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Euro Green Chemistry-2018-Carboxylate-Directed C–H Allylation with Allyl Alcohols or Ethers-Zhiyong Hu- Ruhr Universität Bochum

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Introduction: Allylarene substances are extensively found in natural products and biologically active molecules. The regiospecific introduction of allyl groups into functionalised arene substrates is normally achieved by joining pre-formed or in situ-generated aryl-metal species with pre-activated allyl electrophiles, allyl acetates, carbonates, phosphates, halides, allenes. The regiochemistry of C–H allylations is normally ensured by physically powerful directing groups. The usage 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 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 .Examples for C–H allylations with alcohols as the allyl source are relatively little to Kanai's and Sundararaju's cobalt-catalysed allylation of nitrogen heterocycles,Matsunaga and Yoshino's allylation of 6-arylpurines and benzamides, and Kapur's ruthenium-catalysed C–H allylation of indoles having a pyridine directing group.

All of these reactions employ directing groups that are difficult to install and remove, and it require high loadings of Ag or Cu added groups. In our eyes, the ideal entry to allylarenes would consist of a regioselective C–H allylation directed by a simple, widely possible 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 alot many and can be tracelessly removed or act as anchor point for further transformations. Despite the low coordinating ability of carboxylates, efficient carboxylate-directed C–H functionalisations have been developed, such as arylations, acylations, alkylations, and alkenylations. Allylations are only possible starting from pre-formed allyl esters, and have a limited in size substrate scope even at 135 °C.

There is enough evidence that arenecarboxylates can react with Ru-catalysts to give five-membered ruthenacycles .The first challenge was to tune the catalyst in a way that it would combine a simple allyl alcohol and insert into its non-activated C–C double bond. The resulting ruthena cycle C had to be expected to undergo β-hydride elimination, leading to carbonyl compounds. However, if internal rotation could well organized be suppressed by increasing charge separation, thus strengthening the combination of the OH-group to the Ru centre, the only remaining pathway would be β-hydroxide removing leading to the desired allylarene products. The key difficulty 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 struggles.

Results and discussion:

In search for an productive result 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. We were pleased to see that a combination of $[Ru(p\text{-cymene})Cl_2]_2$ with substoichiometric inorganic bases leads to the formation of allylation products. The solvent turned out to be the critical parameter. Aprotic solvents (toluene or CH_3CN) gave low products and inadequate selectivity for the desired allylarene 3aa over the β-H elimination by-product 3aa′. In protic solvents, in contrast, the reaction was highly selective for the desired product 3aa. Products were optimised by adjusting the pKa of the solvents and bases. A mixture of the acidic alcohol 2,2,2-trichloroethanol (TCE, pKa = 12.24) with potassium phosphate and a reaction temperature of 50 °C were found to be optimal . Assessment of value of Ru pre-catalysts showed the cymene-ligated $[Ru(p\text{-cymene})Cl_2]_2$ to be special effective . The presence of ligands slowly reduced the yields and selectivities. 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. K3PO4, TCE, 50 °C), allylarene 3aa was obtained in 2 : 1 E/Z ratio, along with only small amount of the vinylarene double-bond isomer.

The range covered with regard to the carboxylate substrate was examined using 2a as the joining partner . Benzoic acids bearing electron-donating and electron-withdrawing substituents in ortho-, meta-, and para-positions all afforded comparable results. 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(sp2)–H di-functionalisations. The scope also elaborates to heterocyclic carboxylates.

Conclusion:

This work is partly presented at 9th World Congress on Green Chemistry and Technology, September 17-19, 2018, Amsterdam, Netherlands

Finally, this Ru-catalysed C(sp2)–H allylation gives good 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.

A [Ru(p-cymene)Cl_2]$_2$ catalyst capable of action on 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. The reaction concept combines the usage of Huge reagents and directing groups in a sustainable, waste-minimized method for C–C bond formation.

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