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

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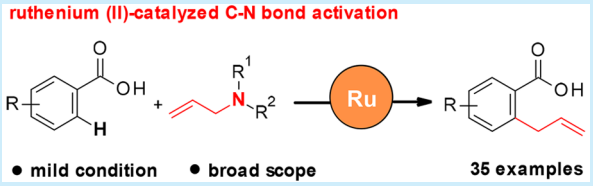
Supporting Information

ABSTRACT: A facile insertion of ruthenium into aromatic C−H and allylic C−N bonds are the key steps in a $[Ru(p\text{-cymene})Cl_2]_2$-catalyzed *ortho*-C−H allylation of benzoic acids. This protocol allows drawing on the large pool of allylic amines for state-of-the-art *ortho*-functionalizations of arenes, turning neutral amines into leaving groups. Concise syntheses of biologically active compounds provide further evidence of the synthetic potential of this methodology.

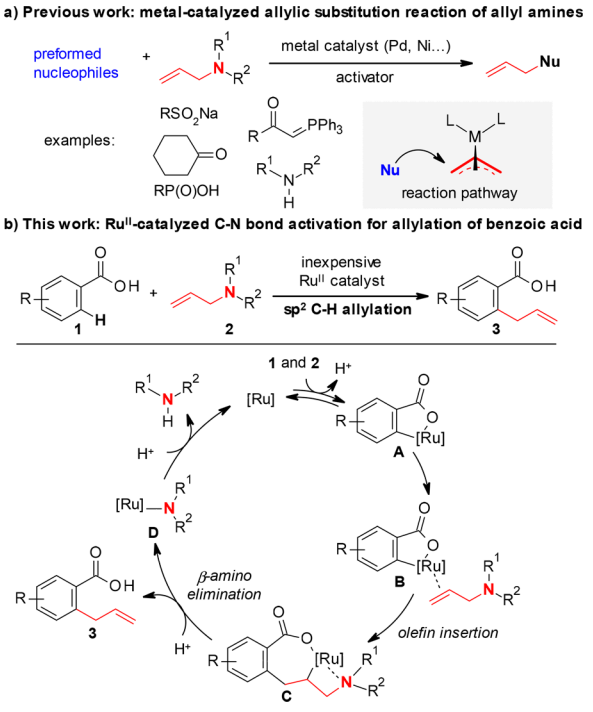


The C−N bond is one of the most prevalent bonds in biological and chemical compounds.[1] Selective transformations of C−N bonds are of substantial interest for the late-stage functionalization of complex molecules in the context of pharmaceutical research and material sciences.[2] However, the cleavage of inert C−N bonds remains a challenging task for scientists due to their thermodynamic stability and relatively high bond dissociation energies (ca. 80 kcal/mol).[3,4] Allyl amines are stable and easy to make in great structural diversity. Tsuji−Trost allylations based on allyl amine electrophiles are comparably well investigated.[5] In 2002, Hartwig et al. reported a nickel-catalyzed amine exchange reaction through oxidative cleavage of C−N bonds.[6] The groups of Yudin,[7] Zhang,[8] Aggarwal,[9] and Tian[10] et al. independently achieved allyl substitutions of allyl amines with the use of various strong nucleophiles, such as amines, carbonyl compounds, sulfinate salts, phosphonium ylides, and phosphinic acids, via η^3-allyl−metal intermediates (Scheme 1a).

In contrast to these cross-couplings, C−H allylations with allyl amines are still in their infancy.[5] Regiospecific *ortho*-C−H functionalizations with allyl substrates mostly require strong directing groups, that in turn require additional steps for their introduction and removal.[11] This limitation was recently overcome in an *ortho*-C−H allylation of benzoic acids.[12−14] Carboxylate groups are particularly desirable directing groups, since they are widely available and can either be tracelessly removed or utilized as anchor points for further transformations.[15]

We believe that the versatility of this synthetic concept would be improved considerably if allyl amines could be used as allylating agents in place of allyl acetates. In addition, we are confident that the challenge of cleaving a C−N bond (ca. pK_a Me_2N−H = 40 vs pK_a MeCOO−H = 4.76) might be overcome based on the mechanistic knowledge gained in related Ru-catalyzed C−H functionalizations.[13,14,16] The reaction is likely to be initiated by a base-assisted *ortho*-C−H activation of the benzoic acid, in which the allyl amine substrate might act as an auxiliary base (Scheme 1b, **A**). Coordination and insertion of the olefinic group of the amine to the ruthenium center would give rise to intermediates **B** and **C**. The key step in the process is the cleavage of the C−N bond in a "β-amine elimination" with formation of the desired product, along with Ru−N complex **D**. We saw a realistic chance that this could succeed, since the coordination of the amine to the ruthenium center would activate it in a similar

Scheme 1. C−H Allylation of Benzoic Acids



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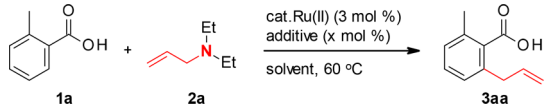
way to a protonation, thus leading to a significant reduction of the C−N bond strength. Clearly, the control of proton activity in the solvent would be a key factor in enabling this intellectually challenging and synthetically useful transformation.

