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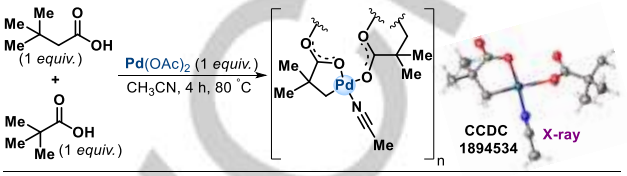
Ligand-Enabled Pd(II)-Catalyzed Iterative γ-C(sp^3)–H Arylation of Free Aliphatic Acid

Pravas Dolui, [§,†] Jayabrata Das, [§,†] Hediyala B. Chandrashekar, [†] S. S. Anjana, [†] Debabrata Maiti*[†]

Abstract: C–H Functionalization of aliphatic carboxylic acids without attaching exogenous auxiliary has been so far limited at the proximal β-position. In this work, we demonstrate a ligand enabled palladium catalyzed first regioselective distal γ-C(sp^3)–H functionalization of aliphatic carboxylic acid without incorporating an exogenous directing group. Aryl iodides containing versatile functional groups including complex organic molecules are well tolerated with good to excellent yields during the γ-C(sp^3)–H arylation reaction. Interestingly, weak coordination of carboxylate group can be further extended for sequential hetero di-arylation. Application of the protocol has been showcased by synthesizing substituted α-tetralone. Mechanistic investigations have been carried out to shed light on the reaction pathway.

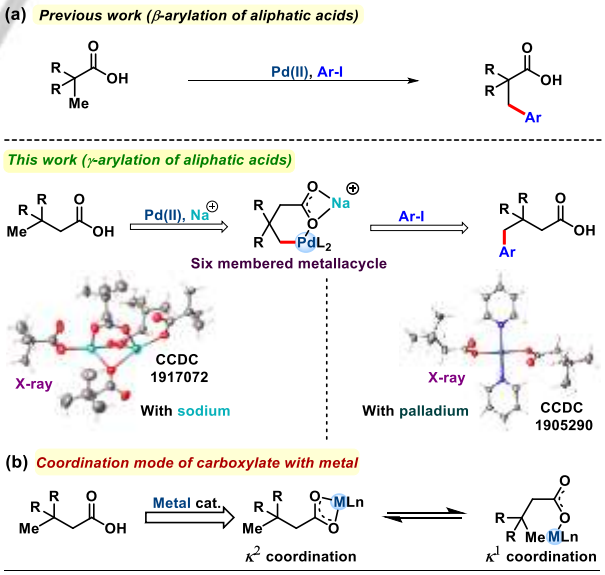
Aliphatic carboxylic acids are versatile synthons in organic synthesis due to their structural diversity and wide availability. Their ubiquitous presence in many natural products as well as in pharmaceutically relevant compounds shows the importance of such molecules. Keeping in mind the diverse range of functions these acids performs in synthetic chemistry,[1] biological processes,[1c] and in rhizosphere ecology,[1d] further transformation of such acids becomes extremely valuable to increase their utility. Over the last decade, directed C–H functionalization using a covalently attached exogenous directing group has contributed significantly for aliphatic systems.[2] Various functionalization such as arylation, oxygenation, iodination, alkylation, silylation, thioarylation, olefination, amidation, carbonylation reactions have been developed *via* attaching a template to the acid substrate covalently.[3] However, this strategy bears certain limitations of using additional steps for pre-installation and removal of directing group post functionalization, as they are not an essential moiety in the target molecules. Exploring the potential of free carboxylic acid without an exogenous directing group is more desirable.[4] Till date, functionalization of free carboxylic acid has been mostly *restricted up to proximal β-position* due to preferred formation of five membered metallacyale.[5]

A crystal structure (CCDC1894534, Scheme 1) we obtained during a competition experiment between pivalic acid and ^{t}butyl acetic acid is quite informative in this regard.



Scheme 1. Our Experimental Evidence in Favour of Five Membered Metallacycle over Six Membered Metallacycle

Preference for a five-membered metallacycle formation over a six-membered one is clearly overwhelming. To attain the functionalization at the distal γ-position regioselectively, a more convenient strategy has to be hypothesized with the help of a suitable ligand since it requires the formation of thermodynamically less favored six membered metallacycle involving weakly coordinating carboxylate group. A free carboxylic acid can coordinate with the transition metal either in κ^2 or κ^1 mode which are in equilibrium (Scheme 2). Of these two, only κ^1 coordination mode, where metal is bound with a single oxygen lone pair may provide a conformation with suitable alignment between the metal center and the C–H bond to be activated. Whereas in κ^2 coordination mode, the active metal catalyst may become inaccessible to further activate γ-C(sp^3)–H bond. The equilibrium thus can be switched towards κ^1 mode by using electropositive alkali metal.[5a] Under such conditions, transition metal possessing a vacant coordination site is expected to facilitate the activation of distal γ-C(sp^3)–H bond *via* formation of a six membered metallacycle.



