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Microwave-assisted Rhodium(I)-Catalyzed C8–Regioselective C–H Alkenylation and Arylation of 1,2,3,4-Tetrahydroquinolines with Alkenyl and Aryl Carboxylic Acids

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Abstract. Rh(I)-catalyzed C8-selective C–H alkenylation and arylation of 1,2,3,4-tetrahydroquinolines with alkenyl and aryl carboxylic acids under microwave assistance have been realized. Using [Rh(CO)$_2$(acac)] as the catalyst and Piv$_2$O as the acid activator, 1,2,3,4-tetrahydroquinolines undergo C8-selective decarbonylative C–H alkenylation with a wide range of alkenyl and aryl carboxylic acids, affording the C8-alkenylated or arylated 1,2,3,4-tetrahydroquinolines. This method enables the synthesis of C8-alkenylated 1,2,3,4-tetrahydroquinolines that would otherwise be difficult to access by means of conventional C–H alkenylation protocols. Moreover, this catalytic system also works well in C8-selective decarbonylative C–H arylation of 1,2,3,4-tetrahydroquinolines with aryl carboxylic acids. The catalytic activity strongly depends on the choice of the *N*-directing group, with the readily installable and removable *N*-(2-pyrimidyl) group being optimal. The catalytic pathway is elucidated by mechanistic experiments.

Keywords: 1,2,3,4-tetrahydroquinoline; C–H activation; microwave-assisted; alkenylation; carboxylic acids

Introduction

1,2,3,4-Tetrahydroquinolines are key motifs in a variety of natural products, biologically active molecules and pharmacologically important compounds (Figure 1).[1] Over the past few decades, extensive efforts have been devoted to developing methods for the construction of these valuable N-heterocycles. While the catalytic reduction of quinolines to 1,2,3,4-tetrahydroquinolines has been of continuing interest in the synthetic community,[2] other types of reactions, including intramolecular cyclization reactions,[3] Povarov-type reactions,[4] functionalization of 1,2-dihydroquinolines[5] and others,[6] have also undergone extensive studies as promising alternatives for the synthesis of 1,2,3,4-tetrahydroquinolines.

In recent years, the development of transition metal-catalyzed direct C–H activation/functionalization have emerged as powerful methods to elaborate heterocycles.[7] Application of these methods to the C–H activation/functionalization of 1,2,3,4-tetrahydroquinolines have been reported.[8] Of particular note, the introduction of *N*-directing groups enable regioselective C8–H chlorination,[8k] arylation,[8o, 8p] acylation,[8l, 8q] amination,[8h, 8i] hydroxylation,[8j] formylation[8m] and even alkylation[8n, 8r] of 1,2,3,4-tetrahydroquinolines in the presence of palladium, rhodium or ruthenium catalysts.

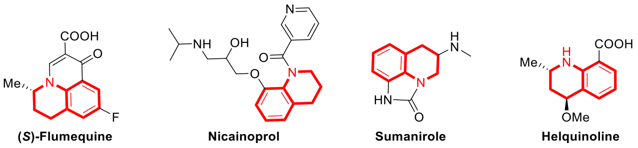
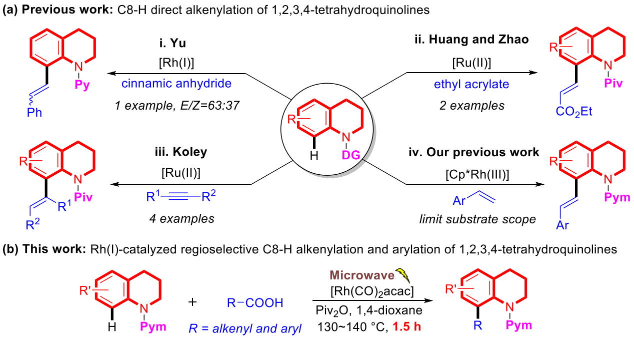


Figure 1. Examples of drug molecules containing 1,2,3,4-tetrahydroquinoline skeletons.

