Remarkable solvent effect of fluorinated alcohols on transition metal catalysed C-H functionalizations

Journal:	*Organic Chemistry Frontiers*
Manuscript ID	QO-HIG-11-2015-000398.R2
Article Type:	Highlight
Date Submitted by the Author:	14-Jan-2016
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Journal Name

ARTICLE

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Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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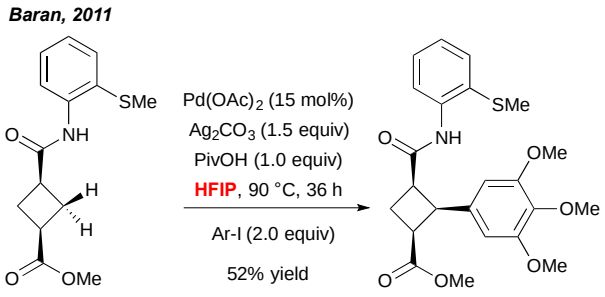
Fluorinated solvents like 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) and trifluoroethanol (TFE) have recently emerged as a remarkable synthetic hint allowing challenging C-H activation reactions. A beneficial effect of these solvents on reactivity, as well as site- and stereoselectivity of various direct functionalization reactions has been observed. Moreover, several catalytic systems specifically require such fluorinated medium. This Highlight is devoted to showcase an exceptional potential of the fluorinated alcohols in the C-H activation field.

Introduction

It is now about a decade since the C-H activation field has attracted an expanding interest of the scientific community, thus opening a new avenue in transition metal catalysis.[1,2] Till recently, several major obstacles have however limited a broad and general utility of this modern strategy. Indeed, the vast majority of the catalytic systems not only required a preinstallation on a substrate of a strongly coordinating directing group (DG)[3] and harsh reactions conditions[1i] but was also almost exclusively limited to an *ortho*-functionalization of aromatic compounds.[4] On the other hand, the direct functionalization of aliphatic molecules,[5] the activation of remote C-H bonds and the stereoselective transformations[6] remained an almost uncovered research field. Nevertheless, since few years, new synthetic solutions have been devised to overcome the above mentioned limitations largely expanding the portfolio of molecular scaffolds that can now be constructed via the C-H activation approach. Interestingly, a panel of solvents commonly employed in the C-H activation field, like alcohols, dichloroethane, aromatic solvents, dioxane and, maybe more sporadically, very polar medium like DMF, DMSO or organic acids, was recently expanded to include polyfluorinated alcohols, such as 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) and 1,1,1-trifluoroethanol (TFE). Owing to their unique properties like their protic but non-nucleophilic character, their high hydrogen bonding donor ability, their high ionizing power, their ability to stabilise cationic species and their extreme polarity, these alcohols were recently recognized as remarkable medium for several types of transformations including oxidations, C-C and C-X bond formations, cycloadditions, etc.[7] On the other hand, the beneficial effect of the acidic solvents to promote C-H activation is commonly acknowledged. Such medium can indeed enhance an electrophilic metallation and accordingly various direct functionalization reaction occur in, or require an addition of strong organic acids such as acetic acid or trifluoroacetic acid. Besides, formation of cationic metallic species during the C-H transformations is frequently suspected. Finally, the DGs embedded within a C-H substrate (amides, carboxylates or nitriles for example), participate easily in hydrogen bonding. Taking into consideration all these points, it becomes quite obvious that polyfluorinated alcohols could advantageously impact the C-H activation reactions by means of various modes of action.



Scheme 1: Diastereoselective direct arylation occurring in HFIP medium.

For the best of our knowledge one of the first to evidence a beneficial effect of TFE as cosolvant for an oxidative olefination was Zhangjie Shi. In 2007, while studying a direct functionalization of *N,N*-dimethylbenzylamines, he discovered that the most active catalytic system was obtained when TFE, together with the acetic acid additive was used.[8] As this reaction was still efficient in other

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solvents (provided that AcOH additive was employed), the origin of this TFE-induced reactivity enhancement was not elucidated. However, it can be hypothesized that when using TFE and AcOH the amine DG is partially protonated yet modifying the features of the reactive species.

