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Ru(II)-Catalyzed Oxidative *Heck*-Type Olefination of Aromatic Carboxylic Acids with Styrenes through Carboxylate-Assisted C−H Bond Activation

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Supporting Information

ABSTRACT: A straightforward synthesis of 2-styrylbenzoic acids from aryl carboxylic acids is disclosed through a carboxylate-assisted coupling under Ru(II) catalysis. This protocol is simple and exhibits broad scope with high tolerance of common organic functional groups, providing good to excellent yields of diverse olefinated products. The efficacy of this protocol has been showcased through sequential syntheses of isochromanone, isocoumarin, and formal synthesis of anacardic acid derivative in good yields.

Alkenyl aromatic carboxylic acids, such as 2-styrylbenzoic acid and derivatives thereof, have profound synthetic importance in light of their existence in many natural products, agrochemicals, pharmaceuticals, and functional materials (Figure 1).[1] They are also high-value synthons for the production of a large number of commodity chemicals and complex molecular architectures including clinical drug candidates.[2] Consequently, devising synthetic protocols toward these scaffolds has remained the focus of general interest. Traditionally, they have been accessed through multistep Wittig and Peterson olefination processes.[2j−l] Although hydroarylation of alkynes[3] and Mizoroki−Heck coupling[1b] of aryl halides are predominant for the synthesis of vinyl arenes, the requirement of prefunctionalized starting materials limits their scope toward this pivotal framework. A straightforward route would be the direct coupling of styrenes with benzoic acids. This approach is advantageous because benzoic acids are inexpensive chemicals with diverse substitution patterns, and styrenes are easily accessible reaction partners. Further, the carboxylic acid functionality can be easily manipulated into various functional groups and also tracelessly removed through protodecarboxylation.[4]

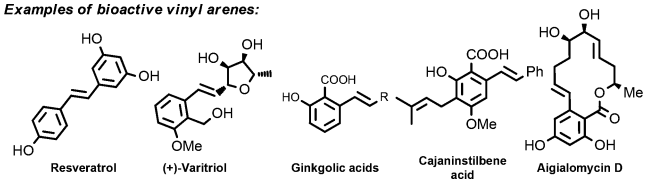
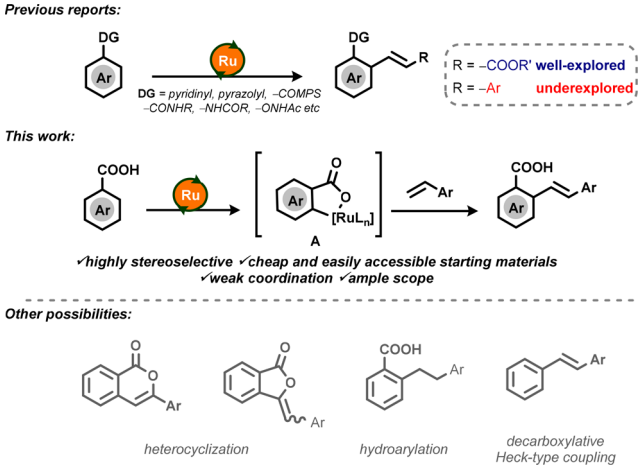


Figure 1. Biologically important 2-styrylbenzoic acid derivatives.

In the past two decades, synthetic chemists have witnessed a radical shift beyond the conventional synthesis toward direct use of otherwise unactivated C−H bonds for the functionalization of organic molecules.[5] In this context, Ru(II)-catalyzed reactions turned out to be very promising.[6] A series of new transformations, particularly oxidative Heck-type coupling, have been developed by exploiting the complex-induced proximity effect with weakly coordinating and synthetically valuable common organic functional groups.[6b,c] While significant advancements on Ru(II)-catalyzed oxidative Heck-type coupling have been accomplished using aromatic amides, esters, anilides, carbamates, and phenol derivatives,[7,8] similar examples with aromatic carboxylic acids are limited (Scheme 1).[9] Furthermore, in a majority of the cases, the choice of coupling partners is largely limited to activated acrylates and only a handful of examples are known with styrene derivatives.[7] There are no reports for the synthesis of 2-styrylbenzoic acids using Ru(II) catalysis.

