Carboxylic Acids

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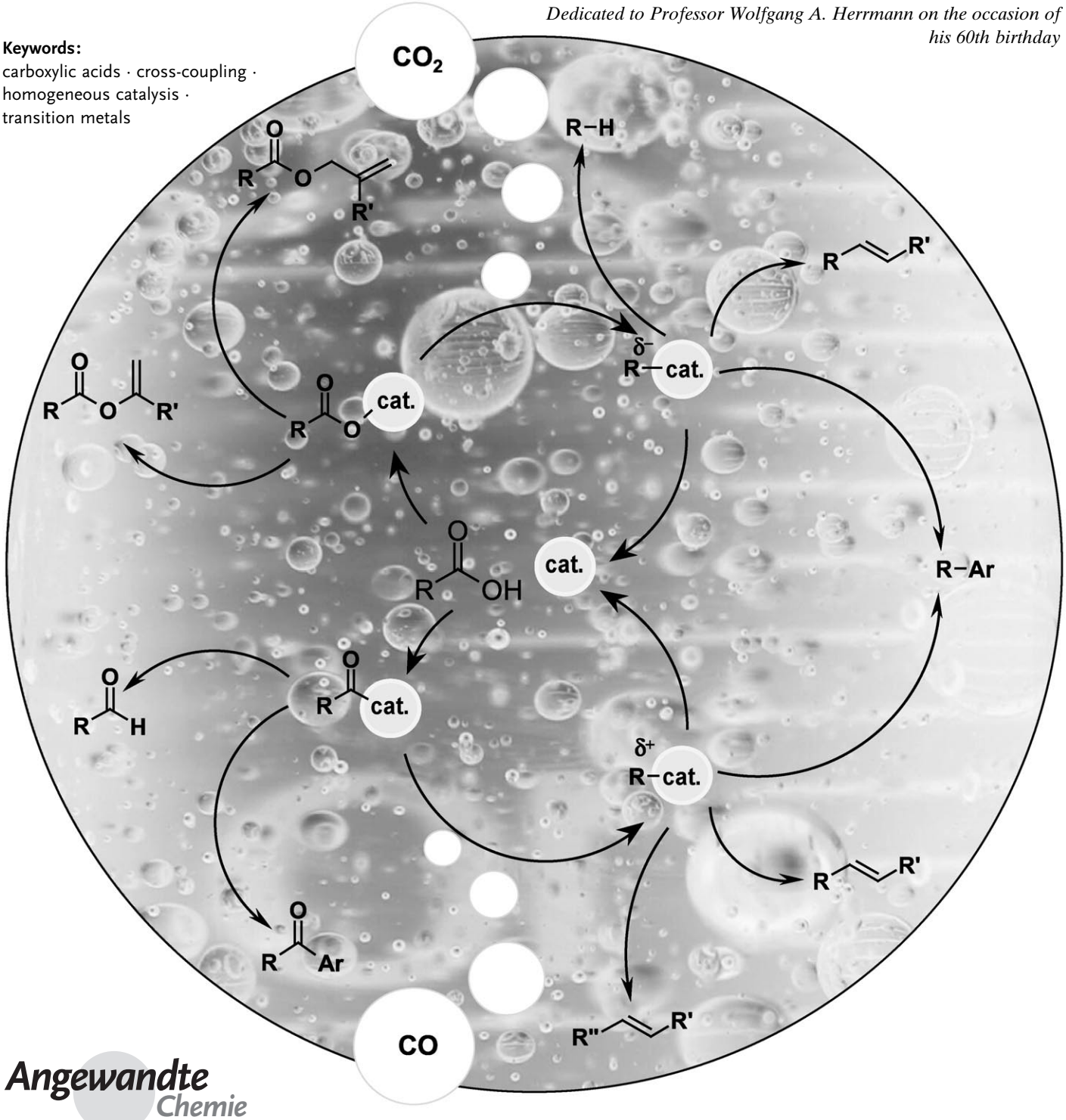
Carboxylic Acids as Substrates in Homogeneous Catalysis

Lukas J. Gooßen, Nuria Rodríguez, and Käthe Gooßen*

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

Keywords:
carboxylic acids · cross-coupling · homogeneous catalysis · transition metals



In organic molecules carboxylic acid groups are among the most common functionalities. Activated derivatives of carboxylic acids have long served as versatile connection points in derivatizations and in the construction of carbon frameworks. In more recent years numerous catalytic transformations have been discovered which have made it possible for carboxylic acids to be used as building blocks without the need for additional activation steps. A large number of different product classes have become accessible from this single functionality along multifaceted reaction pathways. The frontispiece illustrates an important reason for this: In the catalytic cycles carbon monoxide gas can be released from acyl metal complexes, and gaseous carbon dioxide from carboxylate complexes, with different organometallic species being formed in each case. Thus, carboxylic acids can be used as synthetic equivalents of acyl, aryl, or alkyl halides, as well as organometallic reagents. This review provides an overview of interesting catalytic transformations of carboxylic acids and a number of derivatives accessible from them in situ. It serves to provide an invitation to complement, refine, and use these new methods in organic synthesis.

From the Contents

1. Introduction	3101
2. Reactions via Metal Carboxylates	3103
3. Reactions by Extrusion of Carbon Dioxide	3107
4. Reactions via Acyl Metal Species	3112
5. Reactions with Decarbonylation of Acyl Metal Species	3114
6. Summary and Outlook	3117

1. Introduction

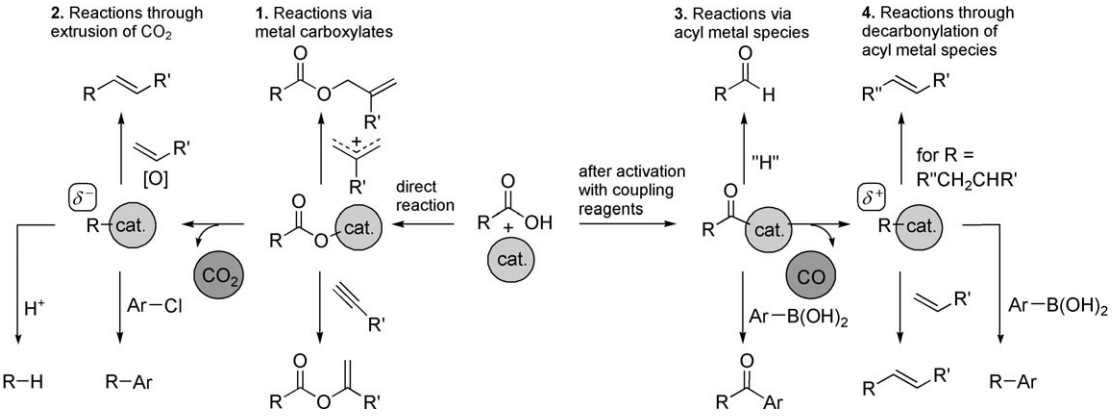
The compound class of carboxylic acids and the most important reactions of the COOH group are known to chemists from as early as the first semester of their studies.[1] Carboxylic acids are commercially available in a large structural variety. They are easy to store, simple to handle, and when necessary, are accessible preparatively by means of a large number of well-established methods. For example, aromatic carboxylate groups can be produced by the oxidation of side chains of the arene ring, ideally through the use of atmospheric oxygen as the reagent with formation of water as the coupling product.[2] This preparative procedure is also suitable for heterocyclic carboxylic acids, although COOH-functionalized heterocycles are often more readily available than the parent compounds, for instance, when they are synthesized by condensation reactions (e.g. from oxoesters).[3] Synthetic strategies starting from carboxylic acids promise ecological advantages with respect to a number of traditional arene functionalizations that originate from halogenation, nitration/reduction/diazotization or Friedel–Crafts reactions, since these are often waste-intensive and the products are formed to some extent as regioisomers.[1] These sustainability aspects also apply to aliphatic carboxylic acids, particularly when they are accessible from natural sources (renewable raw materials) or indirectly by the oxidation of naturally occurring alcohols.[4] Alternatively carboxylic acids may be prepared in a simple manner by, for example, the hydrolysis of nitriles, alkylation of malonic esters, or the carbonylation of alkenes or halogenated compounds.[5]

The ready availability of carboxylic acids makes them extremely promising raw materials for chemical synthesis. However, usually noncatalytic methods are used, whereas the use of carboxylic acids as substrates in transition-metal catalytic methods is currently still more of an exception.

The reactivity of carboxylic acids is determined by the two vicinal oxygen atoms, namely the carbonyl oxygen atom and that of the acidic hydroxy group.[1] Under basic conditions the carboxylic acid group is deprotonated to the resonance-stabilized carboxylate, which significantly impairs nucleophilic attack at the carbonyl carbon atom. Only under acidic conditions is substitution of the hydroxy group possible, for example, in esterifications. Under basic conditions nucleophilic substitution at the carbonyl carbon atom by the addition–elimination mechanism is, on the other hand, possible only when the hydroxy group is replaced by a non-proton-active leaving group, for example, by dehydration to anhydrides or conversion into acid chlorides or active esters.

These fundamental principles also apply to the metal-catalyzed reactions of carboxylic acids and their derivatives, as illustrated in Scheme 1 where they are divided roughly into four groups on the basis of the position and polarity of the bond coupling. In the first reaction mode the O–H bond of the free carboxylic acid is cleaved and the carboxylate residue as a whole is linked up with the coupling partner. The nucleophilicity of the carboxy oxygen atom allows, for example, the reaction with coordinated allyl metal species, as formed, for instance, during the course of allylic substitutions or oxidations (see Section 2.1.2). In the presence of suitable catalysts an insertion into the O–H bond is also

[*] Prof. Dr. L. J. Gooßen, Dr. N. Rodríguez
FB Chemie – Organische Chemie
TU Kaiserslautern
Erwin-Schrödinger-Strasse Geb. 54
67663 Kaiserslautern (Germany)
Fax: (+49) 631-205-3921
E-mail: goossen@chemie.uni-kl.de
Homepage: http://www.chemie.uni-kl.de/goossen
Dr. K. Gooßen
Bayer HealthCare AG, Strategic Planning Pharma
Müllerstrasse 178
13353 Berlin (Germany)



Scheme 1. Carboxylic acids in catalytic transformations.

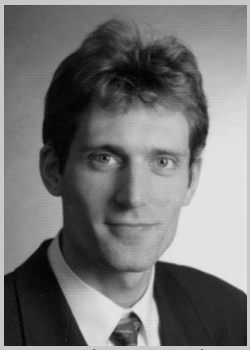
observed, however, in reactions with intrinsically nucleophilic coupling partners, for example, in the metal-catalyzed addition of carboxylic acids to alkenes or alkynes with the formation of (enol) esters (Sections 2.1 and 2.2).

The second reaction mode of carboxylic acids comprises reactions in which metal carboxylates are formed initially, then converted into organometallic compounds with the extrusion of CO_2. This decarboxylation step is usually highly endothermic and only with difficulty can be directed into further catalytic transformations. Even the long-known protodecarboxylation of aromatic carboxylic acids to the corresponding arenes requires a transition-metal mediator such as mercury, silver, or copper, usually in stoichiometric amounts and at high temperatures. Only in recent years have catalytic variants of this reaction been developed (Section 3.1).

Even more valuable for synthesis are reactions in which carboxylic acids are coupled with other substrates after decarboxylation. One of the few examples of this is a biaryl synthesis in which aryl nucleophiles generated by the decarboxylation of aromatic carboxylic acids are coupled with haloarenes on a Pd catalyst (Section 3.2). Following the same mode of reaction carboxylic acids can also react like haloarenes (Sections 3.3 and 3.4), namely when the intermediate aryl nucleophiles undergo umpolung to carbon electrophiles on the metal catalyst before the coupling step. This is observed, for example, in a current variant of the Heck reaction, in which carboxylic acids are coupled to vinyl arenes with alkenes in the presence of a palladium catalyst and Ag^I.

As in classical reactions of carboxylic acids, a nucleophilic attack at the carbonyl carbon atom with subsequent cleavage of the C(O)–O bond in catalytic transformations is possible only when the acid function is activated by substitution of the O–H group. Such activated carboxylic derivatives, including acid chlorides, anhydrides, active esters, and even a few amides and thioesters, react to form acyl complexes, for example, with Pd and Rh complexes under oxidative addition and can thus be made available for catalytic acylation. This third reaction mode forms the basis, amongst others, of the reduction of carboxylic acids to aldehydes, wherein the carboxylic acids are converted into anhydrides in situ with pivaloyl anhydride, which are then hydrogenated to the aldehydes in the presence of Pd catalysts (Section 4.1). Pd-catalyzed cross-couplings of carboxylic acids with boronic acids in the presence of different activating reagents follow the same reaction principle (Section 4.2).