Efforts toward the regioselective C8–H alkenylation of 1,2,3,4-tetrahydroquinolines have met with limited success, despite the potential applications of such products.[8n, 9] Yu and co-workers reported only one case of a Rh(I)-catalyzed decarbonylative alkeynlation of 1-(pyridine-2-yl)-1,2,3,4-tetrahydroquinoline with cinnamic anhydride (Scheme 1a, i).[9a] Huang and Zhao reported two cases of Ru(II) -catalyzed direct alkenylation of *N*-Piv-1,2,3,4-tetrahydroquinoline with ethyl acrylate (Scheme 1a, ii).[9b] Four examples of a Ru(II)-catalyzed C8–H alkenylation of *N*-Piv-1,2,3,4-tetrahydroquinoline with internal alkynes were reported by Koley et al. (Scheme 1a, iii).[9c] Very recently, our group accomplished a Rh(III)-catalyzed C8-selective C–H alkenylation of 1-(pyrimidin-2-yl)-1,2,3,4-tetrahydroquinolines with styrenes (Scheme 1a. iv).[8n] Despite these advances, the substrate generality and functional group tolerance in these reactions were limited. Thus, development of a general catalytic protocol for direct C8–H alkenylation of 1,2,3,4-tretrahydroquinolines remains desirable.

Recently inexpensive, easily accessible, safe and structurally diverse carboxylic acids have been demonstrated as advantageous coupling reagents in transition metal-catalyzed decarboxylative and decarbonylative coupling reactions.[10] In particular, the use of alkenyl carboxylic acids as alkenyl sources in transition-metal catalyzed decarbonylative alkenylation of C–H bonds has captured considerable attention, and a wide variety of alkenylated products including those that would otherwise be difficult to access by means of conventional C–H alkenylation methods could be generated readily. In this context, we were curious if alkenyl carboxylic acids could act as suitable alkenylation reagents for the directed alkenylation of *N*-(pyrimidin-2-yl)-1,2,3,4-tetrahydroquinolines. Based on our previous studies on Rh(I)-catalyzed decarbonylative functionalization of (hetero)arene C–H bonds[11], we herein report the Rh(I)-catalyzed C8-selective C–H alkenylation of *N*-(pyrimidin-2-yl)-1,2,3,4-tetrahydroquinolines using alkenyl carboxylic acids as the alkenyl source (Scheme 1b). This protocol is characterized by an easy-to-handle catalytic system. To enhance the synthetic efficiency, the reaction was conducted under microwave conditions with short reaction times. Moreover, this protocol can be readily extended to C8-selective C–H arylation of 1,2,3,4-tetrahydroquinolines using aryl carboxylic acids as the aryl source.

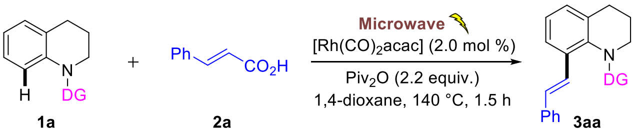


Scheme 1. Catalytic directed C8-alkenylation of 1,2,3,4-tetrahedroquinolines.

Results and Discussion

We commenced our study with directed alkenylation of *N*-(pyrimidin-2-yl)-1,2,3,4-tetrahydroquinoline (**1a**) with *trans*-cinnamic acid (**2a**) using Piv_2O as the activator under Rh(I) catalysis (Table 1). We were pleased to discover that the reaction of **1a** and **2a** in the presence of [Rh(CO)$_2$(acac)] (2.0 mol%) at 140 °C in 1,4-dioxane provided the desired product **3aa** in 91% isolated yield when conducted in a microwave reactor (250 psi, 150 W) for only 1.5 h (Table 1, entry 1). A solvent screen quickly identified 1,4-dioxane as the optimum reaction medium (Table 1, entries 2–4). Changing the rhodium source to $[Rh(CO)_2Cl]_2$, $[Rh(PPh_3)_3Cl]$ or $[Rh(COD)Cl]_2$ did not lead to any improvement in the yield of **3aa** (Table 1, entries 5–7). Poor results were obtained upon replacing Piv_2O with dimethyl decarbonate (DMDC), Boc_2O or PivCl as the acid activator (Table 1, entries 8–10). Further optimization involving decreasing the catalyst loading, reaction time or temperature led to dramatically lowered yields (Table 1, entries 11–13). Notably, the reaction failed in the absence of a rhodium catalyst (Table 1, entry 14). Finally, the effect of the *N*-directing group in this reaction was examined. No reaction occurred when free 1,2,3,4-tetrahydroquinoline or 1,2,3,4- tetrahydroquinoline bearing other substituents on the nitrogen, such as Ac, CF_3CO, PhCO, Piv, Me_2NCO, Me or Ph were employed. Notably, the 2-pyrimidyl resulted in 81% yield and obtained the *trans*-alkenylation product **3a'a**. These results clearly indicated that the judicious choice of the *N*-directing group is critical for catalysis in this transformation (For details see the Supplementary Information, Table S2).

