A Prodigious Behavior of Cycloalkyl Carboxylic Acid to Access 2D Space from 3D Space *via* Multifold C–H Activation

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ABSTRACT: The dehydrogenation chemistry has long prevailed in the paradigm of organic synthesis. More common with carbonyl compounds, many classical reactions evolved around it. The emergence of the transition metal catalysis redefined the dehydrogenation chemistry with strategies such as transfer dehydrogenation, C–H activation and single electron transfer processes. These strategies have been extended to enable multiple dehydrogenations that had led to aromatization depending on the substrate class. On a contrary, dehydrogenative transformations of aliphatic carboxylic acids offers substantial challenges. Engineered ligands in conjunction with metal catalysis can effectuate the dehydrogenation in carboxylic acids initiated by C–H activation with subsequent functionalization or vice versa; however, the reactivity and product formation vary with the substrate structure. Herein, we have developed a catalytic system that enables cyclohexane carboxylic acid to undergo multifold C–H activation to furnish olefinated arenes implying 3D to 2D conversion and thus, completely bypassing the lactone formation, showcasing a display of the change in reactivity of aliphatic carboxylic acids. The reaction occurs *via* a tandem dehydrogenation-olefination-decarboxylation-aromatization sequence which has been proved by various control experiments and isolation of key intermediates. For cyclopentane carboxylic acid which are reluctant to aromatization, the same catalytic system allows controlled dehydrogenation to provide difunctionalized cyclopentene derivatives *via* a tandem dehydrogenation-olefination-decarboxylation-allylic acyloxylation reaction sequence. The transformation is amenable to diversify carboxylic acids to be transformed to molecules of new identity having applications in different fields thus underscoring the importance.

1. INTRODUCTION

The unsaturation in an organic molecule creates multifaceted opportunities to diversify it in a desirable manner. The versatile downstream applications led to the genre of dehydrogenation/unsaturation chemistry flourish over the entire span of organic synthesis. In particular with the carbonyl compounds, the traditional pathway to generate the unsaturation intramolecularly had been predominated by the enolate or enamine chemistry (Scheme 1a).[1] Later, the paradigm of dehydrogenation reaction shifted to newer modes with the classical enolate chemistry being superseded by transition metal catalysis. In this regard, the C–H activation had been a prevailing pathway to initiate the dehydrogenation either through transfer hydrogenation process[2] or β-hydride elimination route.[3] There are also precedences of radical involvement in dehydrogenation processes effectuated by the merger of metal catalysis with photocatalysis or electrocatalysis.[4] While ketones are favorable choices as substrates for dehydrogenation, the aliphatic carboxylic acids in its native form offer more challenges to adopt the similar reactivity. The aliphatic carboxylic acid in its masked enediolates form are amenable to be oxidized to α,β-unsaturated acid by Pd(II) complexes.[5] Also Pd(II) in conjunction with pyridine-pyridone based ligand enables divergent dehydrogenation of carboxylic acids driven by the β-methylene C–H activation. The ligand control helps in inhibiting the over-reaction of the dehydrogenated product by subsequent C–H activation.[6]

The above discussed protocols are relevant for the generation of single unsaturation, however, there are provisions for generating multiple unsaturation in a molecule through subsequent dehydrogenation. This phenomenon is more common with the cyclic ketones as precursors in which a relayed dehydrogenation initiated by C–H activation or through single electron transfer process leads to an aromatic molecule in the form of phenol, anilines or ethers (Scheme 1b).[7] Such dehydrogenative aromatization processes are beneficial in providing certain substituted arenes which are otherwise difficult to access *via* traditional routes. In a very recent report, it has been observed that Pd/ligand combination can also enable the conjugated diene formation in linear aliphatic carboxylic acids.[8] While these methodology developments entail about the creation of double bonds only, a tandem dehydrogenation-functionalization or vice-versa is another facet of C–H activation reactions that are elusive in nature but affords products of high value. This has been witnessed with aliphatic carboxylic acids which upon reaction with alkynyl bromides gives γ-alkylidene butenolides.[6] Further, with α-substituted carboxylic acids, a tandem dehydrogenation−olefination−lactonization affords β-alkylidene-γ-lactones (Scheme 1c).[9] In a recently developed protocol from our group, we have observed a very unique reactivity of cycloalkyl acetic acid having a β-substituent. Such class of substrate in presence of Pd/ligand combination presented a unique reactivity of overriding the usual reactivity mode to form bicyclic lactones bearing an allylic double bond. The same substrate in presence of olefin and allyl alcohols leads to an all-carbon quaternary center at the ring junction (Scheme 1c).[10] Hence a slight change in the substrate class led to different classes of products. Further to our efforts in the area of native aliphatic carboxylic acid diversification, we endeavored to examine the reactivity of cycloalkyl carboxylic acids with olefin under a very similar conditions to that applied for cycloalkyl acetic acid. The cyclohexyl carboxylic acid exhibited a unique reactivity to be transformed to olefinated arenes (Scheme 1d). It may be referred here that with cyclohexyl carboxylic acid bearing an α-substituent a lactone product was observed along with dehydrogenation at the β,γ position.[9] Removing the α-substituent confers a new identity to cyclohexyl carboxylic acid by a tandem dehydrogenation-olefination-

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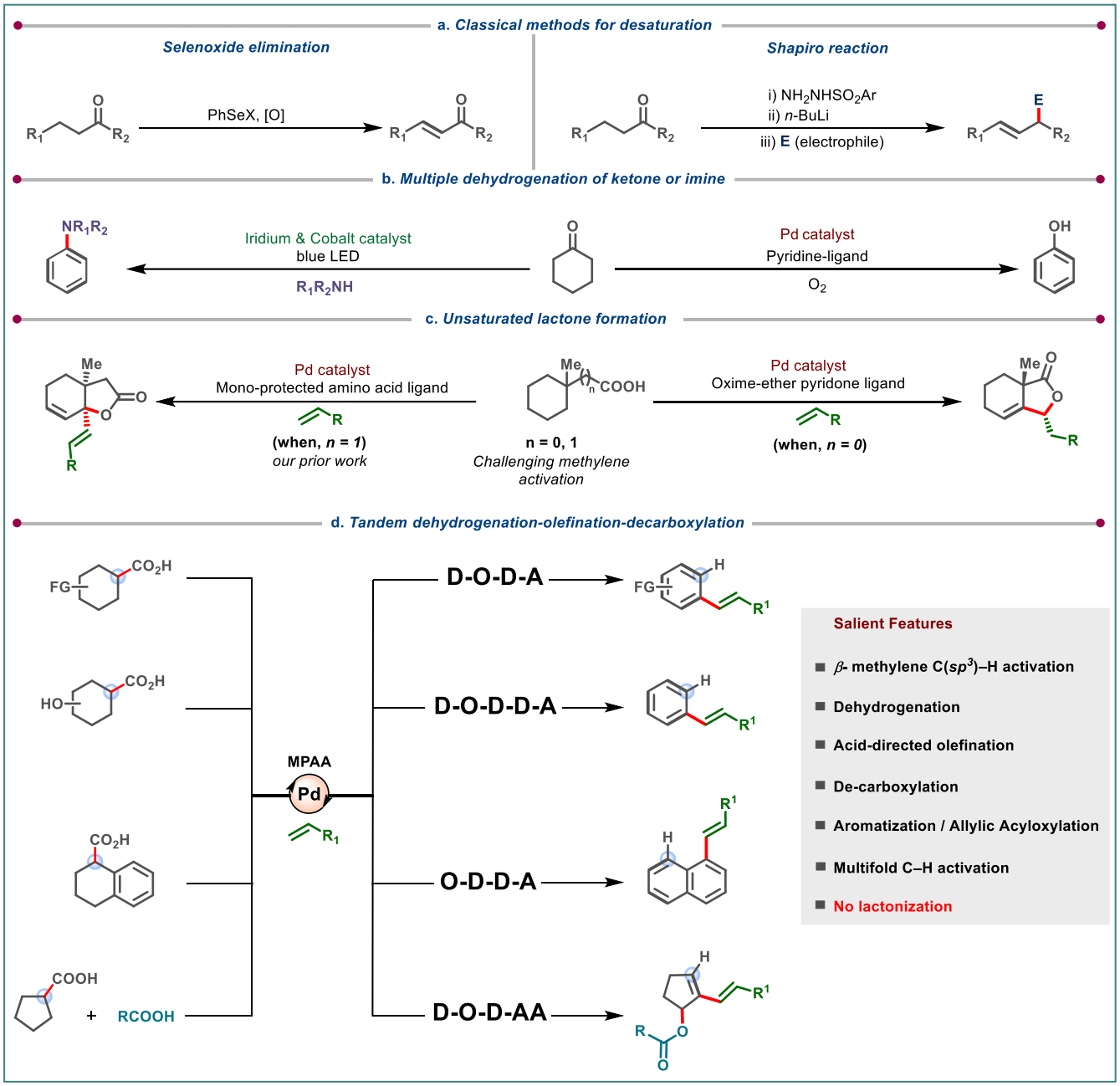
Scheme 1. Evolution and Advancements in Dehydrogenation Strategies of Organic Molecules



