The doping effect of fluorinated aromatic hydrocarbon solvents on the performance of common olefin metathesis catalysts: application in the preparation of biologically active compounds†

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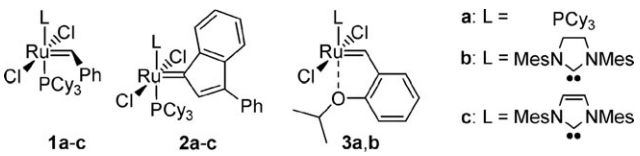
Aromatic fluorinated hydrocarbons, used as solvents for olefin metathesis reactions, catalysed by standard commercially available Ru precatalysts, allow substantially higher yields to be obtained, especially of challenging substrates, including natural and biologically active compounds.

Recent decades have seen burgeoning interest in olefin metathesis, as witnessed by the rapidly growing number of elegant applications.[1] Using this tool, chemists can now efficiently synthesize an impressive range of molecules that only a decade ago required significantly longer and more tedious routes. The development of efficient and selective catalysts **1–3** is the key to the widespread application of olefin metathesis in organic synthesis.[1]



In more advanced applications of olefin metathesis, especially in the total synthesis of natural and biologically active compounds, commercially available Ru catalysts **1–3** do not always lead to satisfactory conversions.[2] To solve this limitation, a lot of research effort has been directed to designing improved catalysts that might allow for better results in "difficult" cases.[3] A recently published total synthesis of largazole, a natural product exhibiting broad anti-cancer activity, represents a convincing example, where improved catalysts were used to counteract the low potency of commercially available initiators for this substrate.[4] Another limitation of commercially available initiators applied to total synthesis is that relatively high loadings of catalysts (up to 25–40 mol%) are often required, resulting in the sub-optimal use of this powerful methodology.[2,5] Nowadays, it is desirable to use expensive and potentially toxic heavy metal-based catalysts more efficiently in order to reduce the costs of industrial processes and fulfil the recent guidelines of green chemistry.[5]

Besides the evolutionary improvement of catalyst structures,[3] research aimed at finding *new* reaction conditions that allow more optimal use of standard commercially available catalysts can be considered as a complementary approach.[6] During a recent profiling study of a set of commercially available Ru catalysts, we noted that the rate of olefin metathesis of some simple dienes was significantly enhanced when fluorinated aromatic hydrocarbons (FAH), such as perfluorotoluene and perfluorobenzene, were used as reaction media.[7] Fluorine-containing aromatic hydrocarbons $PhCF_3$ and C_6F_6 have been used previously as solvents in some metathesis reactions,[8] but no enhancements in metathesis rate were reported in these cases.[9]

Therefore, in the current study, we decided to explore the applicability and the generality of this unexpected activating effect in the metathesis of selected "challenging" olefins, including natural-like substrates. To gain an insight into this new activating effect, a set of comparative metathesis experiments catalysed by commercially available Ru initiators was attempted in "classical" metathesis solvents (toluene and 1,2-dichloroethane) and in FAH under otherwise *identical* conditions (catalyst loading, time, concentration and temperature).‡

The formation of tetrasubstituted double bonds typically requires high catalyst loadings, and even then doesn't lead to quantitative yields.[10] It is believed that di(methylallyl)malonate (**s1**) is a very challenging model substrate for Ru catalysts, giving **1b** and **3b** in only 17 and 6% yield, respectively (5 mol%, CH_2Cl_2, 30 °C, 96 h).[10a] Catalyst **1c**, applied at a higher temperature, was reported to give only 47% of the product (5 mol%, toluene, 80 °C, 24 h; GC yield).[10b] Therefore, we selected this reaction as the first trial in our study. As a result, we found that the observed activating effect was of a quite general nature, as all the catalysts tested lead to higher yields in FAH compared to "classical" conditions (Scheme 1). The activity increase was quite substantial, as in the most pronounced case of **3b**, it was possible to increase the reaction yield 18-fold, simply by changing the solvent from 1,2-dichloroethane to perfluorotoluene. Encouraged by these results, we attempted to test FAH in the metathesis of selected natural or biologically active substrates (Scheme 2). Diene **s2**, a derivative of (−)-isopulegol, a monoterpenic alcohol that is widely employed in the flavour and perfume industry,[11] was chosen as a representative challenging substrate. The ring-closing metathesis (RCM) of **s2**, where a tetrasubstituted double bond is formed, lead to incomplete conversion in 1,2-dichloroethane, while the

