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# Palladium-Catalyzed Direct C−H Arylation of 3-Butenoic Acid Derivatives

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Cite This: *Org. Lett.* 2021, 23, 296−299 Read Online

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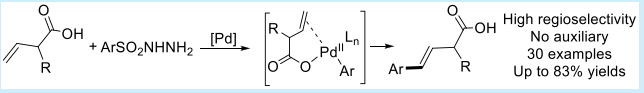
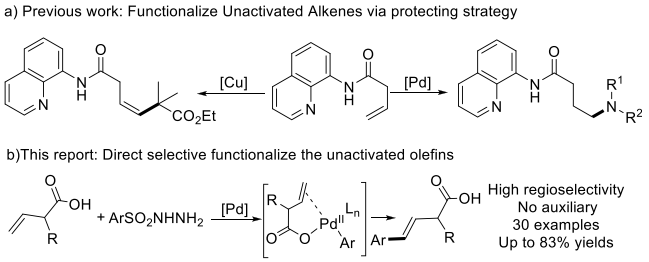
**ABSTRACT:** We report herein a direct method to synthesize 4-aryl-3-butenoic acid through a carboxylic-acid-directed oxidative Heck reaction. The various 4-aryl-3-butenoic acids are easily prepared in moderate to good yields. In view of the promising bioactivity of 4-phenyl-3-butenoic acid previously reported, its derivatives reported here may be bioactive.





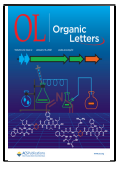

Efficient methods to build various important skeletons are of current interest in organic synthetic chemistry.[1] 4-Phenyl-3-butenoic acid has been found to be anti-inflammatory and an inhibitor of histone deacetylase enzymes and peptidylglycine $\alpha$-hydroxylating monooxygenase (PHM).[2] Such bioactivities have generated interest in 4-phenyl-3-butenoic acid analogues. There are two main approaches to synthesize the analogues.[3] One is the condensation of aryl acetaldehyde with malonic acid and another is through the Wittig reaction of aryl acetaldehyde with 2-(carboxy-ethyl)-triphenylphosphonium bromide as the coupling partner. The research groups of Fu[4] and Wu[5] have transformed cinnamyl alcohol into 4-phenyl-3-butenoic acid derivatives. These methods greatly enrich the synthetic methodology of 4-phenyl-3-butenoic acid derivatives, but the poor availability of prefunctionalized starting material limits the scope of preparing functional-group-substituted 4-aryl-3-butenoic acids. The Mizoroki−Heck reaction is a straightforward way to prepare substituted 4-aryl-3-butenoic acids; however, it usually provides isomeric mixtures, limiting its applications.[6] Recently, Engle's group[7] has demonstrated that 3-butenoic acid is of important synthetic utility and can provide various important organic molecules. In 2018, Zhao's group reported the nickel(0)-catalyzed hydroarylation of unactivated alkenes and styrenes with aryl boronic acids.[8] Subsequently, the group of Bi[9] reported the copper-catalyzed aminoquinoline-assisted Mizoroki−Heck reaction of 3-butenoic acids to form a $Csp^3$−$Csp^3$ bond (Scheme1a). Inspired by these results, we envisage that the 4-aryl-3-butnoic acids can be directly synthesized through a palladium-catalyzed oxidative Mizoroki−Heck reaction assisted by a carboxylic acid group as a weak coordination center. We report herein the synthesis of 4-aryl-3-butenoic acids via carboxylic-acid-group -assisted direct oxidative Heck coupling between 3-butenoic acid and arylsulfonyl hydrazide. A variety of 4-aryl-3-butenoic acids were obtained in moderate to good yields. Preliminary mechanistic studies reveal that the carboxylic acid is very important to realize this transformation in the presence of copper(II) acetate, which plays an important role in activating the arylsulfonylhydrazides to form the key palladium(II) intermediate.

**Scheme 1. Functionalization of the 3-Butenoic Acid Derivatives**




Arylsulfonyl hydrazide has emerged as a highly effective arylation reagent in recent years,[10] which does not require harsh acidic or basic conditions to initiate the reaction. Several protocols have been developed by using arylsulfonylhydrazides as arylating agents. In 2017, Yin's group reported a palladium-catalyzed Sonogashira-type reaction of arylsulfonyl hydrazides with terminal alkynes.[11] However, the arylation of unactivated olefins without a directing group has not been reported. With this background, we first treated 3-butenoic acid with benzenesulfonyl-hydrazide in the presence of $Pd(PPh_3)_2Cl_2$ (2.5 mol %) in *N*,*N*-dimethylamide (DMF) at 100 °C for 10 h. The 4-phenyl-3-butenoic acid was obtained in 7% yield (Table 1, entry 1). When the oxidative silver acetate was added as an oxidant, the conversion of 3-butenoic acid improved, and **3a** was obtained in 12% yield (Table 1, entry 2). Upon screening the oxidants $K_2S_2O_8$, $Cu(OAc)_2$, $Cu(acac)_2$, $Cu(OTf)_2$, $Cu_2O$, and $PhI(OAc)_2$, it was found that with copper acetate, the

