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Decarboxylative Coupling Reactions: A Modern Strategy for C–C-Bond Formation‡

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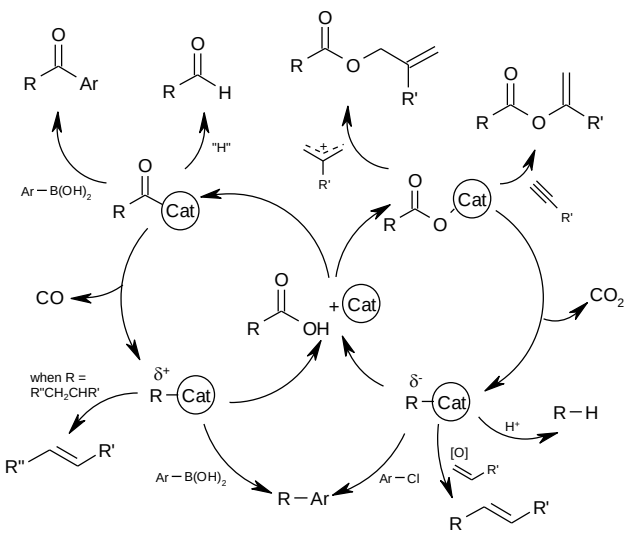
This *critical review* examines transition metal-catalyzed decarboxylative couplings that have emerged within recent years as a powerful strategy to form carbon–carbon or carbon–heteroatom bonds starting from carboxylic acids. In these reactions, C-C bonds to carboxylate groups are cleaved, and in their place, new carbon-carbon bonds are formed. Decarboxylative cross-couplings constitute advantagous alternatives to traditional cross-coupling or addition reactions involving preformed organometallic reagents. Decarboxylative reaction variants are also known for Heck-reactions, direct arylation processes, and carbon-heteroatom bond forming reactions.

1 Introduction

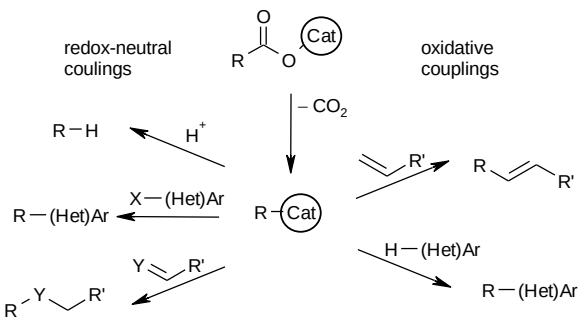
Carboxylate groups have long served as versatile connection points in the construction of carbon frameworks. Carboxylic acids are available at low cost in great structural diversity both from natural and synthetic sources, and are easy to store and handle.[1,2] The last decade, in particular, has seen the development of a wealth of catalytic transformations of carboxylic acids, which give access to various valuable product classes along multifaceted reaction pathways.[3] Scheme 1 illustrates an important reason for this: They can react with metals under formation of either metal carboxylates or acyl metal species, which both can be utilized in catalytic transformations. Moreover, carbon monoxide gas can be released from acyl metal intermediates, and carbon dioxide gas from carboxylate complexes, with different organometallic species being formed in each case. Therefore depending on the catalyst system and the reaction conditions employed, carboxylic acids can serve as synthetic equivalents of acyl, aryl, or alkyl halides, or of organometallic reagents.[4]



Scheme 1. Carboxylic acids as substrates in homogeneous catalysis.

This review focuses on decarboxylative coupling reactions. In this reaction type, organometallic species are formed *via* extrusion of CO_2 from metal carboxylates, and undergo coupling reactions with other organic compounds.

These reactions can roughly be divided into five categories with regard to the position and polarity of the bond formation: 1) redox neutral cross-coupling reactions with aryl, vinyl or allyl electrophiles, 2) Heck-type vinylation reactions, 3) direct arylation processes, 4) conjugate additions and 5) carbon–heteroatom bond forming reactions (Scheme 2).



Scheme 2. Overview on decarboxylative coupling reactions.

The focus of this review is placed on the transition metal-catalyzed decarboxylative cross-coupling reactions that have emerged within the last five years following the discovery of decarboxylative Heck-type reactions and decarboxylative biaryl syntheses. It invites to complement, improve, and use these new methods in organic synthesis. The appropriate discussion of the vast field of enzymatic and radical decarboxylative couplings would have been beyond the scope of a single review article. Decarboxylative allylation reactions have very recently been comprehensively covered by Tunge,[5] and are thus mentioned only briefly herein despite their importance in this context.

2 The decarboxylation step

The decarboxylative carbometalation is the key step in all the decarboxylative coupling reactions. The difficulty connected to this process is that metal salts of simple carboxylates generally require rather forcing conditions to extrude CO_2. Under such conditions, the resulting organometal species are likely to undergo fast protonation by the surrounding medium, giving the corresponding protonated products before a C–C or C–heteroatom bond can be formed.

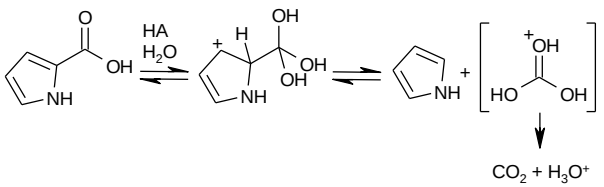
Improving the decarboxylation activity of the catalyst system is often decisive when aiming at lower reaction temperatures, which allow converting a broader scope of carboxylic acids, including sensitive, functionalized derivatives.

The controlled protodecarboxylation of carboxylic acids is a synthetically valuable transformation that allows the removal of carboxylate groups left behind as a result of the chosen synthetic route.[6] Moreover, it is of interest as a test reaction in the development of more effective co-catalysts for decarboxylative coupling reactions.

2.1 Protodecarboxylation

Some highly activated carboxylic acids, for example, *β*-oxoacids, diphenylacetic acids, and polyfluorobenzoic acids, readily decarboxylate even in the absence of metals at moderate temperatures. A range of carboxylic acids, including many heterocyclic, propiolic, and *ortho,ortho*-disubstituted carboxylic acid derivatives decarboxylate using strong Brønsted acids.[7] The mechanism of acid-catalyzed protodecarboxylations was thoroughly investigated by BelBruno *et al.*[8] Ionic liquids have also been found to effectively catalyze the decarboxylation of various *N*-heteroaryl and aryl carboxylic acids with microwave irradiation under aqueous conditions.[9]

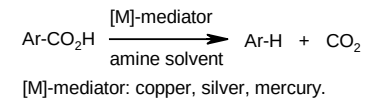
In the studies of protodecarboxylation of heteroaromatic carboxylic acids, Kluger *et al.* found that the release of carbonic acid, formed *via* an associative mechanism, may predominate over the direct release of CO_2 as the driving force for the protodecarboxylation of heterocyclic substrates in acidic solutions (Scheme 3).[10]



Scheme 3. Decarboxylation *via* addition of water to the carboxyl group of pyrrole-2-carboxylic acid.

The downside of these metal-free protodecarboxylations is that they do not proceed *via* organometallic intermediates that could potentially be employed in a coupling step. Moreover, they must always be borne in mind as potential background reactions in metal-catalyzed processes. In fact, the conditions of some protocols reported to be metal-mediated are so similar to those of known acid-catalyzed processes that one might wonder whether the metal is required at all.

In contrast, the extrusion of CO_2 from most other carboxylic acids requires harsh conditions and the addition of a transition-metal mediator, generally a copper or silver salt (Scheme 4). Synthetic applications of milder mercury-mediated processes are limited by the necessity for stoichiometric mercury salts and the intermediacy of toxic organomercury(II) species.[11]

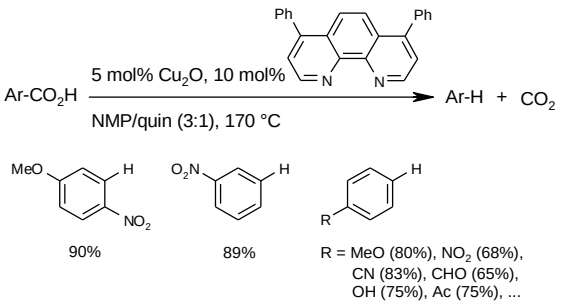


Scheme 4. Metal-mediated decarboxylation of benzoic acids.

Shepard *et al.* made a pioneering contribution to this field when they discovered that halogenated furancarboxylic acids were protodecarboxylated in the presence of copper or copper salts at high temperatures (ca. 250 °C).[12] Nilsson,[13] Sheppard,[14] and Cohen[15] each contributed to optimizing this protocol and extending the scope to activated derivatives, such as benzoic acids with electron-withdrawing *ortho*-substituents, phenyl- or diphenylacetic acids, and 2-thienoic acid. Bipyridine and phenanthroline ligands at the copper center and/or aromatic amine solvents were found to be particularly beneficial. The copper mediator was used mostly in stoichiometric quantities, and only few highly activated derivatives were successfully converted with catalytic amounts.[16]

Based on kinetic investigations, radical trap experiments and stereochemical studies, Cohen *et al.* provided early evidence that the Cu-mediated decarboxylation does not proceed through a radical pathway.[17] The reaction of (*E*)- and (*Z*)-configured vinylic carboxylic acids proceeds predominantly with retention of the configuration.[18] In contrast, for aliphatic carboxylic acids, decarboxylation seems to proceed *via* radical intermediates.[19]

For a long time, copper-mediated protodecarboxylations remained restricted to a narrow range of carboxylic acids. This restriction was overcome with a catalyst system generated *in situ* from copper(I) oxide and 4,7-diphenyl-1,10-phenanthroline in a mixture of *N*-methyl-2-pyrrolidone (NMP) and quinoline (Scheme 5).[20] It allows decarboxylating aromatic carboxylic acids bearing a wide range of functional groups in *ortho*-, *meta*-, or *para*-positions, including oxo, formyl, nitro, cyano, and hydroxy groups. In their associated mechanistic study, Goossen *et al.* show that the addition of TEMPO (10 mol%) as a radical trap has no influence on the yields, confirming that the reaction does not proceed *via* a radical mechanism.



Scheme 5. Copper-catalyzed protodecarboxylation.

With modern microwave technology, which involves using small, contained vessels certified for pressure reactions, protodecarboxylations are particularly easy to carry out.[21] The reaction times are reduced from several hours to a few minutes even when using simple copper/1,10-phenanthroline catalysts. Moreover, the reaction progress can be followed by monitoring

the buildup of carbon dioxide gas on the pressure sensor, and because CO_2 is kept in the vessel, it is no longer able to carry off volatile products.

Patel and Mainolfi *et al.* reported that protodecarboxylations can also been conducted in copper tube flow reactors (CTFR). Many aromatic and heteroaromatic substrates were successfully converted at 250 °C in a CTFR without any added catalysts, ligands, or additives. The reactor itself acts as a source of copper metal.[22]

The mechanism of copper-catalyzed protodecarboxylations of aromatic carboxylic acids was elucidated with DFT calculations. The structure of the calculated transition state for the example of 2-fluorobenzoic acid is shown in Figure 1.[20]

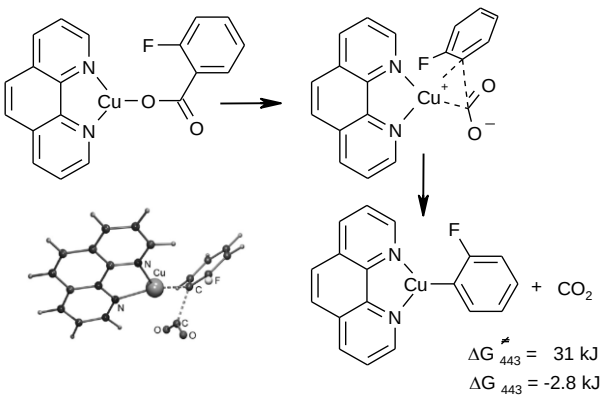
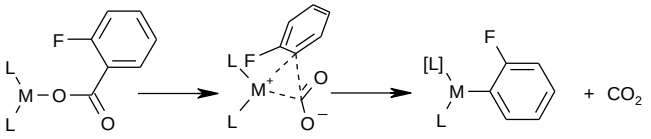


Figure 1. Mechanism of the copper-catalyzed extrusion of CO_2.

The calculations elucidated the beneficial effect of *ortho*-nitro and *ortho*-methoxy groups in the benzoate substrates by showing that the benzoic acid reactivity is dominated by short-range inductive effects transmitted *via* the σ-backbone, whereas long-range mesomeric effects seem to play a subordinate role.

The nitrogen ligand had only a limited influence on the catalyst activity but the central metal proved to have a profound effect on the calculated energies. Thus, the activity of silver and gold catalysts was predicted to be higher than that of copper systems, especially for *ortho*-substituted carboxylic acids. A comparison of the relative energies for the decarboxylation of 2-fluorobenzoic acid with silver and copper catalysts is presented in Table 1.