Table 1. Optimization of the reaction conditions.[a)]

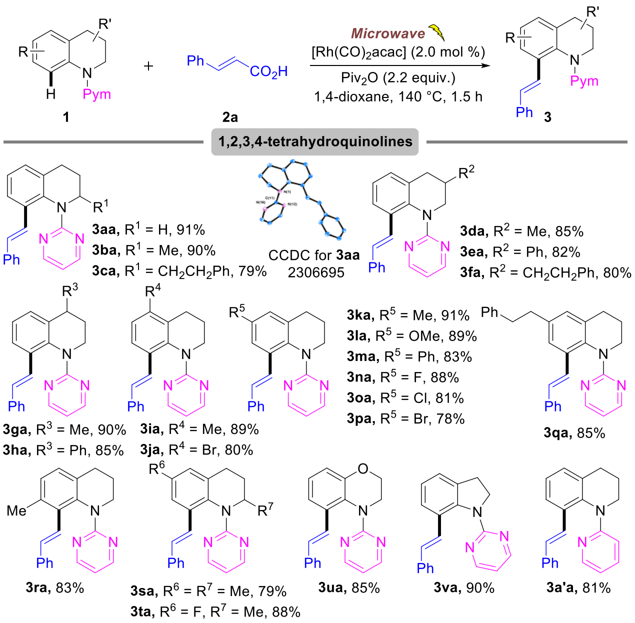


Entry	Deviation	Yield (%)[b)]
1	none	93 (91)[c)]
2	toluene as the solvent	65

3	MeCN as the solvent	0
4	*o*-xylene as the solvent	57
5	[Rh(CO)$_2$Cl]$_2$ instead of [Rh(CO)$_2$(acac)]	77
6	[Rh(PPh$_3$)$_3$Cl] instead of [Rh(CO)$_2$(acac)]	23
7	[Rh(COD)Cl]$_2$ instead of [Rh(CO)$_2$(acac)]	36
8	DMDC instead of Piv$_2$O	89
9	Boc$_2$O instead of Piv$_2$O	18
10	PivCl instead of Piv$_2$O	11
11	[Rh(CO)$_2$acac] (1.0 mol %)	77
12	reaction temperature 130 °C	75
13	reaction time 1 h	81
14	without [Rh(CO)$_2$(acac)]	0

[a] General reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), Piv$_2$O (0.22 mmol), [Rh(CO)$_2$(acac)] (2.0 mol %), 1,4-dioxane (1.0 mL), 140 °C, 250 psi, 150 W, 1.5 h, under air. [b] Yields were determined by ^{1}H-NMR analysis of unpurified reaction mixtures with internal standard CH$_2$Br$_2$. [c] Isolated yield. COD: 1,5-cyclooctadiene, acac: acetylacetone, DMDC: dimethyl dicarbonate.

