

Direct C(sp³)-H Activation of Carboxylic Acids

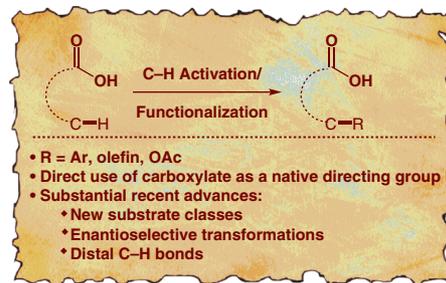
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Abstract Carboxylic acids are important in a variety of research fields and applications. As a result, substantial efforts have been directed towards the C–H functionalization of such compounds. While the use of the carboxylic acid moiety as a native directing group for C(sp²)-H functionalization reactions is well established, as yet there is no general solution for the C(sp³)-H activation of aliphatic carboxylic acids and most endeavors have instead relied on the introduction of stronger directing groups. Recently however, novel ligands, tools, and strategies have emerged, which enable the use of free aliphatic carboxylic acids in C–H-activation-based transformations.

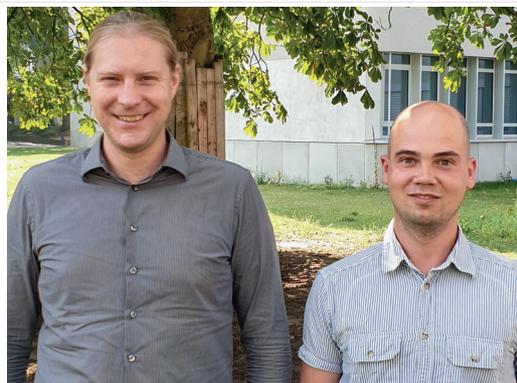
- 1 Introduction
- 2 Challenges in the C(sp³)-H Bond Activation of Carboxylic Acids
- 3 The Lactonization of Aliphatic Carboxylic Acids
- 4 The Directing Group Approach
- 5 The Direct C–H Arylation of Aliphatic Carboxylic Acids
- 6 The Direct C–H Olefination of Aliphatic Carboxylic Acids
- 7 The Direct C–H Acetoxylation of Aliphatic Carboxylic Acids
- 8 Summary

Key words carboxylic acids, C–H activation, native directing group, synthetic methodology

1 Introduction

Carboxylic acids are important building blocks in organic chemistry. They are readily available, cheap and abundant, and are therefore frequently used in organic chemistry as starting materials, synthetic intermediates, or products.¹ In Nature the carboxylic acid moiety is part of amino acids, fatty acids, keto-acids, and a variety of other essential molecules. In industry carboxylic acids serve as bulk chemicals and are converted into solvents, agrochemicals, or pharmaceuticals. Carboxylic acids can be obtained easily via the oxidation of alcohols or alkanes and can be convert-

ed further into a variety of other useful functional groups. Besides this well-known organic chemistry textbook methodology, several further strategies have recently emerged for the use of carboxylic acids.² The photoredox chemistry of carboxylic acids and their corresponding redox active esters has been shown to be a powerful tool to generate alkyl radicals that can be used in a variety of transformations.³



Manuel van Gemmeren (left) studied chemistry in Freiburg, before joining the group of Prof. Benjamin List at the Max-Planck-Institut für Kohlenforschung for his doctoral studies, which he completed in 2014 (summa cum laude). After postdoctoral studies in the group of Prof. Rubén Martín at the ICIQ in Tarragona, he started an independent research group at Westfälische Wilhelms-Universität-Münster in 2016. His group has been supported by a Liebig Fellowship of the Fonds der Chemischen Industrie and the Otto Hahn Award of the Max Planck Society (Max-Planck-Institute for Chemical Energy Conversion). Research in the van Gemmeren lab focusses on the development of novel synthetic methods that enable challenging transformations to proceed with catalyst-controlled reactivity and selectivity. A particular emphasis in the group lies on the conversion of abundant starting materials, such as carboxylic acids, into products of increased value and complexity.

Alexander Uttry (right) is currently conducting his doctoral studies in the van Gemmeren group at Westfälische Wilhelms-Universität-Münster as a member of SFB 858.

Besides these decarboxylative methods, there is a substantial interest in the use of the carboxylic acid moiety as a native directing group for C–H activation/functionalization reactions. Such reactions are highly interesting because they bear the potential to rapidly access complex molecules without the need for prefunctionalization.⁴ Importantly, C–H activation has also found increasing applications in natural product synthesis.⁵ For aromatic carboxylic acids it has been shown that the carboxylic acid functionality can be employed as a directing group in a variety of cases.⁶ However, for the carboxylic acid directed activation of aliphatic C–H bonds, only a limited number of examples have been reported. This type of C–H activation has proven challenging, presumably due to high activation entropies and a lack of pre-coordination of the transition metal to the aromatic π -system, which is often observed for aromatic substrates.

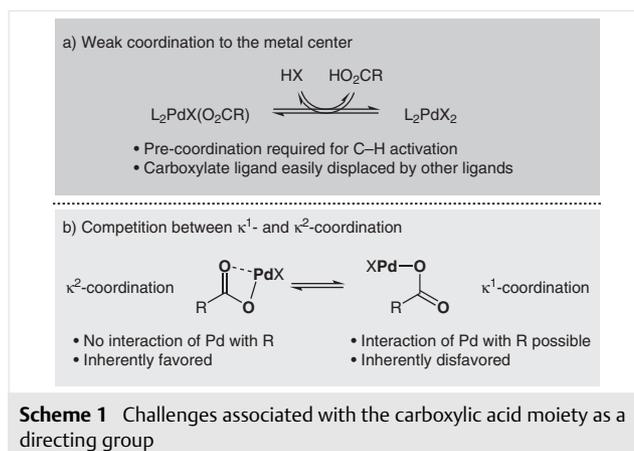
In this short review we discuss the current state of aliphatic carboxylic acid directed C–H activation/functionalization processes, focusing on the major difficulties encountered in catalyst development and the strategies that have been employed to address them.