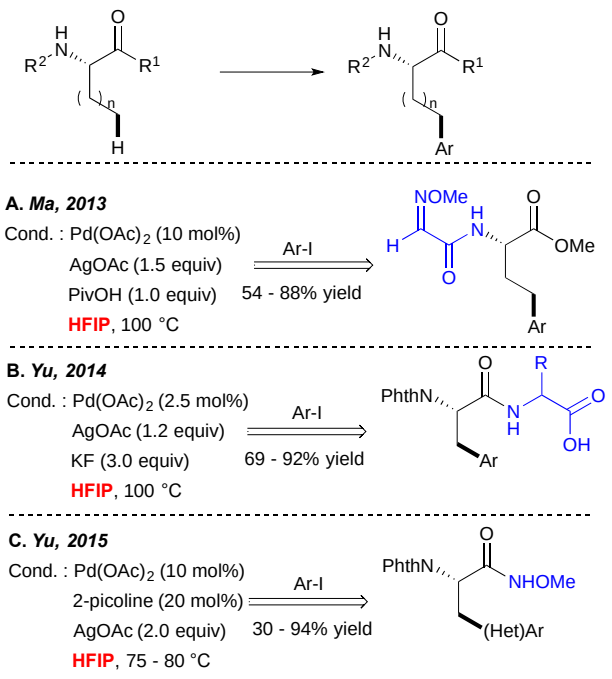
A more meaningful illustration of a unique potential of the polyfluorinated alcohols to mediate C-H activation reactions was reported few years later by Baran *et al*. In the context of a total synthesis of piperarborenine cores, the author noticed that a use of HFIP together with the pivalic acid additive was a critical parameter allowing an efficient arylation of the cyclobutane-derivatives (Scheme 1).[9] Also in this case a selection of this particular solvent rather results from an empirical optimization than a foreseen reactivity. However, although the lack of a rationalized explanation, this work progressively inspired numerous research groups to integrate fluorinated solvents into their "tool-box" and to screen them regularly during an optimization study. Rewardingly, many exiting and efficient transformations progressively emerged.

At this point we would like to highlight several important points. Although the empirical observations showcase a particular role of HFIP and/or TFE in C-H activation reactions, their accurate role has not been studied in-depth and, if any, only very succinct comments are provided by the authors. Accordingly, the herein-presented explanations are rather hypothetical. Secondly, in some cases the authors mention that HFIP or TFE outcompetes other medium but a lack of a detailed optimization study renders the analysis of such results illusive. Finally, it seems that in many cases HFIP solvent was simple not tested. Accordingly, due to all these difficulties, the aim of this review is simple to highlight the different activation modes and beneficial effects that were observed when employing such a medium.

C-H activation of aliphatic substrates

Direct metallation of the C(sp^3)-H bonds is widely recognized as highly challenging and hence particular synthetic hints were needed to facilitate such transformations.[5] Since 2006 Yu and collaborators were particularly actively involved in this field discovering several catalytic systems for direct C(sp^3)-C and C(sp^3)-X couplings.[10,11] They and others observed that many of such transformations performed well in alcoholic solvents like *t*BuOH or *t*AmylOH or even in ether-type medium.

A major step forward in the C(sp^3)-H activation field was achieved when a potential of bidentate DGs to enhance these couplings was evidenced. Such bidentate DGs-induced couplings seem to tolerate well a wide range of solvents such as alcohols, DCE and toluene for example. However, an interesting HFIP-induced reactivity boost was observed independently by Fernández-Ibáñez and Carretero[12], Ma[13] and Yu[14] when alkyl substrates like the amino acid scaffolds bearing a bidentate DG embedded either on the amine ((N-2-pyridyl)sulfonyl or 2-methoxyiminoacetyl auxiliaries (Scheme 2A)) or the carboxylate motif (OH-free dipeptide motif (Scheme 2B)) were submitted to the Pd-catalyzed direct arylation reaction. The truly efficient transformations could be achieved in HFIP while other standard solvents like toluene, non-fluorinated alcohols, dioxane, DCE, THF, etc. enabled formation of the desired product in significantly lower yields. Although the authors did not comment on an exact role of HFIP in these reactions, the "peptide-like" structure of the substrates and strong hydrogen bonding properties of HFIP probably result in a formation of H-bonds between the substrate and the solvent hence favouring an optimal geometry of the metallacyclic intermediates and/or positively influencing the electronic properties of the DG. More recently, HFIP was also selected as an optimal solvent or a key additive in C(sp^3)-H activation of simpler alkanes bearing monodentate auxiliaries like *N*-methoxyamide[15] (Scheme 2C) or oxime ether[16]. In the first case the acidic character of this solvent is believed to prevent a decomposition of the starting material. In the second case an increased efficiency in a presence of the extremely polar HFIP cosolvent (DCE/HFIP 3:1 mixture) is attributed to an accelerated Ar group transfer from a diaryliodonium coupling partner to a palladacyclic intermediate. It's worth of noting that when other commonly used bicoordinating DGs such as 8-aminoquinoline or 2-pyridin-2-ylisopropyl (PIP) moiety were installed on the amino acid scaffold, more standard solvents like hindered alcohols, DCE, acetonitrile or toluene were employed as optimal reaction medium. However, for the best of our knowledge HFIP was generally not tested in these cases (or at least the authors do not mention these testes).[17,18]