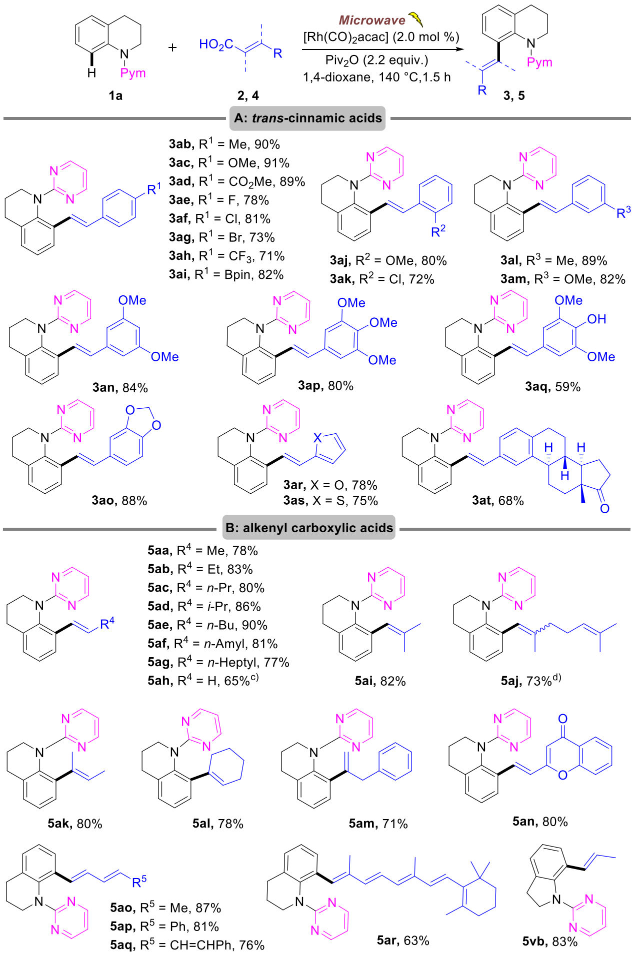
Table 2. Scope of 1,2,3,4-Tetrahydroquinolines.[a,b]



[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), Piv$_2$O (0.44 mmol), [Rh(CO)$_2$(acac)] (2.0 mol %), 1,4-dioxane (2.0 mL, 0.1 M), 140 °C, 250 psi, 150 W, 1.5 h, under air. [b] Isolated yield.

With the optimized conditions in hand, we proceeded to explore the alkenylation of a series of 1,2,3,4-tetrahydroquinolines with *trans*-cinnamic acid **2a** (Table 2). It was found that a series of C2- to C6-substituted 1,2,3,4-tetrahydroquinolines (**1a–1q**) underwent smooth alkenylation with **2a** exclusively at the C8-position to deliver the corresponding products (**3aa–3qa**) in 78–91% yields. A high tolerance of functional groups, including halides at the C5 and C6-positions, was noted. The structure of **3aa** was verified by single-crystal X-ray diffraction (CCDC 2306695). Notably, the C7-substituted *N*-(pyrimidin-2-yl)-1,2,3,4-tetrahydroquinoline (**1r**) was compatible with our Rh(I)-catalyzed system and afforded the alkenylated product **3ra** in 83% yield, despite the increased steric hindrance. The 2,6-disubstituted 1,2,3,4-tetrahydroquinolines (**1s** and **1t**) also readily engaged under the current conditions to give the corresponding products (**3sa** and **3ta**) in 79% and 88% yields, respectively. Substrates could be extended to the 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine **1u** and *N*-(pyrimidin-2-yl)-indoline **1v**, with the products **3ua** and **3va** generated in 85% and 90% yields, respectively. Of note, we investigated the N-(pyridine-2-yl)-1,2,3,4-tetrahydroquinoline **1a'** under our alkenylation method and obtained the *trans*-alkenylation product **3a'a** in 81% yield. High stereoselectivities (*E*/*Z* > 20:1) were observed in all cases studied.

Table 3. Scope of Cinnamic Acids and Alkenyl Carboxylic Acids.[a,b]

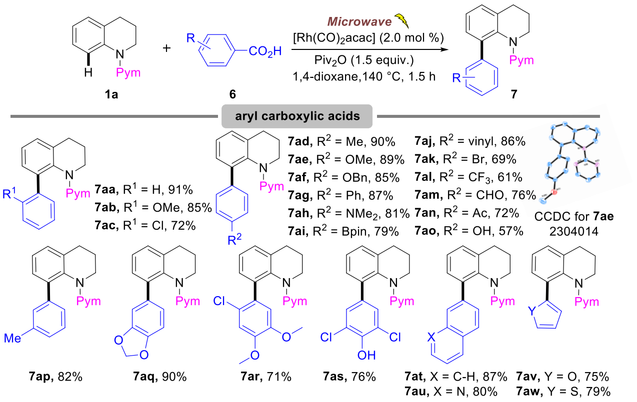


[a] Reaction conditions: **1a** (0.2 mmol), **2** or **4** (0.4 mmol), Piv$_2$O (0.44 mmol), [Rh(CO)$_2$(acac)] (2.0 mol %), 1,4-dioxane (2.0 mL, 0.1 M), 140 °C, 250 psi, 150 W, 1.5 h, under air. [b] Isolated yield. [c] Reaction time: 2 h. [d] Ratio of isomers: *Z*/*E* = 1:2 d.r.