a. Traditional approaches to achieve unsaturation. **b.** Strategies towards metal catalyzed dehydrogenation in cyclohexanones leading to aromatization. **c.** Trends of reactivity in homologous cyclic acids. **d. This work:** One pot dehydrogenation and decarboxylative functionalization *via* multifold C–H activation (D-O-D-A: dehydrogenation-olefination-decarboxylation-aromatization, D-O-D-D-A: dehydrogenation-olefination-decarboxylation-dehydroxylation-aromatization, O-D-D-A: olefination-dehydrogenation-decarboxylation-aromatization, D-O-D-AA: dehydrogenation-olefination-decarboxylation-allylic acyloxylation)

decarboxylation-aromatization (D-O-D-A) sequence. Surprisingly, with smaller alkyl rings, where aromatization is not possible, the reactions led to a difunctionalized cycloalkenes (Scheme 1d). The reaction sequence for such substrates follows dehydrogenation-olefination-decarboxylation-allylic acyloxylation reaction (D-O-D-AA). While the early stages of C–H activation focused on single point functionalization. With the inception of multiple C–H activation in a single molecule and unlocking differential reactivity modes of a substrate with the assistance of ligands, this domain is expected to invade the next phase of organic synthesis and contribute to further advancement in creating valued products.

2. RESULTS AND DISCUSSIONS

Optimization of the Reaction Conditions: The endeavor towards investigating the reactivity of cycloalkyl carboxylic acid commenced with the reaction between 4-^{t}Bu-cyclohexyl carboxylic acid and ethyl acrylate. In all our prior Pd-catalyzed C–H functionalizations of aliphatic carboxylic acids, we have observed that mono-protected amino acids (MPAA) are indispensable parts to enable the functionalization. While a base usually in the form of Na salt is a pivotal requirement to bind the acid functionality in κ^1 mode that can allow a facile C–H activation. Accordingly, the reaction condition comprising of 10 mol% $Pd(OAc)_2$, 20 mol% *N*-Ac-Leu-OH, 2 *equiv*. Ag_2CO_3, 2 *equiv.* Na_2HPO_4 in HFIP solvent

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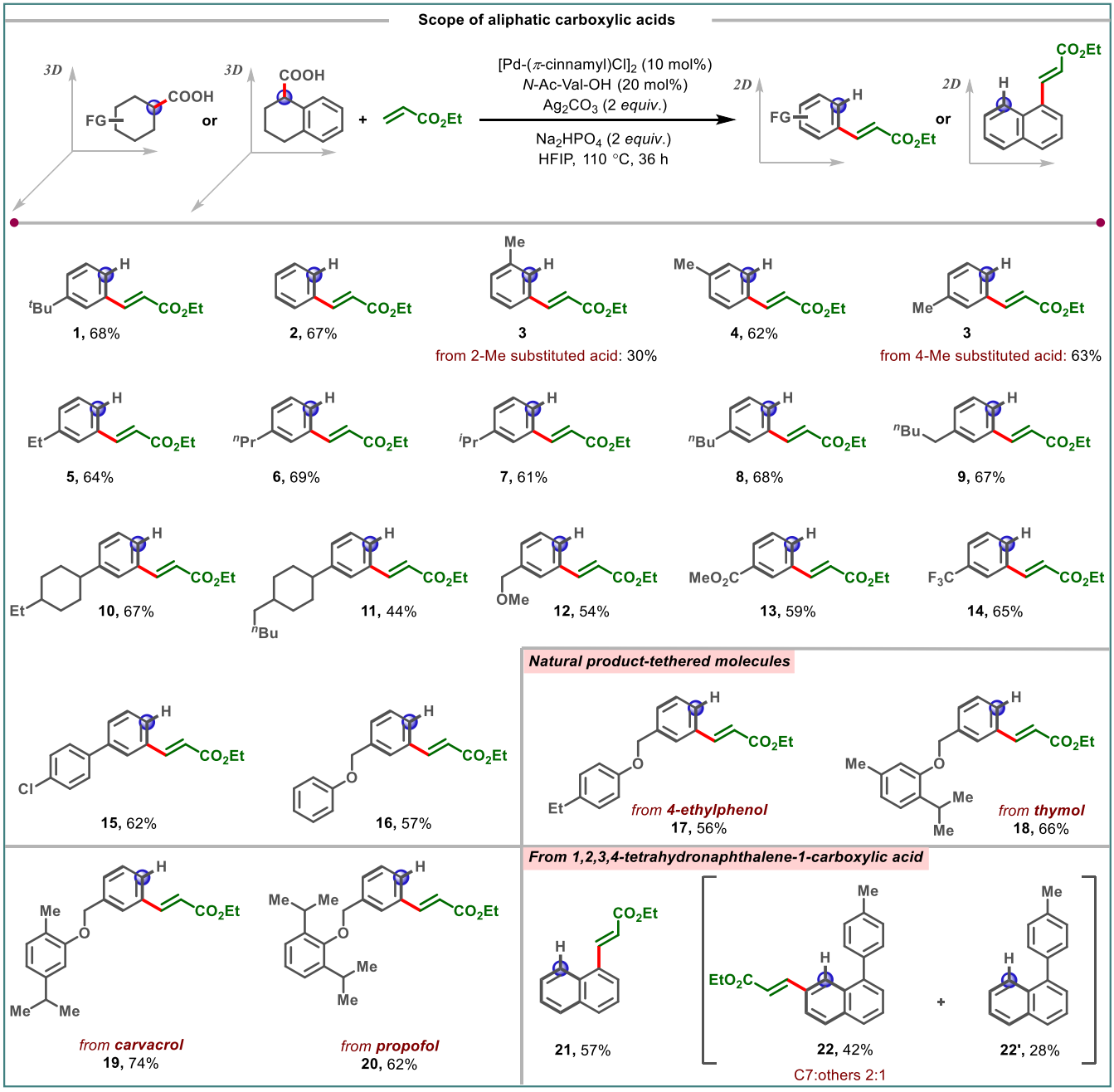
Scheme 2. Prodigious Behaviour of Cyclohexane Carboxylic Acids: Scope of Aliphatic Carboxylic Acids



All reactions were conducted at 0.1 mmol scale and isolated yields are reported. Standard condition: acid (0.1 mmol), olefin (2 *equiv.*), [Pd(π-cinnamyl)Cl]$_2$ (10 mol%), *N*-Ac-Val-OH (20 mol%), Ag_2CO_3 (2 *equiv.*), Na_2HPO_4 (2 *equiv.*), HFIP (1 mL), 110 °C, 36 h.

at 110 °C was chosen for the present transformation; similar to our recent report on the bicyclic lactone formation from cycloalkyl acetic acid. Surprisingly, the initial reaction provided an olefinated arene **1** as the major product *via* multifold dehydrogenation-decarboxylation path. While a bis-dehydrogenated lactone product was obtained as the minor product (see Supporting Information, Table S1).