Scheme 2 HFIP as critical solvent for aliphatic C(sp^3)-H bond activation.

C-H activation using distal DG

For quite a long time the C-H activation field has been almost exclusively limited to the *ortho*-functionalization of the aromatic substrates bearing a coordinating group directly embedded on the aromatic ring and hence accommodating a relatively stable 5-membered metallacyclic intermediates in the key C-H activation step. In contrast, use of distal DGs and subsequent functionalization enabled by a generation of considerably larger metallacyclic intermediates represents a great synthetic challenge. A successful development of such transformations requires overcoming a high entropic barrier (due to the presence of a freely rotating sp^3 carbon centre between the aromatic ring and the DG) necessary for assembling the desired transition state. Impressively, HFIP established itself as the solvent of choice to perform such distal C-H functionalization (Figure 1) as illustrated for the first time by Yu. The author discovered that the fluorinated alcohols (HFIP and TFE) are unique solvents supporting *ortho*-olefination of arenes bearing a distal, weakly coordinating ether DG.[19] This challenging transformation totally failed when performed in other standard medium like *tert*-amyl alcohol and DCE. The superior reactivity was observed in HFIP, permitting the isolation of the desired product in very high yields (even if a non-negligible amount of bifunctionalized products was generated). Importantly, a further work of this research group revealed that other distal, weakly binding DGs such as Weinreb amides, esters and ketones may also be efficiently employed in combination with HFIP solvent permitting direct C-C and C-O couplings.[20] This solvent choice provoked also a drastic change of the reaction outcome when arylation of a mandalic acid was targeted; either any reactivity or only a trace amount of the desired product was generated in DCE, MeCN, toluene, DMF, AcOH and *tert*-amyl alcohol, whereas the use of HFIP, under otherwise identical reaction conditions, yielded the targeted scaffolds.[21] Intriguingly, the authors noticed that the choice of HFIP solvent is especially valuable if the targeted reaction occurs via a Pd(II)/Pd(IV) manifold (arylation, iodination, acetoxylation), whereas the oxidative Heck reaction following a Pd(II)/Pd(0) protocol works well in *tert*-amyl alcohol. In addition, HFIP stood out as the optimal medium when a sulfoxide DG is installed three carbons away from the aromatic ring, like in the case of the phenylpropylsulfoxide.[22]

