far, the reaction conditions were very harsh, often with pressures above 400 bar. However, under milder conditions, the selectivity was on the side of glycol aldehyde (GA) and the hydrogenation product methanol. Only traces of ethylene glycol (EG) could be generated in the presence of a Rh catalyst. We overcame these drawbacks and described a new Rh catalyst system with a pincer ligand, which allows the direct one pot synthesis of EG from paraformaldehyde (PFA) at remarkable mild conditions (70 bar, 100 °C) and overcomes the aforementioned limitations with yield up to 40%.



Scheme 51. Pincer ligand enhanced Rh-catalyzed carbonylation of formaldehyde: direct ethylene glycol production.

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5. Publications

5.1 Manganese-Catalyzed Ring-Opening Carbonylation of Cyclobutanol Derivatives

Tim Meyer, Zhiping Yin, and Xiao-Feng Wu

Tetrahedron Lett. **2019**, *60*, 864; DOI: 10.1016/j.tetlet.2019.02.028

Author contributions:

In this paper, I planned and performed close to all the experiments. I analyzed the data on my own. I wrote the manuscript alone. My contribution as the first author of this paper is more than 70%.

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Manganese-catalyzed ring-opening carbonylation of cyclobutanol derivatives

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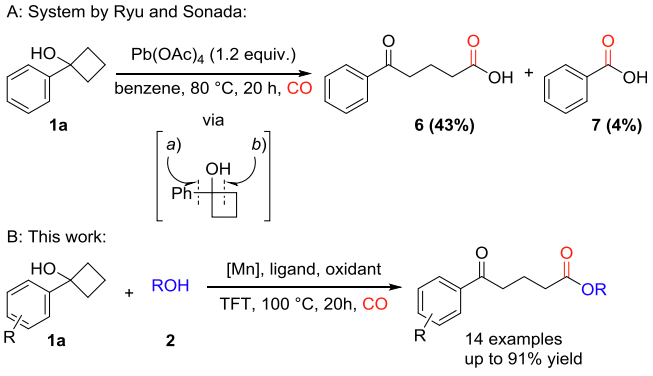
ABSTRACT

Herein, we report a manganese-catalyzed ring-opening carbonylation of cyclobutanol derivatives through cyclic C—C bond cleavage. The reaction happens via a radical-mediated pathway to selectively generate 1,5-ketoesters. A variety of substrates with substituents on the aromatic ring reacted with linear alcohols of different chain lengths. Obtained aliphatic esters are very attractive since they are usually difficult to access.

Introduction

The development of catalysts with abundant and therefore inexpensive 3d transition metal complexes is a good alternative to the extensively researched use of noble metals [1]. Such systems would be particularly attractive in combination with low-cost commercially available ligands and give improved reaction efficiency and reactivity [2]. Catalytic ring-opening reactions are highly efficient because the starting material is fully incorporated into the target molecule. Tertiary cycloalkanols caught our interest, which have proven to be privileged starting materials for oxidative ring opening reactions [3]. The using of palladium catalysts [4] and rhodium catalysts [5] have been well established in this research field. However, early publications showed that it is possible to use non-noble 3d transition metals such as Mn(III) [6], Cr(IV) [7] or V(V) [8] to induce single-electron oxidization of cyclobutanol resulting in a ring-opened free-radical intermediate. Recently, some successes have been reported with catalysts based on Mn [9] or Ag [10] to generate distally functionalized ketones. With regard to carbonylation reactions, ring opening or expansion of epoxides were reported and allow the synthesis of products with high added value (e.g. lactones [11] or succinic anhydrides [12]). The carbonylative cleavage of cyclobutanols is more challenging and much less explored. To the best of our knowledge, only one synthetic pathway was reported by Ryu and Sonada in 1994. The carbonylation could be achieved using 1.2 equivalents of Pb $(OAc)_4$ (LTA) as the one electron oxidation system and catalyst [13]. Phenylcyclobutanol **1a** could be successfully converted into the desired 4-benzoylbutyric acid **6** in 43% yield and benzoic acid **7** as the by-product in 4% yield. From this it was concluded that β-scission *a)* was a minor competitive reaction (Scheme 1). This system faces obvious drawbacks concerning the selectivity and leads to relatively low yields, besides the use of LTA in stoichiometric quantities, which is very toxic and should be avoided concerning green chemistry. In continuation of our research on first row transition-metal-catalyzed carbonylations, we succeeded in designing a new Mn-catalyzed method for 1,5-ketoesters production. The above mentioned drawbacks could be eliminated.



Scheme 1. Ring-opening carbonylation of cyclobutanol.

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0040-4039/

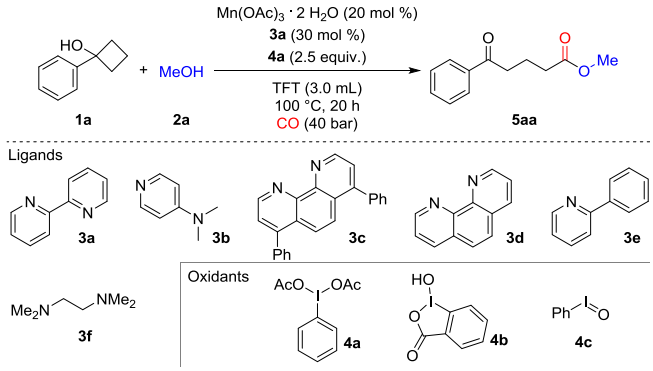
Results and discussion

For our preliminary studies we have chosen 1-phenyl-cyclobutanol **1a** as the model substrate to establish this procedure [9,14]. We conducted comprehensive optimization of the reaction conditions that are outlined in Table 1. Of all the manganese-based catalysts tested, manganese acetate has proven to be the most effective one (entries 1–5). To provide a more efficient catalytic system, we examined various commercially available ligands (entries 6–12, **3a**–**3f**). The *N*,*N*-bidentate ligands (**3c**, **3d** and **3f**) tested all gave worse results. The uses of simple pyridine as the ligand could not futher improve the yield (entries 10–12). In order to demonstrate the importance of the ligand to be bidentate, 2-phenylpyridine **3e** was used, which differs from **3a** only by a missing nitrogen, but the yield was 11% lower. With a monodentate ligand having a strong electron-donating group in unobstructed *para*-position such as DMAP **3b**, it was possible to get the same results as with BiPy (entry 6). The effect of different oxidants was explored subsequently. In line with the recently reported results for oxidative ring-opening reactions [9a], the hypervalent iodine oxidants (entry 13, **4b**) stand out due to their high reactivity. It is noteworthy that $Ce(SO_4)_2$ provided similar results compared to iodosylbenzene **4c** (entries 13–15). PIFA ((bis (trifluoroacetoxy)iodo)benzene) was tested as oxidant in our system as well, but only 15% of the desired product could be obtained. With the suitable ligand and oxidant at hand, we started a thorough screening of solvents. Trifluorotoluene (TFT), which was used from the beginning, emerged as the best solvent. However, the same yield could be achieved with *m*-xylene (51%, entry 16). Interesting regarding green chemistry would be if a mixture of isomers would give comparable results, since xylenes are petrochemically produced on large scale by catalytic reforming. Other tested solvents all gave decreased yields (entries 16–20). Interestingly, the use of less polar "non-fluorinated" toluene resulted in a significantly lower yield (31%, entry 17). In a comparative reaction with methanol as reactant and solvent, only a minor amount of desired product was generated (8%, entry 20). Finally, the CO pressure was increased from 40 to 60 bar and the yield improved dramatically (80%, entry 21). In order to establish direct comparability with the aforementioned system of Ryu and Sonada, LTA was tested under the final conditions and lead to a low yield here (33%, entry 22).

With the optimal conditions in hand, our method was applied on several substrates in combination with different alcohols (Table 2) [15]. The reaction was studied with linear alcohols of different chain lengths (**2a**–**2e**) and several substrates with substituents on the aromatic ring of different electronic properties (**1a**–**1g**) including di-substituted ones (**1e**, **1g**). In general, good yields of the corresponding products with different aliphatic alcohols (**5aa**–**5ae**) can be achieved. Among them, ester product **5ac** could be obtained in an excellent yield of 91% (entry 3). To our delight, it was also possible to use long chained alcohols like *n*-octanol **2e** to generate the elusive aliphatic ester **5ae** in a synthetically useful yield (73%, entry 5). However, only trace amount of the desired product could be detected when i-proponal or *tert*-butanol was tested. Our carbonylation system exhibited functional group tolerance with fluoro and methoxy groups on the aromatic ring. Encouraged by the good results with *n*-butanol, *n*-butanol and methanol were tested with the substrates, respectively. Remarkably, the trend of increased reactivity in combination with *n*-butanol and the associated increased yields also continued for the various substituted cyclobutanols. In case of the alkyl-substituted substrate **1c** together with methanol **2a**, the corresponding product **5ca** was obtained in moderate yield (55%, entry 7) and in presence of *n*-butanol corresponding product **5cc** could be obtained in a good yield (74%, entry 8). This phenomenon could also be observed for single and double substituted products, with a dramatic improvement in yields for *para*-methoxy substituted esters **5da** (40%, entry 9) and **5dc** (89%, entry 10). The same was true for the *meta*-fluoro substituted esters **5fa** (30%, entry 13) and **5fc** (86%, entry 14). In both cases the respective yield has more than doubled when *n*-butanol was used instead of methanol. Di-substituted products with a methoxy group in *para*- and *meta*-position **5ea** (31%, entry 11) and **5ec** (46%, entry 12) also showed an improvement, but less significant. In the case of difluorosubstituted substrate, the desired product could only be isolated in traces, even with *n*-butanol **5gc** (<12%, entry 15). Additionally, alkyl substituted and non-substituted cyclobutanol were tested under standard conditions as well, but no desired products could be detected.

A plausible mechanism is proposed based on experimental observations and literatures (Scheme 2). First the hypervalent iodine reagent oxidizes the catalyst and together with cyclobutanol **a** to give the Mn(V) species **b**. Subsequent single-electron transfer (SET) releases the cyclobutyloxy radical **c**, which undergoes a 'radical clock'-type ring opening tautomerization, leading to alkyl radical **d** [14a]. Under the given pressure, it is likely that together with CO the acyl radical **e** will be formed. It can coordinate to the manganese center to generate **f**. Then X ligand exchange leads to a Mn(V) complex **g** which is able to give the final ester product **h**

Table 1
Optimization of Reaction Conditions.



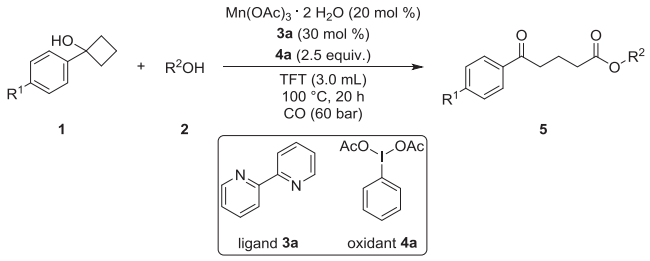
Entry[a]	Deviation from standard conditions	Yield (%)[b]
1	None	51
2	$Mn(CO)_5Br$ as catalyst	41
3	$MnCl_2$ as catalyst	38
4	$Mn(acac)_2$ as catalyst	26
5	$MnBr_2$ as catalyst	19
6	DMAP **3b** as ligand	51
7	Batophen **3c** as ligand	50
8	1,10-Phenantroline **3d** as ligand	41
9	2-Phenylpyridine **3e**	41
10	Pyridine as ligand	36
11	No ligand	34
12	TMEDA **3f** as ligand	27
13	BI-OH **4b** as oxidant	34
14	$Ce(SO_4)_2$ as oxidant	28
15	**4c** as oxidant	27
16	*m*-Xylene as solvent	51
17	Toluene	31
18	Dimethylcarbonate	26
19	Dioxane	25
20	MeOH	8
21	CO (60 bar)	80 (79[c])
22	CO (60 bar), $Pb(OAc)_4$ **4e** as oxidant	33

[a] Unless otherwise noted, all the reactions were conducted on a 0.2 mmol scale in the presence of the alcohol **2** (5.0 mmol) using an autoclave

[b] GC yields were determined by GC-FID analysis using *n*-hexadecane as internal standard

[c] The isolated yield of isolated product **5aa** was obtained from a reaction on a 0.3 mmol scale.

Table 2
Manganese-Catalyzed Ring-Opening Carbonylation of Cyclobutanol Derivatives: Substrate Scope.



