

Catalytic C-N and C-H Bond Activation: *ortho*-Allylation of Benzoic Acids with Allyl Amines

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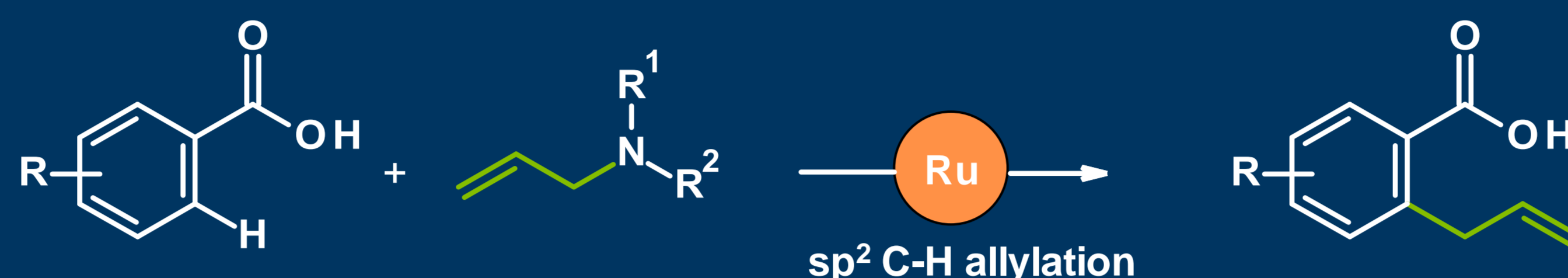
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Abstract

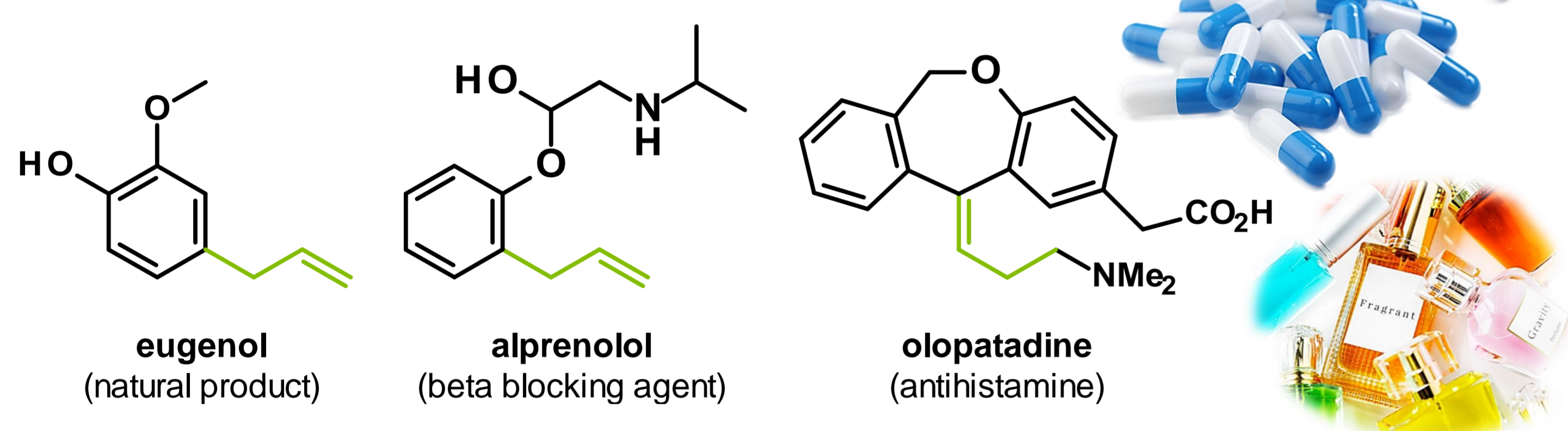
- Widely available starting materials
- Easy to handle and prepare



- Inexpensive catalyst
- Highly regioselective

The selective transformation of C-N bonds, as one of the most prevalent in organic molecules, are of substantial interest for the late-stage functionalization of complex molecules in pharmaceutical research and material sciences. A straightforward *ortho*-allylation of benzoic acids using allyl amines was developed in a sustainable fashion and under mild conditions using a ruthenium-catalyst. The catalyst mediates a carboxylate-directed regioselective C-H cleavage and adds across the double bond of the allyl substrate forming the desired linear alkenyl arenes by enabling a novel simultaneous C-H and C-N Bond activation.