Scheme 2. C(sp^3)–H Arylation of Aliphatic Carboxylic Acid

Herein, we demonstrate the *first example of regioselective γ-C(sp^3)–H functionalization of free aliphatic acids* (Scheme 2). To surmount the challenge of forming thermodynamically less stable

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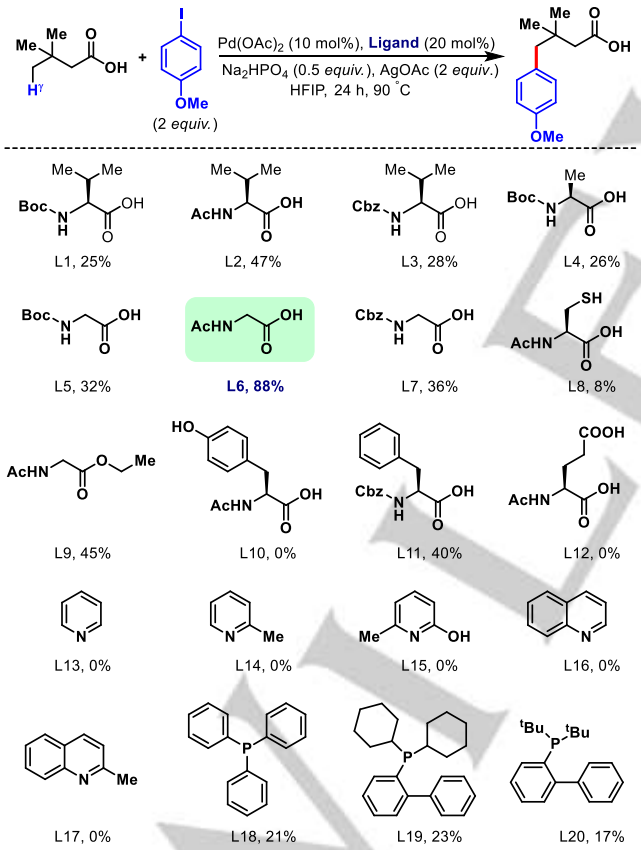
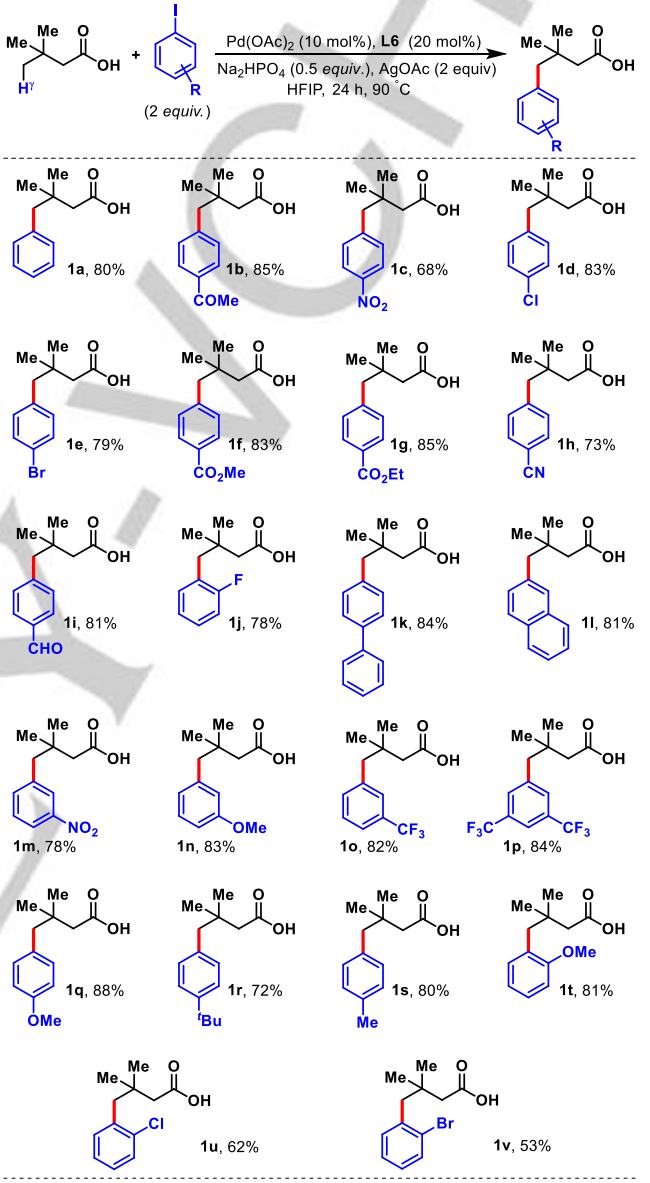
six-membered metallacycle necessary for γ-C(sp^3)–H activation, we initiated γ-arylation of ^{t}butyl acetic acid with 4-iodo anisole as an arylating partner. Interestingly, despite no six membered metallacycle formation during competition with pivalic acid, we found 25% desired γ-arylated product using $Pd(OAc)_2$ as a catalyst and Boc-Val-OH (**L1**) as a ligand in presence of an alkali metal base. However, homo-coupling of 4-iodo anisole was found to form as the major side product in the reaction. Pyridine, quinoline and phosphine based ligands were found to be ineffective. In this context, *N*-Ac-Gly-OH (**L6**, Scheme 3) turned out to be the most effective ligand for the present transformation. Carboxylate group of the carboxylic acid in combination with a bidentate mono-protected amino acid ligand help in γ-C(sp^3)–H activation.[5b] Role of base is thought to be crucial as it facilitates to switch the equilibrium from κ^2 to κ^1 mode and thus palladium have an opportunity to activate the distal γ-C(sp^3)–H bond. Crystal structures obtained with sodium (CCDC 1917072, Scheme 2a) and palladium (CCDC 1905290, Scheme 2a) in this regard are quite informative. Among various bases, Na_2HPO_4 was found to enhance the yield of the γ-arylation product significantly. Additives such as 1-AdCO_2H, I_2, Cu and Ca salts failed to improve the yield of the desired arylated product. After extensive optimization with various reaction parameters it was observed that the use of $Pd(OAc)_2$ (10 mol%), *N*-Ac-Gly-OH (**L6**, 20 mol%), AgOAc (2 *equiv*.), and Na_2HPO_4 (0.5 *equiv.)* in HFIP solvent at 90 °C provided significant formation of γ-arylated product.



