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HIGHLIGHT

Transition metal catalysis and nucleophilic fluorination

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Transition metal catalyzed transformations using fluorinating reagents have been developed extensively for the preparation of synthetically valuable fluorinated targets. This is a topic of critical importance to facilitate laboratory and industrial chemical synthesis of fluorine containing pharmaceuticals and agrochemicals. Translation to ^{18}F-radiochemistry is also emerging as a vibrant research field because functional imaging based on Positron Emission Tomography (PET) is increasingly used for both diagnosis and pharmaceutical development. This review summarizes how fluoride sources have been used for the catalytic nucleophilic fluorination of various substrates inclusive of aryl triflates, alkynes, allylic halides, allylic esters, allylic trichloroacetimidates, benzylic halides, tertiary alkyl halides and epoxides. Until recently, progress in this field of research has been slow in part because of the challenges associated with the dual reactivity profile of fluoride (nucleophile or base). Despite these difficulties, some remarkable breakthroughs have emerged. This includes the demonstration that Pd(0)/Pd(II)-catalyzed nucleophilic fluorination to access fluoroarenes from aryl triflates is feasible, and the first examples of Tsuji–Trost allylic alkylation with fluoride using either allyl chlorides or allyl precursors bearing O-leaving groups. More recently, allylic fluorides were also made accessible under iridium catalysis. Another reaction, which has been greatly improved based on careful mechanistic work, is the catalytic asymmetric hydrofluorination of *meso* epoxides. Notably, each individual transition metal catalyzed nucleophilic fluorination reported to date employs a different F-reagent, an observation indicating that this area of research will benefit from a larger pool of nucleophilic fluoride sources. In this context, a striking recent development is the successful design, synthesis and applications of a fluoride-derived electrophilic late stage fluorination reagent. This new class of reagents could greatly benefit preclinical and clinical PET imaging.

1. Introduction

The value of organofluorine[1] compounds as pharmaceuticals,[2,3] agrochemicals,[4] imaging agents and high performance material is unquestionable and has recently inspired an explosion of interest for synthetic fluorine chemistry.[5,6] One key factor crucial to support this research is the availability of robust synthetic routes relying on a wide range of convenient fluorinating reagents suitable to react with electron rich, electron neutral or electron deficient substrates. Well established and newly developed protocols for nucleophilic and electrophilic fluorination have allowed access to a plethora of high value functionalized molecules, so the challenge today is to develop more efficient reactions for C–F bond formation addressing the problems of reactivity and selectivity for poorly activated substrates. Cost effective protocols are highly sought after for most applications. The criteria to fulfill for the preparation of ^{18}F-radiotracers used for Positron Emission Tomography (PET) imaging are dramatically different compared to the ones to be met for conventional ^{19}F-fluorination. In a retro-radiosynthetic scheme, it is important to introduce the short half-life radioisotope ^{18}F ($t_{1/2}$, 109.8 minutes) as late and as rapidly as possible in the synthetic sequence to achieve maximum efficiency (high radiochemical yield). Moreover, [^{18}F]fluorination should ideally be performed using a [^{18}F]fluoride source in preference to [^{18}F]F_2 (or its derivatives) as most PET centers are not equipped to handle this highly reactive gaseous reagent and the radiotracers generated by [^{18}F]F_2-mediated electrophilic fluorination are typically produced in lower specific activity. Fluorinations catalyzed

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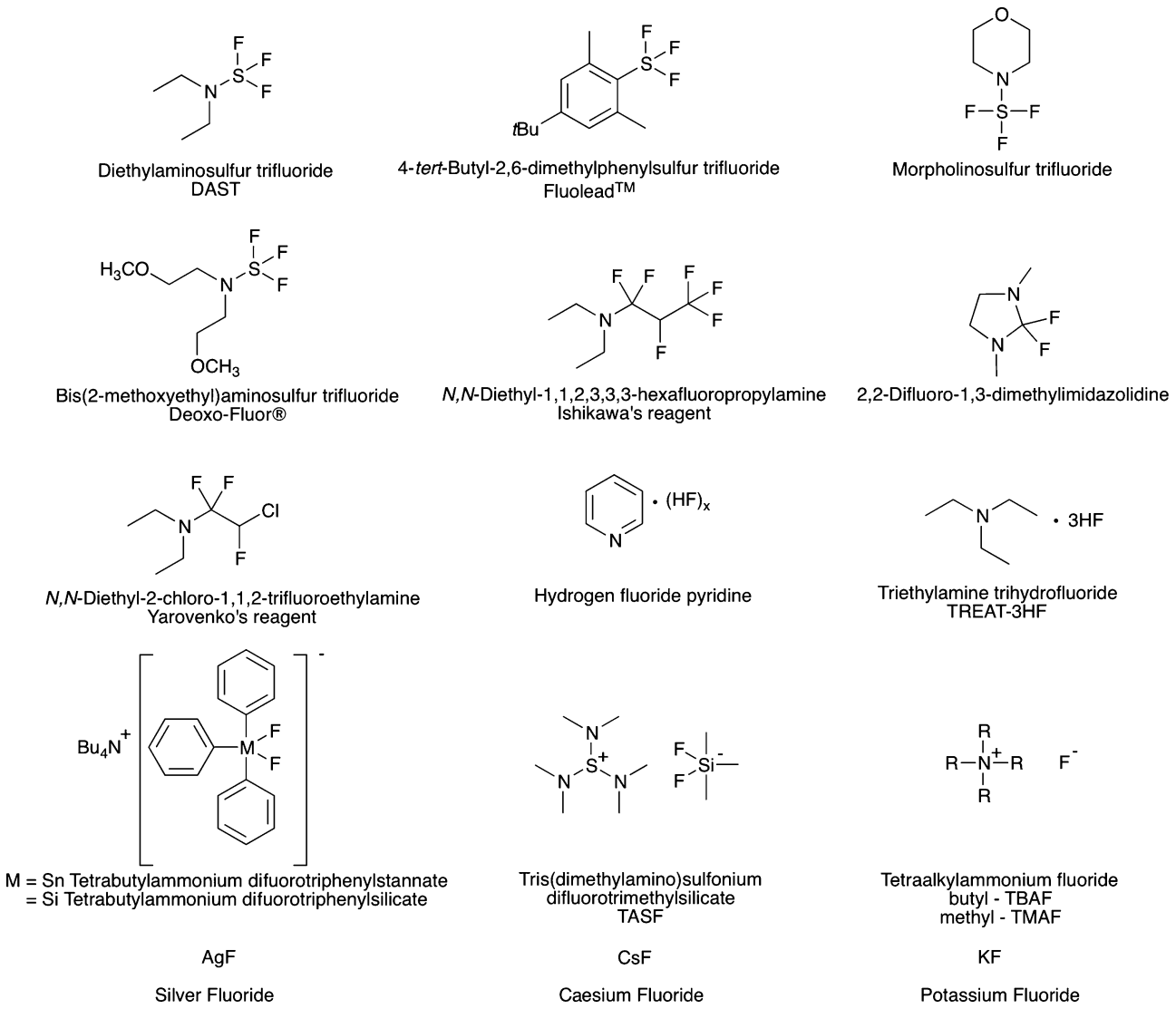

Fig. 1 A selection of nucleophilic fluorinating reagents.

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Véronique Gouverneur

Véronique Gouverneur received her undergraduate degree in chemistry at the Universite Catholique de Louvain (Belgium) where she also did her PhD with Prof. L. Ghosez. In 1992, she moved to a post-doctoral position with Prof. R. Lerner (Scripps Research Institute, USA). Veronique returned to Europe in 1994 with a research and teaching position at the University Louis Pasteur (Strasbourg, France). She started her independent research career at the University of Oxford in 1998, where she developed a research programme aimed at validating new approaches towards fluorinated molecules inclusive of natural products, pharmaceuticals and ^{18}F-labelled probes for imaging.

by transition metals have been extensively scrutinized and reviewed, especially reactions employing electrophilic fluorinating reagents. In this review, we have opted to discuss recent developments in transition metal catalyzed fluorination with nucleophilic fluorinating reagents only, an emerging area in catalysis.

The use of a fluoride ion for fluorination is not straightforward in part due to the challenges associated with poor solubility and its dual reactivity profile both as a nucleophile and a base. In its unsolvated form, fluoride is strongly basic and solvation through hydrogen bonding significantly affects its ability to act as a nucleophile. The successful development of transition metal catalyzed fluorination is directly dependent on the availability of competent, soluble fluoride sources and a clear understanding of the parameters that control nucleophilicity *versus* basicity (Fig. 1). When used in combination with crown ethers, alkali fluorides are suitable reagents for fluorination, the nucleophilicity decreasing with increased ionic strength. Tetraalkylammonium fluorides benefit from increased solubility in organic solvents; in this series, tetrabutylammonium fluoride is commercially available as a trihydrate or can be prepared as a complex with *t*BuOH. The complex TBAF(*t*BuOH)$_4$ displays reduced hygroscopicity and basicity, a set of desirable properties for nucleophilic fluorination.[7] When produced by substitution of hexafluorobenzene with cyanide, anhydrous tetrabutylammonium fluoride is more reactive and capable of nucleophilic aromatic fluorination at room temperature.[8] Anhydrous hydrogen fluoride is one of the most inexpensive fluorinating reagents but the low boiling point (19.6 °C) of this highly corrosive acid leads to logistic complications limiting its use. Stable solutions of HF with amines were reported and in the mid-seventies, Olah and co-workers demonstrated that pyridinium poly(hydrogen fluoride) is a stabilized highly versatile reagent for the fluorination of a large range of functional groups.[9] Various neutral reagents including Yarovenko's reagent,[10] Ishikawa's reagent[11] and 2,2-difluoro-1,3-dimethylimidazolidine have been developed with sulfur trifluoride derivatives such as diethylaminosulfur trifluoride (DAST),[12] bis(2-methoxyethyl)-aminosulfur trifluoride (Deoxofluor)[13] and the more recently-reported 4-*tert*-butyl-2,6-dimethylphenylsulfur trifluoride (Fluolead)[14] being the most common. Taken together, this collection of reagents is suitable for the fluorination of only activated substrates if no catalyst is used; the full potential of these various fluoride sources in transition metal mediated catalytic fluorinations for less activated substrates has not been demonstrated to date. At first glance, the choice of fluoride source is likely to be instrumental for a particular transition metal catalyzed fluorination to proceed as the best outcome may arise from the use of a direct fluoride ion source or *via* slow fluoride release in solution from neutral reagents. This highlight presents the state of play of this emerging field of research and describes how transition metal catalyzed processes have enabled the nucleophilic fluorination of poor electrophiles that cannot be fluorinated in the absence of catalysts and of substrates for which selectivity issues at various levels need to be addressed.