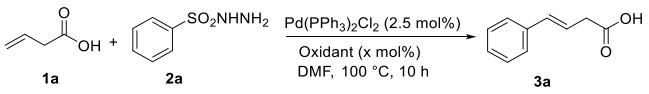
**Received:** November 12, 2020
**Published:** December 28, 2020






https://dx.doi.org/10.1021/acs.orglett.0c03773
*Org. Lett.* 2021, 23, 296−299

**Table 1. Optimization of Reaction Conditions**[a]



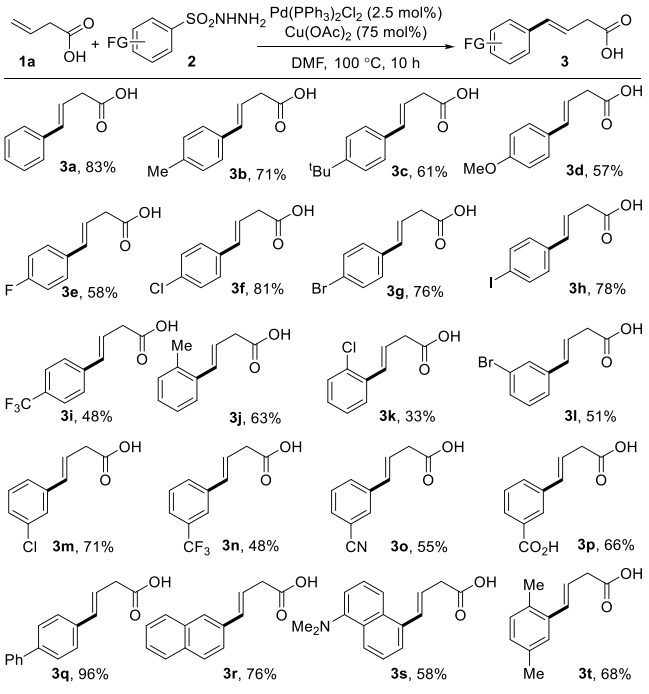

| entry | oxidant | yield (%)[b] |
|---|---|---|
| 1 | none | 7 |
| 2 | AgOAc (75 mol %) | 12 |
| 3 | $K_2S_2O_8$ (75 mol %) | trace |
| 4 | $Cu(OAc)_2$ (75 mol %) | 83 |
| 5 | $Cu(OTf)_2$ (75 mol %) | 71 |
| 6 | $Cu_2O$ (75 mol %) | 34 |
| 7 | $PhI(OAc)_2$ (75 mol %) | 52 |
| 8 | $Cu(OAc)_2$ (50 mol %) | 69 |
| 9 | $Cu(OAc)_2$ (30 mol %) | 47 |
| 10 | $Cu(OAc)_2$ (10 mol %) | 36 |
| 11[c] | $Cu(OAc)_2$ (75 mol %) | 23 |
| 12[d] | $Cu(OAc)_2$ (75 mol %) | trace |

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), $Pd(PPh_3)_2Cl_2$ (2.5 mol %), oxidant (*x* mol %), DMF (1 mL), 100 °C 10 h. [b]Isolated yields are given. [c]Under an $O_2$ atmosphere. [d]No $Pd(PPh_3)_2Cl_2$.

yield of **3a** reached 83% (Table 1,entries 3−7). On reducing the amount of copper acetate below the optimum level, the yield of the product significantly decreased (Table 1, entries 8−10). When a catalytic amount of copper acetate and oxygen was used, the yield of **3a** decreased to 23% (Table 1, entry 11). A control experiment was also performed, and its result showed that the palladium catalyst was indispensable for this transformation (Table 1, entry 12).

Using the optimal conditions, the applicability of arylsulfonyl hydrazides (Scheme 2) to directly convert the readily available 3-butenoic acid to 4-aryl-3-butenoic acids was investigated.

