

The Doping Effect of Fluorinated Aromatic Solvents on the Rate of Ruthenium-Catalysed Olefin Metathesis

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Dedicated to Professor Christian Bruneau on the occasion of his 60th birthday

Abstract: A study concerning the effect of using a fluorinated aromatic solvent as the medium for olefin metathesis reactions catalysed by ruthenium complexes bearing N-heterocyclic carbene ligands is presented. The use of fluorinated aromatic hydrocarbons (FAH) as solvents for olefin metathesis reactions catalysed by standard commercially available ruthenium pre-catalysts allows substantially higher yields of the desired products to be obtained, especially in the case of demanding

polyfunctional molecules, including natural and biologically active compounds. Interactions between the FAH and the second-generation ruthenium catalysts, which apparently improve the efficiency of the olefin metathesis transformation, have been studied by

Keywords: doping effects • fluorinated aromatic hydrocarbons • metathesis • N-heterocyclic carbenes • ruthenium

X-ray structure analysis and computations, as well as by carrying out a number of metathesis experiments. The optimisation of reaction conditions by using an FAH can be regarded as a complementary approach for the design of new improved ruthenium catalysts. Fluorinated aromatic solvents are an attractive alternative medium for promoting challenging olefin metathesis reactions.

Introduction

Olefin metathesis has emerged as a versatile and powerful tool for target-oriented organic synthesis as well as material

science.^[1] Ruthenium-based pre-catalysts **Gru**, **Ind**, and **Hov** (Figure 1)^[2] display a high functional group tolerance and satisfactory to excellent air and thermodynamic stabilities. Unfortunately, relatively high loadings of these ruthenium pre-catalysts are often required, sometimes leading to sub-optimal use of this powerful methodology.^[3,4] In the context of greener chemistry, it is desirable to use these costly and potentially toxic complexes more efficiently in order to pro-

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Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/chem.201100160>.

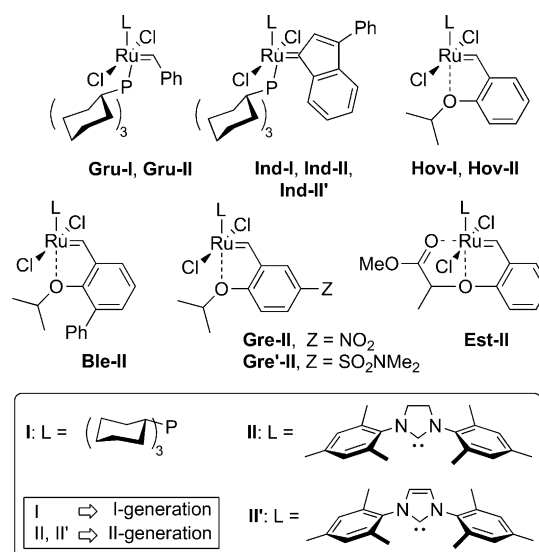


Figure 1. Selected ruthenium-based pre-catalysts for olefin metathesis.

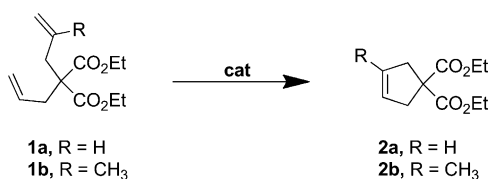
tect the environment and to reduce the costs of industrial processes.^[4] Therefore, further research aimed at the development of new catalysts of improved stability and/or activity is of a vital importance.^[4,5] Alongside evolutionary improvement of the catalyst structure,^[1,5] research aimed at finding new reaction conditions that allow more efficient use of known catalysts can be considered as a complementary approach.^[6]

In particular, we are interested in learning to what extent the solvent used for a metathesis reaction can affect the turnover number (TON) of a given catalyst.^[7] Recently, we reported an unexpectedly strong effect of fluorinated aromatic solvents on olefin metathesis reactions promoted by typical ruthenium catalysts bearing N-heterocyclic carbene (NHC) ligands.^[8] Our initial observation^[9] was also confirmed by Blechert et al.,^[10a] Collins et al.,^[10b] Nolan et al.,^[10c] and Dorta et al.^[10d] These authors reported that the fluorinated aromatic hydrocarbon (FAH) effect is of quite general nature for second-generation ruthenium catalysts, both Grubbs and Hoveyda type complexes, bearing NHCs with mesityl, tolyl, naphthyl and other aromatic substituents. In this article, we assess the practical benefits of using FAHs for challenging olefin metathesis reactions. To provide more data on this interesting effect, X-ray, analytical, synthetic, ³¹P NMR and computational studies have been performed.

Results and Discussion

During our recent studies on the comparative screening of various second-generation ruthenium-based pre-catalysts at low loadings (Figure 1), a strong temperature effect was noted in all of the tested reactions.^[7] In the next step, we attempted to study the effect of different solvents on the rate of olefin metathesis reactions at the same temperature.

For instance, in the case of the ring-closing metathesis (RCM) reactions shown in Scheme 1, the replacement of an aliphatic chlorinated solvent by toluene has a strong effect on catalyst activity, allowing, in the best case, a doubling of yield without increasing the catalyst loading or extending the duration of the reaction (Figures 2 and 3).^[7] The formation of tetrasubstituted double bonds is one of the most challenging transformations for Ru-based olefin metathesis catalysts.^[1,10] This reaction typically requires application of catalysts at high loadings and even then does not lead to quantitative yields.^[11] Therefore, as the first model reaction in the present study, we examined the RCM of diene **1c** (Scheme 2) promoted by a representative set of catalysts.^[11] The reactions were conducted in 1,2-dichloroethane and tol-



Scheme 1. Model RCM reactions.

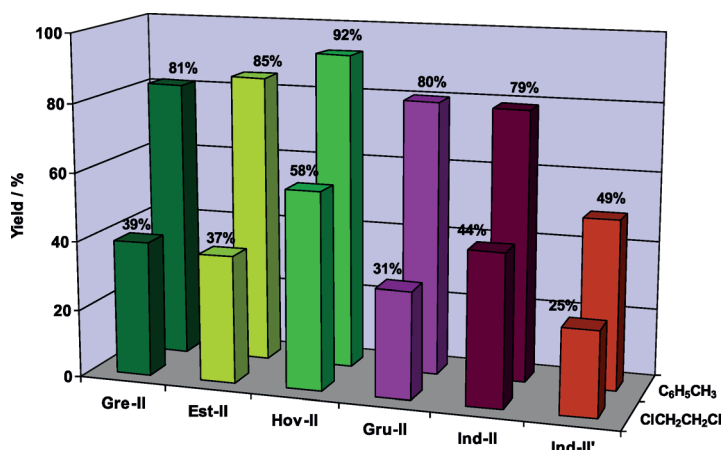


Figure 2. Solvent effect on RCM of **1a**. Conditions: 0.02 mol % of catalyst, $c_{1a}=0.02$ M, 70 °C, 1 h.

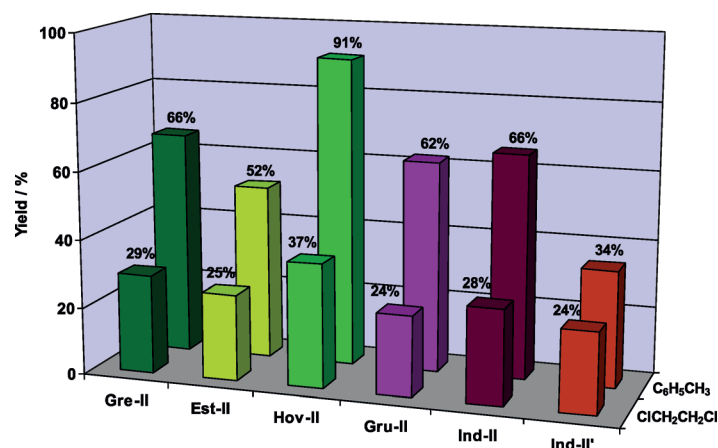
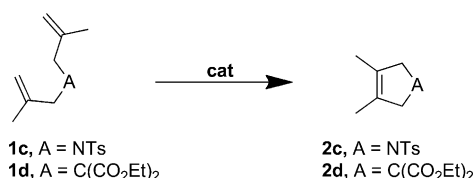


Figure 3. Solvent effect on RCM of **1b**. Conditions: 0.02 mol % of catalyst, $c_{1b}=0.02$ M, 70 °C, 1 h.