Table 1. Relative energies for the decarboxylation of 2-fluorobenzoic acid with silver and copper catalysts.[a]

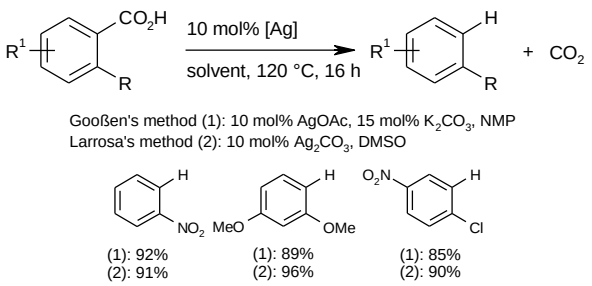


	L	M	ΔE^{R}_{tot}	ΔG^{R}_{393}	$\Delta E^{\neq}_{tot}$	$\Delta G^{\neq}_{393}$	k_{393}
1a → 2a	phen	Cu	13.9	-1.1	32.4	31.3	1.0
1'a → 2'a	phen	Ag	11.0	-3.6	31.4	29.5	9.6
1'b → 2'b	NMP	Ag	13.4	-15.5	29.2	29.2	14.9

[a] *Computational conditions*: Gaussian03;[23] B3LYP[24]/6-311+G(2d,p)[25] //B3LYP/6-31G(d)[26] for H, C, N, O, F; Stuttgart RSC 1997 ECP[27] for Cu, Ag, scaling factor for thermal corrections: f = 0.9804.[28] ΔE^{R}_{tot}, ΔG^{R}_{393}, $\Delta E^{\neq}_{tot}$ and $\Delta G^{\neq}_{393}$ are expressed in kcal·mol^{-1}.

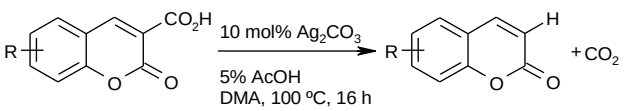
The extrusion of CO_2 from 2-fluorobenzoate at a silver(I)/1,10-phenanthroline catalyst is exergonic both at room temperature (ΔG^{R}_{298} = – 0.5 kcal mol^{-1}) and at 120 °C (ΔG^{R}_{393} = -3.6 kcal mol$^{-)1}$. The activation energies for silver *versus* copper were found to differ by 1.8 kcal mol^{-1} at 120 °C, which would translate to a 10-fold rate acceleration. The lowest activation barrier (29.2 kcal mol^{-1}) was obtained for NMP-ligated silver 2-fluorobenzoate, corresponding to a 15-fold rate acceleration over the copper(I)/1,10-phenanthroline system.

Experimental studies by the same group confirmed that with silver-based catalysts, a new level of activity is reached for certain heterocyclic and *ortho*-substituted benzoic acids.[29] In the presence of catalytic amounts of silver(I) acetate and potassium carbonate, these compounds smoothly decarboxylate already at 80-120 °C – more than 50 °C below those of the best copper catalysts (Scheme 6). Larrosa *et al*. disclosed a closely related Ag(I)-based protodecarboxylation protocol.[30]



Scheme 6. Silver-catalyzed protodecarboxylation.

Jafarpour *et al.* observed that in the presence of catalytic amounts of Ag_2CO_3 and acetic acid, deactivated coumarin-3-carboxylic acids were converted in good to excellent yields and with great preparative ease to the corresponding coumarin derivatives (Scheme 7).[31]

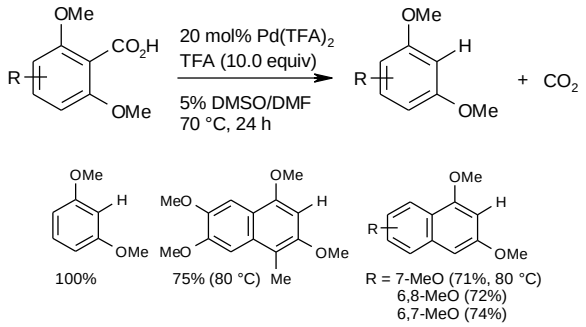


Scheme 7. Silver-catalyzed protodecarboxylation of coumarin 3-carboxylic acid.

In conclusion, silver-based catalyst systems seem to be advantageous for certain substrate classes, including *ortho*-halobenzoic acids, which cannot be converted with copper-based catalysts. The copper systems require higher temperatures, but so far are much more generally applicable.

Under hydrothermal conditions (250 °C/4 MPa), some carboxylic acids protodecarboxylate in the presence of a heterogeneous Pd/C catalyst.[32] This reaction was applied to the preparation of deuterium-labeled compounds.

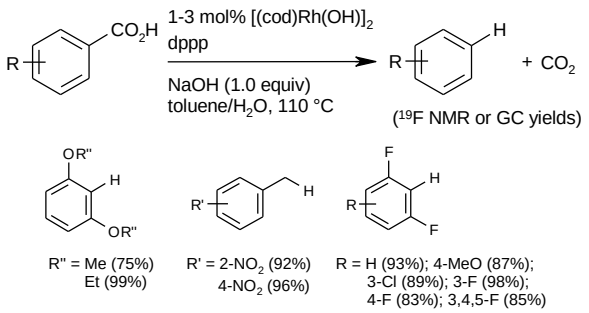
Kozlowski *et al.* showed that homogeneous palladium catalysts operate at much lower temperatures, but their scope is so far restricted to particularly electron-rich bis-*ortho*-substituted aromatic carboxylic acids. These substrates decarboxylate already at 70 °C in the presence of 20 mol% of $Pd(O_2CCF_3)_2$ and excess trifluoroacetic acid (Scheme 8).[33]



Scheme 8. Palladium-catalyzed protodecarboxylation.

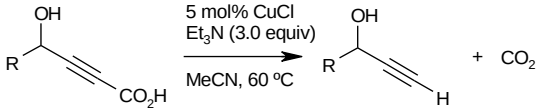
Su, Lin *et al*. modelled the mechanism for the extrusion of CO_2 from several $PdL_2X(\eta^2\text{-}OOCArR)$ complexes of benzoates bearing R-groups in the *ortho*, *meta* or *para* position (L = DMSO; X = $OOCCF_3$; R = H, OMe, NO_2, Me and CN).[34] The results indicate that an *ortho*-substituent on the benzoate is essential, and that electron-donating substituents facilitate the decarboxylation more strongly than electron-withdrawing substituents. The authors conclude that the $^-OOCCF_3$ ligand is not just a spectator ligand but assists the decarboxylation process.

Rhodium-mediated protodecarboxylations also proceed under particularly mild conditions, but are so far restricted to a narrow scope of *ortho*,*ortho*-disubstituted, 2- and 4-nitrophenylacetic and indole-3-carboxylic acids. In the presence of a catalyst system generated from $[(cod)Rh(OH)]_2$ and 1,3-bis(diphenylphosphino)propane (dppp), they smoothly decarboxylate at 90-110 °C in mixtures of aqueous NaOH with THF or toluene (Scheme 9).[35]



Scheme 9. Rhodium-catalyzed protodecarboxylation.

2-Alkynoic acids are another class of carboxylic acids that decarboxylate already at low tempertures. Kolarovič *et al.* reported a copper-catalyzed protocol that allows the decarboxylation of 2-alkynoic acids already at 60 °C, in the presence of a wide range of functional groups (Scheme 10).[36]



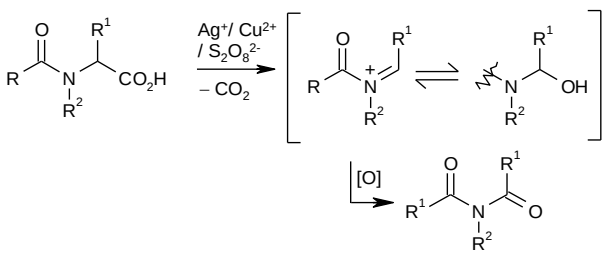
Scheme 10. Copper-catalyzed protodecarboxylation of 2-alkynoic acids.

These compounds also decarboxylate at inductively heated copper wires within flow microreactors.[37]

A recent contibution by Nolan *et al.* demonstrates that the isolated gold(I) complex [Au(IPr)(OH)], leads to the transformation of carboxylic acids to the corresponding decarboxylated gold(I)-aryl complex without the use of silver co-catalyst under mild reaction conditions. It is noteworthy that no protodemetalation is encountered due to the high stability of the gold(I)-aryl species.[38]

Decarboxylations under oxidative conditions

Aliphatic carboxylic acids decarboxylate only *via* radical mechanisms or under oxidative conditions. In the presence of peroxodisulfate, silver salts mediate the oxidative decarboxylation of aliphatic carboxylic acids already at moderate temperatures (60-90 °C).[39] Usually, mixtures of alkenes, alchohols and carbonyl compounds are obtained as products. In contrast, the oxidative decarboxylation of protected amino acids selectively leads to acylimines. Based on stoichiometric protocols employing lead(IV) acetate as oxidant,[40] various catalytic reactions have been developed, e.g. using silver or copper salts in combination with peroxoacids.[41] The reaction proceeds *via in situ* formation of acylimines, which are further oxidized to the imides (Scheme 11).



Reaction conditions: 20 mol% $AgNO_3$, 20 mol% $CuSO_4 \cdot 5H_2O$, $(NH_4)_2S_2O_8$ (3.0 equiv), H_2O, rt

Scheme 11. Oxidative decarboxylation of amino acids.

3 Decarboxylative cross-coupling reactions

If protonolysis of the aryl-metal species generated *via* decarboxylation can be avoided, they can be coupled with various carbon electrophiles, resulting in regioselective carbon-carbon formation. In such decarboxylative cross-coupling reactions, easily available salts of carboxylic acids are used as a replacement of expensive organometallic reagents.

Redox-neutral decarboxylative cross-coupling reactions maintain the advantage of regioselectivity that traditional cross-

couplings have over most C–H activation reactions.

3.1 Synthesis of biaryls

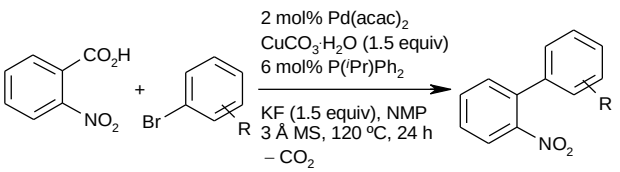
In 1966, Nilsson *et al.*[42] performed a trapping experiment in which they intercepted aryl-copper intermediates generated by thermal decarboxylation of copper benzoates with excess aryl iodide. The detection of unsymmetrical biaryls indicated that there is a thermodynamic basis for such reactions to occur. However, the drastic conditions and intrinsic limitations of copper-catalyzed crossed Ullmann couplings precluded the development of a preparative version of this reaction.

The breakthrough was achieved by combining the decarboxylation catalyst with a two-electron catalyst capable of promoting the cross-coupling of the organocopper species with aryl electrophiles.

3.1.1 Decarboxylative couplings with bimetallic catalysts

3.1.1.1 Cu/Pd-based systems

In the initial protocol of Goossen *et al.*, 2-nitrobenzoic acids and aryl bromides are stirred in NMP for several hours at 120 °C in the presence of stoichiometric amounts of basic copper carbonate and potassium fluoride, an excess of powdered molecular sieves, and 2 mol% of a $Pd(acac)_2/P(^iPr)Ph_2$ catalyst. This way, mixed ArC(O)OCuF salts were generated, which decarboxylate at particularly low temperatures with formation of arylcopper fluoride species. The role of the molecular sieves is to trap the water formed during the *in situ* deprotonation with carbonate bases. This way, the arylcopper species can be coupled with various aryl bromides by the palladium co-catalyst (Scheme 12).[43]

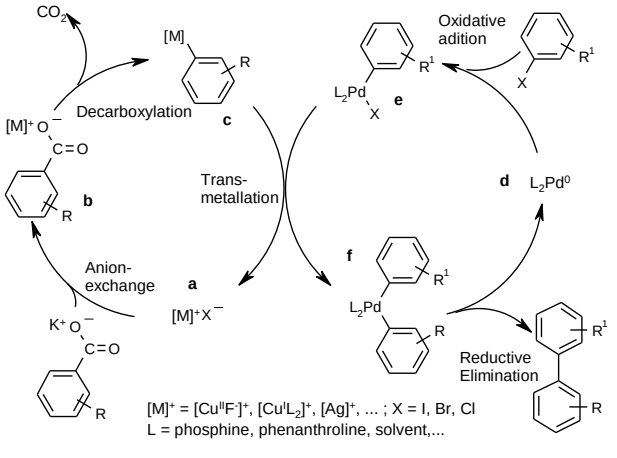


Scheme 12. Biaryl synthesis with stoichiometric amounts of copper.

