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Rh-catalyzed arylation of fluorinated ketones with arylboronic acids

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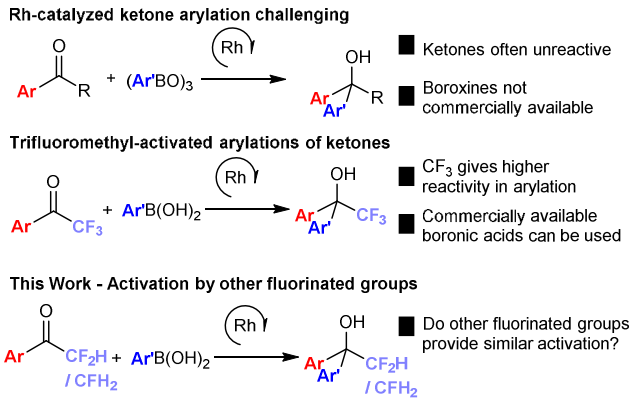
The Rh-catalyzed arylation of fluorinated ketones with boronic acids is reported. This efficient process allows access to fluorinated alcohols in high yields under mild conditions. Competition experiments suggest that difluoromethyl ketones are more reactive than trifluoromethyl ketones in this process, despite their decreased electronic activation, an effect we postulate to be steric in origin.

Fluorinated molecules now appear routinely in a range of applications, ranging from pharmaceuticals to agrochemicals and materials.[1] In particular, the difluoromethyl (CF_2H) group is an important functional group in the study of modern organofluorine chemistry. As an example of fluorine-containing functionality it imparts many of the advantageous properties that has seen fluorine being incorporated in a wide variety of bioactive molecules (such as modulation of pK_a, dipole and lipophilicity, blocking of metabolically-susceptible sites). Yet, compared to the better-studied CF_3 group, the CF_2H group has unique properties of its own. For example, unlike the CF_3 group, a CF_2H group is able to act as a hydrogen bond acceptor,[2] a property which is likely to lead to the discovery of useful functional molecules containing a CF_2H group.

However, the study of difluoromethylated molecules is not well-advanced, largely due to difficulties in their synthesis.[3] The study of the synthesis and reactivity of CF_2H-containing molecules is therefore an active area of research. As part of a developing research program into the synthesis of novel fluorinated moieties,[4] our group recently reported a difluorination-fragmentation of 1-trifluoromethyl-1,3-diketones as an efficient approach for the synthesis of difluoromethyl ketones,[5,6] providing a convenient route for the access of these useful but under-studied building blocks. We are now developing a research program studying the reactivity and utility in synthesis of these ketones.

One potentially useful reaction that is currently under-studied is the addition of nucleophiles to difluoromethyl ketones.[7] Whilst the addition of Grignard and organozinc reagents, as well as reductions of difluoromethyl ketones are known, the full range of nucleophilic addition processes to difluoromethyl ketones have yet to be explored.

An attractive class of nucleophilic species for C-C bond-forming reactions are boronic acids. These are mild, air- and moisture-stable species whose reactions tolerate a broad range of functional groups. They have been typically engaged in additions to carbonyl compounds under rhodium catalysis.[8,9] Whilst the Rh-catalyzed addition of boronic acids to α,β-unsaturated carbonyl compounds (a 1,4-addition process) and aldehydes are well known,[10] the corresponding additions to ketones are under-developed and challenging (Scheme 1). Whilst additions to unactivated ketones are rare, a limited number of examples of intramolecular additions of aryl boronic esters onto unactivated ketones have been reported,[11] along with intermolecular variants of these reactions,[12] generally using arylboroxines as a stabilized form of the corresponding boronic acid. Although boroxines are readily accessible by dehydration of the corresponding boronic acid, they are generally not commercially available, which may limit uptake of this chemistry, particularly by medicinal chemists



Scheme 1: Challenges in Rh-catalyzed ketone arylation

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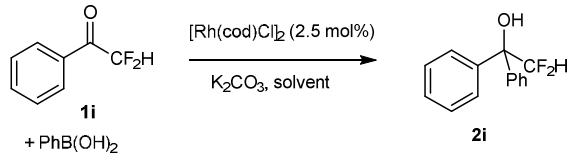
seeking to prepare large numbers of derivatives for screening.

