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Rhodium(III)-Catalyzed C−H Olefination of Aromatic/Vinyl Acids with Unactivated Olefins at Room Temperature

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Cite This: https://dx.doi.org/10.1021/acs.orglett.0c01636 Read Online

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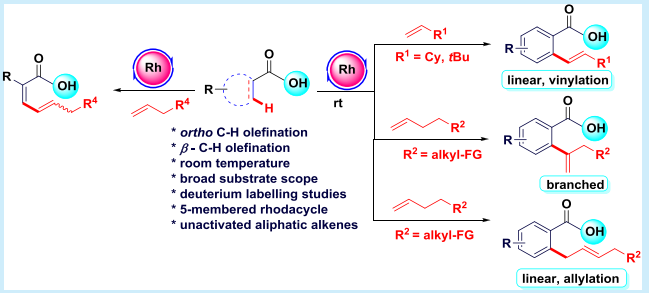
ABSTRACT: A Rh(III)-catalyzed COOH-assisted C−H alkenylation of aromatic acids with unactivated alkenes at room temperature is described. Further, the highly challenging β-C−H olefination of acrylic acids with unactivated olefins was also demonstrated. In these reactions, *ortho*-alkenylated aromatic/vinylic acids were prepared in good to excellent yields. A possible reaction mechanism involving *ortho* C−H activation and a five-membered rhodacycle formation was proposed and supported by the deuterium-labeling studies and isolation of a key rhodacycle intermediate.



The transition-metal-catalyzed chelation-assisted C−H functionalization of organic molecules via a deprotonation pathway has emerged as a powerful synthetic tool in organic synthesis.[1] Several chemical bonds are constructed efficiently in a highly step-economical manner by using this method.[2] A recent observation clearly showed that the C−H activation via a deprotonation pathway can be performed at room temperature.[3] However, in practical terms, most of the known transformations required a higher reaction temperature.

Substituted alkenes are versatile synthetic intermediates and have found widespread application in various organic transformations.[4−7] The metal-catalyzed C−H olefination of substituted aromatics with alkenes is a highly effective method to synthesize arylated alkenes in a stereoselective manner (Figure 1).[4] For this kind of transformation, only activated olefins such as enones, acrylates, acrylonitriles, acrylamides, vinylsulfones, and styrenes are efficiently used (eq 1).[5,6] The C−H olefination with unactivated olefins is very challenging and not well explored in the literature due to the lower reactivity as well as the unbiased nature of unactivated alkenes. Recently, by employing bis chelating group such as 8-aminoquninoline, alkenylation was done with unactivated olefins (eq 2).[7] However, this type of transformation with a monodentate ligand was not well explored.[8] Herein, we report an unprecedented Rh(III)-catalyzed C−H olefination of aromatic/vinyl carboxylic acids with unactivated olefins at room temperature (eq 3). The reaction provides *ortho*-alkenylated aromatic acids and β-C−H-olefinated acrylic acids. In the reaction, the COOH group was not involved in the intramolecular cyclization with an alkene.[5j]

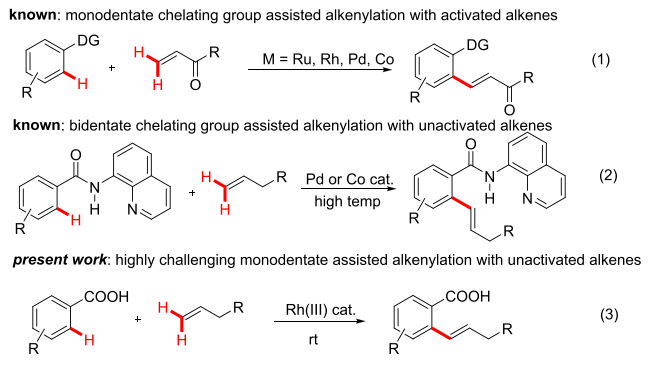
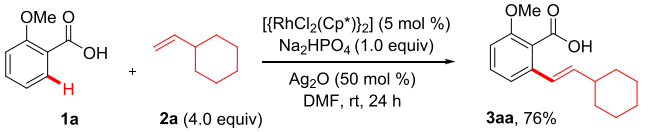


Figure 1. Known C−H alkenylation reaction.