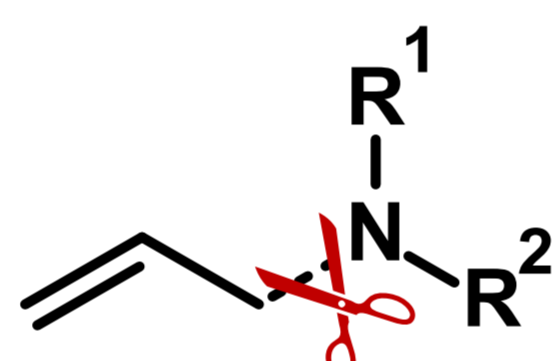
Allyl Arenes



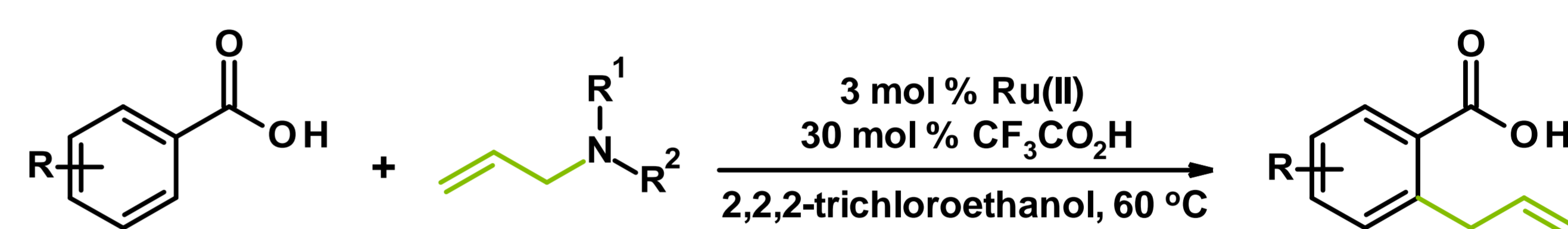
Allyl arenes are structural motifs widely encountered in natural products, pharmaceuticals as well as in the flavor and fragrance industry and material science.