The majority of progress in the field of Rh-catalyzed additions of organoboron compounds to ketones has been made using activated ketones and imines,[13] in particular α-ketoesters[14] and trifluoromethyl ketones.[15] We questioned in particular whether this success with trifluoromethyl ketones could mean that other fluorinated groups, including the difluoromethyl group are also suitable activating groups to promote Rh-catalyzed additions of boronic acids to ketones.

We began our study by examining the addition of phenylboronic acid to difluoromethyl ketone **1i**, varying the solvent system (Table 1). We were pleased to discover that the use of anhydrous toluene provided the arylation product **2i** with essentially quantitative conversion. It has previously been noted that the use of anhydrous toluene imparts very high stability upon the catalyst system in similar Rh-catalyzed processes;[12d] we too noted very little formation of black nanoparticulate Rh under these reaction conditions.



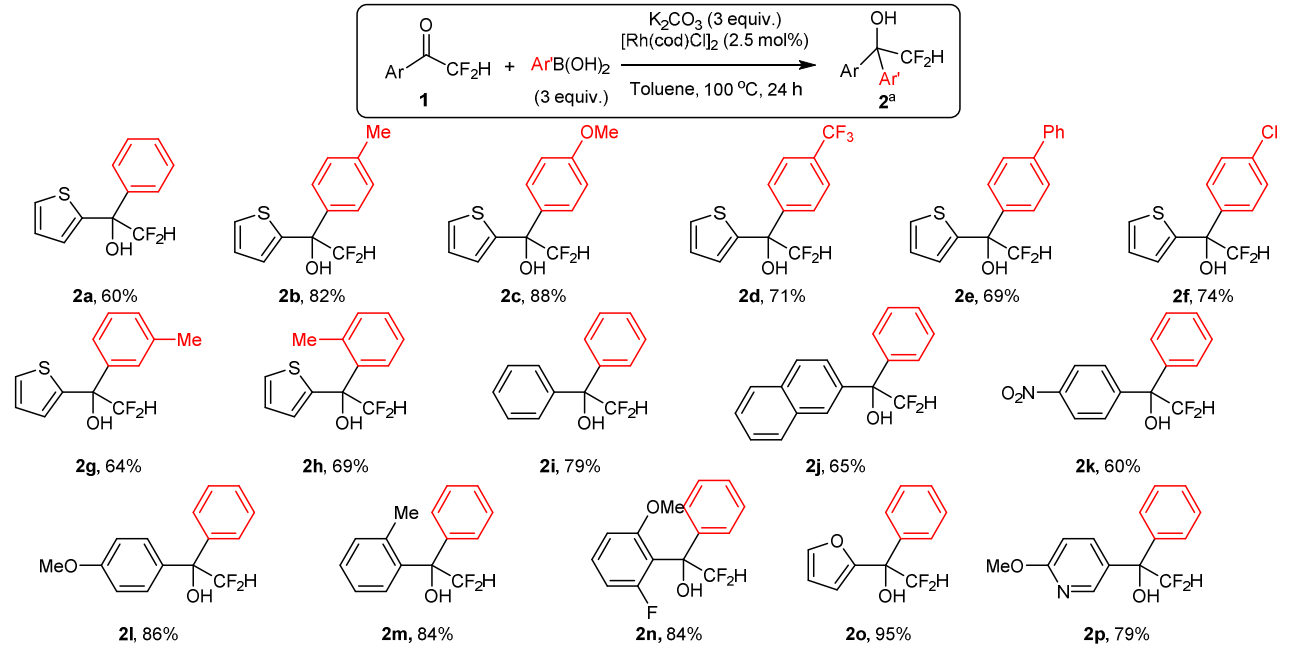
Solvent	Conversion to 2i / %[a]
Toluene	100
Dioxane	61
9:1 Dioxane/Water	67

Table 1: Solvent Optimization. [a] Conversion as measured by ^{19}F spectroscopy against consumption of the starting material