**Scheme 2. Effect of Benzenesulfonyl Hydrazides**[a]

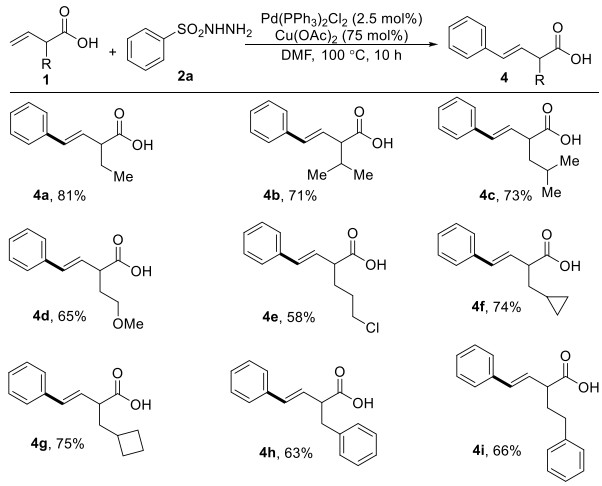



[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.24 mmol), $Pd(PPh_3)_2Cl_2$ (2.5 mol %), $Cu(OAc)_2$ (75 mol %), DMF (1 mL), 100 °C, 10 h. Isolated yields are given.

The para-substituted arylsulfonylhydrazides, including methyl, *tert*-butyl, methoxy, fluorine, chlorine, and bromine (**3b**−**3g**), resulted in the corresponding 4-aryl-3-butenoic acids in moderate to good yields. It is worth mentioning here that the sensitive functional group iodide (**3h**) also gave the corresponding product in 80% yield. However, when there was an electron-withdrawing group such as trifluoromethyl (**3i**) in the para position, the yield was only slightly worse at 48%. Further experiments revealed that the ortho- or meta-substituted arylsulfonylhydrazides gave the corresponding products in moderate to good yields. Gratifyingly, cyano (**3o**) and carboxyl (**3p**) both performed well, yielding the 4-aryl-3-butenoic acids in good yields. The biphenyl (**3q**), naphthyl (**3r**), and dansylhydrazide (**3s**) (a naphthalene ring structure with a $Me_2N$ substituent), were suitable for this transformation, affording the corresponding products in good yields.

Encouraged by these results, we investigated the applicability of the standardized protocol to several α-substituted 3-butenoic acids to understand the functional group tolerance of the transformation (Scheme 3). The ethyl (**4a**), isopropyl

**Scheme 3. Effect of α-Substituted 3-Butenoic Acids**[a]




[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.24 mmol), $Pd(PPh_3)_2Cl_2$ (2.5 mol %), $Cu(OAc)_2$ (75 mol %), DMF (1 mL), 100 °C, 10 h; Isolated yields are given.

(**4b**), isobutyl (**4c**), phenethyl (**4i**), and benzyl group (**4h**) as α-substituents were well tolerated, giving the corresponding product in good to excellent yields. These results suggest that steric hindrance at the α-position has no effect on this transformation. Delightfully, α-substituted 3-butenoic acids containing a functional group at the end of the α-alkyl chain gave a good yield of the desired product when the end group was a methoxy (**4d**), chloride (**4e**), cyclopropyl (**4f**), or cyclobutyl group (**4g**). This highlights the synthetic importance of the present method.

To further test the value of the reaction, we carried out its application on the gram scale for 24 h, and the 4-phenyl-3-butenoic acid (**3a**) was obtained in 74% yield. **3a** could be easily converted into phenylbutyric acid, a bioactive compound **5**, in 78% yield by treating it with palladium in a hydrogen atmosphere (Scheme 4). Furthermore, the bioactive compound Ravicti (**6**), used in the treatment of certain inborn urea cycle disorders, could be easily obtained in 80% yield. These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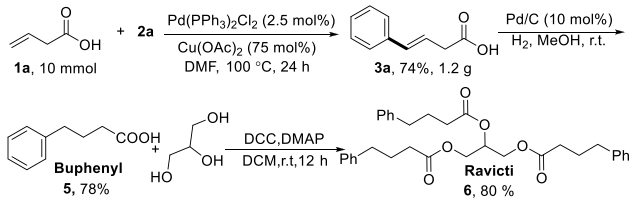
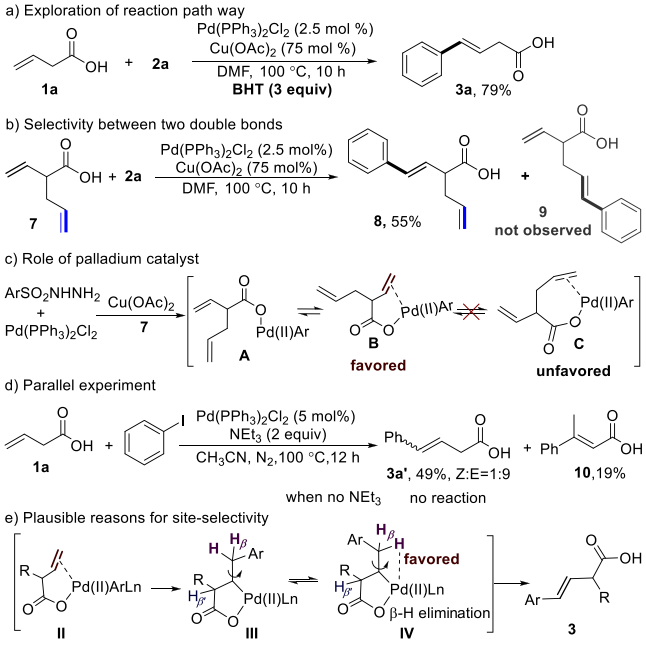
**Scheme 4. Gram-Scale Reaction and Other Applications**