Scheme 3. Effect of Ligand on γ-C(sp^3)–H Arylation of Aliphatic Carboxylic Acid

With optimum condition, we first diversified the scope of aryl iodides (Scheme 4). Aryl partners containing electron withdrawing substituents such as acetyl, nitro, chloro, bromo, and fluoro gave good to excellent yield of monoarylated product (**1b**-**1n**). It was intriguing to find aryl iodides containing functional groups like nitrile, aldehyde and ester underwent the γ-arylation reaction smoothly with synthetically useful yields (**1f**-**1i**). Presence of electron withdrawing trifluoromethyl moiety (**1o** and **1p**) did not affect the efficiency of the protocol. Electron releasing groups like methyl, methoxy and bulkier *tertiary* butyl substituted aryl partner were well tolerated under the standard condition (**1q**-**1t**).



Scheme 4. Ligand-Enabled Pd(II) Catalyzed γ-C(sp^3)–H Arylation of Free Carboxylic Acid with Various Aryl Iodides

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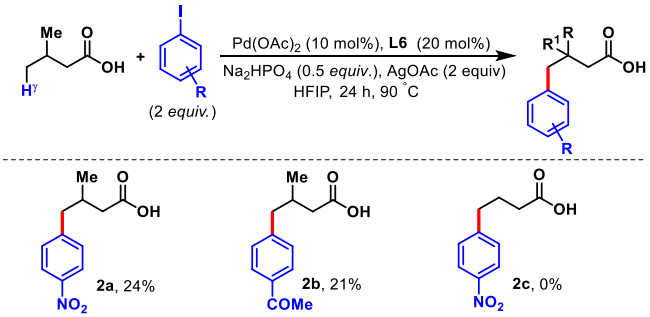
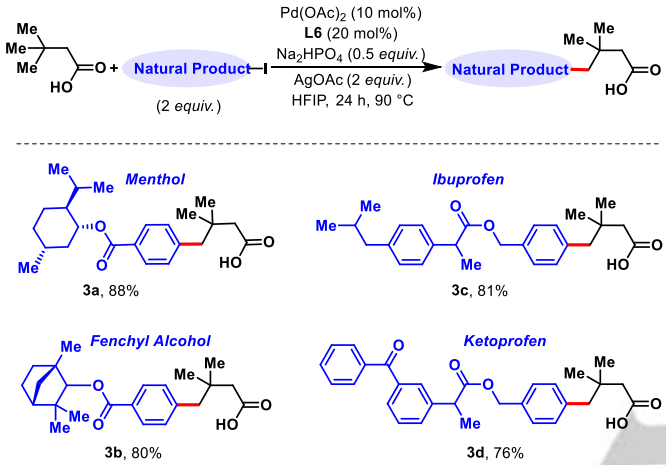