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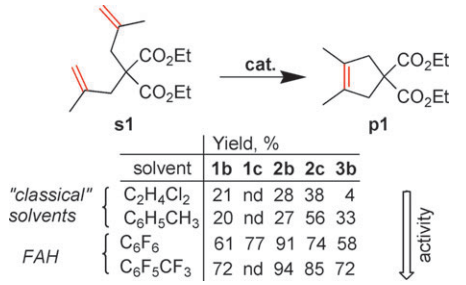
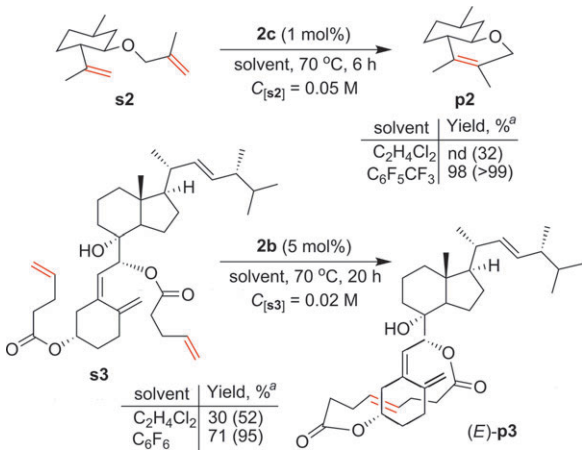
† Electronic supplementary information (ESI) available: Experimental procedures for the preparation of the starting materials, RCM and CM in FAH, and the characterisation of the products. See DOI: 10.1039/b816567j



Scheme 1 Model RCM reaction. Conditions: 2 mol% of catalyst, $C_{[s1]}$ = 0.02 M, 70 °C, 3 h; nd = not determined. Yields calculated by GC.

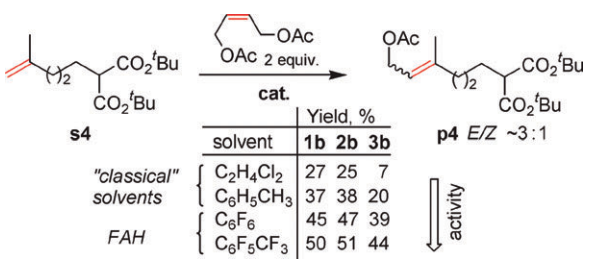


Scheme 2 RCM of (−)-isopulegol (**s2**) and Vitamin D_2 (**s3**) derivatives. [a] Isolated yields after column chromatography. Conversions calculated by ^{1}H NMR are in parentheses; nd = not determined.

use of perfluorotoluene provided quantitative conversion under otherwise identical conditions (loading, temperature, time).

Pentaene **s3**, derived from 7,8-dihydroxy-7,8-dihydrovitamin D_2,[12a] was tested by us previously and considered to be rather problematic under "classical" conditions.[12b] Therefore, we were pleased to find that in the case of this polyfunctional substrate, the use of FAH also lead to much improved results (Scheme 2).

Next, we tested cross-metathesis (CM), the second most popular variant of olefin metathesis.[13] To estimate the potential of our newly developed conditions, we focused only on the most demanding cases, such as the CM of substituted or electron deficient alkenes.[13] The results presented in Scheme 3 show that in 1,2-dichloroethane, the commercially available Ru catalysts were not potent in CM between geminally disubstituted[14] **s4** and (*Z*)-1,4-diacetoxy-2-butene. In 1,2-dichloroethane, the highest yield (27%) was obtained



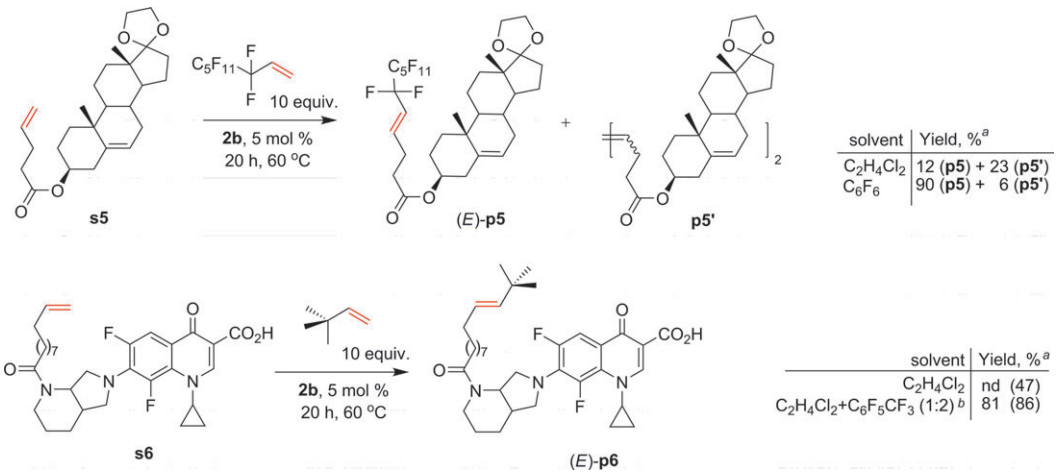
Scheme 3 Model CM reaction. Conditions: $C_{[s4]}$ = 0.02 M, 5 mol% of catalyst, 70 °C, 3 h. Yields calculated by GC.

with **1b**. Importantly, applying perfluorotoluene as the solvent allowed an increase in yield to 50%. Again, the activating effect of the FAHs was observed for all the catalysts tested.

