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Carboxylate-directed C–H allylation with allyl alcohols or ethers†

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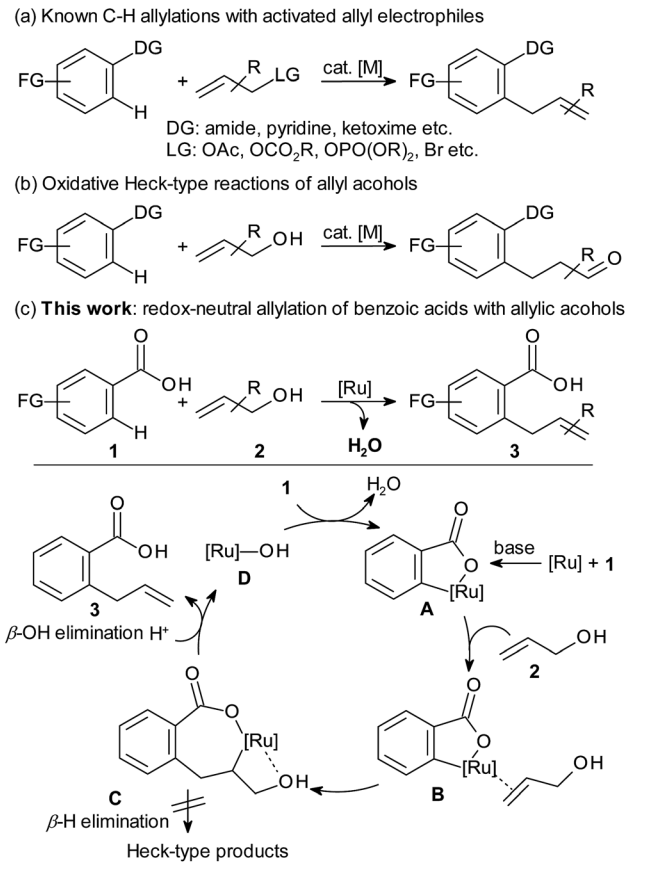
A [Ru(*p*-cymene)Cl_2]$_2$ catalyst activates allyl alcohols and ethers for the regioselective *ortho*-C–H allylation of aromatic and heteroaromatic carboxylates. The reaction is orthogonal to most C–H functionalisations with allyl alcohols in that allyl arenes rather than carbonyl compounds are obtained. 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-minimised method for C–C bond formation.

Introduction

Allylarene motifs are widely found in natural products and biologically active molecules.[1] The regiospecific introduction of allyl groups into functionalised 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,[3] carbonates,[4] phosphates,[5] halides,[6] or allenes.[7] The regiochemistry of C–H allylations is usually ensured by strong directing groups (Scheme 1a). The use in C–H functionalisations 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. Allyl alcohols are widely available and would release only H_2O as a by-product in dehydrogenative arylations.[8] However, OH is such a poor leaving group that allyl alcohols usually react *via* a β-H elimination pathway leading to carbonyl compounds. The resulting Heck-type products are predominant not only in Pd-catalysed couplings of aryl halides, but also in Rh-catalysed oxidative *ortho*-C–H functionalisations (Scheme 1b).[9] Examples for C–H allylations with alcohols as the allyl source are limited to Kanai's and Sundararaju's cobalt-catalysed allylation of nitrogen heterocycles,[10] Matsunaga and Yoshino's allylation of 6-arylpurines and benzamides,[11] and Kapur's ruthenium-catalysed C–H allylation of indoles bearing a pyridine directing group.[12] All these reactions employ directing groups that are arduous to install and remove, and require high loadings of Ag or Cu additives. In our eyes, the ideal entry to allylarenes would consist of a regioselective C–H allylation directed by a simple, widely available substituent, and use non-derivatised alcohols as the allylating agent along with catalytic amounts of an inexpensive metal. In this respect, benzoic acids appeared to be particularly attractive starting materials, because carboxylate groups are abundant and can be tracelessly removed or act as anchor point for further transformations.[13,14] Despite the low coordinating ability of carboxylates, efficient



Scheme 1 Strategies for C(sp^2)–H allylation and reaction design.