Scheme 2. Two models representing challenging RCM reactions.

uene under otherwise identical conditions (catalyst loading, time and temperature).

It is clear from the obtained results that replacing 1,2-dichloroethane by toluene has a strong effect on the turnover numbers, leading to a tenfold increase in yield in the best case (**Hov-II**, Figure 4) at the same temperature. We have become interested in finding an explanation for such a pronounced improvement of activity. It was reported by Fürstner and Nolan that some RCM reactions promoted by the second-generation catalyst [PCy₃(IMes)Cl₂Ru=CHPh] (IMes = 1,3-bis(2,4,6-trimethylphenyl)-2-imidazolylidene) in toluene at 80 °C were not only faster than those in dichloro-

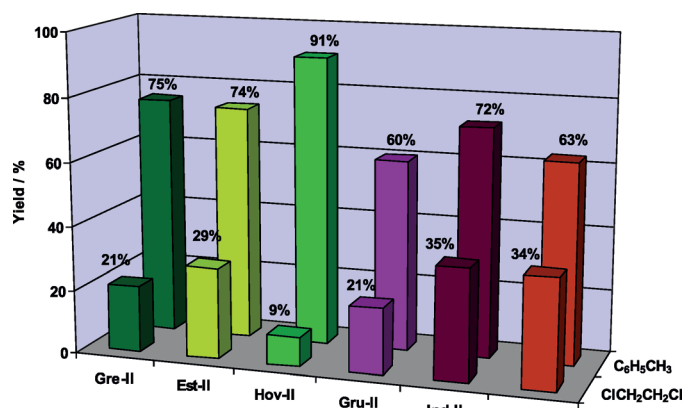


Figure 4. Solvent effects in RCM of **1c**. Conditions: 0.5 mol % of catalyst, $c_{1c}=0.02$ M, 70 °C, 3 h.

methane at 40 °C, but also faster than the reactions conducted in 1,2-dichloroethane at 80 °C.^[12a] Recently, Ledoux et al. noted that in ring-opening metathesis polymerization (ROMP) of cyclooctadiene, the Grubbs pre-catalyst **Gru-II** was unambiguously more active in C₆D₆ than in CDCl₃ at the same temperature.^[12b] A plausible explanation for this effect, based on π - π interactions of the *N*-mesityl group with the aromatic solvent molecules,^[12b] has been proposed.

Encouraged by these reports, we decided to test fluorinated aromatic hydrocarbons as solvents, since these are known to form strong face-to-face π - π complexes with phenyl rings.^[12,13] We set out to focus only on challenging olefin metathesis reactions, specifically RCM and enyne reactions in which a tetrasubstituted C=C double bond is formed. The formation of tetrasubstituted C=C double bonds typically requires high catalyst loadings and even then does not lead to quantitative yields.^[11] Dimethylallyl malonate (**1d**) can be considered as a very challenging substrate for ruthenium catalysts, with **Gru-II** and **Hov-II** giving product yields of only 17 and 6%, respectively (CH₂Cl₂, 30 °C, 96 h).^[11,12a] Therefore, this transformation seemed to be the best model to test the extended palette of aromatic solvents, including toluene, trifluoromethylbenzene, perfluorobenzene, and perfluorotoluene. We decided to perform a comparative study at 70 °C, which was found to be optimal during our previous investigation.^[7] The obtained results (Figure 5) were quite striking. First, we noted that the fluorinated aromatic solvents led in general to much higher TONs as compared to chlorinated aliphatic solvents and toluene. Indeed, the ring closure of **1d** was accomplished in 94% yield within 3 h using only 2 mol % of catalyst **Ind-II** in perfluorotoluene at 70 °C. Under the same conditions but using toluene as the solvent, only 27% of tetrasubstituted product **2d** was furnished.

For some phosphine-containing Ru catalysts (**Gru-II**, **Ind-II**, and **Ind-II'**), we observed that TON increases directly with the number of fluorine atoms in the solvent molecule, reaching the maximum in the case of perfluorotoluene. However, the results obtained with Hoveyda type catalysts

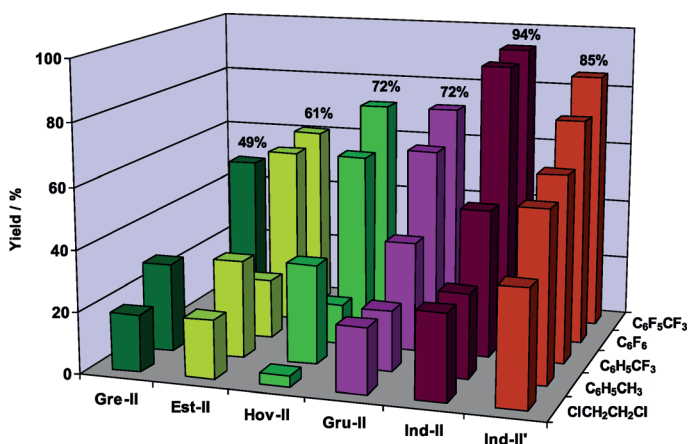
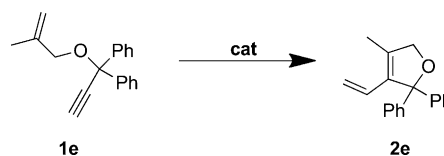


Figure 5. Observed solvent influence on RCM of **1d**. Conditions: 2 mol % of catalyst, $c_{1d}=0.02$ M, 70 °C, 3 h.

(**Est-II**, **Hov-II**) show that this picture is more complicated (Figure 5). Even if not yet fully explained, this observation is very important from a practical point of view because in the most pronounced case of **Hov-II** it was possible to increase the reaction yield 18-fold merely by changing the solvent from 1,2-dichloroethane to perfluorotoluene (Figure 5).

The challenging enyne **1e** was chosen as another excellent forum for evaluation of the scale of this intriguing solvent effect (Scheme 3).^[10,12] Again, the reactions conducted in



Scheme 3. Model enyne reaction.

fluorinated aromatic solvents led to much higher TONs as compared to those conducted in 1,2-dichloroethane and toluene (for example, a sixfold increase in yield in the case of **Gru-II**, or even a 13-fold increase in the case of **Ind-II**) under otherwise identical conditions (catalyst loading, time, and temperature; see Figure 6).

Being aware of the increasing importance of cross-metathesis (CM) in the synthesis of natural and biologically active products, we included this transformation in our study.^[14] To estimate the potential of our newly developed conditions, we focused only on the most demanding cases, such as the CM of geminally disubstituted or electron-deficient alkenes (Scheme 4).^[14,15] The results presented in Table 1 show that in 1,2-dichloroethane none of the second-generation catalysts was sufficiently potent to induce high TONs in the CM between **1f** and (*Z*)-1,4-diacetoxy-2-butene (Scheme 4a). In 1,2-dichloroethane, the highest yield (27%) was obtained with **Gru-II**. Importantly, applying perfluorotoluene as the solvent led to an increased yield of 50%.