Under the same conditions, various Pd salts afforded different ratios of these products but with π-allyl and π-cinnamyl Pd(II) complexes, the minor lactone product could be completely eliminated to provide the olefinated arene as the only product. Considering yields, the π-cinnamyl Pd(II) complex was superior over the π-allyl complex. Although [$Pd_2(dba)_3$] catalyst yielded higher yield (58%) than [Pd(π–cinnamyl)Cl]$_2$ (53%), we continued with [Pd(π–cinnamyl)Cl]$_2$ as it did not produce any side product, unlike the case for [$Pd_2(dba)_3$] (see Supporting Information, Table S1). Noticeable that a subtle variation in the substrate structure from cycloalkyl acetic acid to cycloalkyl carboxylic acid brings forth a significant change in the reactivity. Further, a series of *N*-protected α-amino acids were screened and it was observed that the inclusion of *N*-Ac-Val-OH as ligand improved the yield of **1**. The pyridone and pyridine-based ligands which are widely used for C(sp^3)–H functionalizations were not much effective in the present transformation. The optimization of other parameters such as oxidant, base, solvent and temperature revealed that the ones used for the preliminary reaction was ideal. Deviation from the ideal parameters hampered the product yield. Only upon prolonging the reaction time from 24 h to 36 h was found beneficial in providing the highest achievable yield of **1**. The final reaction conditions constitute of [Pd(π-cinnamyl)Cl]$_2$

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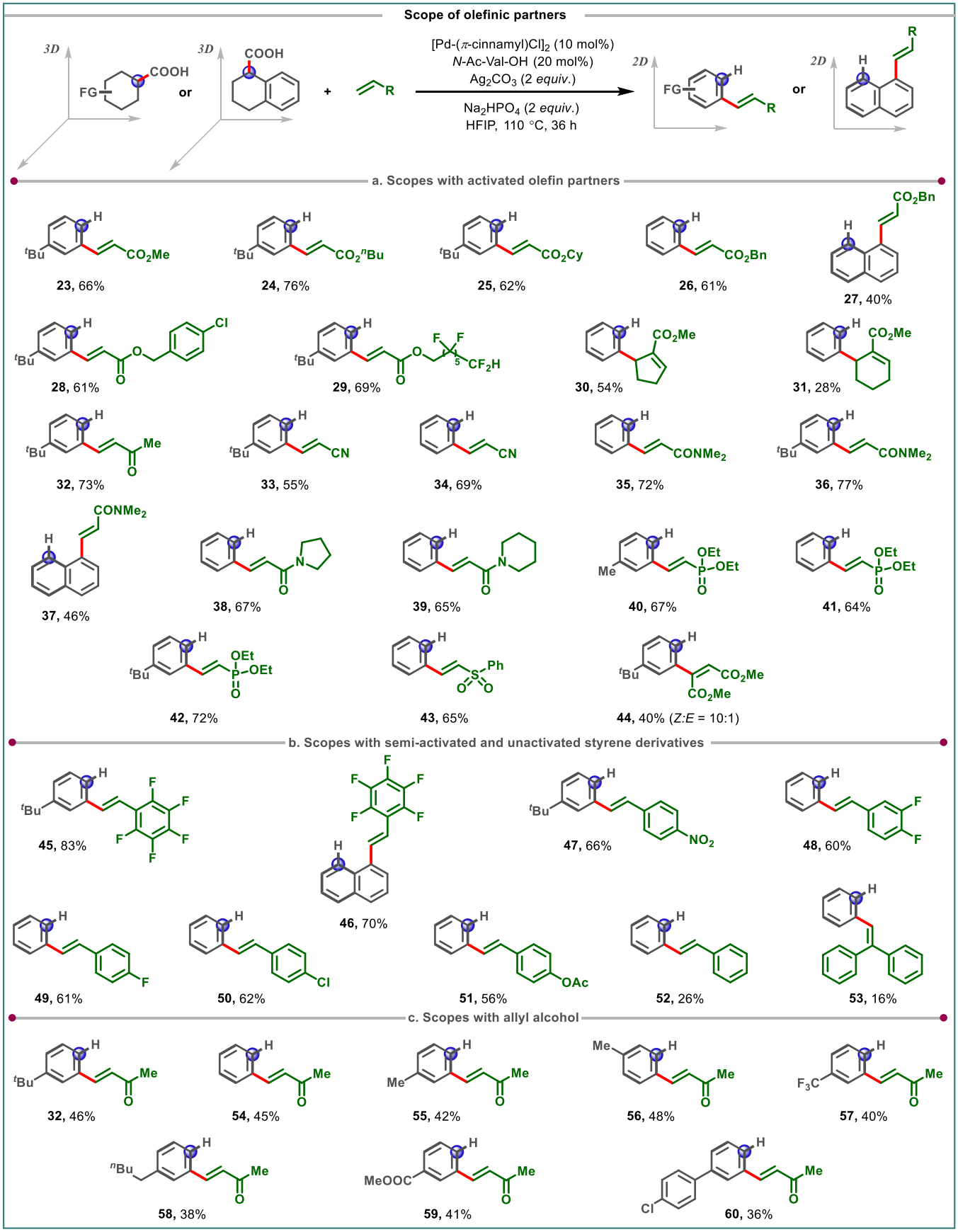
Scheme 3. Diversification of Activated and Semi-activated Olefinic Partners



All reactions were conducted at 0.1 mmol scale and isolated yields are reported. Standard condition: acid (0.1 mmol), olefin (2 *equiv.*), [Pd(π-cinnamyl)Cl]$_2$ (10 mol%), *N*-Ac-Val-OH (20 mol%), Ag_2CO_3 (2 *equiv.*), Na_2HPO_4 (2 *equiv.*), HFIP (1 mL), 110 °C, 36 h.

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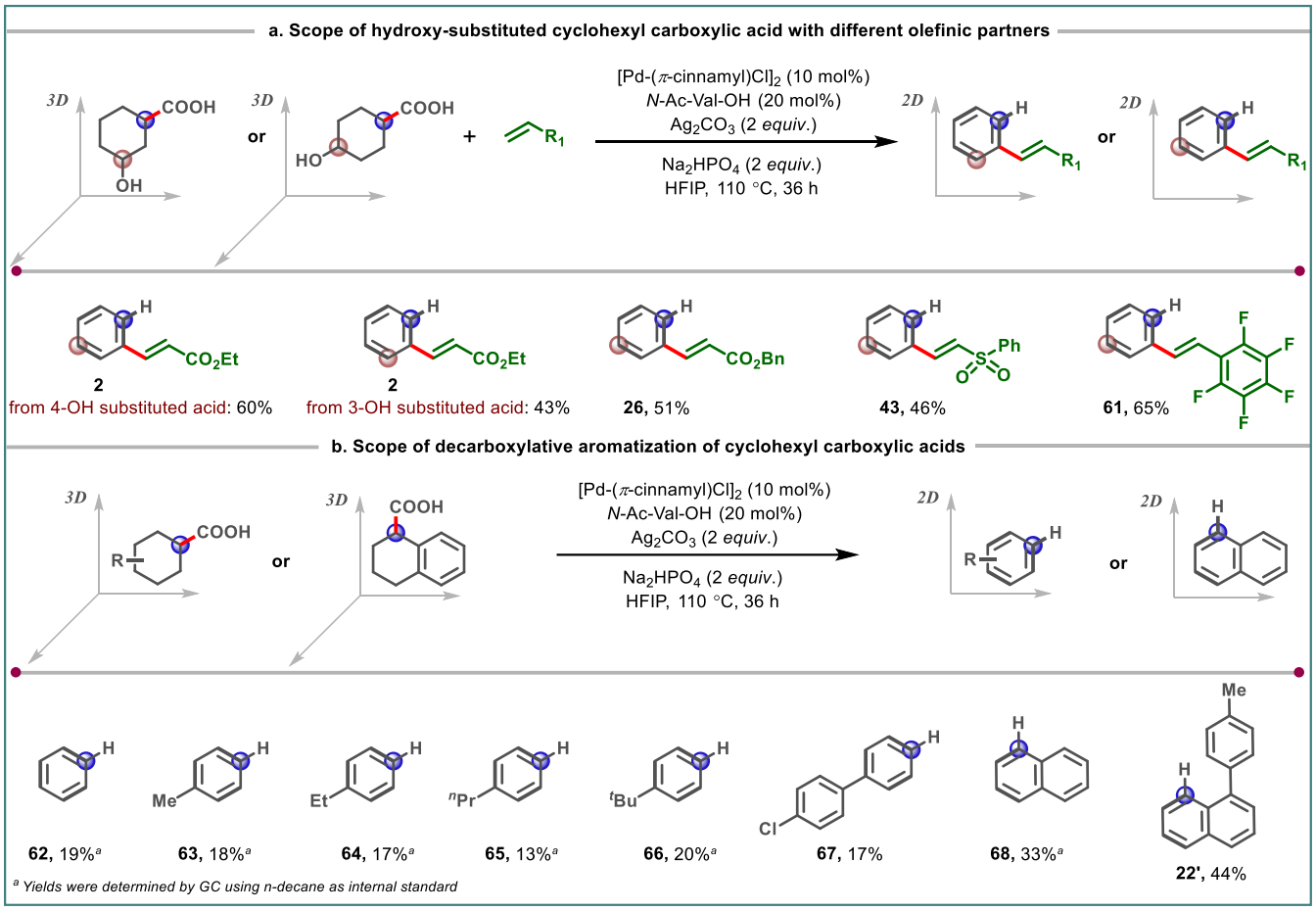
Scheme 4. Strategies for D-O-D-D-A and D-D-A



All reactions were conducted at 0.1 mmol scale and isolated yields or GC yields (mentioned) are reported. Standard condition: acid (0.1 mmol), olefin (2 *equiv*. for Scheme 4.a, not being used for without coupling partner approach Scheme 4.b), [Pd(π-cinnamyl)Cl]$_2$ (10 mol%), *N*-Ac-Val-OH (20 mol%), Ag_2CO_3 (2 *equiv*.), Na_2HPO_4 (2 *equiv*.), HFIP (1 mL), 110 °C, 36 h.