2 Challenges in the C(sp³)–H Bond Activation of Carboxylic Acids

In general, aliphatic C–H activation processes face the challenge presented by the high thermodynamic stability and the relatively non-polar character of the aliphatic C–H bond, which often renders the insertion of the transition metal into the C–H bond the key step of the respective catalytic cycle.⁷ To achieve the C–H activation the transition metal has to be in close proximity to the respective C–H bond. This is often achieved by using directing groups, where a pre-coordination places the transition metal close to the targeted C–H bond. The acceleration by this so-called complexation-induced proximity effect (CIPE) is often required for a reaction to occur.⁸ Additionally, this pre-coordination also dictates the regioselectivity of the C–H activation process. While this directing group approach has been shown to be very successful, the use of the free carboxylic acid moiety as a native directing group remains highly attractive. However, it also features several additional key challenges (Scheme 1).^{9,10}

Compared to ligands and substrates containing strongly binding subunits like nitrogen-based heterocycles, carbenes, or phosphines, the carboxylic acid moiety is only weakly coordinating to transition metals. Therefore, the carboxylic acid can easily be replaced by other anions present in the reaction mixture (Scheme 1, a). This type of equilibrium reduces the amount of reactive species in the system and is thus detrimental to the overall reaction efficiency.

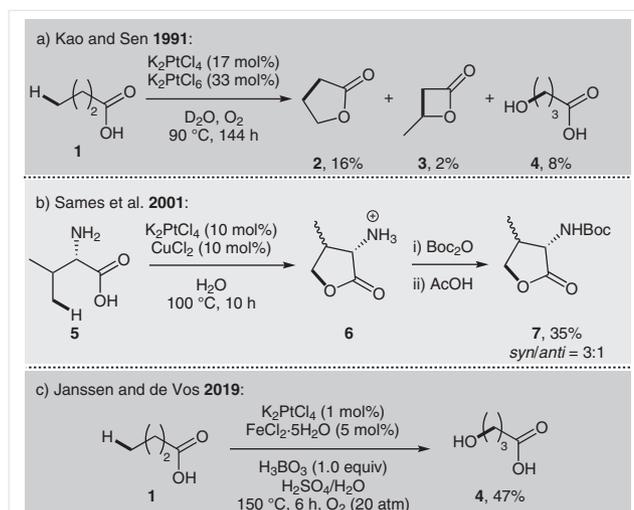
When bound to the transition metal catalyst, the carboxylic acid moiety can engage in two different coordination modes to the metal center (Scheme 1, b). In the typi-



cally favored κ^2 -coordination mode the metal is coordinated to both oxygen atoms of the carboxylate, whereas in the κ^1 -coordination mode only a single lone pair of one oxygen atom coordinates to the metal.¹¹ Of these, only the κ^1 -coordinated complex can adopt a conformation with a suitable alignment between the metal center and the C–H bond to be activated.

3 The Lactonization of Aliphatic Carboxylic Acids

The first studies with the carboxylic acid moiety as a directing group for aliphatic C–H activation were undertaken with lactonization reactions (Scheme 2). In 1991, Kao and Sen demonstrated that various aliphatic carboxylic acids could be converted into lactones using potassium tetrachloro-



platinate(II) as the catalyst.¹² The reaction was conducted in deuterated water, and starting from butanoic acid (**1**) the authors obtained a mixture of γ -butyrolactone (**2**), resulting from γ -methyl C(sp³)-H activation, and β -butyrolactone (**3**), resulting from β -methylene C(sp³)-H activation. Furthermore, the ring-opened hydroxy acid **4** was observed as a side product (Scheme 2, a).

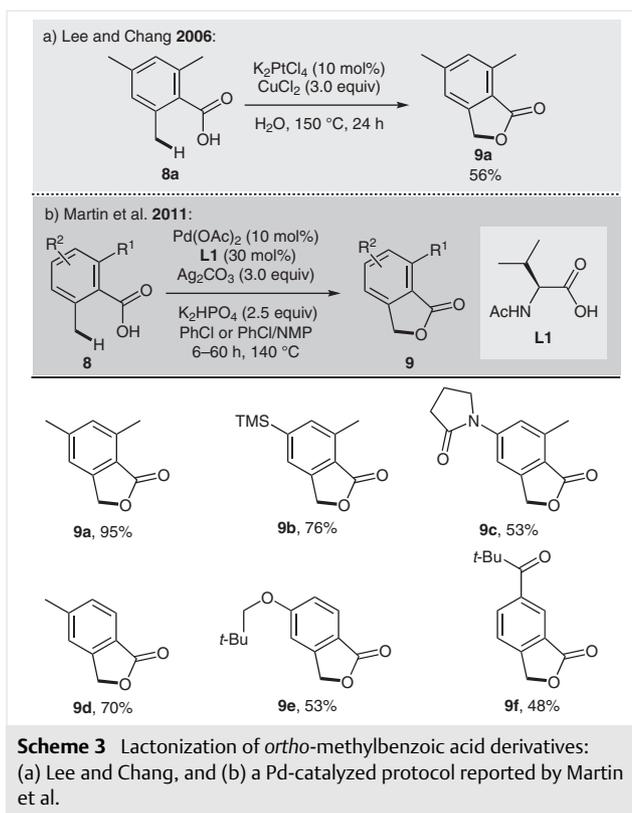
Based on the ratio between the lactones, the authors concluded that under their reaction conditions γ -C-H bonds are preferentially activated, presumably due to the formation of a ring-strain-free six-membered platinacycle. While significant reactivity was observed for β -, δ -, and ε -C-H bonds, α -C-H bonds were dramatically less reactive and no reaction occurred at this position when β -C-H bonds were present in the substrate. Concerning the mechanism, it was postulated that the carboxylate coordinates to the transition metal before the C-H activation step. Reductive elimination would then liberate the product and give a Pt(0) species, which can be reoxidized to the catalytically active Pt(II) species by the terminal oxidant K₂PtCl₆, thereby closing the catalytic cycle. Unfortunately, turnover numbers remained low in all cases studied and stoichiometric platinum was required, since it was indispensable both as catalyst and terminal oxidant.