CM reactions have gained increased importance in the synthesis of natural and biologically active products in recent years.[13] Therefore, the CM reactions of two advanced substrates (Scheme 4) were selected to reveal the potential utility of FAH solvents in target-oriented synthesis.

The functionalisation of steroid cores by olefin CM has become an important tool in the pharmaceutical industry. Recently, we reported the synthesis of new 17β-hydroxysteroid dehydrogenase type 1 inhibitors—drug candidates in estradiol-dependent diseases such as breast cancer or endometriosis—*via* the CM of allylestrone with various acrylic acid derivatives.[15] Kotora *et al.* have published a study on the perfluoroalkylation of some steroid derivatives through CM reactions with (perfluoroalkyl)propenes.[16a] We decided to test the potential of FAHs in similar reactions, because fluorine-containing compounds are popular targets in the pharmaceutical industry.[16b] The CM of functionalised alkenes and fluorinated olefins has previously been studied by Blechert *et al.*[8a] When (perfluorobutyl)ethylene was used as both the CM partner and solvent, it was found that α,α,α-trifluorotoluene could be used as an additive to overcome the insolubility of the Ru catalysts in the reaction medium.[8a] However, no enhancement in the metathesis rate of **3b** was reported in connection with use of this co-solvent. To look more closely at this phenomenon, we executed a CM reaction between 3β-pent-4-enoyloxy-17,17-ethylenedioxy-5-androstene (**s5**)[17] and (perfluorohexyl)ethylene in two solvents, 1,2-dichloroethane and perfluorobenzene, under otherwise identical conditions (Scheme 4). Importantly, it was found that in the latter medium, CM proceeded in a much more productive and selective fashion, while in the "classical" solvent, the reaction suffered from low conversion and selectivity, with the unwanted homo-cross metathesis product, **p5′**, being formed in large quantities (Scheme 4). Finally, to determine the scope of the enabling effect of FAHs with respect to structural variations in substrates, we tested the CM reaction of acid **s6**, a distant relative of the fluoroquinolone antibacterial agent moxifloxacin,[18] with 3,3-dimethyl-1-butene (Scheme 4). Modification at the terminal vinyl positions, leading to the corresponding *tert*-butyl-substituted alkenes, can be problematic in some cases.[19] Therefore, we were pleased to find that our new conditions allowed a much higher yield to be obtained in this case.

In accordance with assumptions made by the groups of Fürstner,[10b] Ledoux,[20] Blechert[9c] and Collins,[9d] we think that the formation of π–π complexes between *N*-mesityl groups of the NHC ligand that is present in second generation Ru catalysts and the FAH solvent molecules plays a role in the observed catalyst activity enhancement. Although the exact nature of the observed effect is not yet clear,[21] we foresee its practical importance as a method for the *in situ* activation of commercial metathesis catalysts.§ We expect that this technique will find applications in the synthesis of advanced natural and biologically active compounds, where any increase in yield is of high importance, especially when the metathesis step is applied at a late stage of a total synthesis. Detailed studies on



Scheme 4 The CM of substrates **s5** and **s6**. [a] Isolated yields after column chromatography; conversions calculated by ^{1}H NMR are shown in parentheses. [b] 1,2-Dichloroethane was used as a co-solvent to increase the solubility of **s6** in the reaction medium; nd = not determined.

the nature and scope of the activating effect of FAHs are ongoing in our laboratory, and will be published in due course.

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Notes and references

‡ Solvents used in comparative experiments were distilled from CaH_2 and stored under argon. A representative procedure for the the CM reaction of **s5**: To a solution of **s5** (132.7 mg, 0.32 mmol) and (perfluorohexyl)ethylene (1.1 g, 3.2 mmol) in deoxygenated anhydrous hexafluorobenzene (6.5 ml) was added **2b** as a solid (0.016 mmol, 5 mol%). The resulting mixture was stirred under argon at 60 °C for 20 h. The solvent was removed under reduced pressure.§ The crude product was purified by flash chromatography, yielding product **p5** as a colourless solid (210.6 mg, 0.287 mmol).

§ It should be noted that the expensive fluorinated solvents can be fully recovered by distillation after reactions and reused.

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