OL | Organic Letters

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

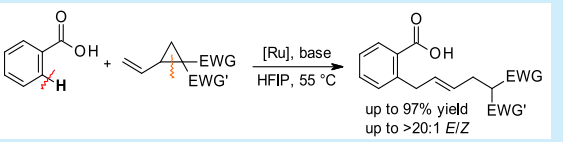
Ring-Opening *Ortho*-C−H Allylation of Benzoic Acids with Vinylcyclopropanes: Merging Catalytic C−H and C−C Activation Concepts

Zhiyong Hu, Xiao-Qiang Hu, Guodong Zhang, and Lukas J. Gooßen*

Lehrstuhl für Organische Chemie I, Ruhr-Universität Bochum, Universitätsstrasse 150, 44801 Bochum, Germany

Supporting Information

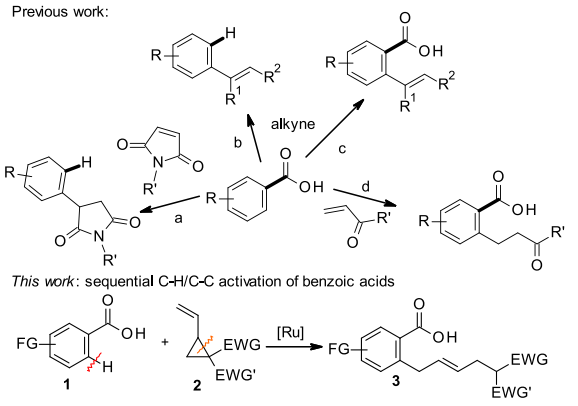
ABSTRACT: A Ru-catalyzed selective and atom-economic *ortho*-C−H allylation of aromatic acids with vinylcyclopropanes is reported. The reaction proceeds with selective cleavage of both a C−H and a C−C bond. A wide range of allylarenes were synthesized in high yields and stereoselectivities. The vinylcyclopropane substrates can optionally be generated in situ from a diazo compound and 1,3-butadiene. Concise syntheses of isocoumarin and 3,4-dihydroisocoumarin derivatives underline the synthetic utility of the reaction.



Transition-metal-catalyzed directed C−H functionalization has become a key technology for the regioselective construction of complex molecules from simple precursors.[1] Initially, the regiospecificity of the transformation was often enforced by strongly coordinating, complex directing groups.[2] In the past decade, new catalyst generations have permitted the use of abundant functionalities, such as carboxylates, as directing groups, with key contributions made by Yu,[3] Miura,[4] Larrosa,[5] Su,[6] Ackermann,[7] our group,[8] and others.[9] The main advantage of carboxylate directing groups is that they are ubiquitously available and can either be tracelessly removed or utilized as leaving groups in decarboxylative couplings.[10]

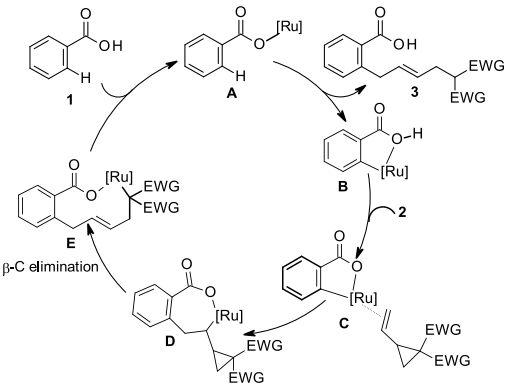
In this context, the Ru-catalyzed *ortho*-hydroarylations[11] of benzoic acids have proven to be a versatile entry point to organoruthenium intermediates that can enter an array of diverse reaction pathways (Scheme 1). Potential products include alkyl- and vinylarenes (a, b)[7a,12] and alkenyl- and alkylcarboxylates (c, d).[13]

Scheme 1. Ru-Catalyzed Hydroarylation Processes with Carboxylates



We have recently found that Ru catalyst systems strongly facilitate C−X over C−H elimination pathways and, thus, permit the selective *ortho*-allylation of benzoic acids with allyl sources of remarkably low intrinsic reactivities, such as allyl alcohols and even amines.[8b,c] Intrigued by the reactivity displayed by this catalyst, we went on to explore its application to allyl sources with carbon-based leaving groups (Schemes 1 and 2).