Treatment of 2-methoxybenzoic acid (**1a**) with vinylcyclohexene (**2a**, 4.0 equiv) in the presence of $[\{RhCl_2(Cp^*)\}_2]$ (5 mol %), Ag_2O (50 mol %), and Na_2HPO_4 (1.0 equiv) in DMF at room temperature for 24 h afforded *ortho*-vinylated benzoic acid **3aa** in 76% yield (Scheme 1). The olefination reaction was examined with oxidants such as AgOAc, Ag_2CO_3, Ag_2O, $Cu(OAc)_2{\cdot}H_2O$, $Cu(OAc)_2$, CuO, $K_2S_2O_8$, and $(NH_4)_2S_2O_8$. Among the tested

Scheme 1. *Ortho*-Vinylation of 2-Methoxybenzoic Acid



Received: May 13, 2020

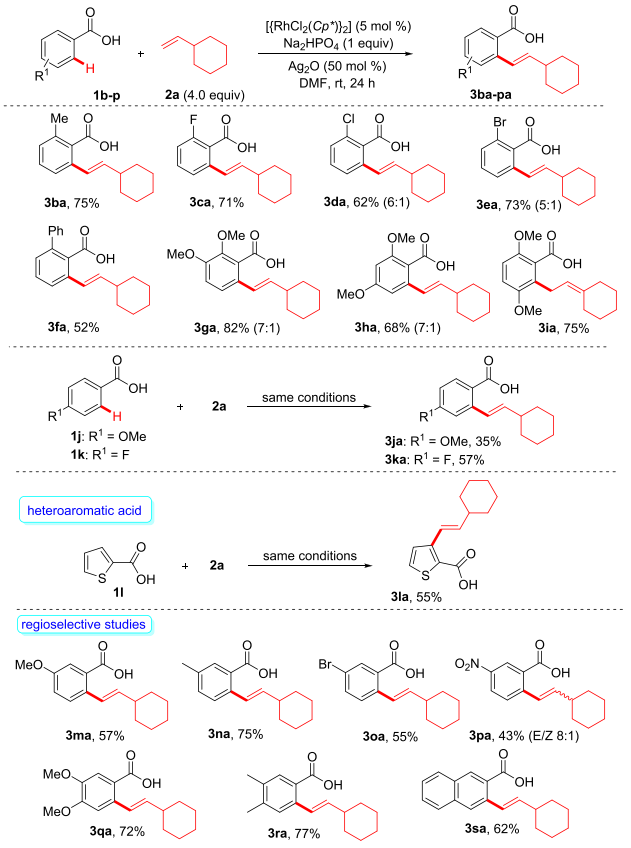
oxidants, Ag_2O was very successful, providing product **3aa** in 76% yield. AgOAc and Ag_2CO_3 were partially effectual, giving **3aa** in 48% and 57% yields, respectively. Other oxidants were not effective. Further, the *ortho*-alkenylation reaction was studied with various bases such as carbonates, acetates, phosphates, and amines. Among them, phosphate base (Na_2HPO_4) was effective, affording **3aa** in 76% yield. Other bases were partially effective or ineffective. The reaction was tested with 2.0 equiv of Na_2HPO_4. In the reaction, product **3aa** was formed in 76% yield. The olefination reaction was examined with solvents such as DMSO, toluene, cyclohexane, CH_3CN, THF, 1,4-dioxane, DME, MeOH, TFE, 1,2-DCE, 1,2-dichlorobenzene, and acetic acid instead of DMF. CH_3CN, THF, MeOH, and TFE were less efficient for the reaction, giving **3aa** in 20−30% yields. Remaining solvents were ineffective.

The alkenylation reaction was tested with substituted aromatic acids **1b−s** (Scheme 2). The reaction of 2-methylbenzoic acid (**1b**) with **2a** delivered *ortho*-alkenylated benzoic acid **3ba** in 75% yield. Halogen substituents such as F, Cl, and Br at the *ortho*-position of benzoic acids **1c−e** reacted with **2a** to yield *ortho*-vinylated benzoic acids **3ca−3ea** in 71%, 62%, and 73% yields, respectively. In the case of 2-Cl and Br benzoic acids, mixtures of *ortho*-alkenylated/allylated products were observed in ratios of 6:1 and 5:1, respectively. The reaction of 2-phenylbenzoic acid (**1f**) with **2a** gave *ortho*-alkenylated aromatic acid **3fa** in 52% yield. The reaction of disubstituted benzoic acids such as 2,3-dimethoxy- (**1g**) and 2,4-dimethoxybenzoic acids (**1h**) with **2a** yielded products **3ga** and **3ha** in 82% and 68% yields, respectively. In **1g** and **1h**, minor amounts *ortho*-allylated products were also observed. Interestingly, in the case of 2,5-dimethoxybenzoic acid (**1i**), exclusively *ortho*-allylated benzoic acid **3ia** was formed in 75% yield. 4-Methoxybenzoic acid (**1j**) and 4-fluorobenzoic acid (**1k**) reacted with **2a** to give products **3ja** and **3ka** in 35% and 57% yields, respectively. Interestingly, thiophene-2-carboxylic acid (**1l**) was also efficiently involved in the reaction, giving product **3la** in 55% yield.

