

Regioselective C–H Alkylation via Carboxylate-Directed Hydroarylation in Water

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Abstract

In the presence of catalytic $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ and using Li_3PO_4 as the base, benzoic acids react with olefins in water to afford the corresponding 2-alkylbenzoic acids in moderate to excellent yields. This C–H alkylation process is generally applicable to diversely substituted electron-rich and electron-deficient benzoic acids, along with α,β -unsaturated olefins including unprotected acrylic acid. The widely available carboxylate directing group can be removed tracelessly or utilized for further derivatization. Mechanistic investigations revealed that the transformation proceeds via a ruthenacycle intermediate.

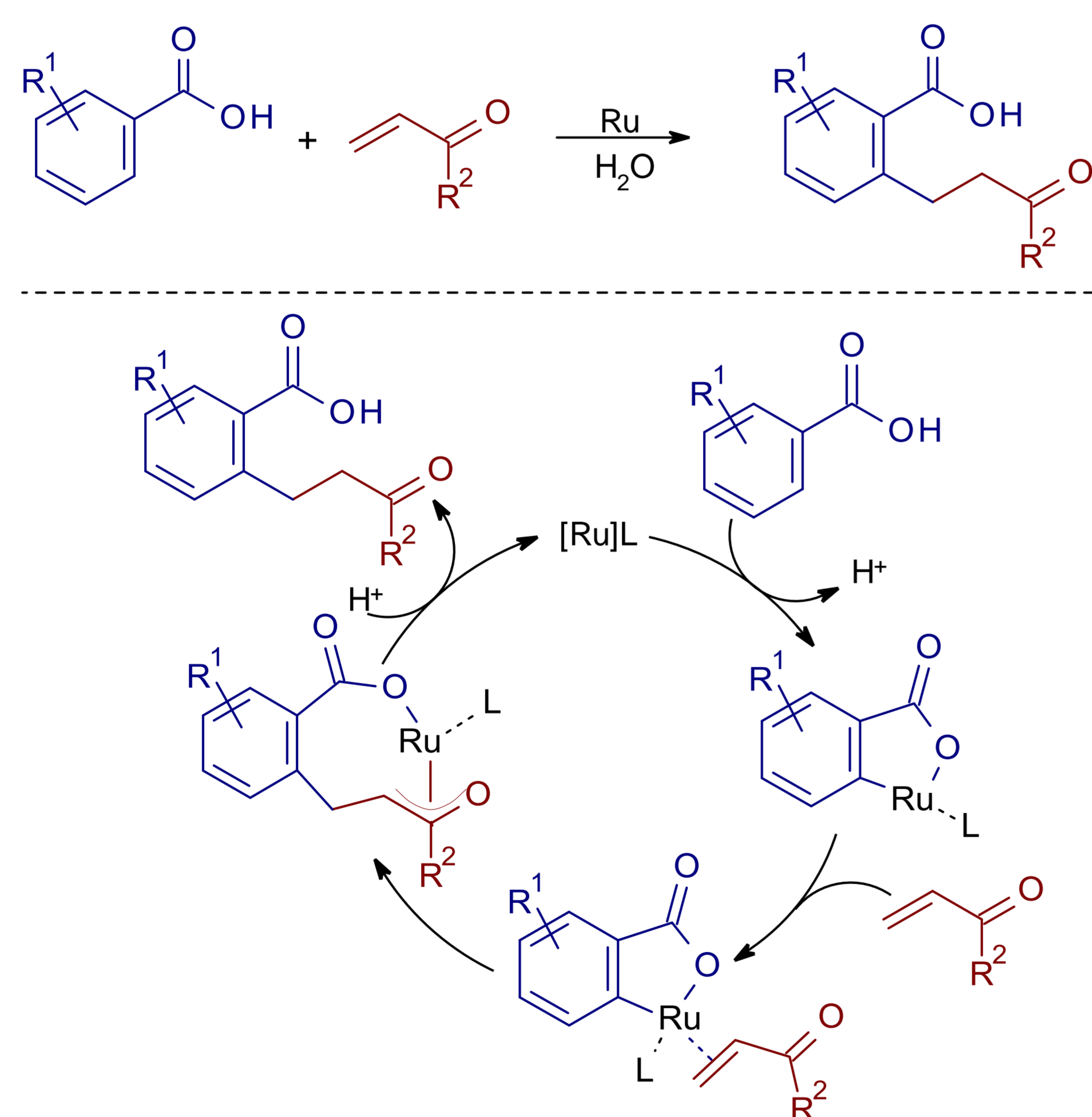
Introduction

Modern reaction development is aiming at the development of catalytic C–H alkylations, ideally based on non-prefunctionalized substrates and without stoichiometric organometallic reagents. Among them, directed hydroarylations of alkenes are particularly advantageous due to their ideal atom-economy. The regioselectivity of the C–H alkylation can be controlled by various directing groups.^[1] However, these directing groups often need to be introduced and later removed in additional reaction steps, increasing the complexity of the overall synthetic sequence.