We subsequently investigated the reactivity of various *trans*-cinnamic acids and alkenyl carboxylic acids with **1a** (Table 3). As shown in Table 3A, a wide range of cinnamic acids (**2b–2m**) with mono-substituted aromatic rings participated in the alkenylation with **1a** to exclusively furnish the desired C8-alkenlayed 1,2,3,4-tetrahydroquinoline products (**3ab–3am**) in 71–91% yields. The alkenylation proved to be insensitive to the nature of the substituents on the aryl ring, with various electron-donating (methyl, methoxy) and withdrawing substituents (CO_2Me, CF_3) participating. Sensitive functional groups, including Bpin and halogens, were all well tolerated, providing products **3an–3ai** in 71–90% yields. Similarly, the more complex cinnamic acids (**2n–2q**), with polysubstituted aromatic rings, displayed good reactivity, affording the target products (**3an–3aq**) in 59–88% yields. Among them, it is worth noting that a trisubstituted cinnamic acid bearing an active hydroxyl group provided the target product **3aq** in 59% yield under the standard conditions. Heteroaryl groups are important substructures in medicinal chemistry.[12] We, therefore, examined the compatibility of heteroaryl cinnamic acids with **1a**. The heteroaryl cinnamic acids bearing 2-furanyl and 2-thienyl (**2r** and **2s**) reacted smoothly with **1a** to give the desired products **3ar** and **3as** in 78% and 75% yields, respectively. Importantly, the estrone-derived cinnamic acid **2t** proved to be equally effective in this transformation, forming **3at** in 68% yield, indicating the robustness of the current catalytic system.

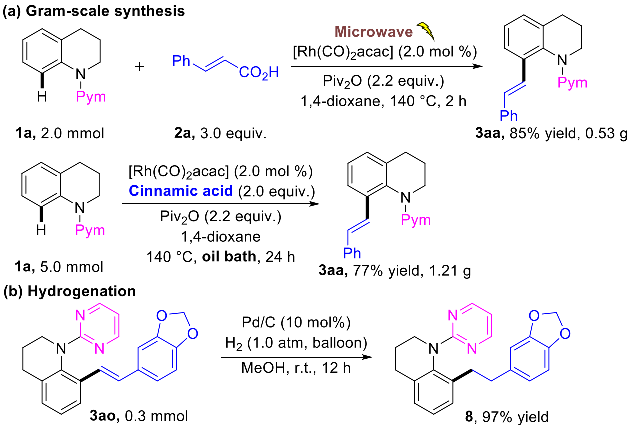
To further demonstrate the potential of this catalytic method, we extended the reaction to substituted alkenyl carboxylic acids (Table 3B). It was found that treatment of various β-alkylated acrylic acids (**4a–4g**) with **1a** resulted in formation of C8-alkenylated 1,2,3,4-tetrahydroquinoline products (**5aa–5ag**) in 77–90% yields, irrespective of the nature of the β-alkyl groups. Notably, acrylic acid **4h** was also reactive, giving rise to the target product **5ah** in 65% yield after prolonging the reaction time to 2 h. Furthermore, trisubstituted acrylic acids (**4i–4l**), including the naturally occurring geranic acid **4j** and tiglic acid **4k** were suitable substrates, producing **5ai–5al** in 73–82% yields. The formation of a mixture of *Z*/*E* isomers in the case of **5aj** was likely due to the low stereochemical purity of the starting geranic acid **4j** (~ 1:2 d.r.). The α-substituted acrylic acid **4m** (2-benzylacrylic acid) was a competent substrate, delivering **5am** in 71% yield. Remarkably, conjugated polyene carboxylic acids (**4o-4r**) were also coupling partners in this transformation. Subjecting the conjugated dienyl carboxylic acids (**4o–4p**) to this protocol afforded the desired products **5ao** and **5ap** in 63–87% yields. The trienyl **4q** reacted to produce the triene product with 76% yield. The bioactive retinoic acid **4r** furnished pentaene **5ar** in 63% yield. Reaction of the indoline-based substrate was also explored. In the event, crotonic acid **4a** reacted with *N*-(pyrimidin-2-yl) indoline **1v** to provide the C7-alkenylated indoline product **5vb** in 83% yield.