Challenge of C-N Bond Cleavage

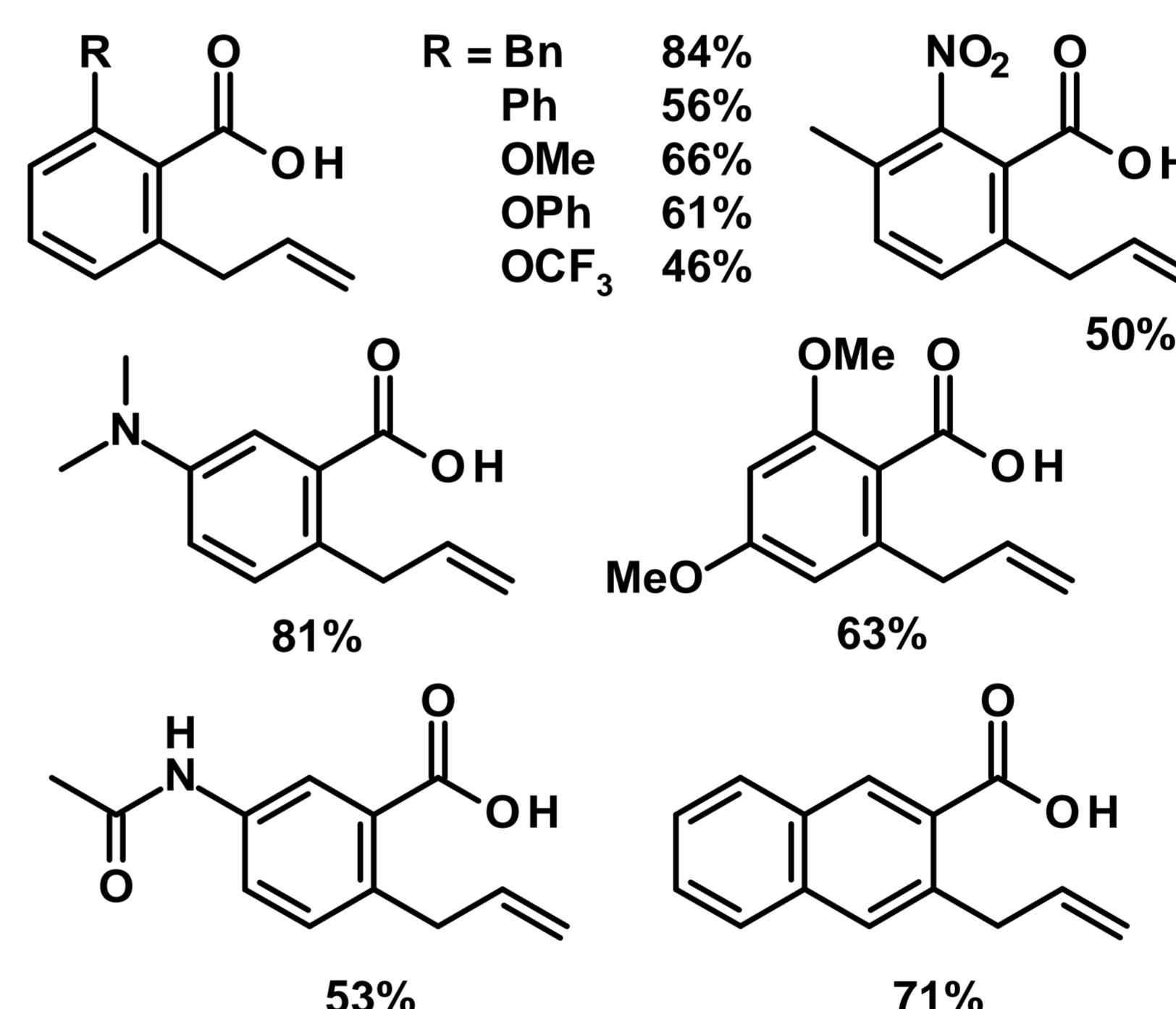
- thermodynamic stability
- relatively high BDE: ca. 80 kcal/mol
- poor leaving groups: ca. pKa Me₂N-H = 40 vs pKa MeCOO-H = 4.76