In the fourth and last reaction mode the tendency of acyl metal complexes, accessible by oxidative addition of activated carboxylic acid derivatives to metal catalysts, to decarbonylate with the formation of alkyl or aryl metal species is exploited. In this way organometallic species are formed from carboxylic acids, just as they are formed by the oxidative addition of haloarenes to metal complexes in the initiating step of many catalytic transformations. Hence, aromatic carboxylic acids can be converted into vinyl arenes with alkenes in Heck reactions (Section 5.2) or coupled to biaryls with boronic acids (Section 5.3).



Lukas J. Gooßen studied chemistry at the University of Bielefeld and the University of Michigan. He received his degree in chemistry working with Prof. K. P. C. Vollhardt and his doctorate in 1997 with Prof. W. A. Herrmann at the TU München. After a postdoctoral fellowship with Prof. K. B. Sharpless and a position as laboratory head at Bayer AG he gained his habilitation with Prof. M. T. Reetz at the MPI für Kohlenforschung. As Heisenberg Fellow he worked at the RWTH Aachen until he took up his current position in 2005 as Professor of Organic Chemistry at the TU Kaiserslautern. He is working on the development of sustainable catalytic transformations.

Nuria Rodríguez was born in 1978 in Valencia (Spain). After completion of her chemistry studies at the University of Valencia she gained her doctorate in the group Prof. G. Asensio and M. Medio-Simon working on palladium-catalyzed cross-couplings with participation of an sp^3-hybridized carbon center in the α-position to a sulfinyl group. Sponsored by a Humboldt Fellowship, she has carried out research in the group of Prof. Gooßen as a postdoctoral fellow since 2006. The emphasis of her work is the development of decarboxylative cross-coupling reactions.

A sequence of oxidative addition and decarbonylation can also be carried out successfully with alkyl carboxylic anhydrides on Pd catalysts. If the alkyl metal species thus formed possess β-hydrogen atoms, alkenes shortened by one carbon atom are released by β-hydride elimination (Section 5.1). This Pd-catalyzed decarbonylation of active carboxylic acids is thus synthetically equivalent to hydrogen halide elimination from haloalkanes.

In this review current developments in the area of transition-metal catalysis are presented in which carboxylic acid derivatives function as substrates. Perspectives are discussed which could be opened up by these conversions in organic synthesis. In view of the large variety of interesting reactions, a choice had to be made about which ones to cover. The main emphasis lies in recently published catalytic transformations that start out either from the carboxylic acids themselves, or from derivatives that are accessible under mild conditions. Catalytic reactions of acyl chlorides are mentioned only as exceptions, for example, when they serve as a basis for the development of such reactions. The extensive literature on the addition of carboxylic acids to multiple bonds is only briefly presented so as to avoid overlap with current review articles.

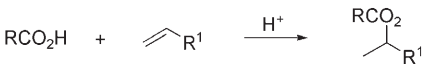
2. Reactions via Metal Carboxylates

2.1. Catalytic Addition of Carboxylic Acids to Alkenes

2.1.1. Hydroacyloxylations

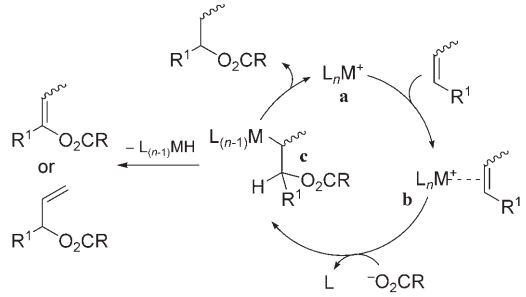
Like hydrogen halides, carboxylic acids can add to alkenes with the formation of Markovnikov products.[6] Such hydroacyloxylations are mediated by Brønsted acids or Lewis acidic metal centers of homo- or heterogeneous catalysts and are used on an industrial scale for the production of simples esters (Scheme 2).[7]

The development of alternative catalysts based on coinage metals and platinum metals is of considerable interest since the selectivity of the reaction could be improved and milder reaction conditions could be permitted with the softer metals. Unfortunately toxic mercury salts have long been the only compounds of this type known to facilitate the addition reaction in the desired manner.[8] The difficulty in the use of transition-metal catalysts is that for many substrates their alkyl complexes tend towards β-hydride elimination, so that the planned redox-neutral catalytic cycle is only too easily diverted into a Wacker-type oxidative process (Section 2.2; Scheme 3).[9]



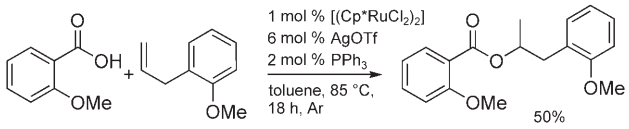
Scheme 2. Hydroacyloxylations of alkenes.

Käthe Gooßen, née Baumann, studied chemistry at the University of Durham (Great Britain) and moved to the group of Prof. J. A. Murphy at the University of Strathclyde (Glasgow) for her PhD studies on palladium-catalyzed alkaloid syntheses. Since 1999 she has been working at Bayer AG, first as laboratory head in the Fluorine Laboratory of Central Research, then in chemical development at Bayer Healthcare, and from 2005 onwards in strategic planning at Bayer Schering Pharma. Since the start of her parental leave in 2006 she has been working with the Gooßen group.



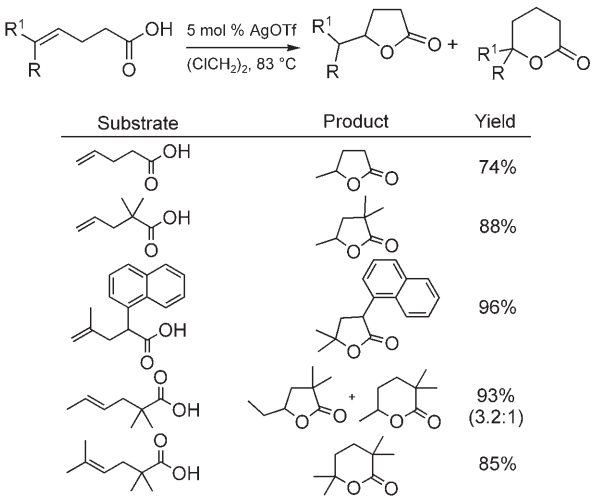
Scheme 3. Mechanism of the transition-metal-catalyzed hydroacyloxylation.

By using a cationic, sterically shielded Ru^{II} complex generated from 1 mol% $[(Cp^*RuCl_2)_2]$ ($Cp^* = C_5Me_5$), 2 mol% 1,1′-bis(diphenylphosphino)butane (dppb) or PPh_3, and 6 mol% silver triflate, Oe et al. were able to suppress this undesired reaction pathway to such an extent that the selective addition of aromatic carboxylic acids to a number of alkenes was possible even with this late-transition-metal catalyst system.[10] In most examples norbornene was used as the alkene component, so that the reaction pathway via β-hydride elimination was unfavorable for geometric reasons. However, an example of a selective alkyl ester synthesis is known (Scheme 4) in which a redox-neutral addition is in direct competition with the oxidative addition.



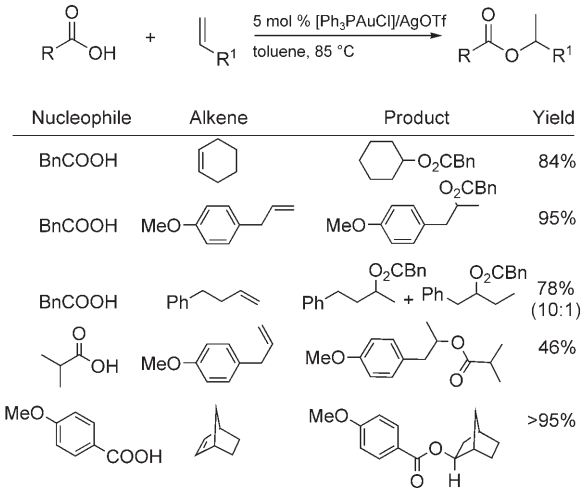
Scheme 4. Ru/Ag-catalyzed hydroacyloxylations as described by Oe et al.

Shortly afterwards He et al. reported an intramolecular variant for the cyclization of γ,δ-unsaturated carboxylic acids to five- and six-membered-ring lactones in which the former cocatalyst silver triflate (5 mol%) acted as the sole mediator (Scheme 5). The reactions also follow the Markovnikov rules selectively, so that, depending on the substitution pattern of the double bond, 6-*endo* and 5-*exo* products are formed, sometimes as a mixture. However, the selective synthesis of larger rings from, for example, δ,ε-unsaturated carboxylic acids, was unsuccessful. Instead, mixtures of five- and six-membered-ring lactones were formed upon double-bond migration.[11]



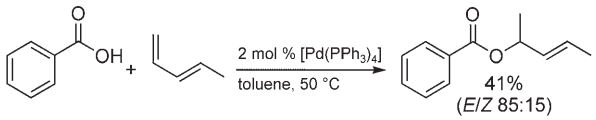
Scheme 5. Examples of Ag-catalyzed hydroacyloxylations.

Such intramolecular addition reactions have meanwhile also been reported for other catalysts, for example, for 2.5 mol% copper(II) triflate[12] and for a mixture of 10 mol% $FeCl_3$ and 30 mol% AgOTf (OTf = trifluoromethane sulfonate).[13] Perhaps the most interesting findings were obtained by He and Yang with cationic gold(I)–phosphine complexes, which also mediate the intermolecular addition of aromatic and aliphatic carboxylic acids to simple alkenes (Scheme 6).[14] Here the lower tendency of this coinage metal to undergo β-hydride elimination probably plays a pivotal role.



Scheme 6. Examples of Au-catalyzed hydroacyloxylations. Bn = benzyl.

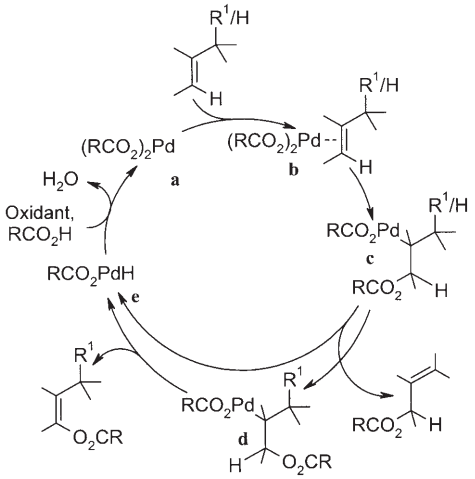
The addition of carboxylic acids to conjugated dienes has also been investigated relatively little so far. In 2003 Hartwig et al. reported that this reaction is mediated by Pd–phosphine complexes, with selective formation Markovnikov products (Scheme 7).[15] However, since this reaction is an equilibrium that does not heavily favor the product thermodynamically, yields of only about 50% were obtained, whereby the carboxylic acid preferentially attacks from the sterically less shielded side to form the *E* product.



Scheme 7. Pd-catalyzed hydroacyloxylation of a diene.

2.1.2. *Oxidative Acyloxylations*

Further pathways for the reaction of carboxylic acids with alkenes are opened up if the additions are carried out under oxidative conditions. Such (usually palladium-catalyzed) oxidative acyloxylations can run via π-allyl complexes (Scheme 13) or are initiated through 1,2-additions of carboxylic acids to coordinated alkenes (Scheme 8), though the precise catalytic cycle has not been completely clarified.[16]

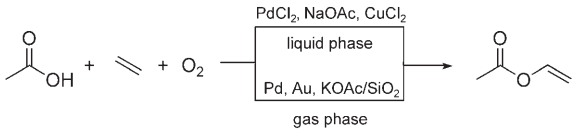


Scheme 8. Pd-catalyzed oxidative acyloxylations of alkenes by 1,2-addition.