Scheme 2. Mechanistic Blueprint



The selective activation of inert C−C bonds is challenging due to their high bond dissociation energy of ca. 90 kcal/mol.[14] In the context of low-valent transition-metal-catalyzed allylations of preformed nucleophiles, the ring strain of vinylcyclopropanes has successfully been utilized to facilitate the cleavage of a C−C bond, leading to the formation of allylmetal intermediates.[15] However, there are very few reactions that combine catalytic C−H functionalizations with C−C bond activation steps,[16] and they all involve high

Received: July 11, 2019

DOI: 10.1021/acs.orglett.9b02393
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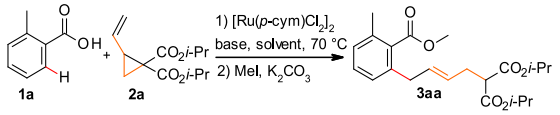
molecular-weight, nitrogen-based directing groups,[17] which often need to be preinstalled and later removed in additional reaction steps. We reasoned that our ruthenium-based system for carboxylate-directed C−H activation should display a similar reactivity toward vinylcyclopropanes as observed, e.g., for allyl alcohols (Scheme 2).

Thus, a benzoic acid **1** should react with a ruthenium complex to form a ruthenacycle (**B**), which would coordinate the C−C double bond of **2**, followed by carbometalation to give **D**. This intermediate is now ideally set up for a concerted C−C bond-cleavage process in which the leaving group is transferred to Ru.[17f,i] The product is liberated from the resulting species **E** by protonation/exchange with the benzoic acid substrate.

In order to probe the viability of this reaction concept, we chose 2-methylbenzoic acid **1a** and diisopropyl 2-vinylcyclopropane-1,1-dicarboxylate **2a** as model substrates (Table 1). Gas chromatographic analysis of the reaction mixtures was

Table 1. Optimization of the Allylation Reaction[a]



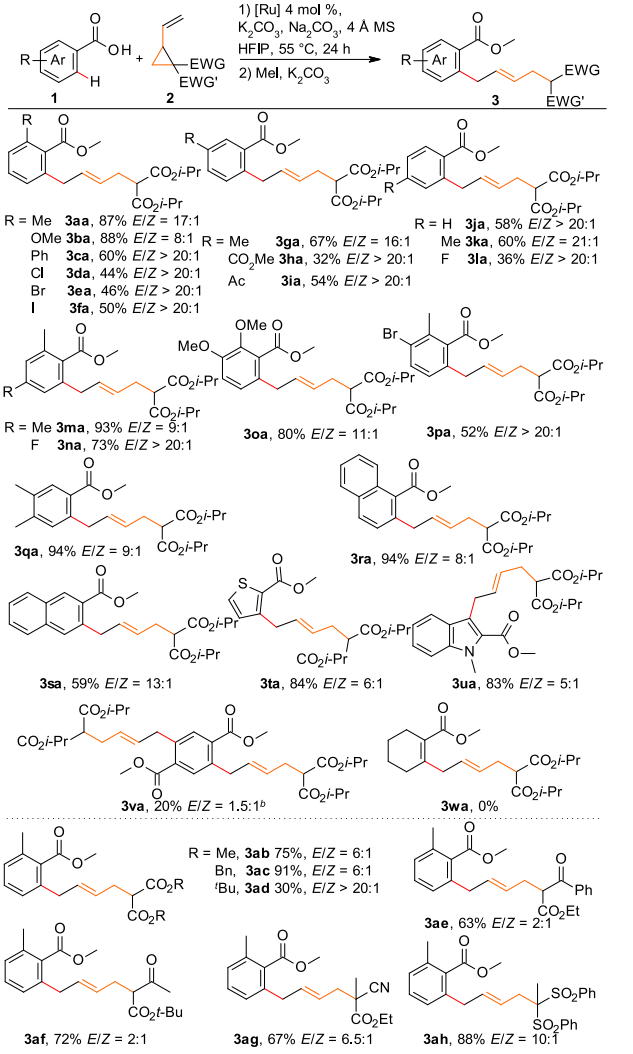
entry	solvent	base	yield[b] (%)	*E*/*Z* ratio
1	TCE	K_3PO_4	5	7:1
2	MeCN	Na_2CO_3	46	4.5:1
3	DCE	Na_2CO_3	15	3:1
4	DME	Na_2CO_3	20	5:1
5	DMF	Na_2CO_3	26	2:1
6	H_2O	Na_2CO_3	trace	
7	^{i}PrOH	Na_2CO_3	32	3.5:1
8	TFE	Na_2CO_3	20	5:1
9	TCE	Na_2CO_3	15	8:1
10	HFIP	Na_2CO_3	67	7.5:1
11	HFIP	K_2CO_3	46	20:1
12	HFIP	Cs_2CO_3	35	15:1
13	HFIP	K_3PO_4	50	14:1
14	HFIP	K_2CO_3 + Na_2CO_3	59	16:1
15[c]	HFIP	K_2CO_3 + Na_2CO_3	68	16:1
16[c,d]	HFIP	K_2CO_3 + Na_2CO_3	76	15:1
17[c,d,e]	HFIP	K_2CO_3 + Na_2CO_3	91	16:1