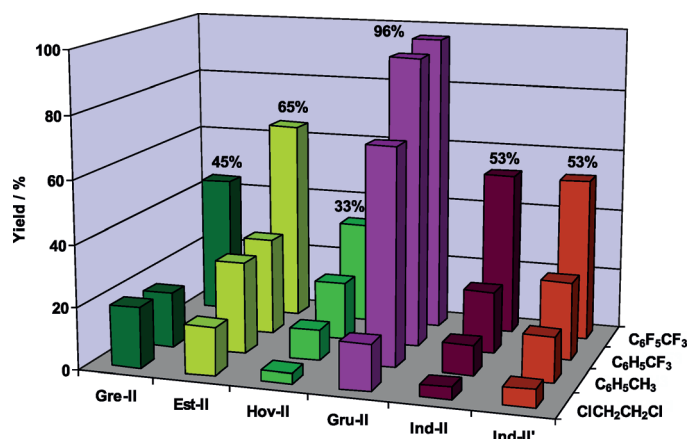
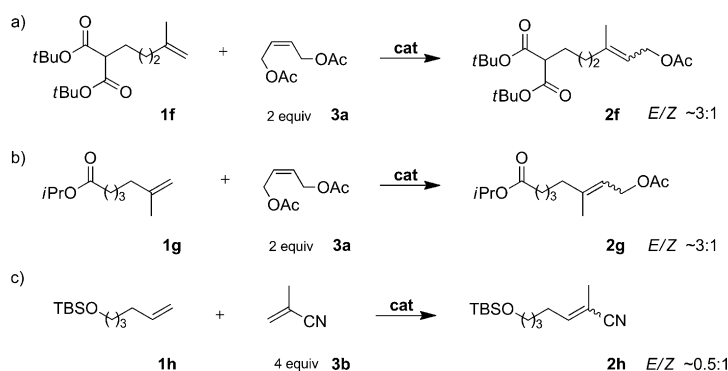


Figure 6. Observed solvent influence on the cycloisomerisation of **1e**. Conditions: 5 mol % of catalyst, $c_{1e} = 0.02$ M, 70 °C, 5 h.



Scheme 4. Models representing challenging CM reactions.

Table 1. Yields [%] observed in the CM of **1f** with **3a**.^[a]

solvent	Est-II	Hov-II	Gru-II	Ind-II	Ind-II'
ClCH ₂ CH ₂ Cl	13	7	27	25	24
toluene	42	20	37	38	39
perfluorobenzene	47	39	45	47	32
perfluorotoluene	50	44	50	51	13

[a] $c_{1f} = 0.02$ M, 5 mol % of catalyst, 70 °C, 3 h.

Table 2. Yields [%] observed in the CM of **1g** with **3a**.^[a]

solvent	Est-II	Hov-II	Gru-II	Ind-II	Ind-II'
ClCH ₂ CH ₂ Cl	24	12	31	27	29
toluene	46	29	40	40	40
perfluorobenzene	52	42	50	n.d.	40

[a] $c_{1g} = 0.02$ M, 5 mol % of catalyst, 70 °C, 3 h; n.d. = not determined.

A similar trend (Table 2) was observed for another challenging geminally disubstituted olefin, **1g** (Scheme 4b).^[5c] It is known that while the Grubbs catalyst (**Gru-II**) is not very efficient in CM reactions of some electron-deficient alkenes, the Hoveyda type catalysts perform particularly well in such cases.^[14b,15b] Therefore, we became interested in ascertaining whether fluorinated aromatic solvents could aid demanding

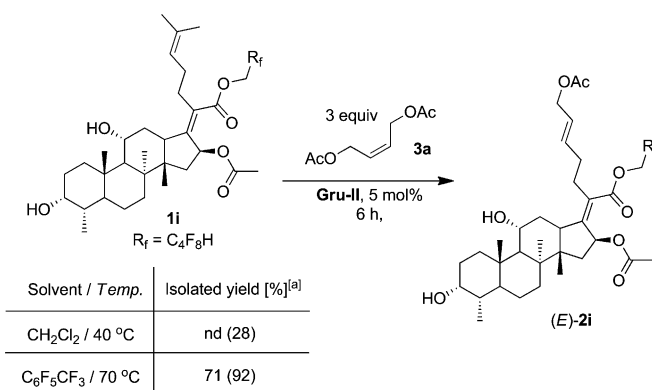
CM reactions by promoting the reactivity of trisubstituted electron-poor substrates (Scheme 4c).^[14] It has been reported that such an effect can be achieved through capturing phosphine from the Grubbs type complexes.^[6b] Methacrylonitrile (**3b**) is one of the most reluctant substrates to undergo CM, especially for **Gru-II** type initiators.^[5b,d,15b,c] For example, in the reaction between **1h** and **3b** in toluene (Scheme 4c), we observed that **Gru-II**, **Ind-II**, and **Ind-II'** gave much lower yields (13, 12, and 16 %, respectively) as compared with **Est-II** and **Hov-II** (56 and 58 %, respectively; conditions: 5 mol % of catalyst, 70 °C, 3 h). Importantly, the replacement of toluene with perfluorotoluene led to an up to fourfold increase in yield (in the case of **Ind-II**) (Table 3).^[16] It should be noted that in the case of CM with **3b**, the enhancing effect of the FAHs was only pronounced in the case of phosphine-containing complexes.

Table 3. Yields [%] observed in the CM of **1h** with **3b**.^[a]

solvent	Est-II	Hov-II	Gru-II	Ind-II	Ind-II'
toluene	56	58	13	12	16
trifluoromethylbenzene	41	39	41	40	25
perfluorobenzene	49	51	50	55	39

[a] $c_{1h} = 0.02$ M, 5 mol % of catalyst, 70 °C, 3 h.

In our initial report on the doping effect of FAHs in olefin metathesis, we studied a set of biologically active compounds.^[9a] It was found that many highly polar molecules, such as a derivative of the antibacterial agent moxifloxacin, are insoluble in pure fluorinated aromatic solvents.^[9a] To solve this problem, we used FAH mixed with chlorinated aliphatic or aromatic co-solvents, and still observed substantial improvements in yields.^[9a] In the current study, we decided to try an alternative strategy that allows us to work in pure FAH media. To do so, we used short fluorinated tags (such as octafluorobutane), which can enhance the solubility of polar substrates in neat fluorinated solvents (Scheme 5).^[17a] One such substrate is the antibacterial steroidal compound, fusidic acid. In the CM reaction between an fluorinated tagged fusidic acid derivative (**1i**) and **3a** catalysed

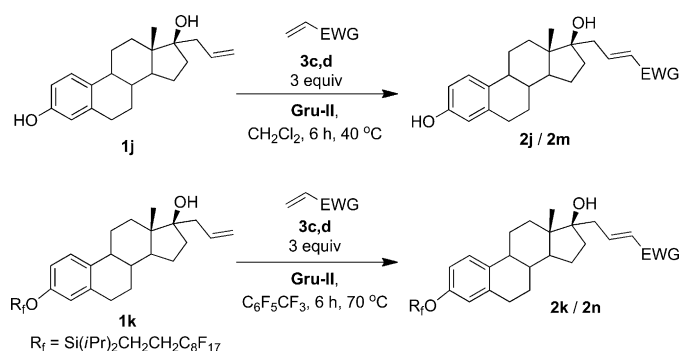


Scheme 5. CM of fusidic acid derivative **1i**. ([a] Isolated yields after column chromatography. Conversions calculated by ¹H NMR are given in parentheses; n.d. = not determined).

by 5 mol % of **Gru-II**, the trisubstituted C–C double bond of **1i** is converted into an allyl acetate fragment (**2i**).^[18] This challenging transformation is significantly improved in octafluorotoluene at 70 °C (reaching 92 % conversion) as compared to “classical” conditions using dichloromethane at 40 °C (only 28 % conversion), under otherwise identical conditions.