In a reaction course proceeding by 1,2-addition, the alkene first coordinates to the Pd^{II} catalyst **b**, followed by nucleophilic addition of the carboxylate to the alkene **c**. The product is released from **c** or **d** by β-hydride elimination; it is dependent upon the structure of the alkene whether this leads to the allyl carboxylate or the enol ester. Allyl carboxylates are usually formed in additions to alkenes with easily accessible allyl hydrogen atoms, since an additional internal rotation would be required to achieve the *syn* conformation necessary for the release of the enol ester by β-hydride elimination.[17] In contrast, the formation of enol esters is mainly observed in the Pd-catalyzed oxidative acyloxylations of ethene or alkenes without allyl hydrogen atoms. In any case, the resulting Pd hydride species **e** must finally be transformed once more into the original Pd^{II} catalyst **a** in an oxidation step.

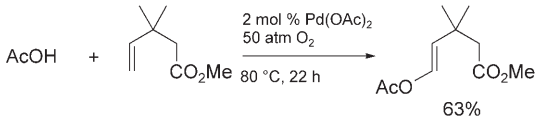
The Pd-catalyzed oxidative synthesis of enol esters, first investigated by Moiseev et al. in 1960,[18] resembles mechanistically the Wacker oxidation of alkenes,[19] except that carboxylic acids are added as nucleophiles instead of water. One example is the addition of acetic acid to ethene, which has been used on an industrial scale since the 1960s for the

production of vinyl acetate (Scheme 9).[20] This reaction was originally carried out in the liquid phase with a $PdCl_2$/NaOAc/$CuCl_2$ catalyst, and was later superseded by a reaction procedure on a Pd/Au heterogeneous catalyst in the gas phase.[21]



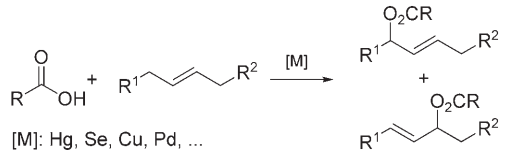
Scheme 9. Industrial production of vinyl acetate.

An early example for the application of this reaction to more complex structures is the synthesis of 2-pyrones by the oxidative cyclization of penta-2,4-dienoic acids in the presence of a mediator consisting of one equivalent $PdCl_2$/LiCl with Na_2CO_3 as the base and water as the solvent, as introduced by Izumi and Kasahara in 1975.[22] A further preparative application is the reaction of a more complex alkene without allyl protons shown in Scheme 10.[23]



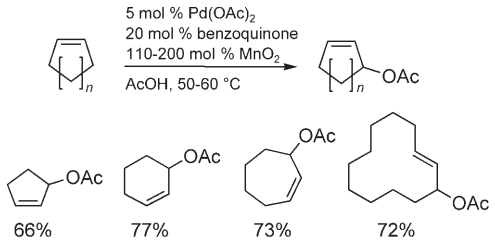
Scheme 10. Preparation of enol esters by oxidative acyloxylation.

As mentioned above, in most oxidative acyloxylations allyl carboxylates are formed selectively. At the start of the development of this reaction, methods were known from, for example, Winstein, Rappoport, et al., mostly with stoichiometric amounts of mercury,[24] selenium,[25] copper,[26] or palladium salts[27] (Scheme 11). Shortly afterwards a reoxidation of the catalysts with oxygen or other oxidizing agents facilitated the development of the first catalytic variants of this reaction.[28]



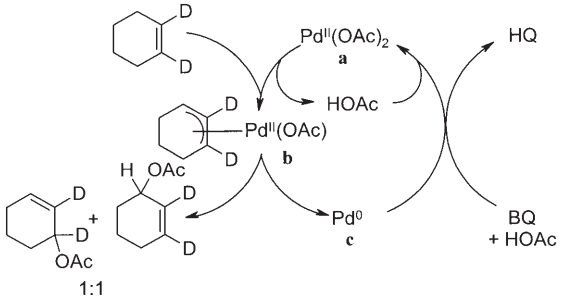
Scheme 11. Preparation of allyl carboxylates from alkenes.

The reaction of propene with acetic acid and oxygen in the presence of heterogeneous palladium catalysts has since become established as an industrial process for the production of allyl acetate.[29] Palladium catalysts in combination with quinone and O_2 or MnO_2 have also been used by Byström and Åkermark for the allylic acyloxylation of more complex molecules; owing to the low regioselectivity this method has been used mainly on unsubstituted cyclic systems.[30] Only a few examples of this reaction type are shown in Scheme 12, as it has been comprehensively treated in recent review articles.[31]



Scheme 12. Allylic acetoxylation of cyclic alkenes.

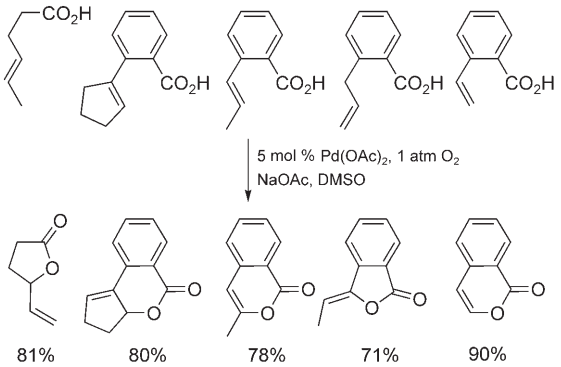
In addition to the 1,2-addition mechanism, a further mechanism via π-allyl complexes may also be formulated for this reaction, which is more probable especially in the reactions of internal alkenes. Studies with deuterated compounds by Grennberg and Bäckvall show that initially the allyl protons of the alkene are activated by the Pd^{II} catalyst **a** and cleaved with formation of an allyl complex **b** (Scheme 13).[32] After addition of the carboxylic acid to the allyl residue the allyl carboxylate is released with formation of a Pd^0 species **c**, and the catalytic cycle is closed by reoxidation of the palladium catalyst.



Scheme 13. Mechanistic investigation of allylic oxidation. HQ = hydroquinone, BQ = benzoquinone.

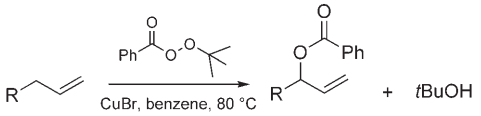
Larock and Hightower have developed a Pd-catalyzed intramolecular oxidative addition of carboxylic acids to alkenes (5 mol% $Pd(OAc)_2$, NaOH as base, in DMSO under 1 atm O_2) as an efficient synthesis of mono-, bi-, and tricyclic five- and six-membered-ring lactones.[33] Depending on the substrate, the reaction results in products that point to a reaction course by 1,2-addition, products that suggest allyl intermediates, and enol esters from substrates without allyl hydrogen atoms (Scheme 14). Since asymmetric carbon centers can be generated in such reactions, the development of an enantioselective variant, in analogy to the oxidative cyclization of *o*-alkenyl phenols,[34] is a worthwhile research target. The stereoselectivity of oxidative acyloxylations has already been efficiently controlled by the use of chiral carboxylic acids.[35]

In addition to these palladium-catalyzed methods, copper-catalyzed acyloxylations, developed primarily by Kharasch



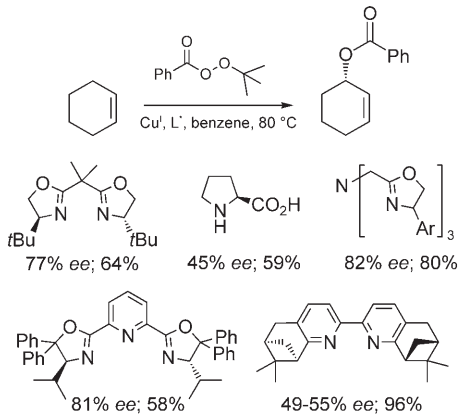
Scheme 14. Intramolecular oxidative acyloxylations.

and Sosnovsky at the end of the 1950s,[36] have become established in which peresters act as oxidants and acyl sources.[37] In the case of terminal alkenes the internal secondary esters are formed selectively (Scheme 15). Effi-



Scheme 15. Example of a Kharasch–Sosnovsky reaction.

cient enantioselective variants of these reactions have been developed in recent years, in which mostly cyclic alkenes have been treated with *tert*-butyl peresters of aryl carboxylic acids in the presence of chiral copper complexes.[38] In these reactions, Denny, Muzart, et al.[39] used camphor and proline derivatives as ligands; Pfaltz,[40] Andrus,[41] and Katzuki et al.[42] used chiral oxazoline copper complexes. Since then the ligand systems have been continually complemented and improved.[43] Since this work is the subject matter of current review articles, only a few selected results are presented in this context.[38] Using the asymmetric oxidative acyloxylation of cyclohexene as an example, Scheme 16 gives an overview of the impressive capabilities of a number of current ligand systems.



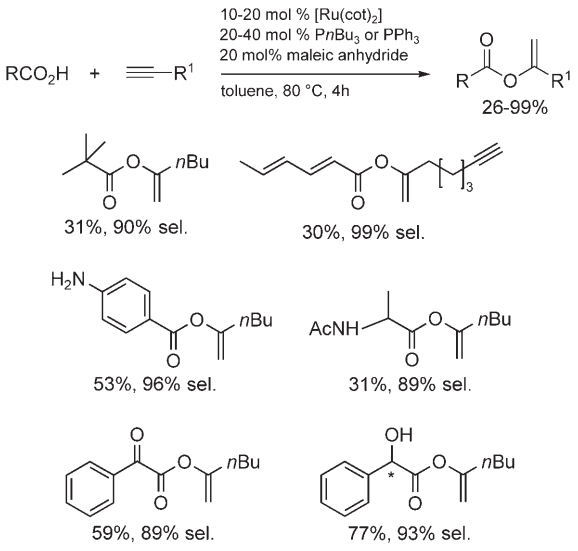
Scheme 16. Current ligands for the asymmetric acyloxylation of cyclohexene.

2.2. Catalytic Addition of Carboxylic Acids to Alkynes

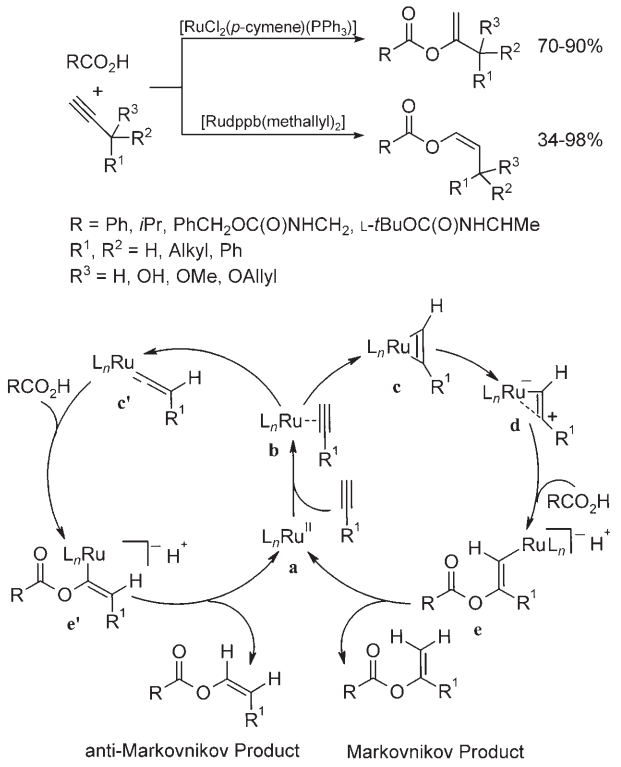
The addition of carboxylic acids to triple bonds with formation of preparatively useful vinyl esters provides an interesting alternative to condensation reactions, which require harsh conditions and yield the products as isomeric mixtures. Rotem and Shvo have introduced the first hydroacyloxylations of alkynes with the formation of vinyl esters, mediated by catalytic amounts of $[Ru_3(CO)_{12}]$ in place of stoichiometric amounts of mercury salts.[44] A mixture of mainly *E* anti-Markovnikov products along with *Z* isomers and rearrangement products were formed. This reaction was optimized by the targeted development of increasingly more active and selective Ru^{II} complex catalysts by the groups of Mitsudo[45] and Dixneuf.[46] The Mitsudo catalyst system consisting of bis(η^5-cyclooctatrienyl)ruthenium, tri-*n*-butylphosphine, and maleic anhydride mediated the addition of a number of complex functionalized carboxylic acids to terminal alkynes and propargyl alcohol derivatives, and provided enol esters in high yields with excellent Markovnikov selectivities (Scheme 17).[47]

Dixneuf et al. described $[RuCl_2(p\text{-cymene})(PPh_3)]$ and $[\{Ru(O_2CH)(CO)_2(PPh_3)\}_2]$ as similarly widely applicable and highly Markovnikov-selective catalysts. Even N-protected amino acids and peptides can be converted smoothly into vinyl esters with these catalysts.[48] The authors also developed a complementary system from bis(methallyl)ruthenium and the chelating phosphine dppb, with which the *Z* anti-Markovnikov products are accessible selectively. According to the postulated mechanism (Scheme 18) the selectivity reversal is brought about by rearrangement of the Ru–alkyne intermediate **b** to an alkylidene complex **c'**, to which the carboxylic acid adds preferentially with anti-Markovnikov selectivity.[49]

Furthermore, kinetic investigations by Mitsudo et al. showed that in the Markovnikov-selective protocol the addition of the carboxylic acid is rate-determining.[47] On the basis of this mechanistic knowledge we have developed

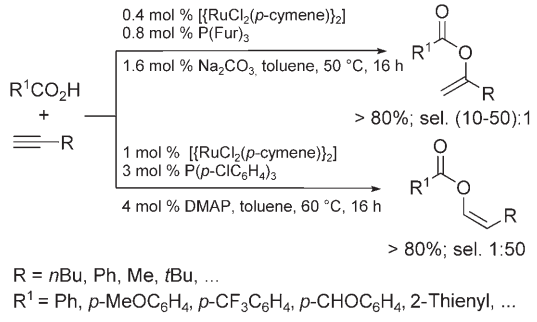


Scheme 17. Ru-catalyzed Markovnikov-selective addition of carboxylic acids to alkynes; cot = cyclooctatrienyl.