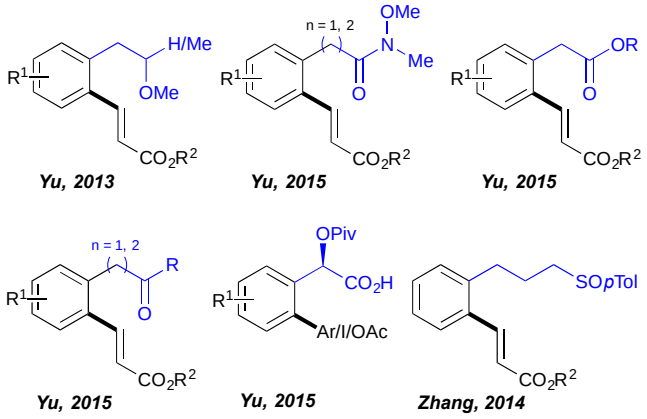


Figure 1 HFIP allowed direct C-H activation in a presence of distal DG

Remote C-H activation

Expanding the scope of the C-H activation reactions beyond a proximity-driven reactivity (*ie. ortho*-functionalization) remained, till the beginning of this decade, an unsolved problem. Several different approaches have been imagined to achieve the *meta*-selective transformations[4] and amongst them a design of "end-on" template allowing formation of larger metallacyclic intermediates and subsequent functionalization on distal positions have attracted a particular attention (Figure 2). In his seminal work, Yu *et al.* reported that a fine design of a removable template bearing a weakly coordinating nitrile group is the key to successfully deliver a metal catalyst to the vicinity of a tethered arene substrate hence promoting the direct olefination of the *meta*-C-H bond.[23] Rewardingly, when the template T1, considered as a U-shaped tethered, was employed, a desired reactivity could be achieved with a high site-selectivity. The solvent selection had a major impact on both selectivity and efficiency of this reaction with HFIP outcompeting other medium. Thereafter, a use of this T1 nitrile template paved also the way to the *meta*-arylation and alkylation of the aromatic substrates (using boronic acid derivatives).[24] Following these seminal works, several different "end-on" tethers (T2-T4) were designed to promote the remote functionalization of various synthetically useful cores such as aniline,[25] phenol,[26] phenyl acetic acid[27] and benzylic alcohol[28] derivatives as well as heterocyclic compounds like tetrahydroquinolines[25] and indolines[29]. Accordingly the key factors governing the geometry of the metallacyclic intermediates and the

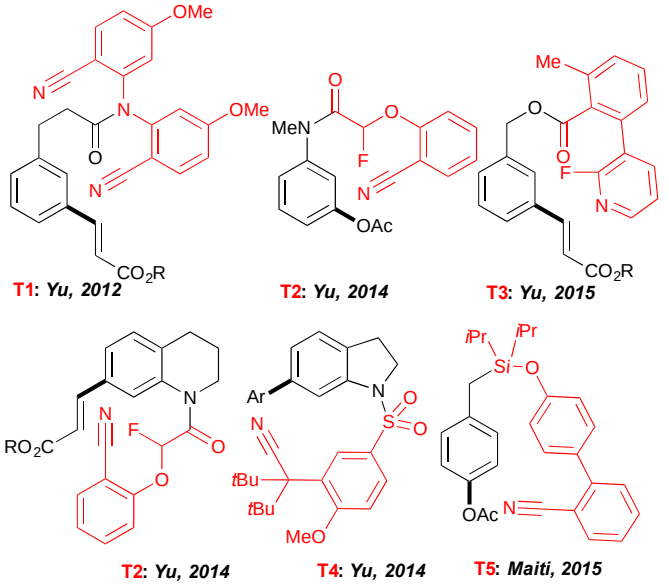


Figure 2 Examples of molecular scaffolds accessible via remote C-H activation occurring in HFIP.

resulting site-selectivity of the overall transformations could be identified. Remarkably, HFIP is still superior to other solvents. For instance only a trace amount of the desired product was observed when acetoxylation of the aniline-derivatives was conducted in DCE, *tert*-amyl alcohol or acetic acid.

Further key achievement in the remote C-H activation was disclosed by Maiti who succeeded in designing a D-shaped template T5 directing a C-H activation to the *para*-position.[30] As previously, HFIP is crucial to insure an excellent site-selectivity. Notwithstanding the lack of theoretical studies to elucidate the particular role of the fluorinated solvents in these exciting transformations, HFIP is believed to coordinate the Pd catalyst hence accommodating a desired pre-transition state and to enhance stabilisation of a macrocyclic intermediates.

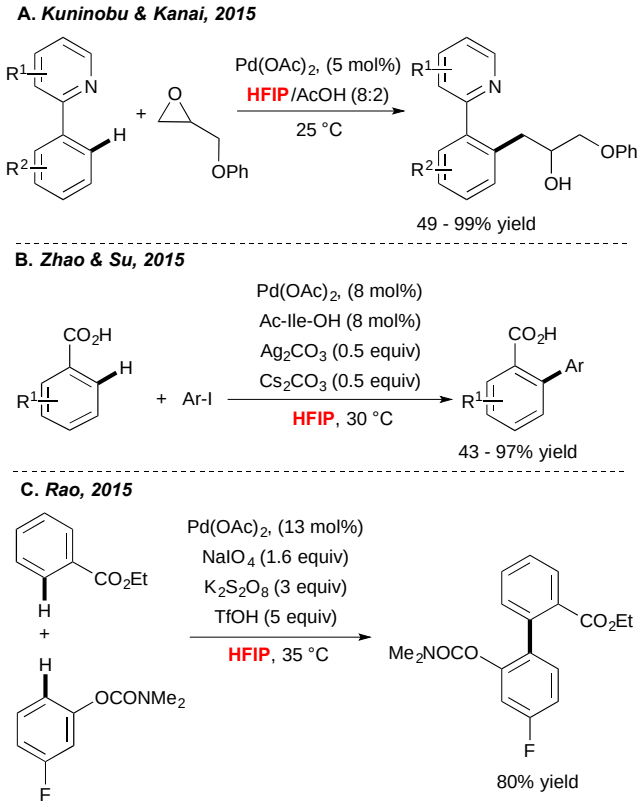
Besides coordinative interactions between this fluorinated alcohol and Pd-catalyst could also account for an enhanced palladation step. Finally, formation of H-bonds between HFIP and the "end-on" nitrile moiety can also be reasonably expected, beneficially impacting both reactivity and selectivity of the overall transformation.