[a]Conditions: 0.2 mmol of **1a**, 0.3 mmol of **2a**, 2.5 mol % of [Ru(*p*-cymene)Cl_2]$_2$, 1 equiv of base, 1 mL of solvent, 70 °C, 24 h. [b]Yields determined by GC using methyl laurate as internal standard; *E*/*Z* ratios determined by ^{1}H NMR. [c]With 50 mg of powdered 4 Å MS. [d]55 °C. [e]4 mol % of [Ru]. K_2CO_3 (1.3 equiv) + Na_2CO_3 (0.3 equiv). HFIP = hexafluoro-2-propanol. TFE = 2,2,2-trifluoroethanol. TCE = 2,2,2-trichloroethanol.

made simpler by converting the products in situ to the methyl esters. Using [Ru(*p*-cymene)Cl_2]$_2$ as a catalyst under the conditions optimized for C−H allylations with allyl alcohol substrates, the desired product was formed in encouraging quantities (entry 1). The solvent system played a key role in yield and *E*/*Z* selectivity (entries 2−10). The best results were obtained using hexafluoro-2-propanol (HFIP). The reaction outcome was strongly influenced also by the base (entries 10−13). The optimal combination of conversion and stereoselectivity was obtained with a 4:1 mixture of potassium and sodium carbonate. Further step-ups in the yield were achieved by employing 4 Å MS as an additive (entry 15), lowering the temperature from 70 to 55 °C (entry 16), and increasing the amount of catalyst to 4 mol % (entry 17). A further control experiment with *p*-methylbenzoic acid (**1k**) bearing no *ortho* substituents revealed that no diallylation occurred even when increasing the excess of **2a** to 2.5 equiv.

Under these optimized conditions (Table 1, entry 17), various aromatic carboxylic acids were successfully allylated with the model substrate diisopropyl 2-vinylcyclopropane-1,1-dicarboxylate **2a** in good yields and high *E*/*Z* selectivities (Scheme 3). Notably, not only *ortho*-substituted benzoates but

Scheme 3. Substrate Scope[a]



[a]Conditions: **1** (0.5 mmol), **2** (0.75 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (4 mol %), K_2CO_3 (0.65 mmol), Na_2CO_3 (0.15 mmol), 4 Å MS (50 mg) in HFIP (2 mL) at 55 °C under Ar; isolated yields of corresponding methyl esters. [b]Based on 0.2 mmol.

also *meta*-, *para*-, and unsubstituted derivatives were selectively monoallylated. Halogen substituents, including even iodo groups, are left unchanged, so that transformation is orthogonal to most transition-metal-catalyzed processes. The reaction also tolerates, e.g., ester, ether, or keto groups. Heterocyclic carboxylates were also smoothly converted, albeit with lower stereoselectivity (**3ta**, **3ua**). Starting from terephthalic acid, the diallylation product (**3va**) was obtained in 20% yield. However, the current catalyst system does not

DOI: 10.1021/acs.orglett.9b02393
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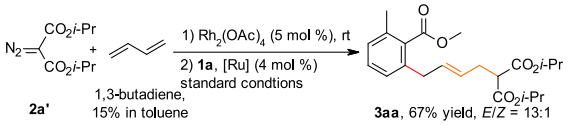
allow the analogous conversion of acrylic acid derivatives such as 1-cyclohexene-1-carboxylic acid **1w**.

Variations of the vinylcyclopropane coupling partner were also investigated. At least two activating groups were found to be required. The reaction is suppressed by alkyl substituents and is senstitive to steric crowding at the vinylcyclopropane substructure. Whereas smaller ester groups gave good yields but only moderate stereoselectivity in favor of the *E* products, the latter were obtained almost exclusively when starting from bulky *tert*-butyl esters, albeit in modest yields (**3ab**, **3ac**, **3ad**). Vinylcyclopropanes bearing ketone (**2e**, **2f**), cyano (**2g**), and sulfonyl groups (**2h**) were smoothly converted, but the diketone **2m** was found to be unreactive (see the SI). Strained heterocycles such as 3,4-epoxy-1-butene (**2n**) and vinyl aziridine (**2o**) did not give the desired allylation products (Scheme S1).