(10 mol%), *N*-Ac-Val-OH (20 mol%), Ag_2CO_3 (2 *equiv.*), Na_2HPO_4 (2 *equiv.*), HFIP (hexafluoroisopropanol) as solvent at 110 °C for 36 hours which were found suitable to execute the tandem D-O-D-A of cyclohexyl carboxylic acid to afford the olefinated arene **1**. It is noteworthy to mention that, that C–H olefination of aliphatic carboxylic acids are always associated by lactone formation.[9-11] However, this is an unchartered territory where the lactone formation could be bypassed to an alternative decarboxylation pathway by selective catalyst screening. The details of the optimization studies are provided in the supporting information (for detailed optimization studies, see Supporting Information, Section 2. Optimization Details).

Substrate scope: We next evaluated the D-O-D-A reactivity for a series of cyclohexyl carboxylic acids under the optimized conditions (Scheme 2). With the unsubstituted cyclohexyl carboxylic acid, the transformation provided decent yield of the respective olefinated benzene **2**. Next, the protocol was applied to alkyl substituted cyclohexyl carboxylic acids. The 2-Me cyclohexyl carboxylic acid afforded low yield of the 3-Me substituted olefinated benzene **3**, owing to the steric hindrance that affects the C–H activation. For the 3-Me substituted substrate having an opportunity of C–H activation at either β and β' position of the carboxylic acid functionality is expected to lead a pair of regioisomeric olefinated products. However, the activation occurred preferentially only at the distal C–H position of the Me group to afford solely **4**. The usual D-O-D-A reactivity was observed with the 4-Me substituted substrate to give the olefinated arene **3**. Hence, **3** can be obtained from both 2- and 4-Me substituted substrate. However, with 4-Me substrate the yield was better. So, the protocol gives a cushion to choose the proper substrate to avail a better yield of a particular regioisomer. A range of other 4-alkyl substituted cyclohexyl carboxylic acid underwent smooth transformations affording the respective *meta*-olefinated arenes (**5-9**) in synthetically useful yields. Thus, this protocol offers an alternate route to form *meta* or *para*-olefinated arenes where commercially available 4- and 3-substituted cyclohexane carboxylic acids could be utilized as starting materials. The reactions of 4-cycloalkyl substituted substrates were also amenable to the D-O-D-A sequence giving moderate to good yields of their respective products (**10-11**). In all the alkyl substituted substrates it was observed that the dehydrogenation remained confined to the cyclohexyl moiety possessing the carboxylic functionality and not relayed to the alkyl substituents. Other functionalities at the 4-position of cyclohexyl carboxylic acids such as ether (**12**), ester (**13**), trifluoromethyl (**14**) and phenyl (**15**) were all tolerated under the present reaction conditions. The tolerance of ester group in **13** can serve as the point of utilization for subsequent derivatization of the arene. The transformation executed on the phenol tethered substrate exhibited the same reactivity to give olefinated arene (**16**). Also, 4-ethylphenol, a botanical agrochemical, tethered with cyclohexane carboxylic acid reacted efficiently to provide corresponding olefinated product (**17**).[12] Further, the robustness of the protocol was demonstrated by generating structurally diverse molecules from the

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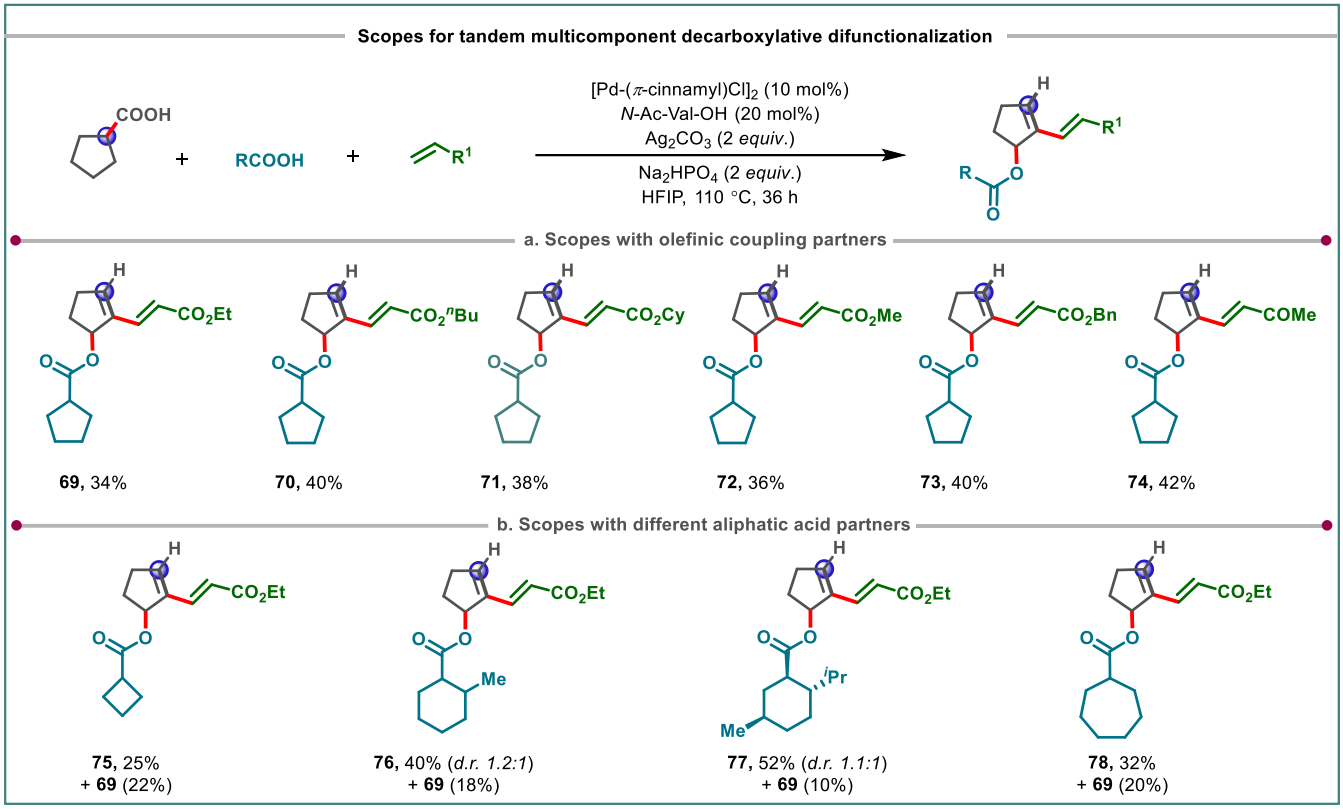
Scheme 5. Unified Strategy for Synthesis of Difunctionalized Cyclopentene Derivatives *via* Controlled Dehydrogenation



All reactions were conducted at 0.1 mmol scale and isolated yields are reported. Standard condition: cyclopentane carboxylic acid (0.1 mmol), cycloalkyl carboxylic acid (4 to 7 membered cycloalkyl carboxylic acid, 1 *equiv.*), olefin (2 *equiv.*), [Pd(π-cinnamyl)Cl]$_2$ (10 mol%), *N*-Ac-Val-OH (20 mol%), Ag_2CO_3 (2 *equiv.*), Na_2HPO_4 (2 *equiv.*), HFIP (1 mL), 110 °C, 36 h.

cyclohexyl substrates with phenolic natural product pendants *viz.* thymol (**18**), carvacrol (**19**) and propofol (**20**) which provided the respective olefinated products in decent yields without any compromise in reactivities (Scheme 2).

