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New catalytic transformations of carboxylic acids*

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Abstract: A series of metal-catalyzed processes are presented, in which carboxylic acids act as sources of either carbon nucleophiles or electrophiles, depending on the catalyst employed, the mode of activation, and the reaction conditions. A first reaction mode is the addition of carboxylic acids or amides over C–C multiple bonds, giving rise to enol esters or enamides, respectively. The challenge here is to control both the regio- and stereoselectivity of these reactions by the choice of the catalyst system. Alternatively, carboxylic acids can efficiently be decarboxylated using new Cu catalysts to give aryl-metal intermediates. Under protic conditions, these carbon nucleophiles give the corresponding arenes. If carboxylate salts are employed instead of the free acids, the aryl-metal species resulting from the catalytic decarboxylation can be utilized for the synthesis of biaryls in a novel cross-coupling reaction with aryl halides, thus replacing stoichiometric organometallic reagents. An activation with coupling reagents or simple conversion to esters allows the oxidative addition of carboxylic acids to transition-metal catalysts under formation of acyl-metal species, which can either be reduced to aldehydes, or coupled with nucleophiles. At elevated temperatures, such acyl-metal species decarbonylate, so that carboxylic acids become synthetic equivalents for aryl or alkyl halides, e.g., in Heck reactions.

Keywords: decarboxylation; enol esters; enamides; aryl-metal intermediates; copper catalyst; carbon nucleophiles; biaryls.

INTRODUCTION

In the last years, the development of new catalytic methods for sustainable organic transformations was the focus of our research. In this context, we viewed carboxylic acids as a highly desirable substrate class, since they are available in great structural diversity at low cost both from natural and synthetic sources, and are easy to store and handle. Nevertheless, they had so far been widely neglected as starting materials for catalytic transformations.

We and others have disclosed a series of catalytic transformations of carboxylic acid derivatives that can roughly be divided into four categories with regard to the position and polarity of bond formation: (1) catalytic addition reactions, in which the carboxylate group is transferred as a whole to C–C multiple bonds; (2) decarboxylative couplings, in which the carbon nucleophiles generated by extrusion of CO_2 from metal carboxylates are coupled with electrophiles, e.g., aryl halides; (3) cross-

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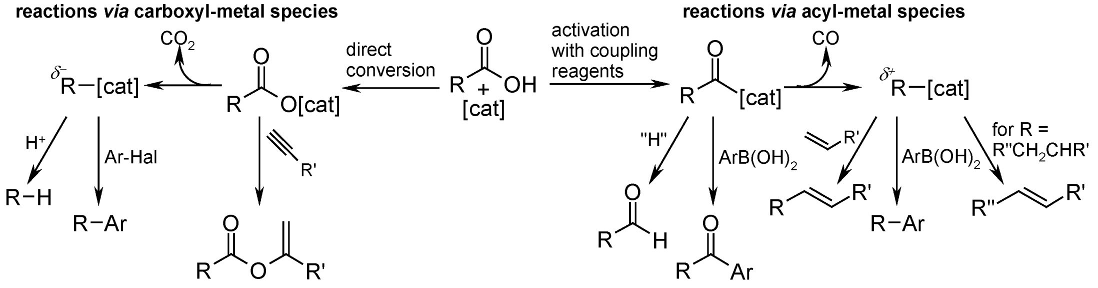
coupling reactions of acyl-metal species generated by insertion of a metal catalyst into the C–O bond of activated carboxylic acid derivatives; and (4) decarbonylative reactions, which involve the loss of carbon monoxide from acyl-metal species under formation of carbon electrophiles. Scheme 1 gives an overview of these reaction modes and the products that can be accessed in the corresponding processes.