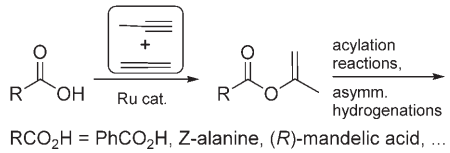
Scheme 18. Postulated catalytic cycles for the Markovnikov and anti-Markovnikov addition of carboxylic acids to alkynes.

particularly simple catalyst systems in which catalytic amounts of base are added to accelerate the reaction and to control its selectivity.[50] A combination of [{$RuCl_2$(*p*-cymene)}$_2$], tri-2-furylphosphine, and sodium carbonate brings about Markovnikov addition with high selectivity even at lower temperatures, while the same Ru precursor in combination with tri-*p*-chlorophenylphosphine and 4-dimethylaminopyridine (DMAP) yields selectively the *Z* anti-Markovnikov products (Scheme 19). The selectivity reversal by the highly coordinating base DMAP may be explained by the mechanism in Scheme 18, in which the coordination of the base increases the electron density at the Ru center and so promotes the rearrangement to the alkylidene complex. As an alternative to the phosphine system, N-heterocyclic carbenes were used as ligands by Verpoort et al. instead of the phosphines for the control of the *E*/*Z* selectivity of the Ru-catalyzed addition of aliphatic carboxylic acids to terminal alkynes.[51]



Scheme 19. Addition of carboxylic acids to terminal alkynes.

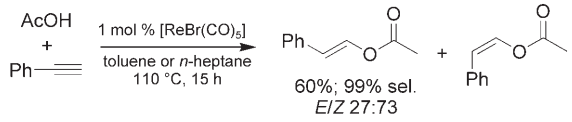
These and mechanistically similar Ru-catalyzed additions to alkynes can be employed in synthesis with considerable flexibility. Examples are the syntheses of dioxolanes from α-hydroxycarboxylic acids,[52] furan derivatives from hydroxyenynes,[53] and enamides from amides and alkynes.[54] The atom economy of these transformations is excellent, which opens up interesting perspectives for the development of sustainable processes. For example, activated carboxylic acid derivatives such as isopropenyl esters can be generated from the reaction of carboxylic acids with a mixture of propyne and allene, which is produced as a by-product in the cracking distillation of natural oil (Scheme 20). In combination with



Scheme 20. Environmentally friendly activation of carboxylic acids. Z = benzyloxycarbonyl.

further reactions that use vinyl esters as substrates (see, for example, Section 5.2) an ecologically advantageous alternative to the activation of acids with thionyl chloride is thus opened up.[55] The development of efficient catalysts for the asymmetric hydrogenation of enol esters provides further possibilities for using the addition of carboxylic acids to alkynes in sustainable organic syntheses since they represent an alternative to the more difficult asymmetric hydrogenation of dialkyl ketones with subsequent esterification.[56]

In addition to ruthenium a number of other metals have been used as catalysts for the addition of carboxylic acids to terminal alkynes, for example, tripodal cationic rhodium(I)–phosphine complexes[57] and bis(η^5-cyclooctadienyl)diiridium(I) dichloride/trimethylphosphite/sodium carbonate systems,[58] from which the Markovnikov products are formed in good or moderate selectivities. In contrast, simple, air-stable pentacarbonylrhenium(I) bromide as catalyst[59] affords almost exclusively the anti-Markovnikov products (Scheme 21). The *E*/*Z* ratio with this first ruthenium system is still largely dependent on the substrate, but presumably could be better controlled by the use of directing ligands.



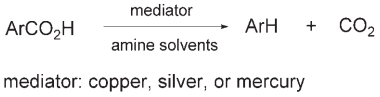
Scheme 21. Example of a Re-catalyzed addition of a carboxylic acid to to an alkyne.

3. Reactions by Extrusion of Carbon Dioxide

3.1. Protodecarboxylations of Carboxylic Acids

The simplest case of a catalytic activation of carboxylic acids by decarboxylation, the thermal protodecarboxylation

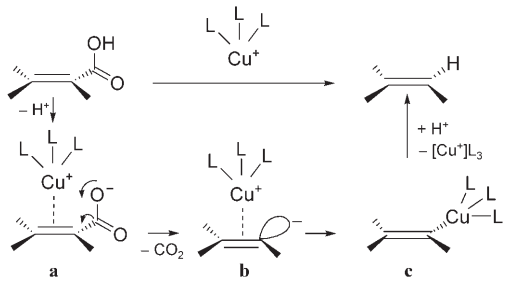
of carboxylic acids, is long established in organic synthesis.[60] It is particularly useful for cases in which there is a need to remove a carboxylic group that is still present in the molecule after a malonic ester or heterocycle synthesis. While highly activated carboxylic acids, for example, β-oxoacids, diphenylacetic acids, or polyfluorobenzoic acids, are also readily decarboxylated in the absence of metals, the release of CO_2 from most other carboxylic acids requires the addition of a transition-metal mediator, generally a copper, silver, or mercury salt (Scheme 22). Usually this mediator is added in



Scheme 22. Decarboxylation of benzoic acids.

stoichiometric amounts, and high temperatures (ca. 250 °C) are necessary. In the original method of Shepard et al. halogenated furancarboxylic acids were reacted in the presence of copper or copper salts.[61] These methods were extended stepwise to activated aromatic and vinylic carboxylic acids by Nilsson,[62] Shepard,[63] and Cohen et al.[64] Bipyridine ligands at the copper center and/or aromatic amine solvents were particularly beneficial.

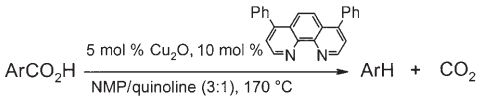
The mechanism of the Cu^I-mediated decarboxylation was investigated intensively by Cohen et al.[65] A number of findings, especially with respect to the stereospecificity of the reaction of vinylic carboxylic acids, make the mechanism in which the copper center is first coordinated by the C–C double bond (Scheme 23) probable for this class of substrates. In contrast, radical reaction pathways have been postulated for aliphatic carboxylic acids.[66]



Scheme 23. Cu-mediated decarboxylation of vinyl carboxylic acids.

Copper-mediated protodecarboxylations have since been used frequently in organic synthesis,[67] although for a long time substrates have been restricted to activated derivatives, for example, benzoic acids with electron-withdrawing *ortho* substituents, phenyl or diphenylacetic acids, and heteroarene carboxylic acids. Only in special cases of highly activated derivatives did the reaction succeed with catalytic amounts of copper.[68,69]

Just recently a method was introduced that also facilitates the decarboxylation of non-activated aromatic carboxylic acids, even *p*-methoxybenzoic acid, with only catalytic amounts of copper.[70] A species formed from copper oxide and 4,7-diphenyl-1,10-phenanthroline in a mixture of *N*-methyl-2-pyrrolidone (NMP) and quinoline functions as the catalyst (Scheme 24). The reactions are mild enough to



Ar = *m*-$NO_2C_6H_4$ (89%), *p*-$MeOC_6H_4$ (80%), *p*-$NO_2C_6H_4$ (68%), *p*-$CHOC_6H_4$ (65%), 2-NO_2-5-$MeOC_6H_3$ (90%), *p*-HOC_6H_4 (75%), *p*-$MeC(O)C_6H_4$ (75%), *p*-$MeC(O)NC_6H_4$ (76%), *p*-CNC_6H_4 (83%)

Scheme 24. Cu-catalyzed protodecarboxylation of aromatic carboxylic acids.

tolerate a number of functional groups, including oxo, formyl, nitro, cyano, and hydroxy groups. DFT calculations on this transformation correctly predicted the observed reactivity sequence of the substrates.[70] The structure of the calculated transition states for the decarboxylation of *o*-fluorobenzoic acid is shown in Figure 1.

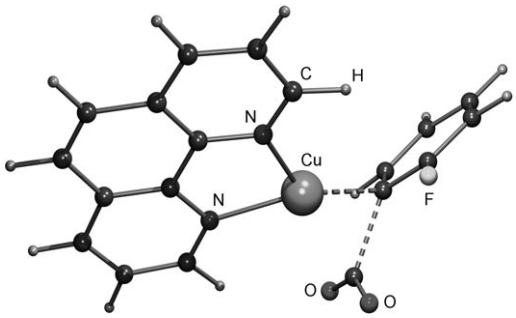


Figure 1. Calculated transition state for the Cu-catalyzed protodecarboxylation.

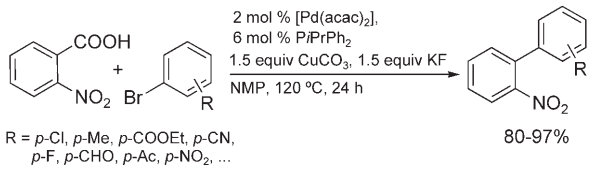
Kozlowski et al. introduced a palladium-catalyzed protodecarboxylation as an alternative to the copper system in which electron-rich, 2,6-disubstituted benzoic acids were reacted at a temperature of just 70 °C in the presence of 20 mol % $Pd(O_2CCF_3)_2$ in DMSO/DMF (1:20).[71] In view of the particularly mild conditions this reaction variant could become an advantageous alternative, especially if it can be run with a smaller loading of palladium.

3.2. The Preparation of Biaryls from Aromatic Carboxylic Acids and Haloarenes

The work by Nilsson and Cohen on copper-mediated decarboxylations shows that intermediate organocopper species are formed in such reactions (Scheme 23).[62,65] Their synthetic potential may be ideally exploited if they are trapped and used as aryl anion equivalents in cross-couplings. Nilsson et al. have already observed that during the pyrolysis of copper(I) 2-nitrobenzoate in the presence of excess

iodobenzene, some 2-nitrobiphenyl is also formed, presumably through a combination of decarboxylation and Ullmann coupling.[62] However, the drastic conditions and the general limitations of crossed Ullmann couplings prevented an extension of this procedure to a preparatively useful synthesis of unsymmetrical biaryls. Only with the combination of a copper or silver decarboxylation catalyst with the classical cross-coupling metal palladium were we successful in the realization of this transformation (Scheme 27).