For further investigations, we selected an estradiol derivative **1j**, which is insoluble in pure octafluorotoluene, and its analogue **1k**, decorated at the phenol moiety with a fluororous tag, which significantly enhances solubility in FAH solvents (Scheme 6). Comparative CM reactions of **1j** and **1k** with challenging olefin metathesis partners, such as *tert*-butyl acrylate (**3c**) and phenyl vinyl sulfone (**3d**), provided some interesting results (Table 4). The CM reactions of **1j** were performed in a chlorinated aliphatic solvent (CH₂Cl₂ at 40 °C), while the reactions of **1k** were conducted in a fluorinated aromatic solvent (octafluorotoluene at 70 °C). In all cases, we observed improved efficiency for the reactions performed in octafluorotoluene as compared to CH₂Cl₂. CM of *tert*-butyl acrylate with estradiol derivatives **1j** and **1k** catalysed by 1 mol % of **Gru-II** led to products **2j** (in CH₂Cl₂) and **2k** (in octafluorotoluene) in isolated yields of 32 and 93 %, respectively. On the other hand, the same CM partners with phenyl vinyl sulfone and 5 mol % of **Gru-II** gave products **2m** (in CH₂Cl₂) and **2n** (in octafluorotoluene) in isolated yields of 29 and 69 %, respectively.^[19]

The results that we obtained in the above model RCM, enyne and CM experiments showed that fluorinated aromatic solvents can modify the properties of commercially available catalysts in a significant manner, allowing the recovery of much higher yields from difficult metathesis transformations compared to “classical” solvents used in olefin metathesis. To gain further insight into this striking solvent



Scheme 6. CM of estradiol derivatives (**1j** and **1k**).

Table 4. CM of estradiol derivatives with challenging partners.

CM partner	Gru-II [mol %]	Solvent (<i>T</i> [°C])	Product (Yield [%]) ^[a]
1 1j + <i>tert</i> -butyl acrylate (3c)	1	CH ₂ Cl ₂ (40)	2j (32)
2 1k + <i>tert</i> -butyl acrylate (3c)	1	C ₆ F ₅ CF ₃ (70)	2k (93)
3 1j + phenylvinylsulfone (3d)	5	CH ₂ Cl ₂ (40)	2m (29)
4 1k + phenylvinylsulfone (3d)	5	C ₆ F ₅ CF ₃ (70)	2n (69)

[a] Isolated yields after column chromatography.

effect, the experiments described in the following subsections were conducted.

Determination of RCM profiles: Detailed RCM profiles for the cyclisation of **1d** promoted by a representative catalyst (**Ind-II**) were measured in selected solvents (Figure 7). The results revealed that the reaction performed in fluorinated aromatic solvents proceeds with an overall increased rate as compared to RCM carried out in 1,2-dichloroethane and toluene, respectively. Indeed, the rate is enhanced in FAH, as evidenced by results obtained in various solvents after 2 h (RCM of **1d** catalysed by 5 mol % of **Ind-II**): perfluorotoluene (◆) 94 %, 1,3-bis(trifluoromethyl)benzene (○) 88 %, chloropentafluorobenzene (●) 83 %, pentafluorobenzene (□) 68 %, trifluoromethylbenzene (△) 55 %, toluene (■) 33 %, 1,2-dichloroethane (▲) 22 % and nitrobenzene (◇) 4 % (Figure 7).

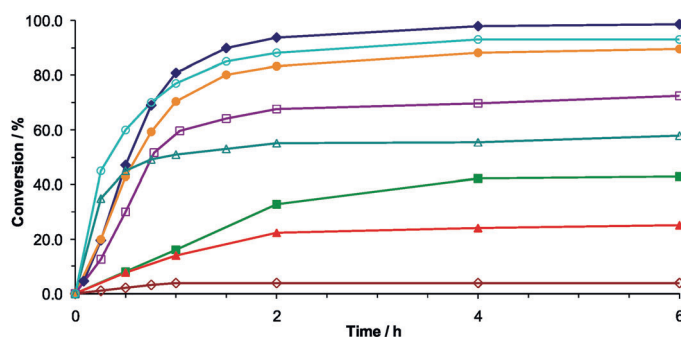


Figure 7. Benchmark RCM activity of **Ind-II** in different solvents (◇ = nitrobenzene, ▲ = 1,2-dichloroethane, ■ = toluene, △ = trifluoromethylbenzene, □ = pentafluorobenzene, ● = chloropentafluorobenzene, ○ = 1,3-bis(trifluoromethyl)benzene, ◆ = octafluorotoluene). Conditions: 5 mol % of catalyst, *c*_{1d} = 0.2 M, 70 °C, 6 h.

In general, a correlation between TONs in RCM of **1d** catalysed by **Ind-II** and the number of fluorine atoms in the solvent molecules was observed. Moreover, solvents such as nitrobenzene, containing strong Lewis base substituents, possibly “arrest” 14-electron Ru active species, leading to low activity.^[20] Interestingly, 1,3,5-tris(trifluoromethyl)benzene was not a suitable solvent for the model RCM reaction, due to insolubility of the ruthenium pre-catalyst (**Ind-II**) in the reaction medium.

Correlation between rate enhancement and volume fraction of FAH:

The overall reaction rate enhancement was correlated with the volume fraction of the fluorinated aromatic solvent present in the reaction medium (Table 5). To do so, the same RCM model reactions of **1d** were independently conducted in toluene and in 1,2-dichloroethane containing variable amounts of perfluorotoluene. It was found that the activating effect is directly linked to the volume fraction of the fluorinated aromatic solvent present in the reaction medium. This challenging transformation was most efficiently conducted in pure perfluorotoluene. These results are in

Table 5. Observed conversions in the RCM of **1d** with **Ind-II** in perfluorotoluene/solvent mixtures of various proportions.^[a]

Fraction of perfluorotoluene (v/v)	0	0.25	0.5	0.75	1
1,2-dichloroethane	28	35	50	75	> 99
toluene	45	65	80	90	> 99

[a] $c_{1d} = 0.2$ M, 5 mol % of catalyst, 70 °C, 6 h.

agreement with those reported by Nolan, who observed only a slight increase of the reaction ratio in model RCM using a mixture of $\text{CH}_2\text{Cl}_2/\text{C}_6\text{F}_6$ (9:1) as compared to the reaction performed in pure CH_2Cl_2 .^[10c]

The effects of different additives in the reaction mixtures:

First, we used 25 mol % of hexachlorobenzene (m.p. 228 °C) dissolved in 1,2-dichloroethane, which did not increase the reaction rate of RCM of **1d** catalysed by 5 mol % of **Ind-II**. We also used CuCl, which is known to be an effective phosphine scavenger,^[6b] but no improvements in the reaction rate were observed compared to the same reaction performed in the presence of CuCl in pure 1,2-dichloroethane. Finally, when 25 mol % of trinitrobenzene (a strong π acceptor)^[23a] was used as an additive in 1,2-dichloroethane, only the starting material **1d** was recovered.

Evaluation of first-generation ruthenium complexes: The NHC-deprived, first-generation ruthenium complexes were tested in selected aromatic and aliphatic solvents (Figure 8). Interestingly, no improvement in the RCM of diethyl allyl-methyl malonate (**1b**) was observed when representative first-generation pre-catalysts (**Gru-I**, **Ind-I** and **Hov-I**) were used in the fluorinated aromatic solvents. These results are in agreement with Fürstner's observation^[12a,21] that the positive influence of toluene on a reaction ratio is observed only for ruthenium catalysts bearing *N*-aryl-substituted NHC ligands, whereas the activity of analogues with *N*-alkyl groups is usually higher in chlorinated media.^[11a,21]

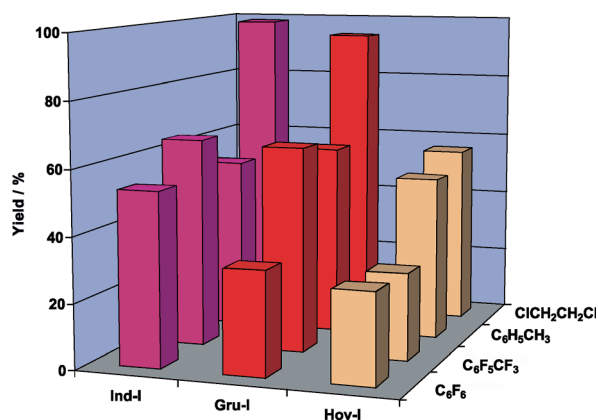


Figure 8. Observed solvent effects in RCM of **1b**. Conditions: 5 mol % of catalyst, $c_{1b} = 0.02$ M, 40 °C, 3 h.

