Advanced Synthesis & Catalysis

Very Important Publication

DOI: 10.1002/adsc.201500321

Palladium-Catalysed C–H Bond Electrophilic Fluorination of Highly Substituted Arylpyrazoles: Experimental and DFT Mechanistic Insights

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Received: March 31, 2015; Revised: June 10, 2015; Published online: September 10, 2015

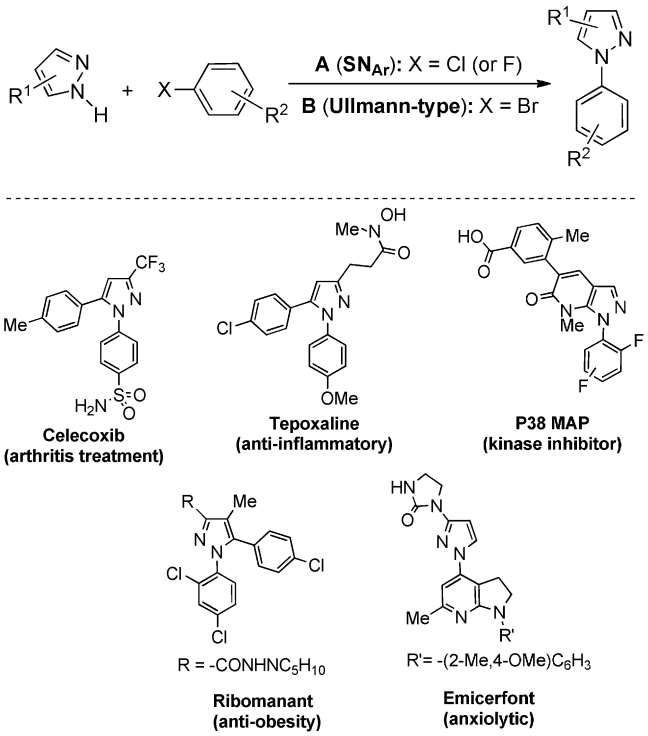
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201500321.

Abstract: A general protocol for palladium-catalysed C–H mono- and di-fluorination of highly substituted arylpyrazoles is reported. Coupling pathways and substrate limitations are discussed in the light of complementary mechanistic experimental and density functional theory (DFT) studies. The mono- and di-*ortho*-fluorination of arylpyrazoles having substituted pyrazole groups and *ortho*-, *meta*-, or *para*-substituted arene moieties is achieved. Various pyrazole groups can efficiently promote the direct C–H activation/fluorination of substrates bearing valuable reactive ester, cyano, halide and nitro functions. The presence of methoxy, methyl and trifluoromethyl is tolerated on the pyrazole directing groups. However, steric substituent effects have a marked influence which is evidenced by calculations. DFT modelling suggested also a previously unseen outer-sphere oxidative addition of *N*-fluorobenzenesulfonimide (NFSI) to Pd(II) as an alternative mechanism to the commonly assumed Pd(II)/Pd(IV) process. This unprecedented proposal, which is supported by the mass spectrometry identification of a key Pd(II) monomer under the stoichiometric conditions deserves more attention. The influence of elaborate highly substituted directing groups on the course of Pd-catalysed fluorination has generally received limited attention although this question has a crucial synthetic utility; herein, appropriate conditions for isolating pure products are reported.

Keywords: arylpyrazoles; C–H activation; fluorination; mechanism; palladium

Introduction

Ligand-directed C–H bond activation/functionalisation by a transition metal has emerged as a powerful method for selectively creating C–C and C–X bonds (X = N, O, S, halogen).[1] While fluorinated compounds are present in pharmaceuticals, agrochemicals, molecular materials and medical imaging radiotracers,[2] synthetic methods to efficiently form carbon–fluorine bonds under mild conditions remained rather limited until recently.[3–7] Directed C–H bond fluorination is an attractive approach obviating substrate prefunctionalisation. The first example of Pd-catalysed C–F bond formation *via* C–H activation has been reported with pyridine as the directing group in the presence of $Pd(OAc)_2$.[8] Direct sp^3 C–H electrophilic fluorination proceeded smoothly upon microwave irradiation with moderate yields.[9] Fluorination of arenes bearing an amide directing group has been then reported,[10] and tuning substituents on this amide allowed fluorination of benzoic amides. The use of *N*-ligand directing groups has been extended mainly to quinoxalines and selective monofluorination can be promoted in nitromethane by the addition of trifluoroacetic acid (TFA).[11] Xu et al. also illustrated three examples of monofluorination of *para*-functionalised arenes using a simple pyrazole as directing group and TFA while our work was ongoing. They noticed serious difficulties to isolate fluorinated compounds from starting materials using arylpyrazoles. Lately a remarkable effect of nitrate as a substoichiometric additive with an *O*-methyloxime directing group, which allowed *ortho*-fluorination of several



Scheme 1. Synthesis of substituted pyrazoles and drugs incorporating substituted arylpyrazoles.

unsubstituted and *para*-substituted arenes at moderate temperature, has been disclosed.[12]

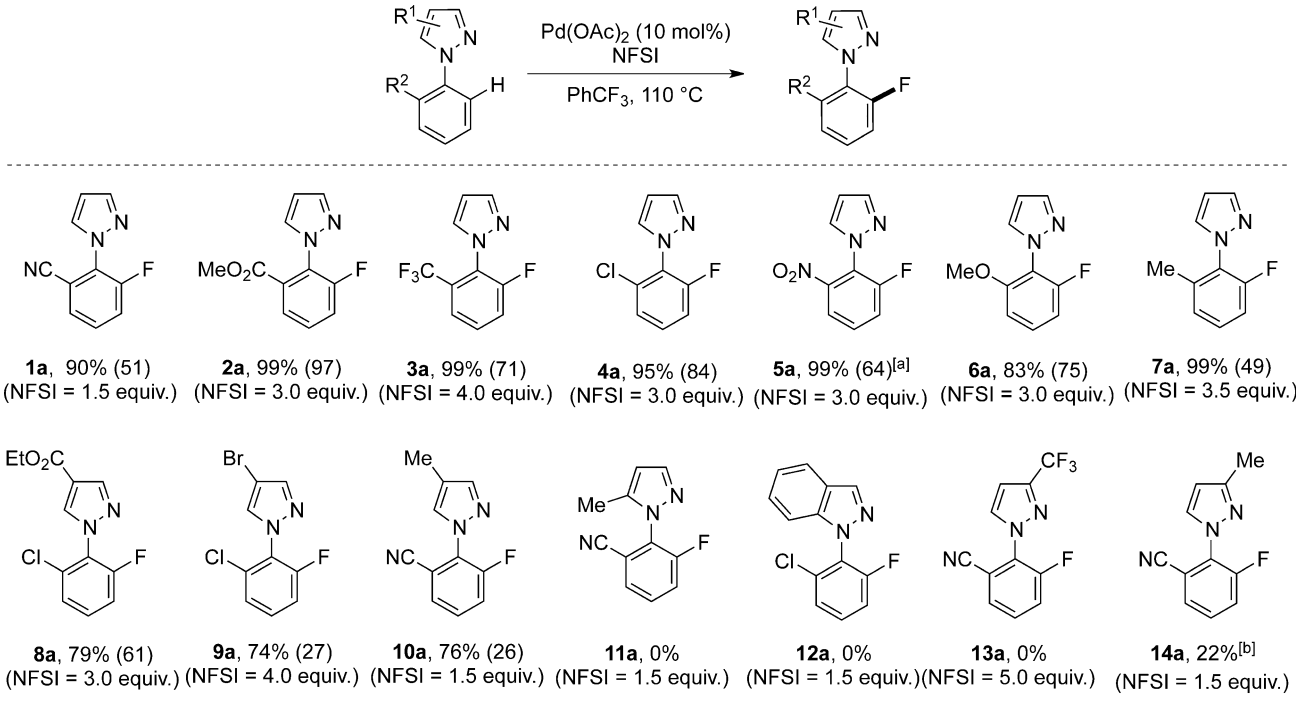
While significant progress has been made in the development of this kind of fluorination reactions, the influence of elaborate substituted directing groups on the course of Pd-promoted fluorination generally received limited attention, although this question has a crucial synthetic utility (see, for instance, sophisticated arylpyrazole drugs, Scheme 1). It had been also suggested that there are intriguing and still unclear limitations for some directing groups involved with the fluorination of *ortho*-substituted arenes.[12] We have investigated herein these issues by introducing new and variously substituted directing groups based on a pyrazole unit. Pertinent mechanistic studies devoted to fluorination have been reported,[13] and to further extend the community effort we also undertook DFT studies specifically paired to our experiments. We now report a catalytic system efficiently performing mono- and di-*ortho*-fluorination of arylpyrazoles with highly substituted pyrazole groups and *ortho*-, *meta*-, and *para*-substituted arene moieties. DFT studies revealed a previously unseen outer-sphere attack of the fluorinating agent, *N*-fluorobenzenesulfonimide (NFSI), onto the intermediate Pd(II), which keeps the metal centre at this oxidation state and might be an alternative to the formation of Pd(IV) intermediates. Our calculations evidenced also the deleterious steric effects of bulky directing groups regarding key fluorination reaction steps.