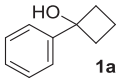
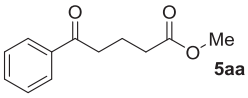
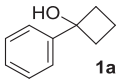
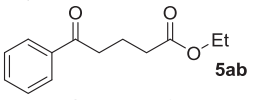
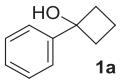
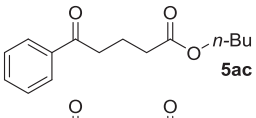
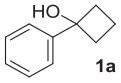
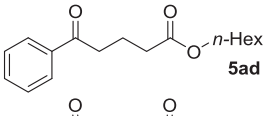
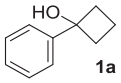
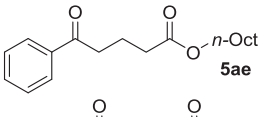
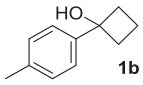
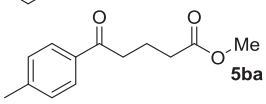
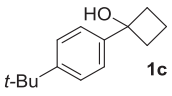
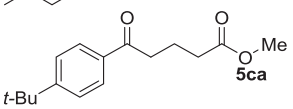
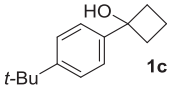
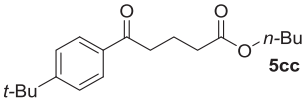
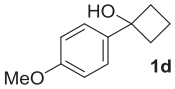
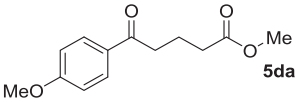
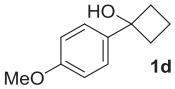
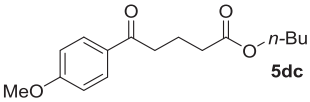
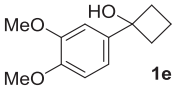
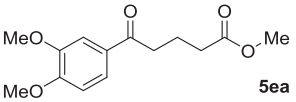
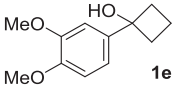
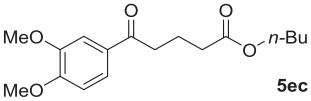
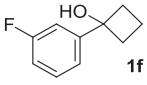
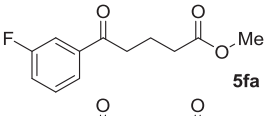
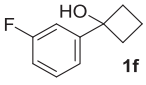
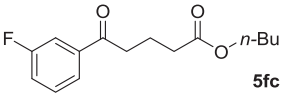
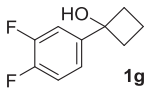
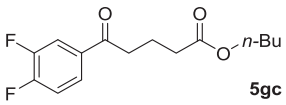
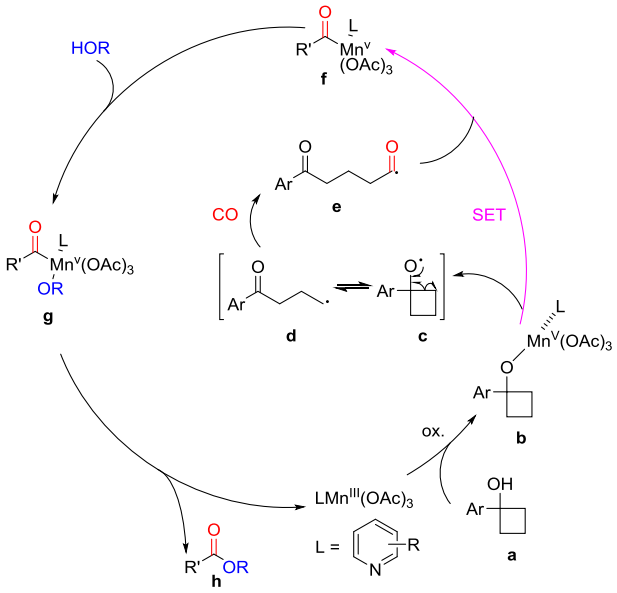
Entry	Cyclobutanol	Alcohol	Product	Yield [%][b]
1	 **1a**	HO–Me **2a**	 **5aa**	79
2	 **1a**	HO–Et **2b**	 **5ab**	61
3	 **1a**	HO–*n*-Bu **2c**	 **5ac**	91
4	 **1a**	HO–*n*-Hex **2d**	 **5ad**	70
5	 **1a**	HO–*n*-Oct **2e**	 **5ae**	73
6	 **1b**	HO–Me **2a**	 **5ba**	47
7	 **1c**	HO–Me **2a**	 **5ca**	55
8	 **1c**	HO–*n*-Bu **2c**	 **5cc**	74
9	 **1d**	HO–Me **2a**	 **5da**	40
10	 **1d**	HO–*n*-Bu **2c**	 **5dc**	89
11	 **1e**	HO–Me **2a**	 **5ea**	31
12	 **1e**	HO–*n*-Bu **2c**	 **5ec**	46
13	 **1f**	HO–Me **2a**	 **5fa**	30
14	 **1f**	HO–*n*-Bu **2c**	 **5fc**	86

Table 2 (*continued*)

Entry	Cyclobutanol	Alcohol	Product	Yield [%][b]
15	 **1g**	HO−*n*-Bu **2c**	 **5gc**	<12

[a] Unless otherwise noted, all the reactions were conducted on a 0.3 mmol scale in the presence of the alcohol **2** (5.0 mmol) using an autoclave.
[b] Isolated yields.



Scheme 2. Proposed mechanism for the ring-opening carbonylation of cyclobutanol.

after reductive elimination. Evidence for the formation of benzoic acid via β-scission as a competitive reaction could not be provided [13]. We assume that our catalytic system selectively generates cyclobutyloxy radical **c** during the step of single-electron transfer. However, we also can not excluded a Mn(III)/Mn(II) catalytic cycle.

In conclusion, we described a method for the ring-opening carbonylation of cyclobutanols. Several elusive aliphatic 1,5-ketoesters could be generated with our system, using simple bipyridine as ligand and manganese acetate as catalyst both from chemical feedstock.

Acknowledgments

We gratefully acknowledge the analytic support of Dr. W. Baumann, Dr. C. Fischer, Dr. A. Spannenberg, S. Buchholz, and S. Schareina. We thank Professor Matthias Beller and Professor Armin Börner for providing a perfect working environment.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2019.02.028.

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[15] General procedure: A 4 mL screw-cap vial equipped with a septum, a small cannula, and a stirring bar was charged with starting material **1** (300 μmol), BiPy (30 mol%, 14.1 mg), $Mn(OAc)_3{\cdot}2H_2O$ (20 mol%, 16.1 mg), TFT (3 mL), PIDA **4a** (750 μmol, 242 mg), and alcohol **2** (5 mmol). The vial was sealed, connected to atmosphere with a cannula, purged with argon three times, placed on an alloy plate, and transferred into a 300 mL stovetop autoclave (4560 series from Parr instrument company®). The autoclave was flushed two times with argon and two times with CO. It was then placed into an aluminum block on a magnetic stirrer. The reaction mixture was stirred (600 rpm) for 20 h at 100 °C and under pressure of 60 bar CO. Then it was cooled to room temperature and the pressure was released carefully. As an internal standard, n-hexadecane (30 μL, 100 μmol) was added to the reaction mixture. An aliquot (1 mL) of the mixture was purified with a pipette flash column using EtOAc (3 mL) as the eluent. Samples prepared in this way were subjected to GC analysis. Isolated products were obtained by column chromatography on silica gel.

5.2 Photocatalytic Synthesis of Stilbenes via Cross-Coupling of Alkenyl Boronic Acids and Arenediazonium Tetrafluoroborate Salts

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Author contributions:

In this paper, I planned and performed close to all the experiments. I analyzed the data on my own. I wrote the manuscript alone. My contribution as the first author of this paper is more than 60%.

Photocatalytic Synthesis of Stilbenes via Cross-Coupling of Alkenyl Boronic Acids and Arenediazonium Tetrafluoroborate Salts

Tim Meyer,[a] Jian-Xing Xu,[a] Jabor Rabeah,[a] Angelika Brückner,[a] and Xiao-Feng Wu*[a]

In this article, we describe the development of a new method for the photocatalytic synthesis of (*E*)-stilbenes by the coupling of alkenyl boronic acids and aryldiazonium salts. In our operatively simple and metal-free system, visible light is used as an energy source and a "green" mixture of water and ethanol is used as solvent. A mechanistic explanation is presented which is supported by several control experiments. The reaction proceeds via a radical pathway, from both the diazonium salt and boronic acid in the presence of visible light.

1. Introduction

In times of increasingly scarce resources, science is addressing an inexhaustible source of clean energy which is independent of planet earth and will continue to exist for another five billion years: the sun.[1] Many research groups are therefore working eagerly to discover new reaction patterns and make known reactions photochemically accessible.[2] Most simple small organic molecules only absorb UV light and activating them by visible light is one challenge of the 21st century. Irradiation with UV light, which is often absorbed by different functional groups, can lead to undesired side reactions like photodegradation, especially on more complex substrates. In contrast, the irradiation with visible light is insufficient to activate these weak bonds. Photo catalytically mediated reactions usually take place under very mild conditions, often at room temperature. Various impressive synthesis methods have been reported about the excitation of transition metal complexes of ruthenium,[3] iridium,[4] but also in combination with cobalt,[5] nickel[6] and gold[7] by visible light. In addition, miscellaneous Earth-abundant metal complexes were successfully used in photocatalysis[8] or are under investigation with regard to their suitability as photocatalysts.[9] When a typical transition metal complex like $Ru(bpy)_3^{3+}$ is excited, it undergoes a MLCT (metal to ligand charge transfer) from the HOMO (highest occupied molecular orbital) of the metal to the LUMO (lowest unoccupied molecular orbital) of the ligand.[10] The resulting photo-excited species has the remarkable property that it is both more oxidizing and reducing than the species in its ground state. To quantify this, a standard reduction potential vs the SCE (saturated calomel electrode) was introduced. Excited photocatalysts (PC*) perform electron or energy transfer with the substrate. Frequently, SET (single-electron transfer) occurs in the mechanisms of photocatalytic reactions. Some reactivities are caused by an energy transfer (EnT). These phenomena are called photosensitization and do not depend on the redox properties of the substrates, but mainly on the triplet state energies of the organic substrate and the excited photocatalyst.[11] Eosin Y is a long known organic dye that was used in medicine to stain blood cells and in everyday products such as lipstick. Already in 1928 Windaus and Brunken reported the photochemical oxidation of ergosterol with eosin Y at room temperature using a filament lamp.[12] Fifty years later the Kellogg group found that eosin Y is a fantastic photosensitizer that is very cost effective, non-toxic, and eco-friendly unlike transition metal catalysts. They described the reduction of phenacyl sulfonium salts by 1,4-dihydropyridines using visible light.[13] Since then, many studies have given a picture of how well eosin Y and other members of the fluorescein family are suited as a photocatalysts in C–C coupling reactions.[14] For an overview and quick introduction into the state-of-the-art in photocatalysis, see the lately published retrospective approach by the König group.[15] However, to highlight some properties, when excited by visible light, eosin Y undergoes rapid intersystem crossing (ISC) to the lowest energy triplet state, having a lifetime of 24 microseconds.[16] The maximum oxidative power of eosin Y is 0.83 V and the maximum reductive power is – 1.11 V.[2c,17] For comparison, in the case of $Ru(bpy)_3^{2+}$ it is 1.29 V and - 1.33 V,[18] respectively (all redox potentials against SCE).[19] Looking at the current prices of eosin Y is very cost effective (0.63 €/mmol) compared to $Ru(bpy)_3Cl_2$ (144 €/mmol). Iridium-based photocatalysts are even more expensive. Also, from a cost point of view, it is consequently a good decision to prefer organic photocatalysts. Many chemists directly associate the term "stilbene" with Resveratrol (3,4′,5-trihydroxystilbene), a major ingredient in wine that has been shown to have strong anti-inflammatory and antioxidant properties and can inhibit platelet aggregation and cancer cell growth.[20] Of obvious fact, stilbenes are a whole class of compounds, and synthetically produced stilbenes have their own properties and applications. The ubiquitous presence of

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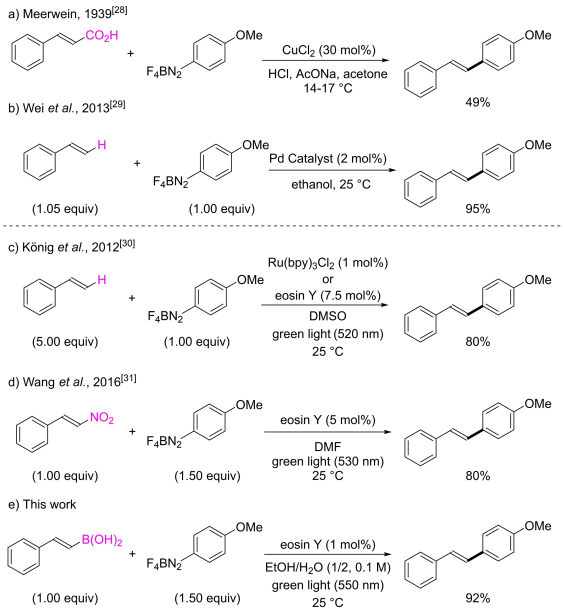
the stilbene motif in materials,[21] natural products,[22] and pharmaceuticals[23] has led to the development of some very mature synthesis methods which are applied in the laboratory and on industrial scale. Some important examples are the already mentioned Heck reaction,[24] the Julia-Olefination,[25] Perkin condensation,[26] and the Wittig-Horner-Reaction.[27] They were traditionally limited by the use of base, metal, and relatively high reaction temperatures. Recently, in the course of a renaissance of photochemical reactions, which has been going on for about 15 years, photochemical methods using visible light have become more and more popular. New selective and intense light sources can as a trace-less reagent to supply photons. In this context it is worthwhile to compare some reactions, more recent and historical ones (Scheme 1). Already in 1939, Meerwein reported the use of diazonium salts in a coupling reaction with cinnamic acid to generate (*E*)-1-methoxy-4-styrylbenzene. Other unsaturated compounds including alkenes were also suitable for the reaction (Scheme 1, a).[28] Without intending to diminish this breakthrough, the disadvantages of the reaction are striking. High catalyst loadings and low yields. In addition, chlorine from the catalyst can bind to the double bond and lead to the generation of by-products. Nowadays, in the presence of small amounts of palladium catalysts, a modified Mizoroki-Heck coupling reaction can provide excellent yields (Scheme 1, b).[29] By using photocatalysis, it is possible to dispense with metal catalysts and carry out the reaction under irradiation with visible light in the presence of eosin Y. In the example reaction the substrate was styrene, which is particularly inexpensive, but had to be used in large excess of five equivalents (Scheme 1, c).[30] In order to overcome this drawback, the need for a suitable leaving group was apparent, which was identified with the conversion of nitroalkenes (Scheme 1, d).[31]



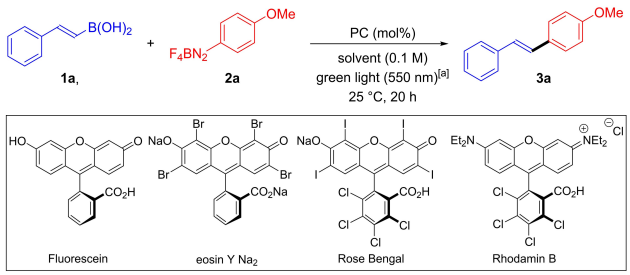
Scheme 1. Evolution of Heck type cross coupling reactions.