Sames et al. developed an improved protocol in 2001 by employing CuCl₂ as the oxidant to achieve the lactonization of amino acids in water (Scheme 2, b).¹³ For L-valine (**5**) the γ -C-H lactonized product **7** could be isolated as a mixture of stereoisomers in 35% overall yield after derivatization of the primary product **6**.

These studies provided a highly important proof of principle. However, from a practical perspective, substantial challenges such as the high catalyst loadings required and the relatively narrow scopes of these processes remained to be addressed. It should be noted that efficient methods for the C-H lactonization of simple aliphatic acids, with low catalyst loadings and for example air as the terminal oxidant, bear substantial industrial potential. Such methods could deliver γ -hydroxybutanoic acid (GHB) (**4**) and related compounds of industrial importance. In 2019, Janssen and de Vos showed that the reaction of butanoic acid (**1**) with a K₂PtCl₄ system could be performed with oxygen as the terminal oxidant by fine-tuning of the reaction conditions (Scheme 2, c). The authors demonstrated that both reactivity and selectivity could be improved either by the addition of 2-pyridone as a ligand or by the addition of boric acid to stop the oxidation process at the stage of GHB.¹⁴

Lee and Chang used a related catalytic system in 2006 to achieve the lactonization of *ortho*-methyl-substituted benzoic acid derivatives (Scheme 3, a).¹⁵

For example, using 2,4,6-trimethylbenzoic acid (**8a**) as the substrate the authors isolated the corresponding lactone **9a** in 56% yield. Lee and Chang also showed that vari-



ous carboxylic acid derivatives such as esters or primary amides reacted under their optimized conditions, presumably via in situ hydrolysis to give the corresponding benzoic acids under the harsh reaction conditions.

In 2011 Martin et al. developed a Pd-based catalyst system for this type of transformation (Scheme 3, b).¹⁶ Key features for the success of this catalyst system were the use of *N*-acetylvaline (**L1**) as a ligand, the addition of silver and potassium salts as additives, and the use of chlorobenzene as a polar aprotic solvent. Concerning the choice of the transition metal for catalysis it should be noted that palladium complexes undergo ligand exchange much faster compared to platinum complexes, which often allows the development of milder reaction conditions and more active catalysts.¹⁷ For 2,4,6-trimethylbenzoic acid (**8a**) the yield of the benzolactone **9a** was close to quantitative. The authors were also able to show that functionalities such as silyl groups (**9b**) and amides (**9c**) were tolerated under the reaction conditions. Moreover, they demonstrated that the reaction was not limited to 2,6-dimethylbenzoic acid derivatives (**9d**) and that substrates bearing strongly electron-withdrawing or electron-donating groups gave the corresponding lactones **9e,f** in moderate yields.

4 The Directing Group Approach

However, after these beautiful studies on lactonization reactions, the extension to other transformations remained challenging. Other C–H activations/functionalizations on aliphatic carboxylic acids were first achieved rather elegantly by indirect approaches based on the conversion of the carboxylic acid moiety into a stronger directing group.¹⁸

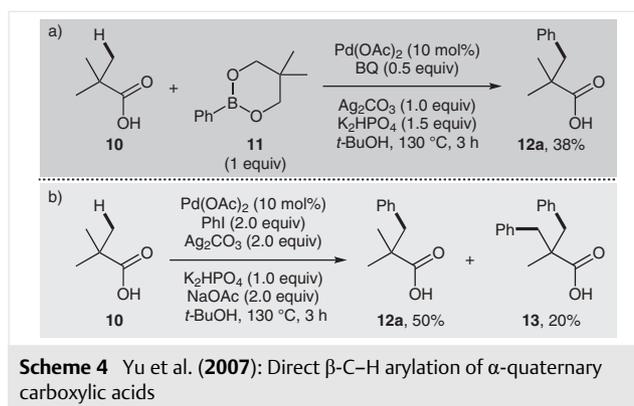
The directing group approach has found widespread application and was quickly extended to a broad variety of synthetic applications, including enantioselective reactions.^{19,20} It should be noted that in most of the cases the directing group is specifically designed to favor the C–H activation step. The use of such groups bears some inherent disadvantages, most importantly, that the directing group is typically introduced for the sole purpose of enabling the C–H activation and subsequently removed, resulting in a poorly step- and atom-economic three-step protocol. Furthermore, the removal of the directing group is in many cases not trivial.²¹ However, recent studies have enabled the use of synthetically more versatile carboxylic acid derivatives, such as simple amides, as directing groups in C–H bond activation reactions.²²

A further strategy to alleviate the disadvantages associated with directing groups is the use of transient directing groups, which are installed and removed under the reaction conditions and can thus often be utilized in sub-stoichiometric amounts. While this strategy has proven highly useful for other challenging substrate classes such as amines or alcohols,²³ no transient directing group for acids has been reported to date.