At this point, it becomes clearly apparent that the observed rate enhancement effect is only realised when second-generation ruthenium complexes, bearing an NHC ligand with aromatic substituents, are combined with aromatic fluorine-containing solvents. This conjecture is also supported by the recent report by da Costa and Gladysz,^[22] who tested some fluorous second-generation Grubbs catalysts in aliphatic fluorous media,^[17] such as perfluorocyclohexane (C_6F_{12}) and perfluoromethylcyclohexane ($\text{CF}_3\text{C}_6\text{F}_{11}$).^[22b] For comparison purposes, the authors also measured the reactivities of the standard Grubbs second-generation pre-catalyst **Gru-II** in the same aliphatic fluorinated hydrocarbons. They concluded that in the case of **Gru-II** no appreciable solvent effect was observed for these media.^[22]

Correlation between physico-chemical properties of solvents and observed conversions in RCM: Initiation rates of **Gru-I/II**^[24] as well as the neat results of model RCM reactions^[25a,b]

have already been correlated with the dielectric constants of the solvents. On the other hand, viscosity plays a significant role in reactions performed in ionic liquids.^[25c] Nolan et al. suggested that the FAH effect in olefin metathesis could be related to the physical properties of the reaction medium.^[10c] In the present work, we have attempted to correlate the observed effect (see Figure 7) with selected physicochemical properties of the reaction medium, such as dielectric constant and viscosity.^[24,25] For instance, dielectric constant values decrease in the following order: 1,2-dichloroethane > trifluoromethylbenzene > 1,3-bis(trifluoromethyl)benzene > pentafluorobenzene > other nonpolar FAH (see Table 6). On the other hand, viscosity is similar for all FAHs at 25 °C, with them being slightly more viscous than “classical” solvents. As the data collected in Table 6 show, it is difficult to find a strong correlation between either viscosity or dielectric constant and the results of challenging olefin metathesis reactions of **1d**. Recently, solvent effects were probed in an RCM reaction using the multiple parameter fitting approach;^[25e] however, we have not yet tried this method.

Table 6. Dielectric constants and viscosities of various solvents, and conversions in the RCM of **1d** with **Ind-II** observed in these media.^[a]

Solvent	Dielectric constant $[\epsilon_r]$ ^[b]	Dynamic viscosity $[\text{mPa s}]$ ^[b]	Conversion in RCM of 1d [%]
nitrobenzene	35.60 ^[c]	1.863 ^[c]	4
1,2-dichloroethane	10.42 ^[c]	0.779 ^[c]	25
toluene	2.38 ^[c]	0.560 ^[c]	43
benzene	2.28 ^[c]	0.604 ^[c]	43
trifluoromethylbenzene	9.22 ^[c]	0.689	58
pentafluorobenzene	4.36	–	73
chloropentafluorobenzene	2.27	1.468	89
1,3-bis(trifluoromethyl)benzene	7.49	1.029	94
hexafluorobenzene	2.03 ^[c]	1.183	99
octafluorotoluene	2.66	1.233	> 99

[a] $c_{1d} = 0.2$ M, 5 mol % of **Ind-II** catalyst, 70 °C, 6 h. [b] Measurements were conducted at 25 °C. [c] Value taken from reference [25f].

Comparison of commercially available non-degassed FAHs with freshly distilled and degassed solvents in RCM experiments: It is known that perfluorohydrocarbons dissolve relatively large amounts of gases, especially oxygen.^[17a] Being aware of a negative influence of oxygen on the catalyst lifetime,^[24] we performed a set of RCM reactions of **1d** in commercially available non-degassed toluene and hexafluorobenzene (the reactions were run in open vessels in air), and compared the results with the outcome of reactions conducted in freshly distilled and degassed solvents (using Schlenk techniques under argon atmosphere). Interestingly, we did not observe a significant influence of air on the rate of RCM performed in FAH (Table 7). Although difficult to explain, the results show some practical advantages of these solvents.

Table 7. Observed conversions in the RCM of **1d** with **Ind-II** in commercially available compared with distilled and degassed solvents.^[a]

Solvent	Commercially available solvent, conversion [%]	Distilled and degassed solvent, conversion [%]
toluene	19	45
hexafluorobenzene	91	99

[a] $c_{1d} = 0.2$ M, 5 mol % of **Ind-II** catalyst, 70 °C, 6 h.

³¹P NMR stability and decomposition studies of Gru-II in solutions containing FAH: Intrigued by the above results, we decided to study decomposition reaction rates of **Gru-II** in “classical” chlorinated solvents and in the presence of FAH. To do so, two sets of ³¹P NMR experiments were conducted by recording spectra from solutions of **Gru-II** (10 mM) in neat C₂D₄Cl₂ and in a mixture C₆F₆/C₂D₄Cl₂ (4:1, v/v). The decay of the characteristic ³¹P NMR signal of **Gru-II** ($\delta = 29$ ppm) was recorded until its complete disappearance. At the same time, a new signal appeared at 48 ppm, which was unambiguously associated with the formation of tricyclohexylphosphine oxide, Cy₃P=O. This signal was the major feature in the ³¹P NMR spectrum, accompanied by two signals at $\delta = 21$ and 31 ppm (for copies of the spectra and calculated thermodynamic data, see the Supporting Information). We have not attempted to characterise other decomposition products.

Three series of spectra were recorded from the respective solutions at temperatures of 30, 40, and 50 °C. The measured decomposition half-lives of **Gru-II** in C₂D₄Cl₂ were 470 min at 30 °C and 170 min at 50 °C. In the solution containing C₆F₆, the catalyst decomposed much more rapidly, with half-lives of 160 min at 30 °C and of only 60 min at 50 °C (see Figure 9). A relatively narrow temperature window was used in these experiments due to the pronounced temperature dependence of the process. Below room temperature, the process becomes very slow, whereas above 50 °C it becomes too fast to be reasonably measured.

The observed faster decomposition of **Gru-II** in solutions containing FAH may seem surprising in the light of the invariably better yields reported for reactions in these solvents, as well as in the presence of oxygen (see Table 7). We

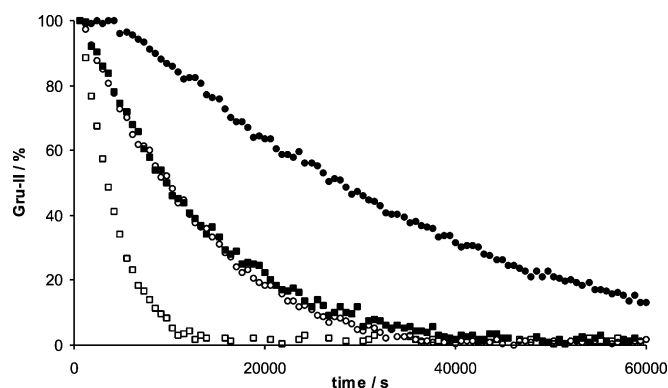


Figure 9. Plots of the relative intensity of the ³¹P NMR signal of **Gru-II** as a function of time in C₂D₄Cl₂ at 30 (●) and 50 °C (○), and in a mixture of C₆F₆/C₂D₄Cl₂ (4:1, v/v) at 30 (■) and 50 °C (□).

suggest that the facile dissociation/oxidation reaction of the phosphine ligand in FAHs allows faster and irreversible formation of catalytically active 14-electron species, which can be subsequently stabilised by π - π stacking interactions between an electron-donating moiety (*N*-mesityl or benzyldiene) and electron-poor solvent molecules,^[23,26] or even by direct fluorine–ruthenium interactions.^[27] In the case of phosphine-free Hoveyda type systems, similar stabilisation of the propagating species can be suggested. We postulate that the interactions with fluorinated solvent molecules can modify the through-space transfer of electron density between the Ru=CHR unit and the aromatic rings on the *N*-substituents of the NHC ligand, thereby accelerating the rate of the metathesis reaction,^[26] such that high TONs can be achieved even for very challenging substrates.