Herein we report on a metal catalyst and base free system, which with the help of green light and only one percent of organic dye, creates a new C–C bond and makes many stilbenes accessible starting from an alkenyl bearing a boronic acid leaving group (Scheme 1, e). Many different functional groups (including nitro group) on the diazonium salt and the other substrates were tolerated. The stereoselectivity was very high in the reactions carried out led nearly exclusively to the (*E*)- stilbene. Mechanistic studies show that under the chosen reaction conditions both reaction partners are activated, and the corresponding radicals were directly detected by EPR experiments and indirectly by side products. The portable Lumatec SUPERLITE S 04 (150 W, 100–240 V, 50–60 Hz)[32] with fiber optic cable was used as a light source in our studies. Control experiments were carried out to determine the output and emission of our specific light source and to compare it with commonly used green LEDs. We have chosen an alkenyl substrate with a boronic acid as leaving group for our investigations, since they are commonly applied in important reactions like the Suzuki-Miyaura coupling due its experimental convenience and commercial availability.[33] Besides, only a couple of examples are known for the use of boronic acids in connection with photocatalysis.[34] It is also necessary to mention that in contrast to alkenyl boronic acids, aryl diazonium salt is well known and has been studied in detail with regard to its properties to generate aryl radicals not only under the exposure to light and is used in many cross-coupling systems, especially with palladium.[35]

2. Results and Discussion

At the beginning of our investigations we tried to identify suitable reaction conditions based on the methods known from the literature for Ru-catalyzed (and eosin Y-catalyzed) photoredox Meerwein arylation and the conversion of nitroalkenes.[30–31] Therefore, various diazonium salts were generated from the corresponding aniline derivatives. Attention was paid to keep the reaction at low temperature, as diazotation is an exothermic reaction and the diazonium salts are usually not thermally stable (depending on the substituents on the aromatic ring). Diazonium salts with electron withdrawing residues were easy to handle. Furthermore, attempts to obtain diazonium salts from heteroaromatic amines failed. Initial studies into the coupling of (*E*)-styreneboronic acid (**1 a**) and 4-methoxybenzenediazonium tetrafluoroborate (**2 a**) were performed with organic dye Fluorescein (15 mol%), with exposure to green light in MeCN (Table 1, entry 1; 13% yield). Investigations were carried out to find the appropriate photocatalyst. Initially, a large amount of catalyst was used, which was further optimized later. Organic dyes of the fluorescein family were compared. Changing the photocatalyst to eosin Y, Rhodamine B or Rose Bengal slightly improved the overall reaction efficiency (Table 1, entries 2–4). We decided to use eosin Y, which has been thoroughly examined in literature, for all subsequent experiments. With eosin Y as the catalyst and acetone as solvent, the reactivity was improved (Table 1,

Table 1. Initial optimization studies.



Entry [b]	PC [mol %]	Solvent	Other deviation	GC Yield [%][c]
1	Fluorescein (15)	MeCN	–	13
2	eosin Y (15)	MeCN	–	16 (15)[d]
3	Rose Bengal (15)	MeCN	–	17
4	Rhodamine B (15)	MeCN	–	16
5	eosin Y (15)	acetone[d]	–	20
6	eosin Y (15)	EtOAc	–	15
7	eosin Y (15)	DCM	–	9
8	eosin Y (15)	THF	–	14
9	eosin Y (15)	MeCN	**2a** (2.0 equiv)	34
10	eosin Y (15)	acetone[d]	**2a** (1.5 equiv)	45
11	eosin Y (15)	extra dry acetone]	**2a** (2.0 equiv)	39
12	eosin Y (15)	acetone[d]	**2a** (2.0 equiv), N*i*Bu$_3$ (1.0 equiv)	27
13	eosin Y (15)	acetone[d]	**2a** (2.0 equiv), EtN*i*Pr$_2$ (1.0 equiv)	21
14	eosin Y (15)	acetone[d]	**2a** (2.0 equiv), DTBP (2.0 equiv) and no light	10
15	eosin Y (1)	acetone[d]	**2a** (2.0 equiv)	48
16	eosin Y (1)	EtOH/H$_2$O (1/1)	**2a** (1.5 equiv)	84
17	eosin Y (1)	EtOH/H$_2$O (1/2)	**2a** (1.5 equiv)	93
18	eosin Y (1)	MeCN/H$_2$O (1/2)	**2a** (1.5 equiv)	70

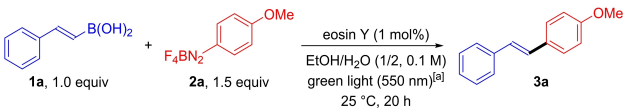
[a] Lumatec SUPERLITE S 04; for more details, refer to the Supporting Information. [b] The reactions in this table were conducted on a 0.2 mmol scale. [b] GC yield was determined by GC-FID analysis using hexadecane as an internal standard. [c] The yield of isolated product obtained from a reaction on a 0.3 mmol scale is given in parenthesis. [d] Acetone contained 0.21% of water (determined by Karl-Fisher titration).

entry 5; 20%), while other tested polar solvents had a negative effect (Table 1, entries 6–8). An excess of diazonium salt **2a** of two equivalents in MeCN as solvent improved the yield to 34% (Table 1, entry 9). One explanation for this could be the formation of dimers, like in this case 4,4′-dimethoxy-1,1′-biphenyl (detected by GC-MS) as a competing reaction. The best solvent to this point, acetone, was used and the amount of **2a** used was reduced to 1.5 equivalents. We used technical grade acetone, which contained 0.2% of water (determined by Karl-Fischer titration) (Table 1, entry 10; 45%) and a control experiment with extra dry acetone showed negative effects on the yield (Table 1, entry 11; 39%). Aryldiazonium salts are known to be capable of being activated even without light, just in the presence of a weak base.[36] To investigate whether such a base-catalyzed system would be suitable for our case, two control experiments were performed.

The two bases TIBA (triisobutylamine) and DiPEA (*N*,*N*-diisopropylethylamine), which are commonly used in photocatalytic systems, could not lead to any improvement. They even decreased the overall efficiency (Table 1, entries 12 and 13). Furthermore, it was investigated whether the reaction could also be initiated by using a radical starter, in the absence of light. The experiment with DTBP (Table 1, entry 14; 10%) gave a similar poor result as a control experiment without organic dye. Next, the amount of organic dye was adjusted. Reducing the amount to only 1 mol% eosin Y even improved the yield slightly (Table 1, entry 15; 48%). Extensive testing with different solvents showed that wet solvents were superior to dry solvents. We hypothesized that on the one hand the solubility of boronic acid **1** in solvents with water is better and on the other hand that diazonium salts can be activated by even small amounts of water. The reaction with water and ethanol in a ratio of 1 to 1 dramatically improved the yield to 84%. Increasing the amount of water to a ratio of water to ethanol of 2 to 1 improved the result further to over 90%. To make a comparison to the previous investigations a mixture of water with MeCN (2:1) was used and 70% yield was obtained (Table 1, entry 18). Other commonly used solvents were also able to achieve yields above 90% (for more detailed information see supporting information), but it was deliberately decided to use the most "green" mixture of solvents for the scope.[37]

In our further optimization studies, the omission of one of the solvents, respectively the performance in pure water or ethanol, and the control experiment in the dark showed that all components of the system are necessary for an efficient product formation (Table 2, entries 2–4). Under these optimised reaction conditions, it was not possible to avoid an excess of diazonium salt **2a** (Table 2, entry 5). A possible reduction of the reaction time to about 6.5 h could be derived from the reaction progress monitoring (Table 2, entry 6, see supporting informa-

Table 2. Further optimization studies.



Entry[b]	Deviation	GC Yield [%][c]
1	none	93 (91)[d]
2	no light	8
3	only H$_2$O as solvent	32
4	only EtOH as solvent	34
5	**2a** (1.0 equiv)	80
6	Reaction time of 6.5 h	93
7	0.05 M	94
8	0.2 M	85
9	white light (400–700 nm)[a]	53
10	blue light (460 nm)[a]	72
11	LEDs (3 W, λ_{max} = 568 nm)[d]	90[e]

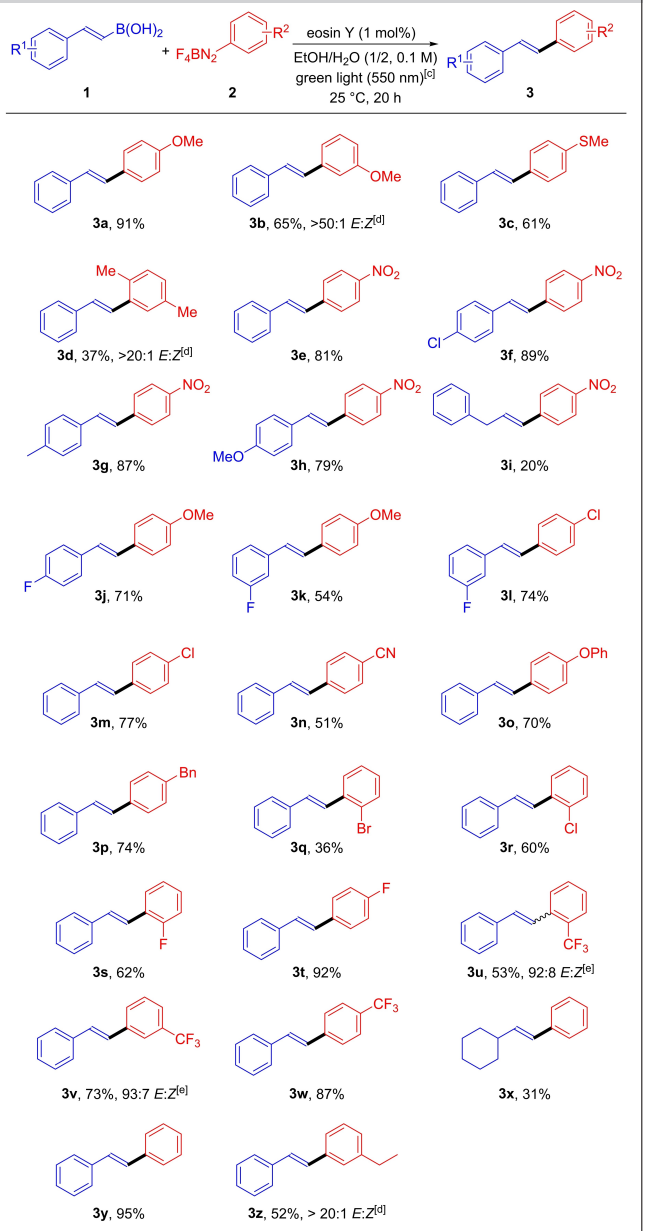
[a] Lumatec SUPERLITE S 04; for more details, refer to the Supporting Information. [b] The reactions in this table were conducted on a 0.2 mmol scale. [b] GC yield was determined by GC-FID analysis using hexadecane as an internal standard. [c] The yield of isolated product obtained from a reaction on a 0.5 mmol scale is given in parenthesis. [d] Innotas LED 568 nm, 300 milli Candela. [e] 95:5 *E*:*Z*.

tion for details). For reasons of convenience and the possible varying reactivity of the different substrates used, the reactions were run overnight (20 h). Different concentrations of the reactants were screened (Table 2, entries 7 and 8). The initially chosen concentration of 0.1 M with respect to the boronic acid **1a** gave a similar result to 0.05 M and was maintained. Our tuneable light source was used with different settings (Table 2, entries 9 and 10, the corresponding spectra can be found in the supporting information). The setting to green light with an emission peak at $\lambda_{max} = 550$ nm resulted in the best efficiency. A control experiment with green LEDs (emission peak at $\lambda_{max} =$ 568 nm), gave a comparable result (Table 2, entry 11; 90%). In this experiment, the reaction temperature did not exceed 30 °C even without active cooling.

We next studied the general validity of this coupling reaction and the results are summarized in Table 3. First, already in our model reaction, an electron donating methoxy group in *para*- position was introduced (**3a**, 91%, >99:1 *E*/*Z*). The same reaction using a diazonium salt bearing the methoxy group in *meta*-position, led to a visible drop in efficiency and *E*/*Z* isomerism (**3b**, 65%, >50:1 *E*/*Z*). Obviously, the reaction is negatively influenced by steric hindrance, whereby the relatively small methoxy group is already enough. This observation is supported by the introduction of an electron-withdrawing group (CF_3) in the same way, in different positions on the ring of the diazonium salt (**3u**–**w**). Again, the trend in terms of yield was *para* > *meta* > *ortho*. Bearing the deactivating nitro group in *ortho*-position lead to a good yield (**3f**, 89%). Driven by this observation and the fact that the NO_2 group on the substrate in the system by Wang *et al.* was completely neglected,[31] we kept the diazonium salt unchanged and varied the boronic acid. Different electron rich and electron poor substituents on the boronic acid all offered the desired product in good yields (**3e**–**h**). An exception represent the conversion of the non-aromatic boronic acid (*E*)-(3-phenylprop-1-en-1-yl)boronic acid (**3i**, 20%) and boronic acid bearing a cyclohexyl instead of phenyl rest (**3x**, 31%). One explanation for this is the lack of stabilization via the resonance effect of the phenyl ring attached to the formed radical. Fluorinated boronic acids generally gave lower yields than their non-fluorinated pendants (compared **3l** and **3m**). Also, in this case, the *para*-substituted substrate outperformed the *meta*- and *ortho*-substituted variant. Different substitutions in *para*-position of the diazonium salt (nitrile-, phenoxy-, and benzyl) were tolerated and gave moderate to good yields of the desired products (**3n**–**p**). To demonstrate the limitation of the reaction in stilbenes with substitution in 1-position, readily halogen rests were introduced (**3q**–**s**). Surprisingly, only low yields were obtained with simple alkyl substituents (**3d** and **3z**). In these cases, the homo coupling of boronic acid was observed by GC-MS leading to the generation of competing 1,4-substituted butadiene products.