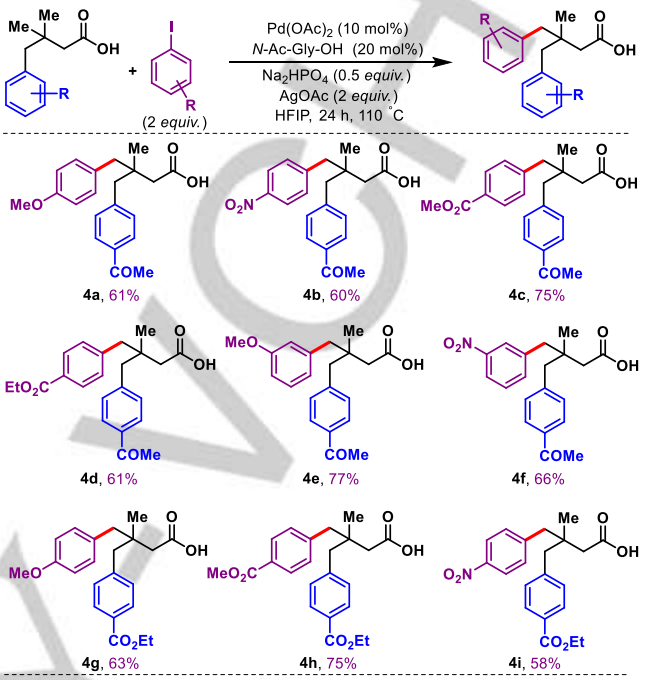
Scheme 5. Scope of various acids



Scheme 6. Complex Organic Molecules Containing Aryl Iodides as Coupling Partner in γ-C(sp^3)–H Arylation of Carboxylic Acid

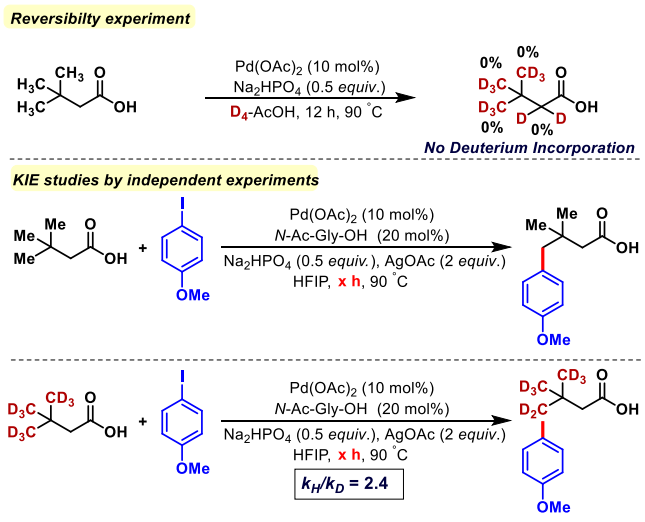
Interestingly, aryl iodides having *ortho*-substitutents such as methoxy, fluoro, chloro, and bromo underwent the reaction well without much compromise in yields (**1j**, **and 1t-1v**). It is worth mentioning that bulkier and electron deficient aryl partners such as biphenyl (**1k**) and naphthyl (**1l**) also performed well under the reaction condition. A range of aryl iodides derived from different complex organic molecules *viz*. menthol and fenchyl alcohol could be effectively utilized in the reaction (Scheme 6, **3a** and **3b**). Also the derivatives of drug molecules, ibuprofen and ketoprofen were successfully incorporated at γ-position of aliphatic acid (**3c** and **3d**). Compatibility of such natural products shows the robustness of the present γ-arylation methodology. To show the compatibility of the protocol, we varied aliphatic free carboxylic acids containing γ-C(sp^3)–H bonds. Expectedly, isovaleric acid was found to be a challenging substrate. Nevertheless, it was found to produce the desired γ-arylated product under the optimized reaction condition, albeit in relatively low yield (**2a**-**2b**). Despite our best effort, butyric acid failed to generate arylated product under the standard reaction condition.