Results and Discussion

Arylpyrazoles are easily made by C–N bond formation (Scheme 1).[14] We reasoned that a pyrazole unit might be an efficient directing group for C–H bond fluorination as it has been nicely demonstrated for C–C bond formation by the introduction of phenyl and nitrile groups.[11,15,16] This approach gives access to a variety of substituted-pyrazoles, usable as directing groups. In preliminary experiments, the direct C–H activation/fluorination of arylpyrazoles was tested under the conditions reported for pyridine and benzoic amide directed reactions.[8–11] Starting with the *ortho*-functionalised arene 2-(1*H*-pyrazol-1-yl)benzonitrile (**1**, Table S1, Supporting Information), these conditions were not general enough to provide the fluorinated compounds in pure form and satisfactory yield. A detailed screening of conditions was undertaken (Table S2, Supporting Information). Various F^+ sources, Pd precursors, acid additives and solvents were tested.[17,18] $Pd(OAc)_2$ in trifluoromethylbenzene ($PhCF_3$) led to **1a** in 90% yield.

With optimised reaction conditions in hands we examined the efficiency of a pyrazole directing group for the fluorination of *ortho*-functionalised arenes with various substituents, including reactive functions like ester, nitro and chloro (Scheme 2). Reactions proceeded nicely with high conversion and good isolated yields (>70%) of **2a**, **3a**, and **4a**, respectively. In the presence of a nitro substituent, the NFSI reagent is stabilised and longer reaction times are possible yielding **5a** in 99% (64% isolated). Methoxy- and methyl-substituted arylpyrazoles were tested in the presence of 3.0 and 3.5 equiv. of electrophilic fluoride to give **6a** in 75% and **7a** in 49% isolated yield, respectively.

Substituents on the pyrazole unit have a dramatic influence on the reaction, rendering it generally more difficult. Nevertheless, C-4 substituted pyrazole units with electron-donating and electron-withdrawing functions such as ester, bromide and methyl are tolerated, yielding **8a** in 79%, **9a** in 74% and **10a** in 76%, respectively. Conversely, substitution of the pyrazole group at C-5 inhibited fluorination towards **11a** and **12a** possibly due to steric reasons. Contrasting results were obtained with C-3 substitued pyrazoles since an electron-withdrawing substituent trifluoromethyl fully inhibited fluorination to **13a** while a donating methyl group allowed a modest conversion of 22% in **14a**. Purification procedures based on chromatography limited the isolated yields despite various work-up efforts (Table S3, Supporting Information).



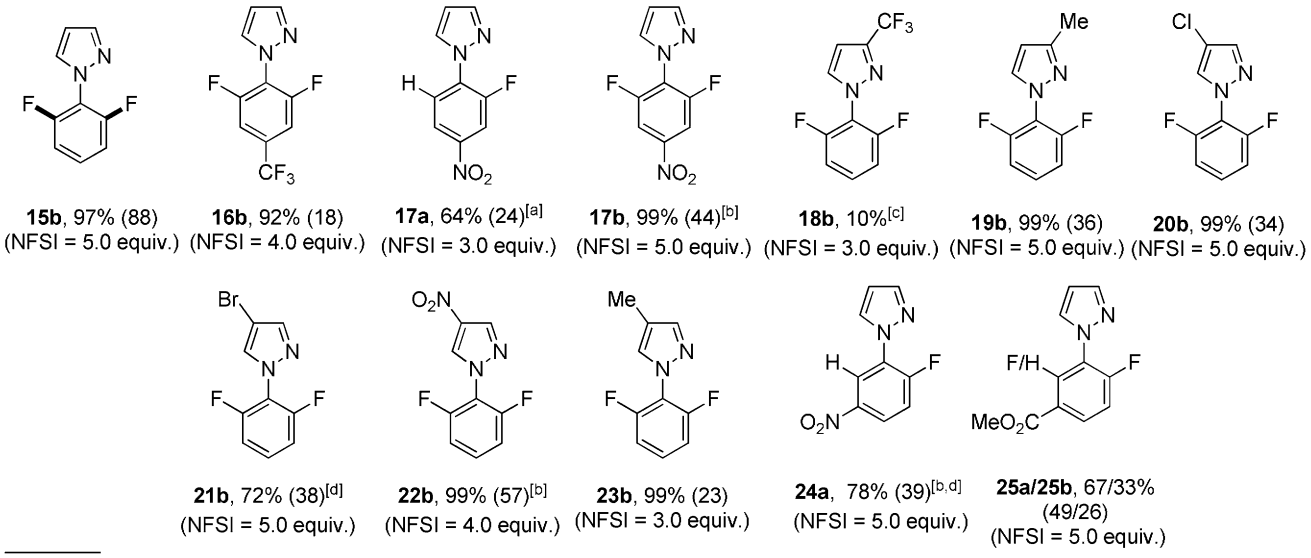
[a] 40 h instead of 17 h.
[b] ^{1}H and ^{19}F NMR yield.

Scheme 2. Pyrazole-directed C–H fluorination of *ortho*-substituted arenes. *Conditions:* arylpyrazole (0.5 mmol), $Pd(OAc)_2$ (10 mol%), *N*-fluorobenzenesulfonimide (NFSI), solvent (5 mL) at 110 °C, under argon, 17 h. ^{1}H and ^{19}F NMR yield and isolated yield in brackets.

The issue of *N*-directed selective monofluoration of non-*ortho*-substituted arenes can be solved by adding a TFA promoter in the presence of CH_3NO_2 or NO_3^-.[11,12] According to our investigation this is due to a kinetic effect which increases the gap existing between the rates of monofluorination and subsequent difluorination reactions. Conversely, little is known on the efficiency of difluorination reactions, and TFA has a deleterious effect on its course. Gratifyingly, the present catalytic system competently addressed complete and selective difluorination of *meta*- and *para*-substituted arenes (Figure 1).

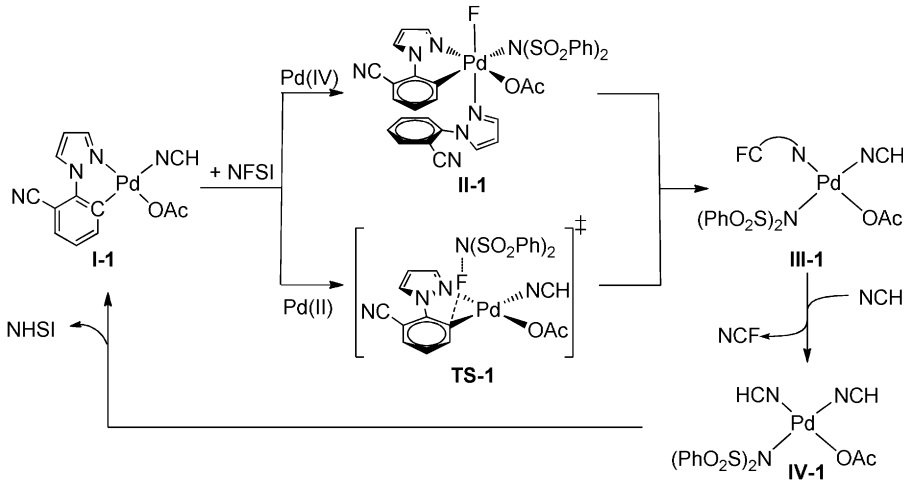
The use of *N*-phenylpyrazole led to difluorinated **15b** in high isolated yield (88%); nevertheless 5 equiv. of NFSI were necessary for full conversion, possibly indicating a relatively low stability in the reaction. Lower amounts of NFSI always led to a mixture of **15a** and **15b**. This was later confirmed in our mechanistic studies (see below). Compound **16** was also converted into **16b** in high yield but was unstable during the purification process. Fluorination of nitro *para*-substituted arene using 3 equiv. of NFSI proceeded more slowly, which was again found to be in favour of a monofluorination to **17a** (64% conversion). By using 5 equiv. of NFSI a fairly good conversion in difluorinated product can be obtained and **17b** was isolated in 44% yield after 40 h of reaction. A similar slow kinetic was observed for the arylpyrazole having a nitro function in the *meta*-position of the arene which allowed the isolation of **24a** in moderate 39% yield. C-3 and C-4 substituted pyrazole units are also suitable directing groups for C–H fluorination. The products **18b** to **23b** were formed in modest to very high yield (10% to 99%), even if lower isolated yields were obtained when high purity (+99%) was sought. With functions at the *meta*-position of the arene, a dominant selectivity for the first fluorination was observed and even an excess of NFSI was ineffective to achieve difluorination. These results raised several questions on the mechanism of the reaction and on the influence of the substituents and their position, which were addressed by DFT calculations.