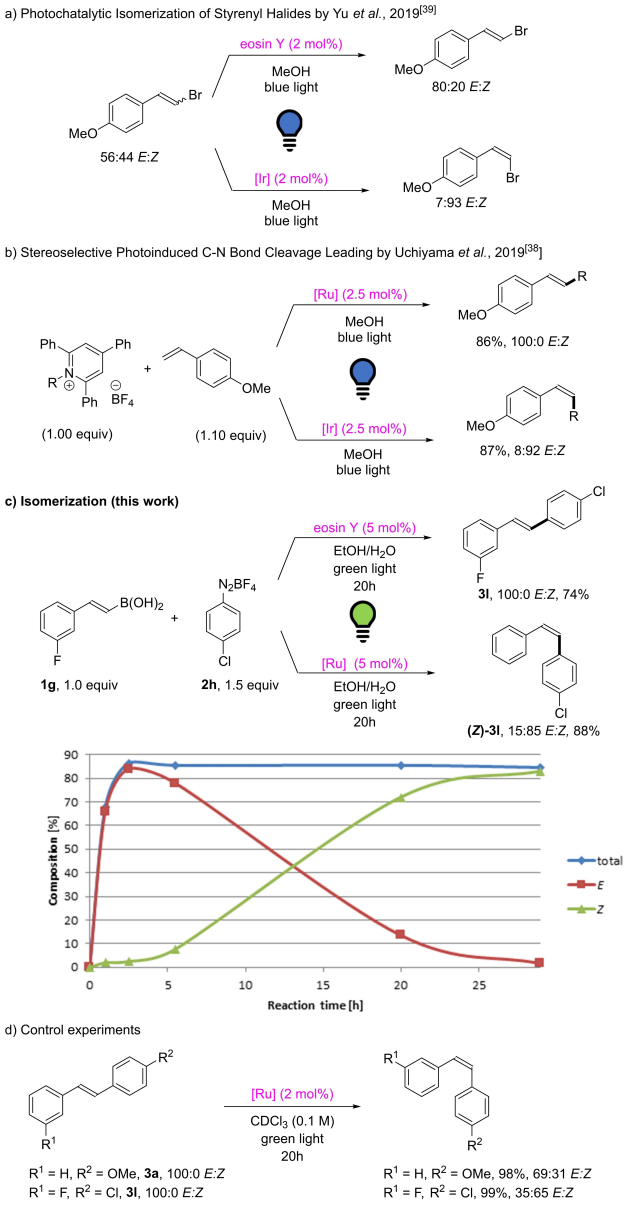
While the selectivities for *E*-stilbenes together with eosin Y were very high, almost pure *Z*-stilbenes could be obtained when using $Ru(bpy)_3Cl_2$ as photocatalyst. This phenomenon has been described most recently by the groups of Uchiyama[38] and Yu[39] (Scheme 2). In order to find out whether the

Table 3. Synthesis of stilbenes.[a,b]



[a] Reaction conditions: Boronic acid **1a** (0.50 mmol), diazonium salt **2a** (0.75 mmol), eosin Y (1 mol%), EtOH/H_2O (1/2, 0.1 M), 25 °C, 20 h. [b] Yields are given of the isolated product after column chromatography. [c] Portable Lumatec SUPERLITE S 04 was used as light source.[32] [d] *E*/*Z* ratio determined by GC-FID. [e] *E*/*Z* ratio determined by ^{19}F NMR spectroscopy.

conversion of (*E*)-boronic acid to *Z*-stilbene in the presence of $Ru(bpy)_3Cl_2$ follows its own mechanism or is a conversion to *E*-stilbene with subsequent isomerization, a monitoring was performed (c). A look at the reaction profile showed that photo-induced isomerization followed the actual coupling step. According to the GC-FID evaluation the reaction is incomplete after 1 h, but it is already evident that almost pure *E*-isomer was formed (*E*:*Z* 97:3, 68% overall yield). After 2.5 h the reaction was complete, and the yield was 88%. It is not expected to increase further during monitoring. The third sample after 5.5 h revealed that part of the *E*-product has



Scheme 2. Mechanistic study. [Ir] = $Ir(ppy)_3$ and [Ru] = $Ru(bpy)_3Cl_2$. All reactions conducted at room temperature.

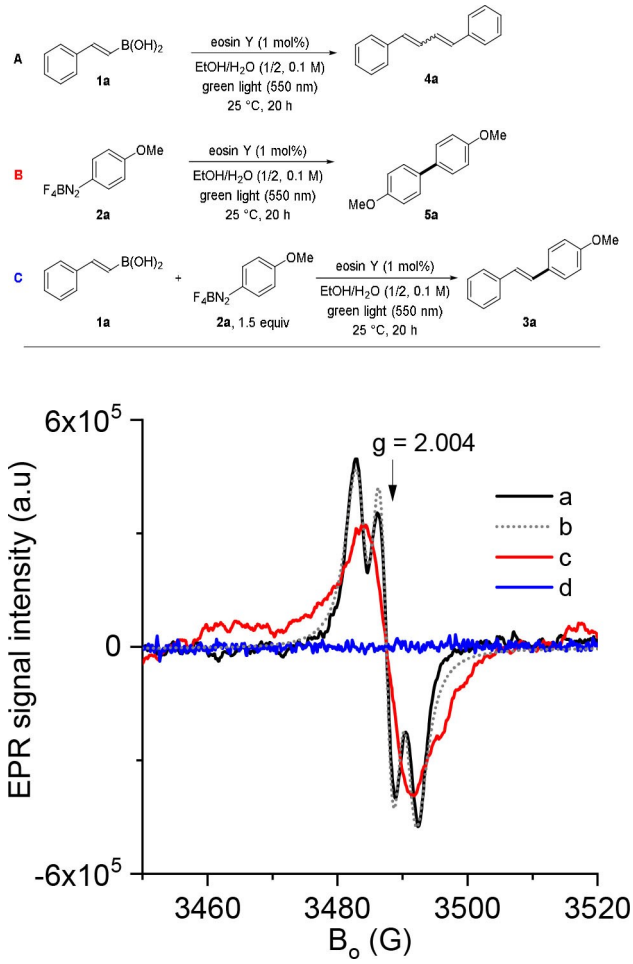


Figure 1. *In situ* EPR measurements for reactions indicated in the top panel. a) *In situ* EPR spectrum for the reaction between boronic acid **1a** (0.10 mmol) and eosin Y (1 mol%); b) EPR spectral simulation of (a); c) *in situ* EPR spectrum for the reaction between diazonium salt **2a** (0.10 mmol) and eosin Y (1 mol%); d) EPR spectrum for the reaction between boronic acid **1a** (0.10 mmol), diazonium salt **2a** (0.15 mmol), and eosin Y (1 mol%); in EtOH/H_2O (1/2, 0.1 M) during irradiation with green light.

already been converted in the subsequent isomerization step (*E:Z* 91:9). The fourth sample after 20 h showed that the *Z*-stilbene was now the main product. The product mixture could be isolated and the exact composition (*E:Z* 15:85) was determined by ^{19}F NMR. After 29 h almost pure (*Z*)-stilbene was found (*E:Z* 2:98). In an additional control experiment the conversion of model substrate **3a** to (*Z*)-**3a** in the presence of $Ru(bpy)_3Cl_2$ was achieved, but much more slowly. After 20 hours of irradiation only 65% converted to (*Z*)-**3a**.

In order to get a better understanding of the mechanistic background, different *in situ* EPR controlled experiments were performed as shown in Figure 1. The EPR spectrum during irradiation a reaction mixture between boronic acid **1a** (0.10 mmol) and eosin Y (1 mol%) catalyst in EtOH/H_2O mixture with green light showed a three-lines signal at g = 2.004 with coupling constant A = 3.5 G (Figure 1 a). This signal can be simulated[40] considering a hyperfine fine splitting due to the interaction between the magnetic moment of the unpaired electron and nuclear spin of two hydrogen atoms (Figure 1 b) suggesting the formation of phenyl vinyl radical. The relatively broad linewidth of the radical signal indicates the presence of dipolar interactions between the paramagnetic species. This could also explain the slow formation of **4a** dimer which was detected by HR-MS. Additionally, we prove the slow formation of phenyl radical by trapping it with TEMPO to form unstable EPR-inactive compound **7** (Figure S10). This results in slowly decreasing of the EPR signal intensity of TEMPO at g = 2.007 with hyperfine splitting A = 16 G (Figure S11, supporting information). When diazonium salt **1a** (0.10 mmol) and eosin Y (1 mol%) irradiated with a green light in the absent of boronic acid, the EPR spectrum of the reaction mixture showed a radical signal without hyperfine splitting at g = 2.004 (Reaction **C**, Figure 1 c, red line), more probably due to the formation of the phenyl radical of **2a** since the corresponding dimer **5a** was

identified by GC-MS. Interestingly, the reaction mixture between boronic acid **1a** (0.10 mmol), diazonium salt **1a** (0.15 mmol) and catalyst eosin Y (1 mol%) did not show any EPR signal (Figure 1 d, blue line) suggesting that the radical intermediates formed in **A** and **B** are rapidly converted to **3a** product.

Based on these results, a plausible reaction mechanism is shown in Scheme 3. In the literature, the formation of a phenyl radical **B** under irradiation of diazonium salts **2** with green light from LEDs in presence of eosin Y, via SET from the excited state of eosin Y, has been extensively described and the phenyl radical **B** could successfully be trapped with the persistent radical TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy).[14a,f, h, i, 30] At the same time, after a SET from eosin Y* to the boronic acid **1**, a short-lived radical **A** could be formed. The corresponding trapping experiment with TEMPO gave traces of 2-phenylacetaldehyde **8**, which is the rearrangement product of unstable intermediate **7** (Figure S11). The dimer **4a** was found to be the major product after 24 h, in an experiment analogue to EPR a (Figure 1). This phenomenon opens an alternative mechanistic pathway I. Depending on the substitution of the compounds **1** and **2**, the amount of recombination to the respective dimers **4a** and **5a** is greater or smaller. From this, it can be deduced that the radical self-reaction rate constants k_s for the radicals are significantly different. The PRE (persistent radical effect) would be the basis for the selective cross-coupling of **A** and **B**, since the respective half-lives differ significantly for both radicals and are form at the same rates.[41] From the GC-MS after 5 min and 30 min of irradiation it can be concluded that there is a significant difference in the radical self-reaction rate of the two radicals ($k_{s,A} \ll k_{s,B}$). Styrene radical **A** is relatively electron-rich and can be considered as a nucleophile in relation to the more electron-poor phenyl radical **B**, especially if it bears an electron withdrawing group. The other possible pathway II would be the formation of intermediate **C** after the phenyl radical **B** gets trapped by alkenyl boronic acid **1** to generate the radical **C**. A molecular weight of compound **9** which produced by capture intermediate **C** by TEMPO, can be detected in our control experiment as well. From intermediate **C**, cationic intermediate **D** will be formed after oxidation process and then followed by an elimination reaction would give product **3**. Moreover, quantum yield ($\varphi =$ 45.5; Figure S12 and S13) and ^{11}B NMR (Figure S14) were measured as well to support the reaction mechanism.

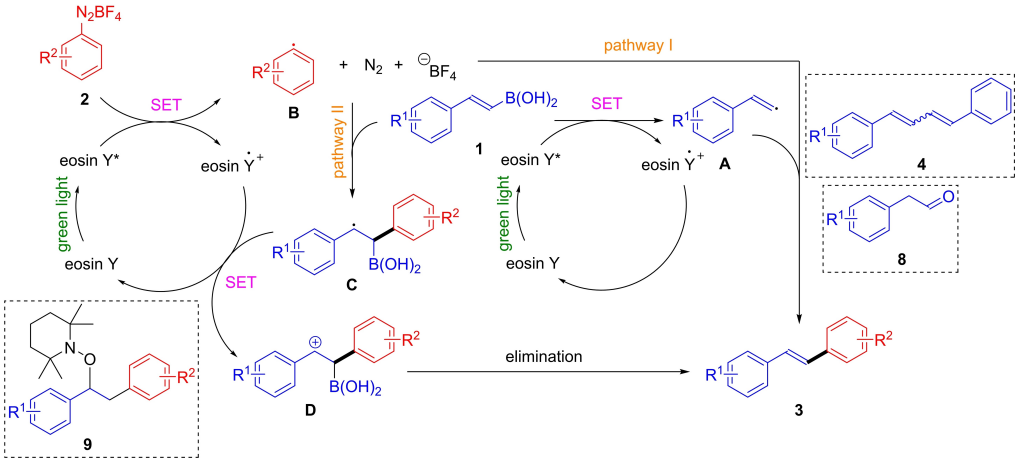
3. Conclusion

In summary, we have developed an environmentally friendly photochemical system for a stereoselective cross-coupling reaction, which, starting from a boronic acid and a diazonium salt, makes a wide range of *E*-stilbenes accessible. A subsequent conversion into or the direct conversion to Z-Stilbenes is possible. This reaction meets the requirements of green chemistry, with very low catalyst loadings of the organic dye eosin Y, no base or metal and excellent solvents are used, according to the solvent selection guide.[42] In this way, stilbenes are operationally simple generated, which are an interesting building blocks for the pharmaceutical industry.

Experimental Section

General Information

All commercial reagents were bought from Acros, Aldrich, Alfa, and TCI. Unless otherwise stated, they were used without further purification and analysis. Air- and moisture-sensitive reactions were performed under argon atmosphere and oven-dried glassware. NMR spectra were recorded on a Bruker Avance 300 MHz or a Bruker ARX 400 MHz spectrometer. The chemical shifts δ (ppm) are given relative to the used solvent. In the case of $CDCl_3$ it is 7.26 ppm for ^{1}H NMR and 77.16 ppm for 13 C NMR. Multiplets were assigned as s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublet), and m (multiplet). Chemicals shifts (δ) are noted in ppm downfield of tetramethylsilane. ^{19}F NMR spectra are not calibrated by an internal reference. All GC yields were calculated using hexadecane as internal standard. All measurements were carried out at room temperature unless otherwise noted.



Scheme 3. Proposed mechanism.

EPR spectra were recorded on an X-band Bruker EMX CW-micro EPR spectrometer equipped with an ER4119HS high-sensitivity resonator using a microwave power of Ca 6.9 mW, modulation frequency of 100 kHz and modulation amplitude up to 5 G. EPR spectrum simulation was made with Bruker SimFonia software[40] using the spin Hamiltonian $H=\mu_B SgB_o+SAI$ in which μ_B is the Bohr magneton, S is the electron spin operator, g is the g tensor, B_o is the magnetic field vector, A is the hyperfine coupling tensor, and I is the nuclear spin operator. Electron impact (EI) mass spectra were recorded on AMD 402 mass spectrometer (70 eV) and the data is given as mass units per charge (m/z). Gas chromatography analysis was performed on an Agilent HP-7890 A instrument with a FID detector and HP-5 capillary column (polydimethylsiloxane with 5% phenyl groups, 30 m, 0.32 mm i.d., 0.25 μm film thickness) using argon as carrier gas. The products were isolated by column chromatography on silica gel 60 (0.063–0.2 mm, 70–230 mesh). For irradiation the light source was placed ca. 15 cm from the reaction vial inside a manufactured box. The reaction temperature was maintained with a fan (see 3.4 for a typical set up). In every reaction the strong light source Portable Lumatec SUPERLITE S 04[32] was used with different set filters: blue (λmax = 460 nm) or green (λmax = 550 nm). The Emission spectra can be found in the supplementary information. They were measured with AvaSpec-ULS4096CL-EVO spectrometer and linked CMOS linear image sensor.[43] The output at the different wavelengths was measured with the electronic actinometer (Thorlabs PM100USB).[44] The attached S405 C measuring cell was placed at a distance usual for a reaction performance (~15 cm from the light source). In the case of green light (550 nm) the measured output intensity was 16 mW cm^{-2}, for blue light (460 nm) it was 18 mW cm^{-2} and for white light (400–700 nm) it was 81 mW cm^{-2}.