X-ray structural analysis of ruthenium complexes with FAH:

Fortunately,^[10b] we were able to grow crystals of Hoveyda pre-catalysts in FAH, which allowed us to study possible solvent–catalyst interactions in the solid phase. The complex of **Hov-II** with perfluorobenzene crystallises in the *P* $\bar{1}$ space group of the triclinic system. There are two independent catalyst molecules in the crystallographic asymmetric unit, which differ with respect to the interactions with the perfluorobenzene solvent molecules.^[29] Both molecules (denoted hereinafter as M1 and M2 according to the ruthenium atom numbering) occupy general positions (Figure 10). One of the *N*-mesityl arms in M2 is disordered over two positions with respective occupancies of 0.45 and 0.55. The asymmetric unit also contains one-and-a-half perfluorobenzene molecules. The solvent molecule containing atoms C101–C103 and F1–F3 (denoted hereinafter as S1) is located in a special position with an inversion center at the middle of the mesityl ring and is perfectly ordered. The other solvent molecule (denoted as S2) displays a complicated disorder. Three alternative positions are occupied by this molecule, with occupancy factors of approximately 0.45, 0.35 and 0.2, respectively. The former two orientations are coplanar and parallel to one of the mesityl moieties in M2. The least occupied position places the C125 atom of perfluorobenzene close to the

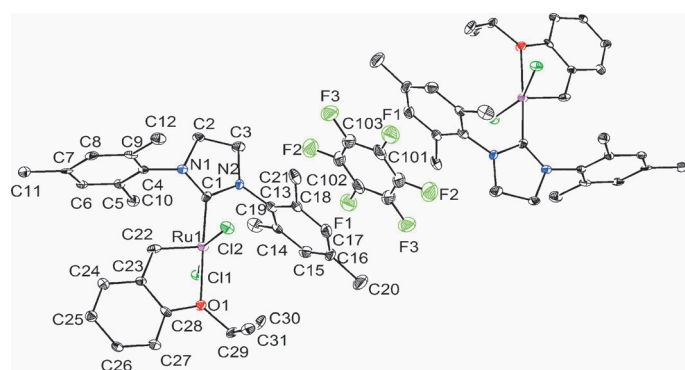


Figure 10. X-ray structure analysis of **Hov-II** with hexafluorobenzene incorporated in the crystal lattice. Ellipsoids represent 50% probability level. Hydrogen atoms have been omitted for clarity.

crystallographic inversion center and the whole molecule in the plane perpendicular to the more occupied positions. An ORTEP representation of the catalyst molecule interacting with perfluorobenzene is presented in Figure 10. The disordered system is illustrated in Figure S1 in the Supporting Information. The structures of both independent molecules of the **Hov-II** catalyst do not differ from the crystal structures of this catalyst crystallised with dichloromethane.^[1e,30] The coordination sphere of the ruthenium ion is particularly well conserved. The most important geometrical parameters characterizing the catalyst are reported in the Supporting Information.

The interactions of perfluorobenzene with the Hoveyda catalyst seem to be important for the crystal formation and are quite different from what has been observed in the case of catalyst crystallised from other solvents. The catalyst molecules M1, together with the solvent molecules S1, which are located exactly between the C13–C21 *N*-mesityl arms of M1 (Figure 10) and the same moiety related by the inversion center, form a well localised stacked structure. The distance between the centroids of the perfluorobenzene molecule and the mesityl moiety is 3.533(3) Å, thus indicating strong interaction between the rings. S1 is rotated with respect to the mesityl ring by 23.6(6)°, so that its carbon atoms are located above the bonds of the mesityl moiety. The fluorine atom F2 is engaged in short contacts to methylene protons H3A (2.650 Å), H57 (2.621 Å), and H60A (2.556 Å) from the disordered part of M2 and F35 from the disordered solvent, which results in a longer C–F distance (1.340 Å, compared with 1.330 Å for F1). The C53–C61 mesityl moiety of M2, analogous to C13–C21 in M1, interacts with perfluorobenzene S2 also mainly by ring stacking (see Figure S1). In this case, S2 is not stacked between two mesityl moieties. However, another S2 molecule, related by an inversion center, is located parallel to the first; therefore, the fluorine atoms from one molecule lie above the carbon atoms from the parallel molecule. The shortest distance between the mesityl moiety and S2 is 3.331 Å, and the shortest distance between the two parallel S2 molecules is 3.429 Å.

The methyl hydrogen atoms of the mesityl group form numerous short contacts with the S2 molecules both parallel and perpendicular to the mesityl ring. The crystal packing depends strongly on the mesityl–perfluorobenzene and perfluorobenzene–perfluorobenzene interactions.^[23] The solvent molecules are gathered on the (110) crystallographic plane. The disordered S2 molecules form a continuous tape along the [100] direction passing through 0¹/₂0, while the S1 molecules are located directly along the [100] axis. Both the formation of the characteristic layer and strong interactions with the catalyst molecules account for the fact that the evaporation of solvent causes slow crystal decomposition.^[29] The catalyst molecules themselves occupy space between the perfluorobenzene layers. The molecules M1 interact with M2 through the methyl groups at the *para*-position in the mesityl moieties, which penetrate the space between the mesityl rings of M2. The interacting mesityl and benzylidene moieties surround a channel, which extends along the [100] direction in the middle of each unit cell.

The structure of Gru-II with perfluorobenzene: The crystals formed from **Gru-II** and C₆F₆ crystallise in the *P* $\bar{1}$ space group with one molecule of the catalyst and two molecules of solvent (S1: C50–C55 ring and S2: C60–C65 ring) in the independent part of the unit cell (Figure 11). The most important structural parameters for this structure are given in the Supporting Information. There are several weak interactions between the perfluorobenzene moieties and the Grubbs pre-catalyst molecule, which may be important for crystal formation and stability. Each catalyst molecule interacts with two perfluorobenzene molecules through quite complex interactions. First of all, the F atoms change the sign of the molecular quadrupole moment. This means that the negative charge in C₆F₆ is located in the plane of the moiety, whereas the positive charge lies above and below this plane. Consequently, the Cl atoms of the catalyst mole-

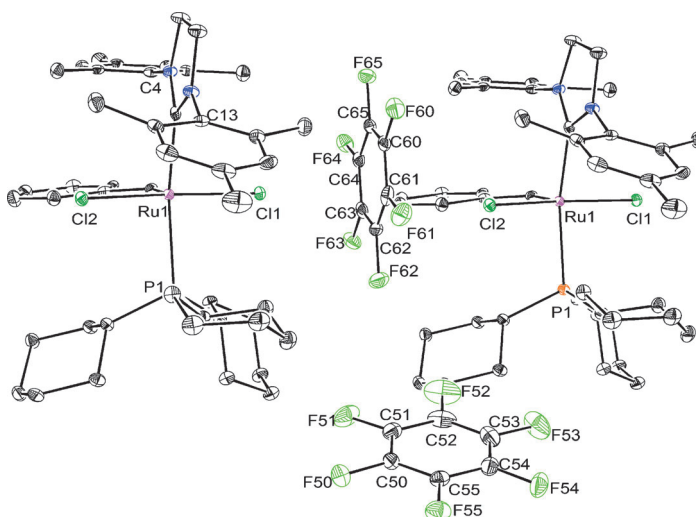


Figure 11. X-ray structure analysis of **Gru-II** with hexafluorobenzene incorporated in the crystal lattice. Ellipsoids represent 30% probability level. Hydrogen atoms have been omitted for clarity.

cule point towards the carbon atoms of the S2 solvent molecule (with Cl...C contacts of length about 3.3–3.4 Å), as might be expected for bond dipole...molecular quadrupole interactions. In this way, catalyst–solvent–catalyst chains are formed in the crystal lattice, which extend along the [100] direction. At the same time, the C₆F₆ molecule S2 is oriented perpendicularly to the plane of the other independent solvent molecule S1 to allow close F...C contacts. This is characteristic of molecular quadrupole...quadrupole interactions. Numerous F atoms of both solvent molecules form several weak H...F hydrogen bonds. Additionally, even short F...F contacts are possible.