results indicate that this transformation may give various phenylbutyric acid analogues having potential for applications in drug discovery.

To understand the mechanism of the reaction, we carried out a series of reactions (Scheme 5). On the basis of previous

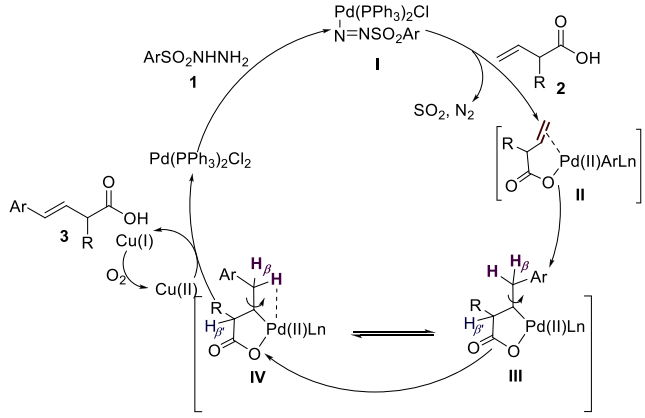
**Scheme 5. Preliminary Mechanistic Study**




reports,[9] control experiments were carried out. First, the reaction was performed in the presence of a free-radical scavenger, 2,6-di-*tert*-butyl-4-methylphenol (BHT). The reaction proceeded efficiently, indicating that it probably did not undergo a free-radical pathway. Subsequently, when the substrate **7**, which has a competitive reaction center, was subjected to standardized reaction conditions, product **8** was observed in 55% yield, whereas **9** was absent. On the basis of the previous reports,[6b] it appeared that the complex **A** was generated with the help of copper(II) acetate. It was easily transformed into complex **B**, rather than complex **C**, due to the ring strain. Interestingly, when 3-butenoic acid was treated with iodobenzene for Heck coupling, the 4-phenylbutenoic acid was obtained in 55% yield as a 9:1 (E/Z) mixture (**3a′**), along with isomeric 3-phenyl-3-methylpropenoic acid (**10**) in 19% yield. These results are consistent with previous reports.[6] On the basis of these results, we may speculate that the complex **II** appears to be formed in the catalytic cycle, which gives intermediate **III**. The $\beta$-H elimination in **IV** leads to a high regioselective product.

On the basis of the existing literature,[10,12] and the above experimental facts, a plausible reaction pathway is proposed in Scheme 6. First, $Pd(PPh_3)_2Cl_2$ and $ArSO_2NHNH_2$ generate

**Scheme 6. Plausible Catalytic Cycle**




intermediate **I**, and it is transformed into **II** by treating with **1**, which concomitantly releases $N_2$ and $SO_2$. Thereafter, the Heck reaction occurs to generate intermediate **III**, which forms the key intermediate **IV**. Its $\beta$-H elimination, results in the highly regioselective formation of product **3**. Palladium(0) further reacts with copper(II) acetate under an oxygen atmosphere to give the palladium(II) complex for the next cycle.

In conclusion, we have developed the palladium-catalyzed direct arylation of 3-butenoic acid, which gives important 4-aryl-3-butenoic acid analogues. A wide variety of functional-group-substituted 4-phenyl-3-butnoic acids have been easily prepared in moderate to good yield. This may result in the discovery of new bioactive compounds. Preliminary mechanistic studies reveal that the reaction follows an oxidative Heck-reaction-type mechanism, assisted by carboxylic acid.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03773.

Detailed experimental procedures and characterization data (PDF)

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https://dx.doi.org/10.1021/acs.orglett.0c03773
*Org. Lett.* 2021, 23, 296−299

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[§]S.Y. and L.L. contributed equally.

## Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

We gratefully acknowledge the Natural Science Foundation of China (no. 21772139), The Jiangsu Province Natural Science Fund for Distinguished Young Scholars (BK20180041), the Prospective Study Program of Jiangsu (17KJA150006), and the PAPD Project. The project was also supported by the Open Research Fund of the School of Chemistry and Chemical Engineering, Henan Normal University.

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