5 The Direct C–H Arylation of Aliphatic Carboxylic Acids

The first intermolecular C–H bond activation/functionalization using the carboxylic acid moiety as a native directing group was developed by Yu et al. in 2007 (Scheme 4).²⁴ The authors showed that α -quaternary carboxylic acids can be arylated using organoboron reagents (Scheme 4, a). The reaction proceeds via a Pd(0)/Pd(II) cycle, with the arylation of pivalic acid (**10**) taking place in the presence of boronic ester **11** to give the product **12a** in 38% yield. Furthermore, the authors also employed aryl iodides as the arylating agent under modified reaction conditions (Scheme 4, b). In this case the reaction was proposed to proceed through a Pd(II)/Pd(IV) cycle. After the C–H activation step, the Pd(II) species oxidatively adds into the carbon iodine bond to form a Pd(IV) intermediate. This species then liberates the product via reductive elimination with concomitant formation of a Pd(II)IL_n species, from which the active catalyst is regenerated by anion exchange with the silver salt. It should be noted that besides the abstraction of I[−] from palladium, the role of the silver salt in this type of reaction is

not fully understood and it is well possible that the silver ions actively engage in the C–H activation transition state.²⁵ For pivalic acid (**10**) the arylated product **12a** could be obtained in 50% yield and the diarylated material **13** was observed as a side product. For both sets of reaction conditions the key factor that enabled reactivity was the addition of sodium and potassium salts. The presence of alkali cations presumably affects the coordination of the carboxylate to palladium to favor κ^1 -coordination, or at least shift the equilibrium towards this coordination mode.⁹

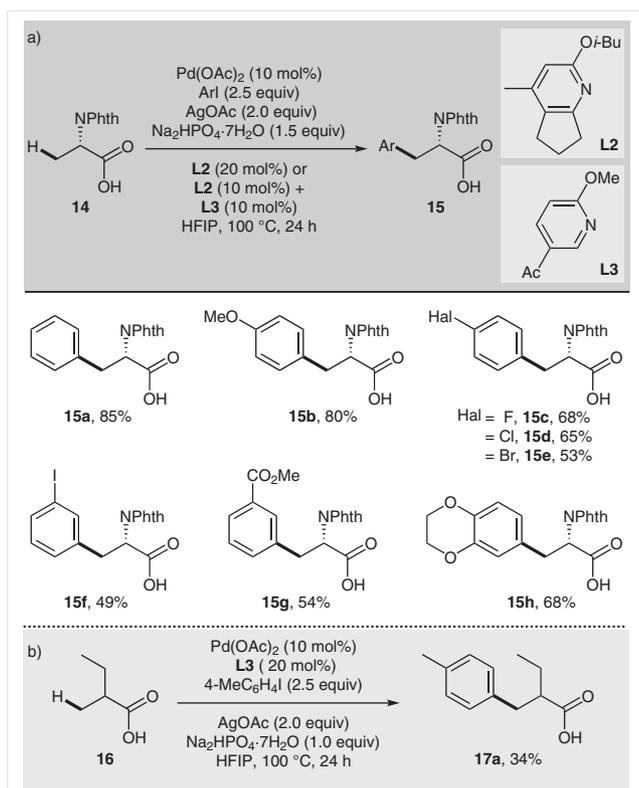


After this milestone, the key challenges to be addressed were the extension to α -non-quaternary substrates and to other transformations. These challenges remained unfulfilled until various groups reported the arylation of α -non-quaternary carboxylic acids in 2017. Such substrates are more challenging to activate since they lack the Thorpe–Ingold effect that accelerates the activation of α -quaternary substrates.²⁶ Furthermore, carboxylic acids featuring α - or γ -hydrogen atoms can potentially undergo β -hydride elimination after the C–H activation step.²⁷ In all of these studies the key finding to enhance reactivity was the introduction of suitable ligands.

Yu et al. have studied the arylation of N-protected amino acids to generate unnatural phenylalanine derivatives (Scheme 5).²⁸

The authors found that the pyridine-derived ligands (**L2** and **L3**) enhanced the reactivity. Besides the ligand, the addition of sodium salts and the use of 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) as solvent were found to be crucial for the desired reactivity. HFIP and other highly fluorinated solvents have a unique combination of properties, such as a high polarity, low nucleophilicity, and the ability of H-bond donation by dimeric and trimeric solvent aggregates, which are favorable for C–H activation processes.²⁹

The authors used a variety of aryl iodides to study the scope of this transformation. Besides the phenyl group (**15a**), arenes with strongly electron-donating groups (**15b**) could be introduced in very good yields. The authors showed that halides (**15c–e**) were well tolerated. Furthermore, substrates with *meta*-, *para*- and multiple substitu-

