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Carboxylate-Directed C–H Allylation with Allyl Alcohols or Ethers

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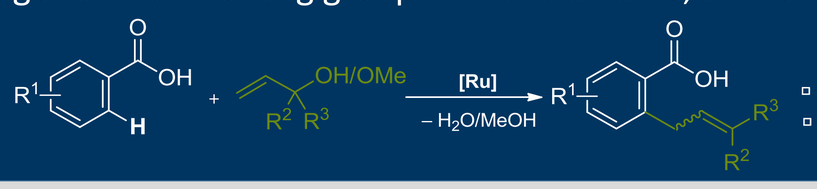
Abstract

A [Ru(p-cymene)Cl_2]$_2$ catalyst activates allyl alcohols and ethers for the regioselective ortho-C–H allylation of aromatic and heteroaromatic carboxylates. The reaction is orthogonal to most C–H functionalizations with allyl alcohols in that allyl arenes rather than carbonyl compounds are obtained. A wide range of substrates are thus smoothly transformed to allylarenes at 50 °C in phosphate-buffered 2,2,2-trichloroethanol. The reaction concept combines the use of abundant reagents and directing groups in a sustainable, waste-minimized method for C–C bond formation.

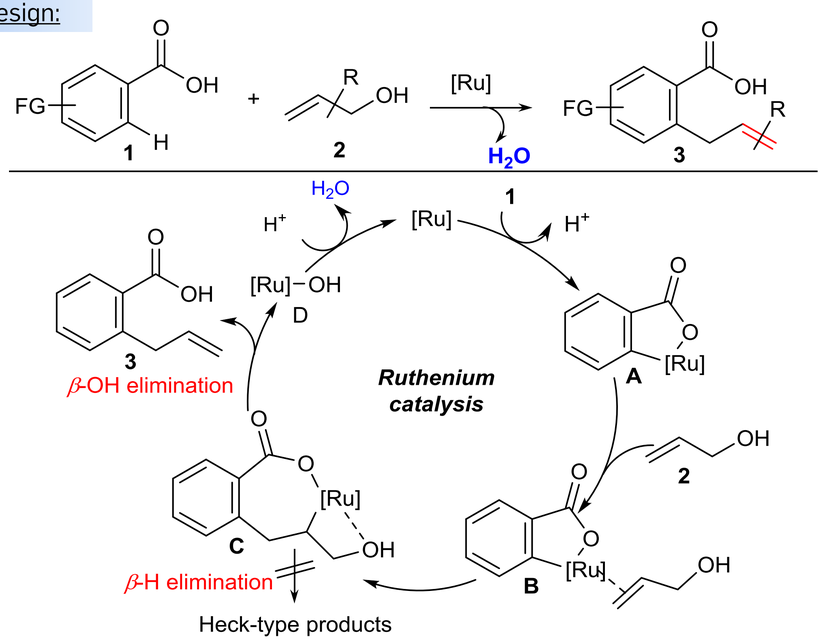


- Broad substrate scope
- Mild conditions
- Easily available materials
- Salt free

Introduction

Allylarene motifs are widely found in natural products and biologically active molecules.[1] The regiospecific introduction of allyl groups into functionalized arene substrates is generally achieved by coupling pre-formed or *in situ*-generated aryl-metal species with pre-activated allyl electrophiles,[2] such as allyl acetates carbonates, phosphates or halides. The use in C–H functionalizations of non-activated allyl alcohols, with OH as the leaving group, would be highly desirable from the point of view of step- and atom economy. However, OH is such a poor leaving group that allyl alcohols usually react via a β-H elimination pathway leading to carbonyl compounds.[3] In the development of C-H functionalization, benzoic acids appeared to be particularly attractive starting materials,[4] because carboxylate groups are abundant and can be tracelessly removed or act as anchor point for further transformations.[5]

Reaction design:

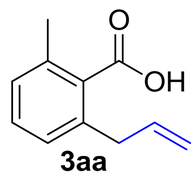


Challenges: the competitive reaction of β-OH and β-H elimination
carboxylic acids as a weak directing group
the formation of ester groups between acids and alcohols