Table 4. Scope of Aryl Carboxylic Acids.[a,b)]



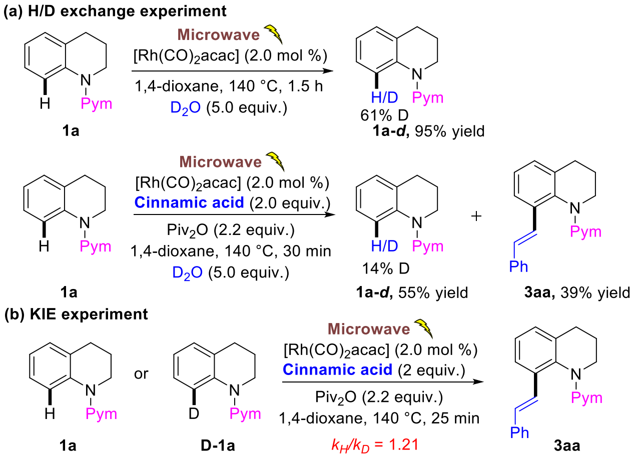
a) Reaction conditions: **1a** (0.2 mmol), **6** (0.24 mmol), Piv_2O (0.3 mmol), $[Rh(CO)_2(acac)]$ (2.0 mol %), 1,4-dioxane (2.0 mL, 0.1 M), 130 °C, 250 psi, 150 W, 1.5 h, under air. b) Isolated yield.

To demonstrate the synthetic utility of this transformation, a scale-up reaction of **1a** with **2a** was evaluated. As can be seen in Scheme 2a, the target product **3aa** was obtained in 85% yield on a 2.0 mmol scale under microwave assistance (Scheme 2a). It is noteworthy that under thermal heating conditions (at 140 °C in an oil bath without microwave irradiation), this reaction could be scaled to 5.0 mmol, furnishing **3aa** in 77% yield, albeit with a long reaction time of 24 h. Moreover, hydrogenation of **3ao** with a Pd/C catalyst at room temperature led to the formation of product **8** in 97% yield (Scheme 2b).

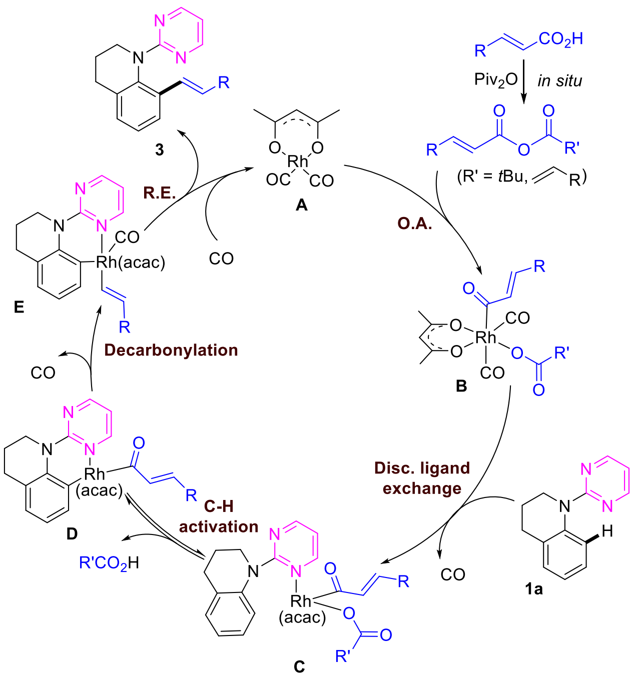


Scheme 2. Synthetic Applications.