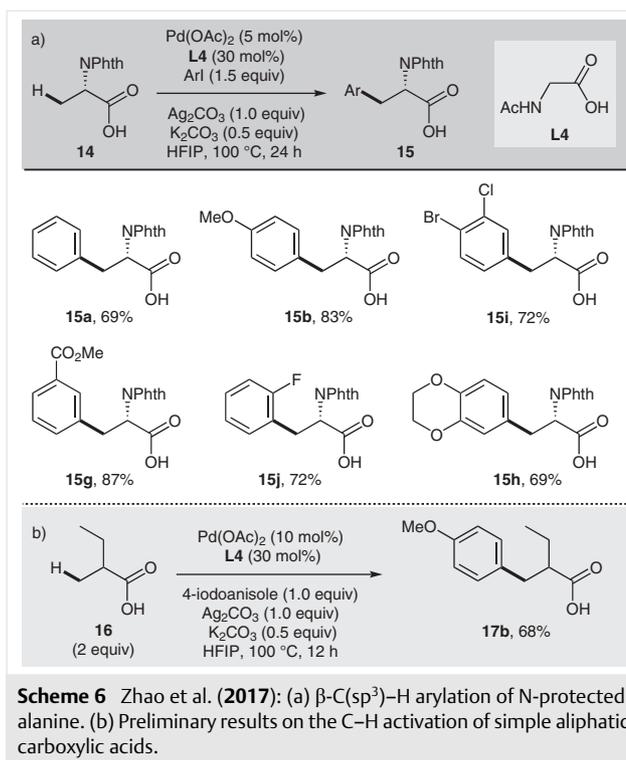


Scheme 5 Yu et al. (2017): (a) β -C(sp³)-H arylation of N-protected alanine. (b) Preliminary results on the C-H activation of simple aliphatic carboxylic acids.

ents (**15f–h**) were also compatible with this protocol. Slightly decreased yields were observed for very electron-poor aryl iodide coupling partners (**15g**). These results correlate with the fact that the rate of the oxidative addition is usually higher for aryl iodides bearing electron-donating groups.³⁰ Considering that a comparably unstable intermediate is formed in the key C-H activation step, it seems reasonable that this intermediate would be trapped quickly by a sufficiently reactive reagent to avoid decomposition. Although this study was focused on the C-H arylation of amino acid derivatives, the authors also reported on the performance of their catalytic system with simple aliphatic acids. For example, 2-methylbutanoic acid (**16**) could be arylated to give product **17a** in moderate yield (Scheme 5, b).

Contemporarily, the group of Zhao studied the same transformation and found that simple N-protected amino acids were also effective ligands for this transformation (Scheme 6, a).³¹

It has been proposed that these ligands aid the C-H activation step, which proceeds via a concerted metalation-deprotonation (CMD) pathway, by acting as an internal base that takes up the proton generated during the C-H activation.³² Zhao et al.³¹ investigated the effect of various nitrogen protecting groups and identified *N*-acetylglycine (**L4**) as the most efficient ligand. The same group demonstrated



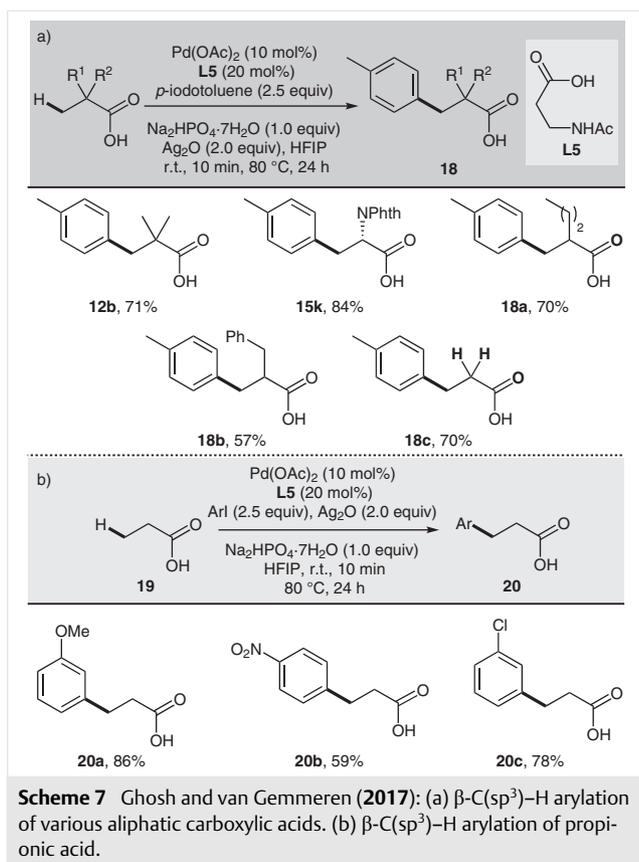
Scheme 6 Zhao et al. (2017): (a) β -C(sp³)-H arylation of N-protected alanine. (b) Preliminary results on the C-H activation of simple aliphatic carboxylic acids.

a broad aryl iodide scope, generally obtaining comparable yields to those reported in the study by Yu et al.²⁸ Besides the phenyl group (**15a**) and electron-rich aryl groups (**15b**), the protocol was found to tolerate halide substituents (**15i,j**) and varied substitution patterns (**15g,h**).

For the even more challenging simple aliphatic acids as substrates, the same authors obtained reasonable yields by changing from an acid-limited to an aryl-iodide-limited reaction. Under these conditions, the authors reported that 2-methylbutanoic acid (**16**) could be converted into the arylated product **17b** in 68% yield (Scheme 6, b). While this change of reaction conditions provides a solution for cheap and abundant acids as substrates, the excess of acid required is an obvious hindrance when considering the application of such a protocol on more sophisticated starting materials.