Aiming a balanced presentation of the above-mentioned research axis, it's important to note that in some cases DCE may also be employed as reaction medium, like in the case of a *meta*-functionalization of benzylic ethers.[31] Moreover, Tan devised a closely related Si-tethered template attached to benzyl ethers and the corresponding remote C-H activation occurs in DCE although an addition of HFIP as additive boosts the efficiency of this reaction and slight improves its selectivity.[32]

Mild C-H activation

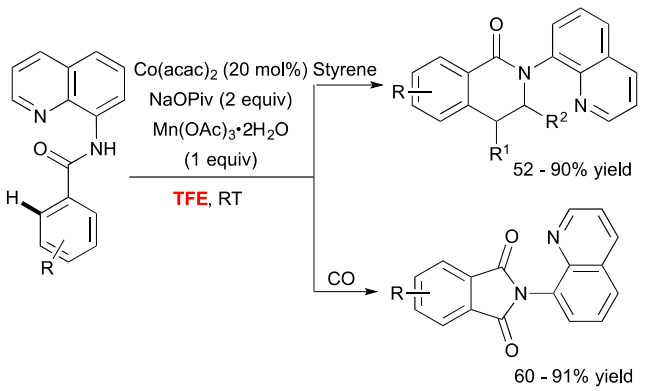
Achieving direct functionalization reactions under mild reaction conditions and in absence of external oxidants gives promise of designing truly synthetically useful transformations. Impressively, as illustrated very recently by Kuninobu and Kanai[33] (Scheme 3A) the choice of the fluorinated alcohol as medium may again be a privileged solution. In this case a Pd-catalyzed C-H activation, followed by a coupling with oxiranes, afforded alkylated compounds under surprisingly mild reaction conditions and at room temperature. In this particular case HFIP is expected to increase the stability of the oxirane coupling partner. In parallel, Zhao and Su[34] discovered that picking HFIP solvent is essential to perform a high-yielding direct arylation of benzoic acid derivatives occurring at ambient temperature (Scheme 3B).

Another example of a mild Pd-catalyzed and HFIP-mediated C–H activation was disclosed very recently by Rao (Scheme 3C).[35] The authors targeted challenging two-fold C-H functionalization allowing coupling of two aromatics bearing weakly coordinating DGs. Their extensive experimental work was rewarded by a determination of an optimal catalytic system. Impressively a choice of both, an oxidant and a solvent, were critical factors. A test reaction, ie. homocoupling of benzophenone, was totally inefficient in DMSO, DMF and EtOH, moderate conversions were observed in DCE and TFE whereas the desired product was isolated in 83% yield when the reaction was performed in HFIP. Taking into consideration the choice of the weakly coordinating DGs, the authors surmised that HFIP serves as a suitable ligand for palladium, stabilizing for example its high-oxidation state intermediates.



Scheme 3 Mild Pd-catalyzed C-H activation occurring in HFIP

In addition to these Pd-catalyzed mild C-H activation reactions, Daugulis astutely employed TFE as a unique medium to perform a cobalt-catalyzed olefination[36] and carbonylation[37] of aminoquinoline derivatives (Scheme 4). The superiority of the fluorinated alcohol over other solvents was likely attributed to an increased solubility of the metal catalyst in this medium.

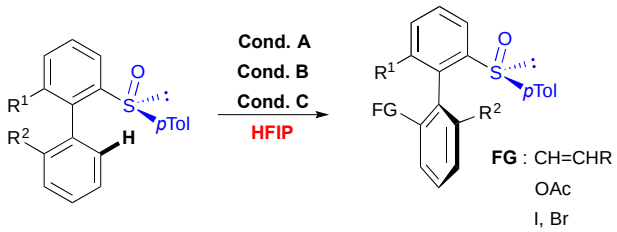


Scheme 4 Cobalt catalysed mild C-H activation.