The proposed reaction mechanism is outlined in Scheme 13. The reaction starts with the extrusion of CO_2 from a metal carboxylate **b**, in this case generated by salt exchange from a potassium carboxylate and a copper salt **a**. The resulting arylcopper species **c** transfers its aryl group to an arylpalladium(II) complex **e** generated by oxidative addition of an aryl halide to a palladium co-catalyst **d**, giving rise to a biarylpalladium species **f**. The catalytic cycle for the palladium is closed by reductive elimination of the biaryl, thus also regenerating the initial palladium(0) species **d**.

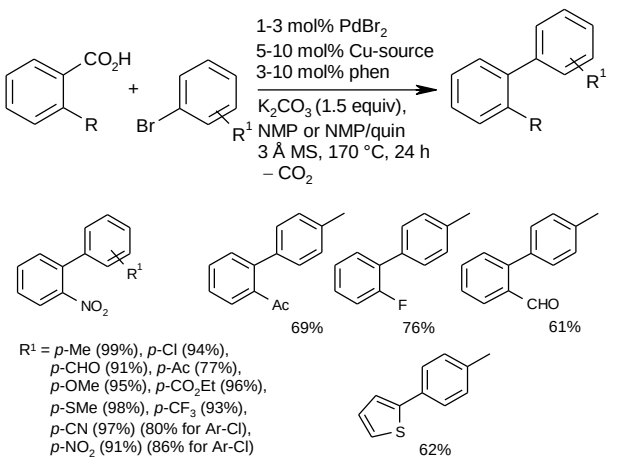
For copper(II) systems, the catalytic cycle for copper could not be closed so that this protocol remained stoichiometric in copper. However, in a second protocol, copper(I)/phenanthroline complexes were used to mediate the decarboxylation, and for these compounds, the carboxylate complexes **f** could be regenerated from the copper bromides **a** released in the cross-coupling step, allowing a process catalytic in both palladium and copper.

As the speed of the rate-determining decarboxylation step strongly depends on the nature of the carboxylic acid, a perfect balance of the rates of decarboxylation and cross-coupling required fine-tuning of the bimetallic catalyst for each substrate combination.



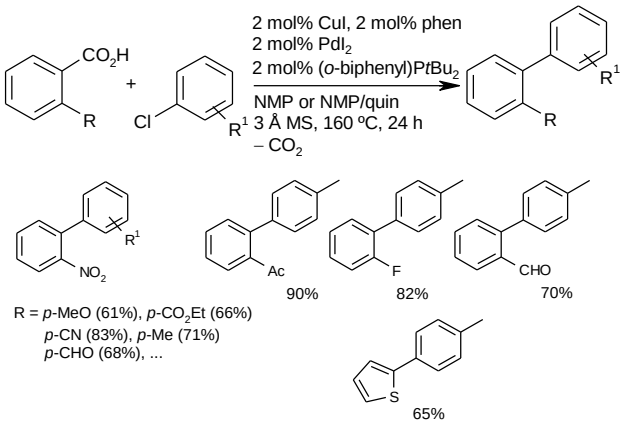
Scheme 13. Decarboxylative biaryl synthesis.

A second-generation catalyst system consisting of 10 mol% of CuBr/phenanthroline and 3 mol% $PdBr_2$ was more broadly applicable to various combinations of carboxylates and aryl halides and led to good yields across a range of substrates (Scheme 14).[44]



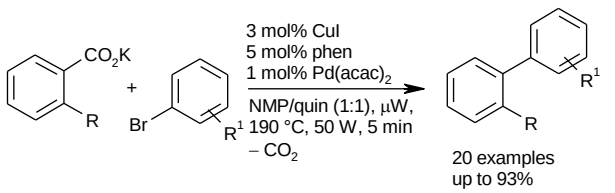
Scheme 14. Biaryl synthesis with catalytic amounts of copper.

The efficiency of the palladium catalysts was improved by the addition of the sterically demanding, electron-rich bis(*t*-butyl)biphenylphosphine, thus allowing the broad use of chloroarenes as the electrophilic coupling partner (Scheme 15).[45]



Scheme 15. Biaryl synthesis using aryl chlorides.

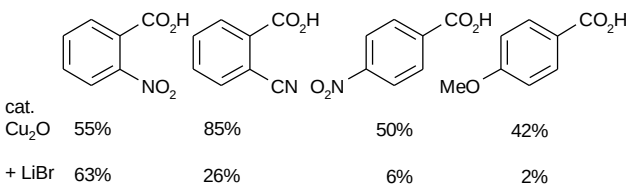
In a simplified reaction protocol particularly suited for applications in parallel synthesis and drug discovery, the decarboxylative cross-coupling of aryl carboxylates with aryl bromides was carried out in sealed vessels in a laboratory microwave (Scheme 16).[46]



Scheme 16. Microwave-assisted protocol for the decarboxylative biaryl synthesis.

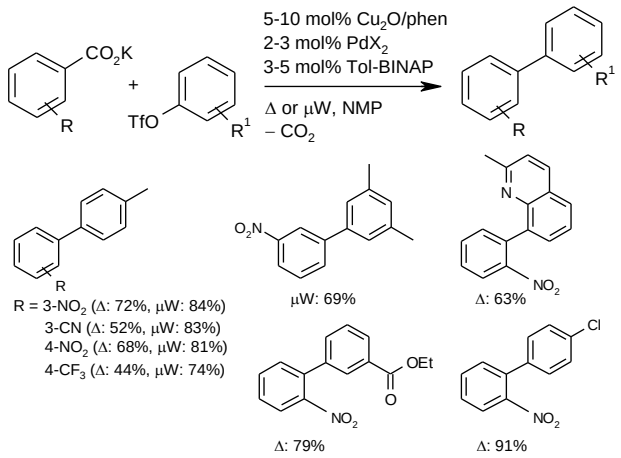
However, at this point, a certain pattern of reactivity became apparent: All protocols were limited to certain *ortho*-substituted or heterocyclic carboxylic acids. This was surprising, as the decarboxylation catalyst developed in this context effectively promoted the protodecarboxylation of an extensive range of benzoic acids regardless of their substitution pattern.[20]

The key to understanding this limitation was provided by the observation that copper-catalyzed protodecarboxylations of non-*ortho*-substituted benzoic acids are stalled when adding halide salts as would form in decarboxylative cross-couplings with aryl halides. The strong affinity of the copper catalyst to the halide ions released in the cross-coupling step makes the salt metathesis (Scheme 13, **a** → **b**) unfavorable for carboxylates without additional copper-coordinating groups in the *ortho*-position (Scheme 17).



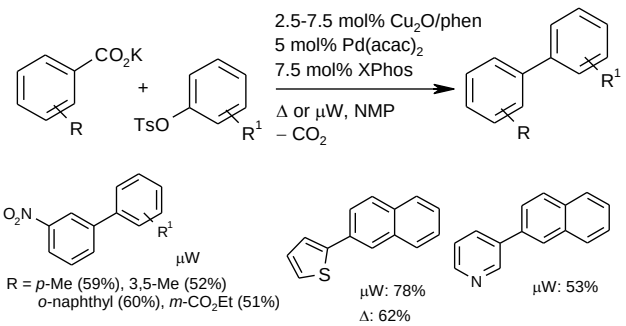
Scheme 17. Effect of halides on protodecarboxylation.

This limitation was overcome by employing aryl sulfonates rather than aryl halides as the coupling partners in combination with a catalyst generated in situ from $Pd(acac)_2$, Tol-BINAP, Cu_2O, and phenanthroline.[47] The weakly coordinating triflate ions released in the cross-coupling step are unable to block the carboxylates out of the coordination sphere of the copper catalyst, thus allowing the cross-coupling of a much broader range of benzoic acids, now also including *meta*- and *para*-substituted derivatives (Scheme 18). The reaction can be performed either using conventional heating (170 °C, several hours) or microwave heating (190 °C, 5-10 min).[48] The microwave protocol is higher-yielding particularly for deactivated carboxylates.



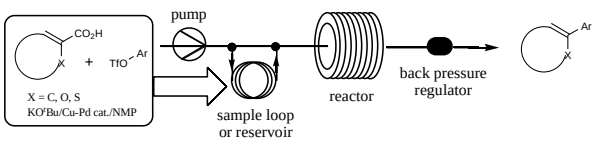
Scheme 18. Decarboxylative coupling of aryl triflates.

Further improvement of the palladium catalysts and the reaction conditions allowed extending the substrate scope of decarboxylative couplings to less expensive aryl tosylates (Scheme 19).[49] Using 5 mol% $Pd(acac)_2$, 7.5 mol% of the sterically crowded monodentate ligand XPhos, and microwave heating (190 °C/150 W/5 min), various biaryls were synthesized in reasonable yields.



Scheme 19. Decarboxylative coupling of aryl tosylates.

Goossen, Underwood *et al.* developed an especially adapted catalyst system and conditions that allow performing decarboxylative cross-coupling reactions in a continuous flow reactor (Scheme 20).[50] This is advantageous for this high-temperature reaction, as in comparison to the batch processes, the reaction time is reduced and the formation of side products is minimized.

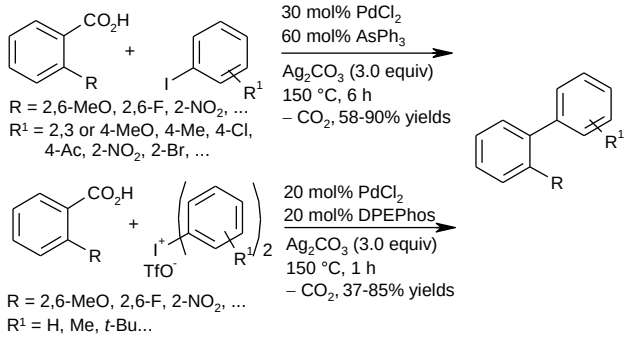


Scheme 20. Decarboxylative biaryl synthesis in a continuous flow reactor.

3.1.1.2 Ag/Pd-based systems

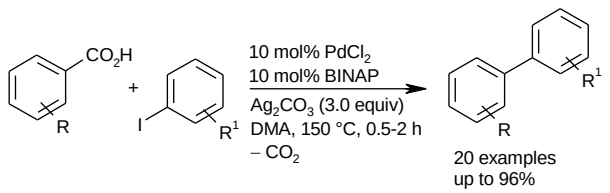
During the development of the initial decarboxylative cross-coupling protocol, which was still stoichiometric in the decarboxylation metal, silver carbonate was also tested in the place of copper(II). In the presence of 2 mol% $Pd(acac)_2$, 6 mol% PPh_3, 1.5 equiv Ag_2CO_3,and 1.5 equiv KF, the biaryl product was obtained in reasonable yields (47% for 4-chloro-2'-nitrobiphenyl, Scheme 21).[43,44]

A higher-yielding silver/palladium-mediated reaction was disclosed by Becht *et al.*, who coupled *ortho*-substituted carboxylic acids with iodoarenes or diaryliodonium salts in the presence of three equivalents of silver carbonate, 30 mol% palladium chloride, and 60 mol% triphenylarsine in DMSO (Scheme 21).[51,52]



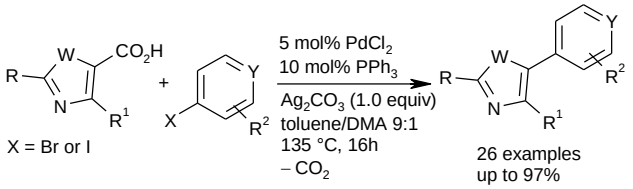
Scheme 21. Biaryl synthesis by Becht et al.

Wu *et al.* reported another protocol for the decarboxylative cross-coupling of arenecarboxylic acids with aryl iodides using a $PdCl_2$/BINAP catalyst and Ag_2CO_3 as the base. Good to excellent yields were achieved for *ortho*-substituted benzoates, and 3,5-dinitrobenzoic acid was coupled with 1-iodo-4-methylbenzene in 40% yield (Scheme 22).[53]



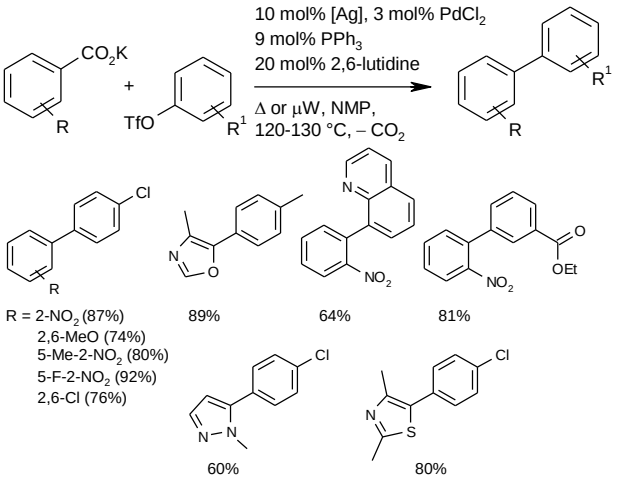
Scheme 22. Biaryl synthesis using a Ag/Pd system.