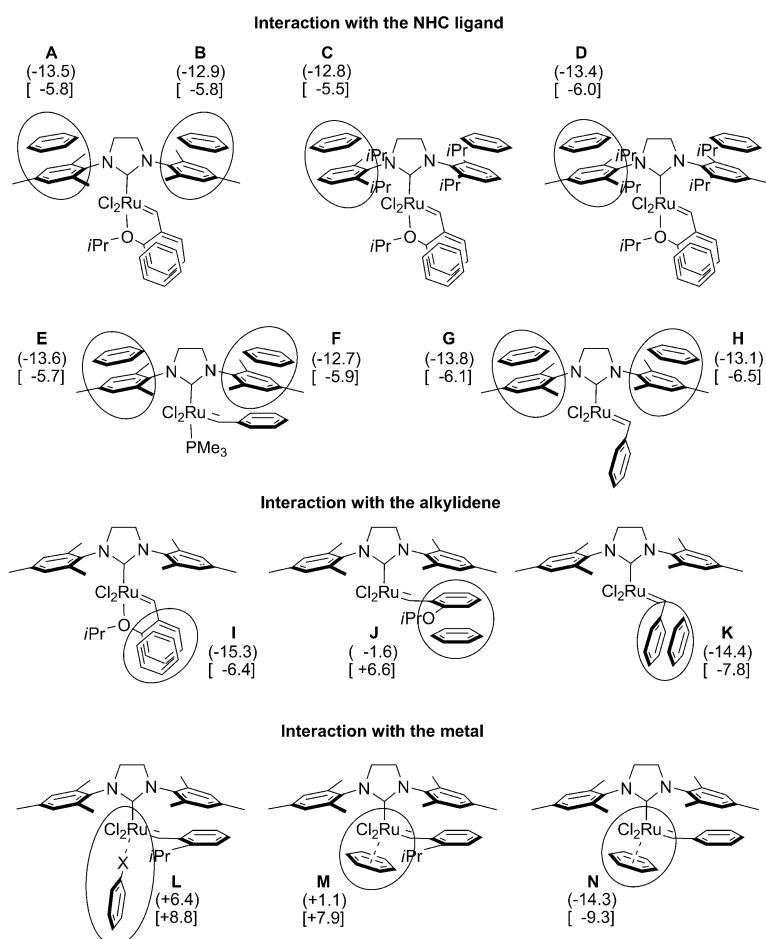
The S1 ring is located almost parallel to the C13–C21 mesityl group of the catalyst molecule, and the distance between their centroids is 3.870 Å, which indicates some stacking-type interactions. This corresponds to the Hoveyda solvates, in which stacking is the main type of interaction between the catalyst and solvent molecules; however, the interaction distances in the Hoveyda derivatives are shorter (about 3.53–3.55 Å for the two independent moieties in the asymmetric unit). The distance between the centroids of the other C4–C12 mesityl ring and the C22–C28 benzyldiene group bound to the Ru atom is 3.799 Å.

The crystal packing depends on perfluorobenzene–Grubbs complex interactions (Figure 11), and likewise in the Hoveyda structure crystallised with C₆F₆. Each molecule of the Grubbs complex forms numerous short contacts with seven solvent moieties and only one contact with another catalyst molecule. Aromatic rings in the lattice, except those of S2 engaged in interactions with chlorine atoms, are located almost perpendicularly to the [100] direction.

Computational results of ruthenium complexes in FAHs: To obtain insights into the energetics of the interactions between aromatic solvent molecules (both C₆F₆ and C₆H₆ rings) and the ruthenium pre-catalysts considered above, we performed density functional theory (DFT) calculations. Since one of the main interactions could be a stacking between the aromatic rings of the Ru complex and of the solvent, we selected the M06L functional,^[31] which is among the best

and recommended functionals for efficiently describing organometallic systems and weak interactions.^[32] The geometries that we examined are drawn in Scheme 7.

Calculations were started from geometry **A** in Scheme 7, since it allows a direct comparison of the DFT-optimised and X-ray structures. Geometrical analysis indicated that the DFT-optimised structure (see Figure 12) is in excellent agreement with the crystallographic structure, with RMSDs (root-mean-square deviations) of only 0.055 Å for distances and 0.9° for angles.^[33] The distance between the centre of the C₆F₆ ring and the aromatic ring of the adjacent mesityl ring is 3.52 Å, in excellent agreement with the experimental value of 3.59 Å. This analysis validates the chosen computational approach for locating the geometry of these particular systems. Replacing C₆F₆ with C₆H₆ results in a strong tilting and shift of the C₆H₆ ring, leading to an offset stacked geometry.^[23a] The distance between the centres of the two aromatic rings increases to 4.51 Å, with the C₆H₆ ring rotated to point towards the nearby methylene group of the backbone of the NHC ligand. This results in the formation of a weak C–H...aromatic interaction, as suggested by the short distance of 2.81 Å between the centre of the benzene and



Scheme 7. Structures examined, and interaction energies, in kcal mol⁻¹, between the Ru complexes and C₆F₆ and C₆H₆, in round and in square parentheses, respectively. For the sake of clarity, the F and H atoms of C₆F₆ and C₆H₆ have been omitted in the drawings.

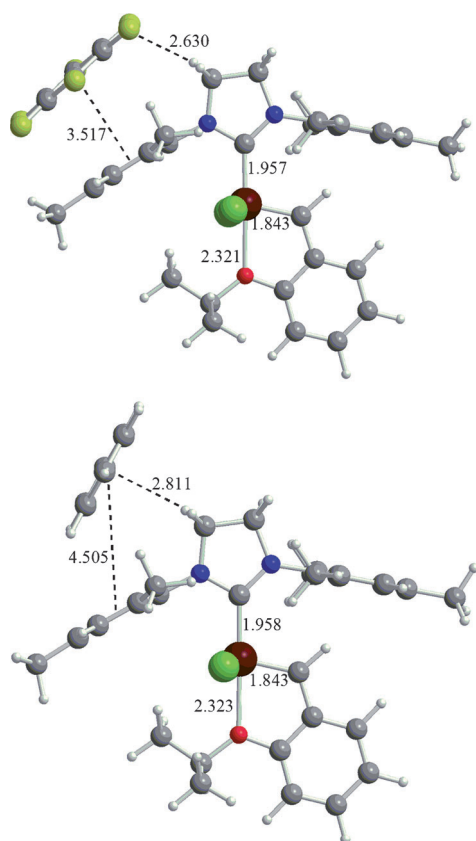


Figure 12. DFT-optimised structures of the complexes between C_6F_6 (top) or C_6H_6 (bottom) and the **Hov-II** catalyst. Distances in Å.

the closest hydrogen atom of the methylene group. From an energetic point of view, the interaction of C_6F_6 with the Ru complex, $13.5 \text{ kcal mol}^{-1}$, is considerably stronger than that involving C_6H_6 , which amounts to just $5.8 \text{ kcal mol}^{-1}$; see Scheme 7.

The formation of a nicely stacked structure in the case of C_6F_6 and of a rather tilted structure in the case of C_6H_6 can be explained in terms of the quadrupole moments of the two molecules. The quadrupole moment of benzene (and similarly of a mesityl ring) is large and negative, while the electronegativity of fluorine makes the quadrupole moment of C_6F_6 large and positive. The opposite quadrupole moments of C_6F_6 and of the mesityl ring maximise the electrostatic interaction energy and favour a stacked arrangement, whereas the same-sign quadrupoles of C_6H_6 and of the mesityl ring electrostatically repel, favouring a T-shaped or offset stacked geometry.^[23a] We also investigated structures in which the C_6F_6 and C_6H_6 rings are placed above the other mesityl ring, that is, on the same side of the $Ru=ylidene$ bond, structure **B** in Scheme 7. In this case as well, the C_6F_6 ring remains well stacked over the mesityl ring, whereas the C_6H_6 ring moves away to engage in an interaction with the NHC bridge backbone. In short, both **B** structures are quite similar to the corresponding **A** structure. The interaction energies between the solvent molecules and the Ru complex in **B**, 12.9 and $5.8 \text{ kcal mol}^{-1}$ for C_6F_6 and C_6H_6 , respectively,

are essentially the same, which indicates that the interaction of a solvent molecule with the mesityl rings is not selective.