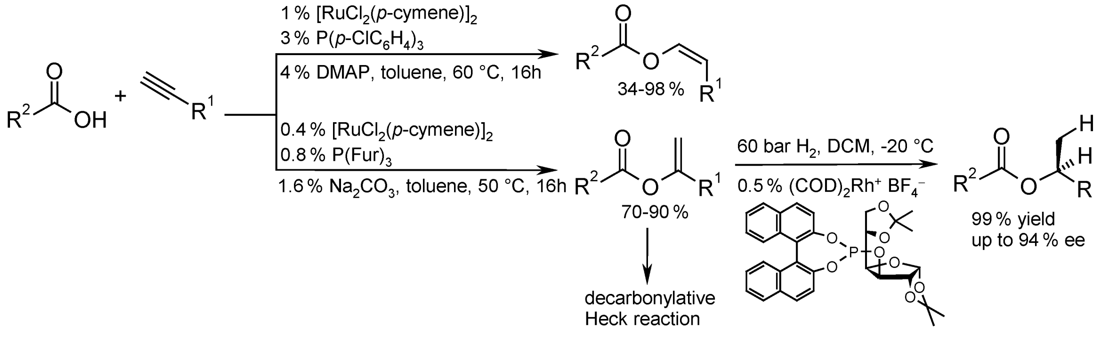


Scheme 1 Catalytic transformations of carboxylic acids.

CATALYTIC ADDITION TO ALKYNES

The most straightforward reaction mode of a carboxylic acid with a metal catalyst is the cleavage of the acidic O–H bond under formation of a metal carboxylate. This is the initial step in the synthetically valuable addition of carboxylic acids to alkynes under formation of enol esters.

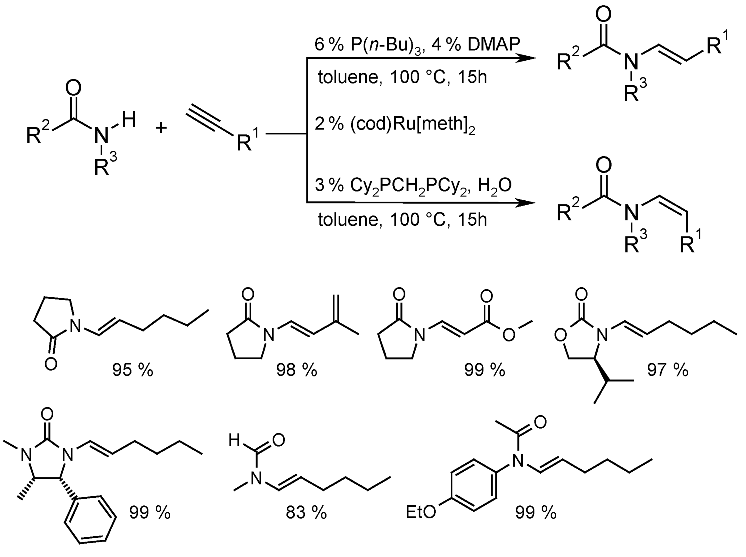
Rotem et al. have shown for the first time that this process is mediated by Ru precursors [1]. Since then, several efficient Ru catalysts have been developed that allow the addition of a range of carboxylic acids to various terminal alkynes [2]. The regioselectivity of this reaction is most often controlled by the choice of Ru precursor and phosphine ligand. We have recently disclosed a particularly robust, inexpensive, and easy-to-use set of protocols, in which a base, added in catalytic amounts, plays a key factor in regiocontrol (Scheme 2) [3]. When the catalyst is generated in situ from $[RuCl_2(p\text{-cymene})]_2$, trifurylphosphine as the ligand and sodium carbonate as the base, the reaction proceeds in Markovnikov fashion (Scheme 2, bottom), while the use of tri-*p*-chlorophenylphosphine and 4-dimethylaminopyridine along with the same Ru precursor results in a complete reversal of selectivity, giving rise to the (*Z*)-configured *anti*-Markovnikov products (Scheme 2, top). Both protocols have successfully been employed for the synthesis of a broad variety of enol esters.



Scheme 2 Catalytic addition of carboxylic acids to terminal alkynes and follow-up reactions.