We chose the reaction of 2-methylbenzoic acid **1a** and *N*-allyldiethylamine **2a** as a model to investigate various catalyst systems, solvents, and additives (Table 1). To our delight, the

Table 1. Optimization of the Allylation Reaction[a]



1a 2a 3aa

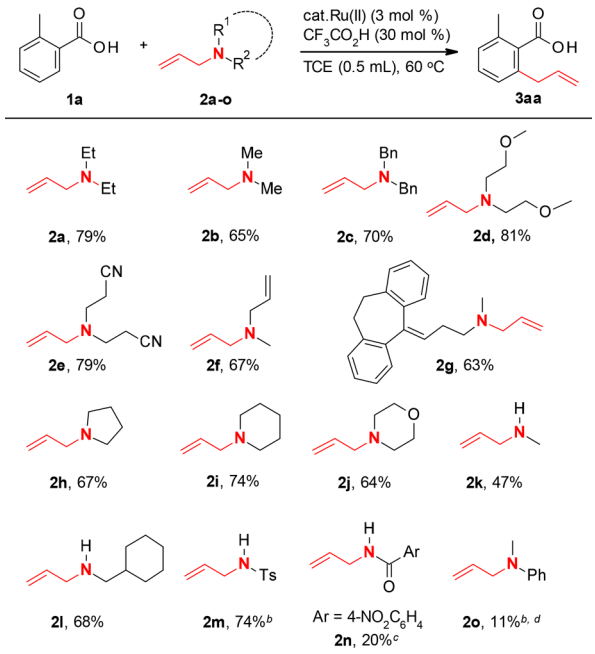
entry	solvent	additive (mol %)	yield (%)[b]
1	^{t}AmOH	–	trace
2	MeOH	–	8
3	TFE	–	30
4	HFIP	–	47
5	TCE	–	52
6	toluene	–	trace
7	dioxane	–	trace
8	TCE	CH_3CO_2H (20)	61
9	TCE	CF_3CO_2H (20)	67
10	TCE	CF_3SO_3H (20)	56
11	TCE	CF_3CO_2H (30)	74
12	TCE	CF_3CO_2H (40)	69
13	TCE	K_3PO_4 (20)	trace
14[c]	TCE	CF_3CO_2H (30)	80

[a]Reaction conditions: 0.5 mmol of **1a**, 0.65 mmol of **2a**, 3 mol % [Ru], 0.5 mL of solvent, 60 °C, 24 h. [b]Yields determined by ^{1}H NMR spectroscopy using dibenzyl ether as internal standard. [c]1.0 mmol scale. [Ru] = $[Ru(p\text{-cymene})Cl_2]_2$. ^{t}AmOH = 2-methylbutan-2-ol. HFIP = hexafluoro-2-propanol. TFE = 2,2,2-trifluoroethanol. TCE = 2,2,2-trichloroethanol.

desired allylation product **3aa** was detected in small quantities when using 3 mol % $[Ru(p\text{-cymene})Cl_2]_2$ in protic solvents (entries 2−5). Intricate optimization of the solvent system was a crucial step toward improved yields. The best yields were obtained in alcohols, particularly in 2,2,2-trichloroethanol (TCE, pK_a = 12.24)[17] (entry 5). In contrast, aprotic solvents were not suitable for this reaction (entries 6 and 7). The yields were further increased by adjusting the pH of the reaction mixture by addition of Brønsted acids (entries 8−12). Inorganic bases, such as K_3PO_4, totally shut down the reaction (entry 13). It proceeds best in a rather concentrated solution (entry 14). It should be noted that a more dilute solution significantly decreased the reaction efficiency (see Supporting Information). Under the optimal conditions (3 mol % $[Ru(p\text{-cymene})Cl_2]_2$, 30 mol % TFA, 0.5 mL of TCE, 60 °C), allylarene **3aa** was obtained in 80% yield. Under these mild conditions, isomerization of the double bond into the vinylic position was completely suppressed at slightly incomplete conversion.[18]