In 2010, Greaney *et al.* developed an effective protocol for the (het)arylation of thiazoles and oxazoles.[54] The reaction is of particular interest due to the importance of the corresponding products in medicinal and agrochemistry (Scheme 23).[55]



Scheme 23. Decarboxylative (het)arylation of thiazoles and oxazoles.

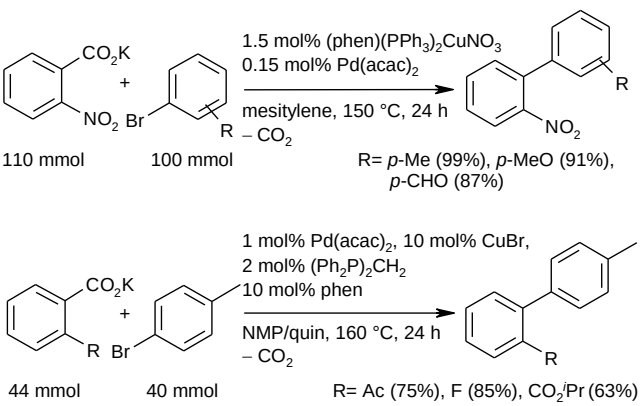
All silver-based decarboxylative cross-couplings are limited by the fact that the stability of silver halides prevents that the silver re-enters the catalytic cycle. Thus, stoichiometric amounts of silver are generally required. On the other hand, when employing arenesulfonates instead of aryl halides, reactions catalytic in silver become possible, as these electrophiles do not release coordinating anions in the cross-coupling step.[56] The Ag/Pd-catalyzed cross-coupling of arenecarboxylates with aryl triflates proceeds already at 120 °C and gives access to various (hetero)biaryls (Scheme 24).



Scheme 24. Decarboxylative biaryl synthesis catalytic in Ag and Pd.

3.1.1.4 Applications in synthesis

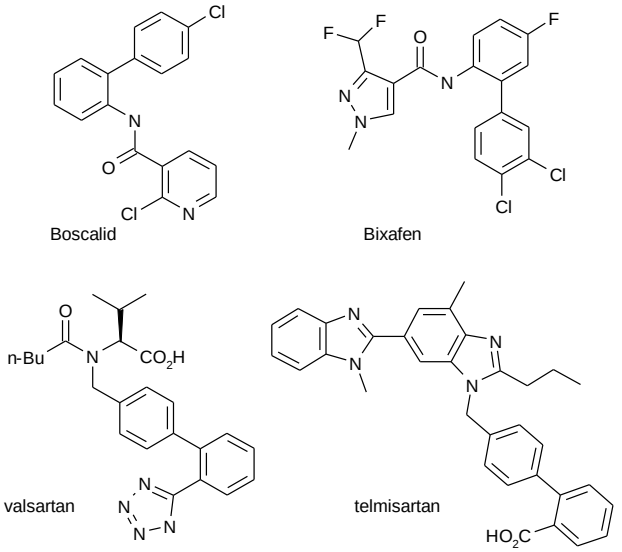
Goossen *et al.* provided two *Organic Syntheses* protocols which were checked by Denmark *et al.* They were specifically designed for preparative-scale applications of decarboxylative cross-couplings, which will help to incorporate such couplings into the toolbox of organic chemists (Scheme 25).[57] The first protocol is suitable for *ortho*-nitro-benzoate derivatives, which decarboxylate particularly fast. The second is applicable to most other *ortho*-substituted or heterocyclic carboxylates.



Scheme 25. Preparative scale of the decarboxylative coupling.

Decarboxylative couplings have successfully been employed in large-scale syntheses of commercially important biaryls, e.g., key intermediates in the syntheses of the agrochemicals Boscalid

and Bixafen.[58] Their principal advantages for industrial application lie in the lower price and the higher stability of benzoic acid salts compared to aryl-metal compounds. They have also been employed in the syntheses of the angiotensin antagonists valsartan[59] and telmisartan.[60]

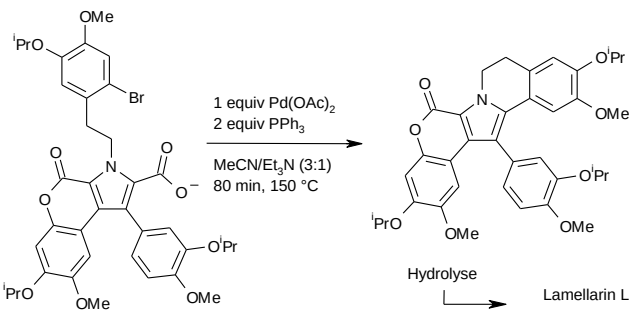


Scheme 26. Biaryl-containing target molecules.

3.1.2 Decarboxylative couplings with monometallic systems

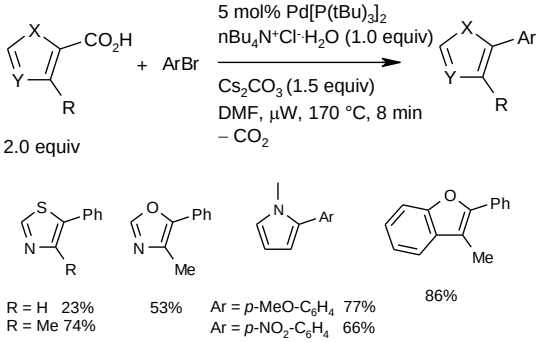
3.1.2.1 Pd-based systems

As discussed in section 2.1, palladium complexes are capable of promoting protodecarboxylations of some particularly activated carboxylates. These substrates also undergo decarboxylative cross-couplings mediated by palladium alone. Thus, Steglich *et al*. reported an intramolecular reaction of this type within a total synthesis (Scheme 27).[61]



Scheme 27. Decarboxylative coupling reported by Steglich *et al.*

Bilodeau and Forgione successfully coupled five-membered heteroarenes bearing carboxylate groups in the 2-position with various aryl halides under extrusion of CO_2 and with formation of the corresponding arylated heteroarenes (Scheme 28).[62]

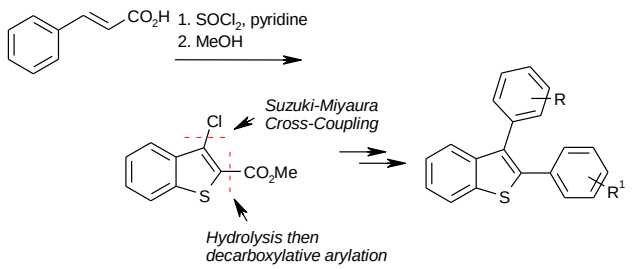


Scheme 28. Pd-catalyzed couplings of five-membered heteroarenes.

Steglich considered this transformation to be a Heck-type reaction, which one could interpret in such a way that the decarboxylation takes place after the carbon-carbon bond forming step. This is supported by the observation that in the examples provided the carboxylate group is located on a carbon atom that would also be the preferred position for a Heck-type carbon-carbon bond formation of such heterocycles. An example is furan-2-carboxylic acid, which is regioselectively monoarylated with decarboxylation in the 2-position. The analogous conversion of furan-3-carboxylic acids was never observed. Forgione *et al*. favor a mechanism, in which the decarboxylation occurs prior to the cross-coupling step.[62b]

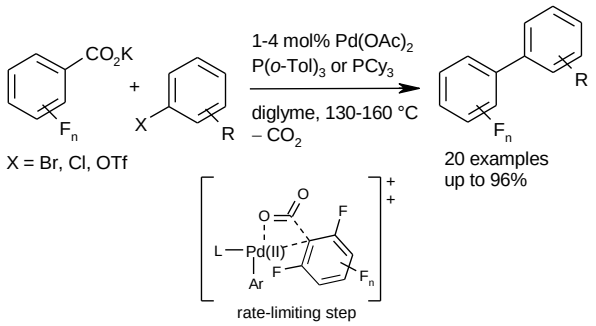
Still, the regiochemistry of the arylation can at least be directed to one of two electronically comparable positions by the carboxylic acid function, and the heterocyclic product are of considerable interest for natural product synthesis and drug discovery.

Miura *et al.* approached the synthesis of 2,3-diarylbenzo[*β*]thiophenes with a nickel-catalyzed Suzuki–Miyaura cross-coupling/palladium-catalyzed decarboxylative arylation sequence of 3-chloro-2-methoxycarbonylbenzo[β]thiophenes, which are readily accessible from the corresponding cinnamic acids (Scheme 29).[63]



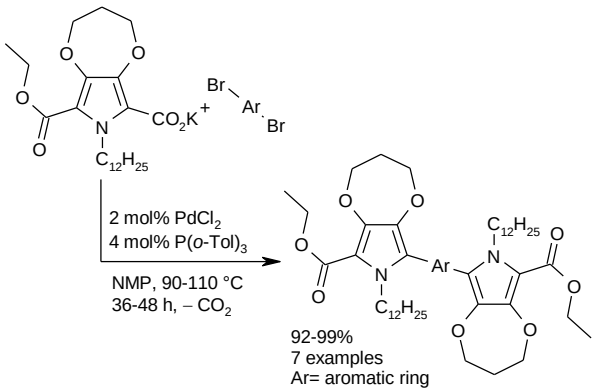
Scheme 29. Decarboxylative synthesis of 2,3-diarylbenzo[*β*]thiophenes.

Liu *et al.* recently reported that a few benzoates with rather special substitution patterns, e.g., polyfluorobenzoates, can undergo decarboxylative cross-coupling with aryl halides and triflates using a monometallic palladium (Scheme 30).[64] With DFT calculations, the authors show that the palladium-catalyzed decarboxylation is the rate-limiting step.



Scheme 30. Palladium-catalyzed decarboxylative biaryl synthesis.

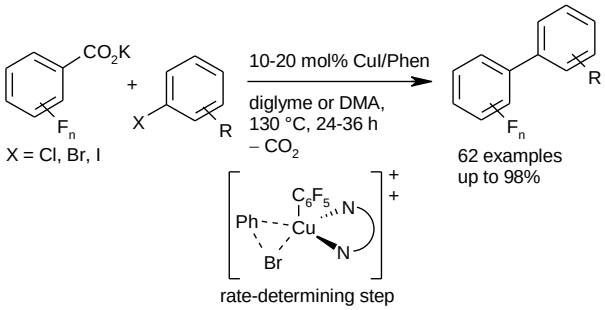
Several conjugated oligomers have also been synthesized by Pd-catalyzed decarboxylative coupling of 3,4-dioxypyrrole with aryl bromides (Scheme 31).[65]



Scheme 31. 3,4-Propylenedioxypyrrole-based conjugated oligomers.

3.1.2.2 Cu-based systems

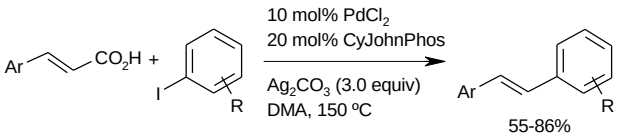
Liu *et al.* showed that monometallic copper can also catalyze the decarboxylative cross-coupling of potassium polyfluorobenzoates with aryl bromides and iodides (Scheme 32).[66] Based on DFT calculations, they proposed a reaction pathway in which the initially formed copper(I) carboxylates extrude CO_2 with formation of polyfluorophenylcopper(I) species, which then react with aryl halides in an oxidative addition/reductive elimination sequence yielding the unsymmetrical biaryls. In contrast to palladium-catalyzed decarboxylative couplings, the oxidative addition step seems to be rate-limiting in copper-catalyzed processes. This conclusion is in agreement with earlier work by Sheppard *et al.*[67]



Scheme 32. Copper-catalyzed decarboxylative biaryl synthesis.

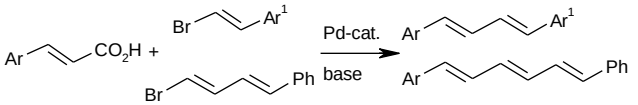
3.1.1.3 Decarboxylative cross-coupling of cinnamic acids

Decarboxylative cross-couplings of vinylic carboxylates are of interest mainly if the carboxylate group is able to direct the arylation into a position opposite to that usually obtained by Heck reactions. Unfortunately, this has not yet been achieved. Otherwise, the products are accessible more easily by Heck-type reactions, and it is hard to exclude that the product formation acutally proceeds *via* protodecarboxylation followed by a starndard Heck reaction. Cinnamic acid was included as an example in one of the initial publications on decarboxylative cross-couplings.[44] Wu *et al.* recently disclosed a protocol specifically adapted to the substrate class of cinnamic acid derivatives that is catalytic in palladium and stoichiometric in silver and gives good yields for a broad range of cinnamic acids and aryl iodides (Scheme 33).[68]



Scheme 33. Decarboxylative cross-coupling of cinnamic acids with aryl iodides.

