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Rhodium-catalysed 1,4-addition–halogenation: the crucial role of lithium halide

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ABSTRACT

The rhodium-catalysed 1,4-addition–iodination or 1,4-addition–bromination of dimethylitaconate has been accomplished in high yield using arylzinc reagents and electrophilic halogenating agents. The product distribution is influenced by the presence of specific lithium halide salts.

The development of multistep syntheses involving two or more transformations in a one-pot reaction is of great utility in organic synthesis.[1] Tandem reactions including catalytic processes have emerged as significant methodology for the formation of new chemical bonds in an efficient manner.[2] In recent years, considerable efforts have been made to use conjugate addition as the initial step of tandem processes,[3] and in particular metal-catalysed 1,4-additions have been combined with a range of different transformations including bromination,[4] aldol reactions,[5] cyclopropanation,[6] cyclisation reactions[7] and enantioselective protonations.[8] Within this context, the α-halogenation of carbonyl compounds represents an area of great interest in organic chemistry.[9] Interestingly, an increasing number of isolated natural products contain halogen atoms in their composition.[10] In recent years, enantioselective halogenation processes have emerged as viable routes to useful building blocks.[11] In medicinal chemistry, the incorporation of halogens (particularly fluorine) can lead to beneficial properties.[12] A number of electrophilic N–F fluorinating agents have been developed to facilitate the synthesis of complex fluorine-containing molecules.[13]

On the basis of reported studies describing a rhodium-catalysed carbometallation–protonation of 1,1′-alkenes,[8] the development of a new protocol for incorporating fluorine was proposed. The tandem approach shown in Figure 1 depicts the quenching of an oxa-π-allylrhodium intermediate with an electrophilic fluorinating agent to install an aryl group and fluorine atom sequentially across an activated alkene. At the outset of the project, it was decided to examine a range of organometallics that could be utilised in the selective fluorination of 1,1′-alkenes triggered by rhodium-catalysed 1,4-addition.[14] We attempted the addition of both organoboron and organosilicon reagents to dimethylitaconate **1** with *N*-fluorobenzenesulfonimide (NFSI) present at the time of addition or introduced afterwards in a separate step.

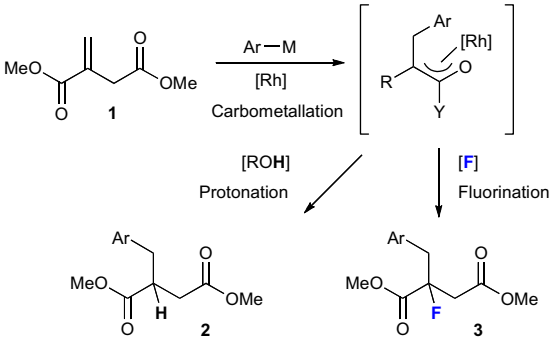

Figure 1. A strategy for the incorporation of fluorine using rhodium-catalysed 1,4-addition of organometallics.

Despite considerable efforts, this approach did not yield the desired product (a wide range of solvents, temperatures, rhodium complexes, other electrophilic fluorinating agents such as Selectfluor® and other important reaction parameters were investigated). In the majority of cases, we observed complex reaction mixtures with only the 1,4-addition–protonation product **2** being isolated cleanly (from trace amounts to modest yields depending on exact conditions). It appeared that the electrophilic fluorinating agents were not effective in this challenging transformation. This could be attributed to a number of possible factors including a slow rate of transmetallation in the absence of water; a slow rate of fluorination (compared to transmetallation or protonation) on what would be a hindered oxa-π-allylrhodium intermediate; deleterious side-reactions of the electrophilic fluorinating agents (preferential reactions with other nucleophilic species in the reaction mixture) and an accelerated catalyst decomposition pathway promoted by the electrophilic fluorinating agent.