Besides its compatibility with Pd and Co, Chang discovered recently that fluorinated alcohols are also a promising medium for Ir-catalyzed C-H transformation as illustrated by a mild arylation of amide using aryldiazonium salts as an arylating agent.[38] In this particular case the lower Lewis basicity of this fluorinated alcohol compared to other conventional alcoholic solvents probably disfavours the coordination of the Ir-catalyst by the solvent yet allowing an efficient binding of the diazonium coupling partner to the metal atom yet expediting the overall transformation.
Notably, sporadic examples of a use of either HFIP or TFE solvents for Ru[39] and Rh[40] based transformations were also disclosed sporadically.

Stereoselective C-H activation

Taking into consideration the unique role of HFIP for both, the C-H activation step, which requires geometrically well-defined metallacyclic intermediates and mild transformations, the choice of this solvent to perform stereoselective transformations appears particularly attractive. This hypothesis is unambiguously confirmed if considering a sulfoxide-directed atropodiastereoselective direct functionalization (Scheme 5).[41] When biaryl substrates bearing a sulfoxide moiety as both DG and chiral auxiliary were submitted to a direct acetoxylation, iodination and olefination reactions, the use of this fluorinated solvent allowed not only to perform the desired transformations under very mild reaction conditions, but also to efficiently control the chiral induction during the overall transformation. Accordingly, the targeted, tri- and tetra-substituted biaryls were generated with excellent atroposelectivity. Notably, the mechanistic studies[41b] firstly proved a unique reactivity of this catalytic system in HFIP (use of other solvents such as DCE, AcOH, $CHCl_3$ and *i*PrOH resulted in a reactivity shut down). Secondly, efficiency and stereoselectivity enhancement observed in HFIP could be attributed to a solvent-induced activation of the substrate by means of a H-bond formation between the sulfoxide moiety and HFIP. Noteworthy, a closely related stereoselective transformation using biaryl substrates bearing a stereogenic phosphonate DG was recently reported and, once more, fluorinated solvent (TFE) was selected as an optimal medium.[42]



Cond. A : $Pd(OAc)_2$ (10 mol%), AgOAc (2 equiv), CH_2=CHR (2 equiv), HFIP, 25 °C
Cond. B : $Pd(OAc)_2$ (10 mol%), $NH_4(S_2O_8)$ (2 equiv), H_2O (2 equiv), HFIP/AcOH (1:1), 25 °C
Cond. C : $Pd(OAc)_2$ (5 mol%), NIS/NBS (1.3 equiv), HFIP/AcOH (1:1), 25 °C

Scheme 5 HFIP induced atropostereoselective C-H activation

Conclusions

Functionalization of the challenging C(sp^3)-H bonds, remote and distal site-selectivity, high reactivity under surprisingly mild reaction conditions and excellent stereoselectivity are highly desirable features of the challenging C-H activation reactions which can be accomplished via numerous catalytic systems employing fluorinated solvents such as HFIP and TFE. Although the particular mode of action of this medium is multiple and ambiguous, several hypotheses may be advanced. Firstly, thanks to the excellent H-bond donor properties of the fluorinated alcohols, these solvents are particularly suited to interact with DGs of the substrates yet accommodating their coordinating properties. Secondly, the coordinating character of this medium could facilitate a controlled assembly of well-defined pretransition states hence enhancing an optimal site- and stereoselectivity. On the other hand this solvent is also prompt to act as an ancillary ligand to coordinate Pd-species and for instance stabilization of the electrophilic catalytic species in HFIP and TFE could also account for an improved overall efficiency.
Nevertheless, although the benefits that may be expected when using HFIP, several disadvantageous need to be taken into consideration. The volatility of HFIP (bp. = 59 °C) renders it unsuitable for high temperature reactions and its elevated price may be prohibitive for its large-scale application (a distillation of HFIP from a crude reaction mixture could however be considered). In this context the use of HFIP and TFE rather as additives and activators than as solvent seems particularly tempting. Nonetheless, the unique potential of these solvents in the C-H activation field make them highly attractive tool to design unprecedented transformations and many exciting discoveries will certainly be reported in a near future.

Acknowledgements

We thank the CNRS (Centre National de la Recherche Scientifique), the "Ministere de l'Education Nationale et de la Recherche", and ANR (Agence Nationale de la Recherche) France for financial support.

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