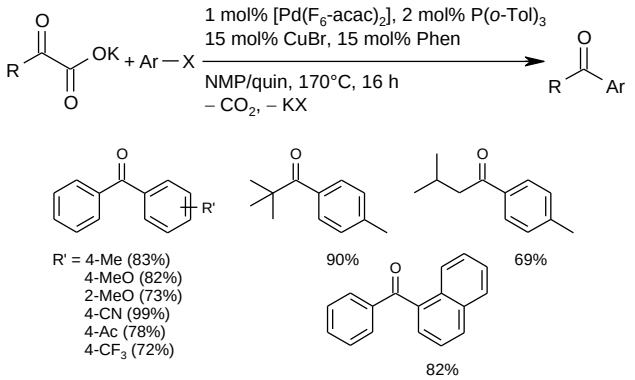
Miura *et al.* developed a decarboxylative coupling of cinnamic acids with β-bromostyrenes with formation of 1,4-diaryl-1,3-butadiene derivatives (Scheme 34).[69] The coupling, which is mediated by a monometallic palladium catalyst, is also applicable to the synthesis of 1,6-diaryl-1,3,5-hexatriene.



Scheme 34. Decarboxylative cross-coupling of cinnamic acids with β-bromostyrenes.

3.2 Synthesis of ketones and azomethines

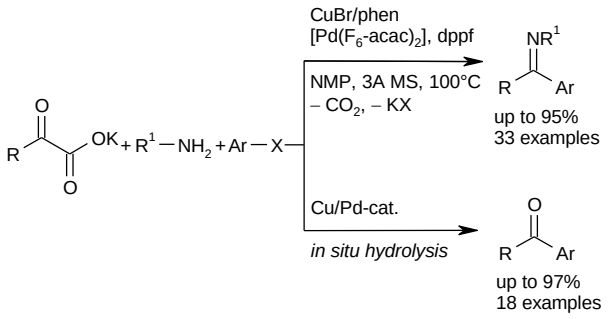
Cu/Pd-catalyzed decarboxylative couplings have successfully been adapted to the reaction of α-oxocarboxylic acids with aryl halides or pseudohalides to give aryl ketones (Scheme 35).[70] This transformation is particularly interesting because it involves the generation and coupling of unprotected acyl anion equivalents with carbon electrophiles. This allows a polarity reversal of the bond formation of traditional ketone synthesis in which carbon nucleophiles are coupled with acyl cations.



Scheme 35. Synthesis of aryl ketones (X = halide, sulfonate).

In the presence of primary amines, α-oxocarboxylic acids react

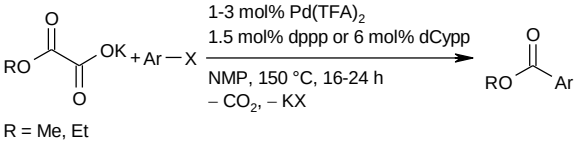
with aryl halides or pseudohalides to the corresponding azomethines (Scheme 36).[71] The presumed intermediate formation of α-iminocarboxylates dramatically lowers the decarboxylation temperature to only 100 °C.



Scheme 36. Decarboxylative azomethine synthesis.

3.3 Synthesis of arenecarboxylate esters

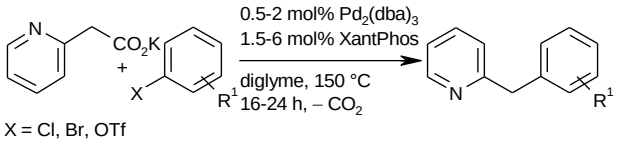
Oxalic acid monoesters are another class of carboxylates that can be decarboxylatively cross-coupled with monometallic palladium catalysts (Scheme 37).[72] This reaction is another example of a cross-coupling of an acyl anion generated *via* the extrusion of CO_2. It allows the conversion of various aryl halides into the corresponding arenecarboxylate esters at 150 °C without the necessity of employing toxic carbon monoxide. As the catalyst, 1-3 mol% $Pd(TFA)_2$ in combination with the bulky chelating ligands 1,3-bis(diphenylphosphino)propane (dppp) or bis(dicyclohexylphosphino)propane (dCypp) were employed.



Scheme 37. Decarboxylative ester synthesis.

3.4 Synthesis of azaarenes

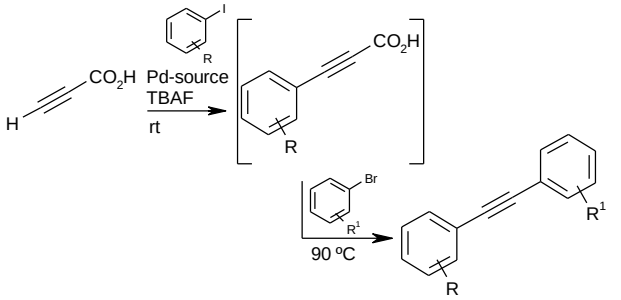
The Pd-catalyzed decarboxylative cross-coupling of 2-(2-azaaryl)acetates with aryl halides and triflates by Liu *et al.* is potentially valuable for the synthesis of functionalized azaarenes (Scheme 38).[73] DFT calculations indicate that the nitrogen atom at the 2-position of the heteroarenes coordinates to Pd(II) in the transition state of the decarboxylation step.



Scheme 38. Synthesis of azaarenes.

3.5 Decarboxylative cross-coupling of alkynyl carboxylic acids

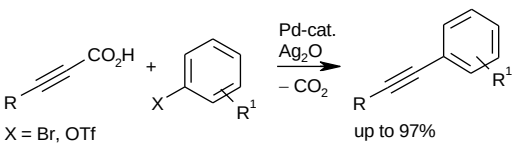
Propiolic acids were converted in one-pot into diarylalkynes by Lee *et al.* In the first step which proceeds at room temperature, the terminal carbon undergoes Sonogashira coupling with aryl halides, and at 90 °C, decarboxylative coupling with another aryl halide occurs at the other sp-carbon (Scheme 39).[74]



Scheme 39. Decarboxylative cross-coupling of alkynyl carboxylic acids.

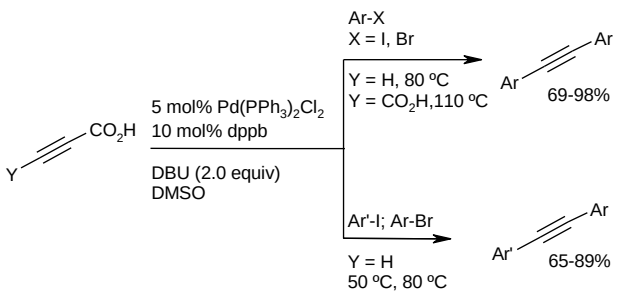
The same authors also reported the decarboxylative coupling reaction of 2-octynoic and phenylpropiolic acids with aryl halides.[75] in the presence of excess tetrabutylammonium fluoride (TBAF) (2–6 equiv.) as the base and a Pd-P(*t*Bu)$_3$ catalyst .

Lee *et al.* disclosed a Pd-catalyzed decarboxylative Sonogashira reaction that takes place under milder conditions and has a higher functional group tolerance but calls for silver oxide in stoichiometric amounts (Scheme 40).[76]



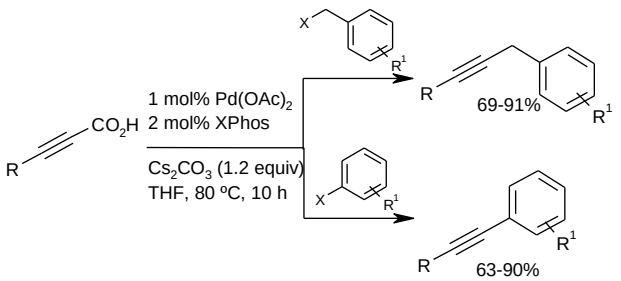
Scheme 40. Pd-catalyzed decarboxylative Sonogashira protocol.

Song, Lee *et al.* showed that propiolic acids can also be coupled with aryl halides in the presence of an inexpensive amine base and a robust ligand system (Scheme 41).[77] Various unsymmetrical diarylalkynes were synthesized in good yields.



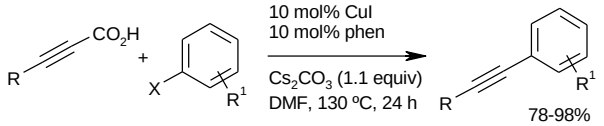
Scheme 41. Optimized decarboxylative Sonogashira protocol.

The decarboxylative coupling of alkynyl carboxylic acids has also been achieved with benzyl halides, cinnamyl halides and aryl chlorides as electrophilic coupling partners (Scheme 42).[78]



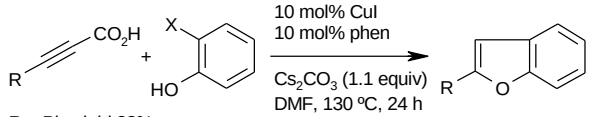
Scheme 42. Decarboxylative coupling of alkynyl carboxylic acids.

Xue *et al.* reported the *via*bility of a copper-catalyzed decarboxylative coupling of alkynyl carboxylic acids with aryl halides under relatively mild reaction conditions (Scheme 43).[79] Based on computational investigations, they propose that in the initiating step of the catalytic cycle, the copper(I) precursor is oxidized to a copper(III) complex, which subsequently reacts with alkynyl carboxylic acid to produce the coupling product through decarboxylation and reductive elimination.



Scheme 43. Cu-catalyzed decarboxylative coupling of alkynyl carboxylic acids.

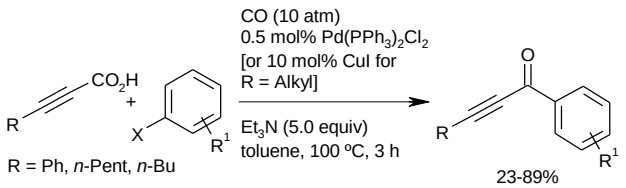
A one-pot domino reaction including a decarboxylative cross-coupling of 2-iodophenol with alkynyl carboxylic acids provides a convenient entry to substituted benzofurans (Scheme 44).



Scheme 44. Decarboxylative furane synthesis.

Park et al. reported that symmetrical diaryl alkynes can be synthesized *via* the decarboxylative coupling of aryl bromides with propiolates in water, in the presence of water soluble palladium catalysts and a phase-transfer reagent $Me(CH_2)_{17}NMe_3Cl$.[80]

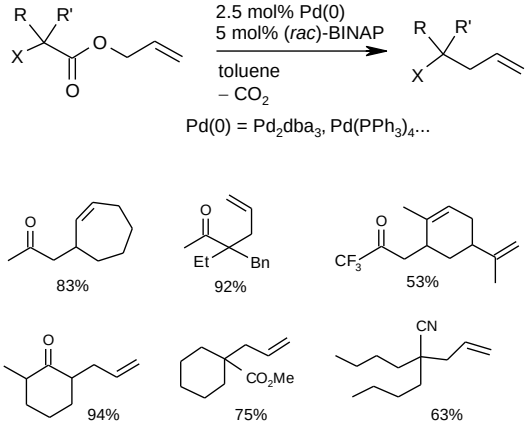
The same authors reported that if the decarboxylative coupling of alkynyl carboxylic acids with aryl iodides is performed under an atmosphere of carbon monoxide (10 atm), carbonylated products were obtained exclusively (Scheme 45).[81] In the case of alkyl-substituted alkynyl carboxylic acids, CuI was required as a cocatalyst, while phenylpropiolic acid gave good yields using a monometallic palladium catalyst.



Scheme 45. Decarboxylative coupling under CO atmosphere.

3.6 Decarboxylative allylation

At temperatures above 170 ºC and in the presence of a base, β-ketocarboxylic acid allyl esters decarboxylate with formation of γ,δ-unsaturated alkyl ketones. This reaction consisting of the thermal rearrangement of the β-keto allyl ester, followed by decarboxylation and an anion-assisted Claisen rearrangement became known as the Carroll rearrangement.[82] In 1980, Saegusa[83] and Tsuji *et al.*[84] reported that palladium catalysts promote this decarboxylative process at much lower temperatures and under neutral conditions. Over the last decade, decarboxylative allylation reactions have become a powerful synthetic methodology which has found broad application in organic syntheisis.[85]



Scheme 46. Decarboxylative allylation reaction.