2. C(sp^2)–F bond construction

Fluoride sources are reluctant to react with weak electrophiles, for example poorly activated aromatic or heteroaromatic derivatives, or common electron rich reagents such as alkenes, motifs that are most useful for synthesis in pharmaceutical or agrochemical chemistry. Thus, the ability to carry out catalytic reactions that form these C–F bonds from fluoride sources would substantially facilitate the synthesis of molecules with important biological functions inclusive of high value ^{18}F-radiotracers featuring aryl motifs currently not amenable to direct nucleophilic ^{18}F-fluorination.

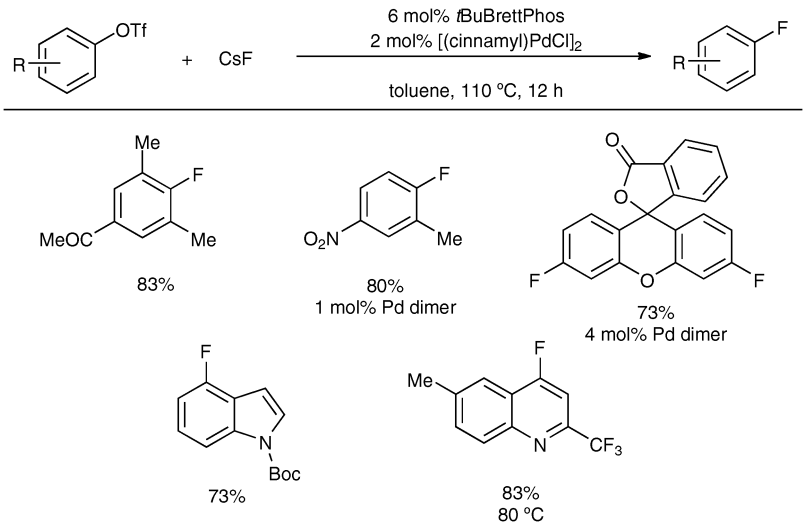
Aryl fluorides

For aryl nucleophilic fluorination, competitive elimination is not a primary concern, although fluoride mediated benzyne formation followed by fluorination has been reported in the literature.[15] Conventional S$_N$Ar nucleophilic substitutions are limited by harsh reaction conditions and substrates bearing an electron-withdrawing group. Transition metal mediated cross-coupling for Ar–F bond formation is an attractive approach to aryl fluorides which has the potential of increasing substrate scope and allowing for milder reaction conditions. The most demanding elementary step in the catalytic cycle of this process is reductive elimination from {Ar–metal–F}; this process has only been thoroughly investigated with late transition metals since they form weaker metal–F bond than early transition metals. Hartwig and co-workers' mechanistic work on the reactivity trend comparing {ArPd(II)–I}, {ArPd(II)–Br} and {ArPd(II)–Cl} would suggest that the equilibrium between {ArPd(II)–F} and ArF disfavours aryl–F bond formation but less so for aryl fluorides than for the other aryl halides.[16] However, reductive elimination to form a C–F bond is much more difficult than for carbon and other heteroatoms due in part to the high electronegativity of fluorine. The demonstration that the use of higher oxidation state {ArPd(IV)F} intermediates reduces the barrier to reductive elimination is a major conceptual advance in aromatic fluorination, which has fuelled intensive research.[17,18] In seminal work conducted by Sanford and co-workers, this catalytic transformation was elegantly validated using an electrophilic fluorinating reagent also acting as the oxidant.[19] In 2009, Buchwald *et al.* reported the first successful reductive elimination from {ArPd(II)F} complexes, which were prepared by halide displacement with nucleophilic fluoride.[20] This breakthrough achievement built on mechanistic work undertaken by Grushin,[21–25] Marshall and Yandulov.[26] Retrospectively, these studies undertaken prior to 2009 revealed that fluoride-bridged dimer formation ({PdArL(μ-F)}$_2$) is the main obstacle to C–F reductive elimination and formation of P–F containing products is a significant side reaction. These problems could therefore be addressed by preventing dimer formation. This could be achieved using ligands sufficiently bulky to induce interligand steric repulsion and the formation of three-coordinated T-shaped {Pd(II)Ar(F)} amenable to preferential C–F bond formation. These key findings emerged *inter alia* from careful theoretical work of Yandulov and co-workers who examined in great detail the activation enthalpies associated with reductive aryl–F bond formation.

In the context of aryl amination reactions, Buchwald *et al.* had identified monomeric complexes {LPdArX} (X = Cl or Br), containing the monophosphine ligand

BrettPhos (L1) as competent species to induce C–N reductive elimination.[27] Thus, the next logical step was to prepare analogous fluoride complexes from the reaction of the corresponding bromide with AgF. A significant finding was that the tricoordinated 14e$^-$ arylpalladium fluoride complexes {L1Pd(*o*-Me, *p*-$CF_3C_6H_3$)F} and {L1Pd(*o*-Me, *p*-CNC_6H_3)F} were found to be monomeric (confirmed by X-ray analysis) (Fig. 2) and thermolysis in toluene induced reductive elimination leading to the desired aryl fluorides in moderate yields (45% and 55%, respectively).

With the stoichiometric reaction in hand, further developments led to the first catalytic C–F bond formation *via* reductive elimination from a Pd^{II} complex using 5 mol% {(COD)Pd($CH_2TMS)_2$}, 10 mol% BrettPhos and 1.5 equivalents of AgF in toluene for 18 h at 130 °C. The more bulky ligand (*t*BuBrettPhos) was necessary to improve catalysis and scope. Under optimum conditions, nucleophilic fluorination of aryl triflates was observed in the presence of an excess of CsF, 2–5 mol% of the pre-catalyst {(cinnamyl)PdCl}$_2$ and 6–15 mol% of *t*BuBrettPhos (L2) at 110 °C in toluene under anhydrous conditions. The reaction led to the formation of aryl fluorides with a large range of electronic properties but has not been applied to substrates with protic functional groups that could engage in hydrogen bonding (Scheme 1). This limitation indicates that such substrates may affect fluoride nucleophilicity. For selected substrates, a mixture of regioisomers was observed. Although the mechanism for the formation of these regioisomers has not been determined, control reactions performed without catalysts show that regioisomer formation is a palladium catalyzed pathway and product distribution is not in keeping with a benzyne mediated process. Some control



Scheme 1 Pd(0)-catalyzed nucleophilic fluorination of aryl triflates.

of selectivity could be gained by the use of an apolar solvent such as cyclohexane, shown to favor the formation of the expected regioisomer. More recent mechanistic studies presented evidence that a modified phosphine (arylated ligand), generated *in situ*, serves as the actual ligand when electron rich aryl substrates are used. This observation suggests that a uniform mechanistic pathway is unlikely to operate over a large range of aryl precursors. Accordingly yields do vary as a function of aryl bromide stoichiometry.[28] The authors carried out further investigation with the view to access ^{18}F–aryl radiotracers for PET. Reaction times were significantly reduced (< 30 min), however only with the use of a large excess of fluoride (6 equivalents of CsF) and in some cases with the addition of a solubilizing agent (poly(ethyleneglycol) dimethyl ether) to give the aryl fluorides with yields up to 79%. Since the stoichiometry of the reaction will be reversed in radiolabelling ([^{18}F]fluoride becomes limiting), this reaction requires further optimization for PET applications.

The Pd(0)-catalyzed nucleophilic fluorination of aryl triflates is a remarkable breakthrough in the field and sets a very high standard for further developments.