Our computational study was first focused on the fluorination of **1** to **1a**. Various isomers were considered for the catalyst resting state (Scheme S1 and Scheme S2, Supporting Information) and the isomer **I-1** (Scheme 3) was identified as the most stable.[19] It is worth noting that the palladium dimer found in previous studies[13d,20] is less stable under our experimental conditions (see Supporting Information). In agreement with reported mechanistic studies,[3d,21] we first considered the oxidative addition of NFSI to the Pd(II) complex **I-1** leading to a Pd(IV) complex **II-1** stabilised by an intramolecular π-staking interaction



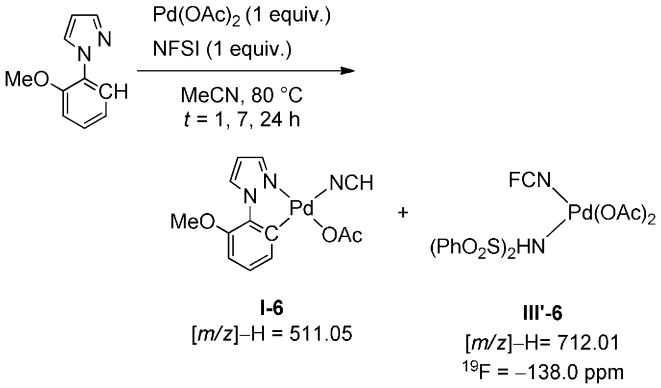
[a] **17b** was formed in 16%.
[b] 40 h instead of 17 h.
[c] ^{1}H and ^{19}F NMR yield.
[d] Fluorination products were identified using ^{1}H, ^{19}F NMR and GC-MS.

Figure 1. Pyrazole-directed C–H fluorination of arenes substituted in *para-* or *meta*-positions. *Conditions:* arylpyrazole (0.5 mmol), $Pd(OAc)_2$ (10 mol%), NFSI, solvent (5 mL) at 110 °C, under argon, 17 h. ^{1}H and ^{19}F NMR yield and isolated yield in brackets.



Scheme 3. Pd(II)/Pd(IV) and Pd(II) outer sphere reaction pathways for the fluorination of **1**. NCH corresponds to the phenyl pyrazole ligand bearing an *o*-CN group on phenyl.

between the two phenylpyrazole moieties. This occurs through a rather high barrier of 46.3 kcal mol^{-1} (Scheme S3, Supporting Information). A reductive elimination from **II-1** leads to the product **III-1** and fluorination of the phenyl ring. The fluorination transition state is similar to those found in studies by Saeys et al.[22] even though the activation energy of 17.8 kcal. mol^{-1} is lower than previous theoretical and experimental values.[19,20] However, in the course of our modelling an alternative pathway emerged that involves an outer-sphere direct fluorination in which the metal centre remains Pd(II): the complex **III-1** is formed through **TS-1** (+29.2 kcal mol^{-1} barrier).[23] Unexpectedly this alternative path appears to be viable since it proceeds with a lower activation energy. Mechanisms involving Pd(II)/Pd(IV) for C–H bond functionalisation have recently emerged and have been intensively discussed.[13d,24] This proposal is unusual but is consistent with the experimental issues related to the fairly high concentration of NFSI required, and as such may be further considered in the coming studies.



Scheme 4. Time-resolved monitoring of the reaction under stoichiometric conditions ($PhCF_3$ solvent can also be used with similar results but MeCN is preferred for clarity in ^1H NMR).

To further explore these DFT results we undertook experimental studies under stoichiometric conditions, including ^1H and ^{19}F NMR and mass spectrometric analysis (Orbitrap ionisation), with the aim to identify key palladium intermediates. In particular we checked the formation and reactivity of complexes **I-6** by monitoring the reaction in time (Scheme 4).

The mass spectrometric analysis of the reaction conducted under the conditions described in the Scheme 4 indicates the formation of monomeric palladium species with a fragmentation corresponding to **I-6**, as detailed in Figure 2. Our results contrast with the studies reported by Xu et al.[11,12] that used quinoxazoline and oxime as *N*-directing ligands, since no isotopic mass m/z above 600 is detected with pyrazole substrates (full range spectra of Figure S4, Supporting Information).

The signature of *monomeric* palladium complex **I-6** is clearly identified (isotopic distribution: Pd^{104} 11%, Pd^{105} 22%, Pd^{106} 27%, Pd^{108} 26%, Pd^{110} 11%) in the mass analyses of reactions under stoichiometric conditions at $m/z = 511.05$, 495.05, 480.03, 469.05 (Figure 2). The palladium signature for dimer compounds is very different and has a typical isotopic mass distribution. The resting state nature of this complex **I-6** was supported by the mass spectra obtained after 1 h, 7 h and 24 h of reaction with, after 24 h, the additional presence of complex **III′-6** ($m/z = 712.0$, ^{19}F NMR, $\delta_F =$

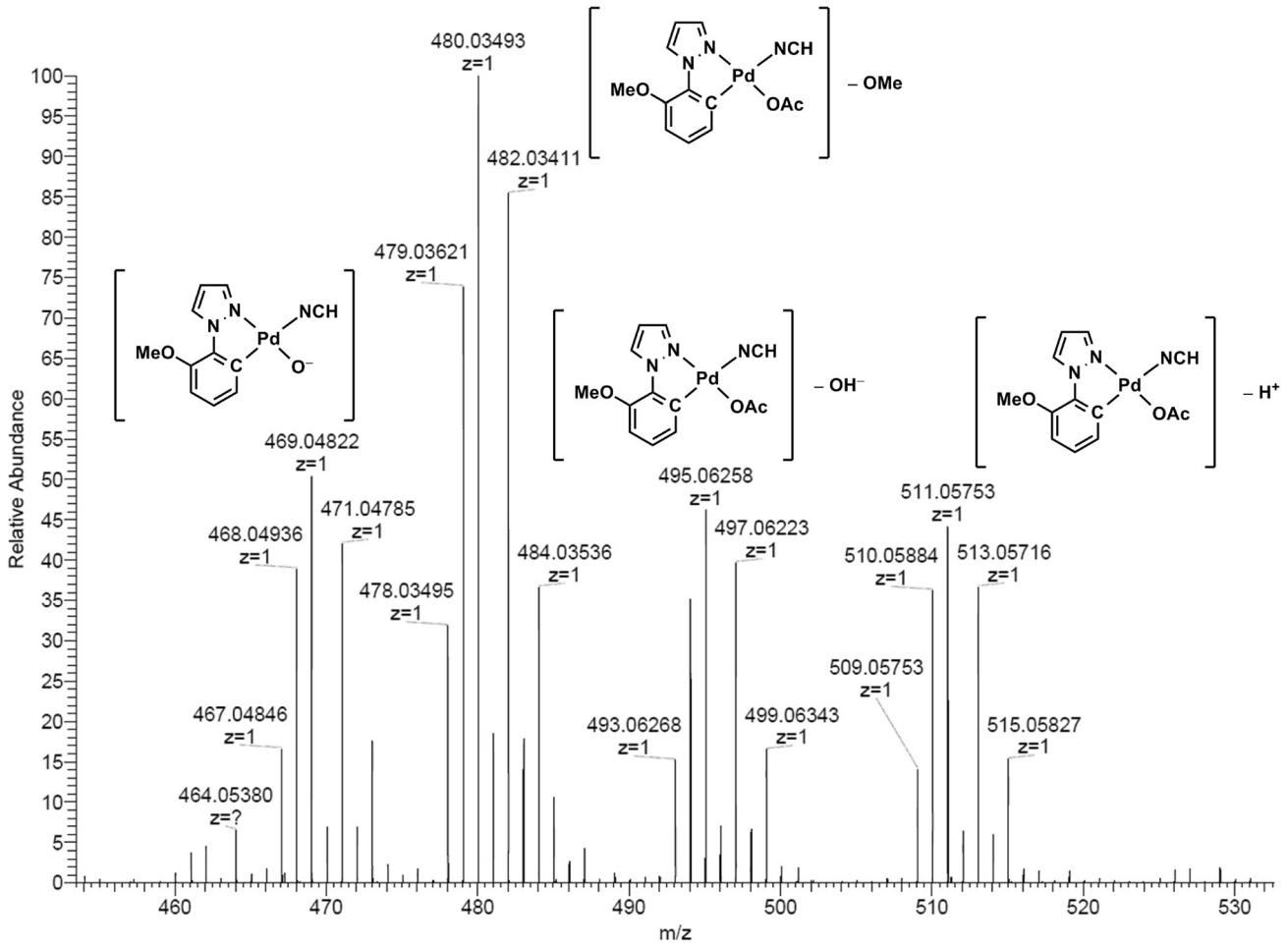
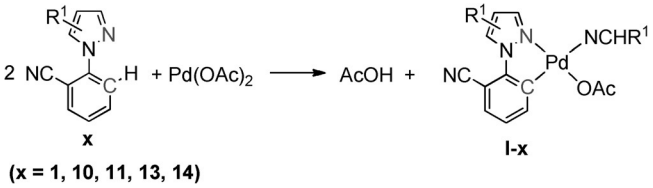


Figure 2. Mass analysis of reactions under stoichiometric conditions.