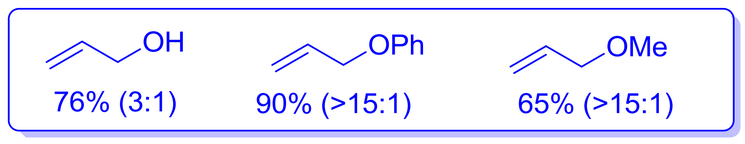
Advantages: easily available carboxylic acids
cheap Ru catalyst
water as an environment-friendly byproduct

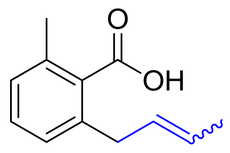
Representative Substrates

Not only allyl phenyl ether but also allyl methyl ether cleanly converted to the desired product with high selectivity (allyl-to-vinyl ratio up to > 15:1). Various 1°, 2°, and even 3° alcohols could run smoothly and give good to excellent yields. Furthermore, this methodology could also be applied in the late-stage functionalization of several nature compounds, affording good yields, even on a gram scale.

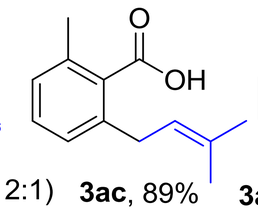


3aa

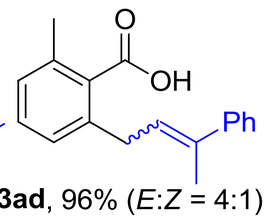




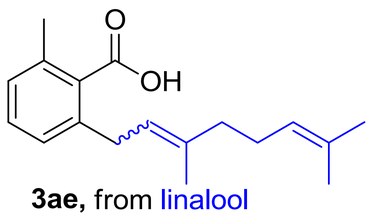
3ab, 87% (*E*:*Z* = 2:1)



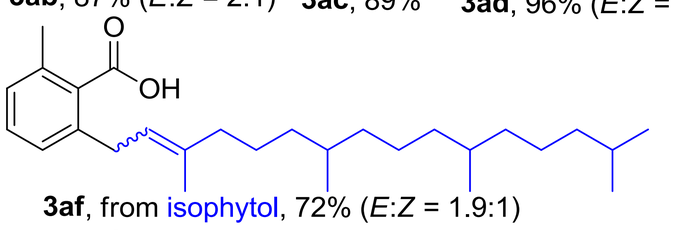
3ac, 89%



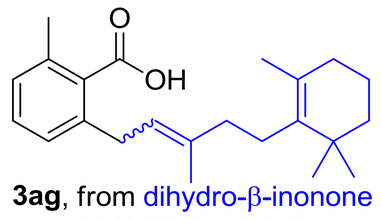
3ad, 96% (*E*:*Z* = 4:1)



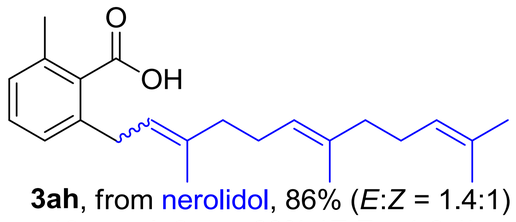
3ae, from linalool
80% (*E*:*Z* = 1.3:1)



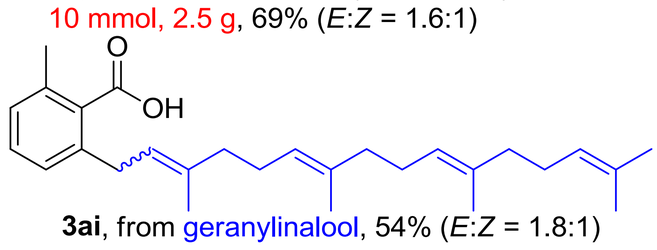
3af, from isophytol, 72% (*E*:*Z* = 1.9:1)