It is useful to note that water is not required for catalyst turnover when arylzinc reagents are employed in rhodium-catalysed 1,4-addition reactions.[15] In a recent study, we noted that in the addition of phenylzinc chloride to dimethylitaconate **1**, the

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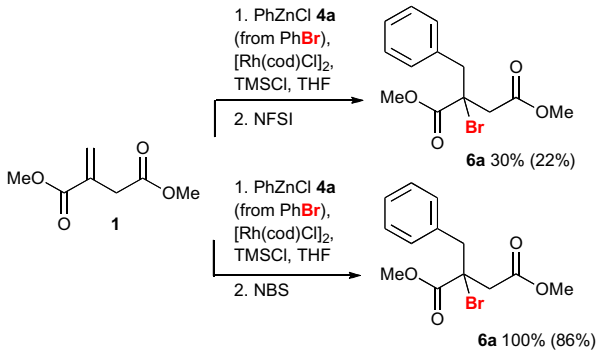
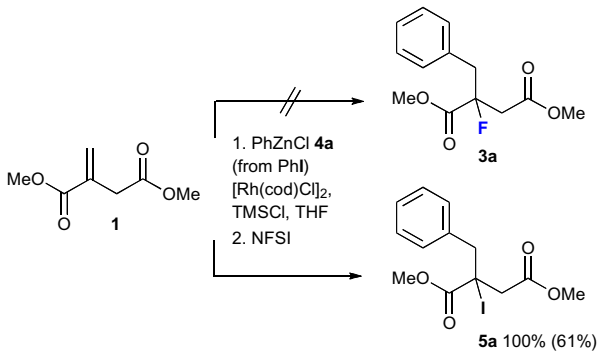
intermediate silylketene acetal could be trapped and observed by NMR.[16] Following this protocol, the addition of phenylzinc chloride to dimethylitaconate followed by treatment with NFSI (after 2 h) furnished a single new product (100% conversion, 61% isolated yield) that was fully characterised as the 1,4-addition–iodination product rather than the desired 1,4-addition–fluorination product (Scheme 1). This result was intriguing, and we sought an explanation for the generation and activation of an iodine source.

The mechanism by which NFSI (and other electrophilic fluorine sources) transfers fluorine is not fully understood. Both single electron transfer (SET) pathways and direct attack of the nucleophile at fluorine (S_N2) have been postulated.[13] It has been established that reagents such as Selectfluor®, NFSI or *N*-fluoropyridinium salts possess good oxidative properties and can be used to activate other halogen sources.[17] An elegant study on the specific reactivity of NFSI towards a wide range of nucleophiles by Crugeiras and coworkers has demonstrated that this molecule has two different electrophilic sites.[18] Oxygen and nitrogen nucleophiles react at the sulfonyl group, whereas halide ions attack the fluorine atom of NFSI. This reactivity pattern can be rationalised in terms of Pearson's principle of hard and soft acids and bases.[19] This observation is significant as the arylzinc reagents used in our study are prepared from the corresponding aryl halides by lithium–halogen exchange (followed by treatment with zinc(II) chloride) resulting in an excess of lithium halide being present in the reaction mixture. A mechanism consistent with the generation of a reactive electrophilic iodine source (when the phenylzinc reagent is prepared from iodobenzene) by attack of iodide ion at the fluorine site of *N*-fluorobenzenesulfonimide is shown in Scheme 2.[20] Interestingly, the NFSI could be replaced by iodine or *N*-iodosuccinimide to obtain the same product but with lower isolated yields alongside some 1,4-addition–protonation product.

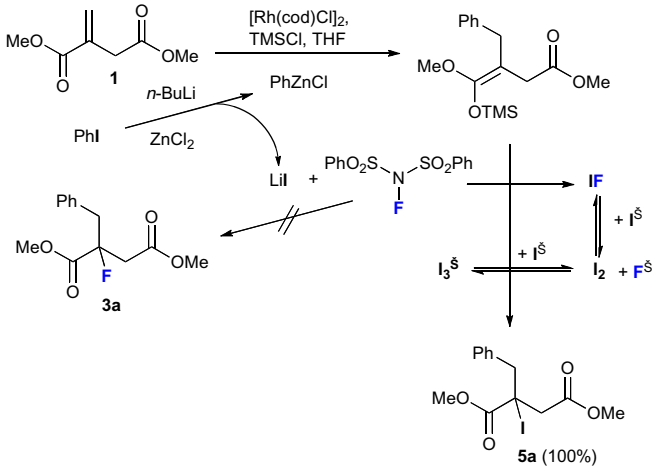
When the phenylzinc reagent was prepared from bromobenzene, the reaction afforded a mixture of products with NFSI: 1,4-addition–protonation (**2** 50%), 1,4-addition–bromination (**6a** 30%) and 1,4-addition–fluorination (**3a** 20%). This suggests that the reaction of bromide at the fluorine site of *N*-fluorobenzenesulfonimide is slower than iodide allowing the oxa-π-allylrhodium intermediate (or enolate) to react with *N*-fluorobenzenesulfonimide. Given the relative ratio of products in the two reactions, it was clear that the order of reactivity of the different electrophilic halogen sources present in the reaction mixture was [I] > [Br] > [F].