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carboxylate-directed C–H functionalisations have been developed,[14] such as arylations,[15] acylations,[16] alkylations,[17] and alkenylations.[18] Allylations are only possible starting from preformed allyl esters, and have a narrow substrate scope even at 135 °C.[19]

There is ample evidence that arenecarboxylates (1) can react with Ru-catalysts to give five-membered ruthenacycles (A).[15c,17c,20] The first challenge was to tune the catalyst in a way that it would coordinate a simple allyl alcohol (2) and insert into its non-activated C–C double bond. The resulting ruthenacycle C had to be expected to undergo β-hydride elimination, leading to carbonyl compounds.[9] However, if internal rotation could efficiently be suppressed by increasing charge separation, thus strengthening the coordination of the OH-group to the Ru centre, the only remaining pathway would be β-hydroxide elimination leading to the desired allylarene products. The key hurdle to this pathway, the low leaving-group ability of hydroxide, might be overcome by its solvent stabilisation. We believed that by adjusting the proton activity within the solvent and the charge at the metal centre, it should be possible to steer the catalyst towards the desired pathway despite these obstacles.

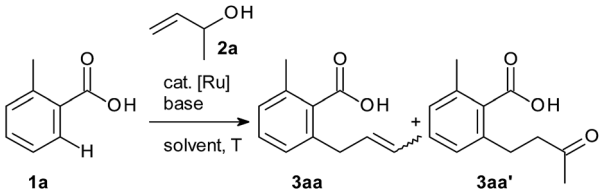
Results and discussion

In search for an effective catalyst system, we used the reaction between 2-methylbenzoic acid **1a** and the secondary allylic alcohol **2a** as the model and systematically investigated various catalysts, additives and solvents (Table 1). We were pleased to see that a combination of $[Ru(p\text{-cymene})Cl_2]_2$ with substoichiometric inorganic bases led to the formation of allylation products. The solvent turned out to be the critical parameter.[21] Aprotic solvents (toluene or CH_3CN) gave low yields and insufficient selectivity for the desired allylarene **3aa** over the β-H elimination by-product **3aa′** (entries 1 and 2). In protic solvents, in contrast, the reaction was highly selective for the desired product **3aa**. Yields were optimised by adjusting the pK_a of the solvents and bases (entries 3–9). A combination of the acidic alcohol 2,2,2-trichloroethanol (TCE, pK_a = 12.24)[22] with potassium phosphate and a reaction temperature of 50 °C were found to be optimal (entry 11). Evaluation of Ru pre-catalysts showed the cymene-ligated $[Ru(p\text{-cymene})Cl_2]_2$ to be uniquely effective (entries 11–13). The presence of ligands dramatically reduced the yields and selectivities (entries 14 and 15). All findings are in agreement with our mechanistic blueprint, which relies on a coordinatively unsaturated metal centre and facile interactions between the hydroxyl group and ruthenium. Under the optimal conditions (2 mol% $[Ru(p\text{-cymene})Cl_2]_2$, 0.5 equiv. K_3PO_4, TCE, 50 °C), allylarene **3aa** was obtained in 2 : 1 *E*/*Z* ratio, along with only traces of the vinylarene double-bond isomer.

When starting from unsubstituted allyl alcohol (**2t**), double-bond migration could not be completely suppressed (Scheme 2). In an attempt to improve this, we also tested ethers as allylation reagents.[23] To our delight, not only allyl phenyl ether (**2u**, pK_a (PhOH) = 9.98)[24] but also allyl methyl ether (**2v**, pK_a (MeOH) = 15.5)[22] cleanly converted **1a** to **3at** with high selectivity (allyl-to-vinyl ratio >15 : 1). This is the first time that the strong alkyl ether bond has been cleaved in a sp^2 C–H functionalisation. This reaction variant may prove useful particularly in total synthesis, since allyl ether intermediates can now be coupled directly without difficult deprotection and activation steps.