Scheme 1. Ru-Catalyzed Direct Styrenylation of Benzoic Acids



In our program on the development of ruthenium-catalyzed C−H bond activation protocols with the aid of weakly

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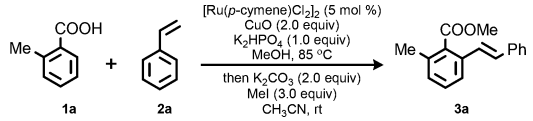
coordinating groups,[10] we envisaged a strategic coupling of styrenes with arene carboxylic acids for the synthesis of 2-styrylbenzoic acids (Scheme 1). Aromatic carboxylic acid, on exposure to Ru(II) catalyst, can form ruthenacycle **A**, which can subsequently undergo facile migratory insertion with styrenes followed by β-hydride elimination to forge the desired product. However, an appropriate reaction condition is necessary to nullify competitive heterocyclization,[11a] hydroarylation,[11b] and decarboxylation[11c] processes.

We instigated our investigation employing commercially available 2-toluic acid (**1a**) and styrene (**2a**) as model substrates. Gratifyingly, when **1a** was reacted to styrene **2a** in the presence of $[Ru(p\text{-cymene})Cl_2]_2$ (5 mol %), K_2HPO_4 (1.0 equiv), and CuO (2.0 equiv) in MeOH solvent at 85 °C for 24 h, oxidative Heck-coupling proceeded smoothly, and the desired product **3a** was obtained in 84% isolated yield after esterification (Table 1, entry 1). It is worth noting that products of other competitive processes depicted in Scheme 1 were not detected under the reaction conditions. Control experiments indicated that all the reagents are necessary for efficient product formation, and ruthenium−copper synergy plays a key role in the transformation (entries 2−4). Alteration of bases provided inferior results (entries 5−6). When CuO was replaced with $Cu(OAc)_2$, yield decreased from 84% to 31% (entry 7). Screening of various organic solvents revealed MeOH as the optimal solvent (entries 8−10). Deterioration in reaction yield was observed when the reaction was performed at lower temperature (entry 11). Further increase of styrene stoichiometry resulted in a negligible improvement in reaction yield (Table 1, entry 12).

Table 1. Optimization of Reaction Conditions[a]

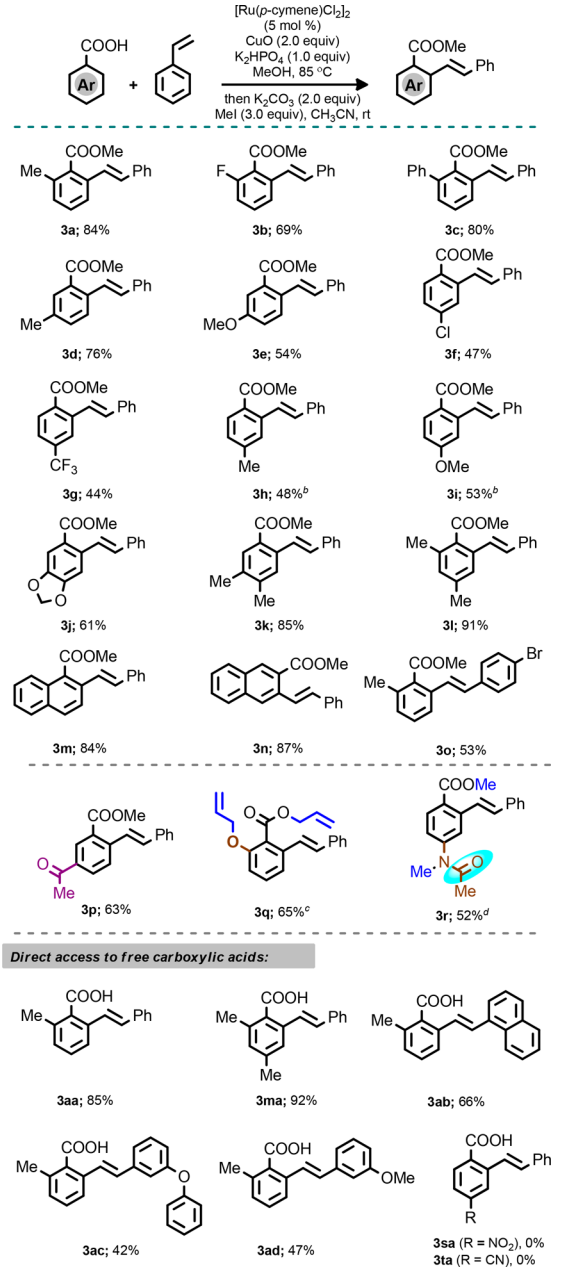


entry	deviation from final catalytic conditions	yield of **3a**
1	none	84%
2	without Ru(II)	
3	without CuO	18%
4	without K_2HPO_4	trace
5	NaOAc instead of K_2HPO_4	73%
6	NaOOCMes instead of K_2HPO_4	mixture[b]
7	$Cu(OAc)_2$ instead of CuO	31%
8	DMF instead of MeOH	trace
9	H_2O instead of MeOH	trace
10	1,4-dioxane instead of MeOH	trace
11	at 75 °C	76%
12	styrene (4.0 equiv)	85%