Having established a convenient and easily scalable entry to vinyl esters, we sought preparative applications of these compounds. Due to their rigid mode of coordination to transition-metal catalysts, we hoped to achieve high enantioselectivities in their hydrogenation, even when using simple and inexpensive ligand systems. In cooperation with the Reetz group, we thus investigated the Rh-catalyzed hydrogenation of prochiral enol esters and identified a system consisting of $(COD)_2RhBF_4$ and a sugar/2,2'-dihydroxy-1,1'-binaphthalene (BINOL)-based phosphite ligand to be particularly effective in terms of both enantioselectivity and yield (Scheme 2, right) [4]. For the synthesis of chiral alkyl esters, the two-step, atom-economic sequence of Ru-catalyzed Markovnikov addition of a carboxylic acid to a terminal alkyne, followed by asymmetric hydrogenation constitutes a valuable alternative to the traditional approach of hydrogenating a prochiral ketone, then reacting it with an activated carboxylic acid derivative.

In continuation of our work on Ru-catalyzed hydroacyloxylations, we developed more active Ru catalysts that allow the selective *anti*-Markovnikov addition of amides and related compounds to terminal alkynes, under formation of the corresponding enamide derivatives [5,6]. With catalyst systems consisting of bis(2-methallyl)-1,5-cyclooctdienylruthenium and suitable ligands, such "hydroamidations" proceed under mild conditions and are widely applicable to amides, anilides, lactams, ureas, bislactams, carbamates, and imides in combination with various terminal alkynes. The stereochemistry of the reaction can efficiently be controlled by the ligand system, so that depending on whether tri-*n*-butylphosphine and dimethylaminopyridine (DMAP) or bis(dicyclohexylphosphino)methane and water are used, either the (*E*)- or the (*Z*)-isomers are selectively formed (Scheme 3). The ideal atom economy in combination with a high chemo-, regio-, and stereoselectivity and the excellent availability of the starting materials makes this enamide synthesis attractive for various applications in synthetic organic chemistry and drug discovery.

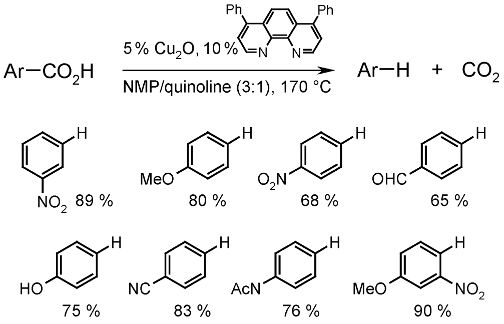


Scheme 3 Catalytic addition reactions of carboxylic acids and derivatives to terminal alkynes.

DECARBOXYLATIVE REACTIONS OF CARBOXYLIC ACIDS

Cu-catalyzed protodecarboxylation

The decarboxylation of metal arenecarboxylates under formation of aryl-metal species is a highly endothermic process and usually requires extreme reaction conditions. Even the widely known Cu-mediated protodecarboxylation of aromatic carboxylates in most cases entails stoichiometric amounts of Cu [7]. Our own process involving Cu(I)oxide and 4,7-diphenyl-1,10-phenanthroline for the first time allows the use of Cu in only catalytic amounts for both activated and non-activated aromatic, heteroaromatic, and vinylic carboxylates (Scheme 4) [8].

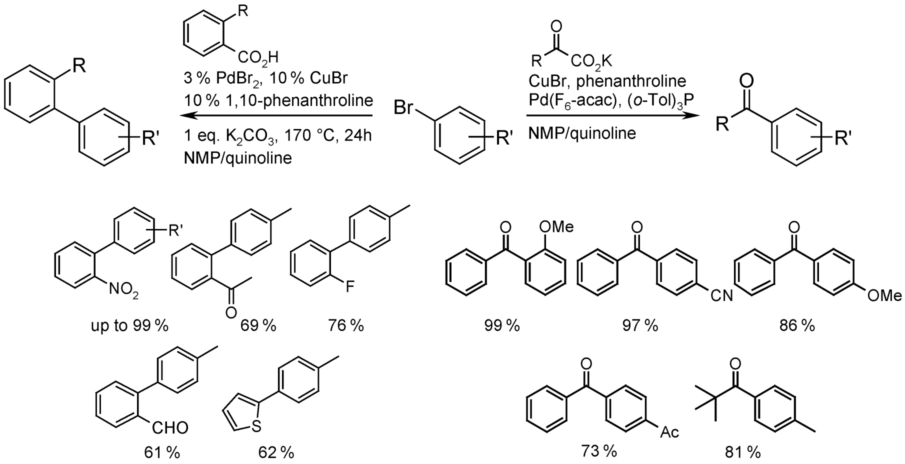


Scheme 4 Catalytic decarboxylative cross-coupling reactions of carboxylates.