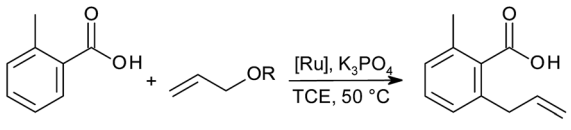
The scope of the C–H allylation with regard to the alcohol substrate is presented Table 2. Various primary, secondary, and even tertiary alcohols were coupled with 2-toluic acid (**1a**) in good yields. Substrates bearing alkyl, aryl, or heteroaryl groups at the carbinol carbon, *e.g.* dimethyl, cyclohexyl and even sterically crowded adamantyl alcohols, were successfully coupled. This, as well as the high selectivity for SN2′-type products, is in good agreement with the proposed β-OH elimination pathway. The *E*/*Z* selectivity correlates with the

Table 1 Optimisation of the allylation conditions[a]



Entry	Base	Solvent	*T* (°C)	**3aa** (%)	**3aa′** (%)
1	K_3PO_4	Toluene	60	13 (2.5 : 1)	6
2	K_3PO_4	CH_3CN	60	8 (2 : 1)	3
3	K_3PO_4	^{t}AmOH	60	16 (1.8 : 1)	—
4	K_3PO_4	HFIP	60	27 (2 : 1)	—
5	K_3PO_4	TFE	60	68 (1.7 : 1)	—
6	K_3PO_4	TCE	60	80 (2 : 1)	—
7	K_2CO_3	TCE	60	73 (2 : 1)	—
8	Cs_2CO_3	TCE	60	68 (2 : 1)	—
9	K_2HPO_4	TCE	60	58 (2 : 1)	—
10	K_3PO_4	TCE	40	81 (2 : 1)	—
11	K_3PO_4	TCE	50	89 (2 : 1)	—
12[b]	K_3PO_4	TCE	50	3 (n.d.)	—
13[c]	K_3PO_4	TCE	50	—	—
14[d]	K_3PO_4	TCE	50	30 (2 : 1)	6
15[e]	K_3PO_4	TCE	50	—	—

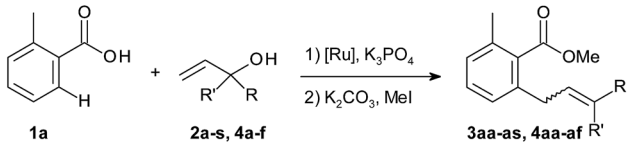
[a] Reaction conditions: 0.5 mmol **1a**, 0.75 mmol **2a**, 2 mol% [Ru], 0.25 mmol base, 0.5 mL solvent, 60 °C, 16 h, yields determined by ^{1}H NMR spectroscopy using dibenzyl ether as internal standard, *E*/*Z* ratios in parentheses. [b] 2 mol% $[Ru(C_6Me_6)Cl_2]_2$. [c] 2 mol% Ru(cod)Cl_2. [d] 4 mol% Ph_3P. [e] 2 mol% dppb. [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.



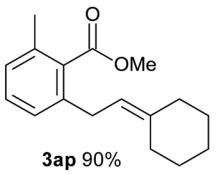
R = H, **2t**, [Ru] (2 mol%) 76% (3:1)
R = Ph, **2u**, [Ru] (4 mol%) 90% (>15:1)
R = Me, **2v**, [Ru] (4 mol%) 65% (>15:1)

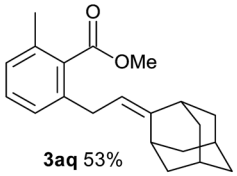
Scheme 2 C–H-allylation with alcohols and ethers as allylating reagents.