The stringent requirement for an excess of dry CsF for this chemistry is limiting and highlights the difficulties associated with nucleophilic fluorination. The low solubility of anhydrous CsF in non-polar solvents also leads to practical complications such as inefficient mixing, yet it was found that increasing the amount of CsF increases the rate of this Pd(0)-catalyzed aromatic fluorination. This observation encouraged the use of a microflow packed-bed reactor. Under optimized conditions, the reaction was performed at 120 °C with a residence time of 20 minutes for all substrates. Excellent results were obtained with a wide variety of aryl precursors with relatively low catalyst loading (1.5–2 mol% Pd). The protocol was found to be suitable for continuous mode production allowing for the fluorination of 3 mmol of 1-naphthyl triflate without a decrease in yield or noticeable microreactor clogging over a period of up to 8 hours.[29]

In 2011, the Cu-catalyzed aryl C–F bond formation was developed.[82] The mechanism proposed is analogous with that of Pd, initial oxidative addition of the metal [Cu(I)–Cu(III)] into an aryl halide, exchange of the halide for F facilitated with the use of AgF, and a terminating reductive elimination releasing the product (Scheme 2). The halide exchange is suggested as the rate-limiting step in this reaction, a conclusion tentatively based on the observation that,

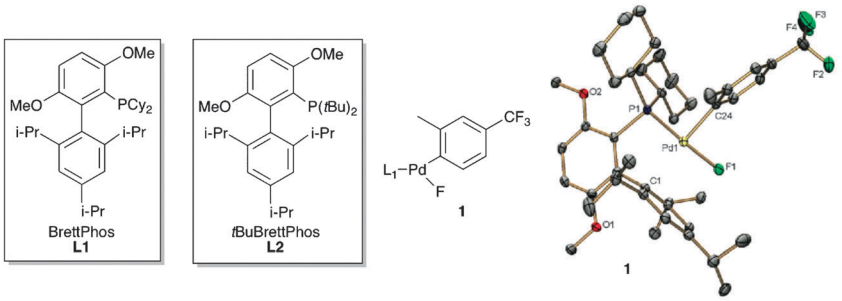


Fig. 2 A competent tricoordinated monomeric Ar–Pd–F species for aryl–F reductive elimination.

unlike other halides (Cl, Br and I), the Cu(III)–F complex could not be detected experimentally. The use of fluoride sources such as TBAF, TMAF and CsF showed no formation of the desired aryl fluoride.

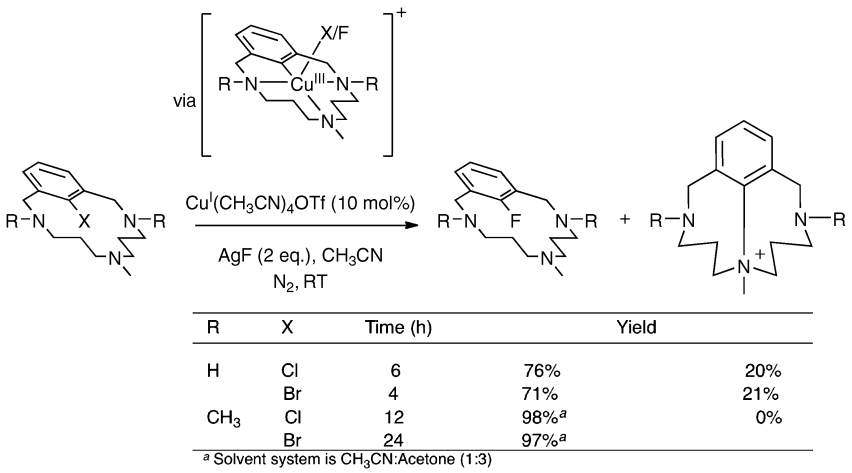
Transition metal mediated fluorination to the formation of ^{18}F–aryl bonds from ^{18}F-fluoride has recently been validated.[30] Nucleophilic [^{18}F]F$^-$ is advantageous for ^{18}F-radiolabeling as it is more widely available, easier to handle and is produced in higher specific activity than [^{18}F]F_2, a reagent which requires a carried-added protocol for its formation. Ritter *et al.* have established a synthesis of a Pd(IV)[^{18}F]fluoride from [^{18}F]fluoride that can be used as an electrophilic fluorinating reagent of high specific activity. This could provide a route to previously unattainable PET tracers as the fluorination step is no longer limited to nucleophilic methodologies. The synthesis is shown to give decay-corrected radiochemical yields (RCY) up to 33% in 10 min, with an overall reaction time of 60 minutes, short reaction times being essential with the short half-life of ^{18}F (109.8 min) (Scheme 3).

Alkenyl fluorides

Catalytic fluorination to access alkenyl fluorides has received less attention. This target structure raises the need to develop transformations that control double bond geometry and regioselectivity. Pd(0) catalyzed alkenyl–F bond forming cross-coupling reactions are not known but Sadighi *et al.* have followed an alternative line of research exploiting the ability of gold complexes to activate alkynes towards nucleophilic attack. The Sadighi group reported the first isolated gold(I) fluoride complex **2** in 2005 (Scheme 4).[31,32] The reaction of an excess of 3-hexyne with this gold complex in CH_2Cl_2 led to the formation of a new fluorinated species which was detected by ^{19}F-NMR after 10 minutes; this species was identified as the β-(fluorovinyl)gold complex, **3**. Removal of the solvent and alkyne at this stage allows for complete recovery of **2** due to the reversibility of this reaction. When the preformed cationic η^2-alkynylgold(I) complex **4** was reacted with $NEt_3{\cdot}3HF$ (triethylamine trihydrofluoride = TREAT-HF), the desired hydrofluorinated alkene **5** was detected in a 64% ^{19}F-NMR yield (Scheme 4). The mechanism of this transformation most likely involves nucleophilic attack of the fluoride onto complex (**4**) and subsequent protodemetalation of the resulting fluorinated alkenyl gold complex (**3**).[33]

For catalysis, the nature of the ligands on the gold was found to be very important. Sterically demanding NHCs were found to be superior for the stabilization of the catalyst and gave respectable yields of the desired fluoroalkenes. The use of $KHSO_4$ with $PhNMe_2{\cdot}HOTf$, as a CH_2Cl_2-soluble acid cocatalyst was also necessary to allow for higher levels of conversion. Under these reaction conditions, the hydrofluorination of alkynes bearing alkyl, aryl and heteroaryl substituents was possible. Moderate to good control over regioselectivity was observed for unsymmetrical alkynes. The nature of the (hetero)aryl groups flanking the starting alkyne was found to impact regioselectivity, the best outcome being observed with the electron-withdrawing *para*-acetylphenyl group or the thienyl substituent (Scheme 5).

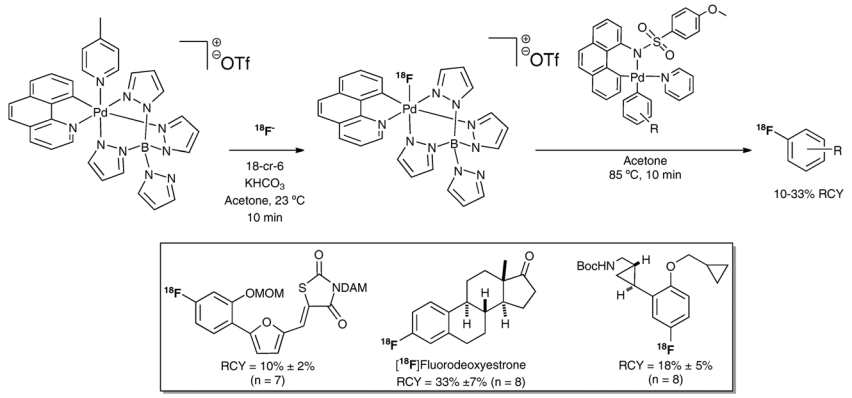
Further developments of this reaction by Miller *et al.*[34] allowed for reversal of regioselectivity by including ester or nitrogen-containing directing groups onto the alkyne. The best regioselectivities were seen with the carbamate containing a 2,2,2-trichloroethoxycarbonyl (Troc) sub-motif (Scheme 6).



R	X	Time (h)	Yield	
H	Cl	6	76%	20%
	Br	4	71%	21%
CH_3	Cl	12	98%[a]	0%
	Br	24	97%[a]	

[a] Solvent system is CH_3CN:Acetone (1:3)

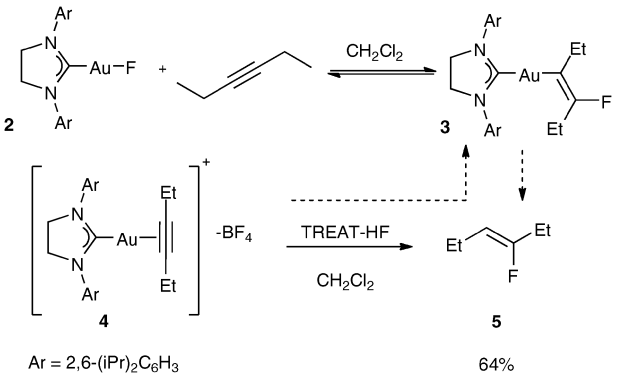
Scheme 2 Nucleophilic fluorination mediated by a Cu(I)/Cu(III) cycle.



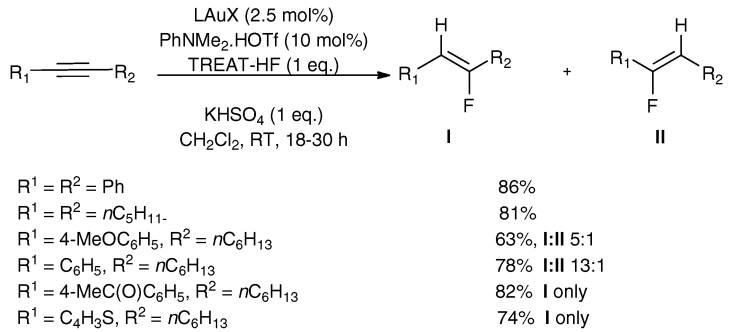
Scheme 3 Electrophilic late-stage fluorination reagent derived from [^{18}F]F$^-$.