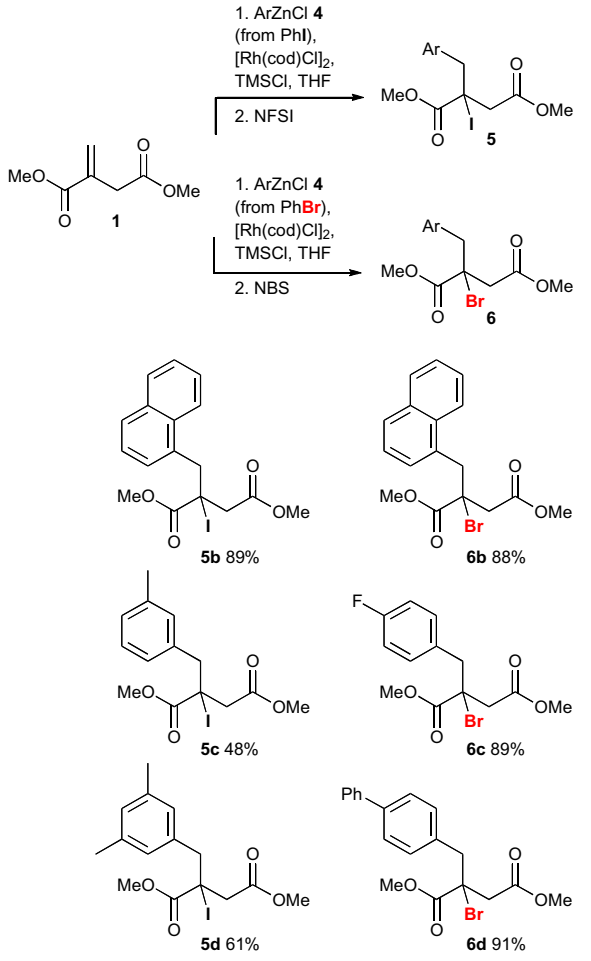
Scheme 3. Rhodium-catalysed 1,4-addition–bromination.



Scheme 1. Rhodium-catalysed 1,4-addition–iodination with NFSI.



Scheme 2. A plausible mechanism for rhodium-catalysed 1,4-addition–iodination with NFSI.



Scheme 4. Examples of rhodium-catalysed 1,4-addition–halogenation.

An efficient catalytic 1,4-addition–bromination process could be realised by switching from NFSI to *N*-bromosuccinimide (NBS) as shown in Scheme 3. The 1,4-addition–bromination product **6a** was isolated as the sole product of the reaction (100% conversion, 86% isolated yield). Persistent attempts to achieve an efficient catalytic 1,4-addition–fluorination process using arylzinc reagents were not successful. A number of alternative strategies to prepare 'halide-free' organometallic donors were attempted (including directed metallation and catalytic carbometallation) without success. Low yields and mixtures of products thwarted the introduction of fluorine in this manner.

Having established distinct conditions for an efficient catalytic 1,4-addition–iodination or 1,4-addition–bromination process, a selection of arylzinc reagents (derived from the corresponding aryl iodide or aryl bromide) was demonstrated to be effective (Scheme 4). In each case, the reactions proceeded to 100% conversion to furnish a single product as judged by NMR analysis of the crude material. The lower isolated yields of **5c** and **5d** result from elimination processes during purification.

In conclusion, the product distribution in the addition of an arylzinc derivative and halogen atom across an activated alkene using rhodium catalysis is dictated by the presence of specific lithium halide salts and an electrophilic halogen source. We have established suitable conditions for the selective 1,4-addition–iodination or 1,4-addition–bromination of dimethylitaconate in high yield. Interestingly, it was possible to use this process to ascertain if a commercial solution of arylzinc reagent had been prepared from the aryl iodide or bromide from the product(s) of the reaction with dimethylitaconate and NFSI.

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Supplementary data

Experimental procedures and compound characterisation data are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.08.047.

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