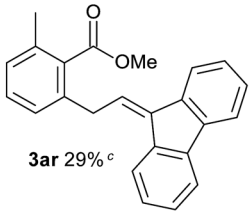
Table 2 Scope of allylic alcohols[a]

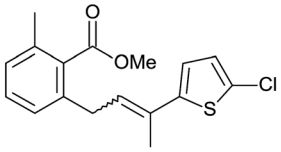


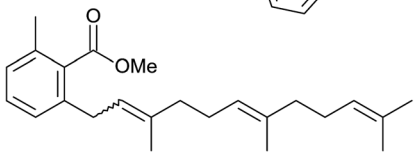
R = H, R' = Me, **3aa** 87% (2:1)
R = H, R' = Et, **3ab** 89% (3:1)
R = H, R' = ^{n}Pr, **3ac** 86% (4:1)
R = H, R' = ^{n}Hept, **3ad** 84% (4:1)
R = H, R' = Ph, **3ae** 79% (1:1)
R = H, R' =1 -naphthyl, **3af** 82% (1.9:1)
R = H, R' = 2-furyl, **3ag** 67% (1.5:1)
R = R' = Me, **3ah** 89%, 65%[b]
R = R' = Ph, **3ai** 90%
R = R' = 4-MeC_6H_4, **3aj** 92%
R = R' = 3-FC_6H_4, **3ak** 85%
R = Ph, R' = Me, **3al** 96% (4:1)
R = Ph, R' = ^{i}Pr, **3am** 97% (>20:1)
R = Ph, R' = Cy, **3an** 92% (>20:1)
R = Ph, R' = cyclobutyl, **3ao** 92% (9:1)

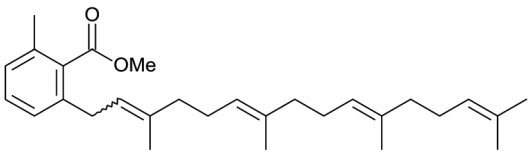

3ap 90%

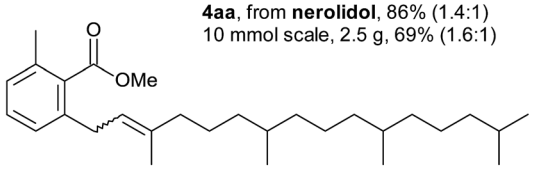

3aq 53%

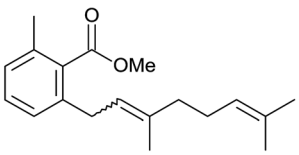

3ar 29%[c]

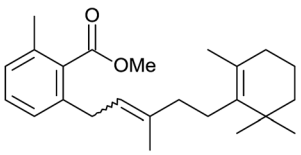

3as 73% (1.3:1)

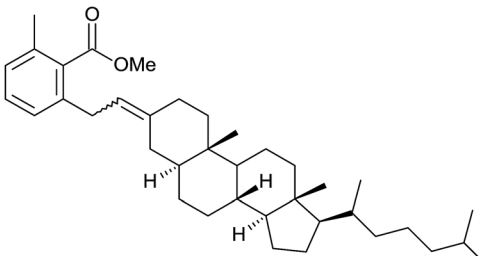

4aa, from **nerolidol**, 86% (1.4:1)
10 mmol scale, 2.5 g, 69% (1.6:1)


4ab, from **geranyllinalool**, 54% (1.8:1)[c]


4ac, from **isophytol**, 72% (1.9:1)


4ad, from **linalool**, 80% (1.3:1)


4ae, from **dihydro-b-inonone**, 89% (2.4:1)


4af, from **3-keto-5a-cholestane**, 44% (1.5:1)