[a]Reaction conditions: **1** (0.15 mmol), styrene (2.0 equiv), $[Ru(p\text{-cymene})Cl_2]_2$ (5 mol %), K_2HPO_4 (1.0 equiv), CuO (2.0 equiv), MeOH (0.5 mL) at 85 °C for 24 h; then K_2CO_3(2.0 equiv), MeI (3.0 equiv), MeCN (1.0 mL) at room temperature for 4 h; olefination reactions were performed under aerial atmosphere in a screw cap reaction tube, and esterification was performed for the ease of purification via column chromatography. [b]Complex mixture of uncharacterized compounds.

Having established the suitable conditions, we next explored the scope of the reaction (Scheme 2). The reaction is quite general, and a series of benzoic acids having electron donating or withdrawing substitutions at *ortho*-, *meta*-, and *para*-positions effectively participated in this reaction, affording moderate to good yields of desired products (**3a−i**, 44−84%). Disubstituted benzoic acids also underwent smooth transformation, producing **3j−l** in 61−91% yields. Reactions of α- and β-naphthoic acids proceeded regioselectively at the less sterically hindered site, rendering monostyrylated products **3m** and **3n** in 84% and 87% yields, respectively. Olefination was also successful with 4-

Scheme 2. Ru-Catalyzed Mono-olefination of Benzoic Acids[a]



[a]Reaction conditions: **1** (0.15 mmol), styrene (2.0 equiv), $[Ru(p\text{-cymene})Cl_2]_2$ (5 mol %), K_2HPO_4 (1.0 equiv), CuO (2.0 equiv), MeOH (0.5 mL) at 85 °C for 24 h; then K_2CO_3 (2.0 equiv), MeI (3.0 equiv), MeCN (1.0 mL) at room temperature for 4 h; olefination reactions were performed under aerial atmosphere in a screw cap reaction tube. [b]Reactions were performed using 1.5 equiv of styrene, where bis-olefination products were also obtained in 15% and 11% yields for **3h** and **3i**, respectively. [c]Allylation of carboxylic acid and hydroxyl functionalities were performed using allyl bromide (3.0 equiv) instead of MeI. [d]Esterification was performed using NaH (1.2 equiv), MeI (3.0 equiv), THF, 0 °C−rt under N_2 atmosphere.

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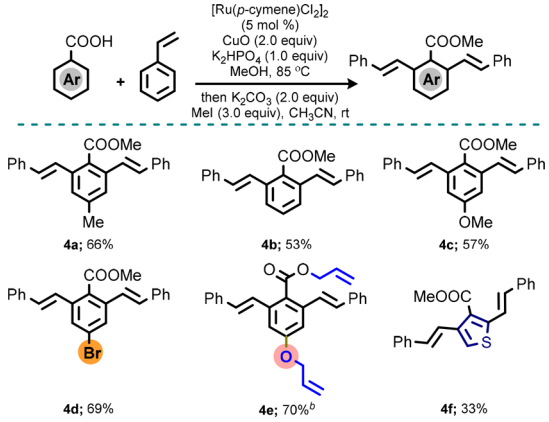
bromostyrene producing **3o** in 53% yield. Interestingly, benzoic acid bearing acetyl group at 3-position offered 63% yield of olefinated product **3p**. To our delight, salicylic acid possessing free hydroxy group was also a good substrate for this process, furnishing **3q** in 65% yield. Notably, the presence of 4-acetamido functionality (**3r**), a known weakly coordinating directing group in C−H bond activation reactions, did not inhibit the reactivity and selectively furnished the mono-olefination at the *ortho*-position of the carboxylic acid group.[12]

The importance of 2-styrylbenzoic acids was showcased through the isolation of 2-styrylated free carboxylic acid derivatives **3aa** and **3ma** in 85% and 92% yields, respectively. Reactions were also fruitful with other styrene derivatives; 1-naphthtyl (**3ab**), 3-phenoxy (**3ac**), and 3-methoxy (**3ad**) derivatives of styrene gave synthetically useful yields of desired carboxylic acids. However, catalytic conditions were ineffective for strongly electron withdrawing nitro- (**3sa**) and cyano-substituted (**3ta**) benzoic acids.