In the small-scale reactions above, the products were isolated by column chromatography as their methyl esters following in situ esterification. However, it is also possible to isolate the carboxylic acids themselves. This was demonstrated by the gram-scale (4 mmol) synthesis of allylation product **3aa′** yielding 85% of the free acid.

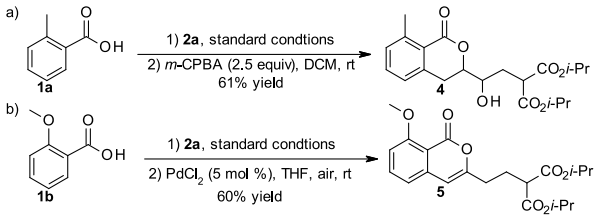
We next probed whether the synthesis of the vinylcyclopropane substrates from widely available starting materials could be performed as a one-pot process with the C−H allylation. To our delight, the Rh-catalyzed cyclopropanation of 1,3-butadiene with diazo ester **2a′** turned out to be mutually compatible with the Ru-catalyzed allylation. Thus, the allylbenzoic acid **3aa** was synthesized in respectable yield in one pot from *o*-toluic acid (**1a**), diazo ester **2a′**, and a toluene solution of butadiene (Scheme 4).[18]

Scheme 4. One-Pot for Cyclization, C−H Activation, and Ring-Opening



The allylation reaction can also be combined with follow-up steps. For example, the 3,4-dihydroisocoumarin derivative **4** was obtained in 61% yield via allylation followed by an epoxidation/ring-opening cascade (Scheme 5a). Allylation

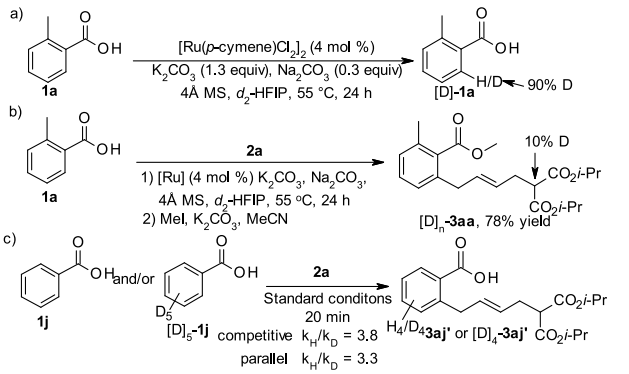
Scheme 5. In Situ Product Derivatization



followed by Pd-catalyzed intramolecular aerobic cyclization led to the isocoumarin **5** (Scheme 5b). Both of these bicyclic product classes are of interest due to their antibacterial, antifungal, anti-inflammatory, antioxidant, and anticancer activities.[19]

The mechanism of the allylation reaction was investigated by deuterium-labeling experiments. Upon stirring the benzoic acid **1a** in the presence of catalyst and base in d_2-HFIP, rapid *ortho*-deuteration was observed, confirming that the C−H activation step is reversible (Scheme 6a). When the allylation was carried

Scheme 6. Mechanistic Insights



out in the presence of d_2-HFIP, deuterium uptake in the α-postion of dicarboxylate groups was observed, pointing toward a protodemetalation rather than a hydride-transfer mechanism (Scheme 6b). Taken together with the high kinetic isotope effect, one can conclude that C−H cleavage is rate-determining, whereas the hydroarylation is much faster (Scheme 6c). All of these findings are in good agreement with the mechanism shown in Scheme 2.

In conclusion, simple *p*-cymene ruthenium catalyst allows the *ortho*-C−H allylation of aromatic carboxylates with vinylcyclopropanes under mild, redox-neutral conditions. This use of a carbon-based leaving group represents a major advance in the field of carboxylate-directed reactions. The new allylation has considerable synthetic potential, particularly due to its tolerance of halo functionalities, which makes it orthogonal to most catalytic C−C and C−heteroatom bond-forming reactions. Moreover, it can be combined with an up front diene cyclopropanation or with follow-up reactions such as oxidative lactonizations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02393.

Experimental procedures, full analysis data for new compounds, and NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: lukas.goossen@rub.de.

ORCID

Lukas J. Gooßen: 0000-0002-2547-3037

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) under Germany's Excellence Strategy, EXC-2033, Projektnummer 390677874, SFB-TRR 88 "3MET", and GO 853/12-1, and BMBF and the state of NRW (Center of Solvation Science "ZEMOS"). We thank

DOI: 10.1021/acs.orglett.9b02393
Org. Lett. XXXX, XXX, XXX−XXX

UMICORE for donating chemicals and the CSC for fellowships to G.Z. and Z.H.

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DOI: 10.1021/acs.orglett.9b02393
Org. Lett. XXXX, XXX, XXX−XXX