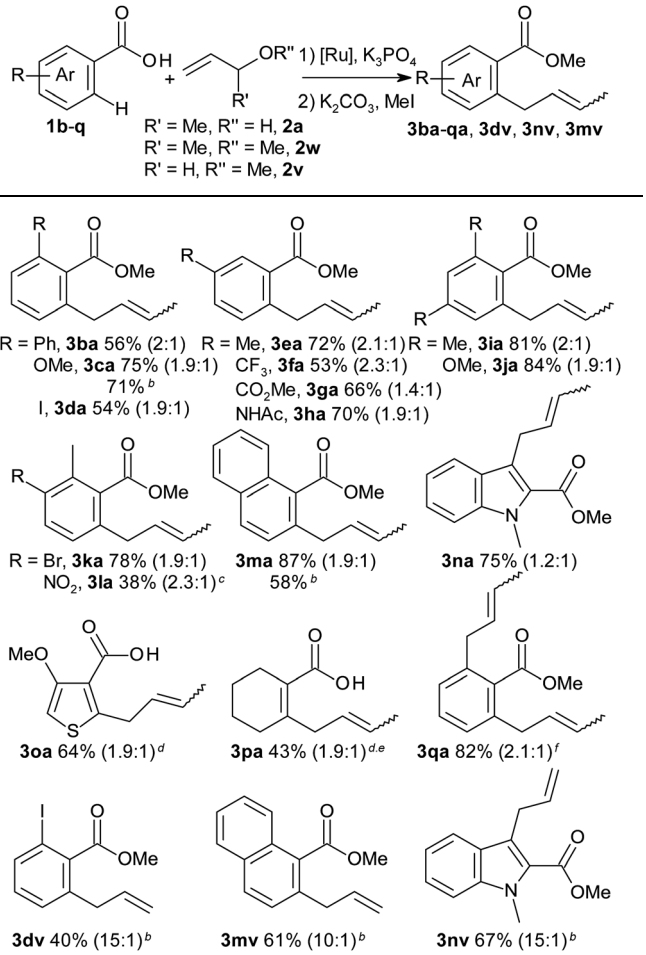
[a] Reaction conditions: 0.5 mmol **1a**, 0.75 mmol **2**, 2 mol% [Ru(*p*-cymene)Cl_2]$_2$, 0.25 mmol K_3PO_4, 0.5 mL TCE, 50 °C, 16 h. After the reaction was complete, 2 mL MeCN, 1.5 mmol K_2CO_3 and 2.5 mmol MeI were added and the mixture was stirred at 50 °C for 2 h, isolated yields of corresponding methyl esters, *E* : *Z* ratios in parentheses. [b] Using TMS analogue of **2h** in the presence of KF. [c] 0.5 mmol K_2CO_3, 0.5 mL CH_3CN, 80 °C, 16 h.

magnitude of steric interactions between the two substituents at the carbinol carbon, which is particularly high for **3am** and **3an**. The reaction is well-suited for naturally occurring allyl alcohols. The sensitive terpene alcohols nerolidol, geranyllinalool, isophytol and linalool were smoothly coupled, as were allylic alcohols obtained by vinylation of dihydro-β-ionone and 3-keto-5α-cholestane. The reaction was successfully performed on gram scale (**4aa**, 2.5 g, 69% yield). In the presence of potassium fluoride, allyl trimethylsilyl ethers also become effective allylating agents in this reaction. Thus, the TMS analogue of **2h** was converted to product **3ah** in 65% yield. A remaining limitation of this prototype protocol is that no substituents are tolerated at the double bond.

The scope with regard to the carboxylate substrate was investigated using **2a** as the coupling partner (Table 3). Benzoic acids bearing electron-donating and electron-withdrawing substituents in *ortho*-, *meta*-, and *para*-positions all afforded comparable yields. Sensitive functionalities, such as ester, nitro and CF_3 groups and reactive leaving groups such as bromo and even iodo substituents are left intact. Moreover, functional groups that are efficient directing groups in other C–H functionalisations, such as amide groups, were tolerated, opening up opportunities for orthogonal C(sp^2)–H difunctionalisations. The scope also extends to heterocyclic carboxylates. The conversion of the vinylic carboxylate 1-cyclohexene-1-carboxylic acid required only minor deviations from the standard conditions. *Para*- and non-substituted benzoic acids reacted with competing diallylation. The diallylation product was obtained selectively when using 2.5 equivalents of the allyl alcohol (**3qa**).