Polyarylated products are of utmost importance in functional organic materials and material chemistry due to their exceptional physical properties.[6] These structures are also a frequent constituent of natural products and pharmaceuticals. Having realized the importance of such compounds, we wished to arylate the acid substrate sequentially. To the best of our knowledge, there are no reports of sequential arylation of free carboxylic acids or carboxamide at distal γ-position even with covalently attached directing group approach.[7] Interestingly, we found the present protocol with weakly coordinating carboxylate group was able to activate γ-C(sp^3)–H bonds sequentially. Initial attempt to get sequential diarylation was unsuccessful at 90 °C temperature. Diarylated product was obtained by slight increase in temperature to 110 °C (*see supporting information*). Aryl iodides containing electron withdrawing group as well as electron releasing group were well tolerated to give moderate to good yield of diarylated product (Scheme 7, **4a**-**4i**).



Scheme 7. Ligand-Enabled Pd(II) Catalyzed Diarylation of γ-C(sp^3)–H Bond of Free Carboxylic Acid

To gain mechanistic insight of the present transformation, we carried out several kinetic experiments (Scheme 8). Reversibility studies involving C–H activation step with ^{t}butyl acetic acid in presence of deuterated acetic acid showed no deuterium scrambling in the recovered substrate. This observation indicates irreversible nature of C–H activation step. Order determination study both w.r.t. substrate and aryl iodide were performed. The reaction follows first order kinetics w.r.t. aliphatic acid and fractional order w.r.t. aryl iodide. These result further support C–H activation as the rate determining step of the reaction. A first order rate dependency was obtained with respect to catalyst *via* a



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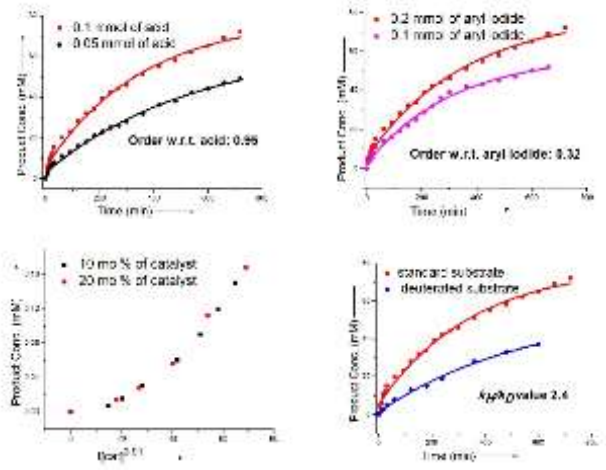
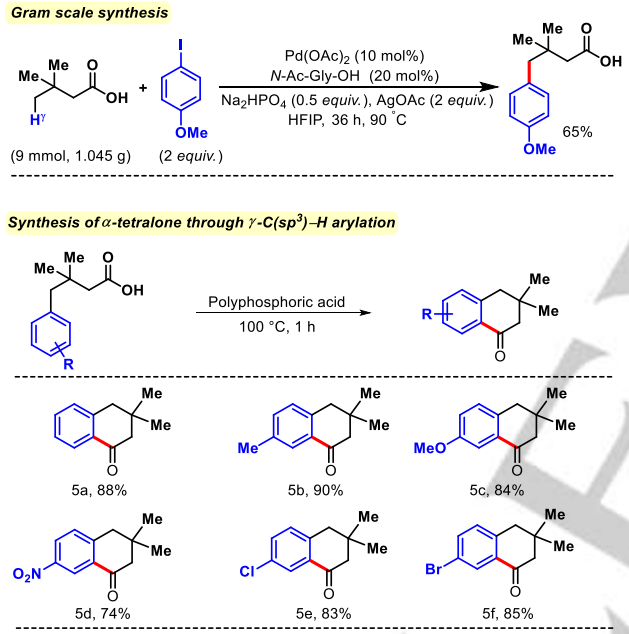