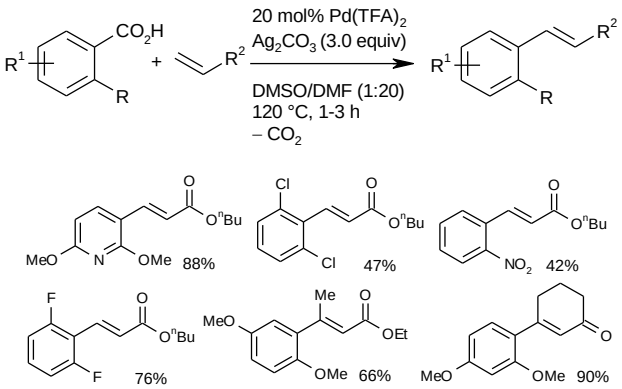
It would have been impossible to apropriately address this rapidly growing field within this article. Fortunately, a review article specifically on this topic has recently been published.[5]

4 Oxidative decarboxylative couplings

In all above reactions, the carboxylic acids serve as sources of carbon nucleophiles which are further functionalized *via* a metal-catalyzed coupling with a carbon electrophile. The addition of stoichiometric amounts of an oxidant also permits the combination of the decarboxylation step with a metal-catalyzed coupling involving a nucleophilic coupling partner. Examples of such *oxidative* transformations are decarboxylative Heck reactions or direct arylation processes.

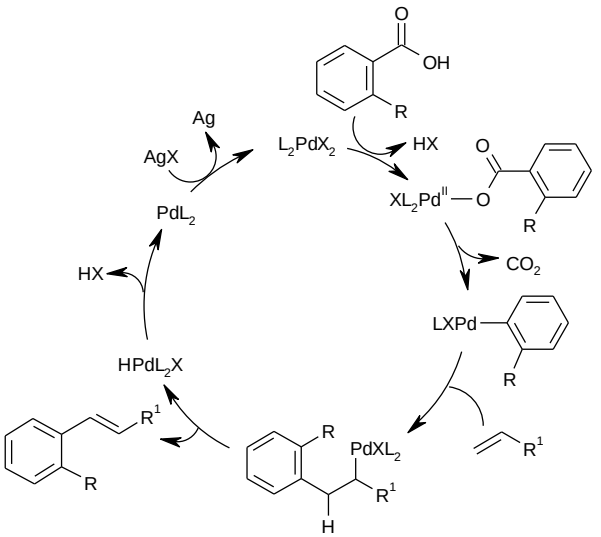
4.1. Decarboxylative Heck reaction

In 2002, Myers *et al.* introduced a novel palladium-catalyzed decarboxylative coupling of arene carboxylic acids with olefinic substrates with formation of vinylarenes (Scheme 47).[86] The methodology is applicable to heteroaromatic-2-carboxylic acids or aromatic carboxylic acids bearing a substituent in the *ortho* position. The scope with regard to the olefinic substrate includes styrene, acrylates, (*E*)-ethyl crotonate and cyclohexenone. It is worth mentioning that *ortho*-vinylation is observed as a side reaction when non-*ortho*-substituted benzoic acids are employed.



Scheme 47. Decarboxylative Heck reaction using a silver salt as oxidant.

Based on NMR studies and X-ray crystallographic analysis,[87] the authors proposed a catalytic cycle outlined in Scheme 48. It starts with the formation of an aryl palladium(II) intermediate *via* extrusion of CO_2 from a palladium(II) carboxylate species. In the traditional Heck-reaction, an analogous intermediate is formed *via* the oxidative addition of palladium(0) to an aryl halide. Subsequent elementary steps – insertion of the alkene, internal rotation, and β-hydride elimination – are common to both processes. However, in the decarboxylative Heck reaction, an additional oxidation step is required to reoxidize the Pd(0) back into Pd(II), and close the catalytic cycle. In the initial protocol, this reoxidation was effected by silver carbonate added in excess.

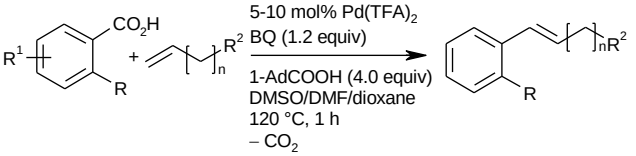


Scheme 48. Decarboxylative Heck-reaction.

The decarboxylation is believed to be initiated by the intramolecular shift of thes electron-deficient palladium(II) center to the *ipso*-carbon of the arene ring. The extrusion of CO_2 leading to the arylpalladium(II) intermediate seems to be the most favorable in the case of electron-rich substrates.

These observations were supported by DFT calculations.[34, 88] They predict that $Pd(TFA)_2$ is a particularly active catalyst, and that the exchange of Cl or Br by a carboxylate is thermodynamically favorable for $PdCl_2$ and $PdBr_2$. Moreover, DMSO is a good ligand that facilitates both the carboxyl exchange and the decarboxylation steps. Phosphines and *N*-heterocarbenes were found to retard the decarboxylation, whereas pyridine ligands hamper the carboxyl exchange.

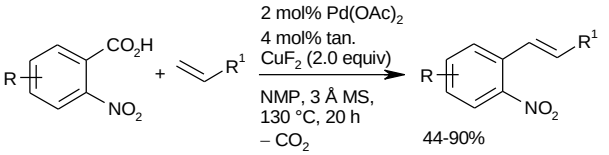
Su *et al.* recently reported a silver-free catalyst system for decarboxylative Heck reactions. They used *para*-benzoquinone as the oxidant in the presence of a catalyst system consisting of 5-10 mol% $Pd(TFA)_2$ and 1-adamantanecarboxylic acid as additive (Scheme 50).[89] The protocol is applicable even to unactivated alkenes, but seems to be strictly limited to the activated benzoates that can be protodecarboxylated with palladium alone. This might be seen as evidence that the excess silver salt used in the protocol by Myers *et al.* also helps in the decarboxylation of less reactive substrates.



n = 1, R^1 = CO_2Et, regioselectivity = 13:1-63:1, *E:Z* > 16:1
n = 0, R^1 = Ph or $CO_2{}^i$Bu, 48-99% yield
n = 0, R^1 = OAc, regioselectivity = 8:1-29:1

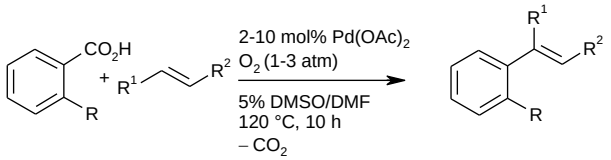
Scheme 49. Decarboxylative coupling using *para*-benzoquinone as oxidant.

Goossen *et al.* developed a Cu/Pd catalyst for decarboxylative Heck reactions. The catalyst system consists of $Pd(OAc)_2$ (2 mol%), CuF_2 (2 equiv), and benzoquinone (0.5 equiv) and allows the coupling of 2-nitrobenzoates with various olefins (Scheme 50).[90]



Scheme 50. Decarboxylative Heck coupling of *ortho*-nitro substituted benzoates.

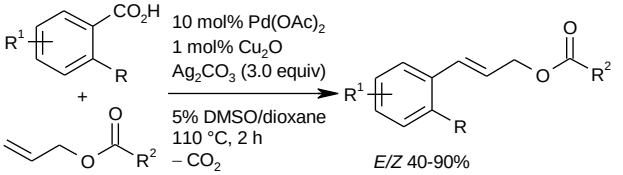
Su *et al.* found that Pd catalysts mediate decarboxylative Heck couplings of both electron-rich and electron-deficient aromatic carboxylic acids without the need for any Ag or Cu salt when dioxygen is used as the oxidant (Scheme 51).[91] A catalyst system based on $Pd(OAc)_2$ efficiently works for electron-rich aromatic carboxylic acids, while a $Pd(OAc)_2$/SIPr system (SIPr: 1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene) is optimal for electron-deficient aromatic carboxylic acids.



R = electron-donating group; no ligand is required
R = electron-withdrawing group; SIPr

Scheme 51. Decarboxylative Heck coupling of electron-rich and electron-poor carboxylic acids.

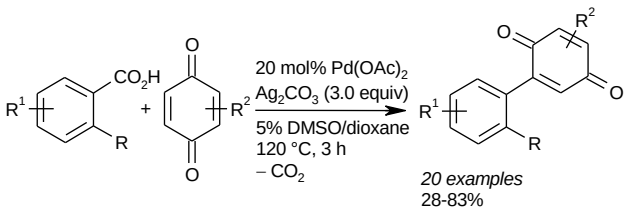
The substrate scope of this methodology with respect to the olefins have been expanded beyond simple olefins. In this context, it has been reported that the palladium-catalyzed decarboxylative Heck coupling of aromatic carboxylic acids with allylic esters alows the efficient synthesis of aryl-substituted allylic esters (Scheme 52).[92]



Scheme 52. Synthesis of aryl-substituted allylic esters.

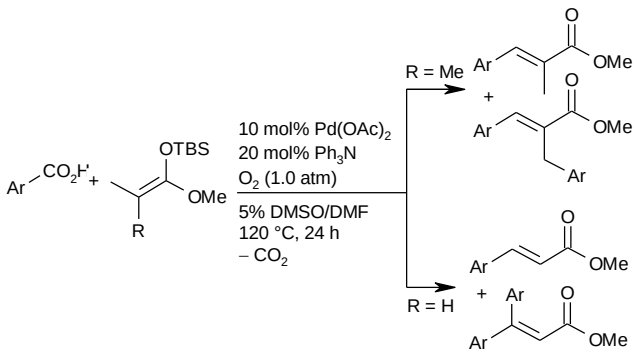
Liu *et al.* have also used a palladium(II)-catalyzed decarboxylative cross-coupling to prepare aryl-substituted 1,4-benzoquinone derivatives from electron-rich arene carboxylates

and 1,4-benzoquinones (Scheme 53).[93]



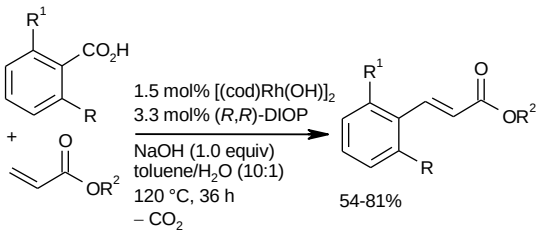
Scheme 53. Decarboxylative coupling with 1,4-benzoquinone derivatives.

Su *et al.* reported a Pd-catalyzed aerobic oxidative coupling of various benzoic acids with silyl enol esters (Scheme 54).[94] Mechanistic studies reveal that this coupling involves the *in situ* generation of an olefin from aerobic oxidation of the silyl enolate, followed by a decarboxylative Heck coupling.



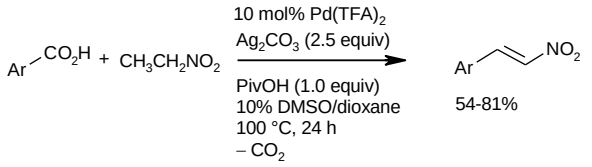
Scheme 54. Pd-catalyzed aerobic oxidative coupling of carboxylic acids with silyl enol esters.

Zhao *et al* found that Rh(I) catalysts effectively mediate the decarboxylative Heck reaction of *ortho*-fluorinated benzoic acids.[95]



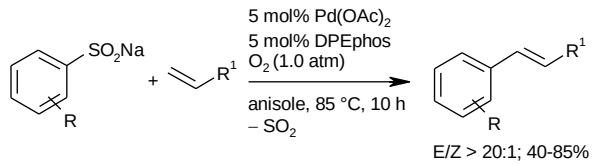
Scheme 55. Rh(I)-catalyzed decarboxylative Heck-reaction.

Su *et al.* disclosed a coupling reaction of an aromatic carboxylic acid with nitroethane with stereoselective formation of (*E*)-*β*–nitrostyrenes. It is believed to proceed *via* the *in situ* generation of nitroethylene followed by a decarboxylative Heck coupling (Scheme 56).[96] Stoichiometric amounts of $Pd(TFA)_2$ mediate the reaction of electron-rich benzoic acids with nitroethane in the absence of Ag_2CO_3. However, Ag_2CO_3 alone did not mediate the decarboxylation of electron-rich benzoic acids. This indicates that the decarboxylation of the electron-rich benzoic acids resulted from the contribution of $Pd(TFA)_2$ rather than Ag_2CO_3.



Scheme 56. Decarboxylative synthesis of (*E*)-*β*–nitrostyrenes.

The concept of decarboxylative couplings has meanwhile been translated also to other substrate types. Examples are the Pd-catalyzed oxidative Heck reaction of arylphoshonic acids by Oshima *et al.*,[97] and the desulfitative Heck coupling of aromatic sulfinic acids by Deng *et al.* (Scheme 57).[98] They use dioxygen as the oxidant and $PdCl_2$/DPEphos as the catalyst. Remarkably, the extrusion of SO_2 occurred already at 85 °C.



Scheme 57. Pd-catalyzed desulfitative Heck coupling.