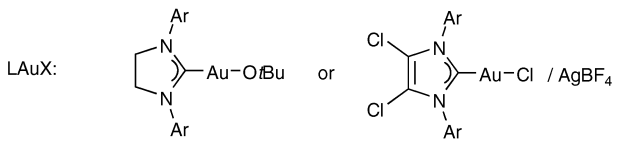
3. C(sp^3)–F bond construction

Uncatalyzed nucleophilic fluorination to install the fluorine substituent on an sp^3-hybridized carbon is a vast research field well reviewed in the literature.[35–38] Recently, catalytic fluorinations inclusive of asymmetric variants were developed using electrophilic fluorine sources. Electron-rich π-systems such as metal enolates,[39] enamines,[40–42] various organosilanes[43–45] and indoles[46] have been investigated in this context. Catalytic nucleophilic fluorinations are less common but are emerging at an increasing pace. To date, efforts were mainly (but not solely) focused

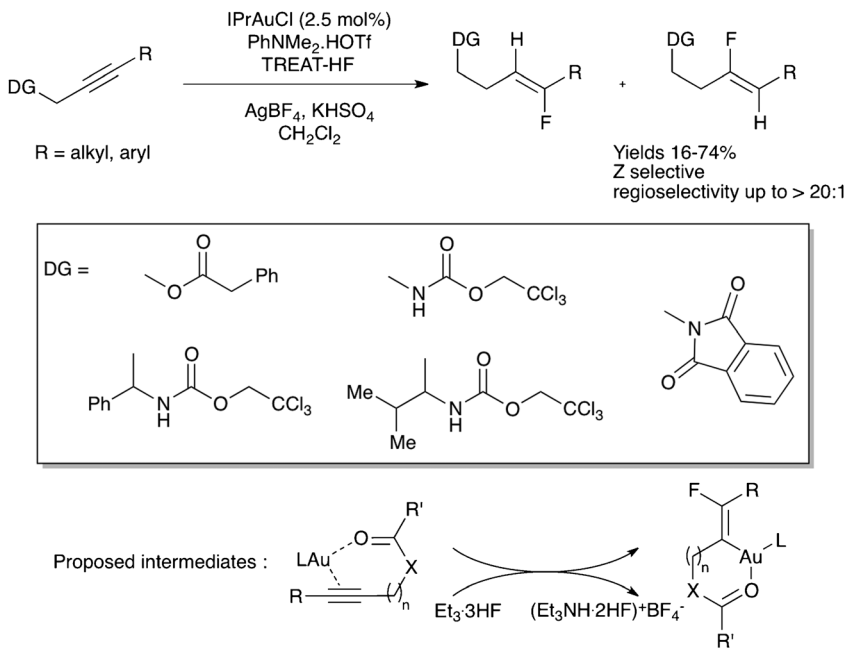


Scheme 4 Sadighi gold catalyzed hydrofluorination of alkynes.





Scheme 5 Substrate scope of gold-catalyzed hydrofluorination.



Scheme 6 Miller gold-catalyzed regiodirected hydrofluorination of alkynes.

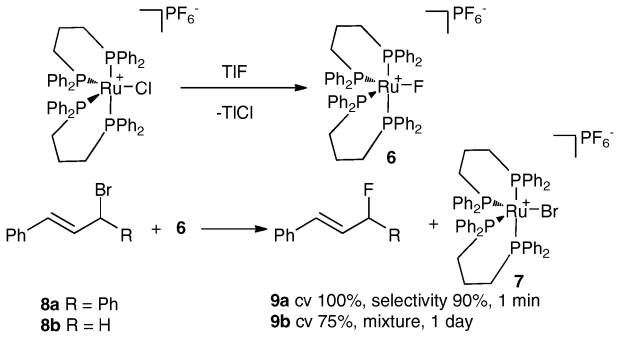
on transition metal catalyzed allylic fluorination of pre-functionalized substrates and on the opening of epoxides.

Allylic fluorides

The most common synthesis of allylic fluorides is the DAST-mediated fluorination of allylic alcohols reported by Middleton in 1975.[12] However, there are limitations to this method as only sterically or electronically biased substrates undergo fluorination with good levels of selectivity.[47] In electrophilic mode, these issues have been addressed using alkenes temporarily activated at the allylic position with a trimethylsilyl substituent, a group which also serves to induce regiocontrol upon fluorination with either Selectfluor or NFSI.[43] This approach is wide in scope and delivered a large collection of functionalized fluorinated compounds inclusive of enantiopure building blocks featuring the fluorine substituent on a stereogenic centre. In search of alternative regio- and stereoselective nucleophilic allylic fluorinations (ideally not requiring allylic pre-functionalization of the starting alkenes), late transition metallic species have been considered as catalysts to address these issues of reactivity and selectivity.

In 1999, Togni *et al.*[48] reported C–F bond formation *via* halide metathesis between the 16-electron penta-coordinated ruthenium fluoride complex, {[RuF(dppp)$_2$]PF$_6$} **6** (dppp = 1,3-bis(diphenylphosphino)-propane), and 1,3-diphenylallyl bromide **8a**, a process leading to the desired allyl fluoride in >80% ^{19}F NMR yield within a minute (Scheme 7). The only other successful synthesis of this sensitive allylic fluoride is the reaction of **8a** with fluoride sources such as TBAT or KF in DMF under rigorously dry conditions (complete exclusion of O_2 and H_2O). The Ru–F **6** mediated reaction is limited in scope as (*E*)-3-bromo-1-phenylpropene was found to be much less reactive than 1,3-diphenylallyl bromide and upon fluorination forms unidentified organic products.[49] Although a catalytic variant was not established for allylic fluorination, this work demonstrates that a metal–fluoride reagent is competent for nucleophilic allylic fluorination under mild conditions.

An attractive route to allylic fluorides is the Pd(0)-catalyzed Tsuji–Trost allylic



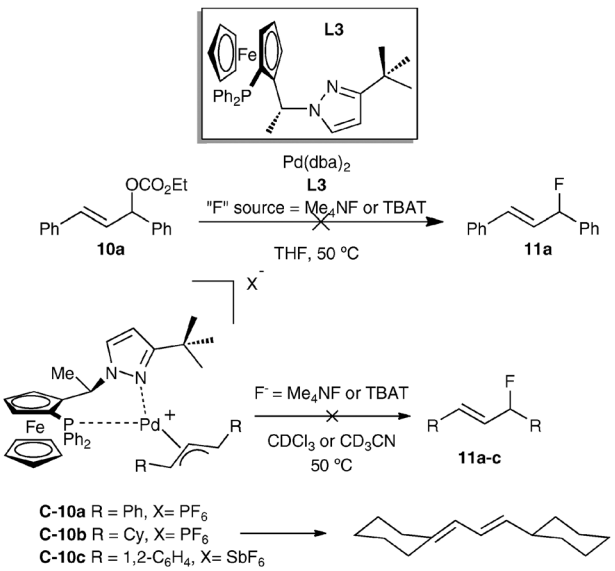
Scheme 7 Ruthenium fluoride complex **6** and its use in nucleophilic fluorination.

alkylation with fluoride as the nucleophilic reactant. The Tsuji–Trost reaction is a very powerful transformation for the attachment of a variety of carbo- and heteroatom nucleophiles to allylic electrophiles.[50] Asymmetric variants have increased the value of this reaction, which has found numerous applications in natural product synthesis.[51] Pd-catalyzed allylic alkylations are well documented especially with soft carbon nucleophiles. The use of heteroatom nucleophiles is much more challenging for various reasons. These nucleophiles can have significant affinities for the transition metal, a preference that may be detrimental for catalytic turnover or may interfere with productive complexation of the substrate to the metal catalyst. Heteroatoms are also typically harder nucleophiles and, if successfully introduced onto the substrates, may lead to products that are themselves susceptible to undergo the reverse reaction, a process that could affect control over enantioselectivity. All these challenges stand true for fluoride. In fact, fluoride salts have been used as additives in Pd-catalyzed allylation but not as the reacting nucleophile. For example, the presence of fluoride was found to improve control over enantioselectivity for allylic alkylation with amine nucleophiles.[52] More recently, Stang and White have used tetra-*n*-butylammonium fluoride (TBAF) to modulate the stereochemical outcome of an oxidative C–H macrolactonisation.[53] In both cases, the fluoride is believed to enhance the rate of π–σ–π isomerization of the η^3-allyl Pd complexes, presumably by interacting with a vacant coordination site on Pd.

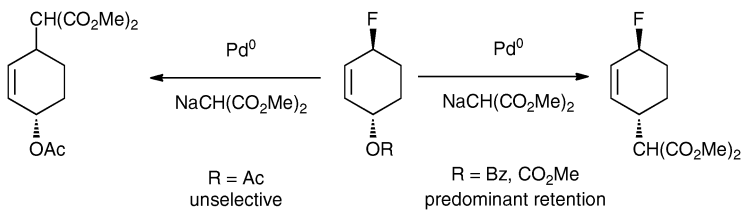
Togni *et al.* investigated the feasibility of a Pd-catalyzed allylic nucleophilic fluorination in 2006.[54] In a mechanistically oriented study, it was found that exposure of cationic Pd(II) allyl complexes **10a–c** to various fluoride sources at room temperature and 50 °C in $CDCl_3$ or CD_3CN showed no conversion to allylic fluoride (Scheme 8). However, diene formation was observed for substrates able to undergo elimination reactions, such as 1,3-dicyclohexyl-substituted Pd(II) allyl complexes, when exposed to fluoride. The analogous Pt(II) allyl complex of **C-10a** also failed to give the desired allylic fluoride when treated with Me_4NF in toluene, with anion exchange of PF_6^- and F^- taking place instead. Togni *et al.* came to the conclusion that the stoichiometric fluorination of these η^3-allyl Pd or Pt complexes is not thermodynamically feasible as oxidative addition of the allylic fluoride to Pd(0) was shown also to be facile.