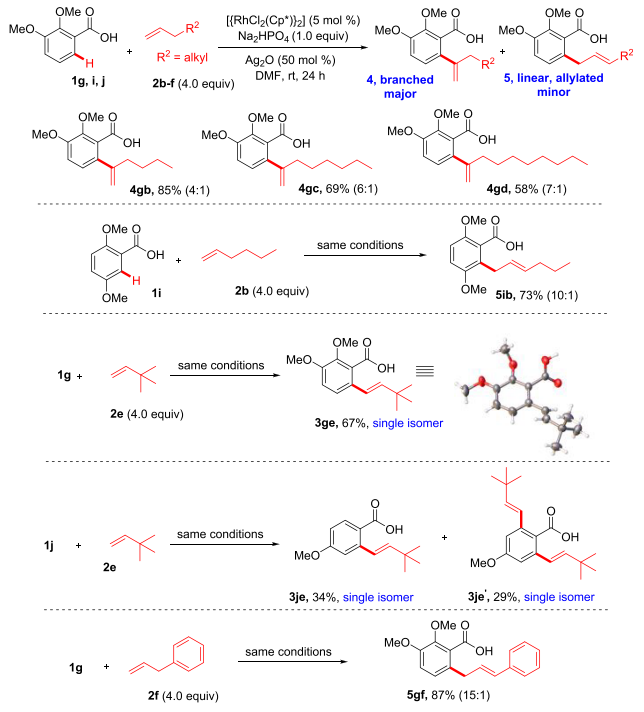
The vinylation reaction was further examined with substituted benzoic acids **1m−s**. The alkenylation reaction is highly regioselective, and the vinylation selectively takes place at the less hindered side. The reaction of 3-methoxy- (**1m**), 3-methyl- (**1n**), and 3-bromobenzoic acids (**1o**) with **2a** afforded *ortho*-olefinated products **3ma**, **3na**, and **3oa** in 57%, 75%, and 55% yields, respectively. Gratifyingly, the strong electron-withdrawing 3-NO_2 benzoic acid (**1p**) was also involved in the reaction, furnishing product **3pa** in 43% yield with an 8:1 *E*/*Z* ratio. In these reactions, alkenylation selectively takes place at the less hindered C6 position. 3,4-Dimethoxy (**1q**) and 3,4-dimethylbenzoic acids (**1r**) reacted with **2a** to afford *ortho*-olefinated products **3qa** and **3ra** in 72% and 77% yields, respectively. In the reaction, the C−H activation takes place at the C6 position of aromatic acids. Similarly, 2-naphthoic acid (**1s**) reacted with **2a** to give product **3sa** in 62% yield. In the reaction, vinylation takes place at the C3 position.

The olefination reaction was examined with unactivated α-substituted olefins (4.0 equiv) (Scheme 3). In the reaction, mixtures of branched vinylated as well as linear allylated or vinylated products were observed. These α-substituted olefins are substantial starting materials for the preparation of synthetic fatty acids, synthetic lubricants, polymers, and plasticizers. The reactions of 1-hexene (**2b**), 1-octene (**2c**), and 1-decene (**2d**) with **1g** afforded the corresponding vinylated products **4gb**, **4gc**, and **4gd** in 85%, 69%, and 58% yields, respectively. In the reaction, linear type allylated