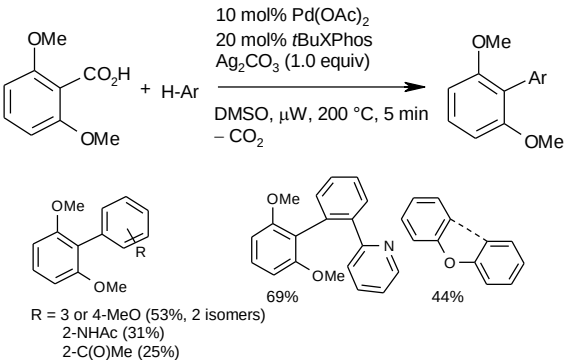
4.2 Decarboxylative coupling with C–H activation.

The generation of organometallic species generated *via* a decarboxylative metalation step has been combined also with palladium-catalyzed oxidative arylation processes. This reaction mode merges modern C–H functionalization processes with state-of-the-art decarboxylation protocols, opening up attractive new strategies for C–C bond formation without the need of using organohalides or sensitive organometallic reagents.

As in most other C–H functionalizations, the control of the regiochemistry is one of the major challenges to be mastered. Solely on the side of the carboxylate substrate the position of the C–C bond formation is predefined., while the C–H activation is not always regioselective.

4.2.1 Direct arylation.

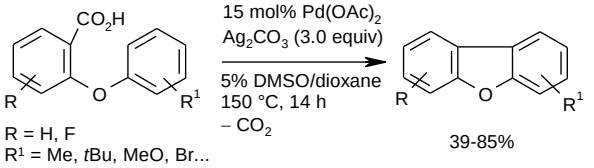
In a pioneering contribution, Crabtree *et al.* coupled electron-rich aromatic carboxylates with arenes in the presence of 10 mol% $Pd(OAc)_2$, 20 mol% *t*BuXPhos and excess silver carbonate in moderate to good yields (Scheme 58).[99] The validity of this concept was confirmed for both intramolecular and intermolecular applications.



Scheme 58. Decarboxylative coupling under C–H activation.

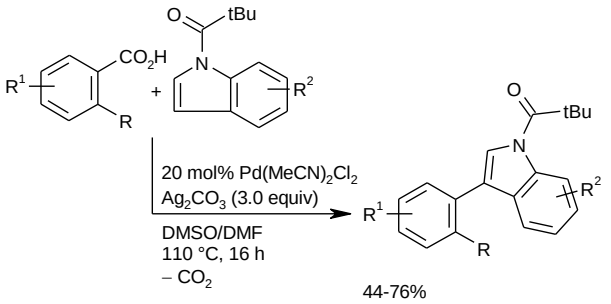
Glorius *et al.* utilized this strategy for the synthesis of various

dibenzofurans *via* an intramolecular arylation of 2-phenoxybenzoic acid derivatives (Scheme 59).[100]



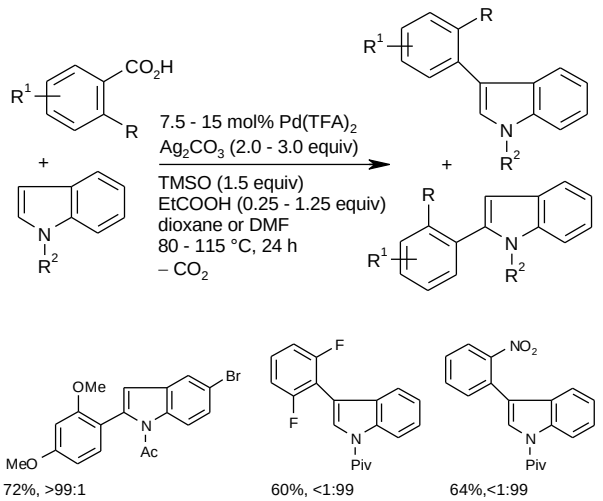
Scheme 59. Intramolecular decarboxylative coupling under C–H activation.

Larrosa *et al.* employed similar reactions for the arylation of indoles in the 3-position with electron-deficient benzoic acids (Scheme 60).[101]



Scheme 60. Direct C-3 arylation of indoles.

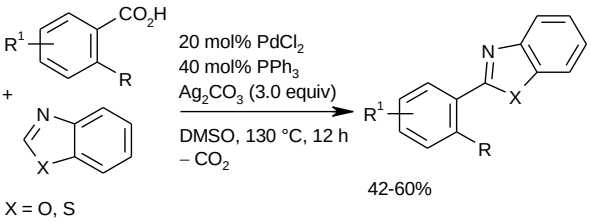
Su *et al.*[102] disclosed an effective catalyst system that promotes the coupling of a wider range of electron-rich and -deficient *ortho*-substituted benzoic acids with various indoles. Interestingly the indoles are arylated in the 3-position with electron-deficient benzoic acids, whereas 2-arylindoles are formed in decarboxylative arylations with electron-rich benzoic acids (Scheme 61).



Scheme 61. Selective C-3 and C-2 arylation of indoles.

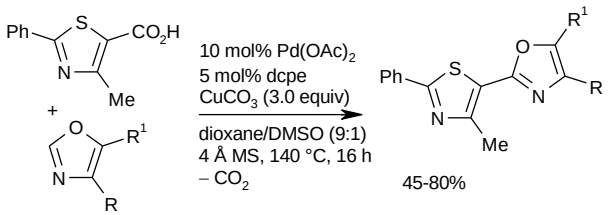
Preliminary mechanistic studies suggest that the switching of the regioselectivity might be the result of two competing catalytic pathways. In the absence of $Pd(TFA)_2$, Ag_2CO_3 does not decarboxylate the electron-rich 2,4-dimethoxybenzoic acid in dioxane, suggesting that in the indole arylation involving electron-rich benzoic acids, Ag_2CO_3 is not responsible for the decarboxylation. In the case of electron-deficient benzoic acids, however, the decarboxylation might be mediated by Ag_2CO_3 rather than $Pd(TFA)_2$.

Tan *et al.* reported that in the presence of a Pd catalyst and excess Ag_2CO_3 substituted benzoic acids arylate thiazoles, benzoxazole and polyfluorobenzenes in the 2-position (Scheme 62).[103]



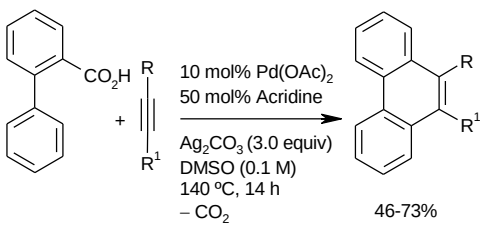
Scheme 62. Direct arylation of heteroaromatics.

Greaney *et al.* disclosed a related intermolecular decarboxylative C–H cross-coupling between oxazoles and thiazoles (Scheme 63).[104]



Scheme 63. Pd-catalyzed direct arylation of oxazoles and thiazoles.

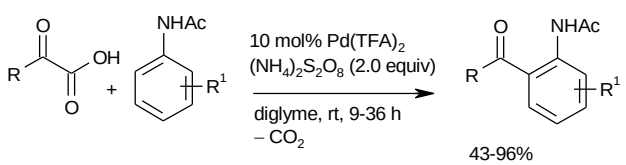
A palladium-catalyzed intermolecular formal [4+2] annulation of 2-phenylbenzoic acids with alkynes affording phenanthrenes (Scheme 64) was reported by Glorius *et al.*[105] This method might find application in the synthesis of polycyclic aromatic hydrocarbons (PAHs) for material science.[106]



Scheme 64. Combined C–H activation, insertion and decarboxylation.

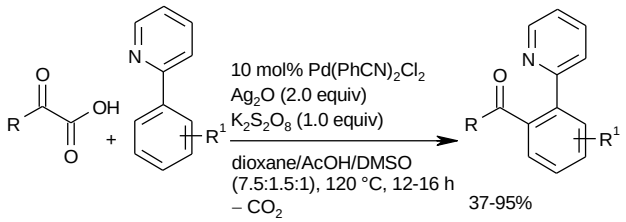
4.2.2 Oxidative acylation

Besides aromatic carboxylic acids, α-oxocarboxylic acids, can be used as substrates in decarboxylative reactions with C-H activation. Ge *et al.* thus reported an interesting Pd-catalyzed decarboxylative *ortho*-acylation of acetanilides with α-oxocarboxylic acids (Scheme 65).[107] Remarkably, the reaction takes place already at room temperature. It provides an efficient entry to *ortho*-acyl acetanilides.



Scheme 65. Pd-catalyzed decarboxylative *ortho*-acylation.

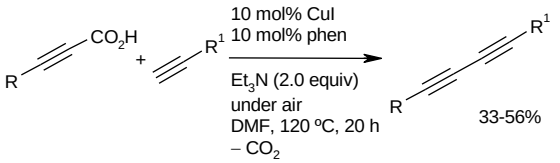
This reaction concept was extended to the acylation of arenes with other directing groups, namely 2-phenylpyridines (Scheme 66).[108]



Scheme 66. Decarboxylative acylation of 2-phenylpyridines.

4.2.3 Oxidative coupling of terminal alkynes with propiolic acids

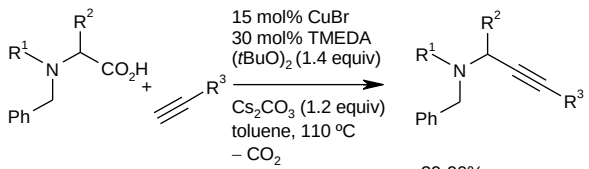
Not only arenes and heteroarenes but also alkynes have successfully been used as substrates in decarboxylative couplings with C-H functionalization. Thus, the copper-catalyzed decarboxylative cross-coupling reaction of propiolic acids with terminal alkynes gives rise to unsymmetric 1,3-conjugated diynes under mild conditions. (Scheme 67).[109]



Scheme 67. Oxidative coupling of propiolic acids.

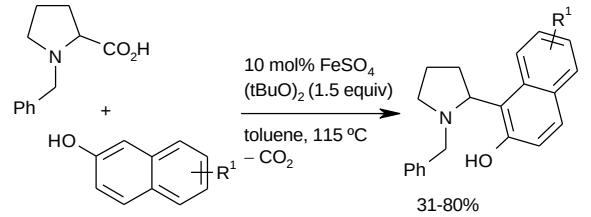
4.2.5 Coupling of α-amino acids

α-Amino acid carboxylate group can be used as a handle to obtain a range of interesting amine products from this ubiquitous substrate class by way of decarboxylative coupling reactions. Thus, Liang, Li *et al*. have used copper(I) to oxidatively couple *α*-amino acids with alkynes in high yields (Scheme 68).[110] Propargylamines, indolyl pyrrolidines and piperidines, as well as *β*-nitroamines are accessible with this method.



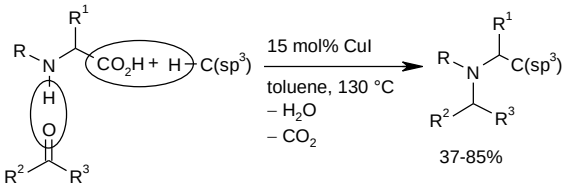
Scheme 68. Decarboxylative coupling of α-amino acids.

With iron-based catalyst systems, a related process has been developed by the same authors for the decarboxylative coupling of *α*-amino acids with naphthols and phenols to give aminonaphthol derivatives.[111] In both methods, the oxidant employed is *tert*-butyl peroxide.



Scheme 69. Decarboxylative coupling of amino acids.

Liang, Yao, Li *et al.* reported a copper-catalyzed one-pot reaction of secondary *α*-amino acids with aldehydes or ketones and alkynes, consisting of imine formation and decarboxylative coupling to afford propargylic amine derivatives *via* an internal redox reaction (Scheme 70).[112]

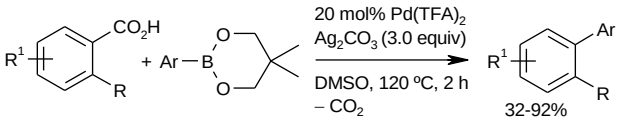


Scheme 70. Aldehyde- and ketone-induced tandem decarboxylation-coupling.

4.3 Decarboxylative couplings with boronic acids

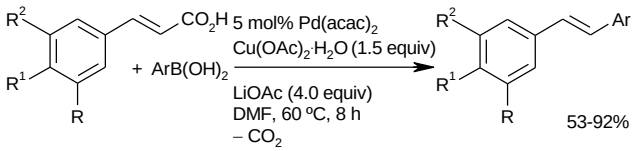
The carbon electrophiles formed by oxidative decarboxylation of carboxylic acids have successfully been coupled with boronic acids in a Suzuki-type fashion.

These decarboxylative Suzuki couplings between aromatic carboxylic acids and aryl boronates using silver(I) as the oxidant proceed in the presence of diverse functional groups. This includes chloro and bromo groups that generally do not remain intact in classical Suzuki couplings (Scheme 71).[113]



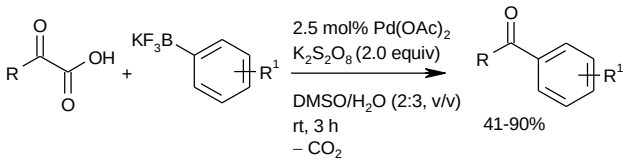
Scheme 71. Decarboxylative Suzuki-coupling.