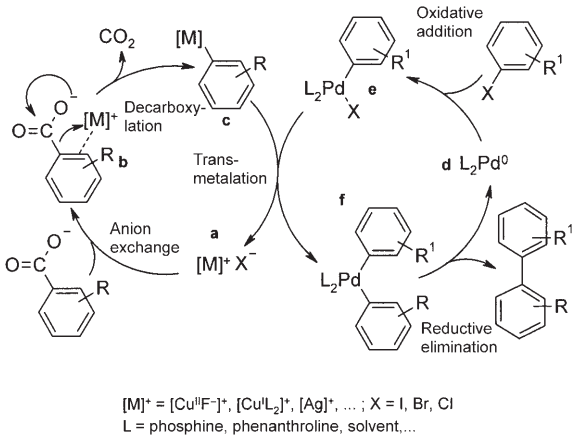
In the original reaction variant *o*-nitrobenzoic acid is initially converted into a particularly reactive Cu^{II} salt by the reaction with basic copper(II) carbonate and potassium fluoride with the removal of water that is formed. Decarboxylation then affords an aryl copper species at only 120 °C which couples with a series of bromoarenes in the presence of 2 mol % $[Pd(acac)_2]$ and 6 mol % P*i*PrPh$_2$ in NMP in high yields (Scheme 25). This first version of a decarboxylative



Scheme 25. Biaryl synthesis with stoichiometric amounts of copper salt.

biaryl synthesis was also carried out under similar conditions with silver carbonate as the base (2 mol % $[Pd(acac)_2]$, 6 mol % PPh_3, 1.5 equiv $AgCO_3$, 1.5 equiv KF), albeit in somewhat lower yields (47 % for R = *p*-Cl).[72,73] The silver/palladium-mediated reaction variant was recently taken up by Becht et al.,[74] who achieved good yields in the coupling of a number of *ortho*-substituted carboxylic acids with iodoarenes by increasing the amount of silver carbonate to three equivalents and by using 30 mol % palladium chloride/60 mol % triphenylarsine as the catalyst and DMSO as the solvent.

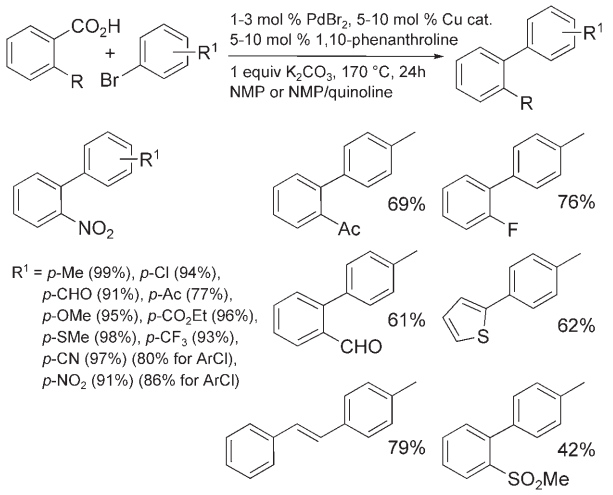
The postulated mechanism of the decarboxylative biaryl synthesis (Scheme 26) begins analogously to the Cu-mediated



Scheme 26. Proposed mechanism of the decarboxylative biaryl synthesis.

protodecarboxylation (Scheme 23). It is assumed that the copper species **a** first coordinates to the carboxylate oxygen atom and then inserts into the C–C(O) bond via the aryl π-system with extrusion of CO_2 and the formation of an aryl–Cu species (**c**). At the same time the haloarene adds oxidatively to a coordinatively unsaturated Pd^0 species **d**. As in a classical cross-coupling, a transmetalation then folllows in which the aryl group is transferred from the copper center to the palladium center (**f**) with the release of copper halide. The unsymmetrical biaryl is released by reductive elimination, thereby closing the palladium catalytic cycle. To be able to run the reaction catalytically with respect to copper, a salt exchange between fresh potassium carboxylate and the copper halide **a** is all that is necessary, but this is hampered by the high affinity of halides for copper ions. In the alternative Ag/Pd system a reduction in the amount of silver appears to be hardly feasible in view of the considerable stability of silver(I) halides.

A second reaction variant has already been developed for the Cu/Pd system in which not only palladium but also copper is used in catalytic amounts (Scheme 27).[72] In this variant, *o*-

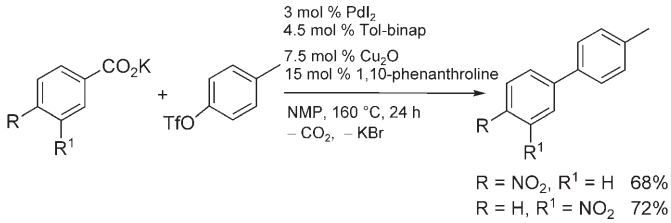


Scheme 27. Biaryl synthesis with catalytic amounts of Cu.

nitrobenzoic acids were coupled in good yields to the corresponding biaryls with a number of bromo-, iodo-, and even some chloroarenes in the presence of a catalyst system consisting of 3 mol % Cu^IBr, 5 mol % 1,10-phenanthroline, and 1 mol % $[Pd(acac)_2]$ at 160 °C.[75] In the presence of 10 % copper catalyst, less activated carboxylic acids also couple, including *ortho*-substituted benzoic acids and heterocyclic derivatives. In contrast, only modest yields were obtained with non-*ortho*-substituted benzoic acids, even with the use of stoichiometric amounts of copper. The key to understanding this limitation was provided by the observation that copper-catalyzed protodecarboxylations of non-*ortho*-substituted benzoic acids are blocked by the addition of halides that are unavoidably formed in decarboxylative cross-coupling.[73]

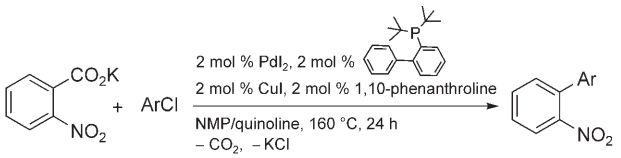
The hypothesis that it is indeed only the salt exchange which has hitherto hindered the general applicability of the reaction was confirmed when the decarboxylative cross-

coupling of aryl triflates also achieved in good yield with *meta*- and *para*-substituted benzoic acids in the presence of catalytic amounts of copper (Scheme 28).[76] Instead of halide salts weakly coordinating triflate salts are released, which do



Scheme 28. Decarboxylative cross-coupling of non-*ortho*-substituted benzoic acids. Tol-binap = (1,1′-binaphthalene)-2,2′-diylbis(di-*p*-tolylphosphine).

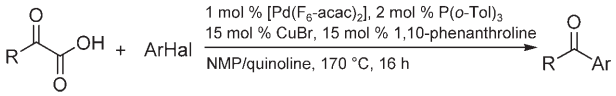
not hinder the decarboxylation. The Pd catalyst has also been developed further, and the spectrum of substrates has been significantly improved with respect to electrophilic coupling partners. A catalyst system of palladium iodide/bis(*tert*-butyl)biphenylphosphine and copper iodide/phenanthroline facilitates, for example, the coupling even of notoriously nonreactive electron-rich chloroarenes in high yields (Scheme 29).[77]



Scheme 29. Decarboxlative cross-coupling of chloroarenes.

The large number of commercially important biaryls such as valsartan, boscalid, or telmisartan, which currently are produced by multistep syntheses that involve for example, Suzuki couplings, suggest the economic potential of decarboxylative biaryl syntheses. Their principal advantages for industrial application lie in the lower price and the higher stability of benzoic acid salts compared to aryl metal compounds. Saltigo GmbH has already produced a special *ortho*-nitro-substituted biphenyl on a multikilogram scale, for which it was possible to reduce the amount of copper to 0.3 mol% and the amount of palladium to 0.06 mol%.

Recent results show moreover that the basic reaction principle of this decarboxylative cross-coupling is not restricted to the synthesis of biaryls. In the presence of a modified copper/palladium system it has also been shown that α-oxocarboxylic acid salts can be treated with haloarenes to give ketones under decarboxylation, as illustrated in the examples in Scheme 30.[78] The novelty of this access pathway is that, reversing the polarity of the bond coupling compared to traditional ketone synthesis, acyl anion equivalents are here coupled with aryl electrophiles.

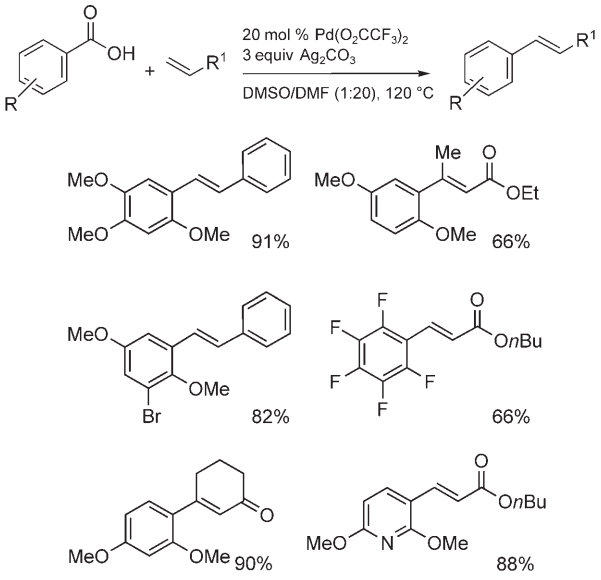


R = Ph; Ar = *p*-MeC$_6$H$_4$ (83%), *p*-MeOC$_6$H$_4$ (82%), *p*-CNC$_6$H$_4$ (99%), *p*-AcC$_6$H$_4$ (78%), *o*-MeOC$_6$H$_4$ (73%), ...
R = *t*Bu; Ar = *p*-MeC$_6$H$_4$ (90%)

Scheme 30. Decarboxylative ketone synthesis from α-oxocarboxylic acid salts and haloarenes. *o*-Tol = *o*-tolyl, F$_6$-acac = hexafluoroacetylacetonate.

3.3. Heck Reaction of Aromatic Carboxylic Acids with Alkenes

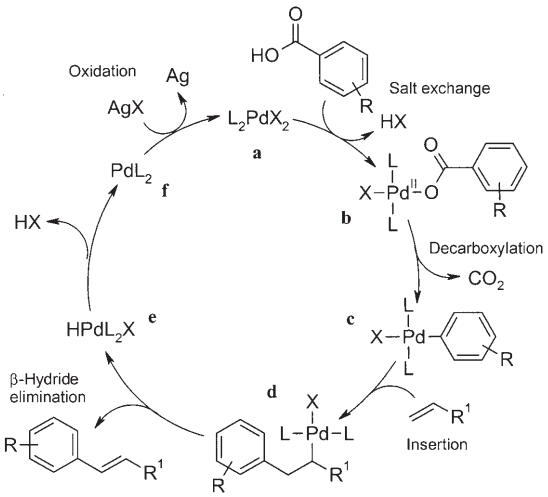
In 2002 Myers et al. introduced a novel Heck reaction in which the aromatic carboxylic acids are treated with alkenes in the presence of silver carbonate and a palladium catalyst with the release of CO_2 to form vinyl arenes (Schema 31).[79]



Scheme 31. Oxidative Heck olefination of aromatic carboxylic acids.

The mechanism of this reaction is outlined in Scheme 32. Unlike the classical Heck reaction,[80] the catalytic cycle begins with a Pd^{II} species **a**, which takes up the carboxylate by salt exchange. An aryl palladium(II) species **c** is subsequently formed by decarboxylation, as would also be formed by the oxidative addition of a haloarene. Thus, the insertion of the alkene, the internal rotation, and the β-hydride elimination can follow the traditional mechanism, although an additional oxidation step is required to convert the released Pd^0 (**f**) back into Pd^{II} (**a**) and thus close the cycle. Through this oxidation, which is brought about by the silver carbonate added in excess, the aryl nucleophiles formed by decarboxylation of carboxylic acid salts actually become reversed in polarity and thus behave as aryl electrophiles.

Compared to mechanistically related oxidative vinylations of arenes by C–H activation (Fujiwara reaction)[81] this reaction offers the considerable advantage of regiospecificity through the use of aromatic carboxylic acids. However, silver carbonate is a very expensive reagent, so the

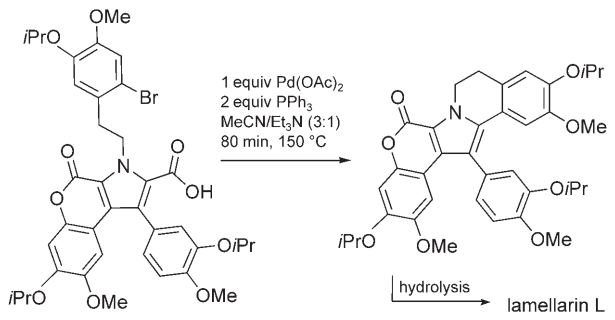


Scheme 32. Mechanism of the oxidative Heck olefination of carboxylic acids.