In order to elucidate the reaction mechanism, a series of experiments were conducted. First, as exemplified in Scheme 3a, an H/D exchange experiment with substrate **1a** and D_2O, but in the absence of an unsaturated carboxylic acid coupling partner and the activator Boc_2O, revealed that a significant H/D scrambling was observed at the C8 position of **1a** by ^1H NMR. Furthermore, when the standard vinylation reaction was conducted with 5 equiv D_2O and quenched at low conversion, starting **1a** was recovered in 55% yield and contained 14% C8-D incorporation. These results support the reversibility of the C–H activation step. Moreover, a minor kinetic isotope effect (KIE, k_H/k_D) of 1.2 was observed, suggesting that the C–H bond cleavage may not be involved in the turnover-limiting step (TLS) (Scheme 3b).



Scheme 3. Experiments to Elucidate the Reaction Mechanism.



Scheme 4. Proposed Reaction Mechanism.

Based on the aforementioned results, and previous reports,[11] the key steps in a plausible mechanism for the alkenylation is proposed in Scheme 4. First, the acid reacts with Piv_2O to generate an anhydride, which undergoes oxidative addition to a Rh(I) species **A** to yield the Rh(III) intermediate **B**. Then, ligand exchange for the substrate follows, giving intermediate **C**. The C8-selective C−H activation of *N*-(pyrimidin-2-yl)-1,2,3,4-tetrahydroquinoline generates the acid and the six-membered rhodacycle **D**, rather than a second oxidative addition, we prefer a concerted metalation deprotonation (CMD) by the carboxylate ligand. Then, rhodacycle intermediate **D** subsequently undergoes decarbonylation to release CO and deliver the Rh-alkenyl intermediate **E**. Finally, **E** undergoes reductive elimination to liberate the product **3**, and regenerate the active catalyst Rh(I) species **A**.

Conclusion

In conclusion, we have developed a Rh(I)-catalyzed decarbonylative alkenylation and arylation at the C8 position of 1,2,3,4-tetrahydroquinolines with inexpensive carboxylic acids under air. This method is applicable to a wide range of substituted cinnamic acids, acrylic acids, conjugated polyene carboxylic acids and aryl carboxylic acids, enabling facile access to C8-alkenylated and arylated 1,2,3,4-tetrahydroquinolines in 57–91% yields. This protocol is anticipated to have promising applications in the production of biologically active molecules and natural products.

Experimental Section

To an oven-dried 10 mL pressure vessel equipped with a stir bar were sequentially added 1-(pyrimidin-2-yl)-1,2,3,4-tetrahydroquinolines **1** (0.2 mmol), alkenyl carboxylic acids **2** or **4** (0.4 mmol), $[Rh(CO)_2acac]$ (1.1 mg, 0.004 mmol), Piv_2O (89.3 µL, 0.44 mmol) and 1,4-dioxane (2.0 mL). Then the vessel was sealed, and the reaction mixture was irradiated in a monomodal microwave reactor with power of 150 W and pressure of 250 Psi at 140 °C for 1.5 h. After that, the tube was cooled to room temperature, saturated sodium bicarbonate (3.0 mL) was added and the resulting solution stirred to quench the excess acid. The resulting mixture was extracted three times with DCM (3 × 5.0 mL). The organic phases were combined and dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by flash column chromatography (hexane/EtOAc) to give the pure product.

Acknowledgements

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[13] Deposition Numbers CCDC 2306695 (**3aa**), CCDC 2304014 (**7ae**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and FachinformationszentrumKarlsruhe Access Structures service.

RESEARCH ARTICLE

Microwave-assisted Rhodium(I)-Catalyzed C8–Regioselective C–H Alkenylation and Arylation of 1,2,3,4-Tetrahydroquinolines with Alkenyl and Aryl Carboxylic Acids

Adv. Synth. Catal. **Year**, *Volume*, Page – Page

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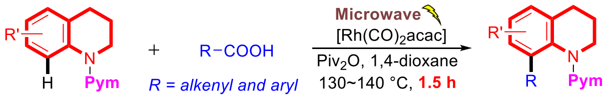

- *Microwave-assisted*
- *Short reaction time*
- *High stereoselectivity (E/Z > 20:1 d.r.)*
- *Regioselective C8-alkenylation and arylation*

85 examples
57-91% yields