The reactivity of 1,2,3,4-tetrahydro-1-naphthoic acid with ethyl acrylate was ventured next (Scheme 2). 1,2,3,4-tetrahydro-1-naphthoic acid is fused bicyclic substrate which has the provision for C–H activation at both C2- and C8-positions. Hence the olefin counterpart can be coupled either at the C2-position (which is the usual reactivity observed so far with the cyclohexyl carboxylic acid) or at the C8-position. In this case olefination took place at the C8-position (**21**) suggesting that acid directed olefination occurred initially subsequently followed by decarboxylation and aromatization. However, if the C8-position is blocked by another group, then the olefin was inserted at the C2-position (**22**) by usual D-O-D-A sequence; albeit other regioisomeric olefinated products formation were observed. Further, this substrate underwent a dehydrogenation-decarboxylation-aromatization (D-D-A) sequence pathway to form naphthalene derivative (**22'**). Subsequently, the scope of activated olefins as coupling partners was explored employing the optimal conditions (Scheme 3a). An array of diversely substituted acrylates including alkyl (**23**-**24**), cyclohexyl (**25**), benzyl (**26**-**28**), perfluoroalkyl (**29**) were effective coupling partners in this transformation to give the desired olefinated products in moderate to good yields, irrespective of the kind of carboxylic acid substrates. The cyclic *α,β*-unsaturated esters led to the formation of allylic esters (**30**-**31**) instead of the olefin products. Apart from the acrylate derivatives, the present transformation was equally efficient with activated olefins possessing ketone (**32**), nitrile (**33**-**34**), amide (**35**-**39**), phosphonate (**40**-**42**) and sulfone (**43**). These activated olefins afforded corresponding olefinated arenes *via* tandem D-O-D-A sequence in good yields. Dimethyl fumarate, which is an internal olefin is deemed as a challenging substrate in olefination. However, the compatibility of this internal olefin under the present catalytic system was showcased by the formation of the corresponding olefinated product (**44**) in 40% yield with a *Z:E* ratio of 10:1. While activated olefins are preferred choices as coupling partners in C(sp^3)–H activation reactions, they fail to accommodate semi-activated styrene substrates. There are no reports known for employing styrenes as olefin partner in carboxylate mediated C(sp^3)–H activation. The current protocol could be extended to a series of styrene substrates, the reactivity is governed by the kind of substitution present in the phenyl ring (Scheme 3b). Pentafluoro styrene with 4-^{t}Bu cyclohexane carboxylic acid provided excellent yield of 83% for the unsymmetrically substituted stilbene derivative (**45**). High yields of the respective stilbene derivatives were obtained for the reaction with 1,2,3,4-tetrahydro-1-naphthoic acid (**46**). Other than pentafluoro styrene, 4-nitro styrene (**47**), 3,4-difluoro styrene (**48**), 4-fluorostyrene (**49**), 4-chloro styrene (**50**) and 4-acetoxy styrene (**51**), reacted efficiently with cyclohexyl carboxylic acids to form corresponding unsymmetrically substituted stilbene derivatives with a range of 56% to 66% yields. Styrene and 1,2-gem-diphenylethylene were also found to be amenable under the reaction conditions to produce trans-stilbene (**52**) and triphenylethylene (**53**) albeit their reactivity dropped to give lower yields. Another class of olefins that could be encompassed under the present transformation is allyl alcohol (Scheme 3c). Though allyl alcohols are well known as a coupling partner in C(sp^2)–H activations, reports for its practical applications in the field of unactivated C(sp^3)–H functionalization remain scarce.[10,13] However, the successful utilization of allyl alcohols as olefinic partner with cyclohexyl carboxylic acids (with or without substitution) under the optimized conditions gave access to *α,β*-unsaturated ketones incorporated arenes in moderate yields (**32**, **54**-**60**, Scheme 3c).

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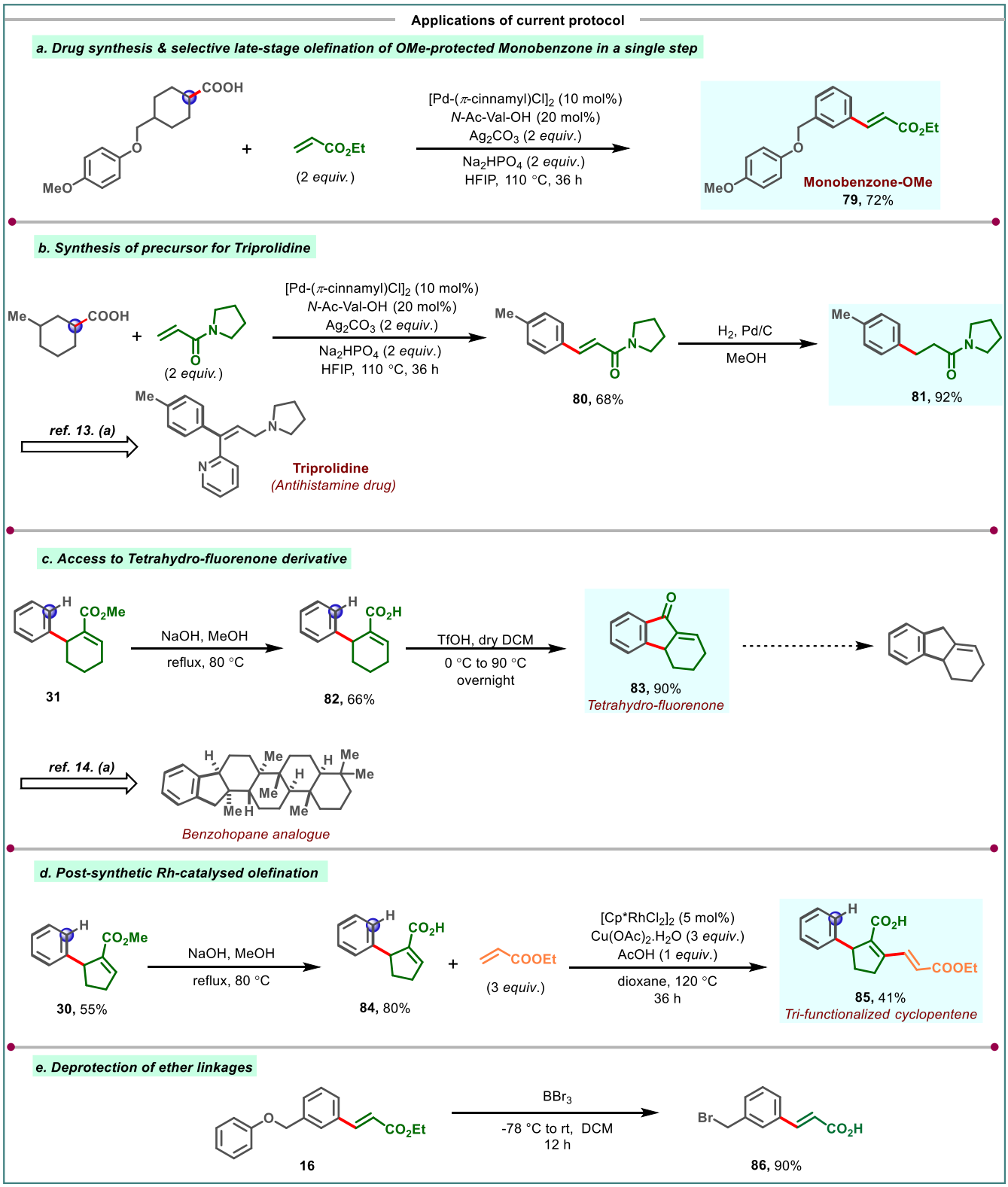
Scheme 6. Applicability and Post-synthetic Modification of Current Protocol



a. Expedited synthesis of Monobenzone derivative with exclusive regioselectivity. **b.** Synthesis of Tripolidine synthon. **c.** Access to tetrahydro-fluorenone, an important building block for benzohopane analogue. **d.** Synthesis of trifunctionalized cyclopentene derivative. **e.** Post-synthetic deprotection strategy to synthesis *meta*-olefinated benzyl bromide.