To gain insight into the role of the N-substituents of the NHC ligand, the SIMes (1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene) ligand of **Hov-II** was replaced by the popular SIPr (1,3-bis(2,6-diisopropylphenyl)-2-imidazolidinylidene) ligand, structure **C** in Scheme 7. Even in the presence of the bulkier *ortho* isopropyl substituents, the solvent molecules can effectively approach the aromatic ring of the N-substituents. Indeed, the distance between the centre of the C_6F_6 ring and the nearby N-substituent of the SIPr-based Ru complex, 3.85 Å , compares well with the analogous distance in the SIMes-based Ru complex. The interaction energy between C_6F_6 and the SIPr-based Ru complex, $12.8 \text{ kcal mol}^{-1}$, is essentially the same, giving a further indication that the bulkier *ortho* *i*Pr groups do not sterically destabilise the interaction. In line with this trend, adding a methyl group *para* to the N atoms in the SIPr-based Ru complex, structure **D** in Scheme 7, stabilises the interaction with C_6F_6 from 12.8 to $13.4 \text{ kcal mol}^{-1}$. In all of these cases, the interaction with C_6H_6 is noticeably weaker. To assess the role of the alkylidene unit, as well as the saturation of the metal, we calculated the same kind of interactions in the prototype second-generation Ru catalyst, and in the 14-electron species formed after phosphine dissociation, structures **E–H**. The interaction energies reported in Scheme 7 for **E–H** are rather similar to those calculated for **A–D**, indicating that the nature of the alkylidene group or the metal saturation have no role in determining the strength of the interaction between the N-substituents and the solvent molecules.

Next, we examined the interactions of C_6F_6 and C_6H_6 with the aromatic ring of the alkylidene moiety, structures **I–K** in Scheme 7. Even with the *i*PrO group coordinated to the Ru centre, structure **I**, a solvent molecule is able to engage properly with the aromatic group of the alkylidene unit, and the interaction is even slightly stronger. This interaction is of course preserved after dissociation of the *i*PrO group, which gives the opportunity to investigate the influence of a solvent molecule on the activation step. In the absence of an explicit solvent molecule coordinated to the Ru complex, dissociation of the *i*PrO group has an energy requirement of $16.1 \text{ kcal mol}^{-1}$. Considering a solvent molecule coordinated to the alkylidene group, dissociation incurs 13.7 and $13.0 \text{ kcal mol}^{-1}$ on going from **I** to **J** in the presence of C_6F_6 and C_6H_6 , respectively, indicating that a solvent molecule may slightly promote activation, since a better geometry of interaction can be established between the solvent molecule and the alkylidene aromatic group after dissociation of the *i*PrO group. A rather strong interaction is also calculated for that between a solvent molecule and the aromatic ring of the phenylidene group; see structure **K**. In these cases as well, C_6F_6 interacts with the Ru complex considerably more strongly than C_6H_6 .

Moving finally to the interaction of C_6F_6 or C_6H_6 with the Ru centre in the 14-electron complexes derived from dissociation of the *i*PrO group or of the phosphine, we first assessed whether the solvent could interact with the metal

through direct coordination of one of the F or H atoms; structure **L** in Scheme 7. This interaction is clearly disfavoured relative to solvent interaction with the alkylidene aromatic group in **J**, but is still attractive, since the energies of solvent binding to the simple 14-electron species formed by dissociation of the *i*PrO group from **Hov-II** amount to 9.7 and 7.3 kcal mol⁻¹ for C₆F₆ and C₆H₆, respectively. Coordination of a solvent molecule to the Ru centre through the aromatic ring of C₆F₆, structure **M**, is even more favoured, and it allows recovery of almost all of the energy lost in the dissociation of the *i*PrO group. The rather strong interaction between the π -system of the solvent and the Ru centre is confirmed by the strong interaction with the Ru centre in the phenylidene-based 14-electron structure **N**.

Conclusion

The presented results demonstrate that interactions with aromatic fluorinated solvent molecules can significantly influence the activity of NHC-ruthenium catalysts in olefin metathesis. This effect is of high practical importance since it offers a complementary method for activating already existing metathesis catalysts.^[34] In addition, unlike freon[®] and some aromatic hydrocarbons, FAHs do not seem to pose much environmental or biological risk.^[35]

FAHs can improve the efficiency of the initiation step of phosphine-containing Ru pre-catalysts, as was indicated by much faster decomposition of the Grubbs catalysts **Gru-II** in solutions containing FAH. One of the parameters that may be responsible for the enhanced activity of the propagating catalyst is the formation of π - π stacking interactions between the N-aromatic substituent and the aromatic fluorinated solvent molecules. A number of interactions, including π - π stacking, have been observed between FAHs and second-generation ruthenium catalysts in the solid state. Independent calculations have indicated that an aromatic solvent molecule can engage in a variety of possible interactions with a ruthenium complex, stabilizing it and even protecting the 14-electron species by direct coordination to the Ru centre. This contributes to a higher stability of the ruthenium active species, which may be responsible for the remarkable activation effect observed experimentally. Further, the calculations indicated that C₆F₆ interacts remarkably more strongly than C₆H₆, which is in line with the experimental results. Finally, there is no reason to rule out the possibility that the interactions described above could work cooperatively.^[36]

Experimental Section

Experimental details of the catalytic procedures, with complete characterisation of all new compounds, including copies of the NMR spectra, X-ray crystallographic tables, the data in crystallographic information file (CIF) format, and all other information are included in the Supporting Information. CCDC-759842 (**Hov-II** with perfluorobenzene) and 782769 (**Gru-II** with perfluorobenzene) contain the supplementary crystallo-

graphic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Static calculations: Static DFT calculations were performed at the GGA level with the Gaussian 09 package using the M06L functional.^[31] The electronic configurations of the molecular systems were described with the standard split-valence basis set with a polarisation function due to Ahlrichs and co-workers for H, C, N, O, F, and Cl (SVP keyword in Gaussian 09).^[37] For Ru, we used the small-core, quasi-relativistic Stuttgart/Dresden effective core potential, with an associated (8s7p6d)/(6s5p3d) valence basis set contracted according to a (311111/22111/411) scheme (standard SDD keywords in Gaussian 09).^[38] The geometry optimisations were performed without symmetry constraints, and the located stationary points were characterised by analytical frequency calculations. Solvent effects, including contributions of non-electrostatic terms, have been estimated by single-point calculations on the gas-phase-optimised structures, based on the polarisable continuum solvation model PCM using benzene and perfluorobenzene as solvents.^[39]

Acknowledgements

C.S. thanks the Foundation for Polish Science ("Ventures" Program) for financial support. The project "Ventures/2008-1/5" is realised within the "Ventures" program of the Foundation for Polish Science, co-financed from the European Union Regional Development Fund. K.W. thanks the Foundation for Polish Science for the award of a "Mistrz" professorship. A.M. is also thankful for financial support in the form of a Polish Ministry of Science and Higher Education grant for Ph.D. students, no. NN204030233. Special thanks are due to Dr. R. Kadyrov (Degussa-Evonik) for initiation of the project, Prof. R. Holyst (IChF PAN) for assistance with viscosity measurements, and Dr. H. Szatyłowicz (Faculty of Chemistry, Warsaw University of Technology) for assistance with the dielectric constant measurements. A.P. is grateful for the allocation of a Ramón y Cajal contract by the Spanish MICINN. We thank the HPC team of Enea (www.enea.it) for the use of the ENEA-GRID and the HPC facilities of CRESCO (www.cresco.enea.it) in Portici, Italy.

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Received: January 17, 2011

Revised: June 25, 2011

Published online: September 29, 2011