This collection of data encouraged the Gouverneur and Brown groups to examine allylic C–F bond activation under Pd(0) catalysis in more detail. This work was carried out with the aim to probe the leaving group propensity of an allylic fluoride in Pd-catalyzed substitutions with a malonate nucleophile. For the allylic systems investigated, carbonate was found to be a superior leaving group to fluoride, and fluoride more labile than acetate (Scheme 9).[55]

This discovery prompted further studies and led to the demonstration that allylic fluorination of allyl carbonates with TBAF·4*t*BuOH is feasible.[56] A *p*-nitrobenzoate was identified as a superior leaving group than carbonate, an interesting observation since the use of this leaving group in classical palladium chemistry is sparse in the literature.[57,58] Allylic nitrobenzoates containing aryl groups substituted with electron withdrawing or

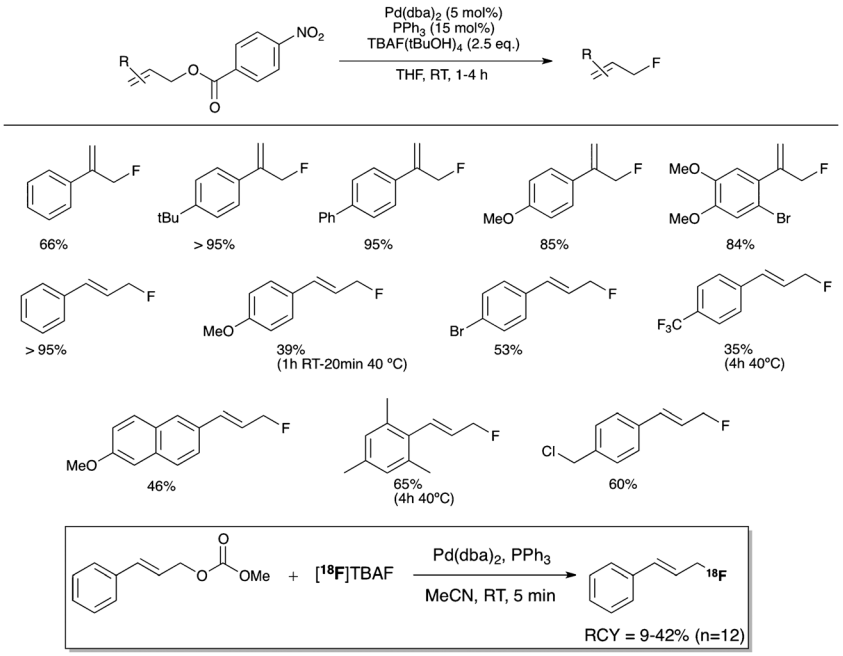


Scheme 8 Togni mechanistic studies towards allylic fluorination.



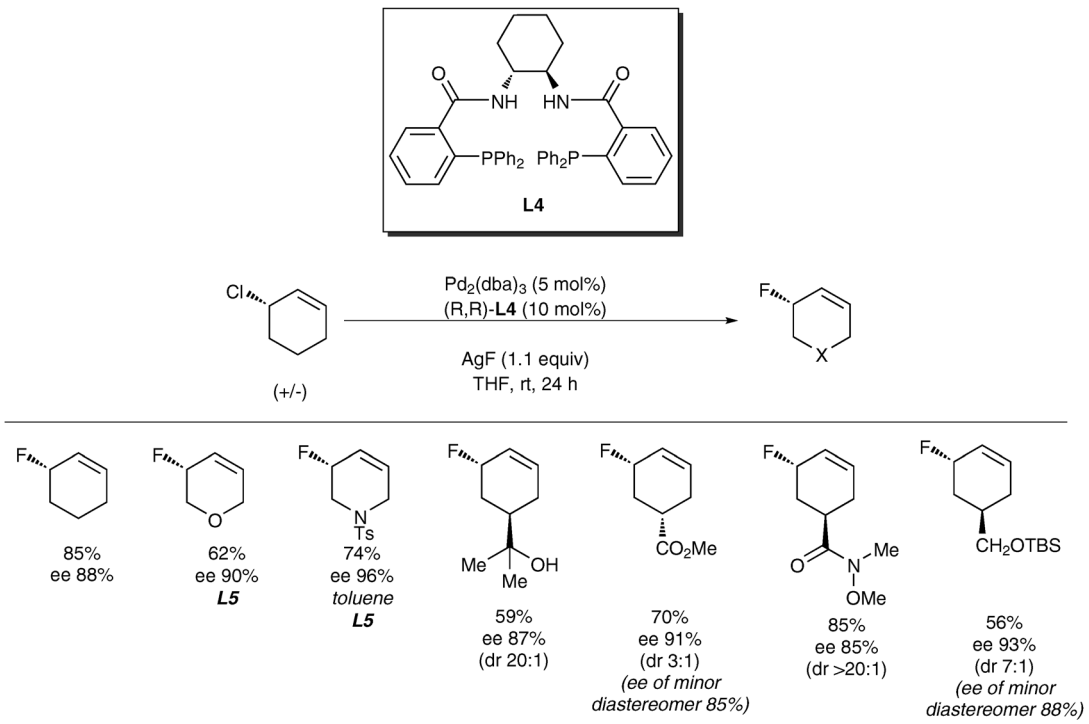
Scheme 9 Leaving group propensity of F, AcO^-, BzO and $MeOCO_2$ for Pd-catalyzed allylic alkylation.

donating groups were suitable substrates as reflected by the high yields of products; allyl fluorides conjugated with electron rich substituents were formed in lower yields as these compounds are more sensitive to work-up conditions. Nonetheless, the mildness of this reaction is demonstrated by the synthesis of cinnamyl fluoride in a >95% isolated yield, a compound known to be unstable on standing at room temperature.[59] This methodology was tolerant of sterically hindered substrates (mesityl groups) and those containing easily modified functional groups such as aryl bromide or benzylic chloride sub-motifs. For precursors that could lead to two regioisomeric products, only the linear allylic fluoride was formed with no detectable trace of branched allylic fluoride as determined by ^{19}F NMR of the crude reaction mixture prior to purification. A further benefit of this transformation is the availability of the starting nitrobenzoates, which can be obtained easily from the corresponding allylic alcohols. Problems were seen with substrates capable of competing elimination reactions as large amounts of diene were formed predominantly. In accordance with the findings of Togni *et al.*,[54] the reactions of ethyl-1,3-diphenylallyl carbonate/benzoate under the optimized reaction conditions did not furnish any fluorinated product. Further development of this reaction led to the first palladium mediated ^{18}F-fluorination at an allylic position. For the radiochemistry work, the methyl carbonate was found to be the superior leaving group. This development is the first step towards the transition metal mediated synthesis of ^{18}F-radiolabelled compounds (Scheme 10).



Scheme 10 Pd(0)-catalyzed ^{19}F and ^{18}F fluorination of allylic *para*-nitrobenzoates and carbonates.

Doyle and co-workers reported an alternative solution for Pd(0)-catalyzed allylic fluorination.[60] In a preliminary investigation, a cyclic palladium(II)allyl complex[61,62] formed from the corresponding allyl chloride[63] underwent fluorination with AgF, delivering the product in 49% yield (NMR yield) along with 4% yield of the undesired product of elimination.



Scheme 11 Pd-catalyzed asymmetric allylic fluorination of cyclic allylic chlorides.