Miura *et al.* obtained hydroxylated stilbenes by the palladium-catalyzed vinylogous decarboxylative Suzuki reaction of hydroxyl-substituted cinnamic acids with arylboronic acids using a copper(II) salt as the oxidant (Scheme 72).[114]



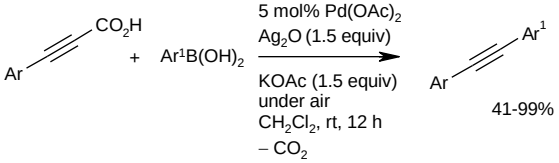
Scheme 72. Direct decarboxylative coupling of cinnamic acids with arylboronic acids.

Ge *et al*. recently reported an aryl ketone synthesis *via* palladium-catalyzed decarboxylative cross-coupling of potassium aryltrifluoroborates with *α*-oxocarboxylic acids at room-temperature (Scheme 73).[115]



Scheme 73. Decarboxylative coupling of potassium aryltrifluoroborates with α-oxocarboxylic acids.

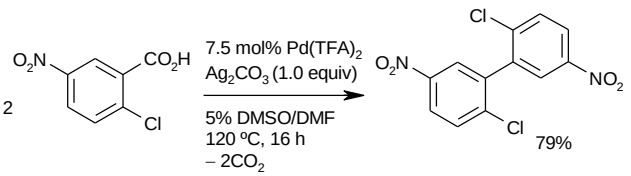
Unsymmetrically substituted alkynes are accessible *via* palladium-catalyzed decarboxylative coupling of arylboronic acids and alkynyl carboxylic acids (Scheme 74).[116]



Scheme 74. Decarboxylative synthesis of unsymmetrical diarylalkynes by Loh *et al.*

4.4 Decarboxylative homocoupling of (hetero)aromatic carboxylic acids

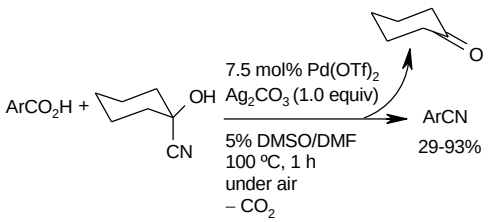
A variety of hetero(aromatic) carboxylic acids undergo decarboxylative homocoupling, mediated by Pd/Ag-systems (Scheme 75).[117] This methodology provides access to a variety of symmetric biaryls starting from inexpensive and stable arenecarboxylates. However, the scope is limited to 2-heteroaromatic carboxylic acids or aromatic carboxylic acids with an *ortho* electron-withdrawing substituent, i.e. the same carboxylic acids that decarboxylate in the presence of Ag(I)-systems (see Section 2.1).



Scheme 75. Decarboxylative homocoupling of arenecarboxylates.

4.5 Decarboxylative cyanation

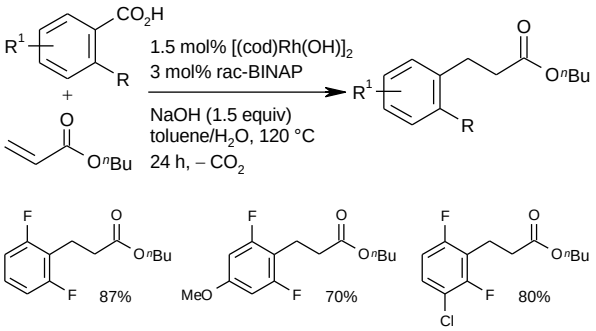
Taran *et al.* developed a conversion of arenecarboxylic acids into aryl nitriles by a palladium-catalyzed decarboxylative cyanation that makes use of cyanohydrins as the source of soluble cyanide (Scheme 76).[118] It is applicable to a variety of substrates bearing at least one *ortho* substituent.



Scheme 76. Decarboxylative cyanation reaction.

5 Decarboxylative addition reactions

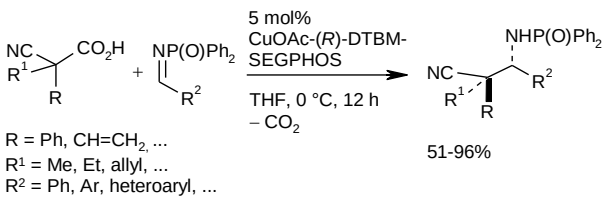
The rhodium-catalyzed decarboxylation discussed in Section 2.1 has been combined with 1,4-additions previously reported with boronic acids as the carbon nucleophiles. In the presence of 1.5 mol% $[(cod)Rh(OH)]_2$, carboxylic acids thus undergo a decarboxylative addition to acrylic esters or amides at 120 °C.[119] So far, the range of carboxylates is limited to *ortho,ortho*-disubstituted or otherwise particularly activated benzoates (Scheme 77).



Scheme 77. Decarboxylative conjugate addition.

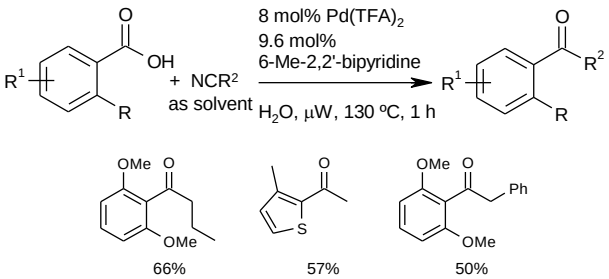
Similarly, carbon nucleophiles generated by Pd-catalyzed decarboxylation of arenecarboxylic acids have also been used in 1,2-additions to aldehydes to give the corresponding alcohols.[120] The catalyst system consists of 10 mol% $PdCl_2$ and 20 mol% AgOTf.

Another example of a decarboxylative 1,2-addition reaction is Kanai and Shibasaki's copper-catalyzed Mannich-type reaction (Scheme 78).[121] In this tramsformation, a chiral copper(I) complex is used to convert α-cyanocarboxylic acids to α-amino acid derivatives with quaternary stereocenters. Enantiomeric excess values in the range of 70-97% e.e. are obtained.



Scheme 78. Decarboxylative Mannich-type reaction.

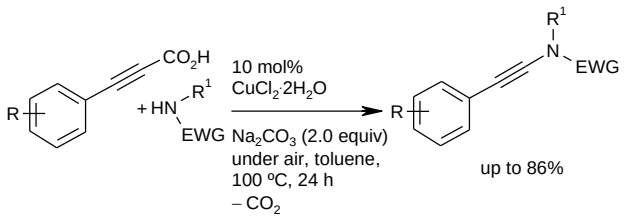
Larhed *et al.* reported a palladium(II)-catalyzed addition of *ortho*-functionalized benzoic acids to nitriles, leading to aryl ketone derivatives (Scheme 79).[122] The inexpensive nitriles are used as the solvent in this process.



Scheme 79. Decarboxylative addition of benzoic acids to nitriles.

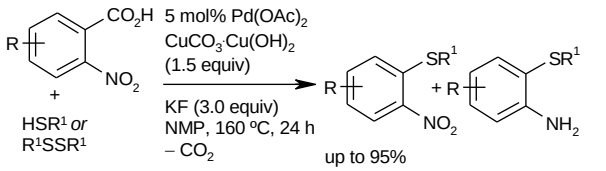
6 Decarboxylative couplings with formation of C-heteroatom bonds

While the overwhelming majority of decarboxylative couplings proceed with formation of C–C bonds, there are also a few examples of C–heteroatom bond forming reactions. Jiao *et al.* disclosed a Cu-catalyzed oxidative amidation of propiolic acids *via* decarboxylation under air (Scheme 80).[123] The use of propiolic acid derivatives rather then the alkynes efficiently inhibits the formation of diynes, common byproducts in oxidative reactions of alkynes.

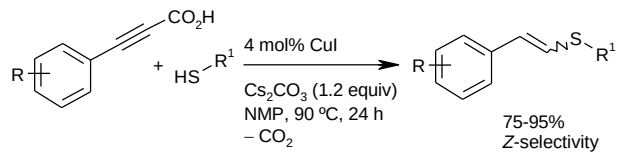


Scheme 80. Decarboxylative C–N bond formation.

Liu *et al.* reported the direct decarboxylative coupling of *ortho*-substituted carboxylic acids with thiols as a synthethic entry to sulfides.[124] The products were obtained as mixtures of nitrobenzene and aminobenzene sulfides.



The same authors reported that the synthesis of vinyl sulfides can be achieved by a copper-catalyzed coupling of arylpropiolic acids with thiols (Scheme 81).[125] The corresponding vinyl sulfides were obtained in good to excellent yields with a high selectivity towards the *Z*-isomers.

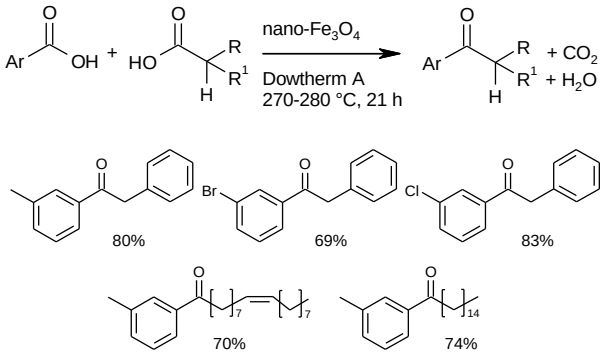


Scheme 81. Decarboxylative synthesis of vinyl sulfides.

7 Decarboxylative ketonization

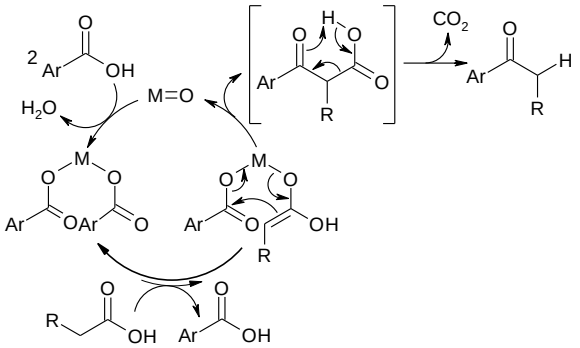
Libavius found already in 1595 that acetic acid reacts under extrusion of carbon dioxide with formation of acetone when pyrolyzed in the presence of lead. Since then, the decarboxylative homoketonization of aliphatic carboxylic acids has been developed into an effective method for the synthesis of symmetrical dialkyl ketones or cyclic alkanones.[126] The homoketonization is mediated by numerous metal oxides. State-of-the-art protocols involve gas phase transformations at temperatures above 350 °C at solid catalysts, e.g. CaO, ZnO, MgO,[127] TiO_2,[128] ZrO_2,[129] MnO,[130] Fe_2O_3,[131] or rare earth metal oxides[132] on SiO_2-, Al_2O_3-, or pumice-based supports.

One of the challenges in this field is to selectively promote the cross-ketonization of two different carboxylic acids. When equimolar mixtures of aromatic and aliphatic carboxylic acids are subjected to the above catalysts, dialkyl and aryl alkyl ketones are obtained at best in a 1:1 ratio. Gooßen *et al.* recently disclosed an iron-based catalytic method for the decarboxylative cross-ketonisation of aromatic with aliphatic carboxylic acids.[133]



Scheme 82. Decarboxylative cross-ketonization.

In the proposed mechanism, an iron(II) oxide molecule reacts with a mixture of aromatic and aliphatic carboxylic acids. Due to its higher acidity, the carboxylate derived from the aromatic carboxylic acid forms preferentially. However, it cannot enolize as it possesses no α-protons. The reaction can proceed further only with the mixed carboxylate. The aromatic acyl residue shifts to the β-position of the aliphatic carboxylate, forming a β-keto acid, which decarboxylates *via* a retro-oxo-ene reaction with formation of the aryl ketone.



Scheme 83. Decarboxylative cross-ketonization.

With nano-scale magnetite powder, aryl alkyl ketones are obtained in remarkable selectivities from a mixture of aryl and alkyl carboxylic acids, releasing water and CO_2 as the only byproducts.

8 Conclusion

In conclusion, decarboxylative transformations have reached an impressive level of performance and versatility within just a few years. Almost every week, a new decarboxylative transformations is disclosed that gives access to another interesting substrate class starting from easily available carboxylic acids. Still, several challenges must be met to fully establish decarboxylative couplings as standard tools in organic synthesis.

It is of high priority to lower the reaction temperature required for the decarboxylation step. New, more effective catalyst generations are thus required.

Another important development will be to extend the substrate scope particularly of monometallic Pd and Rh-catalyzed

decarboxylative couplings. One strategy is to incorporate new co-catalysts, another one to design new ligand systems for the cross-coupling catalysts that facilitate their decarboxylation activity. It will be interesting to see how this active field of research will develop in the coming years.

Notes and references

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