Cu/Pd-catalyzed cross-coupling reactions

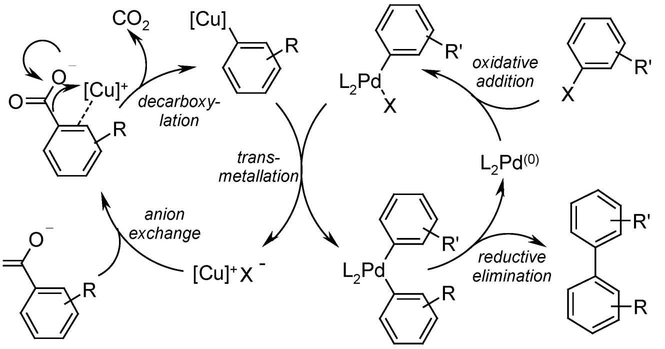
The above investigation set the stage for the development of a new type of cross-coupling reactions in which the carbon nucleophiles are generated in situ from easily available metal carboxylates via the extrusion of CO_2. A first example for this was our biaryl synthesis from aromatic carboxylic acids and aryl halides [9]. This process is catalyzed by a bimetallic system consisting of a Cu-phenanthroline decarboxylation catalyst, and a coordinatively unsaturated Pd(0)-containing cross-coupling catalyst. Following Cu-mediated decarboxylation of the arenecarboxylates under formation of an aryl-Cu species, the aryl residue is transferred onto an aryl-Pd halide species generated in the reaction of the aryl halide with the second catalyst component. Finally, the two aryl groups reductively eliminate under formation of an unsymmetrical biaryl, regenerating the original Pd species.

The new reaction is broadly applicable with respect to the aryl halide component and has successfully been applied to a growing number of aromatic carboxylic acids, including *ortho*-substituted benzoic acids, heterocyclic carboxylates, and cinnamic acid (Scheme 5, left).



Scheme 5 Catalytic decarboxylative cross-coupling reactions of carboxylates. The residues originating from the carboxylic acid are depicted on the left-hand sides.

In our proposed mechanism, a decarboxylation catalyst, e.g., a Cu or Ag complex, initially coordinates to the carboxylate oxygen, then shifts to the aryl π-system and inserts into the C–C(O) bond under extrusion of CO_2 to form a stable aryl-Cu intermediate. A Pd catalyst then cross-couples this species with an aryl electrophile to form the desired biaryl and the corresponding metal halide (Scheme 6).



Scheme 6 Proposed mechanism for catalytic decarboxylative cross-coupling reactions of carboxylates.

Whereas the first-generation catalyst allowed the coupling of aryl iodides, bromides, and some electron-poor chlorides, the latest systems currently under development in our group can smoothly convert even notoriously unreactive electron-rich aryl chlorides such as 4-chloroanisole [9c]. The main factors in this increased activity were optimized steric and electronic properties of the phosphine ligands.

When using aryl halides as coupling partners, the coupling of *meta*- and *para*-substituted benzoic acids has not yet been achieved in satisfactory yields. However, ongoing research indicates that this structural limitation can be overcome when employing aryl triflates instead of halides.

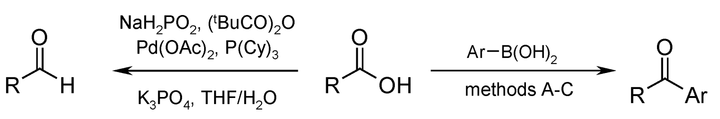
Another exciting development was the extension of the concept of decarboxylative cross-coupling to other substrate classes, as exemplified by a new ketone synthesis that draws on easily available potassium α-oxocarboxylates as sources of acyl nucleophiles in a coupling reaction with aryl bromides (Scheme 5, right) [10]. It is broadly applicable to the synthesis of various aryl and heteroaryl ketones and compares favorably with traditional syntheses of ketones via organometallic reagents.