Scheme 5. Formation of Pd(II) complexes **I-x**. The $NCHR^1$ group corresponds to the N-bonded arylpyrazole. Relative energies for these reaction are gathered in Table 1 for **x** = **10**, **11**, **13** and **14**.

−138 ppm) incorporating a fluorinated pyrazole ligand after this time (Scheme 4).

We also carefully considered the effect of pyrazole substituents and focused our calculations on molecules **10**, **11**, **13** and **14** (Scheme 2). In order to specifically isolate the influence of a given substituent on pyrazole moieties, we compared the formation energy of the Pd(II) complexes **I-10**, **I-11**, **I-13** and **I-14** to that of complex **I-1** (Scheme 5 and Scheme S1 in the Supporting Information).[18] Complex **I** is representative of the intramolecular interactions at play in key intermediates and transition states (Scheme S3, Supporting Information).

Table 1. Relative formation energy for the various complexes: **I-10**, **I-11**, **I-13**, and **I-14**.

	1	**10**	**14**	**11**	**13**
Pyrazole substituent	–	4-Me	3-Me	5-Me	3-CF_3
Fluorinated product	**1a**	**10a**	**14a**	**11a**	**13a**
Yield	90%	76%	22%	0%	0%
ΔE (kcal mol^{-1})	0[a]	−3.9	−2.2	+0.9	+8.4

[a] Formation energy of **I-1** = −30.5 kcal. mol^{-1} (see also Scheme S1, Supporting Information).

The corresponding reaction energies are gathered in Table 1 (line 4). A positive energy implies that the complex **I-x** is more difficult to form than **I-1** because of a deleterious influence of its substituent. Consequently, a positive energy should correlate with significant reaction limitations while a negative energy should indicate a moderate to good yield.

In good agreement with the experimental results (Figure 1, Table 1, line 3), we found that the 5-Me and 3-CF_3 groups prevent the reaction to occur with **11** and **13** because of their positive relative energy of formation ΔE (+0.9 and +8.4).

To evidence the influence of steric parameters we plotted the *non-covalent interactions* (NCI) existing in the two intermediates **I-10** (4-Me, 76%) and **I-11** (5-Me, 0%).[25] The 5-Me group clearly induces a larger intramolecular steric hindrance between the pyrazole and the phenyl moiety as shown by the larger NCI area for **I-11** (Figure 3, *top right*). This is also illustrated by the strong deviation from planarity between the two cycles in **I-11**.

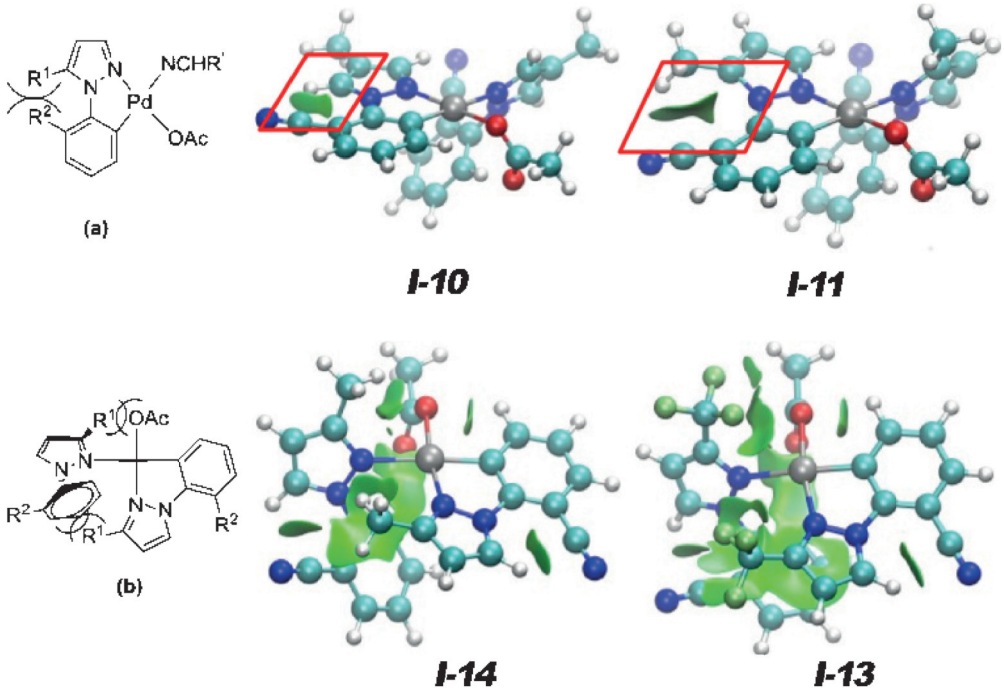


Figure 3. Non-covalent interaction (NCI) plots: the extent of the green areas specifies the degree of steric interactions (H atoms in white, C pale blue, O red, N blue, F green, Pd grey). In (**a**) intramolecular NCI interactions are shown inside the red box (*top*).

The 3-CF_3 (or 3-Me) group creates an inter-ligands steric hindrance with the other pyrazole entity (Figure 3b, *bottom*). The 3-CF_3 group also withdraws electrons of the Pd-bonded N-2 atom whose charge evolves from −0.32 e in **1** to −0.35 e in **14** and to −0.27 e in **13**. Both effects contribute to destabilise the Pd(II) intermediates and are assumed to be major factors hampering the reaction. Concerning fluorination regioselectivity, further DFT calculations supported that fluorination on the opposite site of a *meta*-substituted arene is preferred since for compound **24** forming the Pd–C bond on C-2 costs 5.0 kcal mol^{-1} more than the attack on C-6. This is in agreement with the experimental results for which a regioselectivity above 80% was found in favour of **24a**.

Conclusions

We have reported a general catalytic system for mono- and di-*ortho*-fluorination of arylpyrazoles having substituted pyrazole groups and *ortho*-, *meta*-, or *para*-substituted arene moieties. Pyrazole groups can efficiently promote the direct C–H fluorination of substrates bearing valuable reactive ester, cyano, halide and nitro functions. Methoxy, methyl and trifluoromethyl groups are tolerated but steric substituent effects have a marked influence. Our DFT calculations suggested a previously unseen outer-sphere addition of NFSI to the palladacycle(II) resting state complex as an alternative mechanism to the commonly assumed Pd(II)/Pd(IV) process. This unprecedented proposal deserves more attention from the community. Further experimental and DFT studies on this alternative proposal are ongoing in our groups and will be reported in due time.

Experimental Section

General Conditions

All reagents were purchased from commercial suppliers and used without purifications. All reactions were performed in Schlenk tubes under argon. Unless otherwise stated, the starting pyrazole derivatives were synthesised according to the literature.[14] ^{1}H (300 MHz), ^{13}C (75 or 125 MHz), ^{19}F (282 or 470 MHz) spectra were recorded on Bruker AVANCE III instrument in $CDCl_3$ solutions. Chemical shifts are reported in ppm relative to $CDCl_3$ (^{1}H: 7.26 and ^{13}C: 77.16) and coupling constants *J* are given in Hz. GC experiments were performed with a Shimadzu GC 2010 instrument. GC-MS experiments were performed with a Trace GC Ultra equipped with a mass-selective detector, high resolution mass spectra (HR-MS) were obtained on a Thermo LTQ-Orbitrap XL with ESI source. Flash chromatography was performed on silica gel (230–400 mesh). Elemental analysis experiments were performed with a Thermo Electron Flash EA 1112 Series apparatus.

All reactions were performed under an inert argon atmosphere using conventional vacuum-line and Schlenk techniques. Arylpyrazole substrates were synthesised in one-step from Ullmann coupling or aromatic nucleophilic substitution with commercial halides and pyrazoles. The fluorinated products were isolated and purified (+99%) *via* procedures detailed in the Supporting Information.

Computational Methods

Quantum mechanics calculations were performed with the *Gaussian 09* software package.[26] Energy and forces were computed by density functional theory with the range separated wB97X-D[27] exchange-correlation functional. This range separated functional was selected because it properly describes charge transfers and dispersion effects (such as π-stacking) are taken into account. A polarisable continuum model[28] (PCM) of toluene was used as implemented in Gaussian 09 to describe the trifluoromethylbenzene medium. Transition states were localised using the string theory as implemented in Opt′n Path.[29] Geometries were optimised and characterised with the LANL2DZ basis set and associated pseudopotentials for all atoms. Electronic energies were then refined using single point calculations with the LANL08(f) basis set and associated pseudopotentials for Pd[30] and the 6–311++G(2d,p) basis set for other atoms. In the following this basis set will be denoted BS1, and the single point energies will be denoted by BS1//LANL2DZ. We show in the Supporting Information that this level gives relative energies very close to the full optimisation at the BS1 level, see Table S4 in the Supporting Information. The LANL08(f) basis set and pseudopotentials were taken from the EMSL Basis Set Exchange Web site.[31] All structures were optimised and frequency calculations were performed to ensure the absence of any imaginary frequencies on local minima, and the presence of only one imaginary frequency on transition states. Reactants and products were localised again starting from the transition states (IRC calculations followed by optimisations) to ensure that no TS were forgotten. Populations analyses were conducted using the Natural Bond Orbital analysis (NBO) version 3.[32]

Catalytic Fluorination Reactions

The pyrazole derivative (0.5 mmol), NFSI (1.5 equiv.), and $Pd(OAc)_2$ (0.05 mmol) were introduced in a Schlenk tube, equipped with a magnetic stirring bar. Dry trifluoromethylbenzene (5 mL) was added, and the Schlenk tube purged several times with argon. The Schlenk tube was placed in a pre-heated oil bath at 110 °C and reactants were allowed to stir for 17 h. After cooling to room temperature, the reaction mixture was filtered through a plug of silica and washed with ethyl acetate. The solvent was removed under vacuum and the residue was analysed by NMR and gas chromatography to determine the conversion of the fluorinated product. Then, the residue was diluted with dichloromethane, and was washed three times with water+3% TEA. The combined organic layer was washed with water and dried over $MgSO_4$. The solvent was removed under vacuum and the crude product was purified by silica gel

column chromatography using an appropriate ratio of the eluent.