General Procedure A: Generation of Diazonium Salts

The respective arylamine (5 mmol) was suspended in distilled water (2 mL), mixed with fluoroboric acid (1.7 mL, 50% in water) and cooled down to 0 °C using an ice bath. Sodium nitrite (0.35 g in 1 mL) was slowly added over a period of 5 min. The reaction mixture was stirred for 60 min at 0 °C. If initially no precipitate was formed, iced diethyl ether (5 mL) was then added. The precipitate was separated by filtration and dissolved again in a small amount of acetone. The diazonium tetrafluoroborate was precipitated several times with ice-cooled diethyl ether, filtered, dried under vacuum and washed with small amounts of diethyl ether.

General Procedure B: Photocatalytic Preparation of Stilbenes

A 8 mL snap vial containing a magnetic stirring bar was charged with boronic acid **1** (0.50 mmol, 1.0 equiv), aryldiazonium salt **2** (0.75 mmol, 1.5 equiv), and photocatalyst eosin Y disodium salt (3.5 mg, 0.005 mmol, 1 mol%). The vial was evacuated and back-filled with argon to remove the residual air. In the absence of light, the degassed solvents EtOH (1.7 mL) and H_2O (3.3 mL) were added under an argon stream to give a 0.1 M solution. This solution was irradiated with green light (550 nm) from a portable Lumatec SUPERLITE S 04[32] (15 cm away, with cooling fan attached to keep the reaction near 25 °C) and thoroughly stirred (1200 rpm) for 20 h. The reaction mixture was transferred to a separating funnel, diluted with dichloromethane and washed with water (10 mL). The aqueous layer was washed with dichloromethane (3 × 10 mL). The combined organic phases were dried over Na_2SO4, filtered and concentrated under vacuum. The crude product was purified by column chromatography on silica gel (eluent: pentane/ethyl acetate 100:0–10:1) to afford product **3**.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: alkenes · cross coupling · eosin Y · green chemistry · photocatalysis

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5.3 Visible Light Induced Palladium-Catalyzed Dehydrogenative Carbonylation of Amines to Oxalamides

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Author contributions:

In this paper, I planned and performed close to all the experiments. I analyzed the data on my own. I wrote the manuscript alone. My contribution as the first author of this paper is more than 80%.

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Catalysis

Visible-Light-Induced Palladium-Catalyzed Dehydrogenative Carbonylation of Amines to Oxalamides

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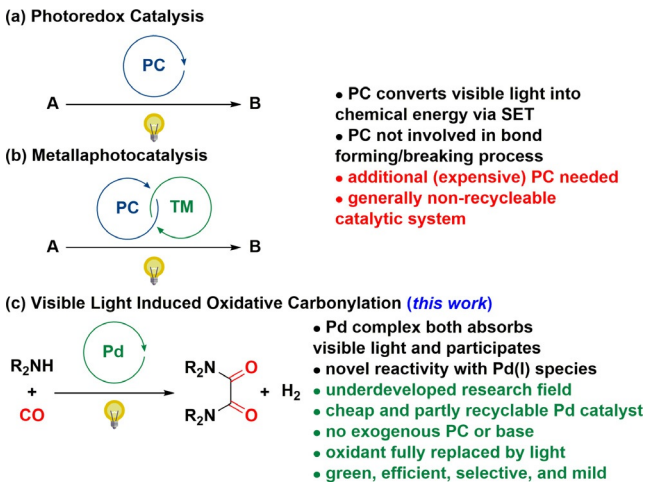
Abstract: The palladium-catalyzed oxidative carbonylation of amines toward the synthesis of oxalamides has been established around 30 years ago and it usually needs the presence of (over)stoichiometric amounts of oxidant. In this work, the first transformation of this type in which the oxidant was replaced by visible light is described. The new approach uses a simple robust Pd complex, which can even be partially recycled. A mechanistic reason is provided and supported by control experiments and EPR studies, showing that Pd^{I} was formed and Pd^{0} was the active species. Both nitrogen- and the intermediate acyl radical can be detected. Moreover, the formation of hydrogen was confirmed by gas GC.

Compared to the use of UV light, which has already found many applications in industry, visible light is a potentially less harmful energy source for chemical reactions. The application of photoredox catalysis (PC) in organic synthesis has already been explored extensively (Scheme 1 a).[1] Organic dyes or rigid and coordinatively saturated metal complexes of Ru and Ir are the typical PC. They engage a single-electron transfer (SET) process with the organic substrate and do not directly participate in the bond forming/breaking process.[1b] The photoexcited species involved has the interesting property of being both more oxidizing and reducing than its ground state. This property is usually quantified by the reduction potential vs. the saturated calomel electrode (SCE).[1b] A novel powerful tool is the dual catalysis, which combines photocatalysis and TM catalysis (metallaphotocatalysis) and makes new chemical transformations accessible.[2] Their two corresponding catalytic cycles are involved (Scheme 1 b). It requires an exogenous PC which harvests light and undergoes a SET or energy transfer to the TM catalyst, the latter is directly involved in the formation or breakage of a chemical bonds. Under comparably mild conditions, reactive radical species are accessible from native functional groups. New pathways for direct coupling of non-traditional nucleophilic partners afforded by new complementary activation modes. Recently, in the context of carbonylation visible-light excitation Arndtsen et al. described the capability of palladium to drive both oxidative addition (OA) and reductive elimination (RE) in their carbonylative transformations of organic halides.[3] However, visible light (400–760 nm) can itself provide energy in a range from 71 to 38 kcal mol^{-1}.[4] This lies within the energy barriers of many TM-catalyzed reactions that traditionally require a heat source. Circumventing this macroscopic element, visible light provides a potentially cleaner energy source for reactions and access to high-energy species. Important elementary steps in classic organometallic chemistry such as ligand dissociation, OA, RE, transmetallation, and migratory insertion could all be influenced by visible light without any additional PC.[5] Herein, we report on a novel visible light induced TM catalysis, a new underdeveloped research field (Scheme 1 c).[6] Nevertheless, already some examples of visible light induced systems with Mn,[7] Fe,[8] Co,[9] Ni,[21] Cu,[10] Ru,[11] Rh,[12] Pd,[13] and Au[14] catalysts are known. In the context of CO chemistry, the number of publications is rather limited,[15] except several examples on carbonylative photoredox catalysis,[16] metallaphotocatalysis,[3,17] and light-induced systems[18] exist. Our showcased yellow Pd complex absorbs visible light and participates directly in the bond forming process of the oxidative carbonylation. Under the oxidant-free conditions, hydrogen gas was formed and detected by gas GC.



Scheme 1. Photocatalysis involving transition metals.

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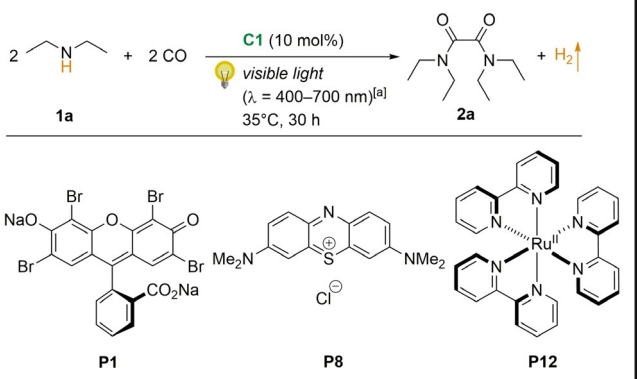
Oxalamide is a class of building block that can be found in various molecules of synthetic relevance including pharmaceuticals,[19] ligands,[20] and precursor in the production of ethylene glycol (EG).[21] Oxidative carbonylations have the considerable advantage over the classical approaches of for example, condensation reaction of avoiding toxic oxalyl chloride. However, these reactions usually lead to mixtures with the corresponding urea, as described by Costa et al. in the presence of PdI_2/KI.[22] Pioneering work in terms of selectivity for oxalamides was already done in 1990 by Pri-Bar and Alper with the carbonylation of secondary (and primary) amines in the presence of iodide ions as a promoter and oxygen to the corresponding oxamides (Scheme 2).[23] The reaction was performed at room temperature and low pressures ($CO:O_2$, 3.7 bar), with stoichiometric amounts of promoter, oxidant, and base as well as high catalyst loadings (7 mol%). An improved catalytic system was reported by Gabriele et al., using lower amounts of KI in an ionic liquid at moderate pressure (CO:air, 20 bar) and low Pd loading (1 mol%).[24] Later, Dong et al. further improved the catalytic efficiency dramatically to an industrial useful level. Featuring low catalyst loadings (0.01 mol%) and high turnover number (TON) (26500), the presence of base (10 mol%) and nBu$_4$NI (5 mol%) was still necessary.[21a] Despite the synthetic value of these methods, the palladium-catalyzed synthesis of oxalamides from amines has been limited by the requirement of additives (often in stoichiometric amounts) and the need of O_2:CO mixtures. The latter involves the risk of explosion and requires special handling. Hence, new alternative procedure for oxalamides synthesis is still in demand.

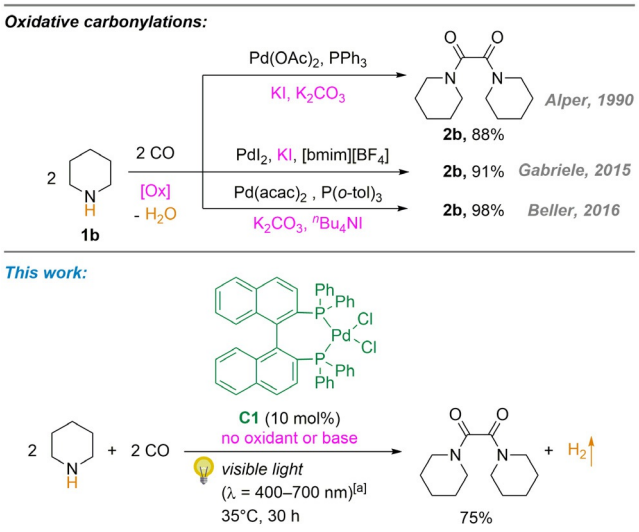
With this information in mind, we started our investigations to find suitable reaction conditions (for optimization details, see Supporting Information). For our model substrate diethylamine (**1a**), the target oxalamide (**2a**) can be isolated in 76% yield (Table 1, entry 1; palladium catalyst **C1** (10 mol%), diethylamine (0.2 mmol) in DMAc (*N*,*N*-dimethylacetamide) (0.05 M), irradiated (400–700 nm) for 30 h at 35 °C). No urea product could be detected in GC-MS. Control experiments showed catalyst and light were all individually necessary (Table 1, entry 2 and 3). In agreement with our previous studies, catalyst **C1** proved to be superior to a mixture of $PdCl_2$/BINAP and their in situ coordination. Notably, simple $PdCl_2$ without additional ligand was moderately effective in catalyzing our reaction. A reaction stopped after 20 h showed that palladium black was clearly formed. The corresponding GC-MS spectrum of the reaction mixture showed no by-products (Table 1, entry 4; 42%). Unfortunately, increasing the reaction time to 30 h did not increase the yield (43%). To our delight, in the presence of the simple bidentate phosphine catalyst *rac*-BINAP, extending the reaction time to 30 h could increase the yield significantly (Table 1, entry 5; 64%). We conducted extensive investigations photocatalysts and additives in a homogenous system. With particular focus on photocatalysts and the possible synergistic catalysis of PC and TM (Scheme 1b). However, they did not lead to an improvement in the efficiency of our system. This observation was also confirmed during the composition of our final optimization. The most notable of these are eosin Y **P1** (Table 1, entry 6) and ruthenium catalyst **P12** (Table 1, entry 7), both of which either reduced the yield or remained within the error tolerance. Interestingly, methylene blue **P8** (Table 1, entry 8; 93%) led to excellent yield. No oxidants were screened since this would have contradicted our initial idea. The addition of base NaOAc (Table 1, entry 9) could slightly improve the overall efficiency. We decided to keep our catalytic system as simple as possible. Although DMAc proved to be the superi-

Table 1. Optimization studies.[a]

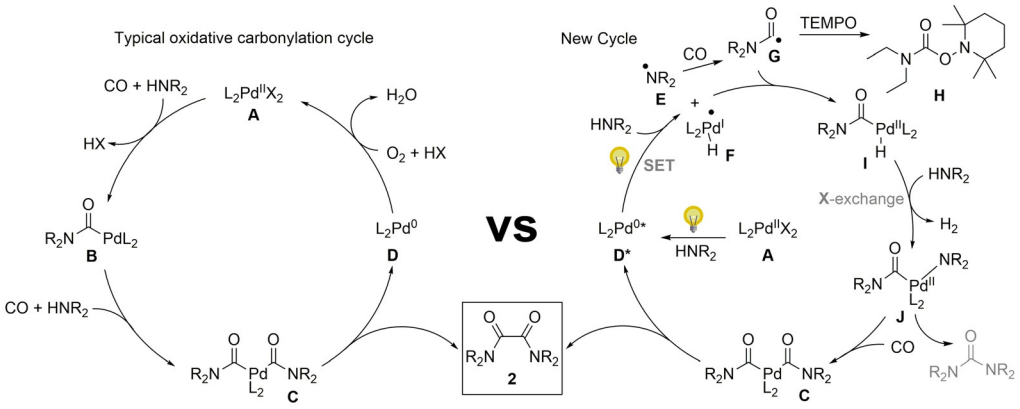


Entry	Variation	Yield [%][b]
1	none	74
2	no **C1**	0
3	no light	6
4	$PdCl_2$ (10 mol%) instead of **C1**	43(42)[c]
5	$PdCl_2$ (10 mol%) and BINAP (10 mol%) instead of **C1**	64(52)[c]
6	additional **P1** (5 mol%)	58
7	additional **P12** (5 mol%)	70
8	additional **P8** (5 mol%)	93
9	additional NaOAc (1.0 equiv)	81
10	**C1** (5 mol%)	65

[a] Reactions in this table were conducted on a 0.1 mmol scale. [b] GC yields were determined by GC-FID analysis using hexadecane as an internal standard. [c] The yield of **2a** after reaction time = 20 h is given in parenthesis.



Scheme 2. Generation of oxamides via oxidative carbonylation and novel light mediated synthetic pathway.