We then sought to establish the scope of this arylation process (Scheme 2), so a range of difluoromethyl ketones were prepared and reacted with boronic acids under the optimized reaction conditions. In general, the reactions proceeded to complete conversion and were broadly applicable to a range of systems; electron-donating groups such as methoxy substituents were tolerated on the aryl ring of the ketone and boronic acids containing either *ortho*-substituents and electron withdrawing groups, including halogen atoms for further cross-coupling processes and a trifluoromethyl substituent, were excellent nucleophilic partners. However, boronic acids known to be less stable, particularly to protodeboration (or indeed protoderhodation after transmetallation), which included alkenyl and pyridyl examples failed to provide the arylation product under these reaction conditions. A sterically hindered 2,6-dimethylated arylboronic acid was also unreactive.

We also examined the reactivity of α-monofluorinated ketones in similar processes (Scheme 3). Pleasingly, we found that fluoromethyl ketone **3a** and α-fluoroethyl ketone **3b** could both be arylated in high yield under conditions that were identical to those used with difluoromethyl ketones. However, the attempted arylation of acetophenone under these reaction conditions led simply to the return of the starting material, with no arylation observable. This demonstrates clearly the activating effect fluorine substitution has on Rh-catalyzed ketone arylation processes.

To gain a better understanding of this activating effect by fluorine, a series of competition experiments were performed which would allow the degree of activation by a CF_3, CF_2H and CFH_2 substituent to be compared. Interestingly, these showed that in all cases examined, a difluoromethyl ketone provided higher reactivity in Rh-catalyzed arylation with boronic acids than a trifluoromethyl ketone (Scheme 5). This is despite the higher degree of electronic activation afforded by a



Scheme 2: Substrate scope in Rh-catalyzed arylation of difluoromethyl ketones. [a] Isolated yields of pure material.

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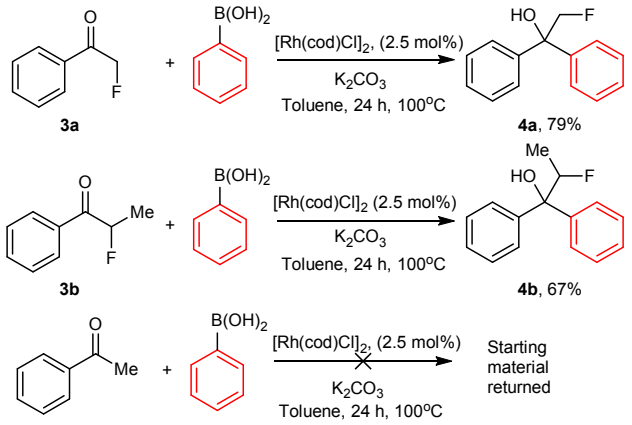
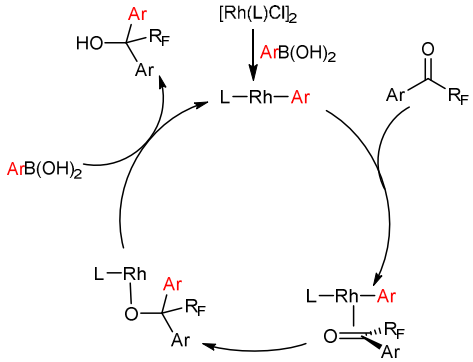


Scheme 3: Rh-catalyzed arylation of monofluorinated ketones



Scheme 4: Likely key steps of reaction mechanism

trifluoromethyl substituent compared to a difluoromethyl group (σ_p (CF_3) = 0.53; σ_p (CF_2H) = 0.35). We therefore postulate that this effect is steric in origin. The size of the CF_2H group is smaller than the CF_3 group, which may lead in the CF_2H case to more facile complexation of the ketone to Rh and enhanced insertion of the Rh-aryl species into the C=O bond (Scheme 4).[15d] Further support for this hypothesis is provided by comparison of entries A-D which suggest that the reactivity difference between a CF_2H- and a CF_3-ketone is exacerbated by increasing the steric demand of the aryl substituent on the ketone(compare thiophenyl (entry B, 57:43) to 2-MeC_6H_4 (entry D,75:25)). Comparison of a difluoromethyl ketone to a monofluoromethyl ketone (entry G) demonstrates significantly higher reactivity in the difluoromethyl case, suggesting that increased electronic activation by CF_2H (σ_p (CF_2H) = 0.35; σ_p (CFH_2) = 0.10) is now outweighing any steric effects. Finally, comparision of the reactivity of a difluoromethyl ketone to an aldehyde (entry H) shows the aldehyde to be significantly more reactive.