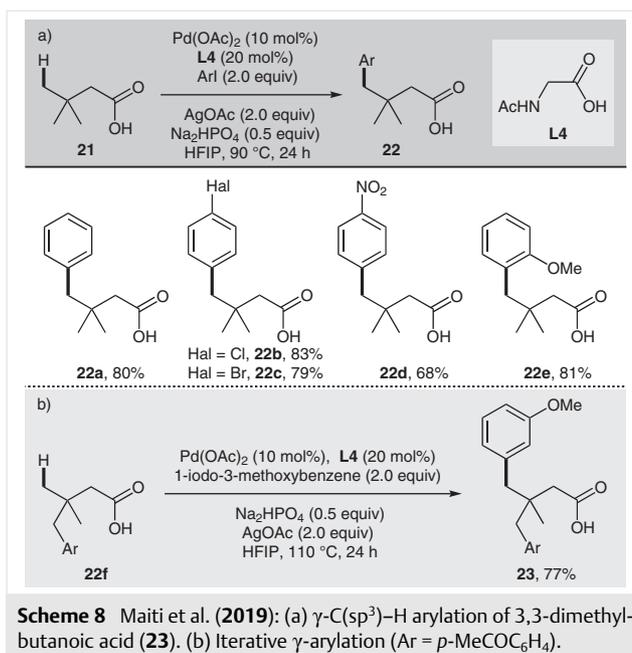
In parallel to the abovementioned studies, Ghosh and van Gemmeren studied the arylation of simple α -non-quaternary carboxylic acids (Scheme 7).³³

The authors identified *N*-acetyl- β -alanine (**L5**) as the ligand of choice for this type of substrate. Furthermore, silver(I) oxide was found to deliver substantially better results than the more typically used acetate or carbonate analogs, likely due to the presence of fewer anions competing for the coordination to palladium, leading to an increased concentration of the required Pd-substrate complex. The improved performance of **L5** compared to *N*-acetyl- α -amino acids is presumably related to the fact that it forms a six-membered rather than five-membered chelate complex.¹⁸ Under their



optimized reaction conditions, the authors obtained β -arylated products derived from a variety of acid substrates ranging from the pivalic acid derivative **12b** and the phenyl alanine derivative **15k** to a series of α -non quaternary carboxylic acids **18a–c**, all of which were formed in good yields using the acid as the limiting reagent. Importantly, even the entropically challenging substrate propionic acid (**19**) could be handled using this catalytic system and was chosen by the authors to demonstrate the aryl iodide scope of the reaction. A broad range of aryl iodides with varied electronic properties could be employed, for example giving access to products **20a–c**.

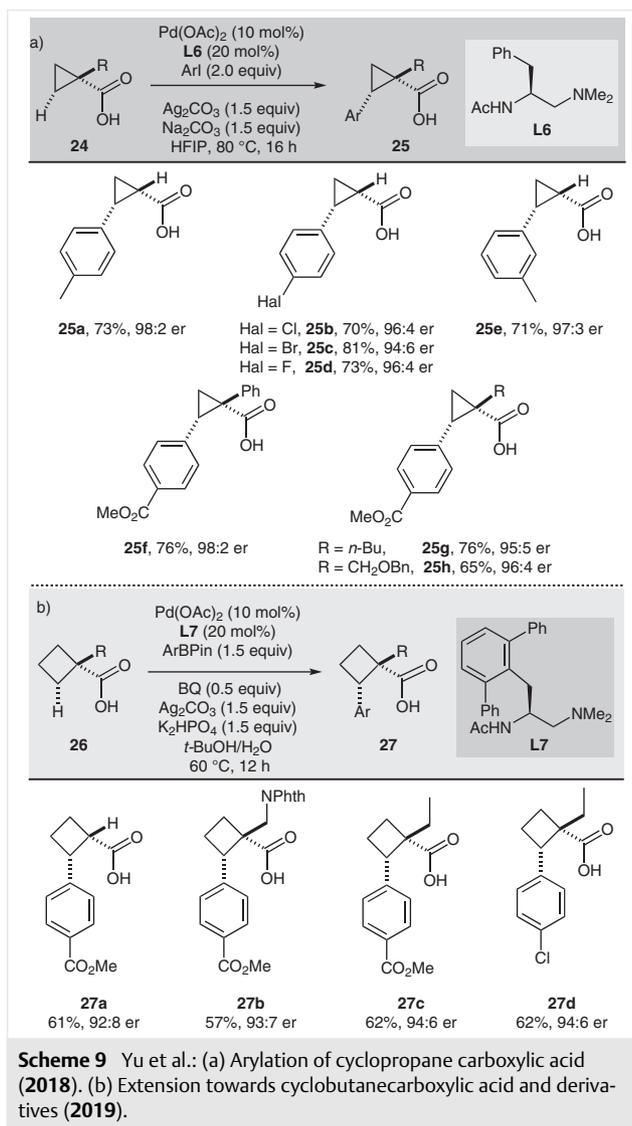
In 2019, Maiti et al. tackled one of the major challenges in the field, by aiming to activate more distal C–H bonds relative to the carboxylic acid directing group. In this study, the authors extended the C–H arylation of aliphatic carboxylic acids to the γ -C–H bond using a catalytic system based on palladium bearing *N*-acetylglycine (**L4**) as the ligand (Scheme 8).³⁴ With this catalytic system, 3,3-dimethylbutanoic acid (**21**) could be functionalized with a variety of aryl iodides. Interestingly, besides the simple phenyl group (**22a**), halide substituents (**22b,c**) and electron-withdrawing groups (**22d**), this protocol also tolerates *ortho*-substituents on the aryl iodide reagent (**22e**).