With the optimal conditions established, we proceeded to investigate the influence of leaving groups in allyl amines. As shown in Scheme 2, allyl amines bearing different alkyl groups were suitable reagents, affording the desired allylarene products in good yields. The allyl amine **2g** derived from Nortriptyline participated well in this transformation, delivering the expected product **3aa** in 63% yield. Commercially available cyclic

Scheme 2. Investigation of the Leaving Groups[a]



[a]Reaction conditions: 1.0 mmol of **1a**, 1.3 mmol of **2**, 3 mol % $[Ru(p\text{-cymene})Cl_2]_2$, 30 mol % CF_3CO_2H, 0.5 mL of TCE, 60 °C, 24 h, isolated yields. [b]4 mol % $[Ru(p\text{-cymene})Cl_2]_2$, ^{1}H NMR yield. [c]3 mol % $[Ru(O_2CMes)_2(p\text{-cymene})]$, 0.5 mL of HFIP and 65 °C, ^{1}H NMR yield. [d]Without CF_3CO_2H.

amines such as 1-allylpyrrolidine, 1-allylpiperidine, and 4-allylmorpholine were smoothly coupled. N-Protected or unprotected secondary allyl amines were also efficiently converted. For example, *N*-allyl-4-methylbenzenesulfonamide **2m** gave the desired product **3aa** in 74% yield. Carboxamides, in contrast, gave lower yields. Even after adapting the reaction conditions and leaving out the trifluoroacetic acid, *N*-allyl-*N*-methylaniline **2o** gave only a low yield. However, at the current stage, no substituents are tolerated at the double bond (see SI)

The scope of the C−H allylation with respect to the benzoic acids is outlined in Scheme 3. The electron-donating and electron-withdrawing substituents at the *ortho*-, *meta*-, and *para*-positions of benzoic acids are tolerated, and the desired products are mostly obtained in satisfactory yields. Sensitive groups, such as amino and nitro substituents, were retained unchanged in the final products (**3na** and **3qa**). Even under harsh conditions, i.e. higher temperature (80 °C) and using an excess of **2a**, monoallylation products were formed exclusively from *meta*-substituted benzoic acids, demonstrating the high selectivity of this reaction variant. Strongly coordinating thioether substituents are not tolerated, and a methanesulfonyl group led to a low yield (**3la**). Notably, other directing groups such as amides are well-tolerated in this reaction and do not affect the regioselectivity (**3ma**), opening up an opportunity for further, orthogonal C(sp^2)−H functionalizations. Remarkably, even strongly coordinating pyridinecarboxylic acids were selectively converted (**3ua**). Using simple benzoic acid, a mixture of the mono- and diallylation products was obtained in 55% and 25% yields, respectively.

The current reaction was successfully scaled up to 7.5 mmol, and the desired product **3pa** was obtained in 75% yield (Scheme 4a). The preparative utility of the process was also

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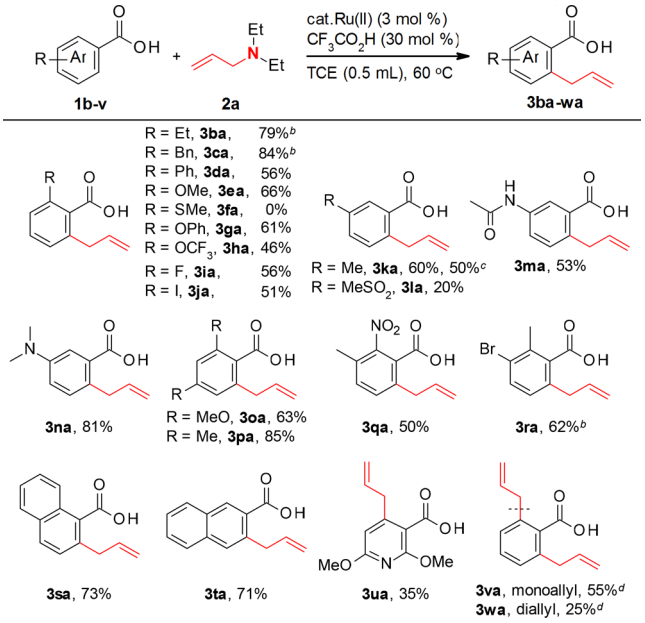
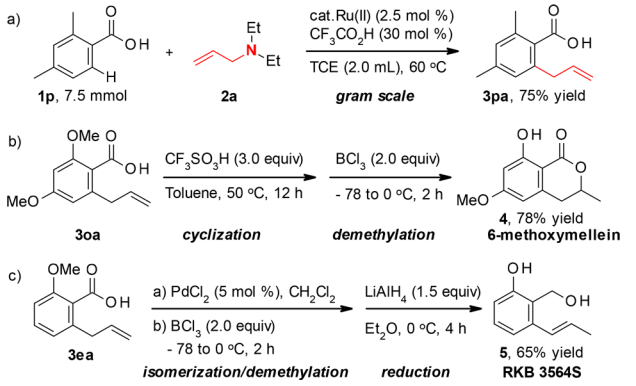
Scheme 3. Scope of Allyl Benzoic Acids[a]