Starting from allyl methyl ethers, the reaction proceeded similarly well (**3ca**, **3ma**). Their use is advantageous for

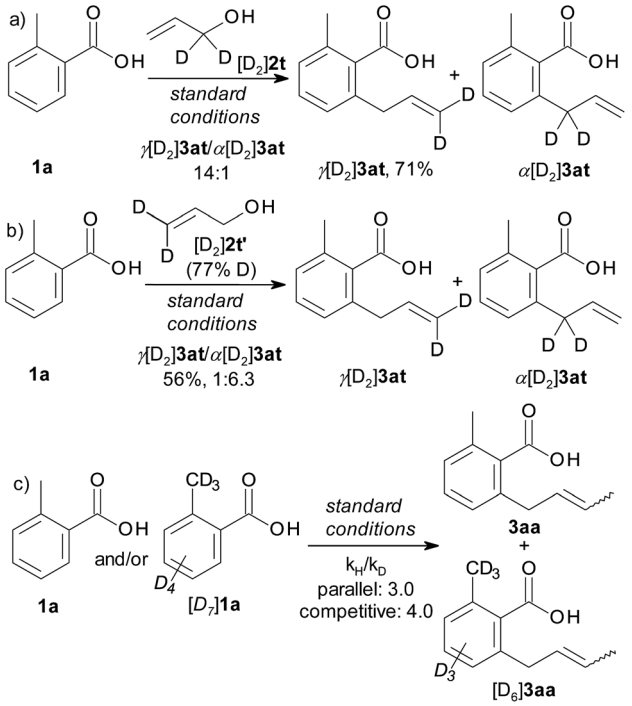
Table 3 Scope of benzoic acids[a]



[a] Reaction conditions: 0.5 mmol **1**, 0.75 mmol **2a**, 2 mol% [Ru(*p*-cymene)Cl_2]$_2$, 0.25 mmol K_3PO_4, 0.5 mL TCE, 50 °C, 16 h. After the reaction was complete, 2 mL MeCN, 1.5 mmol K_2CO_3 and 2.5 mmol MeI were added and the mixture was stirred at 50 °C for 2 h isolated yields of methyl esters, $E:Z$ ratios in parentheses. [b] Starting from methyl allyl ether, ratios of terminal to internal alkene in parentheses. [c] 60 °C. [d] Isolated as acid. [e] 0.5 mmol K_2CO_3, 60 °C. [f] 1.25 mmol **2a**.

introducing unsubstituted allyl groups, since double-bond isomerisation is efficiently suppressed (**3dv**, **3mv**, **3nv**).

Deuterium-labelling experiments were conducted to elucidate the reaction mechanism. The allylation of **1a** with 1,1-dideuterio-allyl alcohol [D_2]**2t** afforded a 14 : 1 mixture of γ[D_2]**3at** (71% yield) and α[D_2]**3at** (Scheme 3a). When 3,3-dideuterio-allyl alcohol [D_2]**2t′** (77% D incorporation) was employed, a 1 : 6.3 mixture of γ[D_2]**3at** and α[D_2]**3at** was observed (Scheme 3b). These results further support that the β-OH elimination is the dominant 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 (Scheme 3c). These observations agree with the proposed catalytic cycle.



Scheme 3 Mechanistic studies.

Conclusions

In conclusion, this Ru-catalysed C(sp^2)–H allylation gives efficient and sustainable access to a wide range of allylarenes from benzoic acids and non-activated allylic alcohols or ethers along with water or methanol as the only by-product.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgements

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