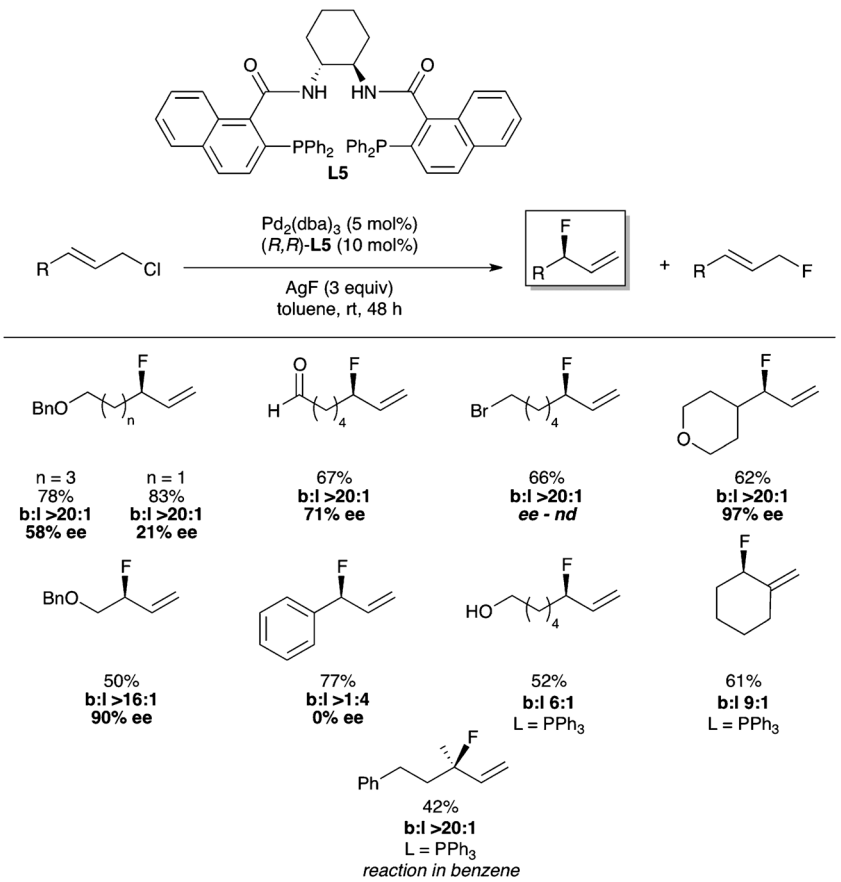
The subsequent successful development of a catalytic variant for this reaction offered the possibility to define a protocol for enantioselective fluorination. A chiral biphosphine-ligated palladium catalyst derived from the commercially available Trost ligand,[64] (1*R*,2*R*)-(+)-1,2-diaminocyclohexane-*N*,*N*′-bis(2-diphenylphosphinobenzoyl), **L4** promoted the fluorination of a series of cyclic fluorides with synthetically useful yields and enantiomeric excesses (up to 96%). For this reaction, alternative leaving groups conventionally used in palladium catalyzed allylic alkylations were not reactive. When a bifunctional substrate offering the possibility to react at either the allylic chloride or the allylic carbonate was subjected to fluorination, chemoselective attack of the fluoride on the allyl chloride was the sole process taking place. Since this reaction is clearly limited to allylic chlorides, the formation of AgCl is likely to provide the driving force for C–F bond formation. Control reactions confirmed that direct S_N2 reaction is suppressed at room temperature in non-polar solvents, suggesting that this uncatalyzed process is not affecting control of enantioselectivity. The reaction was shown to be tolerant of a wide range of functional groups inclusive of those potentially amenable to react with fluoride (*e.g.* silyl-protected alcohols). In this study, the reaction appeared to be limited to six-membered allylic chlorides with initial results on five and seven-membered rings showing reduced yields and enantiomeric excesses. Mechanistically, the authors proposed that oxidative addition of Pd(0) into the allyl chloride is followed by an S_N2-type outer-sphere attack of the fluoride on the allyl ligand to give the product with overall retention of configuration. This would suggest that the stereochemical outcome of this process is in line with what would be typically expected from the use of a soft nucleophile, not a hard nucleophile such as fluoride (Scheme 11).

This work was extended to the $Pd_2(dba)_3$/**L5** catalyzed fluorination of acyclic linear allylic chlorides, a reaction leading to branched allylic fluorides in good yields, good to high branched/linear ratios (1 : 4 to > 20 : 1) and poor to high level of enantioselectivity (0–97%).[65] The preference for the formation of branched products is unclear but proposed to arise due to the small size of the fluoride and possible hydrogen bonding interaction with the chiral ligand. The regiodirected delivery of nucleophile (other than fluoride) facilitated by hydrogen-bonding with the concave orientated amide N–H in cationic Pd–η^3-allyl and Pd–η^3-cyclohexenyl bearing *trans*-cyclohexylenediamine-based Trost 'Standard Ligand' has been discussed previously by the research groups of Lloyd-Jones and Norrby.[66] In accordance with cyclic allylic fluorides, the use of toluene as the solvent was essential to avoid competing background reactions and allow for control over enantioselectivity. The reaction was shown to be tolerant of a wide range of functionalities with some exceptions; the presence of a free alcohol in the starting allylic chloride led to competitive intramolecular capture of the transiently formed Pd–η^3-allyl complex and the chemical yield of tertiary fluorides did not exceed 45% due to unwanted diene formation (Scheme 12).

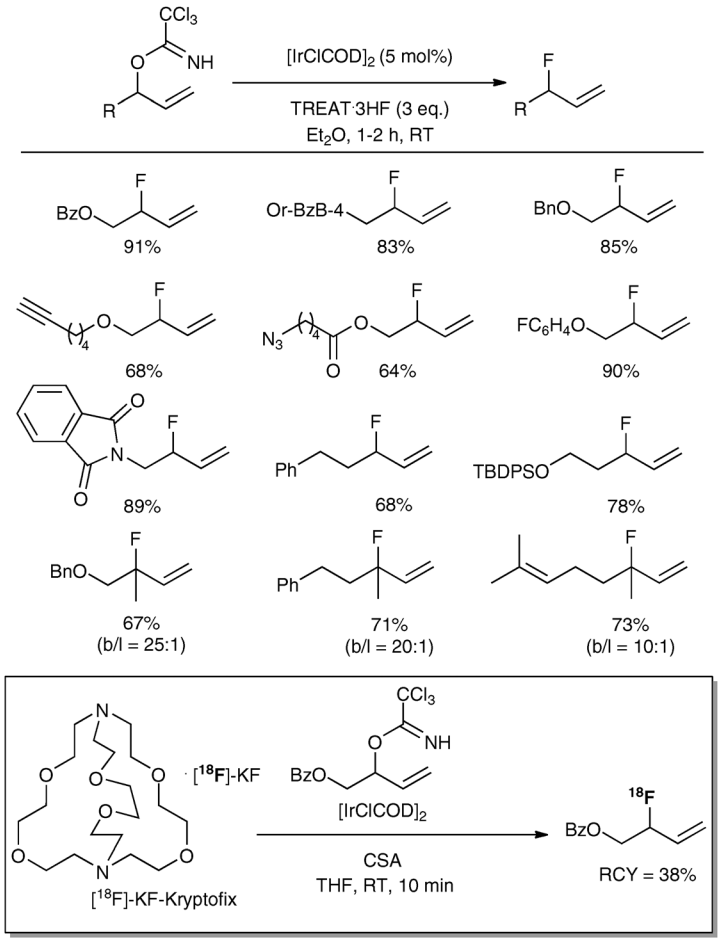
Nguyen *et al.* have also recently reported the preparation of secondary and tertiary racemic allylic fluorides from allylic trichloroacetimidate under iridium catalysis (5 mol% $\{Ir(COD)Cl\}_2$) (Scheme 13).[67] Triethylamine trihydrofluoride (TREAT·3HF) was found to be the optimized source of fluoride allowing moderate to good yields of secondary branched allylic fluorides to be obtained. Tertiary allylic fluorides though accessible by this route could not be isolated owing to polymerization or decomposition. This rapid and functionally tolerant reaction has also been extended to the preparation of a representative [^{18}F]-allylic fluoride in 38% RCY (decay-corrected).

Benzylic and alkyl fluoride

Few examples of transition metal catalyzed nucleophilic fluorination of benzyl and alkyl halides were reported in the literature. Early investigations revealed that $\{PdF(Ph)(PPh_3)_2\}$ undergoes halide metathesis with CH_2Cl_2 to afford a mixture of CH_2ClF and CH_2F_2.[68] This process has not been further investigated for catalysis. Bergman *et al.* described the synthesis of $Cp^*(PMe_3)Ir^{III}(Ph)F$ in 1995 (Scheme 14).[69] This complex was



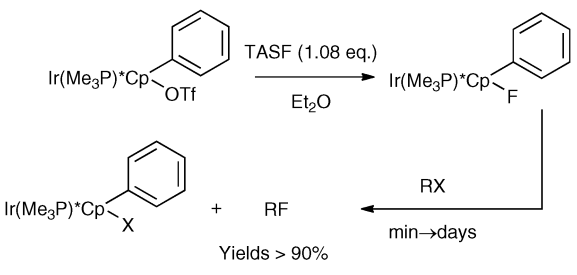
Scheme 12 Asymmetric catalytic fluorination of linear allyl chlorides leading to branched allyl fluorides.



Scheme 13 Ir-catalyzed fluorination of allylic trichloroacetimidates.

shown to undergo reactions with organic halides to yield the corresponding fluoride including benzyl fluoride in >90%.

In 2001, Togni *et al.* reported the catalytic nucleophilic fluorination of S_N1-type substrates in the presence of 1–10 mol% of the 16 electron ruthenium(II) complex $\{[RuCl(dppe)_2]PF_6\}$ (***cat*A**) and thallium fluoride, a reagent which acts both as the source of fluoride and as halide scavenger.[70] Various benzylic and *tert*-butyl alkyl fluorides were formed with chemical yields ranging from 31% to 83%. The fluorination of *trans*-1,2-dibromo-1,2,3,4-tetrahydronaphthalene is highly regioselective and gives *trans*-1-fluoro-2-bromo-1,2,3,4,-tetrahydronaphthalene **15** in 68% yield after three days (Scheme 15). The retention of configuration at C(1) can be explained by a neighboring group mechanism involving the formation of a bromonium intermediate. Alkyl halides such as 2-iodopropane and cyclohexyl bromide are completely unreactive suggesting significant charge separation in the transition state of the halogen transfer reaction. This is consistent with the lack of reactivity of ketones bearing a halide on the α-position. A further limitation of this chemistry is the poor tolerance for functional groups. Protic substrates such as alcohols and carboxylic acids do not undergo fluorination owing to the formation of HF. The chiral complex $\{[RuCl(PNNP)_2]PF_6\}$ (PNNP = (1*S*, 2*S*)-*N*,*N*′-bis[2-(diphenylphosphino)benzylidene]diaminocyclohexane) (***cat*B**) is a competent catalyst for the fluorination of PhCH(Me)Cl into PhCH(Me)F, **14** (49% yield after 24 h). Monitoring of this reaction showed that at 1% conversion the product **14** is obtained with an enantiomeric excess of 16%.