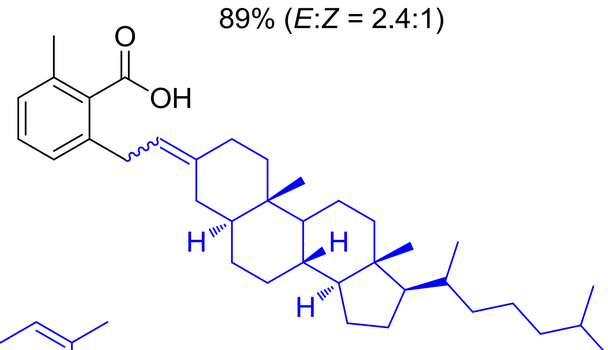
3ag, from dihydro-β-inonone
89% (*E*:*Z* = 2.4:1)



3ah, from nerolidol, 86% (*E*:*Z* = 1.4:1)
10 mmol, 2.5 g, 69% (*E*:*Z* = 1.6:1)



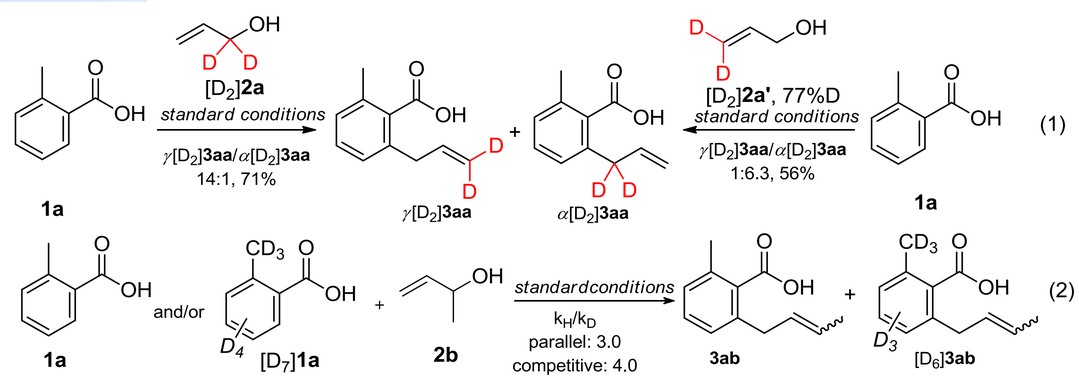
3ai, from geranylinalool, 54% (*E*:*Z* = 1.8:1)



3aj, from 3-keto-5α-cholestane,
44% (*E*:*Z* = 1.5:1)

Mechanism Study

Deuterium-labeling experiments were conducted to elucidate the reaction mechanism. The allylation of **1a** with 1,1-dideuterio-allyl alcohol [D_2]-**2a** afforded a 14:1 mixture of γ[D_2]-**3aa** (71% yield) and α[D_2]-**3aa** (eq. 1 left). When 3,3-dideuterio-allyl alcohol [D_2]-**2a'** was employed, a 1 : 6.3 mixture of γ[D_2]-**3aa** and α[D_2]-**3aa** was observed (eq. 1 right). There are evidences against the intermediacy of π-allyl metal-complex and for a β-OH elimination pathway. The significant kinetic isotope effects in intermolecular competition (k_H/k_D = 4.0) and parallel experiments (k_H/k_D = 3.0) indicate that C–H activation rather than β-OH elimination is the rate-determining step (eq. 2).



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[1] G. Ni, Q.-J. Zhang, Z.-F. Zheng, R.-Y. Chen, D.-Q. Yu, *J. Nat. Prod.* **2009**, *72*, 966.
[2] J. D. Weaver, A. Recio, III, A. J. Grenning, J. A. Tunge, *Chem. Rev.* **2011**, *111*, 1846.
[3] L. Huang, Q. Wang, J. Qi, X. Wu, K. Huang, H. Jiang, *Chem. Sci.* **2013**, *4*, 2665.
[4] M. Pichette Drapeau, L. J. Gooßen, *Chem. Eur. J.* **2016**, *22*, 18654.
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