Scheme 2. Scope of Aromatic and Heteroaromatic Acids



Scheme 3. Scope of Unactivated Aliphatic Alkenes



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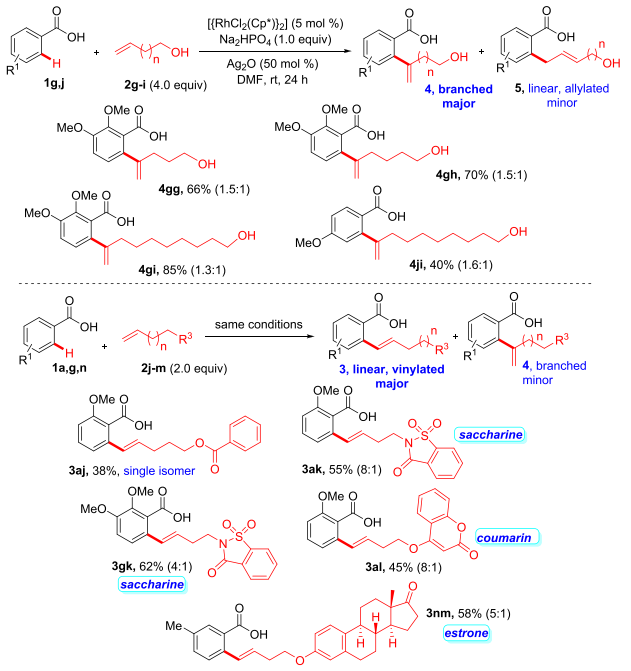
product **5** was observed in a minor amount. It is important to note that as the length of carbon chain of α-olefin increases the selectivity of branched vinylated product increases. In 1-hexene (**2b**), 1-octene (**2c**), and 1-decene (**2d**), branched/linear alkenes were observed in 4:1, 6:1, and 7:1 ratios. The position of the substituent on the aromatic acid also plays a crucial role for the control of selectivity of branched vs linear alkenes. In the reaction of 2,5-dimethoxybenzoic acid (**1i**), linear *ortho*-allylated benzoic acid **5ib** was observed in 73% yield with high selectivity. 3,3-Dimethylbut-1-ene (**2e**) reacted with **1g** at 80 °C for 24 h to give exclusively *ortho*-vinylated benzoic acid **3ge** in 67% yield. The structure of product **3ge** was confirmed by single-crystal X-ray crystallography (CCDC 1990502). Similarly, 4-methoxybenzoic acid (**1j**) with **2e** at 80 °C for 24 h gave the expected product **3je** in 34% yield. In addition, dialkenylation product **3je′** was also observed in 29% yield in the reaction. Allylbenzene (**2f**) reacted with **1g** to afford *ortho*-allylated benzoic acid **5gf** in 87% yield along with a minor amount of branched alkene in a 15:1 ratio.

Subsequently, the olefination reaction was tested with functional group substituted unactivated olefins (Scheme 4).

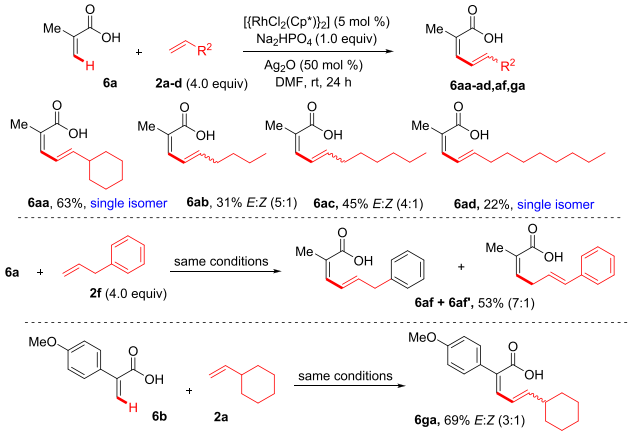
Scheme 4. Scope of Functionalized Unactivated Alkenes



Hydroxy group substituted alkenes such as pent-4-en-1-ol (**2g**), hex-5-en-1-ol (**2h**), and dec-9-en-1-ol (**2i**) reacted with **1g** to furnish branched as well as allylated products **4gg**, **4gh**, and **4gi** in 66%, 70%, and 85% yields, respectively. Similarly, 4-methoxybenzoic acid (**1j**) reacted with **2i** to provide branched as well as allylated products **4ji** in 40% yield. Further, ester-, amine-, and ether-substituted unactivated olefins (2 equiv) were examined. The reaction of ester-functionalized alkene **2j** with **1a** provided exclusively vinylated product **3aj** in 38% yield in a highly regioselective manner. Heterocyclic functionalized alkenes such as saccharine **2k** react with **1a** or **1g** to afford olefinated products **3ak** and **3gk** in 55% and 62% yields, respectively. In the reaction, a minor amount of branched alkene was also observed. Furthermore, unactivated alkenes containing a coumarin **2l** or estrone **2m** group reacted with **1a** or **1n** to provide olefinated products **3al** and **3nm** in 45% and 58% yields, respectively. In the reaction, a minor amount of branched alkene product was observed.