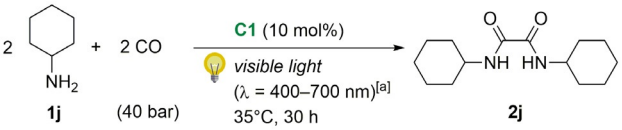
Scheme 3. Proposed mechanism. Oxidative carbonylation vs. light-induced oxidant free system (this work).

or solvent, our product could be found in nonpolar (Ph-H, Ph-Me) as well as polar solvents (ethyl acetate (EA), acetone, MeCN) in medium to low yields (Table S4, entry 14–21). Moreover, early investigations with model substrate piperidine **2a** on different Pd sources showed comparable activity for $PdCl_2$, PdI_2, and $PdBr_2$ (Table S3) indicating, that the halogen ions most likely do not act as promoters in our reaction. In accordance with our proposed mechanism (Scheme 3), the reaction was catalyzed by Pd^0. We investigated the soluble Pd^0 sources $Pd(PPh_3)_4$ and $Pd_2(dba)_3$. Both were capable to catalyze the target transformation (Table S3, entry 11 and 12). Maybe due to its heterogeneous nature or obstruction of light, Pd/C could only give traces of oxamide product **2b**. A Pd/C-BINAP system could not improve these results.

Halving the catalyst loading of our final catalyst **C1** to 5 mol% resulted in the loss of efficiency (Table 1, entry 10). However, in close to every reaction a significant amount of the catalyst could be recovered by column chromatography and the NMR data were in agreement (Figure S6). It can therefore be assumed that our reaction is very slow and the large surface area with 10 mol% catalyst loading leads to acceptable TON in the given time. Extensive testing has shown EA to be the best solvent for primary amines and **2j** could be obtained in 75% yield (Table S5, entry 1). It could be observed that amines **1** generally dissolve well in EA, whereas the formed oxamides **2** dissolve very poorly. A possible explanation for the superiority of EA is that according to Le Chatelier's principle, the insoluble product is removed from the equilibrium. Interestingly, nonpolar solvent toluene could also provide **2j** in good yields (Table S5, entry 4, 68%).

To demonstrate the recyclability of our catalytic system, we performed an experiment with primary cyclohexylamine **1j**. After exposure to our standard protocol, the resulting oxalamide **2j** was easily separated from the slightly green suspension by a short column. The catalyst **C1** was recovered smoothly and found to be relatively stable to oxidation (in solution). **C1-R** (recovered) was isolated to 74% and was reused without additional "new" **C1** (see Table 2). The second run gave product **C1-R'** in 56% yield. After the third run, the recycle experiments were stopped, as only 44% of the catalyst **C1-R''** could

Table 2. Recycling of catalyst **C1**.



1j 2j

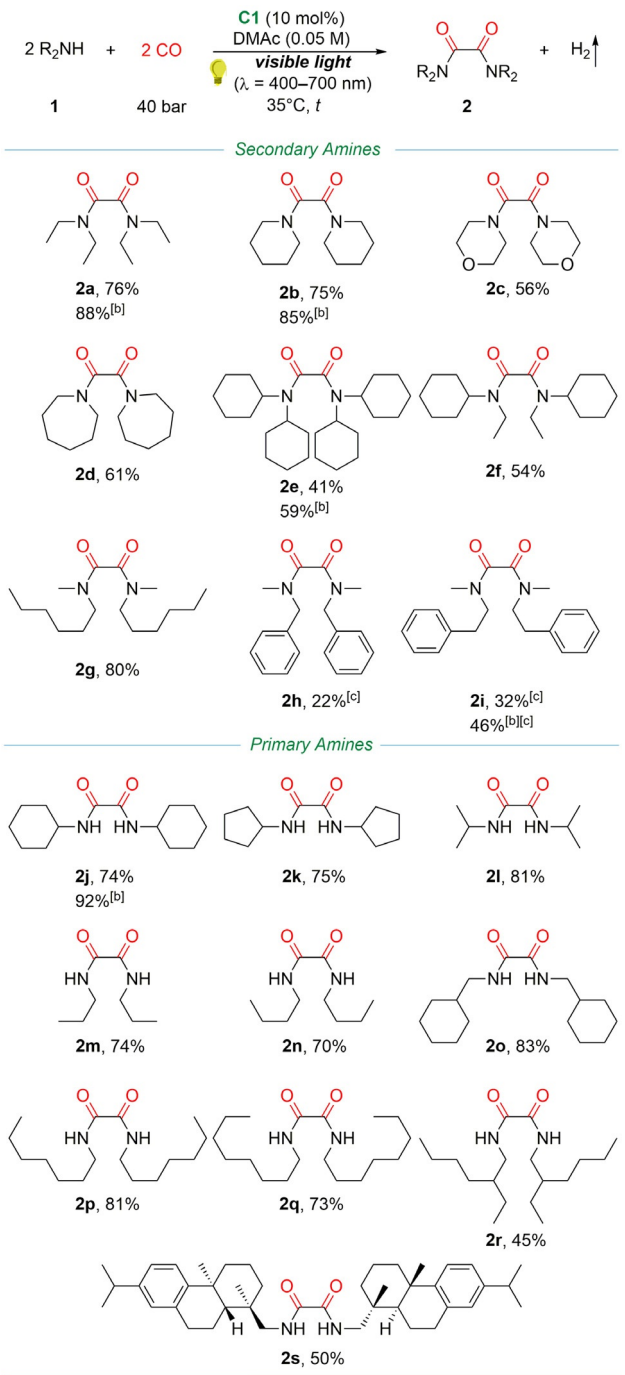
Run	Amount of **1j** [mmol][a]	S/C	*c* [M]	Recovered **C1-R** [%][b]	Yield **2j** [%]	TON[c]
1	0.40	10	0.05	74	75	3.8
2	0.30	10	0.05	56	76	3.9
3	0.17	10	0.05	44	75	3.8
4	0.07	10	0.05	–	75	3.8

[a] Initially 40 μmol of **C1** were used and no additional **C1** was added in the four runs presented. The amount of **2j** injected was adjusted to the amount of **C1-R** keeping S/C = 10. [b] Recovered **C1** [%] always refers to the amount of **C1** used in the previous run (for more information see Supporting Information). [c] TON = mol of **2j** formed per mol of **C1**.

be recovered. Over all runs only a very minor loss of activity could be observed. A part of the catalyst becomes palladium black, which is an irreversible step. To ensure comparability, the substrate to catalyst ratio (S/C) was kept at 10 and the reaction concentration 0.05 M.

Under our standard conditions, the scope of amines was assessed (Table 3). Various secondary amines can be transformed into the corresponding oxamides in moderate to good yields. Benzylic amines can be also transformed successfully because the benzyl bond can be easily oxidized in the presence of oxidant (**2h**). The addition of photosensitizer can hardly improve the yield of oxamide in this case and by-products from benzyl amines decomposition can be obtained. The results with anilines as substrate turned out to be discouraging since merely traces of the desired product could be observed. The main by-product was the corresponding urea. We next tested different primary amines. In contrast to the methods known in the literature, oxalamide could be found as the main product.[22] We were delighted to find that small simple primary amines gave respective oxalamides in overall good yields (**2j**–**o**, 70–83%). In the case of **2j** excellent yield was achieved when a catalytic amounts of methylene blue (5 mol%) was added. The choice

Table 3. Scope of primary and secondary amines.



[a] Performed with **C1** (10 mol%) and **1** (0.2 mmol) in DMAc (0.05 M) and irradiated (400–700 nm) for 30 h at room temperature (< 35 °C). In case the of primary amines EA (0.05 M) was used as solvent (see Supporting Information for full experimental details). Isolated yields. [b] Performed with additional methylene blue as photosensitizer (5 mol%). [c] Performed on 0.4 mmol scale in DMAc (0.05 M).

of solvent had a significant influence on the ratio oxalamide **2j** to urea **3j** (see Table S5). When acetone was used as a solvent, urea **3j** was the main product (55% yield). Long chain primary amines (**1p–r**) gave the respective oxalamides in good yields for **2q** and **2p**. In the case of **2r**, 45% of the corresponding product can be also isolated. Finally, we applied our method to a more complexed molecule, a diterpene amine, Leelamine **1s** and the desired oxalamide was also isolated in acceptable yield (**2s**, 50%). It is also worthy to mention that amino acid was tested as well under our standard conditions, but not target product could be detected with low conversion of the substrate (for a list of failed substrates, see the Supporting Information).

Based on previous reports on oxidative carbonylations[24] and with the data from our studies, we proposed a plausible mechanism for our novel catalytic system (Scheme 3). First, amine **1** reacts with Pd^0 to give complex **I** after CO insertion. Then, it reacts with another amine via X-ligand exchange to give intermediate **J** which subsequently been transformed into bis(carbamoyl)palladium intermediate **C** after the insertion of another molecular of CO. Followed by a reductive elimination step to give Pd^0 **D** for the next cycle and the target oxamide product.

In our failed testing with cyclopropyl amine, ring opening side products were obtained (for detailed information see Figure S9). Together with the results from our control experiment with TEMPO, we believe radical intermediates were involved. This suggestion is consistent with the results from several performed in situ EPR radical trap experiments using 5,5-dimethyl-1-pyrroline *N*-oxide (DMPO) as a spin-trapping agent (Figure 1). Thus, we further proposed that the visible light promotes the generation of active photoexcited Pd^0 complex **D*** from complex **A**. In a SET process with amine **1**, the nitrogen radical **E** and Pd^I-radical species **F** are formed. Both intermediates were detected in our EPR studies in the absence of CO (Figure 1). An axial signal of Pd^I species at $g_{\parallel} = 2.085$ and $g_{\perp} = 2.013$ ref. and featureless radical signal at 2.001 were detected at −178 °C after irradiation **C1** and **1a** reaction mixture in DMAc with visible light (cut-off filter 395 nm) at 20 °C for 5 min. The EPR spectrum of DMPO spin trapping experiment in toluene at 20 °C revealed to the formation of DMPO-$^{\bullet}$N spin adducts[25] indicating the formation of *N*-centered radical, see Figure 1. The nitrogen radical is captured very fast by CO to give acyl radical **G** (could successfully be trapped with TEMPO and DMPO to give product **H** and EPR-active DMPO-R spin adduct, respectively). Recombination of Pd^I-radical **F** with acyl radical **G** gives Pd^{II} intermediate **I**, which undergoes a ligand exchange to form Pd^{II} species **J** and hydrogen gas (detected by gas GC). Finally, addition of another CO molecule leads to the formation of bis(carbamoyl)palladium intermediate **C**, which smoothly converts to product **2** and Pd^0 species **D** is regenerated. We calculated a quantum yield of $\varphi = 0.59$. Only 0.59 equivalents of product are formed for every photon absorbed **C1**. Which would be consistent a closed catalytic cycle but could not exclude an inefficient chain reaction. In this process, dimerization of radical **G** to give oxalamide can co-exist as well.

In summary, we have developed a novel sustainable catalytic system for the generation of oxamides from amines. Generated products are of high value since they could be used as potential ligands and more important as starting material for the Ru- or Fe catalyzed synthesis of bulk chemical ethylene glycol (EG).

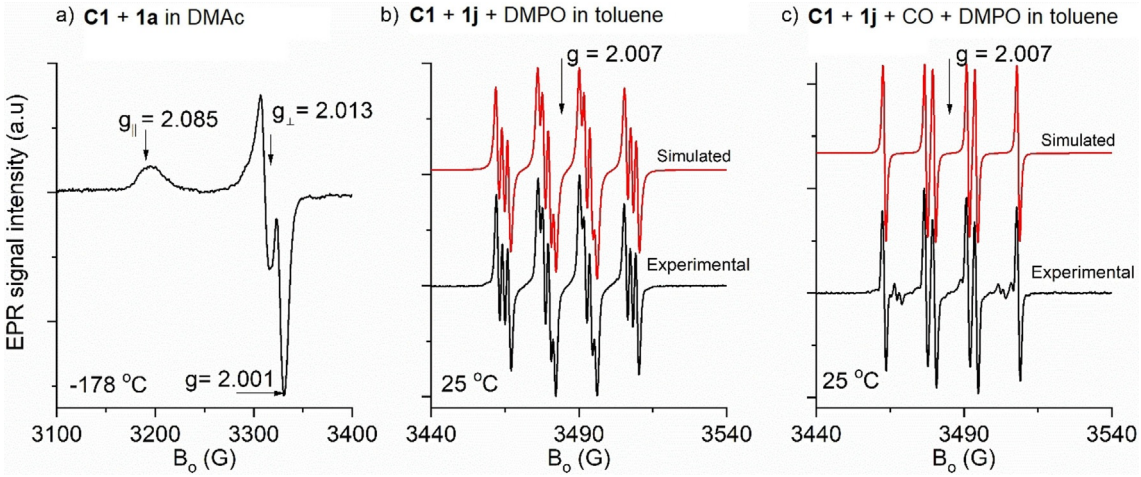


Figure 1. a) EPR spectrum of **C1** (10 mol%) + **1a** (0.1 mmol) in DMAc (2 mL) measured at −178 °C after irradiation the mixture with visible light (cut-off filter 395 nm) for 5 min at 20 °C; b) experimental (black-line) and simulated (red-line) spectra of DMPO-N spin adducts which formed after visible-light irradiation of **C1** (10 mol%) + **1j** (0.1 mmol) solution in toluene in the presence of 15 μL DMPO. The hyperfine fit parameters obtained from spectral simulation were a_N = 14.1 G, a_H = 15.38 and $a_{N(amine)}$ = 1.9 G; c) experimental (black-line) and simulated (red-line) spectra of DMPO-R spin adducts which formed after visible light irradiation of **C1** (10 mol%) + **1j** (0.1 mmol) solution in toluene in the presence of 15 μL DMPO CO (a_N = 14.2 and a_H = 17.0 G). note that the g values present in Figure 1a it appeared in different position from those in b and c due to the different MW frequency used to measure the EPR spectra at low temperature (9.33 vs. 9.79 GHz).

On an industrial level, oxamide **2a** would give ethylamine **1a**, which could be easily separated from EG due to the difference in boiling points. Future work could lead to an immobilized system and irradiation in a continuous flow reactor to overcome the drawback of high catalyst loadings.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: amine · carbonylation · oxalamide · palladium · photocatalysis

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5.4 Pincer Ligand Enhanced Rhodium-Catalyzed Carbonylation of Formaldehyde: Direct Ethylene Glycol Production

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Author contributions:

In this paper, I planned and performed close to all the experiments. I analyzed the data on my own. I wrote the manuscript alone. My contribution as the first author of this paper is more than 70%.