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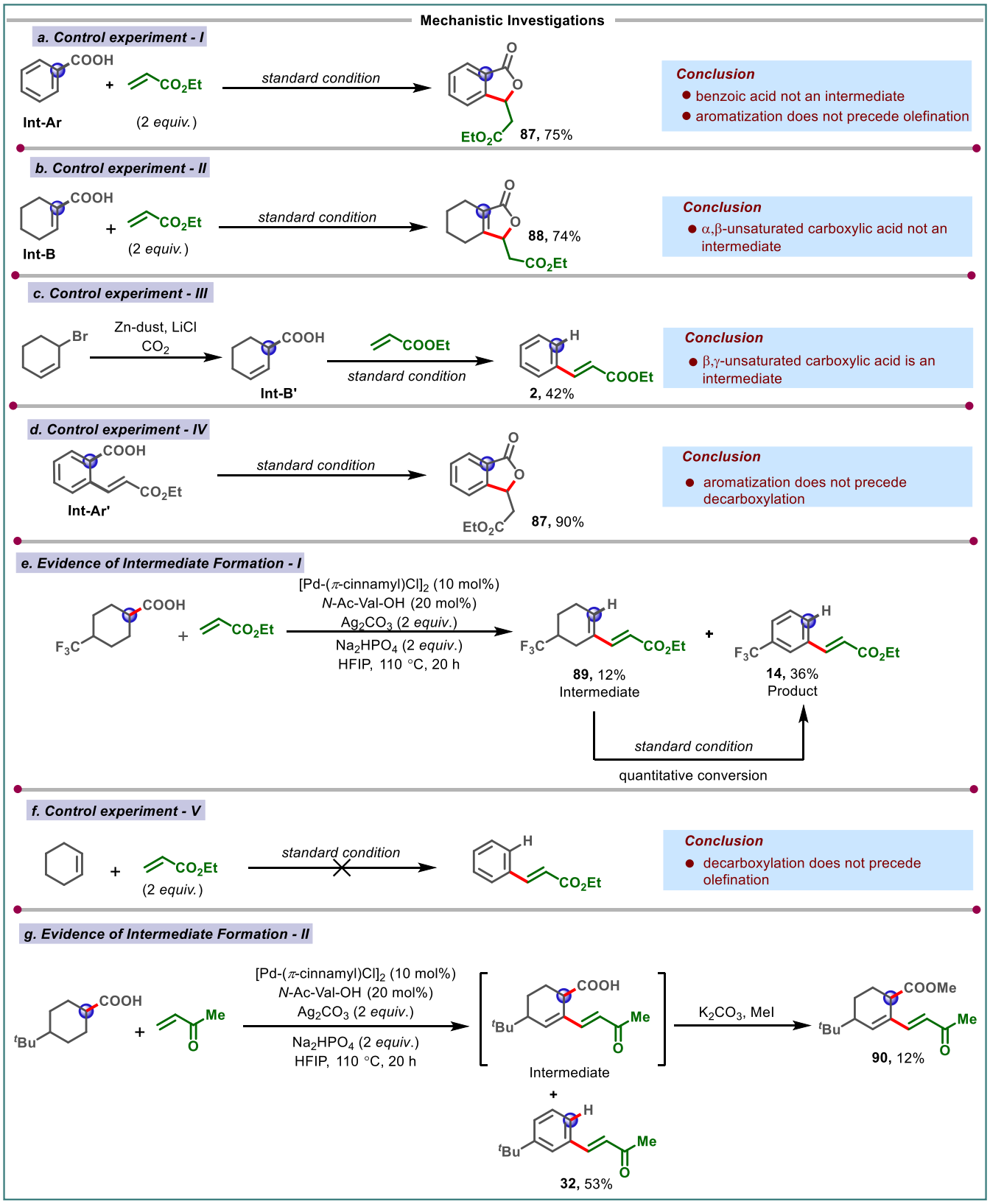
Scheme 7. Mechanistic Investigation



Standard condition: acid (0.1 mmol), olefin (2 *equiv.*), [Pd(π-cinnamyl)Cl]$_2$ (10 mol%), *N*-Ac-Val-OH (20 mol%), Ag_2CO_3 (2 *equiv.*), Na_2HPO_4 (2 *equiv.*), HFIP (1 mL), 110 °C, 36 h.

We were curious to inspect the reactivity of 4-hydroxy-substituted cyclohexyl carboxylic acid under the present reaction conditions. If the substrate reacts via the usual D-O-D-A pathway, then a phenol derivative was expected while the presence of free -OH group

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could also poison the catalyst and inhibit the reaction. Intriguingly, all the above possibilities were over-ridden and a dehydroxylation-pathway took over and resulted in the olefinated arene **2** (Scheme 4a). Analogous observation was also made with the 3-hydroxy substituted substrate which provided the same olefinated product **2**. Hence, these substrates underwent three different de-functionalizations: dehydrogenation-dehydroxylation-decarboxylation which is a rare event in C–H activation-initiated transformations (Scheme 4a). The same reactivity of hydroxy substituted cyclohexane carboxylic acid prevailed for its reaction with other activated olefins (**26**, **43**) and styrene (**61**). Next, our quest was to find out what would be the outcome and how would be the reactivity if coupling partners (olefins) were not introduced for the reaction with cyclohexyl carboxylic acids. We observed that cyclohexane carboxylic acids undergo a decarboxylation-aromatization sequence to give arenes (**62-68**, **22'**, Scheme 4b), albeit in low yields. Only for 1,2,3,4-tetrahydro-1-naphthoic acids, the yields for the corresponding naphthalene product (**68**, **22'**) were slightly higher since the aromaticity drives the decarboxylation in this case. This observation varies from a very recent report where only dehydrogenation occurred to provide benzoic acids.[8] Hence, the reactivity depends on the catalytic system employed for a transformation.

The reactivity of cyclohexyl carboxylic acid or its analogues were studied initially under the optimized conditions; all of which followed the D-O-D-A sequence preferentially to give the olefinated arenes. However, our quest was to study the behavior of cycloalkyl acids for which aromatization is not favored. Towards this goal, cyclopentyl carboxylic acid was chosen as the substrate of interest and executed to the present transformation with ethyl acrylate. Interestingly, the reaction led to a decarboxylated difunctionalized cyclopentene derivative (**69**) with olefin being introduced at the vinylic position and the cyclopentyl carboxylic acid itself is incorporated at the allylic position (Scheme 5a). The yield was moderate considering that acid substrate itself undergoes self-coupling. The same pathway was followed upon reaction of the same cyclopentyl carboxylic acid with a set of other acrylates and methyl vinyl ketone (**70-74**, Scheme 5a). Following the fact that acid itself undergoes as a coupling partner in this reaction we wanted to introduce other acids in the reaction to see if they can effectively couple at the allylic position of cyclopentene. In presence of other cycloalkyl acids which are not or less susceptible to aromatization under present conditions, a tandem multicomponent reaction occurred in which the other acid partner underwent efficient cross-coupling to give the difunctionalized cyclopentene products (**75-78**, Scheme 5b). However, along with the formation of hetero coupling products some minor amount of self-coupled product **69** also formed (Scheme 5b).

Applications: The development of tandem D-O-D-A sequence gives ample opportunity to utilize such a protocol for direct synthesis of bio-relevant molecules of pharmaceutical interest or its precursor. The newly developed catalytic system expedited the synthesis of late stage-functionalized regioselectively olefinated monobenzone derivative, used for the treatment of vitiligo (**79**, Scheme 6a).[14] The protocol thus allows to conduct a late-stage functionalization without actually resorting to the actual drug molecule which would otherwise have given a mixture of regioisomers upon direct olefination. The reaction of 3-Me cyclohexyl carboxylic acid and acryl amide gave the respective olefinated arene (**80**, Scheme 6b), the reduction of which generated the precursor **81** for the synthesis of triprolidine, an antihistamine drug (Scheme 6b).[15] The allyl ester **31** on hydrolysis gave the corresponding carboxylic acid **82** which when treated with triflic acid resulted in the formation of the tetrahydro-fluorenone derivative **83** (Scheme 6c). This compound could have a potential pharmaceutical significance having antifungal activity.[16] Also, such tetrahydro-fluorenone can serve as precursor for the synthesis of pharmaceutically significant benzohopane (Scheme 6c).[17] The allylic acid **84** obtained by hydrolysis of allyl ester **30** was subjected to further diversification by Rh catalyzed olefination at the vinylic position, thus resulting in a tri-functionalized cyclopentene derivative **85** (Scheme 6d).[18] The olefinated arene **16** upon treatment with BBr_3 led to deprotection of ether and ester, to give quantitative yield of *meta*-olefinated benzyl bromide (**86**, Scheme 6e). It is noted that Heck reaction of benzyl bromides are difficult to conduct, hence to avail the olefinated benzyl bromide this can be utilized as an alternative route.