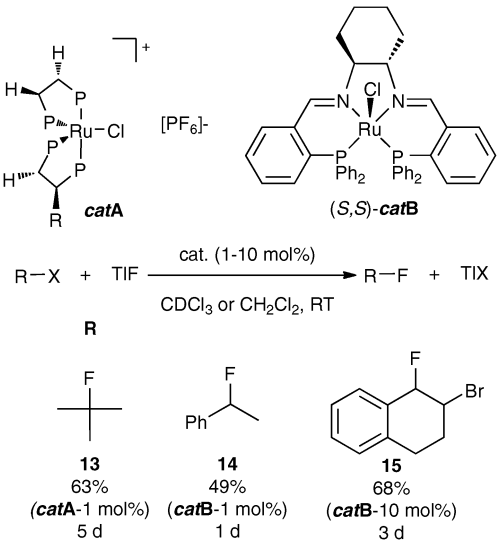


Scheme 14 Bergman *et al.* Cp*(PMe$_3$)Ir(Ph)F complex.

The formation of enantioenriched **14** led the authors to suggest the involvement of the chiral metal complex in the reaction. Two mechanistic scenarios are cautiously proposed. Coordination of the metal centre could increase the polarization of the C–X bond and promote σ bond metathesis (M1). Alternatively, the five coordinate Ru complex could act as a TlF carrier and the resulting $\{Tl(\mu\text{-}F)_2Ru(P\text{–}P)_2\}^+$ could then act as chloride scavenger and fluoride source as depicted in **M2**. Preliminary control experiments seem to favor **M1** (Fig. 3). This work is significant as it represents an early example of transition metal catalyzed nucleophilic fluorination *via* substitution despite its narrow scope and the necessity to use the toxic and expensive fluoride source TlF.

Fluorohydrins

The hydrofluorination of epoxide **16** is a well-documented reaction accelerated by various catalysts inclusive of metal species. HF-containing reagents such as pyridine·*n*HF are suitable for the ring opening of epoxides but, when used in combination with chiral Lewis acids, problems arise due to competitive uncatalyzed pathways and catalyst inhibition. Well-aware of these complications, Haufe desymmetrized cyclohexene oxide using KHF_2/18-crown-6 in the presence of 100 mol% of Jacobsen's (*S*,*S*)-(+)-(salen)chromium chloride complex **24a** in DMF at 60 °C.[71] *trans*-2-Fluorocyclohexanol **17** was formed in 55% ee along with *trans*-2-chlorocyclohexanol **18** (20% ee) (Scheme 16). Using 10 mol% of



Scheme 15 Ruthenium catalyzed allyl fluorination.

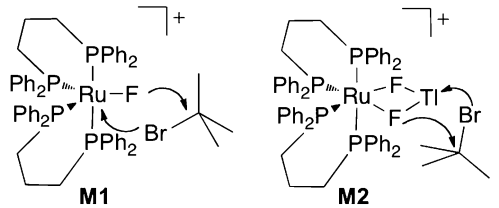
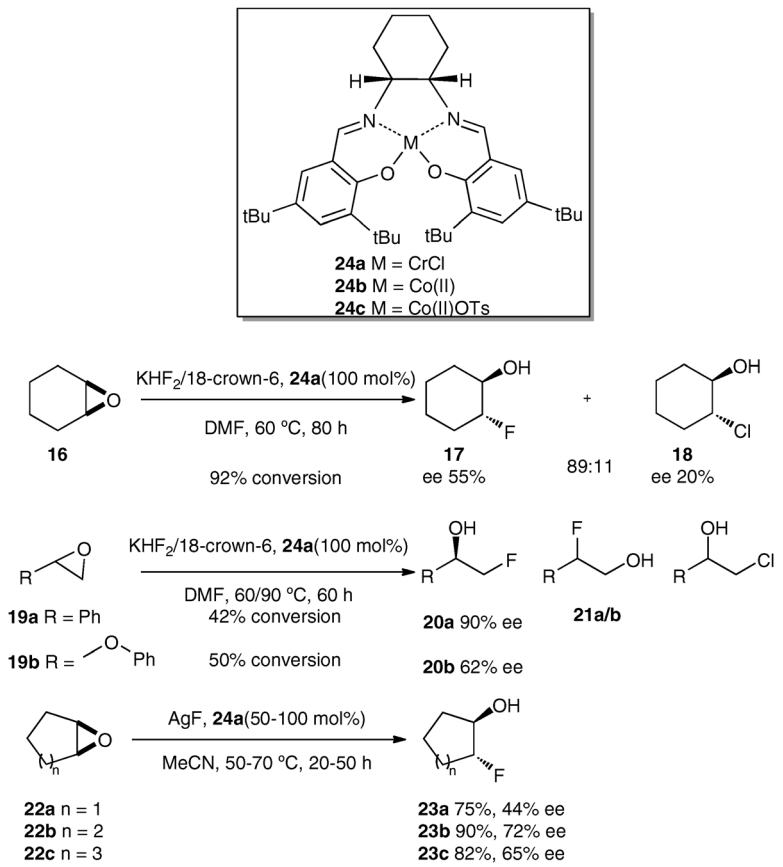


Fig. 3 Proposed mechanism for the Ru-catalyzed fluorination of *tert*-butyl bromide.

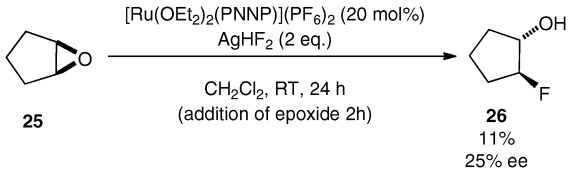


Scheme 16 Enantioselective fluorination *via* epoxide opening with a (*S*,*S*)-(+)-(salen)Cr/Co complex.

24a, the ee of the fluorohydrin decreased to 11%. These reactions constitute the first enantioselective nucleophilic fluorination by desymmetrization of *meso* precursors. When subjected to fluorination, the racemic epoxide styrene oxide **19a** and phenyl glycidylether **19b** led to preferential attack of the fluoride at the less substituted carbon. The products **20a** and **20b** were formed in 90% and 62% ee respectively. Further investigations explored the value of different fluoride sources; for some substrates, silver fluoride was found to be a superior reagent by preventing the formation of undesired chlorohydrin and delivering the fluorocyclohexanol **23b**, fluorocyclopentenol **23a** and fluorocycloheptanol **23c** with ee of 72%, 44% and 65% respectively.[72,73] The clear drawback of these reactions is the necessity to use 100 mol% or at best 50 mol% of the metal complex.

In 2009, Mezzetti *et al.* revisited the catalytic enantioselective desymmetrization of *meso* epoxides with the aim to define a more efficient catalytic system.[74] Cyclopentene oxide **25** underwent ring opening with $AgHF_2$ in the presence of 20 mol% of either $\{[RuCl(PNNP)_2]PF_6\}$ or the dicationic complex $\{[Ru(OEt_2)_2(PNNP)](PF_6)_2\}$. The best results were obtained by adding the epoxide over 2 h to a solution of $\{[Ru(OEt_2)_2(PNNP)](PF_6)_2\}$ (20 mol%) in CH_2Cl_2 and 2 equivalents of $AgHF_2$. Under these conditions, the ring opened fluorinated product **26** was isolated in 11% yield and 25% ee (Scheme 17). Competing polymerization was responsible for the low isolated yield of this transformation. Alternative fluoride sources such as $Et_3N{\cdot}3HF$, $(Bu_4N)H_2F_3$, KHF_2 and PhCOF led only to epoxide polymerization or gave no conversion at all.

The same reaction on *cis*-stilbene oxide gave fluorodiphenylacetaldehyde, a product likely formed *via* a Meinwald rearrangement involving a [1,2]-phenyl shift followed by α-fluorination of the resulting aldehyde. This mechanistic pathway was supported by control experimentation confirming that the treatment of diphenylacetaldehyde with $AgHF_2$ in the presence of 20 mol% of $\{[Ru(OEt_2)_2(PNNP)](PF_6)_2\}$ did not lead to the formation of fluorohydrins but gave 31% yield of fluorodiphenylacetaldehyde. In essence, this reaction is an oxidative fluorination of an aldehyde, a unique process complementing the numerous

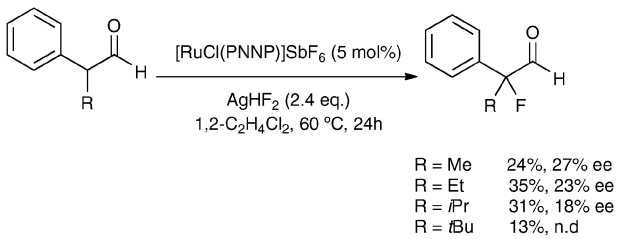


Scheme 17 Ru-catalyzed fluorination of cyclopentene oxide.