In addition, a highly challenging β-C−H olefination of substituted acrylic acids with unactivated alkenes was also examined (Scheme 5). The reaction of α-methyl acrylic acid

Scheme 5. Scope of Acrylic Acids with Unactivated Alkenens



(**6a**) with vinylcyclohexene (**2a**) under similar reaction conditions provided *trans*-diene derivative **6aa** in 63% yield in a highly stereoselective manner. Similarly, 1-hexene (**2b**), 1-octene (**2c**), and 1-decene (**2d**) reacted with **6a** to give expected diene derivatives **6ab**−**ad** in moderate 31%, 45%, and 22% yields, respectively, with 4:1 to 5:1 *E*/*Z* ratios. When α-methyl acrylic acid (**6a**) was treated with **2f**, the corresponding olefinated products **6af** + **6af′** were observed in 53% yield with a 7:1 ratio. An α-substituted acrylic acid such as (2-(4-methoxyphenyl)acrylic acid (**6b**) efficiently reacted with **2a** to deliver β-C−H olefinated product **6ga** in 69% yield with a 3:1 *E*/*Z* ratio. The reaction was not compatible with acrylic acid and β-methyl- and phenyl-substituted acrylic acids.

To understand the reaction mechanism, the following mechanistic studies were carried out (Scheme 6). Treatment of **1j** with CD_3COOD under the optimized reaction conditions provided **D-1j** in 96% yield with 37% deuterium incorporation at both *ortho* carbons. Further, the reaction of **1j** with **2a** afforded *ortho*-olefinated product **D-3ja** in 32% yield with 20% deuterium incorporation at the *ortho*-carbon of benzoic acid. This result clearly explains that the *ortho* C−H bond activation is a reversible process. Later, a rhodacycle intermediate **7a** was isolated in 52% yield in the reaction of **1r** with a stoichiometric amount of $[Cp^*RhCl_2]_2$, $KHCO_3$, and DMSO in MeOH solvent under air at 60 °C for 1 h. Later, a rhodacycle intermediate **7a** was treated with **2a**, giving *ortho*-olefination product **3ja** in 75% yield. This result clearly reveals that the five-membered rhodacycle intermediate is formed in the reaction. Finally, the intermolecular competitive experiment between **1j** and **1k** with **2a** was carried out. In the reaction, products **3ja** and **3ka** were observed in 33% and 30% yields, respectively. This result suggests that the electronic effect of benzoic acids has no apparent impact on the reaction and it proceeds via an acetate-assisted deprotonation pathway.

To account for the present alkenylation reaction, a plausible reaction mechanism is proposed in Scheme 7. The reaction of aromatic acid **1** with $[Cp^*RhCl_2]_2$ in the presence of Ag_2O and

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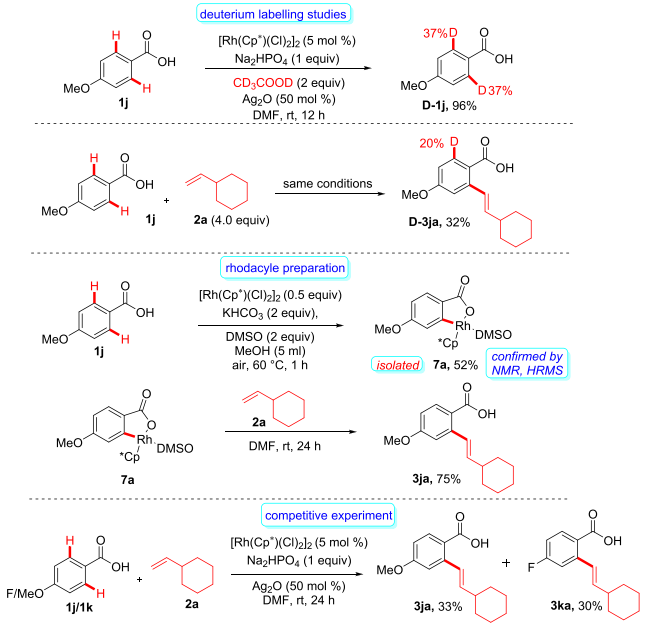
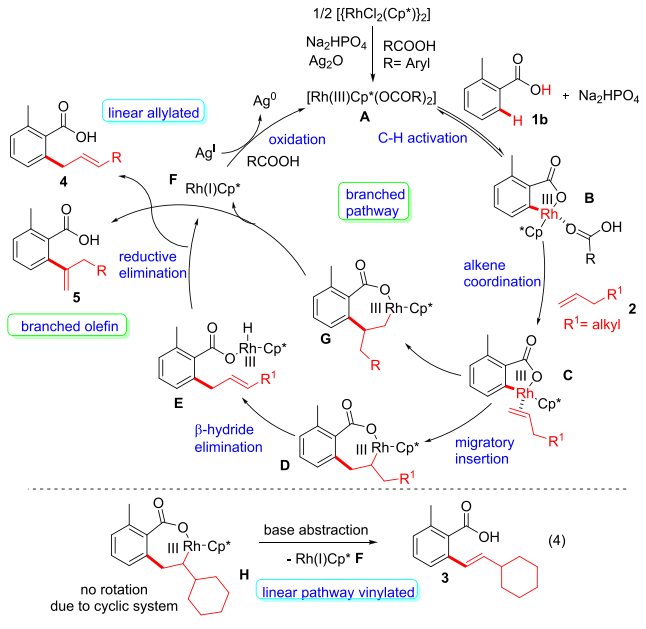
Scheme 6. Mechanistic Studies