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Full Paper

Pincer Ligand Enhanced Rhodium-Catalyzed Carbonylation of Formaldehyde: Direct Ethylene Glycol Production

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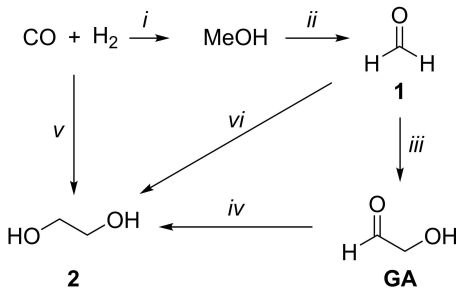
Abstract: Formaldehyde is one of the most important bulk chemicals and is produced on a million tone scale (52 million tons in 2017).[1] Since the middle of the last century, the challenge has remained to produce the valuable ethylene glycol (EG) directly from the C1 building block formaldehyde in a single step. In the systems reported so far, the reaction conditions were very harsh, often with pressures above 400 bar. However, under milder conditions, the selectivity was on the side of glycol aldehyde (GA) and the hydrogenation product methanol. Only traces of EG could be generated in the presence of a Rh catalyst. Herein, we describe a new Rh catalyst system with pincer ligand, which allows the direct one pot synthesis of EG from easy to handle paraformaldehyde (PFA) at remarkable mild conditions (70 bar, 100 °C) and overcomes the aforementioned limitations with yield up to 40%.

Introduction

Wurtz's discovery of ethylene glycol (EG) in 1855 enabled the success of the simplest diol up to the present day.[2] However, this was not to begin until the 20th century. During World War I it was produced in Germany from ethylene chloride and later used as a cheaper alternative in dynamites. Today, the importance of EG is mainly limited to its use in polyester fibers and for antifreeze formulations. One main application of EG is in the production of polyethylene terephthalate (PET), which is a component of almost every plastic bottle. The combination of properties, namely the low freezing point and the ability to mix with water, enables the latter to be applied as antifreeze agent. Of outstanding importance would be an efficient system for the direct synthesis of EG from syngas (Scheme 1, pathway *v*) and attempts have been made in the past to facilitate this synthesis with moderate success. Already in 1953, a patent was applied for by the company Du Pont for the cobalt-catalyzed synthesis of EG at about 3000 bar.[3] Following this pioneering work, efforts were made to find a more efficient catalyst system. Indeed, Rh-based catalysts proved to be more active and selective concerning homogeneous syngas conversions.[4] Certain activity was also found for simple Ru-based catalysts.[5] In these systems only selectivity for methanol and methyl formate was observed. The Ru-hydride species formed is responsible for the fact that most reactions take place via a methoxy intermediate, which makes "dimerization" to the EG impossible. In every case, harsh reaction conditions were necessary. In this context, the ruthenium melt catalysis of Knifton as an example



Scheme 1. Pathways of EG synthesis from syngas.

of heterogeneous catalysis shall be mentioned, which also only succeeded at high temperatures and pressures (e.g. 220 °C, 430 bar), but with comparable good yields for EG (up to 56%). A tertiary phosphonium salt was used as a promoter.[6] Later on, other groups continued this work and comprehensive studies were published by Matsuda.[7] More recently, the Beller group has presented a two-step synthesis of EG directly from CO. In their system, the coupling and reduction steps were separated, which allowed the completely selective formation of EG from CO. A Pd-catalyzed oxycarbonylation of piperidine to oxamide is followed by a Fe-catalyzed hydrogenation. Piperidine could be recycled in this process.[8] Industrial state-of-the-art is still the hydrolysis of ethylene oxide, which is produced by the oxidation of ethylene. The efficiency of this reaction is very high and the initial problems of selectivity, the formation of oligomers, were overcome by the ingenious OMEGA process developed by Shell, in which ethylene oxide is converted with the C1 building block CO_2 to ethylene carbonate. In a second step, base catalysed hydrolysis is carried out, EG is produced with a selectivity of 98% and released CO_2 can be returned to the process cycle.[9] The inherent disadvantage of these otherwise extremely efficient methods of obtaining EG is that two steps are required. Our intellectual interest was to overcome this drawback. We questioned whether it would be possible to obtain EG in a single step with good efficiency under relatively mild conditions. To achieve this goal, we

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considered another easily accessible C1 source, which is produced on a large scale: formaldehyde. Hendriksen demonstrated early on a possible alternative route via the stepwise conversion of syngas (Scheme 1).[10] Starting with CO, it proceeds via its hydrogenation (*i*) to methanol, the subsequent oxidation to formaldehyde **1** (*ii*), its hydroformylation to GA (*iii*), and finally the hydrogenation to EG **2** (*iv*). Our approach corresponds to path *vi* of the GA route, the realization of which has so far suffered from selectivity problems.

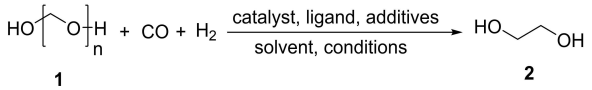
So far, only a few methods have been described for the transition metal catalyzed direct conversion from PFA to EG.[11] Common to all these reports were harsh reaction conditions such as pressures above 200 bar and high temperatures. With the synthesis of the first reported Nitrogen Phosphorus Tridentate (PNP) Dahlhoff and Nelson in 1971, the pincer ligands as another powerful tool for hydrogenation reactions entered the stage,[12] Milstein's group has advanced the detailed understanding this ligand class and its applications.[13] In the field of hydrogenation catalysis, significant progress was made, using Rh,[14] Ir,[15] and earth-abundant first row metals like Mn,[16] Fe,[17] or Ru.[18] Today, many working groups are almost exclusively concerned with the synthesis of multidentate ligands and their coordination on transition metals. The properties and thereby the reactivity of the newly generated potential catalysts, their stability, steric and electronic properties are highly tunable.[18b]

Herein, we present the successful development of a one-step Rh-catalyzed method for the carbonylation of PFA, which breaks the previous selectivity for GA by applying a novel pincer ligand system generation and provides EG as one of the major products.

Results and Discussion

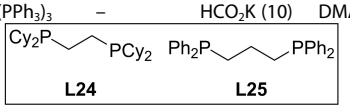
Innovations in the development of a mild synthesis of EG from the C1 building block formaldehyde **1** have decreased in the last decades. Pioneer in this field was Spencer, who described the direct synthesis of GA from PFA already in 1980 (Table 1, entry 1).[11a] He used $RhH(CO)(PPh_3)_3$ which was the most efficient catalyst for hydroformylation of alkenes at that time. For the selective synthesis of GA and methanol, which was present in all reactions, he found DMA to be the superior solvent. EG was detected only in traces and solely in ethyl acetate and acetonitrile. In general, no hydrogenation of glycol aldehyde took place. Interestingly, the activity of the catalyst type $RhX(CO)(PPh_3)_3$ was exactly the opposite of the known hydroformylation of alkenes, in fact X = Cl > X = H. Various monodentate ligands with different electronic properties (for example triphenylphosphine, tri-*p*-fluorophenylphosphine and also strong π-acceptor ligand such as triphenylphosphite) also did not give selectivity for EG. Subsequent work by Okana showed that switching to picoline as solvent significantly improves the activity of the catalyst. The yield for GA reached 90% for the first time under otherwise similar mild conditions (Table 1, entry 2).[11b] First success regarding EG selectivity was achieved with the help of bimetallic catalyst systems (Rh and Co) but under otherwise relatively harsh reaction conditions.[11c,19] After initial careful evaluation of all reaction parameters we discovered that the introduction of a simple bidentate ligand DPPP (4 mol%) in combination with $RhCl_3$ (4 mol%) and a weak inorganic base HCO_2K, to act as a HCl scavenger, (10 mol%) leads to a yield of 9% in terms of EG (Table 1, entry 3). It is possible that the potassium salt of formic acid acts as an additional H-donor or reductant for the active rhodium(I) complex formation. The use of other bases, also of organic nature, of additives such as Lewis acids led to equal or reduced yields (Table S1). Moreover, the increase in the amount of HCO_2K (50 mol%; compared to PFA) or the switch to HCO_2Na had no positive effect. To our surprise, the investigation of various commercially available ligands led to a dramatic improvement if DPPP **L25** was replaced by 1,2-bis(dicyclohexylphosphino)ethane **L24** (Table 1, entry 6; 21%). With our new system in hand, we investigated different catalysts. Unfortunately, the addition of $CoCl_2$ as co-catalyst did not improve the efficiency of our system (Table 1, entry 7). The change of the metal to Ru led to the complete inactivity (Table 1, entry 8). With regard to the solvent, the superiority of *N*,*N*-disubstituted amides was confirmed. In 4-picoline, the second-best result was observed (Table 1, entry 9; an extensive screening is given in the Supporting information). Various Rh-based catalysts were tested, of which $RhCl_3$ turned out to be the cheapest and at the same time as one of the most efficient catalyst (Table S2). The reaction also took place in the presence of Rh(I) catalysts, which is an indication for the presence of Rh(I) species in our catalytic cycle (Scheme. 2).

Table 1. One-step synthesis of EG via carbonylation of formaldehyde **1**.



1 **2**

Entry[a]	Catalyst [mol%]	Ligand [mol%]	Additives [mol%]	Solvent	Yield [%][a]
1 (ref. [11a])[b]	$RhH(CO)(PPh_3)_3$ (0.2)	–	none	MeCN (2.0 M)	trace
2 (ref. [11b])[c]	$RhCl(CO)(PPh_3)_2$ (0.3)	–	none	picoline (1.9 M)	trace
3[d]	$RhCl_3$ (4)	**L25** (4)	HCO_2K (10)	DMA	9
4[d]	$RhCl_3$ (4)	**L25** (4)	HCO_2K (50)	DMA	8
5[d]	$RhCl_3$ (4)	**L25** (4)	HCO_2Na (50)	DMA	7
6[[d]	$RhCl_3$ (4)	**L24** (4)	HCO_2K (10)	DMA	21
7[d]	$RhCl_3$ (4) $CoCl_2$ (10)	**L24** (4)	HCO_2K (10)	DMA	18
8[d]	$RuCl_3$ (4)	**L24** (4)	HCO_2K (10)	DMA	–
9[d]	$RhCl_3$ (4)	**L24** (4)	HCO_2K (10)	4-picoline	13
10	$RhCl(PPh_3)_3$	–	HCO_2K (10)	DMA	1



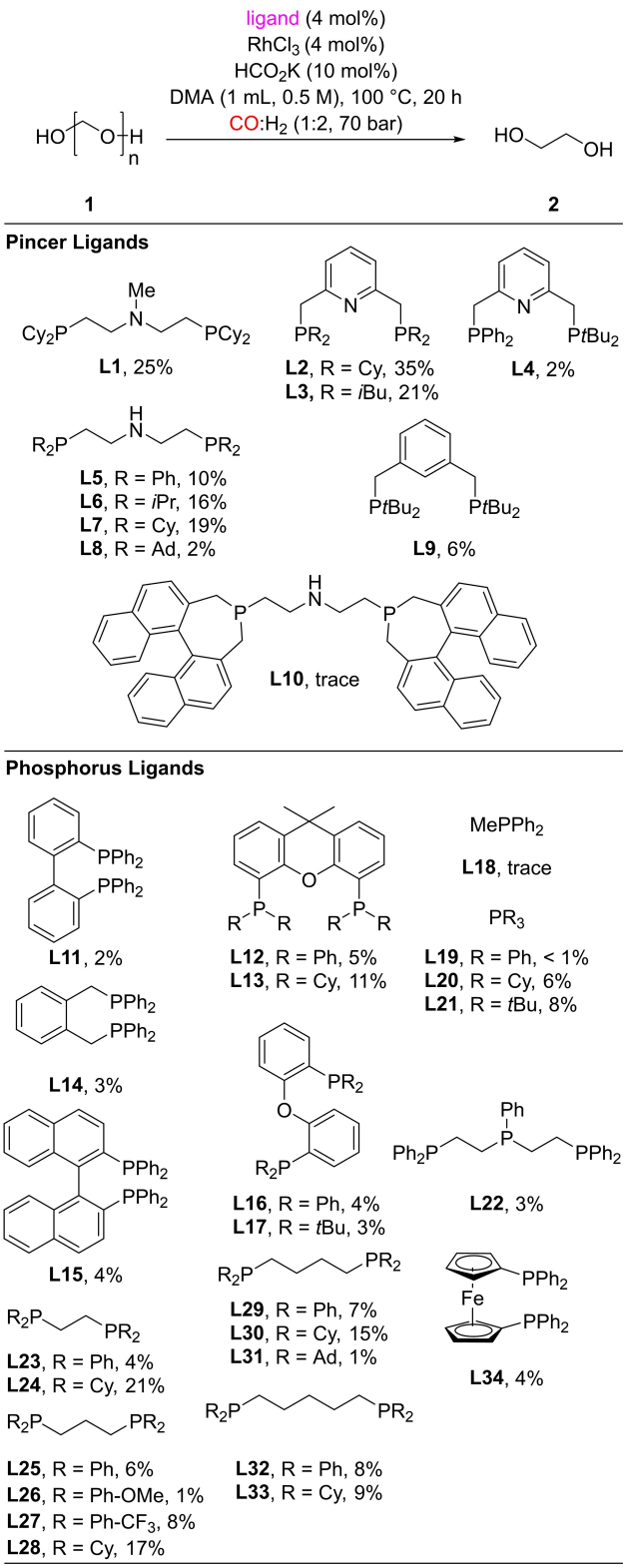
L24 **L25**

[a] All yields are given in respect of **2**. Formaldehyde **1** was applied as PFA in all reactions. [b] CO (40 bar), H_2 (40 bar), 110 °C, 3 h; yielded MeOH (43%) and GA (3%). MeOH (4%) and GA (6%) with DMA as solvent and no EG detected. [c] CO (25 bar), H_2 (25 bar), 70 °C, 3 h; GA could be obtained with a yield of 42%. [d] Reaction conditions: PFA **1** (0.5 mmol), catalyst (4 mol%), ligand (4 mol%) in solvent (1 mL), charged with CO (24 bar), H_2 (46 bar) and stirred at 100 °C for 20 h (see General Procedure I).