Moreover, the same authors have demonstrated an iterative diarylation.³⁴ For example, using acid **22f**, obtained from **21** using the standard protocol, in a second arylation under slightly modified reaction conditions gave the doubly functionalized product **23** (Scheme 8, b). Finally, the authors used more complex aryl iodides, derived from natural products and bioactive molecules, to obtain the corresponding arylated products in good yields. Unfortunately, the reaction remains limited by a very narrow acid scope. All substrates used are β -quaternary carboxylic acids, which favor the desired reaction through a Thorpe–Ingold effect and in which no competing C–H activation can occur at the β -position.

In 2018, Yu et al. reported the enantioselective arylation of cyclopropanecarboxylic acids **24** (Scheme 9, a).³⁵ In this reaction two chiral centers are formed through a desymmetrization process, in which the two previously identical methylene groups are differentiated into methylene and methine groups. This desymmetrization strategy has previously been used as a powerful approach in enantioselective C–H functionalization reactions of analogous substrates bearing other directing groups.³⁶ The authors found that for this transformation *N,N*-donor ligands with one tertiary amine and one *N*-acetyl group, as in ligand **L6**, were most effective with respect to yield and stereoselection. Various substitution patterns on the backbone of the ligands were studied and it was shown that a benzyl residue next to the *N*-acyl group delivered the highest enantioselectivity. Methyl groups were found to be best at the tertiary amine. The authors showed a broad aryl iodide scope, including arenes bearing electron-donating groups (**25a,e**), halides (**25b–d**), and electron-withdrawing groups (**25f**). Concern-

ing the acid scope, the authors were able to use various α -substituted cyclopropanecarboxylic acids (**25f–h**). In all cases, this reaction was highly enantioselective with enantiomeric ratios typically at or above 95:5. Furthermore, the authors demonstrated that heteroaryl iodides could be used in this transformation.



In 2019, the same group extended their methodology to the enantioselective C–H arylation of cyclobutanecarboxylic acid and derivatives thereof (Scheme 9, b).³⁷ Notably, in this transformation, the authors used arylboronic acid pinacol esters as arylating agents and the solvent was switched to a *tert*-butanol/water mixture. In agreement with these changes, a Pd(0)/Pd(II) catalytic cycle was proposed. As ligands, both *N*-protected amino acid derived ligands and *N,N*-donor ligands such as **L7** were shown to be active catalysts. In contrast to the desymmetrization of cyclopropanecarboxylic acids, the optimum ligands were in this case

found to require a very bulky substituent on the side chain. In addition to the arylation of cyclobutanecarboxylic acid (**27a**), the authors demonstrated a broad range of α -substituted cyclobutanecarboxylic acid derivatives (**27b–d**). By using the corresponding vinyl boronate species under slightly modified reaction conditions, the scope of this reaction could also be extended to an analogous enantioselective vinylation. It should be noted that the C–H activation of methylene C–H bonds is generally considered to be more challenging than of analogous methyl C–H bonds, however, for cyclobutane- and cyclopropanecarboxylic acids the C–H activation step is strongly facilitated by ring strain, the π -character of the C–C bond, and the reduced activation entropy due to the pre-alignment of the acid moiety and the bond to be activated.³⁸

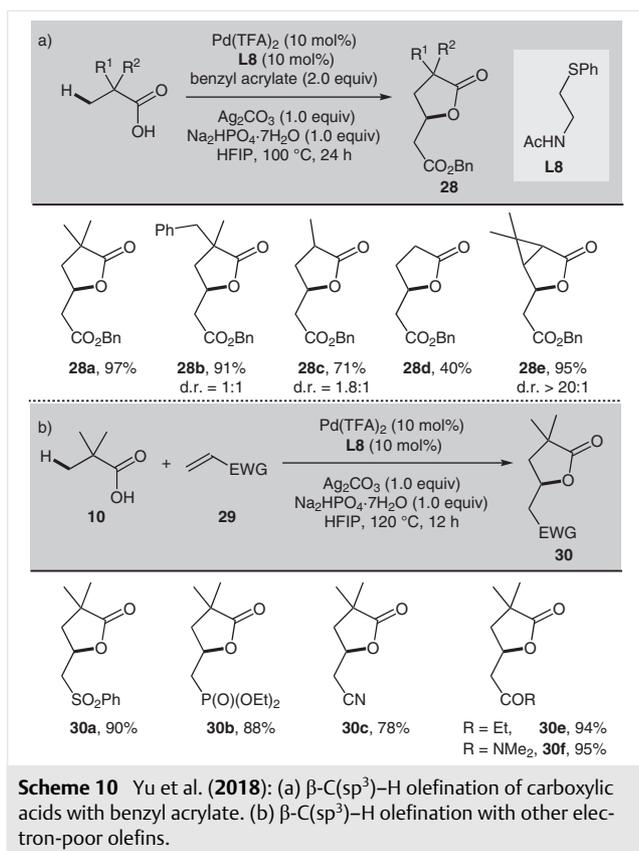
6 The Direct C–H Olefination of Aliphatic Carboxylic Acids

In 2018, Yu et al. reported the first extension of the catalysts presented above to a transformation other than arylation, i.e., the direct olefination of carboxylic acids.³⁹ After extensive ligand optimization, the authors found that *N*-acyl-aminoethyl phenyl thioether (**L8**), which acts as an *N,S*-bidentate ligand, is superior to the typically used amino acid derived *N,O*-bidentate ligands. This shows that depending on the reaction at hand, fine-tuning of the ligand properties is very important. The reaction proceeds via a C–H olefination followed by an intramolecular 1,4-addition to give γ -lactones **28** (Scheme 10).