In summary, we have developed the Rh-catalyzed arylation of fluorinated ketones with boronic acids, which provides an efficient and mild route to fluorinated alcohols. Interestingly, we have shown that difluoromethyl ketones are more reactive than their trifluoromethyl ketone counterparts, an effect we believe to be steric in origin. Future work will concentrate on the development of an enantioselective variant of this reaction,[16] as well as the further use of difluoromethyl ketones as under-studied building blocks for the synthesis of useful fluorinated molecules.

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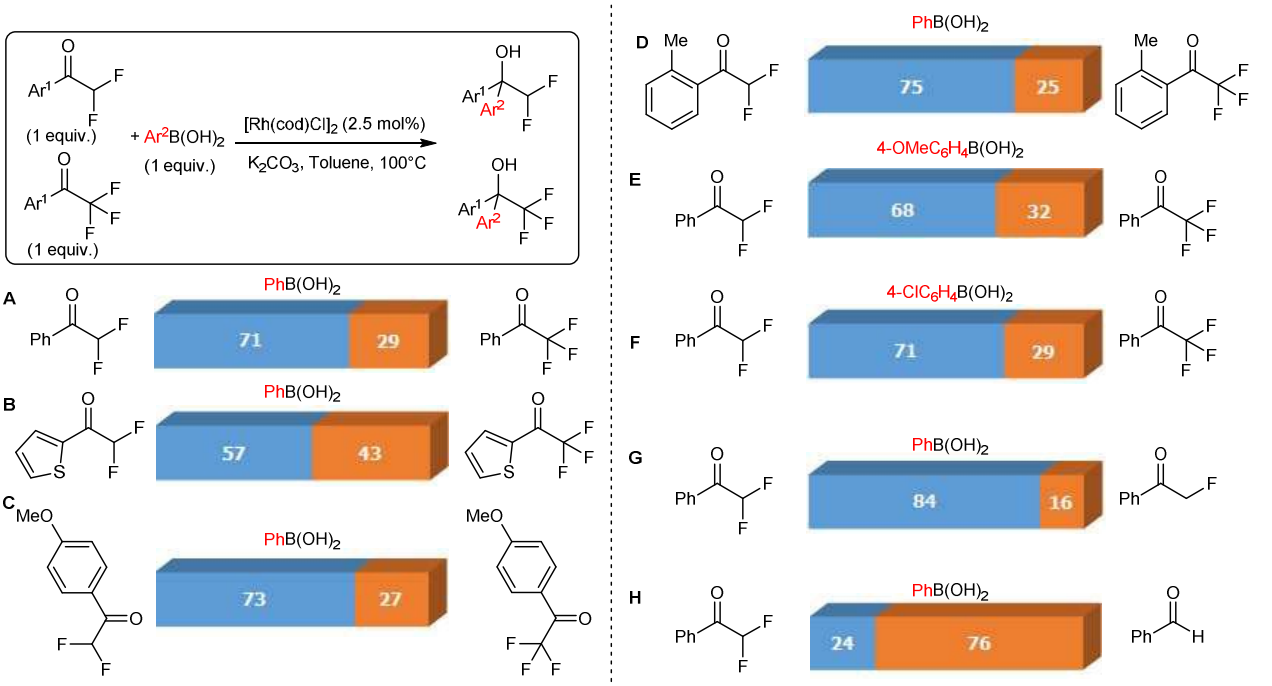

Scheme 5: Competition Experiments. [a] Ratios measured by ^{19}F NMR integration (Reactions G/H measured by ^{1}H NMR integration)

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16. Preliminary work on the development of an enantioselective variant of this reaction has given low enantioselectivities. See supporting information.