3-Fluoro-2-(1*H*-pyrazol-1-yl)-benzonitrile (1a): The reaction of 2-(1*H*-pyrazol-1-yl)-benzonitrile (52 μL, 0.5 mmol) and NFSI (236.5 mg, 0.75 mmol) affords **1a**; yield: 47.9 mg (51%); yellow oil; (ethyl acetate-heptane = 3:7); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.87 (d, J = 1.70 Hz, 1H), 7.83 (t, J = 2.52 Hz, 1H), 7.63–7.60 (m, 1H), 7.51–7.45 (m, 2H), 6.56 (dd, J = 2.52, 1.88 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ = −120.4; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.5 (d, J = 254.0 Hz), 142.3, 131.7 (d, J = 4.5 Hz), 131.0 (d, J = 13.5 Hz), 130.3 (d, J = 4.0 Hz), 129.5 (d, J = 8.4 Hz), 121.8 (d, J = 20.6 Hz), 115.5 (d, J = 4.1 Hz), 111.5 (d, J = 1.9 Hz), 108.4; elemental analysis: calcd (%) for $C_{10}H_6FN_3$: C 64.17, H 3.23, N 22.45; found: C 63.33, H 3.16, N 21.68; HR-MS (+p ESI): m/z = 188.061 [M + H$^+$], calcd for $C_{10}H_6FN_3$: 188.060.

3-Fluoro-2-(1*H*-pyrazol-1-yl)-phenyl acetate (2a): The reaction of 2-(1*H*-pyrazol-1-yl)-phenyl acetate (62 μL, 0.5 mmol) and NFSI (473 mg, 1.5 mmol) affords **2a**; yield: 106.8 mg (97%); yellow oil; (dichloromethane-heptane = 8:2 + 3% TEA); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.73–7.72 (m, 2H), 7.64–7.61 (m, 1H), 7.47–7.33 (m, 2H), 6.48 (dd, J = 2.14 Hz, 1H), 3.68 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$): δ = −123.0; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.0 (d, J = 3.2 Hz), 158.1 (d, J = 252.0 Hz), 141.1, 131.9 (d, J = 3.4 Hz), 131.1, 129.4 (d, J = 8.2 Hz), 128.1 (d, J = 13.2 Hz), 126.0 (d, J = 3.8 Hz), 119.7 (d, J = 20.6 Hz), 107.1, 52.6; elemental analysis: calcd (%) for $C_{11}H_9FN_2O_2$: C 60.00, H 4.12, N 12.72; found: C 59.61, H 4.23, N 12.89. HR-MS (+p ESI): m/z = 243.053 [M + Na$^+$], calcd. for $C_{11}H_9FN_2O_2$: 243.050.

3-Fluoro-2-(1*H*-pyrazol-1-yl)-trifluoromethylbenzene (3a): The reaction of 2-(1*H*-pyrazol-1-yl)-trifluoromethylbenzene (73 μL, 0.5 mmol) and NFSI (631 mg, 2 mmol) affords **3a**; yield: 81.4 mg (71%); yellow oil; (dichloromethane-heptane = 8:2 + 3% TEA, and then diethyl ether-heptane = 1:1 + 3% TEA); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.80 (dd, J = 1.83, 0.38 Hz, 1H), 7.63–7.54 (m, 3H), 7.49–7.42 (m, 1H), 6.50 (dd, J = 2.46, 1.89 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ = −59.8, −119.4; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.6 (d, J = 254.6 Hz), 141.6, 132.7, 130.9 (dd, J = 30.5, 8.5 Hz), 130.5 (q, J = 31.9 Hz), 127.9 (qd, J = 272.4, 3.6 Hz), 127.5 (d, J = 14.0 Hz), 122.5 (m, J = 4.6 Hz), 120.6 (d, J = 20.3 Hz), 107.0:; elemental analysis: calcd. (%) for $C_{10}H_6F_4N_2$: C 52.18, H 2.63, N 12.17; found: C 52.56, H 2.80, N 12.26; HR-MS (+p ESI): m/z = 231.054 [M + H$^+$], calcd. for $C_{10}H_6F_4N_2$: 231.050.

3-Fluoro-2-(1*H*-pyrazol-1-yl)-chlorobenzene (4a): The reaction of 2-(1*H*-pyrazol-1-yl)-chlorobenzene (62 μL, 0.5 mmol) and NFSI (473 mg, 1.5 mmol) affords **4a** ; yield: 82.6 mg (84%); purple oil; (dichloromethane-heptane = 8:2 + 3% TEA); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.80 (d, J = 1.72 Hz, 1H), 7.60 (d, J = 2.46 Hz, 1H), 7.40–7.30 (m, 2H), 7.18–7.12 (m, 1H), 6.49 (dd, J = 2.34, 2 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ = −118.6; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.5 (d, J = 255.4 Hz), 141.5, 133.5, 132.2, 130.6 (d, J = 9.2 Hz), 127.8 (d, J = 14.7 Hz), 125.9 (d, J = 3.8 Hz), 115.4 (d, J = 20.5 Hz), 106.9; elemental analysis: calcd. (%) for $C_9H_6ClFN_2$: C 54.98, H 3.08, N 14.25; found: C 54.78, H 3.38, N 14.32; HR-MS (+p ESI): m/z = 197.027 [M + H$^+$], calcd. for $C_9H_6ClFN_2$: 197.020.

3-Fluoro-2-(1*H*-pyrazol-1-yl)-nitrobenzene (5a): The reaction of 2-(1*H*-pyrazol-1-yl)-nitrobenzene (189 mg, 1 mmol) and NFSI (946 mg, 3 mmol) affords **5a** after 40 h; yield: 132.9 mg (64%); yellow solid; (dichloromethane-heptane = 8:2 + 3% TEA, and then ethyl acetate-heptane = 3:7); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.78 (dd, J = 2.60, 0.33 Hz, 1H), 7.76 (d, J = 1.78 Hz, 1H), 7.73–7.69 (m, 1H), 7.56–7.46 (m, 2H), 6.53 (dd, J = 2.48, 1.90 Hz, 1H); ^{19}F NMR (470 MHz, $CDCl_3$): δ = −120.2; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.0 (d, J = 255.5 Hz), 146.6 (b), 142.5, 132.0 (d, J = 3.7 Hz), 129.4 (d, J = 8.6 Hz), 123.3 (d, J = 15.3 Hz), 120.8 (d, J = 17.9 Hz), 120.7 (d, J = 6.7 Hz), 108.1; elemental analysis: calcd. (%) for $C_9H_6FN_3O_2$: C 52.18, H 2.92, N 20.28; found: C 51.56, H 3.29, N 18.23; HR-MS (+p ESI): m/z = 208.051 [M + H$^+$], calcd. for $C_9H_6FN_3O_2$: 208.050.

3-Fluoro-2-(1*H*-pyrazol-1-yl)-methoxybenzene (6a): The reaction of 2-(1*H*-pyrazol-1-yl)-methoxybenzene (68 μL, 0.5 mmol) and NFSI (473 mg, 1.5 mmol), affords **6a**; yield: 72.2 mg (75%); yellow oil; (dichloromethane-heptane = 8:2 + 3% TEA, and then ethyl acetate-heptane = 45:65); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.77 (d, J = 1.60 Hz, 1H), 7.58 (d, J = 2.41 Hz, 1H), 7.33–7.7.28 (m, 1H), 6.86–6.79 (m, 2H), 6.45 (dd, J = 2.07 Hz, 1H), 3.78 (s, 3H); ^{19}F NMR (470 MHz, $CDCl_3$): δ = −121.6; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.2 (d, J = 251.7 Hz), 156.2 (d, J = 3.3 Hz), 140.8, 132.5, 130.1 (d, J = 10.3 Hz), 118.8 (d, J = 14.2 Hz), 108.7 (d, J = 20.5 Hz), 107.6 (d, J = 3.2 Hz), 106.1, 56.5; elemental analysis: calcd. (%) for $C_{10}H_9FN_2O$: C 62.49, H 4.72, N 14.58; found: C 62.15, H 4.51, N 14.89; HR-MS (+p ESI): m/z = 193.076 [M + H$^+$], calcd for $C_{10}H_9FN_2O$: 193.070.