[a]Reaction conditions: 1.0 mmol of **1**, 1.3 mmol of **2a**, 3 mol % [Ru(*p*-cymene)Cl_2]$_2$, 30 mol % CF_3CO_2H, 0.5 mL of TCE, 60 °C, 24 h, isolated yields. [b]Isolated yields of corresponding methyl esters. [c]80 °C and 2.0 mmol **2a** were used. [d]^{1}H NMR yield.

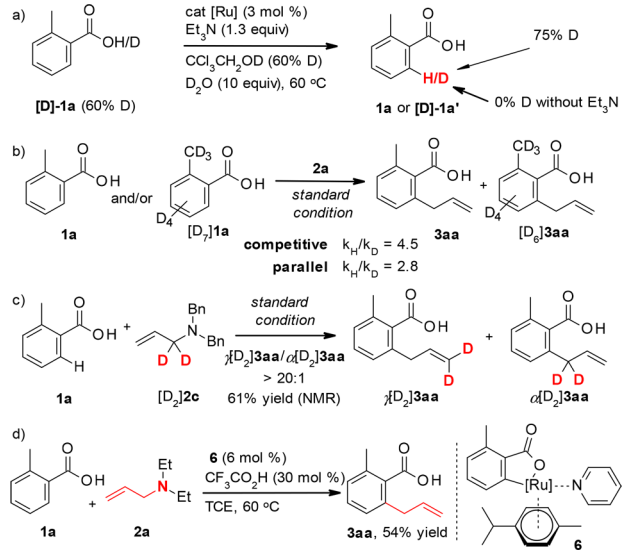
Scheme 4. Synthetic Applications of This Method



demonstrated by a sequential cyclization/demethylation to give 6-methoxymellein **4**, which is known for its antiproliferative activity (Scheme 4b).[19] Moreover, product **3ea** was transformed to the biologically active compound **RKB 3564S** through three simple, sequential operations (Scheme 4c).[20] The latter exhibits significant antiangiogenesis and antitumor activities and has been used for the treatment of diabetes, Alzheimer's, and Parkinson's diseases, as well as neuroses.

To obtain additional insight into the reaction mechanism, a series of deuterium-labeling experiments were conducted. In control H/D exchange experiments, 75% starting material was deuterated at the *ortho*-position in the presence of Et_3N, while, in the absence of a base, no deuterium incorporation occurred, which indicates that the base is necessary for C−H cleavage and this process is reversible (Scheme 5a).[21] The significant kinetic isotope effects (KIE) in parallel experiments (k_H/k_D = 2.8) and the competitive reaction (k_H/k_D = 4.5) demonstrated that C−H activation is the rate-determining step in this reaction (Scheme 5b). The fact that the C−H rather than the

Scheme 5. Mechanistic Studies



C−N bond cleavage is still rate-determining is in agreement with the experimentally determined relative bond strength of 100 vs 80 kcal/mol. When 1,1-dideuterio-allyl amine [D_2]**2c** was used, γ[D_2]**3aa** was obtained exclusively in 61% yield (Scheme 5c), which is in agreement with a β-amino elimination pathway.[22] GC and ^{1}H NMR analysis of the reaction mixture confirmed that the alkylamine and its corresponding ammonium salt are formed as byproducts (see SI). When using 6 mol % ruthenacycle **6** as the catalyst, the reaction proceeded smoothly yielding 54% of the desired product **3aa**, which supports the intermediacy of a ruthenacycle in this transformation (Scheme 5d). Although all our studies agree with the proposed mechanism, a pathway via an η^3-allyl metal-complex intermediate cannot be completely ruled out at this stage.

In summary, we have developed a regiospecific allylation of benzoic acids with allyl amines that proceeds via [Ru(*p*-cymene)Cl_2]$_2$-catalyzed C−N bond activation. This protocol enables the construction of various allylarene motifs in reasonable yields under mild conditions. The succinct synthesis of active compounds 6-methoxymellein and **RKB 3564S** further demonstrate the synthetic potential of this reaction.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01762.

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

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Notes

The authors declare no competing financial interest.

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