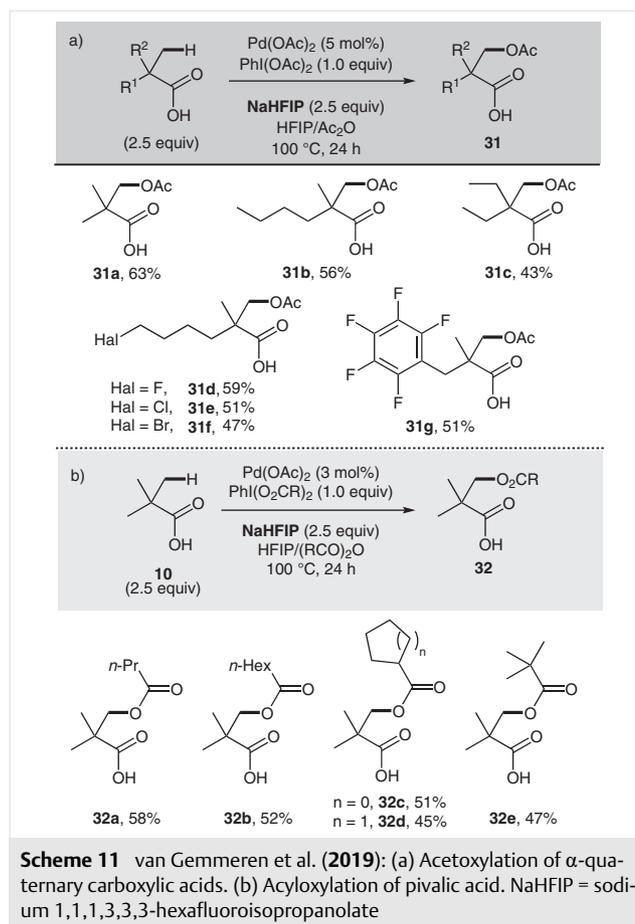
Using benzyl acrylate as their standard olefin the Yu's group studied the carboxylic acid scope (Scheme 10, a). Quaternary carboxylic acids gave the best results in this transformation and the olefinated products **28a,b** could be isolated in nearly quantitative yields. While α -tertiary acids still provided good results (**28c**), a decreased efficiency was observed with propionic acid and the olefinated product **28d** was obtained in 40% yield. Besides acrylates, various other olefins bearing strong electron-withdrawing groups could be used, giving products **30a–f** in good to excellent yields (Scheme 10, b).

7 The Direct C–H Acetoxylation of Aliphatic Carboxylic Acids

In 2019, van Gemmeren et al. reported the first intermolecular C–O bond formation based on the direct C–H activation of aliphatic carboxylic acids.⁴⁰ The authors used (diacetoxyiodo)benzene as the oxidant and limiting reagent, an excess of the acid component being required for satisfactory yields. The reaction proceeds in a mixture of acetic anhydride and HFIP as the solvent to give β -acetoxy-ated carboxylic acids **31** (Scheme 11).



During the development of the reaction conditions, the authors studied the effect of the base additive required for the in situ generation of carboxylate anions and found that many of the concomitantly introduced anions were detrimental to the reaction outcome. The alkali salts typically employed in C–H activation reactions of carboxylic acids gave substantially worse results than a control experiment with preformed sodium carboxylate. The authors found that using the sodium salt of the solvent HFIP as a traceless base restored the desired reactivity. For various α -quaternary carboxylic acids, the corresponding acetoxyated products could be obtained in moderate to good yields (Scheme 11, a). Besides different alkyl substitution patterns (**31a–c**), halide substituents (**31d–f**) and electron-poor aryl groups (**31g**) were tolerated in this transformation. Furthermore, the authors have extended their protocol to analogous acyloxylation reactions by changing the oxidant and the anhydride (Scheme 11, b). Using pivalic acid (**10**) as the substrate, the authors demonstrated that various ester residues could be introduced in good yields (**32a–e**).



8 Summary

While the C–H activation of aliphatic carboxylic acids is still underdeveloped compared to reactions with stronger directing groups, research towards the use of the carboxylic acid functionality as a native directing group has intensified in recent years. Reports have shown that the weak directing group ability of the carboxylic acid moiety can be addressed by employing tailor-made ligands and reaction conditions. The extension of these methods to a broad range of electrophiles, which have already been used with strong directing groups, now seems to be within reach. However, the key C–H activation step is still highly challenging, and it should be noted that a detailed mechanistic understanding of the key factors influencing these transformations is not yet available. Mechanistic studies on such reactions are highly challenging, due to, amongst other reasons: (a) the heterogeneity of typical reaction mixtures, (b) the presence of silver salts, which might be involved in the C–H activation step, (c) complex equilibria between monomeric and higher-aggregated palladium complexes, (d) various coordination modes between catalyst and sub-

strate, as well as catalyst and ligands, and (e) the use of highly polar solvents with the potential to form H-bonds that influence the reaction outcome. Nevertheless, it can be expected that an increased mechanistic understanding will be instrumental in future developments such as extending these transformations to γ -C–H bonds or β -methylene C–H bonds in unbiased substrates. Addressing these substrate classes will likely require the systematic development of novel ligand classes and reaction conditions. Additionally, many current protocols employ stoichiometric amounts of silver salts and specialized solvents, which pose substantial hurdles to the scalability of these reactions. Thus, even for those reactions that have already been enabled, further research will be required towards second generation protocols before a widespread acceptance by the synthetic community, or even large-scale applications, can be expected.

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