Mechanistic investigations: The structural pattern of the product formed with cyclohexyl carboxylic acid indicates that the initiation of C–H activation is followed by three fundamental events: dehydrogenation, olefination and decarboxylation. In order to delve the mechanistic intricacies of this transformation it is important to probe the sequence of the aforementioned events. With our prior knowledge on dehydrogenative C–H-activation in aliphatic carboxylic acid, we hypothesized multiple routes that are feasible to enable the product formation. We conducted a series of control experiments and isolated various intermediates to validate the reaction pathway for this transformation. The occurrence of dehydrogenation by β-hydride elimination is most likely the initial step for this transformation following C–H activation. However, there are two possibilities for dehydrogenation which could either lead to an α,β-unsaturation (Int-B) or the β,γ-unsaturation (Int-B'). Since, the α,β-unsaturated carboxylic acid (Int-B) is thermodynamically more stable than its regioisomer Int-B', Int-B was considered for further investigation. The Int-B can subsequently undergo aromatization followed by olefination or the vice-versa. As per the former sequence, aromatization will first lead to benzoic acid (Int-Ar) which will then undergo *ortho*-olefination of benzoic acid followed by decarboxylation. To check the viability of this hypothesized route, benzoic acid (Int-Ar) had been subjected to reaction with an olefinic coupling partner under the standard conditions. The reaction afforded a lactone derivative (**87**, Scheme 7a) rather than the desired olefinated arene **2**. This suggests that benzoic acid is not an intermediate and this pathway is unlikely. An alternate sequence is where the olefination precedes the aromatization. To verify this route, cyclohex-1-ene-1-carboxylic acid (Int-B) was subjected to standard reaction conditions with ethyl acrylate as coupling partner. However, the α,β-unsaturated cyclohexene carboxylic acid did not produce our desired olefinated-aryl product **2**, albeit furnished an lactone derivative (**88**, Scheme 7b) with 74% yield. This proves that cyclohex-1-ene-1-carboxylic acid (Int-B) is not an intermediate involved in the mechanistic cycle and it is highly probable that the reaction proceeds *via* Int-B'. As with Int-B, the same reaction sequence is possible with Int-B'. Since benzoic acid did not afford the olefinated arene, the previous argument that aromatization does not precede olefination holds good for Int-B' as well. An alternative possibility following the formation of Int-B' may involve early-stage olefination and subsequent aromatization in the penultimate stages. To assess the feasibility of the suggested reaction sequence, we conducted experiments with the pre-synthesized β,γ-unsaturated cyclohexene carboxylic acid (Int-B'). To our satisfaction, it furnished the desired olefinated benzene **2** in 42% yield (Scheme 7c). This outcome strongly indicates the involvement of Int-B' in the proposed reaction pathway and olefination precedes over aromatization. Further, to gain insights about the order in which decarboxylation and aromatization occurs, the present reaction condition was executed on *ortho*-olefinated benzoic acid (Int-Ar') (Scheme 7d). The formation benzolactone **87**, product instead of the anticipated decarboxylated olefinated product **2** rules out the possibility of aromatization prior to decarboxylation. Based on the cumulative control experiments conducted, the following conclusions can be drawn: (a) the reaction pathway involves the intermediacy of β,γ-unsaturated cyclohexene carboxylic acid (Int-B');

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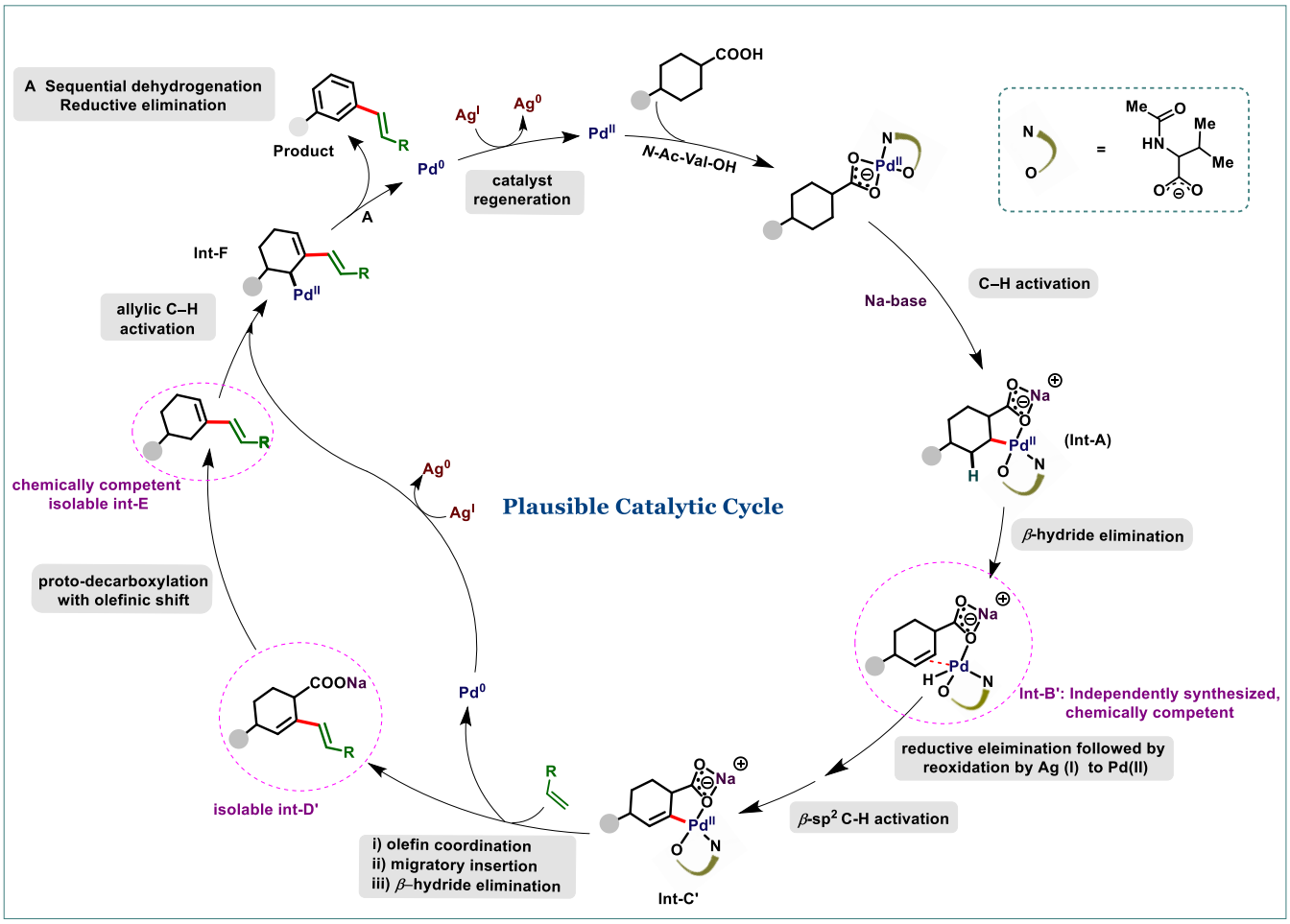
Scheme 8. A Plausible Mechanism for D-O-D-A



(b) olefination takes place prior to the aromatization step; (c) decarboxylation does not occur subsequent to the aromatization step and (d) aromatization is likely the final phenomenon in the entire reaction sequence. (For details of the control reactions and the mechanistic studies please see Supporting Information, Section 7. Detailed mechanistic investigation)

Worth-mentioning, when the reaction of 4-trifluoromethyl substituted cyclohexane carboxylic acid was intercepted after 20 h reaction time, along with the desired olefinated arene 14, the formation of a decarboxylated-olefinated-cyclohexene **89**, in 12% yield was observed (Scheme 7e). Traces of the similar intermediates were also observed for 4-ethyl substituted and thymol tehthered cyclohexane carboxylic acids (see Supporting Information, Section 7.b). Expecting the decarboxylated-olefinated-cyclohexene (**89**) to be an intermediate, we tested the side product under our standard reaction protocol and to our delight, we found our desired product **14** formation in quantitative yield; confirming involvement of **89** as an intermediate of the reaction protocol. However, the intermediacy of **89** raises a query about the sequence of event between (a) Pd-catalyzed olefination at the β–C(sp^2)–H centre, followed by decarboxylation or (b) decarboxylation followed by C(sp^2)–H olefination. The occurrence of the latter pathway would lead to cyclohexene which is expected to undergo further olefination. However, the non-compatibility of cyclohexene to provide either the olefinated cyclohexene or the olefinated arene **2** eliminates the opportunity of the latter pathway (Scheme 7f). Also, the formation of regiospecific olefinated arenes at the β-position with respect to carboxylic acid in cases of substituted cyclohexane carboxylic acid clearly indicates that olefination is driven by the directing assistance of carboxylic acid. Noteworthy, the low yield observed for the formation of arene products without the olefin coupling partner suggests that the olefination accelerates the decarboxylative aromatization. Hence the intermediacy of olefinated-cyclohexene **89** observed for 4-trifluoromethyl substituted cyclohexane carboxylic acid is occurring *via* decarboxylation induced double bond migration of the initially formed β,γ-unsaturated olefinated cyclohexyl carboxylic acid. Indeed, such an intermediate (β,γ-unsaturated olefinated cyclohexyl carboxylic acid, **90**, Scheme 7g) could be intercepted in case of the reaction of 4-^{t}Bu cyclohexyl carboxylic acid with methyl vinyl ketone, further strengthening our hypothesis for the mechanistic cycle.