Scheme 7. Proposed Mechanism



Na_2HPO_4 afforded complex **A**. Complex **A** reacts with benzoic acid **1** to provide a five-membered rhodacycle intermediate **B** via a carboxylate-assisted deprotonation pathway. Then the replacement of RCOOH by unactivated olefin **2a** forms intermediate **C**. Coordinative 1,2-migratory insertion (less hindered side) of an alkene bond into the Rh−carbon bond of intermediate **C** gives a rhodacycle intermediate **D**. Then intermediate **D** undergoes β-hydride elimination at the freely rotatable CH_2 side to form intermediate **E**. Later, intermediate **E** undergoes reductive elimination to give a Rh(I) complex **F** and *ortho*-allylated benzoic acid **4**. Later, the active Rh(III) species **A** is regenerated in the reaction of a rhodium(I) complex **F** with Ag_2O and RCOOH. Intermediate **G** is crucial for the formation of branched type vinylated product **5**. Intermediate **G** is formed by the coordinative insertion of the Rh−C bond of intermediate **C** with the β-carbon of an alkene **2**. Intermediate **G** undergoes base-prompted dehydrometalation to give intermediate **F** and a branched-type vinylated product **5**.[7e] Later, the rhodium(I) complex **F** was oxidized into active Rh(III) species **A** in the presence of Ag_2O and RCOOH. A similar type of base-assisted proto-demetalation is involved in the formation of linear-type vinylated product formation **3**. For a typical β-hydride elimination, the *syn* coplanarity arrangement of metal with Cβ-H is needed. The rotation to achieve *syn* coplanarity in intermediate **G** is restricted due to the cyclic system. In this case, Na_2HPO_4 or Ag_2O could deprotonate the benzylic proton of intermediate **H** (eq 4). It is important to note the possibility that typical β-hydride elimination in eq 4 for the formation of product **5** from intermediate **G** cannot be completely excluded. In OH group substituted alkenes **2g−i**, linear as well as branched products were observed equally. It is assumed that the OH group coordinates with a metal in intermediates **D** and **G** to provide linear as well as branched products.

In conclusion, we have described an unprecedented C−H alkenylation of commercially available aromatic/vinylic acids with unactivated olefins in the presence of a rhodium(III) complex at room temperature. The olefination reaction has broad substrate scope, and various substituted aromatic acids as well as functionalized unactivated alkenes were compatible for the reaction. A convincing reaction mechanism is proposed and supported by deuterium-labeling studies and isolation of a five-membered rhodacycle intermediate.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01636.

General experimental procedures and characterization details, ^{1}H NMR and ^{13}C NMR spectra of all compounds, single-crystal X-ray diffraction data for compound **3ge** (PDF)

Accession Codes

CCDC 1990502 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

https://dx.doi.org/10.1021/acs.orglett.0c01636
Org. Lett. XXXX, XXX, XXX−XXX

■ ACKNOWLEDGMENTS

We thank the DST-SERB (CRG/2018/000606), India, for the support of this research. S.J. thanks IITM for an HTRA Fellowship.

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