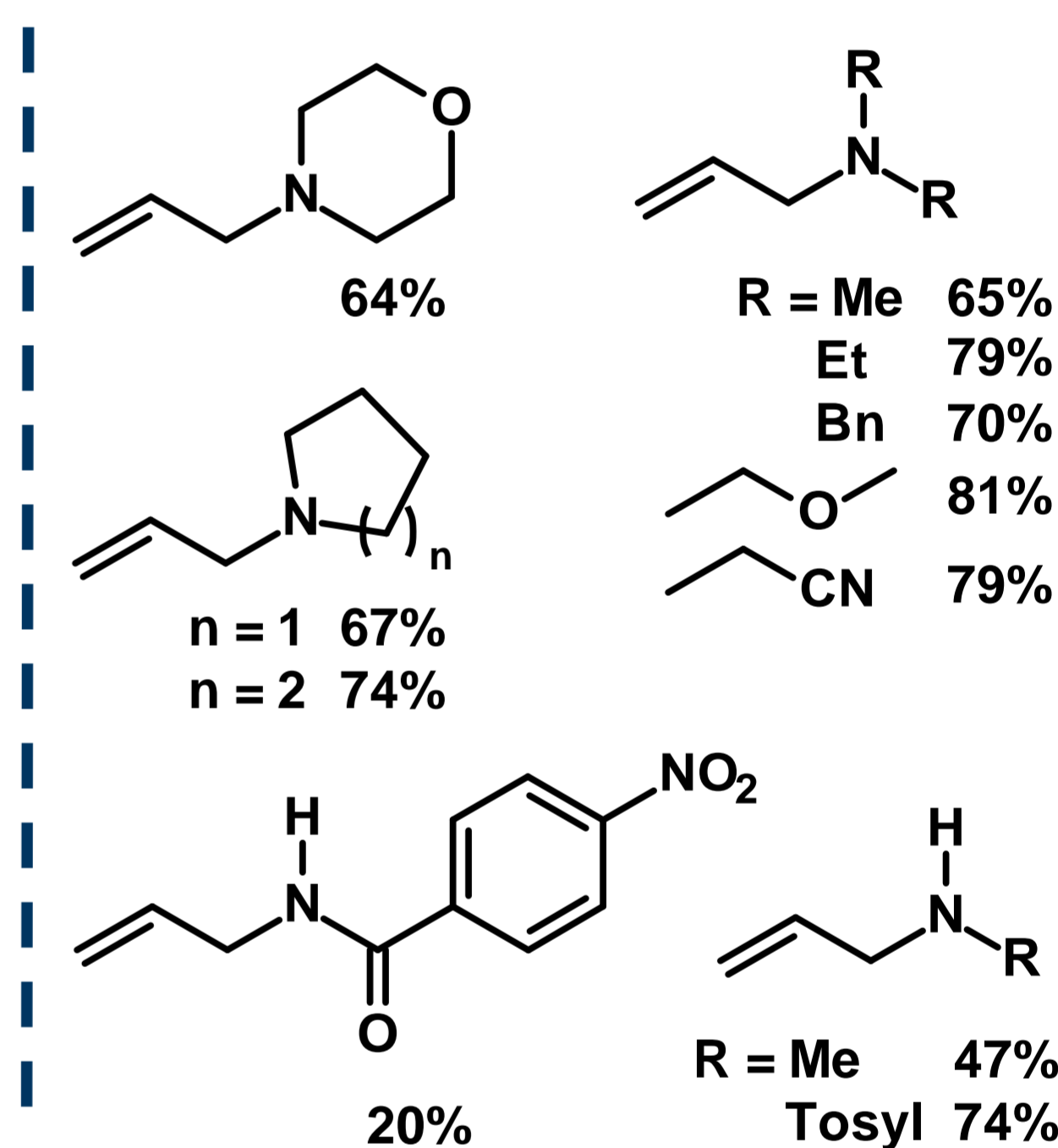
Ruthenium-Catalyzed *ortho*-Allylation



Broad scope of benzoic acids



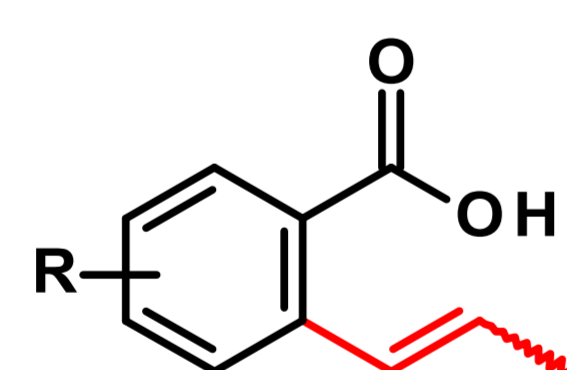
Various amine substituents



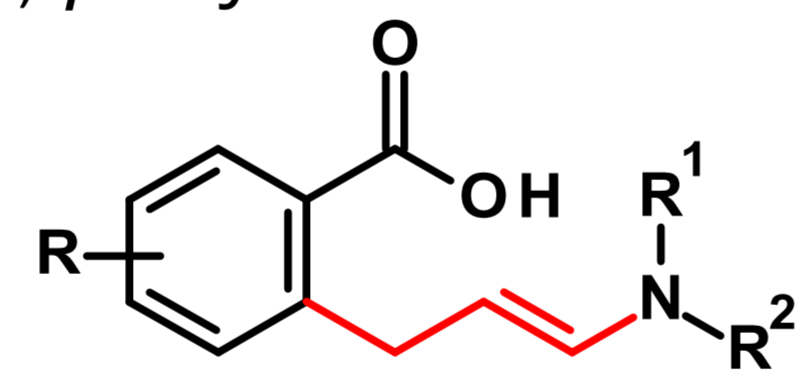
Mechanistic Blueprint and Challenges

Prevent:

1) Double Bond Isomerization

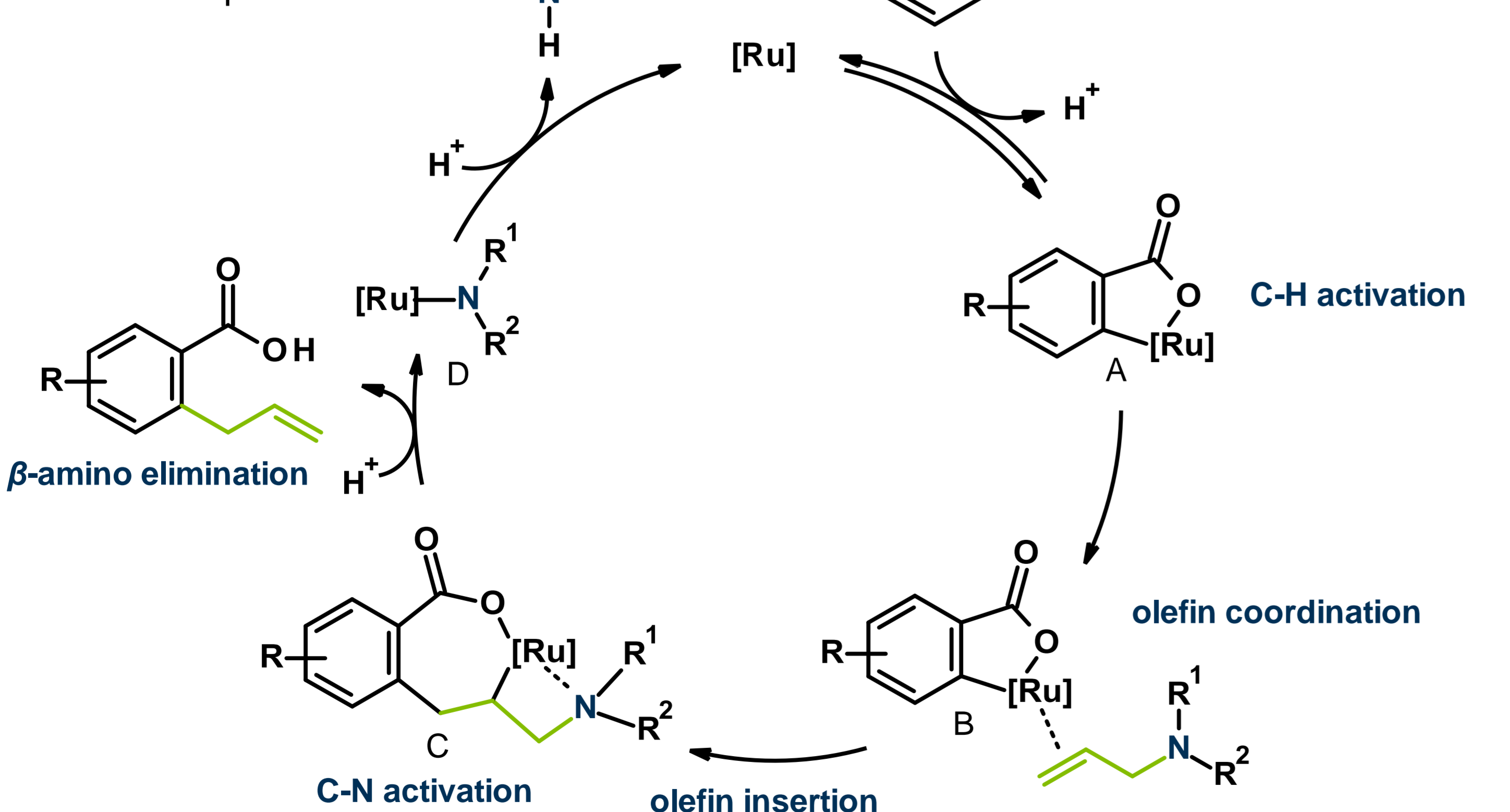


2) β -Hydride Elimination

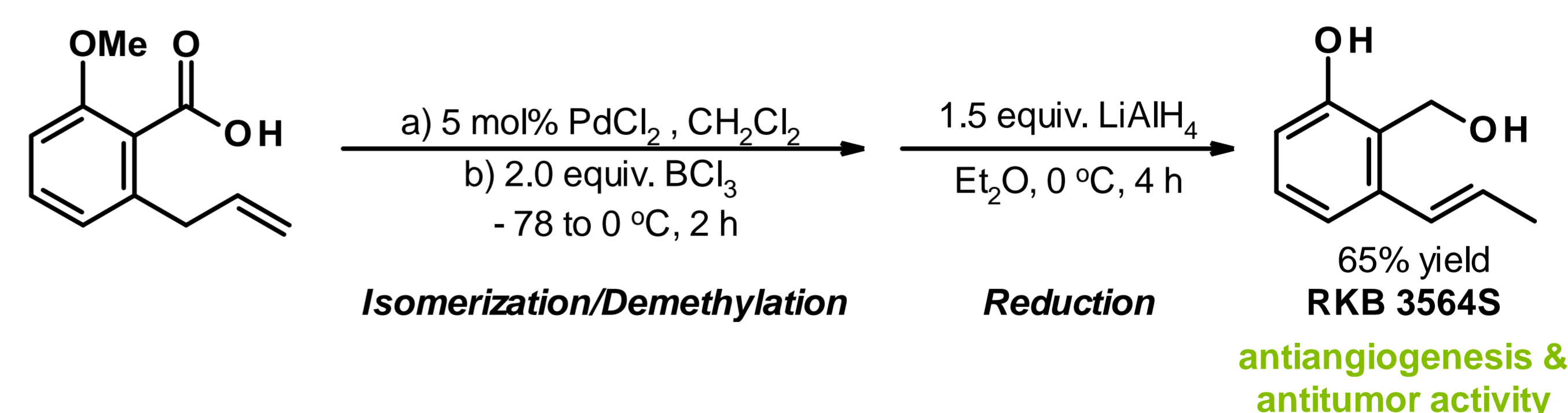
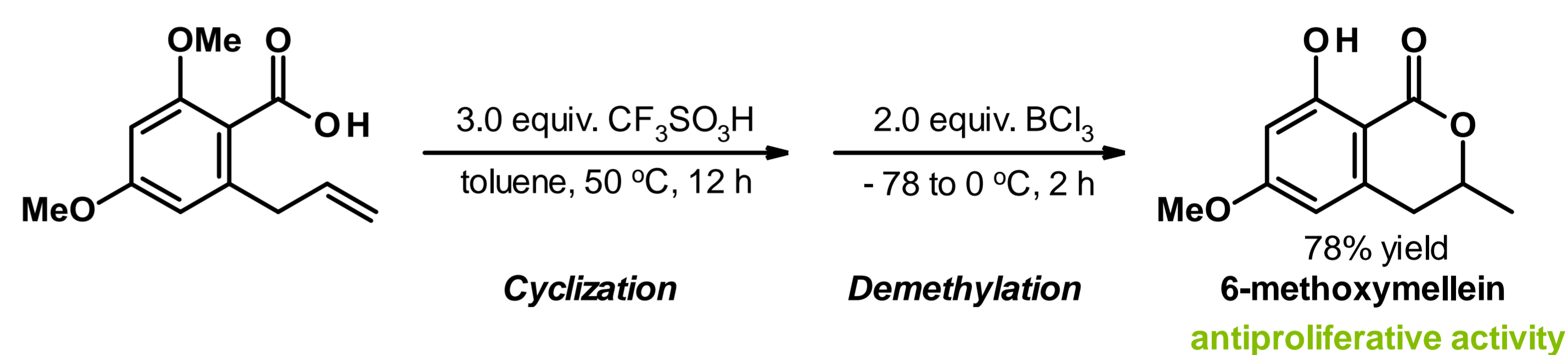


Solution:

- Ru(II) catalyst
- mediation of pH
- low temperatures



Synthetic Application of the Reaction Protocol



Conclusion

The formidable challenge of C-N bond cleavage was successfully tackled via a mild *ortho*-allylation of widely available aromatic carboxylic acids and easily accessible allylic amines, leading to various allyl arenes including biologically active compounds.

References:

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- A. S. Trita, A. Biafora, M. Pichette Drapeau, P. Weber, L. J. Gooßen, *Angew. Chem.* **2018**, DOI 10.1002/ange.201712520; b) X.-Q. Hu, Z. Hu, A. S. Trita, G. Zhang, L. J. Goossen, *Chem. Sci.* **2018**, *9*, 5289–5294.9, 2548.
- X.-Q. Hu, Z. Hu, G. Zhang, N. Sivendran, L. J. Goossen, *Org. Lett.* **2018**, *20*, 4337–4340



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