From the observations of control experiments and the intercepted intermediates it is evident that the sequence of reaction follows dehydrogenation-olefination-decarboxylation-aromatization pathways. A plausible mechanistic cycle is proposed based on D-O-D-A sequence (Scheme 8). The acid substrate initially binds with the catalyst with the help of bidentate ligand. Next, the alkali metal Na^+ displaces Pd(II) from κ^2 coordination to κ^1 coordination and assists in C–H activation to generate Int-A. A β-hydride elimination from palladacycle Int-A delivers β,γ-dehydrogenated Int-B'. After the regeneration of the Pd(II) species by Ag(I) oxidant, acid directed C(sp^2)–H activation provides vinyl palladium species Int-C'. This intermediate subsequently couples with olefin through olefin insertion, migratory insertion and β-hydride elimination to generate Int-D'. Int-D' undergo subsequent proto-decarboxylation[19] with an olefinic shift to form Int-E. Thereafter Int-E, in presence of Pd(II), undergoes two consecutive allylic C(sp^3)–H activations / β-hydride elimination steps to deliver the olefinated benzene derivatives. The re-oxidation of Pd(0) to Pd(II) by Ag(I) carry forwards the next catalytic cycle. While for the five-membered carboxylic acids, the

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initial dehydrogenation-olefination-decarboxylation occurs as demonstrated for six-membered carboxylic acids. The olefinated cyclopentene then undergoes an allylic C(sp^3)–H activation to π-allyl palladium species. At this stage instead of undergoing a further β-hydride elimination to give the diene product, the catalytic system controls the dehydrogenation and follows an alternative allylic acyloxylation[13,20] with the acid (either self-coupling or cross-coupling) to afford the difunctionalized cyclopentene derivatives (see Supporting Information, Section 7.d for the D-O-D-AA mechanistic cycle of cyclopentane carboxylic acid).

3. CONCLUSIONS

In summary, we have devised a catalytic system which forges multifold C–H activation to afford 2D space of olefinated arenes starting from cyclohexyl carboxylic acids (3D space) *via* sequential dehydrogenation-olefination-decarboxylation-aromatization. This protocol demonstrates the variation in reactivity of cyclohexane carboxylic acid with a subtle variation in their structural pattern. While reactions of carboxylic acids with olefins are more known for lactone formation, in the present case the lactone formation could be eliminated by passing over to decarboxylation pathway. A number of acrylates, acryl amides, vinyl phosphonate, diesters, acrylonitrile, vinyl sulfones, unsaturated ketone have been successfully utilized in the reaction. Unactivated and semi-activated olefins, such as styrenes and allyl alcohols were also found to be compatible for our reaction protocol. Very unusual reactivity was observed for cyclohexane carboxylic acids possessing hydroxy substituent which underwent dehydroxylation instead of dehydrogenation step. Cycloalkyl carboxylic acids for which aromaticity is disfavored formed difunctionalized cycloalkene by controlled dehydrogenation following dehydrogenation-olefination-decarboxylation-allylic acyloxylation reaction sequence. The intricacies of the transformation were resolved by thorough control experiments and isolation of intermediates. These findings provide valuable insights into the mechanistic pathway and the sequential order of the key transformations involved. The protocol could also be applied for the synthesis of late-stage functionalized drugs or important precursors for synthesis of various bio-relevant molecules. Such an exhibition of reactivity changes in acid substrates can be harnessed to create a paradigm for diverse applications.

4. EXPERIMENTAL SECTION

General Procedure for the Synthesis of Olefinated Arenes: A clean, oven-dried screw cap reaction tube with previously placed magnetic stir–bar was charged with aliphatic cyclohexane carboxylic acid (0.1 mmol, *1 equiv*.), olefinic partner (0.2 mmol, 2 *equiv.*), [Pd(π-cinnamyl)Cl]$_2$ (0.01 mmol, 10 mol%), *N*-Ac-Val-OH (0.02 mmol, 20 mol%), Ag_2CO_3 (0.2 mmol, 2 *equiv.*) and Na_2HPO_4 (0.2 mmol, 2 *equiv*.) followed by addition of HFIP (1 mL). The reaction mixture was vigorously stirred for 36 h in a preheated oil bath at 110 °C. After stipulated time, the reaction mixture was cooled to room temperature and filtered through a celite bed using ethyl acetate as the eluent (15 mL). The diluted ethyl acetate solution of the reaction mixture was subsequently washed with saturated brine solution (2 x 10 mL) followed by water (2 x 10 mL). The ethyl acetate layer was dried over anhydrous Na_2SO_4 and the volatiles were removed under vacuum. The crude reaction mixture was purified by column chromatography using silica gel and petroleum-ether /ethyl acetate as the eluent to give the desired olefinated-arene as the product.

General Procedure for the Synthesis of Arenes (without olefin): A clean, oven-dried screw cap reaction tube with previously placed magnetic stir–bar was charged with aliphatic cyclohexane carboxylic acid (0.1 mmol, 1 *equiv*.), [Pd(π-cinnamyl)Cl]$_2$ (0.01 mmol, 10 mol%), *N*-Ac-Val-OH (0.02 mmol, 20 mol%), Ag_2CO_3 (0.2 mmol, 2 *equiv*.) and Na_2HPO_4 (0.2 mmol, 2 *equiv.*) followed by addition of HFIP (1 mL). The reaction mixture was vigorously stirred for 36 h in a preheated oil bath at 110 °C. After stipulated time, the reaction mixture was cooled to room temperature and filtered through a celite bed using ethyl acetate as the eluent (15 mL). The diluted ethyl acetate solution of the reaction mixture was subsequently washed with saturated brine solution (2 x 10 mL) followed by water (2 x 10 mL). The ethyl acetate layer was dried over anhydrous Na_2SO_4 and the volatiles were removed under vacuum. The crude reaction mixture was purified by column chromatography using silica gel and petroleum-ether / ethyl acetate as the eluent to give the desired arenes as the product.

General Procedure for the Multicomponent Difunctionalization Reaction: A clean, oven-dried screw cap reaction tube with previously placed magnetic stir–bar was charged with cyclopentane carboxylic acid (0.1 mmol, 1 *equiv.*), cycloalkyl carboxylic acid (4 to 7 membered cycloalkyl carboxylic acid) (0.1 mmol, 1 *equiv.*), olefinic partner (0.2 mmol, 2 *equiv*.), [Pd(π-cinnamyl)Cl]$_2$ (0.01 mmol, 10 mol%), *N*-Ac-Val-OH (0.02 mmol, 20 mol%), Ag_2CO_3 (0.2 mmol, 2 *equiv.*) and Na_2HPO_4 (0.2 mmol, 2 *equiv*.) followed by addition of HFIP (1 mL). The reaction mixture was vigorously stirred for 36 h in a preheated oil bath at 110 °C. After stipulated time, the reaction mixture was cooled to room temperature and filtered through a celite bed using ethyl acetate as the eluent (15 mL). The diluted ethyl acetate solution of the reaction mixture was subsequently washed with saturated brine solution (2 x 10 mL) followed by water (2 x 10 mL). The ethyl acetate layer was dried over anhydrous Na_2SO_4 and the volatiles were removed under vacuum. The crude reaction mixture was purified by column chromatography using silica gel and petroleum-ether / ethyl acetate as the eluent to give the desired difunctionalized cyclopentene derivative.

Supporting Information. "Experimental procedures, analytical data (^{1}H NMR, ^{13}C NMR, ^{19}F NMR, HRMS). This material is available free of charge *via* the Internet at http://pubs.acs.org."

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Competing interests

The authors declare no competing interest(s).

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