3-Fluoro-2-(1*H*-pyrazol-1-yl)-toluene (7a): The reaction of 2-(1*H*-pyrazol-1-yl)-toluene (65 μL, 0.5 mmol) and NFSI (552 mg, 1.75 mmol), affords **7a**; 43.2 mg (49%); yellow oil; (dichloromethane-heptane = 8:2 + 3% TEA): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.78 (d, J = 1.47 Hz), 7.57–7.55 (m, 1H), 7.33–7.26 (m, 1H), 7.11–7.02 (m, 2H), 6.48 (dd, J = 2.33, 1.95 Hz, 1H), 2.16 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$): δ = −123.7; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.6 (d, J = 250.8 Hz), 140.9, 138.5, 131.9, 129.9 (d, J = 8.5 Hz), 128.3 (d, J = 12.1 Hz), 126.3 (d, J = 3.6 Hz), 113.9 (d, J = 20.3 Hz), 106.4, 17.6 (d, J = 2.4 Hz); elemental analysis: calcd. (%) for $C_{10}H_9FN_2$: C 68.17, H 5.15, N 15.90; found: C 67.11, H 6.02, N 15.97; HR-MS (+p ESI): m/z = 177.082 [M + H$^+$], calcd. for $C_{10}H_9FN_2$: 177.080.

Ethyl 1-(2-chloro-6-fluorophenyl)-1*H*-pyrazole-4-carboxylate (8a): The reaction of ethyl 1-(2-chlorophenyl)-1*H*-pyrazole-4-carboxylate (86 μL, 0.5 mmol) and NFSI (473 mg, 1.5 mmol), affords **8a**; yield: 81.4 mg (61%); yellow oil; (ethyl acetate-heptane = 3:7); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.16 (s, 1H), 8.10 (s, 1H), 7.47–7.32 (m, 2H), 7.20–7.14 (m, 1H), 4.32 (q, J = 14.28, 7.14 Hz, 2H), 1.35 (t, J = 7.13 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$): δ = −118.2; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.6, 160.2 (d, J = 256.4 Hz), 142.5, 135.8, 133.2, 131.3 (d, J = 9.0 Hz), 128.8, 126.9 (d, J = 14.7 Hz), 126.0 (d, J = 3.8 Hz), 115.5 (d, J = 20.2 Hz), 60.6, 14.4; elemental analysis: calcd. (%) for $C_{12}H_{10}ClFN_2O_2$: C 53.64, H 3.75, N 10.43; found: C 53.69, H 4.65, N 10.73; HR-MS (+p ESI): m/z = 269.048 [M + H$^+$], calcd. for $C_{12}H_{10}ClFN_2O_2$: 269.040.

3-Fluoro-2-(4-bromo-1*H*-pyrazol-1-yl)-chlorobenzene (9a): The reaction of 2-(4-bromo-1*H*-pyrazol-1-yl)-chlorobenzene (146 μL, 0.5 mmol) and NFSI (631 mg, 2 mmol), affords **9a**; yield: 39.5 mg (27%); yellow oil; (ethyl acetate-heptane = 3:7). During the purification process some decom-

position occurs and even a recrystallisation was not efficient. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.76 (s, 1H), 7.63 (s, 1H), 7.41–7.32 (m, 2H), 7.21–7.15 (m, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ = –118.4; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.3 (d, J = 256.1 Hz), 142.2, 133.4, 132.2, 131.1 (d, J = 9.0 Hz), 127.6 (d, J = 6.8 Hz), 126.0 (d, J = 3.7 Hz), 115.5 (d, J = 20.3 Hz), 95.0; HR-MS (+p ESI): m/z = 276.934 [M+H$^+$], calcd. for $C_9H_5BrClFN_2$: 276.930.

3-Fluoro-2-(4-methyl-1*H*-pyrazol-1-yl)-benzonitrile (10a): The reaction of 2-(4-methyl-1H-pyrazol-1-yl)-benzonitrile (91.6 mg, 0.5 mmol) and NFSI (236.5 mg, 0.75 mmol), affords **10a**; yield: 26.3 mg (26%); yellow oil; (ethyl acetate-heptane = 3:7); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.67 (s, 1H), 7.61–7.57 (m, 2H), 7.50-.38 (m, 2H), 2.18 (s, 3H); ^{19}F NMR (470 MHz, $CDCl_3$): δ = –120.6; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.3 (d, J = 253.6 Hz), 143.3, 131.2 (d, J = 15.3 Hz), 130.3 (d, J = 4.0 Hz), 130.0 (d, J = 4.8 Hz), 129.0 (d, J = 8.5 Hz), 121.7 (d, J = 20.8 Hz), 119.0, 115.8 (d, J = 4.0 Hz), 111.1 (d, J = 2.0 Hz), 9.0; elemental analysis: calcd. (%) for $C_{11}H_8FN_3$: C 65.66, H 4.01, N 20.88, found: C 65.13, H 4.36, N 19.16; HR-MS (+p ESI): m/z = 202.077 [M+H$^+$], calcd. for $C_{11}H_8FN_3$: 202.070.

1-[2,6-(Difluoro)phenyl]-1*H*-pyrazole (15b): The reaction of 1-phenyl-1*H*-pyrazole (66 μL, 0.5 mmol) and NFSI (788.4 mg, 2.5 mmol), affords **15b**; yield: 79 mg (88%): yellow oil; (ethyl acetate-heptane = 3:7); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.80 (d, J = 1.73 Hz, 1H), 7.67–7.65 (m, 1H), 7.38–7.29 (m, 1H), 7.09–7.01 (m, 2H), 6.48 (dd, J = 2.32, 2.03 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ = –120.2; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.2 (d, J = 254.3 Hz), 159.1 (d, J = 254.3 Hz), 141.6, 132.3, 129.7 (t, J = 9.8 Hz), 118.9 (t, J = 14.9 Hz), 112.5 (AA′X, N = 12.0 Hz), 107.0: elemental analysis: calcd. (%) for $C_9H_6F_2N_2$: C 60.00, H 3.36, N 15.50; found: C 59.62, H 3.33, N 16.10; HR-MS (+p ESI): m/z = 181.056 [M+H$^+$], calcd. for $C_9H_6F_2N_2$: 181.050.

3,5-Difluoro-4-(1*H*-pyrazol-1-yl)-trifluoromethylbenzene (16b): The reaction of 4-(1*H*-pyrazol-1-yl)-trifluoromethylbenzene (212 mg, 1 mmol) and NFSI (1.26 g, 4 mmol), affords **16b**; yield: 44.1 mg (18%); white solid; (dichloromethane-heptane = 8:2 + 3% TEA, and then ethyl acetate-heptane = 3:7 + 3% TEA); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.85 (d, J = 1.71 Hz, 1H), 7.73–7.72 (m, 1H), 7.41–7.35 (m, 2H), 6.54 (dd, J = 2.44, 1.98 Hz, 1H); ^{19}F NMR (470 MHz, $CDCl_3$): δ = –63.2, –116.1; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.0 (d, J = 257.3 Hz), 158.0 (d, J = 257.3 Hz), 142.4 (s), 132.2 (s), 131.8 (dt, J = 35.1, 9.3 Hz), 123.6 (dt, J = 272.5 Hz, 3 Hz), 121.9 (t, J = 14.1 Hz), 110.6 (m), 107.8; elemental analysis: calcd. (%) for $C_{10}H_5F_5N_2$: C 48.40, H 2.03, N 11.29; found: C 49.20, H 2.57, N 10.94; HR-MS (+p ESI): m/z = 249.044 [M+H$^+$], calcd. for $C_{10}H_5F_5N_2$: 249.040.

3-Fluoro-4-(1*H*-pyrazol-1-yl)-nitrobenzene (17a): The reaction of 4-(1*H*-pyrazol-1-yl)-nitrobenzene (94 mg, 0.5 mmol) and NFSI (473 mg, 1.5 mmol), affords **17a** after 17 h; yield: 26.8 mg (24%); white solid; (ethyl acetate-heptane = 3:7); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.30–8.27 (m, 1H), 8.20–8.13 (m, 3H), 7.82 (d, J = 1.63 Hz, 1H), 6.57 (dd, J = 2.65, 1.79 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ = –120.6; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.5 (d, J = 252.4 Hz), 145.5 (b), 142.5, 133.5 (d, J = 8.8 Hz), 131.4 (d, J = 14.3 Hz), 123.8 (d, J = 1.2 Hz), 120.7 (d, J = 3.4 Hz), 113.6 (d, J = 26.2 Hz), 109.4; elemental analysis: calcd. (%) for $C_9H_6FN_3O_2$: C 52.18, H 2.92, N 20.28; found: C 52.19, H 2.98, N 20.05; HR-MS (+p ESI): m/z = 208.051 [M+H$^+$], calcd. for $C_9H_6FN_3O_2$: 208.050.