The use of carboxylates as directing groups represents a tremendous advance in this area.^[2] Benzoic acids are widely available in great structural diversity, and after *ortho*-alkylation, the carboxylate group can be tracelessly removed,^[2] or utilized as a leaving group in further functionalization steps.^[3] However, the low coordinating ability of this group poses substantial challenges with regard to reactivity and selectivity of the C–H activating step.

Ru-Catalyzed *ortho*-Alkylation of Benzoic Acids

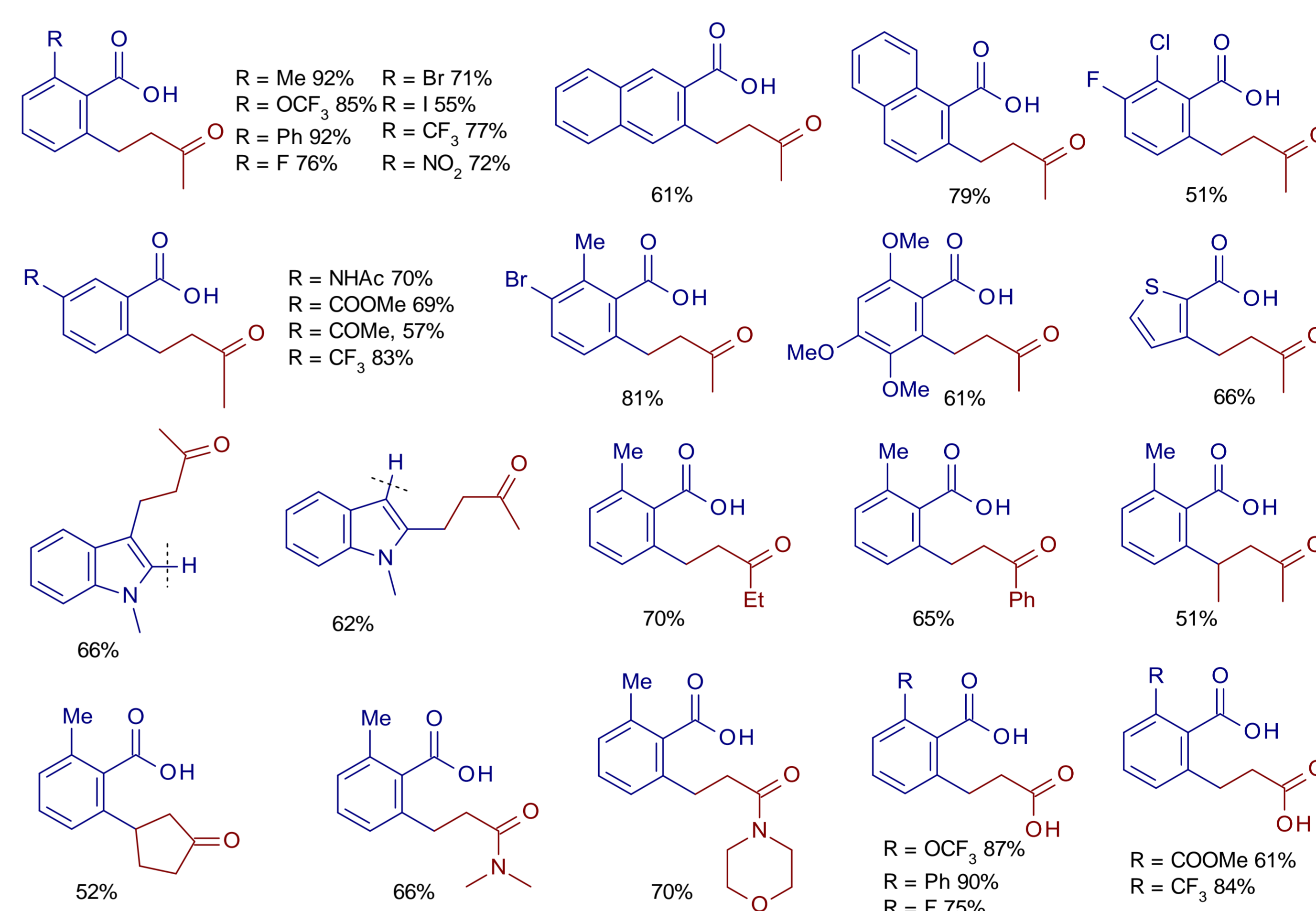
We have disclosed a straightforward Ru-catalyzed *ortho*-alkylation of benzoic acids with α,β -unsaturated olefins including unprotected acrylic acid in water.^[4] It is noteworthy that olefins are generally cheaper and more readily available than dihalogenoalkanes, epoxides, alkyl trifluoroborates, or trimethylaluminium, which served as alkylating agents in advanced transformations.