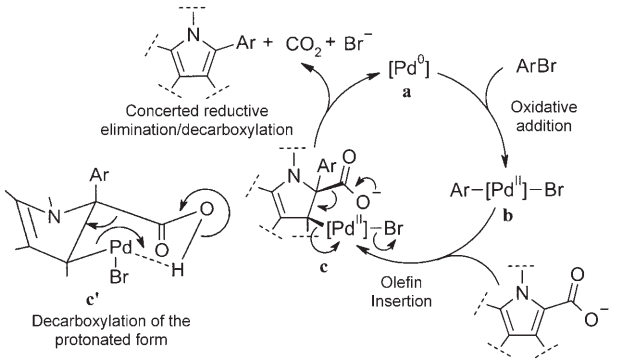
development of alternative oxidizing agents is an urgent goal for making this trendsetting reaction more economical. This has already been successful for the analogous reaction of aromatic phosphonic acids; here the reoxidation of the palladium can be achieved with 4-methylmorpholine-*N*-oxide.[82]

3.4. Heck Reaction of Haloarenes with Heteroaryl Carboxylic Acids

The ability of carboxylates to function as leaving groups on both the arene and the alkene components in the Heck reaction was demonstrated for the first time by Steglich et al. as part of the total synthesis of lamellarin L (Scheme 33).[83] In the palladium-mediated ring-closing synthesis shown in Scheme 33 the bromoarene reacts intramolecularly with a pyrrole carboxylic acid with extrusion of CO_2 and HBr. The authors called this transformation a "Heck cyclization", but unfortunately did not elucidate the mechanism further. Considering that the reactivity of five-membered-ring arenes corresponds to that of double-bond systems rather than to that of aromatic compounds, and considering that Heck reactions are characterized by the insertions of C–C multiple bonds into metal–carbon bonds, we have illustrated in Scheme 34 what such a Heck mechanism could look like.



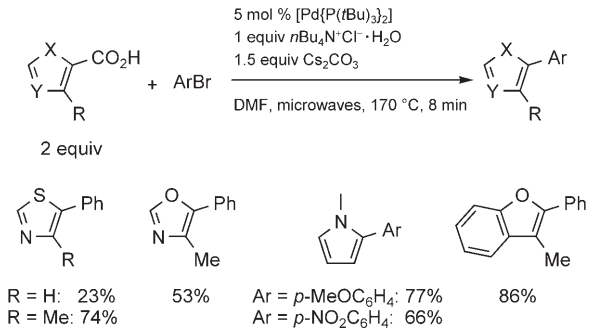
Scheme 33. Decarboxylative intramolecular Heck reaction reported by Steglich et al.



Scheme 34. Mechanistic proposal for a decarboxylative arylation through a Heck reaction.

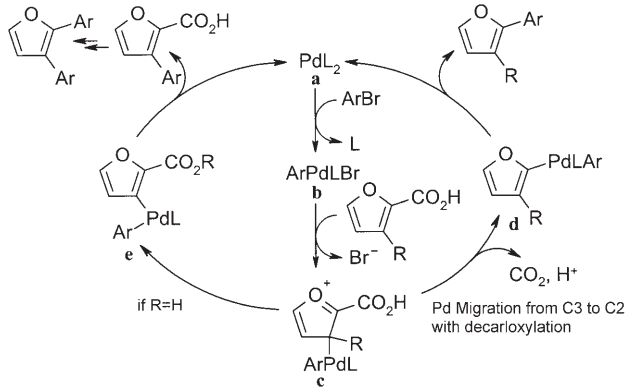
Our postulated reaction pathway corresponds essentially to the Heck reaction of a cyclic alkene. In such a reaction a β-hydrogen atom must be present in the *cis* position to the palladium center for the *syn*-β-hydride elimination to take place;[84] otherwise additional isomerization steps or a temporary shift of the palladium atom onto the heteroatom is necessary to be able to close the catalytic cycle. A carboxylate group at the α-position to the heteroatom opens up an advantageous alternative for this last step (Scheme 34). As with other heteroatom-substituted alkenes (e.g. enol ethers), after the oxidative addition of the haloarene to a Pd^0 species (**a**) the insertion of the double-bond system takes place preferably into the Pd–aryl bond of **b** such that the aryl residue is inserted into the position α to the heteroatom. In this case the catalytic cycle cannot be closed by β-hydride elimination since there is no β-hydrogen atom, whereas a decarboxylation step would be geometrically favorable. In the deprotonated form the decarboxylation/reductive elimination may be formulated as a concerted fragmentation reaction (**c**); in the protonated form of the carboxylic acid group or with inclusion of an ammonium nitrogen atom in place of the proton a presumably energetically favorable six-membered-ring transition state in the chair form can be formulated (**c′**) as an alternative. Overall we consider such a mechanism to be more plausible in this case, rather than a reaction pathway in which the decarboxylation precedes the C–C bond formation.

Recently Forgione et al. succeeded in extending this type of reaction to the intermolecular case by arylating a series of five-membered heterocyclic carboxylic acids of the furan, pyrrole, thiophene, oxazole, and thiazole type with different bromoarenes (Scheme 35).[85] In this reaction the carboxylic acid group specifies the position of the C–C bond formation, but it must always be located on a carbon atom that would also be preferred for a C–C bond formation for electronic reasons. Furan-2-carboxylic acid would therefore be monoarylated regioselectively under decarboxylation, whereas no analogous conversion of furan-3-carboxylic acid is possible. This procedure holds much promise since, unlike in Heck arylations of nonfunctionalized heterocycles, the regiochemistry of the arylation can at least be directed to one of two electronically comparable positions by the position of the carboxylic acid group. Further advantages are the ready availability of heterocyclic carboxylic acids and the large preparative importance of the products accessible from them.



Scheme 35. Decarboxylative arylation of five-membered-ring arenes.

If this transformation takes place according to a Heck-type mechanism (Scheme 34), the substrate spectrum is restricted to a few heterocyclic carboxylic acids with pronounced double-bond character. Forgione et al. regard the reaction, however, as a mechanistically discrete decarboxylative cross-coupling and suggest the following catalytic cycle (Scheme 36, right). The aryl palladium(II) complex **b** formed by oxidative addition of the bromoarene acts as an electro-



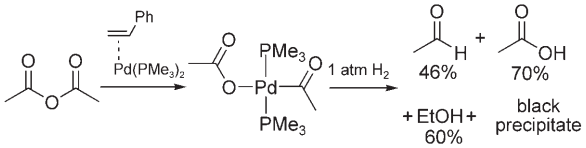
Scheme 36. Postulated mechanism of the decarboxylative arylation of five-membered-ring arenes.

phile and attacks the heterocycle in the *meta* position. A σ bond is thus formed, the oxygen atom assumes a positive charge, and the bromide counterion is displaced from the coordination sphere of the palladium center (**c**). The Pd atom is then moved into the *ortho* position in a C3–C2 migration as CO_2 is simultaneously eliminated (**d**). The product is then released by reductive elimination, and the catalytic cycle is closed. The formation of diarylated by-products is explained by an alternative pathway which takes place by C–H activation and whose product is then arylated quantitatively a second time (Scheme 36, left). If this unusual mechanism is shown to be correct, a transference of this reaction to a broader substrate spectrum, for example, also to electron-rich benzoic acids, would be conceivable.

4. Reactions via Acyl Metal Species

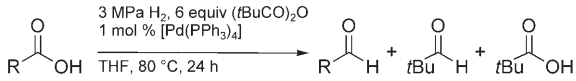
4.1. Reduction of Carboxylic Acids to Aldehydes

The direct reduction of carboxylic acids to aldehydes is very difficult since the products are readily reduced further to alcohols. Heterogeneous catalysts which facilitate the hydrogenation of the carboxylic acid or carbonyl chloride (Rosenmund reduction) to be captured at this stage have been developed as alternatives to complex metal hydrides.[86] A homogeneous catalytic alternative appeared for the first time in 1971 when Wakamatsu et al. succeeded in converting anhydrides into aldehydes in the presence of cobalt octacarbonyl.[87] The breakthrough was subsequently achieved by Yamamoto et al., who demonstrated that anhydrides react with coordinatively unsaturated Pd^0 complexes to form acyl complexes which are reductively cleaved with hydrogen, thereby releasing aldehydes and carboxylic acids (Scheme 37).[88]



Scheme 37. Hydrogenolysis of an acyl–Pd complex.

Since the reactivity of the anhydrides towards Pd–phosphine complexes is heavily dependent upon their steric demand, the direct high-pressure hydrogenation of a mixture of homo- and heteroanhydrides that is formed in the reaction of a carboxylic acid with the sterically demanding pivalic anhydride leads to the preferential formation of the sterically less demanding aldehyde (Scheme 38).[89] The formation of pivaldehyde as a by-product cannot be totally avoided, but this presents no separation problems in the synthesis of more

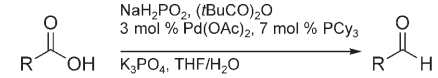


RCO_2H	Yield of:[a]	RCHO [%]	*t*BuCHO [%]
oleic acid		99	26
Ph, CO_2H		84	>1
CO_2H		64	39
NC, CO_2H		99	26
MeO, CO_2H		95	38
CO_2H		30	20
N, CO_2H		99	53
O, CO_2H		87	42

Scheme 38. Hydrogenation of carboxylic acids to aldehydes. [a] Based on the amount of starting carboxylic acid.

complex compounds owing to the high volatility of this compound.

The Yamamoto process is thus a thoroughly elegant method for the synthesis of aldehydes, particularly since it starts directly from carboxylic acids. However, it is a disadvantage for many applications that a high-pressure apparatus must be used. We have therefore developed an alternative method in which sodium hypophosphite is used as a stable and easy-to-handle reducing agent (Scheme 39).[90] In this procedure the carboxylic acid is treated with a mixture of sodium hypophosphite and potassium phosphate in the presence of excess pivalic anhydride in a defined THF/water mixture. The catalyst is generated in situ from palladium acetate and tricylohexylphosphine.



R = *o*-MeC_6H_4 (70%), *m*-MeC_6H_4 (73%), *p*-EtC_6H_4 (74%), *p*-$AcOC_6H_4$ (73%), *m*-CNC_6H_4 (54%), *p*-HOC_6H_4 (68%), $C_{11}H_{23}$ (63%), Cy (59%), ...

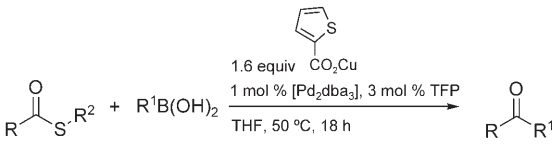
Scheme 39. Reduction of carboxylic acids with hypophosphite. Cy = cyclohexyl.

In all these reactions it is critical that the palladium phosphine complex remains intact since its decomposition product, Pd black, has high catalytic activity for the undesired reduction of the aldehyde to the alcohol.

4.2. Synthesis of Aryl Ketones

Phosphine-stabilized acyl palladium species cannot only be hydrogenolyzed, but the acyl group can also be transferred to carbon nucleophiles. The Pd-mediated cross-coupling of acyl chlorides with organometallic compounds, for example, organic zinc, tin, and boron compounds, is based on this principle.[91] These methods are an interesting alternative to classical ketone syntheses that are carried out by reaction of activated carboxylic acid derivatives, for example, Weinreb amides[92] or nitriles,[93] with aggressive organometallic reagents, but are themselves limited by the high reactivity of the acid chlorides, which makes application to sensitive derivatives difficult.

Liebeskind et al. took an unusual path in their ketone synthesis, which is based on thioesters as less reactive carboxylic acid derivatives and the equally less reactive boron acids. They used an excess of Cu^I in the form of the thiophene carboxylate salt to activate the soft thiolate leaving group.[94] The thiophene carboxylate group at the same time supports the transmetalation step so that, unlike the classical Suzuki reaction, no auxiliary base is needed. The mild reaction conditions facilitated the synthesis of a large variety of sensitive compounds, for example, aryl(chloromethyl)ketone (Scheme 40). The disadvantage, however, is the need to prepare the thioester in a separate reaction step as well as the use of a stoichiometric amount of the heavy metal copper, which is difficult to separate from the heterocyclic products.[121]

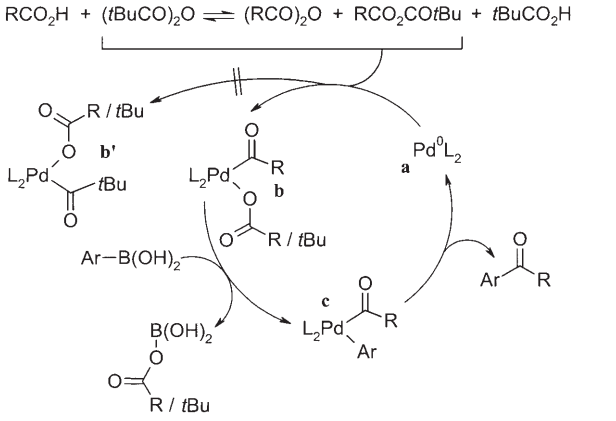


R, R^1 = Ph, *o*-$MeOC_6H_4$ (88%); Ph, *m*-$MeOC_6H_4$ (83%); Ph, 2-naphthyl (79%); *p*-HOC_6H_4, Ph (81%); $C_{11}H_{23}$, *m*-$NO_2C_6H_4$ (79%); $AcOCH_2$, *p*-$MeO_2CC_6H_4$ (88%); ...