3,5-Difluoro-4-(1*H*-pyrazol-1-yl)-nitrobenzene (17b): The reaction of 4-(1*H*-pyrazol-1-yl)-nitrobenzene (94 mg, 0.5 mmol) and NFSI (788 mg, 2.5 mmol), affords **17b** after 40 h; yield: 49.5 mg (44%); white solid; (ethyl acetate-heptane = 3:7); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.04–7.97 (m, 2H), 7.88 (d, J = 1.73 Hz, 1H), 7.79–7.77 (m, 1H), 6.58 (dd, J = 2.57, 1.88 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ = –114.1; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.9 (dd, J = 259.1, 3.94 Hz), 146.6 (m), 142.8, 132.2 (t, J = 2.7 Hz), 124.3 (t, J = 14.0 Hz), 109.1 (m), 108.2; elemental analysis: calcd. (%) for $C_9H_6F_2N_3O_2$: C 48.01, H 2.24, N 18.66; found: C 47.98, H 2.66, N 18.03; HR-MS (+p ESI): m/z = 226.041 [M+H$^+$], calcd. for $C_9H_6F_2N_3O_2$: 226.030.

1,3-Difluoro-2-(3-methyl-1*H*-pyrazol-1-yl)-benzene (19b): The reaction of 3-methyl-1-phenyl-1*H*-pyrazole (79 mg, 0.5 mmol) and NFSI (788 mg, 2.5 mmol), affords **19b**; yield: 34.7 mg (36%); yellow oil; (ethyl acetate-heptane = 3:7); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.47 (m, 1H), 7.27–7.19 (m, 1H), 7.00–6.92 (m, 2H), 6.20 (d, J = 2.36 Hz, 1H), 2.31 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$): δ = –120.0; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.3 (d, J = 254.0 Hz), 159.2 (d, J = 254.0 Hz), 151.1, 133.0, 129.4 (t, J = 9.8 Hz), 119.0 (t, J = 14.6 Hz), 112.5 (AA′X, N = 12.0 Hz), 107.1, 13.8; elemental analysis: calcd. (%) for $C_{10}H_8F_2N_2$: C 61.85, H 4.15, N 14.43; found: C 62.10, H 4.85, N 14.75; HR-MS (+p ESI): m/z = 195.072 [M+H$^+$], calcd. for $C_{10}H_8F_2N_2$: 195.070.

1,3-Difluoro-2-(4-chloro-1*H*-pyrazol-1-yl)-benzene (20b): The reaction of 4-chloro-1-phenyl-1*H*-pyrazole (89 mg, 0.5 mmol) and NFSI (788 mg, 2.5 mmol), affords **20b**; yield: 36.8 mg (34%); white solid; (ethyl acetate-heptane = 3:7); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.73 (s, 1H), 7.66 (m, 1H), 7.44–7.35 (m, 1H), 7.12–7.04 (m, 2H); ^{19}F NMR (282 MHz, $CDCl_3$): δ = –120.1; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.5 (d, J = 255.2 Hz), 158.5 (d, J = 255.2 Hz), 140.4, 130.2 (t, J = 9.8 Hz), 130.1 (s), 118.3 (t, J = 14.0 Hz), 112.7 (AA′X, N = 11.9 Hz), 112.1; elemental analysis: calcd. (%) for $C_9H_5ClF_2N_2$: C 50.37, H 2.35, Cl 16.52, F 17.71, N 13.05; found: C 48.65, H 2.41, N 12.62; HR-MS (+p ESI): m/z = 215.017 [M+H$^+$], calcd. for $C_9H_5ClF_2N_2$: 215.600.

1,3-Difluoro-2-(4-bromo-1*H*-pyrazol-1-yl)-benzene (21b): The reaction of 4-bromo-1-phenyl-1*H*-pyrazole (111 mg, 0.5 mmol) and NFSI (788 mg, 2.5 mmol), affords **21b**; yield: 49.9 mg (38%); yellow oil; (ethyl acetate-heptane = 3:7); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.76 (s, 1H), 7.69 (m, 1H), 7.44–7.34 (m, 1H), 7.12–7.04 (m, 2H); ^{19}F NMR (282 MHz, $CDCl_3$): δ = –120.0; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.1 (d, J = 255.2 Hz), 159.1 (d, J = 255.2 Hz), 142.4, 132.3, 130.4 (t, J = 9.7 Hz), 118. 5 (t, J = 16.5 Hz), 112.7 (AA′X, N = 11,9 Hz), 95.3; elemental analysis: calcd. (%) for $C_9H_6BrF_2N_2$: C 41.73, H 1.95, N 10.81; found: C 41.78, H 2.21, N 11.06; HR-MS (+p ESI): m/z = 258.967 [M+H$^+$], calcd. for $C_9H_6BrF_2N_2$: 258.960.

1,3-Difluoro-2-(4-nitro-1*H*-pyrazol-1-yl)-benzene (22b): The reaction of 4-nitro-1-phenyl-1*H*-pyrazole (64.1 mg, 0.34 mmol) and NFSI (428.9 mg, 1.36 mmol), affords **22b** after 40 h; yield: 44.2 mg (57%); yellow oil; (ethyl acetate-heptane = 3:7); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.41 (b, 1H), 8.34 (s, 1H), 7.55–7.45 (m, 1H), 7.19–7.15 (m, 2H); ^{19}F NMR (282 MHz, $CDCl_3$): δ = –119.6; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.0 (d, J = 255.2 Hz), 158.9 (d, J =

255.2 Hz), 142.4, 132.2, 130.2 (t, $J=9.7$ Hz), 118.2 (t, $J=16.6$ Hz), 112.6 (AA′X, N=11,7 Hz), 95.3 (s); elemental analysis: calcd. (%) for $C_9H_5F_2N_3O_2$: C 48.01, H 2.24, F 16.88, N 18.66, O 14.21; found: C 48.27, H 2.82, N 17.78; HR-MS (+p ESI): $m/z=226.042$ $[M+H^+]$, calcd. for $C_9H_5F_2N_3O_2$: 226.150.

1,3-Difluoro-2-(4-methyl-1*H*-pyrazol-1-yl)-benzene (23b): The reaction of 4-methyl-1-phenyl-1*H*-pyrazole (158 mg, 1 mmol) and NFSI (946 mg, 3 mmol), affords **23b**; yield: 43.2 mg (23%); yellow oil; (ethyl acetate-heptane=3:7); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.51$ (b, 1H), 7.32 (b, 1H), 7.24–7.16 (m, 1H), 6.98–6.89 (m, 2H), 2.06 (s, 3H); ^{19}F NMR (470 MHz, $CDCl_3$): $\delta=-120.3$; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=159.2$ (d, $J=254.1$ Hz), 159.1 (d, $J=254.1$ Hz), 142.5, 130.7, 129.3 (t, $J=9.8$ Hz), 119.2 (t, $J=14.6$ Hz), 117.5, 112.5 (AA′X, N=12.0 Hz), 8.9; elemental analysis: calcd. (%) for $C_{10}H_8F_2N_2$: C 61.85, H 4.15, N 14.43; found: C 61.30, H 4.92, N 14.56; HR-MS (+p ESI): $m/z=195.072$ $[M+H^+]$, calcd. for $C_{10}H_8F_2N_2$: 195.070.

4-Fluoro-3-(1*H*-pyrazol-1-yl)-nitrobenzene (24a): The reaction of 3-(1*H*-pyrazol-1-yl)-nitrobenzene (94.5 mg, 0.5 mmol) and NFSI (788 mg, 2.5 mmol), affords **24a**; yield: 40.9 mg (39%); yellow solid; (ethyl acetate-heptane=3:7). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=8.93$ (dd, $J=6.44$, 2.44 Hz, 1H), 8.16 (ddd, $J=9.08$, 3.96, 2.87 Hz, 1H), 8.11–8.09 (m, 1H), 7.80 (d, $J=1.67$ Hz, 1H), 7.40 (dd, $J=10.78$, 9.09 Hz, 1H), 6.55 (dd, $J=2.58$, 1.84 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): $\delta=-114.8$; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=158.0$ (d, $J=258.8$ Hz), 145.0 (b), 142.1, 131.0 (d, $J=12.2$ Hz), 129.3 (d, $J=10.3$ Hz), 122.6 (d, $J=9.5$ Hz), 120.2 (d, $J=2.9$ Hz), 118.2 (d, $J=23.5$ Hz), 108.9 (d, $J=2.1$ Hz); elemental analysis: calcd. (%) for $C_9H_6FN_3O_2$: C 52.18, H 2.92, N 20.28; found: C 51.60, H 3.18, N 19.08; HR-MS (+p ESI): $m/z=208.051$ $[M+H^+]$, calcd. for $C_9H_6FN_3O_2$: 208.040.