The proposed mechanism maybe involve a ruthenacycle intermediate, which would coordinate to the olefin. 1,4-conjugate addition of the arylruthenium species to the double bond should then yield the ruthenium-oxa- π -allyl species that preferentially undergoes protonolysis to release the alkylarene and regenerate the ruthenium catalyst.

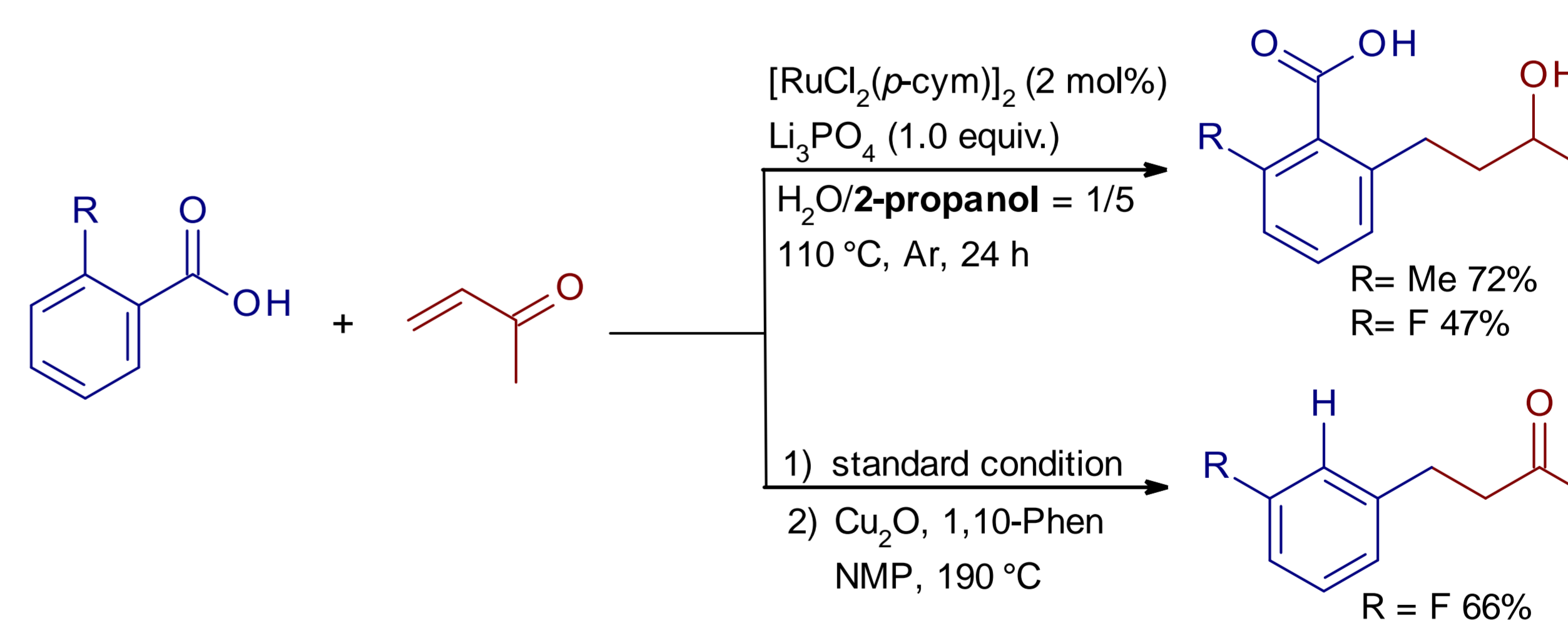
Substrate Scope

The C–H alkylation process is generally applicable to diversely substituted substrates. The tolerance of acetamido, methoxycarbonyl, and acetyl groups opens up opportunities for further functionalization. The reaction is also applicable to a range of substituted benzoates in combination with acrylic acid.



Optional Functionalizations

Further investigations revealed that the ketone could be reduced in situ to hydroxyl group using isopropanol as the hydride source, and that protodecarboxylation was possible in a one-pot process.



Conclusion

In summary, the carboxylate-directed hydroarylation of olefins in the presence of $[\text{RuCl}_2(p\text{-cymene})]_2$ provides a convenient and sustainable access to various 2-alkylbenzoic acids. This transformation proceeds smoothly in water. It tolerates various functional groups, including even standard directing groups, which opens up opportunities for further functionalization. The catalyst system is compatible with unprotected acrylic acid.

References:

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