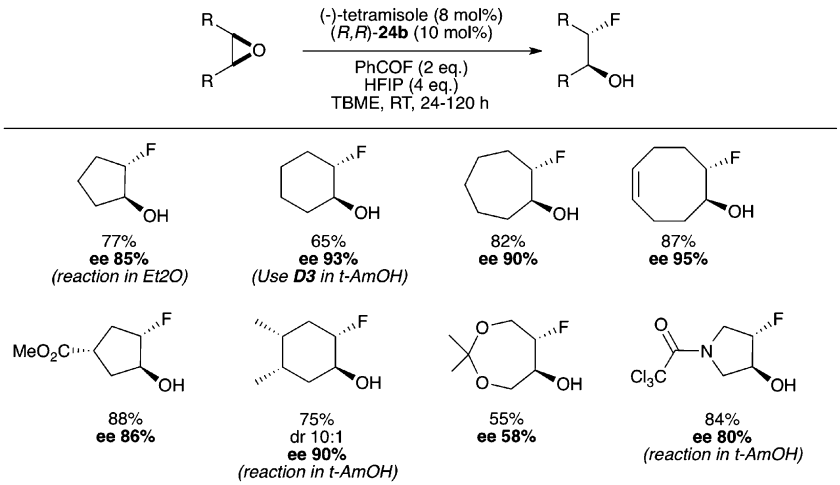
asymmetric catalytic protocols known for electrophilic fluorination of carbonyl derivatives.[37,75–79] Optimization studies indicate that the fluorination of diphenylacetaldehyde was best performed with the pentacoordinated complex {[RuCl(PNNP)$_2$]SbF$_6$} (5 mol%) and 2.4 equivalents of AgHF$_2$ in 1,2-dichloroethane at 60 °C for 24 h. The scope for this reaction is restricted to secondary aldehydes bearing both an aryl and an alkyl in the α-position. The catalyst {[RuCl(PNNP)$_2$]SbF$_6$} (5 mol%) induced some level of enantiocontrol for the fluorination of 2-phenylpropionaldehyde but the reaction is globally inefficient as the product was only isolated in 24% yield and 27% ee. Mechanistically, the author proposed a chemical oxidation (Ag^+ as the oxidant) followed by nucleophilic fluorination of an *in situ* generated oxa-allyl complex of Ru(IV) or the corresponding Ru(II) complex of an α-carbonyl cation (Scheme 18).

In 2010, Kalow and Doyle reinvestigated the catalytic asymmetric fluorination of *meso* epoxides with a strategy aimed at releasing a reactive form of HF *in situ* upon addition of 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) to benzoyl fluoride in the presence of an amine catalyst.[80] An asymmetric variant of this protocol was successfully implemented (yields up to 88% and ee ranging from 58% to 95%) performing the hydrofluorination of various *meso* epoxides in TBME using both the chiral isothiourea (−)-tetramisole (8 mol%) and the chiral (salen)Co complex **24b** (10 mol%) as catalysts (Scheme 19). The limitation of this chemistry is the long reaction time (24–120 h). Control reactions with achiral amines or the use of a mismatched Lewis acid/amine pair had a detrimental impact both on yield and enantioselectivity, an observation supporting the synergic cooperative effect of the two chiral co-catalysts. *Meso* cyclic epoxides containing alkene, ester and protected amine functionalities were all amenable to hydrofluorination under the optimized reaction conditions or slightly readjusted variants (*t*-AmOH or diethylether as the solvent). When applied to racemic terminal epoxides, kinetic resolution took place delivering the fluorohydrins (regioselective opening at the terminal position) with ee ranging from 88 to 99% (k_{rel} up to > 300) (Scheme 20).

Further studies shed light on the mechanism of this hydrofluorination.[81] The rate limiting step, the fluoride ring opening event, is proposed to proceed *via* a bimetallic mechanism based on non-linear effect studies with monomeric (salen)Co catalysts and experiments using a linked catalyst. A kinetic profile with apparent first-order dependence on (salen)Co was observed. To account for these data, the authors propose a mechanism involving a cobalt fluoride as the active nucleophilic fluorine species that forms a resting state dimer. In this mechanistic scenario, axial ligation of the amine cocatalyst to (salen)Co can facilitate dimer dissociation and is accounting for the observed cooperativity. Taken together, these insights led to the design of a second generation dimeric catalyst displaying dramatically improved efficiency (shorter reaction time).



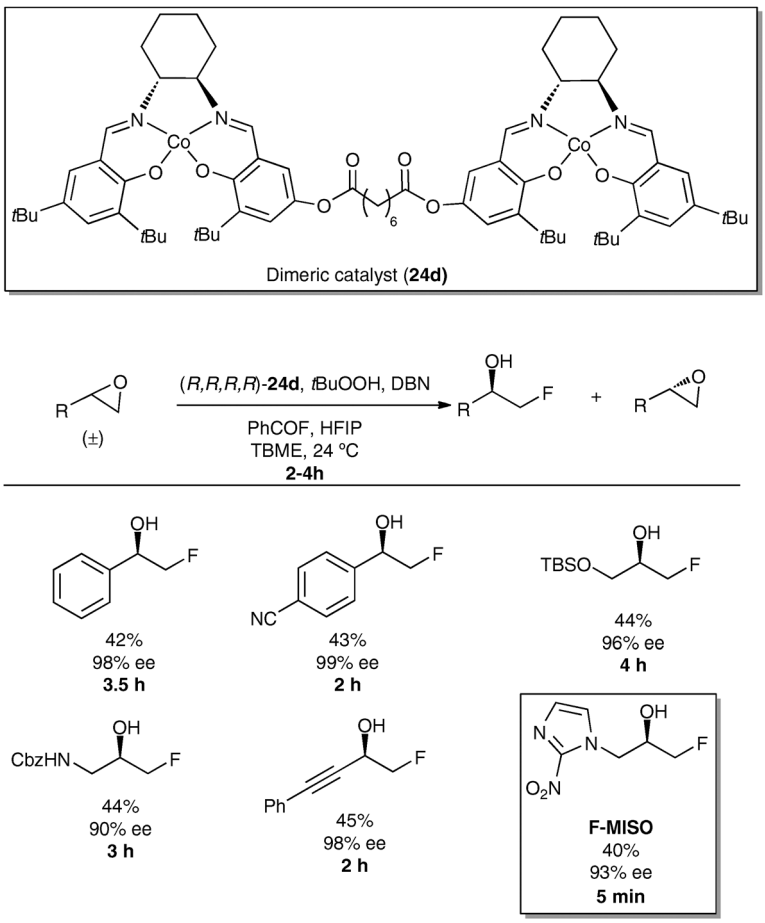
Scheme 18 Ru-catalyzed asymmetric oxidative α-fluorination of aldehydes.



Scheme 19 Cooperative co-catalyzed asymmetric fluorination of *meso* epoxides.

4. Conclusion

Although great progress has been made in the field of transition metal catalyzed fluorination, the dominance of processes relying on electrophilic fluorine sources is clear with only a handful of reactions using fluoride based reagents. However, the reactions presented in this review indicate that transition metal catalysis is emerging as a powerful tool to facilitate the nucleophilic fluorination of poorly activated substrates. Important breakthroughs include the demonstration that Pd(0)/Pd(II)-catalyzed nucleophilic fluorination to access fluoroarenes from aryl triflates is feasible, and the first examples of Tsuji–Trost allylic alkylation using either allyl chlorides or allyl precursors bearing O-leaving groups under Pd or Ir catalysis. Another reaction, which has been greatly



Scheme 20 Improved catalytic enantioselective fluorination of epoxides (kinetic resolution).

improved, based on careful mechanistic work, is the catalytic asymmetric hydrofluorination of epoxides. The body of work accomplished to date establishes that this chemistry is heavily dependent on the nature of the fluoride source. It is remarkable to note that each known transformation uses a different fluoride source, an inorganic fluoride salt for aryl and allylic fluorination, an ammonium fluoride salt for the allylic fluorination of allyl carbonates and allyl *para*-nitrobenzoates, triethylamine trihydrofluoride for the gold-catalyzed *trans*-hydrofluorination of alkynes and benzoyl fluoride, a reagent releasing fluoride upon treatment with an alcohol under amine catalysis for the fluorination of epoxides. Currently, the choice of the reagent is typically the result of extensive optimization studies but, ideally, a better understanding of the precise factors that enhance nucleophilicity/basicity and fluoride affinity for a defined transition metal species should drive this selection process. The field could benefit from the availability of a wider range of fluoride sources allowing researchers to make a more rational choice on which reagent to use. A deeper insight of the elementary steps of the reaction mechanism under investigation will also accelerate the development of catalytic nucleophilic fluorination for synthetic applications. This has already been elegantly demonstrated with the fluorination of *meso* epoxides under Lewis acid/amine cooperative catalysis. As for other catalytic processes, the wish list for the ideal nucleophilic fluorination process is long and includes a broad scope of substrates, tolerance for functional groups, fast rates, high turnover numbers, high control over selectivity, low cost and minimal side reaction pathways. At present, substrates that feature functional groups capable of hydrogen bonding are problematic and the necessity for some of these reactions to be conducted under anhydrous conditions is limiting as these conditions enhance fluoride basicity. Another important goal is the development of new catalytic systems for the direct fluorination of feedstock substrates by C–H bond functionalization. Finally, it is noteworthy that transition metal mediated fluorination has the potential to greatly advance ^{18}F-radiochemistry. The first Pd-mediated ^{18}F–C bond formation has been validated with a representative allylic alkylation. $\{Ir(COD)Cl\}_2$ was also found to be a competent complex for the allylic [^{18}F]fluorination of an allylic trichloroacetimidate. More recently, an additional Pd-mediated ^{18}F–C reaction has been disclosed allowing for electron rich aryl motifs to be fluorinated using a [^{18}F]fluoride source. These accomplishments are highly significant as they indicate that transition metal mediated nucleophilic fluorination can facilitate the production of ^{18}F-labelled radiotracers for Positron Emission Tomography (PET) imaging.

Acknowledgements

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