Implementing $RhCl(PPh_3)_3$ as catalyst gave only traces of EG, which is in accordance with the aforementioned literature (Table 1, entry 10). Considering this preliminary work, we questioned whether it is possible to produce a polyalcohol like EG in acceptable yields under mild conditions and what role a ligand could play in this context. The use of known cheaper amino ligands was our starting point and under our set conditions (100 °C, 70 bar) no EG was obtained. This did change with tests of phosphorus-based ligands, as shown in the lower part of Scheme 2. The use of simple monodentate ligands resulted in low yields of EG (ligands **L17**–**L20**). It can be observed here that the introduction of more basic alkyl groups has a positive impact.[20] The electronic properties of the groups at the phosphorus atoms have an important influence on the reaction outcome, as the change to the electron-rich cyclohexyl moiety (Cy) in the case of ligand **L24** clearly shows (R = Ph 4% vs R = Cy 21%). The change to the Cy group on the phosphorus also leads to better results with the shown ligands of the Xantphos type (**L13** > **L12**). In the case of the linear ligands bearing a Cy group, the bite angle seems to play a decisive role, since the yields increase inversely proportional to the angle of bite (**L24** > **L28** > **L30** > **L33**). Small bite angle can favour the oxidative addition step. However, the possibility of dimeric complexes formation in the case of long chain ligands should be considered as well. We sought to improve the selectivity further by using PNP ligands, which, as a relatively new class of ligands, were not accessible to the pioneering group and could meet our exact specifications. We started with the commercially available **L5**, which is known to be an effective ligand in transition metal-catalyzed hydrogenation reactions.[21] Initial studies with this ligand showed low activity but better selectivity than PPP ligand Triphos **L22**. To improve the performance, the moiety on the phosphor was modified. As expected, the introduction of a Cy group (**L7**) improved the activity (10 to 19%). A sterically demanding Ad Rest (**L8**) led to worse results. This trend was also evident in experiments with the phosphorus ligand **L31**. Next, we modulated the N-donor by introducing a basic Me group, which further improved the activity and yield of the catalyst system (**L1**, 25%). The switch to more rigid symmetrical pyridine-based PNP pincer ligands was made and we were pleased with the best result of EG yield 35% with ligand **L2**.

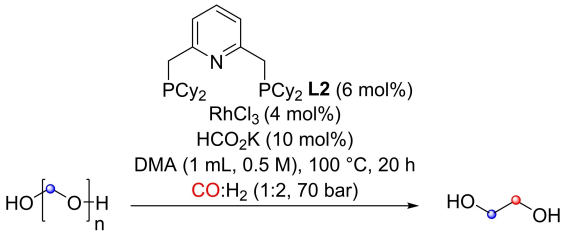
After extensive optimization of the reaction conditions, we selected the best performing ligand **L2** in an excess with respect to the catalyst (6 mol%). This resulted in the reaction conditions shown in Table 2 (entry 1, 40%). A significant reduction of the catalyst loading to 1 mol% was possible (Table 2, entry 2) without loss of yield. Control experiments in the absence of the catalyst, the base and in the absence of a ligand (Table 2, entries 3–5), showed that all three components are necessary for the efficiency of our catalytic system. However, under these optimized conditions, commercially available phosphorus ligand **L24**, which had already been used in our original optimization reactions, also gave acceptable results (Table 2, entry 6).

To meet the mild reaction conditions we specified, the total pressure of the reaction should not exceed 70 bar. However, the optimum ratio of P_{H2} to P_{CO} could be identified. Unfortunately, for pincer ligand **L2** as well as for phosphorus ligand **L24**



Scheme 2. Ligand Screening. [a] All yields are given in respect of **3**. [b] Reaction conditions: PFA **1** (0.5 mmol), catalyst (4 mol%), ligand (4 mol%) in solvent (1 mL), charged with CO (24 bar), H_2 (46 bar) and stirred at 100 °C for 20 h (see General Procedure I).

Table 2. Final optimization and control experiments.



	1	2
Entry[a]	Deviation	GC Yield [%][b]
1	none	40 (36)[c]
2	**L2** (1.5 mol%) and $RhCl_3$ (1 mol%)	40
3	no $RhCl_3$	–
4	no HCO_2K	7
5	no ligand	<1
6	**L24** (1.5 mol%) as ligand and $RhCl_3$ (1 mol%)	21 (18)[c]

[a] Reaction conditions: PFA **1** (15.0 mg, 500 µmol), $RhCl_3$ (4.2 mg, 4 mol%), HCO_2K (4.2 mg, 10 mol%), ligand **L2** in solvent (1 mL), 100 °C, 20 h. [b] GC yields were determined by using a calibration on a GC-FID with hexadecane as an internal standard. [c] Isolated yield of a reaction conducted on a 0.5 mmol scale is given in parentheses.

no positive effect could be achieved by changing the composition of CO:H_2 (1:2). Both increase of the reaction temperature (T = 120 °C) and decrease (T = 80 °C) deteriorated the activity of our catalyst (Figure 1).

Attempts to prepare Pincer-Rh complex failed in our case. However, in a ^{31}P NMR experiment, pincer-Rh complexes with carbonyl group might be formed (Figure S1).

The detection of EG in GC on a commonly used HP5 column is only successful at high concentrations, and EG was transformed into ester for accurate yield measuring. The *in situ* transfer of the EG in a second step to the ethane-1,2-diyl dibenzoate **3** with an average efficiency of 88% also proved to be precise and suitable. As mentioned above, the direct synthesis of EG from synthesis gas is possible and the CO used could also play a less obvious role, such as acting only as a ligand. Our aim was to find out what role paraformaldehyde **1** plays in the reaction, or rather how many carbon atoms in the products **2** or **3** originate from PFA. For this purpose, an experiment with ^{13}C-PFA was carried out. From the NMR data of the isolated product, it was easy to recognize that in the ethane-1,2-diyl dibenzoate **3** obtained in this manner, the signal associated with the EG component in the ^{13}C NMR at $\delta = -62.89$ ppm is much stronger than in an experiment with ordinary PFA. In combination with the high-resolution mass of this sample ($[C_{15}(^{13}C)H_{14}O_4Na]^+$ ($[M+Na]^+$): 294.0823, measured: 294.0825), it was found that exactly one labelled carbon atom was incorporated from PFA and the other carbon atom from CO. On this basis, it could be concluded that one mole of PFA reacts to one mole of product (see supporting information for details).

Regarding the possible reaction pathway: it is probably related to hydroacylation and hydrogenation (Scheme 3). Due to the stabilization effect from pincer ligand, the active rhodium complex was generated and stabilized as an active species for the following up steps. After oxidative addition with hydrogen, rhodium hydride complex was generated. The formyl–rhodium complex will be produced after CO inserts into the Rh–H bond. Glycol aldehyde will be eliminated after formylmetalation[22] of formaldehyde and reductive elimination steps. Finally, rhodium-catalyzed hydrogenation of glycol aldehyde produces the final desired ethylene glycol product. It is also important to mention that attempting to hydoformylate of benzaldehyde and hexanal failed under our standard conditions. Only small amount of alcohol was formed due to rhodium-catalyzed hydrogenation of aldehyde.

Conclusion

In summary, we have designed a catalytic system which under mild conditions (70 bar, 100 °C), with rhodium as the catalyst and symmetrical pyridine-based PNP ligands, shows a higher selectivity for the direct one-step synthesis of EG from formaldehyde than, to the best of our knowledge, all previously reported systems. From this innovation potentially new oppor-

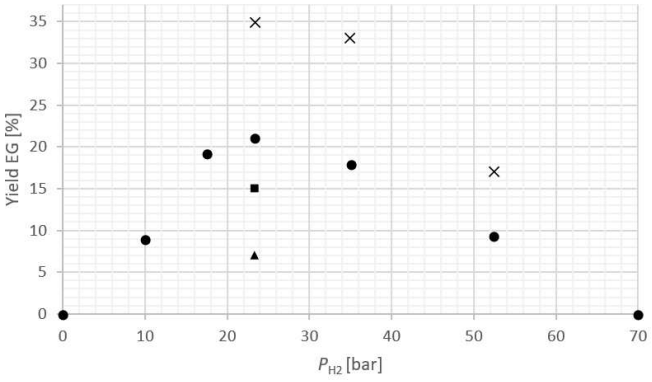
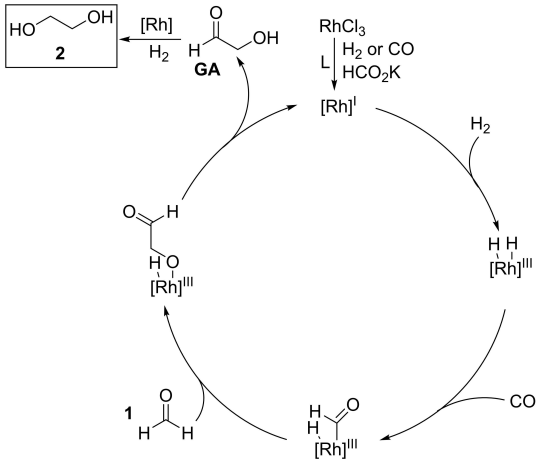


Figure 1. Effect of hydrogen pressure. [a] Total pressure $P_{H2}+P_{CO}=70$ bar in each case. [b] Reaction conditions: PFA **1** (15.0 mg, 500 µmol), $RhCl_3$ (4.2 mg, 4 mol%), HCO_2K (4.2 mg, 10 mol%), ligand (4 mol%) in DMA (1 mL), 100 °C, 20 h. [c] ● ligand **L24**, ■ T = 120 °C, ▲ T = 80 °C; × ligand **L2**.



Scheme 3. Possible reaction pathway.

tunities for carbonylation and hydrogenation of bulk chemicals such as PFA can be derived. Especially the ligand design, which is very advanced for symmetric PNP ligands with one *N*-donor and two identical phosphorus moieties and the possible transition to heterogeneous reaction with immobilized pincer systems, are a promising future application in CO chemistry.

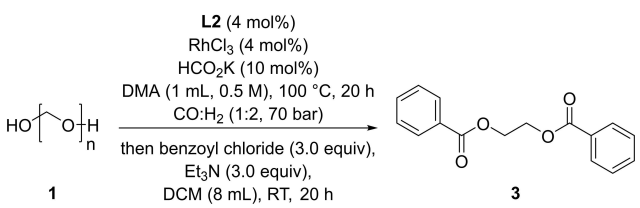
Experimental Section

General Information

Experimental Details All commercially available ligands and other reagents were bought from Acros, Aldrich, Alfa, Strem, and TCI. Unless otherwise stated, they were used without further purification and analysis. Air- and moisture-sensitive reactions were performed under argon atmosphere and in oven-dried glassware. NMR spectra were recorded on a Bruker Avance 300 MHz or a Bruker ARX 400 MHz spectrometer. The chemical shifts δ (ppm) are given relative to the used solvent. In the case of $CDCl_3$ it is 7.26 ppm for ^{1}H NMR and 77.16 ppm for ^{13}C NMR. In the case of benzene–d6 (C_6D_6) it is 7.15 ppm for ^{1}H NMR and 128.62 ppm for ^{13}C NMR. Multiplets were assigned as s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublet), and m (multiplet), and br. s (broad singlet). Chemicals shifts (δ) are noted in ppm downfield of TMS.^{31}P NMR spectra are not calibrated by an internal reference. All GC yields were calculated using hexadecane as internal standard. All measurements were carried out at room temperature unless otherwise noted. Electron impact (EI) mass spectra were recorded on AMD 402 mass spectrometer (70 eV) and the data are given as mass units per charge (m/z). Gas chromatography analysis was performed on an Agilent HP-7890A instrument with a FID detector and HP-5 capillary column (polydimethylsiloxane with 5% phenyl groups, 30 m, 0.32 mm i.d., 0.25 μm film thickness) using argon as carrier gas. The products were isolated by column chromatography on silica gel 60 (0.063–0.2 mm, 70–230 mesh). Compounds **S1**,[23] **S2**,[24] **L1**,[25] **L2**,[18a] and **L3**[18a] were prepared according to literature procedures.

General Procedure I – Isolation

An oven dried 4 mL screw-cap vial equipped with a septum and a stirring bar was charged with PFA **1** (15.0 mg, 500 μmol), $RhCl_3$ (4.2 mg, 4 mol%), HCO_2K (4.2 mg, 10 mol%), and the free (not borane adduct) ligand **L2** (15.0 mg, 4 mol%). The vial was sealed, connected to atmosphere with a needle, evacuated, backfilled with argon three times, and DMA (1 mL) was added by syringe. The vial was placed on an alloy plate and transferred into a 300 mL stovetop autoclave (4560 series from Parr instrument company®). The autoclave was flushed one time with argon and three times with CO. The autoclave was then charged with CO (24 bar) and subsequent with H_2 (46 bar) to reach the desired pressure of 70 bar. It was then placed into an aluminum block on a magnetic stirrer. The reaction mixture was stirred (550 rpm) for 20 h at 100 °C. Then it was cooled to room temperature and the pressure was released carefully. The reaction mixture was transferred into a test tube, diluted with DCM (8 mL), and *n*-hexadecane was added as an internal standard. Then Et_3N (215 μL, 1.5 mmol) was added and subsequent benzoyl chloride (175 μL, 1.5 mmol) was dropped slowly to the stirring solution. The reaction mixture was stirred at room temperature for an additional 20 h. Then most of the solvent DMA was removed in vacuo (< 1 mbar and 60 °C), the residue was taken-up with water and extracted with DCM (3 × 10 mL). Combined organic phases were washed with brine (10 mL), water (10 mL), dried over Na_2SO_4, concentrated in vacuo, and purified by column chromatography. Product **4** was obtained as a white solid (31.0 mg, 32%). With an efficiency factor of 0.88 for the second step, the overall produced amount of EG should be 11.2 mg, 180 μmol, 36% (For calculation of the factor, see Supporting information). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.10–8.04 (m, 4H), 7.59–7.53 (m, 2H), 7.48–7.40 (m, 4H), 4.67 (s, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.5, 133.3, 129.9, 129.8, 128.5, 62.9. **EI-MS**: m/z calculated for $[C_{16}H_{14}O_4]^+$ ($[M]^+$): 270.0892, measured (%): 270 (2), 227 (8), 105 (100), 77 (40), 51 (10). In accordance with reported literature data.[26]



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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Pincer Ligand · Rhodium Catalysis · Ethylene Glycol · Carbonylation · Hydroformylation

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Tim Meyer, J. Rabeah, A. Brückner, X.-F. Wu, *Chem. Eur. J.* **2021**, *27*, 5642.

4 *Pincer Ligand Enhanced Rhodium-Catalyzed Carbonylation of Formaldehyde:Direct Ethylene Glycol Production*
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1 *Dual Ligand-Enabled Non-Directed C-H Olefination of Arenes*
H. Chen, P. Wedi, Tim Meyer, G. Tavakoli, M. van Gemmeren, *Angew. Chem. Int. Ed.* **2018**, 2497.

4. Erklärung gemäß § 4 Absatz 1 Buchstaben g und h der Promotionsordnung

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Ich habe eine Dissertation zum Thema

Studies Towards Radical and Metalhydride Mediated Carbonylation Reactions

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

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