Scheme 8. Kinetic Studies to Provide Mechanistic Insights

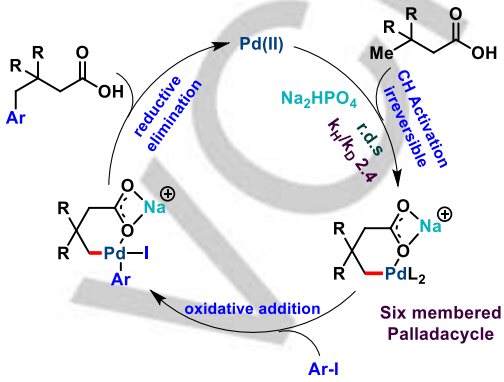


Scheme 9. Synthetic Applications of γ-C(sp^3)–H Arylation

graphical normalized time scale method (*see supporting information*).[8] Further, kinetic isotope study showed k_H/k_D value to be 2.4, which is consistent with C–H activation being the rate determining step of the overall transformation.

The practicality of the developed protocol has been demonstrated by scaling up the reaction up to gram scale. To further exhibit the application of the arylation reaction, we have utilized the γ-arylated acids as the starting material to form α-tetralone, which is prevalent in many natural products and biologically active compounds.[9] The intramolecular cyclization of arylated acid has been achieved by heating it in polyphosphoric acid for one hour. Unsubstituted arene as well as arene containing different substitutions like methoxy, methyl, bromo, chloro, and nitro have been cyclized to form substituted α-tetralone (Scheme 9, **5a-5f**), which can act as a building block to further synthesize complex molecules.

We propose a Pd(II/IV) catalytic cycle (Scheme 10), where aliphatic acid initially coordinate with metal center. Further, γ-C(sp^3)–H bond activation takes place to form a six membered metallacycle with the assistance of an alkali metal ion. Oxidative addition of the aryl iodide to the metal center results a Pd(IV) intermediate, which upon reductive elimination generates the γ-arylated product regioselectively. However, there is also a finite possibility of Pd(II)/(III) cycle to be operative in absence of strong donor ligands.[10]



Scheme 10. Plausible Mechanism of γ-C(sp^3)–H Arylation of Free Carboxylic Acid

In conclusion, for the first time, a method for γ-C(sp^3)–H functionalization of free aliphatic acids without installing exogenous directing group has been developed. The protocol exhibits high levels of monoselectivity for ligand-enabled palladium catalyzed distal γ-arylation. This methodology is compatible with a variety of aryl iodides including complex organic molecule containing aryl partners. Sequential arylation has been promoted by utilizing weakly coordinating carboxylate group. Iterative arylation introducing varied aryl groups at other γ-positions will tune the properties of polyarylated acids for use in functional material. Application of the protocol has been showcased by converting the arylated acids into α-tetralone. Additionally, we have also investigated the reaction mechanism to get insights into the the γ-C(sp^3)–H arylation of free carboxylic acids. Efforts to further understand the mechanism and application of the γ-arylation protocol with free carboxylic acids are currently underway in our laboratory.

Acknowledgements

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Keywords: • γ-arylation • natural product incorporation • iterative arylation • α-tetralone synthesis • mechanistic studies

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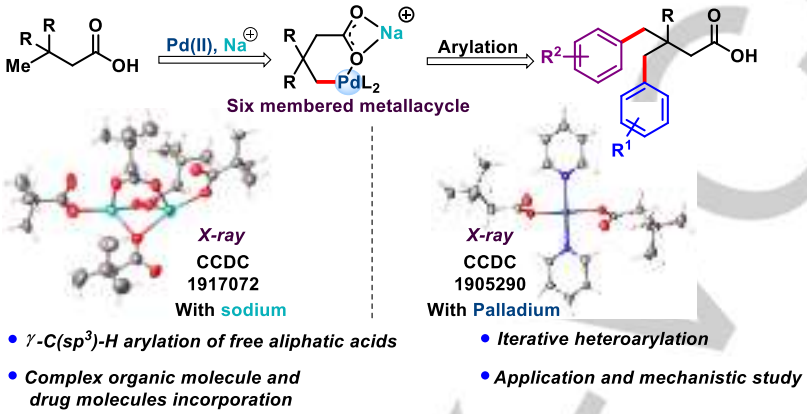
A ligand enabled palladium catalyzed protocol has been developed for regioselective γ-C(sp^3)–H functionalization of aliphatic carboxylic acid without incorporating any exogenous directing group for the first time. The multi-faceted aspects of this transformation have been illustrated through: (i) synthesis of various γ-C(sp^3)–H arylated acids (ii) incorporation of complex organic molecules and drug molecules in the acid. (iii) iterative heteroarylation and (iv) synthesis of substituted α-tetralone from arylated acids.



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