TFP = tri-2-furylphosphine

Scheme 40. Copper-mediated coupling of arylboronic acids with thioesters.

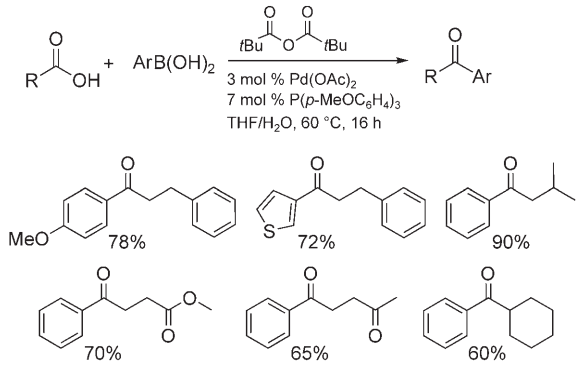
Our own research work in this area originated from efforts to carry out an analogous cross-coupling starting directly from carboxylic acids. This approach succeeded by in situ activation of the carboxylic acid with pivalic anhydride and subsequent cross-coupling to the aryl ketones with boronic acid.[95] The mechanism of this reaction is shown in Scheme 41.[96] With the addition of pivalic anhydride to a



Scheme 41. Mechanism of the ketone synthesis from carboxylic acids and boronic acids.

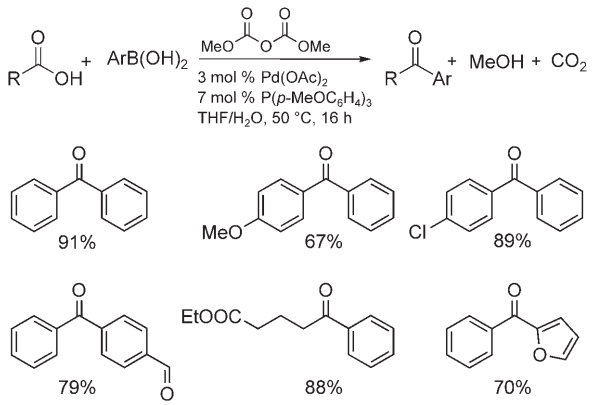
carboxylic acid an equilibrium mixture of pivalic acid and homo- and heteroanhydrides is formed. Since the catalyst **a** only inserts into the C–O bond of the sterically less shielded homoanhydride or the less shielded side of the mixed anhydride (**b**), the desired ketone is formed selectively after transmetalation and reductive elimination, whereas *tert*-butyl ketones are formed in only trace amounts. The exact mechanism of this reaction was investigated by comprehensive DFT calculations,[97] from which is it was concluded that anionic Pd^0 species of the Amatore–Jutand type[98] make particularly advantageous reaction pathways accessible.

This transformation, too, is free of base and thus compatible with many functional groups (Scheme 42). With the use of moist THF as the solvent and a catalyst system that is generated in situ from palladium(II) acetate and moderately electron-rich phosphines such as tri-4-methoxyphenylphosphine, the basicity of the cleaved carboxylate is sufficient to mediate the transmetalation. By reconverting the coupling product pivalic acid into the anhydride a waste-minimized reaction procedure is conceivable.



Scheme 42. Pivalic anhydride one-pot reaction for the coupling of carboxylic acids with boronic acids.

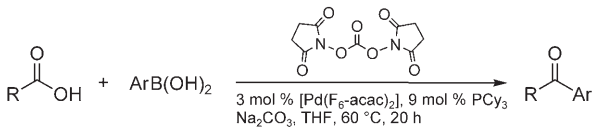
One problem with the original procedure comes from the competitive dehydration of a number of boronic acids to boroxines, as the latter can only be coupled slowly under the reaction conditions. In the reaction variant introduced subsequently by Yamamoto et al. somewhat higher temperatures were used with dioxane as the solvent, which leads to improved yields with aromatic carboxylic acids.[99] The more reactive dimethyl dicarbonate can also be used as activating reagent as an alternative to pivalic anhydride, in which case only the volatile coupling products CO_2 and methanol are formed (Scheme 43). As was shown in the work of Yamamoto et al.[100] and ourselves[101] this reaction variant has advantages for more robust substrates, although is not compatible with quite so large a number of functional groups.



Scheme 43. Dimethyl dicarbonate variants of the ketone synthesis.

A more widely applicable reaction variant that is also compatible with basic heterocycles was developed by ourselves in which the carboxylic acids are activated with *N,N′*-disuccinimidyl carbonate.[102] Here a catalyst system of palladium hexafluoroacetylacetonate and tricyclohexylphosphine is used which is stabilized by the addition of solid sodium carbonate as a proton trap (Scheme 44). This reaction is the first example of the use of peptide-coupling reagents in palladium catalysis.

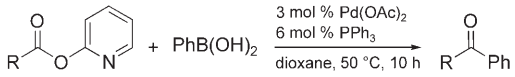
Chatani et al. recently introduced a further reaction variant in which preformed *o*-hydroxypyridyl esters act as



Ar = Ph; R = *p*-AcC_6H_4 (88%), Cy (81%), *p*-$MeOC_6H_4$ (68%), *p*-CNC_6H_4 (95%), *p*-$CF_3C_6H_4$ (89%), *m*-CNC_6H_4 (90%), ...
R = 2-phenylethyl; Ar = *o*-MeC_6H_4 (90%), *p*-$MeOC_6H_4$ (91%), *p*-AcC_6H_4 (56%), ...

Scheme 44. Disuccinimidyl carbonate variant of the ketone synthesis.

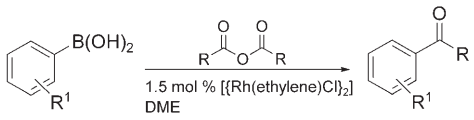
substrates (Scheme 45).[103] The advantage here is that the slightly higher reactivity of this substrate allows the use of a more robust catalyst system comprising $Pd(OAc)_2$ and PPh_3. A similar catalyst is also used in the synthesis of ketones from mixed carboxylic acid/phosphoric acid anhydrides.[104] The high acidity of perfluorocarboxylic acids also allows an analogous Pd-catalyzed synthesis of perfluoroalkyl ketones from their phenyl esters and arylboronic acids.[105]



R = *p*-$MeOC_6H_4$ (97%), *p*-FC_6H_4 (93%), *p*-$NO_2C_6H_4$ (94%), *p*-$MeOC(O)C_6H_4$ (90%), *m*-ClC_6H_4 (89%), *o*-MeC_6H_4 (90%), $C_{15}H_{31}$ (72%), Cy (71%), ...

Scheme 45. Ketone synthesis from *o*-hydroxypyridyl esters and phenylboronic acid.

Frost and Wadsworth showed that the cross-coupling of carboxylic anhydrides with boronic acid is also efficiently mediated by rhodium catalysts at 65 °C in 1,2-dimethoxyethane (DME; Scheme 46).[106]



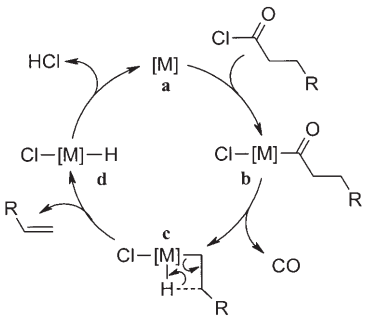
R = Me; R^1 = *p*-Ac (86%), *m*-Me (68%), *p*-MeO (67%), *m*-NO_2 (56%), ...
R = Ph; R^1 = H (76%), ...

Scheme 46. Rh-catalyzed ketone synthesis from anhydrides.

5. Reactions with Decarbonylation of Acyl Metal Species

5.1. Elimination Reactions with Decarbonylation

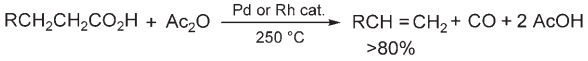
The decarbonylation of activated carboxylic acid derivatives or even aldehydes has been known for a long time from the work of Tsuji and Ohno,[107] among others. To a certain extent such reactions correspond mechanistically to the reversal of frequently used carbonylation processes (Scheme 47). Thus, decarbonylations of acid chlorides are induced by the oxidative addition of these compounds to a transition-metal catalyst **a** with the formation of an acyl metal species **b**; the decarbonylation takes place by migratory



Scheme 47. Mechanism of the decarbonylative elimination of activated carboxylic acid derivatives.

deinsertion of carbon monoxide. Depending on whether the substrate contains β-hydrogen atoms, either a reductive elimination of the corresponding organohalide subsequently takes place, or β-hydride elimination occurs with release of hydrogen halide and the corresponding alkene.

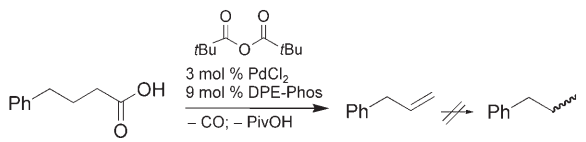
Miller et al. provided evidence that an analogous reaction can also be carried out directly with carboxylic acids. They converted long-chain fatty acids into a mixture of anhydrides by the addition of acetic anhydride and heated the mixture to 250 °C in a nitrogen current in the presence of Pd–phosphine catalysts (Scheme 48). The terminal alkene products distilled



Scheme 48. Pd-catalyzed decarboxylation of fatty acids.

off so rapidly that isomerization of the double bond essentially did not take place.[108] This method is of considerable interest gives access to the preparation of preparatively useful 1-alkenes from renewable raw materials. However, for use in organic synthesis it has the disadvantage that extreme temperatures, an elaborate reaction procedure, and products with a definite volatility are required, since double-bond isomerization is suppressed by the process setup alone.

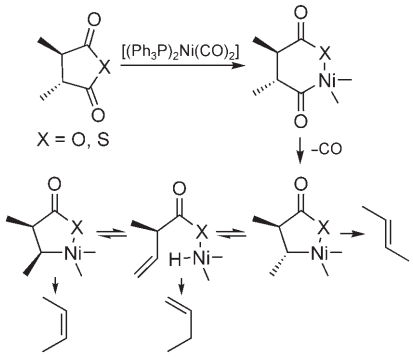
In the reaction variant developed by ourselves pivalic anhydride is used as a dehydrating agent to improve the regioselectivity of the oxidative addition. By the use of bis(2-diphenylphosphinophenyl) ether (DPE-Phos) as ligand the decarbonylative activity of the palladium catalyst is increased and the isomerization activity is suppressed to such an extent that the reaction takes place at just 120 °C in high yield, and no separation of the products by distillation is required.[109] The efficiency of the catalyst system is demonstrated with the example of elimination of 4-phenylbutyric acid (Scheme 49). The terminal alkene is formed with high selectivity, although



Scheme 49. Example of a decarbonylative elimination without isomerization.

double-bond isomerization would lead to the thermodynamically far more stable styrene derivative.

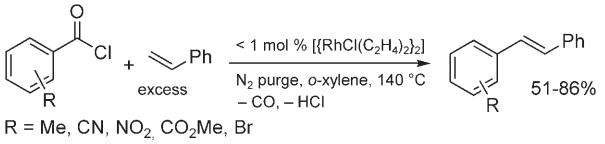
Trost and Chen discovered a reaction pathway along which cyclic anhydrides or thioanhydrides can also be transformed into alkenes by decarbonylation and decarboxylation (Scheme 50).[110] The selectivity of this mechanistically interesting conversion, which is mediated by stoichiometric addition of $[(Ph_3P)_2Ni(CO)_2]$, was not further optimized, but it served as the basis for the development of cross-couplings in which intermediates of this reaction cascade are captured (Scheme 57).



Scheme 50. Conversion of (thio)anhydrides into alkenes.