While the catalytic conditions are generally suitable for mono-olefination process, minor bis-olefinated products were also detected specifically in case of benzoic acids having electron-donating substitution at the *para*-position (Scheme 2, **3h,i**). Intrigued by the importance of conjugated vinyl arenes in chemical and material sciences,[13] we reinvestigated the protocol toward the synthesis of bis-olefinated benzoic acids. Pleasingly, when *para*-substituted benzoic acids were treated with excess styrene (3.5 equiv) under standard conditions, bis-styrylated products **4a−d** were obtained in 53−69% yields (Scheme 3).

Scheme 3. Ruthenium-Catalyzed Diolefination of Benzoic Acids[a]

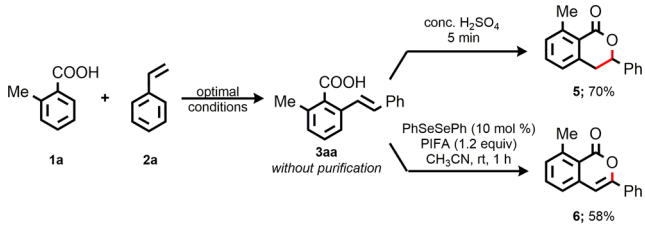


[a]Reaction conditions: **1** (0.15 mmol), styrene (3.5 equiv), [Ru(*p*-cymene)Cl_2]$_2$ (5 mol %), K_2HPO_4 (1.0 equiv), CuO (2.0 equiv), MeOH (0.5 mL) at 85 °C for 24 h; then K_2CO_3 (2.0 equiv), MeI (3.0 equiv), MeCN (1.0 mL) at room temperature for 4 h; olefination reactions were performed under aerial atmosphere in a screw cap reaction tube. [b]Allyl bromide (3.0 equiv) was used instead of MeI.

Substitutions such as bromo (**4d**) and free-hydroxy (**4e**) were well-tolerated in the reaction. Reactions with heteroaromatic carboxylic acid such as thiophene-3-carboxylic acid gave the product **4f** in 33% yield.[14]

Synthetic utility of the process was highlighted through the functionalization of styrylated benzoic acids. Accordingly, the crude product **3aa**, obtained from the reaction of **1a** with **2a** under optimized conditions, was exposed to conc. H_2SO_4, and the isochromanone[15a] **5** was obtained in 70% yield (Scheme 4). Similarly, isocoumarin[15b] **6** was prepared by the treatment of

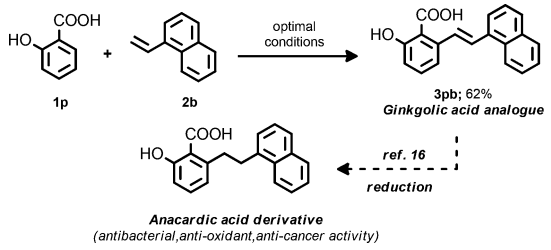
Scheme 4. Sequential Synthesis of Isochromanone and Isocoumarin



crude **3aa** with catalytic amount of diphenyl diselenide in the presence of bis(trifluoroacetoxy)iodobenzene (PIFA) in 58% yield (Scheme 4).[15c]

To extend the applicability of the Ru(II)-catalyzed Heck-type olefination methodology, formal synthesis of anacardic acid derivative was accomplished (Scheme 5).[16] Thus, reaction of

Scheme 5. Formal Synthesis of Anacardic Acids



commercially available salicylic acid with alkene **2b** rendered the key intermediate **3pb**, a ginkgolic acid analogue, in 62% isolated yield. The reduction of **3pb** to anacardic acid derivative was a procedure reported in the literature.[16]

In conclusion, we have developed a straightforward Heck-type styrylation of aromatic carboxylic acids based on Ru(II)-catalyzed weak coordination assisted coupling. The catalytic reaction is operationally simple, highly regioselective, and provides direct access to versatile 2-styrylbenzoic acids in good to excellent yields. The present protocol is also viable toward functionalization of salicylic acid derivatives. It is also interesting to note that the weak coordination of the acid group is effective in the presence of acetamido functionality under the catalytic conditions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03852.

Experimental details and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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