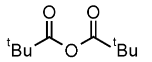
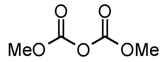
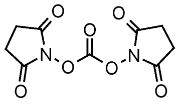
CATALYTIC REACTIONS OF ACTIVATED CARBOXYLIC ACID DERIVATIVES

Cross-coupling reactions of acyl-Pd-complexes

The activation of carboxylic acids by their conversion into anhydrides, or *N*-hydroxysuccinates, permits an insertion of transition-metal catalysts into the acyl-oxygen bond. The resulting acyl intermediates can be hydrogenated to the corresponding aldehydes (Scheme 7, left) [11], or coupled with boronic acids to give aryl ketones (Scheme 7, right).

Based on this mechanistic concept, we have developed a Pd-catalyzed ketone synthesis directly from carboxylic and boronic acids. In this process, an equilibrium mixture of acids and anhydrides is generated in situ from carboxylic acids and pivalic anhydride [12]. The steric bulk of the *tert*-butyl groups precludes an insertion of the Pd-phosphine catalyst into the sterically highly encumbered C(O)–O bond on the pivalate side, so that the less hindered aryl ketone is exclusively obtained in the coupling with the areneboronic acids, releasing pivalic acid as the by-product. The mild, base-free conditions allow the synthesis of various sensitive ketones. Besides pivalic anhydride, dimethyl dicarbonate can also be used as an activator, with the advantage that only volatile by-products are formed, thus allowing even easier product isolation at the cost of a slightly reduced substrate scope [13]. For partic-



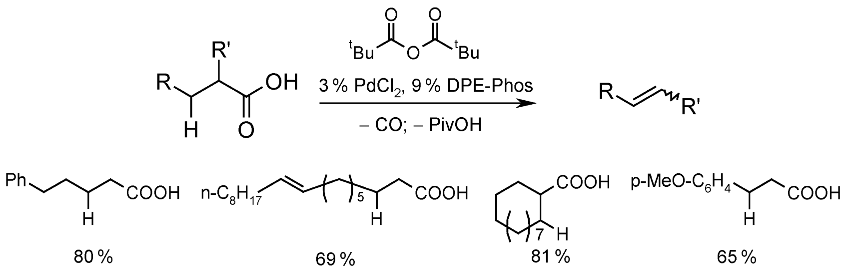
	coupling reagent	catalyst	conditions
method A		3 % Pd(OAc)$_2$ 7 % P(p-MeOC$_6$H$_4$)$_3$	DME-H$_2$O 60 °C, 16h
method B		3 % Pd(OAc)$_2$ 7 % P(p-MeOPh)$_3$	THF-H$_2$O 50 °C, 16h
method C		3 % Pd(F$_6$-acac)$_2$ 9 % PCy$_3$	Na$_2$CO$_3$, THF 60 °C, 20h

Scheme 7 Catalytic transformations of acyl nucleophiles generated using coupling reagents.

ularly sensitive substrates, a third reaction variant was designed involving in situ activation of the carboxylic acids with disuccinimidyl carbonate (DSC) [14]. In this process, we demonstrated the first application of easy-to-use peptide coupling reagents in transition-metal catalysis.

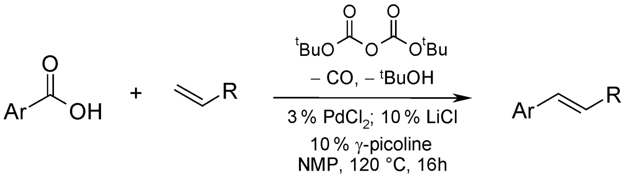
Reactions involving a decarbonylation step

At elevated temperatures, acyl-metal species resulting from the above-mentioned insertion into the C(O)–O bond of activated carboxylic acids tend to decarbonylate, giving rise to alkyl- or aryl-metal complexes. This behavior is exploited in the Pd-catalyzed decarbonylative elimination reaction of alkylcarboxylic acids in the presence of pivalic anhydride, which gives the corresponding alkenes, pivalic acid, and carbon monoxide [15]. The general outline of this reaction along with selected examples of suitable starting materials is given in Scheme 8.