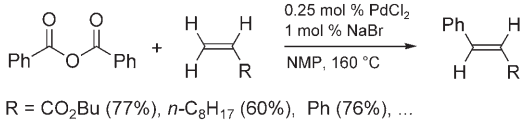
5.2. Decarbonylative Heck Reactions

In traditional Heck reactions haloarenes are converted into vinyl arenes with alkenes by palladium catalysts, and the eliminated hydrogen halide is bound by a base. Blaser and Spencer discovered that in the analogous coupling of aromatic acid chlorides with alkenes vinyl arenes are also formed since the intermediate acyl palladium species quickly decarbonylate.[111] Miura et al. were able to carry out this reaction without a base so that only the gaseous byproducts CO and HCl are formed. They used this method to develop a salt-free and potentially waste-minimized variant of the Heck reaction (Scheme 51); $[\{RhCl(C_2H_4)_2\}_2]$[112] or $[PdCl_2(PhCN)_2]/(PhCH_2)Bu_3NCl$ was used as the catalyst.[113]



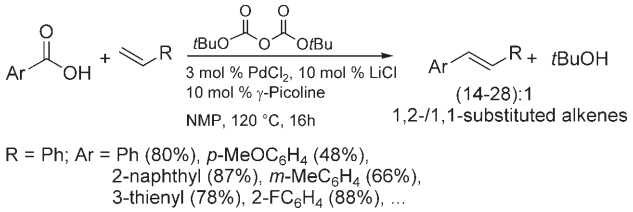
Scheme 51. Rh-catalyzed base-free decarbonylative Heck reaction.

De Vries et al. used a different strategy to avoid the problematic salt formation of traditional Heck reactions by exploiting anhydrides of aromatic carboxylic acids as the aryl source. Using $PdCl_2$/NaBr systems, they treated, for example, benzoic anhydride with acrylic esters to give cinnamic esters and benzoic acid with extrusion of carbon monoxide (Scheme 52).[114] However, it has unfortunately not been possible so far to dehydrate the benzoic acid, which is formed



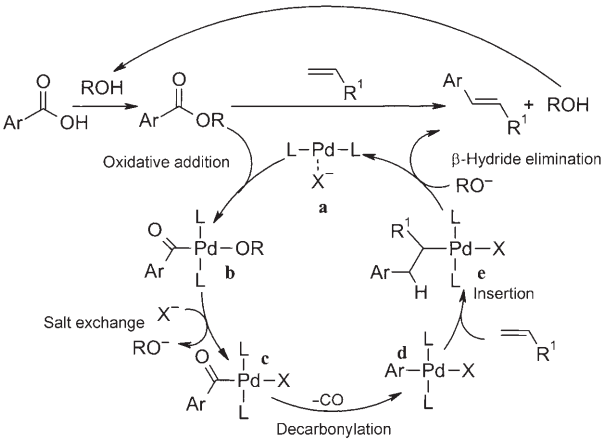
Scheme 52. Heck reaction of carboxylic anhydrides.

as a byproduct in place of a salt, into benzoic anhydride without forming waste; thus, the highly sought-after waste-minimized Heck reaction could not be achieved with this system. A reaction variant developed in our research group allowed the direct transformation of aromatic carboxylic acids in which they are converted into mixed anhydrides by the addition of di-*tert*-butyl dicarbonate (Boc_2O) and coupled with alkenes to give the vinyl arenes. Here, only the volatile byproducts *tert*-butyl alcohol, CO, and CO_2 are formed (Scheme 53).[115]



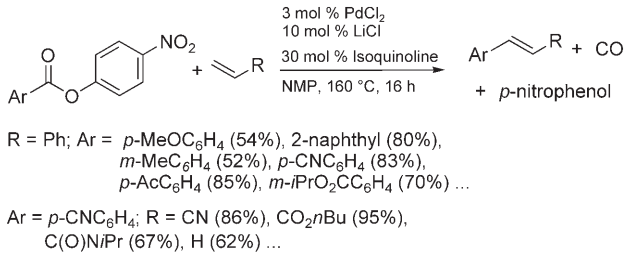
Scheme 53. One-pot procedure for the Heck reaction of carboxylic acids.

Real waste minimization in such Heck reactions could most likely be achieved with esters as substrates since these are thermodynamically more stable than anhydrides and are therefore in part directly accessible from carboxylic acids and alcohols. Thus, with direct recycling of the released alcohol an overall reaction is achieved in which aromatic carboxylic acids are coupled with alkenes give vinyl arenes, CO, and water. A plausible mechanism for such a conversion is outlined in Scheme 54. A starting point for the realization of such a concept was achieved with the Heck reaction of *p*-nitrophenyl esters of aromatic carboxylic acids prepared



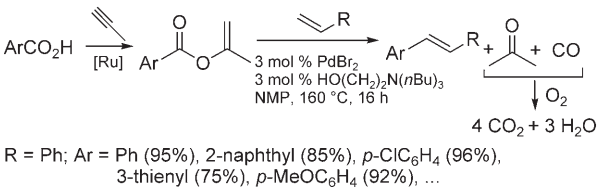
Scheme 54. Proposed mechanism of the Heck reaction starting from esters.

directly from the carboxylic acid and *p*-nitrophenol.[116] Thus, in the presence of a $PdCl_2$/LiCl/isoquinoline catalyst system the *p*-nitrophenyl esters of a series of functionalized aromatic, heteroaromatic, and vinylic carboxylic acids were converted into the corresponding vinyl arenes (Scheme 55). The conversion of further active esters derived from pentafluorophenol, imidazole, and even *m*-chlorophenol, among others, was equally successful with this system. The last step needed for an optimal method has, however, not yet been achieved, namely the extension to simple alkyl esters, which would be in equilibrium with carboxylic acids and alcohols under the reaction conditions. In this way the reaction could be carried out directly with carboxylic acids and alkenes in the presence of a catalytic amount of an alcohol, whereby CO and H_2O would have to be removed by continuous distillation.



Scheme 55. Heck olefination of *p*-nitrophenyl carboxylates.

For an ecologically advantageous alternative we have developed the decarbonylative Heck olefination of isopropenyl esters of aromatic carboxylic acids to vinyl arenes, CO, and acetone with more advanced catalysts from $PdBr_2$ and hydroxy-functionalized tetra-*n*-alkylammonium bromides.[117] If the isopropenyl esters are produced from carboxylic acids and propyne/allene, which are by-products in natural oil refining (see Scheme 20), the whole method is likewise salt free (Scheme 56). Apart from CO only acetone is produced as a coupling product, and this can be incinerated in an almost environmentally neutral manner. An energy-consuming recovery of the coupling product is avoided, and since no stoichiometric inorganic reagent is used, the amount of solvent required can be drastically reduced. The substrate spectrum of this transformation is similar to that of the olefination of *p*-nitrophenyl esters.

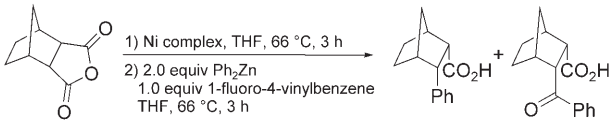


Scheme 56. Two-stage, salt-free synthesis of vinyl arenes from carboxylic acids.

5.3. Decarbonylative Cross-Coupling Reactions

As already mentioned in Section 5.1, Ni complexes formed by the oxidative addition of cyclic anhydrides

decarbonylate particularly, easily forming nickelacycles. Work by Echavarren et al. shows that the reaction of these species with haloalkanes leads to the formation of $C(sp^3)$–$C(sp^3)$-coupled cross-coupled products.[118] Since the oxidation state of nickel is raised here from 0 to II, a catalytic variant of this reaction is hardly realizable. Rovis et al. chose a complementary approach in which the cyclic anhydrides are reacted with diphenylzinc in the presence of stoichiometric amounts Ni^0 complexes (Scheme 57).[119] A mixture of simple

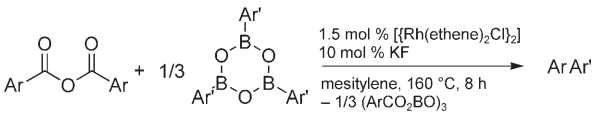


1.0 equiv $[Ni(cod)_2]$ / neocuproine (1:1) 66:33
1.0 equiv $[Ni(cod)_2]$ / neocuproine/ dppb (1.5:1.0:0.5) >95:5 (77% yield)

Scheme 57. Ring opening of cyclic anhydrides with decarbonylation. cod = cyclooctadienyl.

and decarbonylated cross-coupled products is formed, although the authors achieved high selectivity in favor of the decarbonylated product only with the use of stoichiometric amounts of nickel. Whereas succinic anhydride derivatives react comparably smoothly and stereospecifically, interesting ring contraction products are formed with derivatives of glutaric anhydride.

In contrast, our own strategy for the realization of a catalytic decarbonylative cross-coupling is built upon the ketone synthesis in Section 4.2. To achieve a cross-coupling by decarbonylation the reactivity of the metal catalyst must on the one hand be increased with respect to decarbonylation; this was achieved by the use of a Rh catalyst instead of a Pd catalyst at a higher reaction temperature. On the other hand the reactivity of the organometallic components was inhibited in that boroxines were used in place of boronic acids, and a nonpolar solvent was used.[120] In this way a variety of aromatic anhydrides were coupled with different arylboroxines in the presence of a catalyst system of 1.5 mol% $[\{Rh(ethene)_2Cl\}_2]$ and 10 mol% potassium fluoride, with which selectivities of greater than 10:1 in favor of the decarbonylated cross-coupled product were obtained in some cases (Scheme 58).



Ar = *m*-MeC_6H_4; Ar' = Ph (64%), *p*-$CF_3C_6H_4$ (66%), *o*-FC_6H_4 (48%), 2-naphthyl (55%), *m*-$NO_2C_6H_4$ (61%), ...
Ar' = Ph; Ar = Ph (55%), *p*-$MeOC_6H_4$ (35%), 3-thienyl (21%), ...

Scheme 58. Cross-coupling of carboxylic anhydrides and arylboroxines.

6. Summary and Outlook

The versatility of the methods described above foreshadows the high synthetic potential of catalytic transformations based on carboxylic acids. The excellent availability of carboxylic acids from renewable raw material sources, amongst others, is an important argument to intensify research in this area over the next few years.[66] By recombination of elemental steps of the catalytic cycles many further catalytic transformations may yet be conceived, the synthetic potential of which is currently difficult to imagine. Likewise, most of the methods presented here are by no means fully optimized and offer extensive research possibilities for catalyst and process developers.

An important target of future research on the (oxidative) addition reactions of carboxylic acids to multiple bonds is the efficient control of the chemo-, regio-, and stereoselectivity by new catalyst systems. In the reactions proceding via acyl metal complexes, for example, the reduction of carboxylic acids to aldehydes or the cross-coupling of ketones, it is of particular interest to increase further the activity of the catalysts and thus to exploit less activated, more accessible carboxylic acid derivatives, such as phenyl or even alkyl esters, as substrates. This also applies to the methods derived therefrom which take place with the extrusion of carbon monoxide, for example, decarbonylative Heck reactions or elimination reactions. With a new generation of catalysts able to generate acyl species under mild conditions from carboxylate derivatives that are accesible from the parent carboxylic acids (e.g. alkyl esters), numerous possibilities arise for the realization of waste-minimized, sustainable synthetic methods.

In the case of decarboxylative cross-couplings it has been possible over the last two years to confirm their principal suitability for transformations which would formerly have been regarded as hopeless by most chemists. How widely this new concept may now be applied in synthesis is essentially dependent upon the extent to which the activity of the decarboxylation catalysts can be increased. The breadth of applications of the biaryl synthesis is growing continuously, and applications in industry are already being intensively investigated. The ketone synthesis from α-oxocarboxylic acids shows that the potential of this concept already extends beyond the biaryl class of compounds with the current catalysts. The lower the temperatures at which future catalyst generations can decarboxylate carboxylic acid salts to carbon nucleophiles are, the broader the spectrum of reaction steps which can be resultantly combined in situ will be. Examples of this would be further substitution reactions, 1,4-additions to Michael acceptors, 1,2-additions to multiple bonds, and nucleophilic opening of stressed rings. It will be exciting to see how this interesting research area will develop over the next years.

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[121] Note added in proof: A related procedure has very recently been published in which copper is required only in catalytic amounts: J. M. Villalobos, J. Srogl, L. S. Liebeskind, *J. Am. Chem. Soc.* **2007**, *129*, 15734 – 15735.