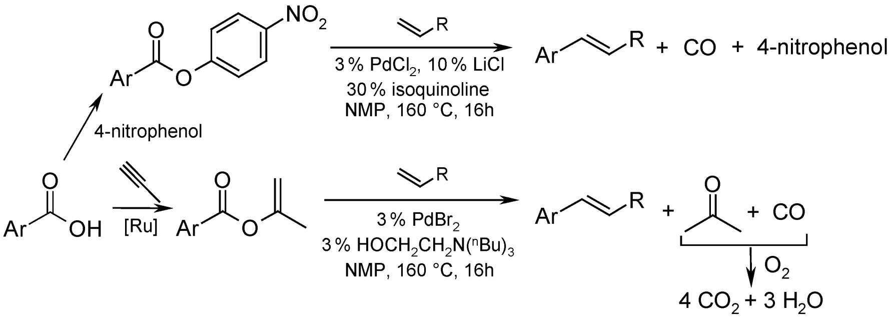
Scheme 8 Catalytic decarbonylative elimination of alkylcarboxylic acids.

A similar decarbonylation is observed in the Heck reactions of aromatic anhydrides [16]. In the process depicted in Scheme 9, aromatic carboxylic acids are activated in situ with di-*tert*-butyl dicarbonate and vinylated under extrusion of CO. All by-products are volatile, which makes product isolation particularly easy [17].



Scheme 9 Catalytic decarbonylative Heck reaction of carboxylic acids.

With especially developed Pd catalysts, even poorly reactive carboxylates can serve as substrates in such decarbonylative Heck reactions. We have demonstrated the coupling of various electron-deficient phenol esters with olefins to give the vinyl arenes, along with CO and the corresponding phenols (Scheme 10, top) [3,18]. The latter were successfully recycled into the starting material in an esterification step with fresh carboxylic acid. With this reaction sequence, it was demonstrated for the first time that the production of waste salts is avoidable in Heck reactions [19].



Scheme 10 Catalytic decarbonylative Heck reactions of carboxylic esters.

Further development of the catalysts enabled the decarbonylative Heck reaction of aryl isopropenoates to give the vinyl arenes, CO, and acetone. Combined with the formation of the isopropenyl esters from the carboxylic acids and propyne (see Scheme 2)—a side product in oil refining—this represents our third approach to salt-free Heck reactions (Scheme 10, bottom): Besides CO, acetone is the only by-product and can be incinerated without much negative impact on the environment [20].

The scope of the decarbonylative Heck reactions is visible from the examples depicted in Fig. 1, the given yields are those obtained starting with isolated 4-nitrophenol esters.

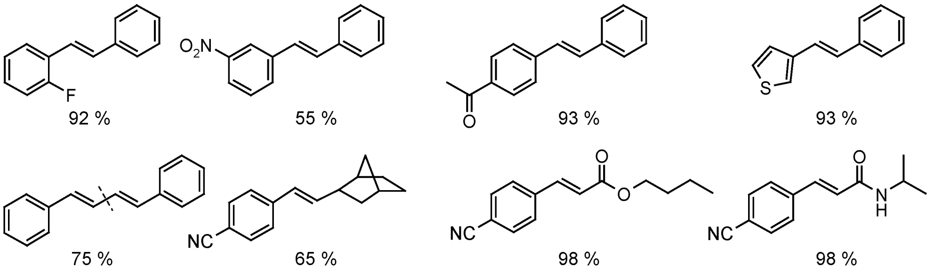


Fig. 1 Selected examples demonstrating the scope of the decarbonylative Heck reactions. The residues originating from the 4-nitrophenol ester are depicted on the left-hand sides.

CONCLUSION

The catalytic transformations outlined in this paper exemplify the rich chemistry of carboxylic acids as substrates in transition-metal catalysis that has evolved in recent years. Most of these reactions could serve as prototypes for a new generation of more sustainable organic processes based on naturally occurring carboxylic acids as renewable feedstocks. Some reactions, such as the ketone synthesis, are already highly developed, while others still require substantial optimization efforts until they reach synthetic maturity. Notably, the decarboxylative cross-coupling reactions, though yet in their infancy, are already the focus of industrial process research, as they have the potential to one day replace cross-couplings of expensive organometallic reagents. It will be interesting to follow future innovation in this emerging field of method development.

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