4-Fluoro-3-(1*H*-pyrazol-1-yl)-phenyl acetate (25a): The reaction of 3-(1*H*-pyrazol-1-yl)-phenyl acetate (148.4 mg, 0.73 mmol) and NFSI (1.15 g, 3.65 mmol), affords **25a**; yield: 53.9 mg (49%); yellow oil; (ethyl acetate-heptane=3:7); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=8.61$ (dd, $J=7.68$, 2.19 Hz, 1H), 8.02 (ddd, $J=2.95$, 0.39 Hz, 1H), 7.99–7.94 (m, 1H), 7.77 (d, $J=1.70$ Hz, 1H), 7.28 (dd, $J=11.22$, 8.65 Hz, 1H), 6.50 (dd, $J=2.51$, 1.85 Hz, 1H), 3.92 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$): $\delta=-118.3$; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=165.6$, 157.9 (d, $J=256.1$ Hz), 141.4, 130.9 (d, $J=10.6$ Hz), 129.3 (d, $J=9.0$ Hz), 128.6 (d, $J=10.0$ Hz), 127.6 (d, $J=3.3$ Hz), 126.1 (d, $J=2.1$ Hz), 117.3 (d, $J=21.8$ Hz), 108.1 (d, $J=1.6$ Hz), 52.5; elemental analysis: calcd. (%) for $C_{11}H_9FN_2O_2$: C 60.00, H 4.12, N 12.72; found: C 58.83, H 4.60, N 11.93; HR-MS (+p ESI): $m/z=221.071$ $[M+H^+]$, calcd. for $C_{11}H_9FN_2O_2$: 221.060.

2,4-Fluoro-3-(1*H*-pyrazol-1-yl)-phenyl acetate (25b): The reaction of 3-(1*H*-pyrazol-1-yl)-phenyl acetate (148.4 mg, 0.73 mmol) and NFSI (1.15 g, 3.65 mmol), affords **25b**; yield: 30.5 mg (26%); orange oil; (ethyl acetate-heptane=3:7); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=8.07$–8.00 (m, 1H), 7.82 (d, $J=1.61$ Hz, 1H), 7.67 (m, 1H), 7.13 (td, $J=8.85$, 1.81 Hz, 1H), 6.52 (dd, $J=2.47$, 1.91 Hz, 1H), 3.94 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$): $\delta=-114.7$, -111.2; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=163.6$ (d, $J=4.3$ Hz), 162.0 (dd, $J=262.1$, 2.9 Hz), 159.3 (dd, $J=268.5$, 3.7 Hz), 142.0 (s), 132.6 (dd, $J=10.4$, 2.3 Hz), 132.4, 119.7 (b), 116.3 (dd, $J=9.6$, 3.8 Hz), 112.5 (dd, $J=20.6$, 4.3 Hz), 107.4, 52.8, elemental analysis: calcd (%) for $C_{11}H_9F_2N_2O_2$: C 55.47, H 3.39, N 11.76; found: C 56.09, H 4.13, N 11.09; HR-MS (+p ESI): $m/z=239.062$ $[M+H^+]$, calcd. for $C_{11}H_9F_2N_2O_2$: 239.060.

Acknowledgements

This work was supported by the Université de Bourgogne (MESR PhD grant for CT), the ERASMUS program (SS), the Région Bourgogne (PARI SMT8) and the CNRS (3MIM and the "Délégation-CNRS" of PFL). ENS de Lyon and C. Andraud are sincerely thanked for their support. This work was granted access to the HPC resources of IDRIS under the allocation 2014-087259 made by GENCI. Calculations were performed using HPC resources from DSI-CCUB (Université de Bourgogne). Referees are acknowledged for suggestions about complementary experiments.

References

[1] For selected reviews on the ligand directed C–H bond activation, see: a) K. Hirano, M. Miura, *Top. Catal.* **2014**, *57*, 878; b) N. Kuhl, M. N. Hopkinson, J. Wencel-Delord, F. Glorius, *Angew. Chem.* **2012**, *124*, 10382; *Angew. Chem. Int. Ed.* **2012**, *51*, 10236; c) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147; d) L. Ackermann, *Top. Organomet. Chem.* **2007**, *24*, 35.

[2] a) K. Hirano, M. Miura, in: *Sustainable Catalysis: Challenges and Practices for the Pharmaceutical and Fine Chemical Industries*, (Eds.: P. J. Dunn, K. K. (Mimi) Hii, M. J. Krische, M. T. Williams), John Wiley & Sons, Inc., Hoboken, New Jersey, **2013**, p 233; b) J. Wang, M. Sanchez-Rosello, J. L. Acena, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, *114*, 2432; c) M. G. Campbell, T. Ritter, *Org. Process Res. Dev.* **2014**, *18*, 474; d) I. Ojima, *J. Org. Chem.* **2013**, *78*, 6358.

[3] For selected reviews on the formation of Ar–F bonds, see: a) T. Liang, C. N. Neumann, T. Ritter, *Angew. Chem.* **2013**, *125*, 8372; *Angew. Chem. Int. Ed.* **2013**, *52*, 8214; b) C. Hollingworth, V. Gouverneur, *Chem. Commun.* **2012**, *48*, 2929; c) X. Mu, G. Liu, *Org. Chem. Front.* **2014**, *1*, 430; d) Y. Li, Y. Wu, G.-S. Li, X.-S. Wang, *Adv. Synth. Catal.* **2014**, *356*, 1412; e) A. Lin, C. B. Huehls, J. Yang, *Org. Chem. Front.* **2014**, *1*, 434.

[4] a) T. Furuya, A. E. Strom, T. Ritter, *J. Am. Chem. Soc.* **2009**, *131*, 1662; b) Y. Ye, M. S. Sanford, *J. Am. Chem. Soc.* **2013**, *135*, 4648.

[5] a) T. Furuya, H. M. Kaiser, T. Ritter, *Angew. Chem.* **2008**, *120*, 6082; *Angew. Chem. Int. Ed.* **2008**, *47*, 5993; b) P. S. Fier, J. Luo, J. F. Hartwig, *J. Am. Chem. Soc.* **2013**, *135*, 2552; c) Y. Ye, S. D. Schimler, P. S. Hanley, M. S. Sanford, *J. Am. Chem. Soc.* **2013**, *135*, 16292.

[6] P. Tang, T. Ritter, *Tetrahedron* **2011**, *67*, 4449.

[7] a) D. A. Watson, M. Su, G. Teverovskiy, Y. Zhang, J. Garcia-Fortanet, T. Kinzel, S. L. Buchwald, *Science* **2009**, *325*, 1661; b) H. G. Lee, P. J. Milner, S. L. Buchwald, *J. Am. Chem. Soc.* **2014**, *136*, 3792; c) P. S. Fier, J. F. Hartwig, *J. Am. Chem. Soc.* **2012**, *134*, 10795.

[8] K. L. Hull, W. Q. Anani, M. S. Sanford, *J. Am. Chem. Soc.* **2006**, *128*, 7134.
[9] K. B. McMurtrey, J. M. Racowski, M. S. Sanford, *Org. Lett.* **2012**, *14*, 4094.
[10] a) X. Wang, T.-S. Mei, J.-Q. Yu, *J. Am. Chem. Soc.* **2009**, *131*, 7520; b) K. S. L. Chan, M. Wasa, X. Wang, J.-Q. Yu, *Angew. Chem.* **2011**, *123*, 9247; *Angew. Chem. Int. Ed.* **2011**, *50*, 9081.
[11] S.-J. Lou, D.-Q. Xu, A.-B. Xia, Y.-F. Wang, Y. Liu, X.-H. Du, Z.-Y. Xu, *Chem. Commun.* **2013**, *49*, 6218.
[12] S.-J. Lou, D.-Q. Xu, Z.-Y. Xu, *Angew. Chem.* **2014**, *126*, 10490; *Angew. Chem. Int. Ed.* **2014**, *53*, 10330.
[13] a) V. V. Grushin, *Chem. Eur. J.* **2002**, *8*, 1006; b) V. V. Grushin, W. J. Marshall, *Organometallics* **2007**, *26*, 4997; c) V. V. Grushin, W. J. Marshall, *Organometallics* **2008**, *27*, 4825; d) for discussions on Pd(IV) and Pd(III) chemistry, see: M. G. Campbell, T. Ritter, *Chem. Rev.* **2015**, *115*, 612.
[14] V. Rampazzi, A. Massard, P. Richard, M. Picquet, P. Le Gendre, J.-C. Hierso, *ChemCatChem* **2012**, *4*, 1828.
[15] T. Lv, X.-H. Zhang, J.-S. Han, P. Zhong, *J. Fluorine Chem.* **2012**, *137*, 44.
[16] For selected publications on arylpyrazole directed C–H bond activation with palladium catalysts, see: a) D. Shabashov, O. Daugulis, *Org. Lett.* **2005**, *7*, 3657–3659; b) X. Jia, D. Yang, W. Wang, F. Luo, J. Cheng, *J. Org. Chem.* **2009**, *74*, 9470–9474; c) S. Hernandez, I. Moreno, R. SanMartin, G. Gomez, M. T. Herrero, E. Domınguez, *J. Org. Chem.* **2010**, *75*, 434–441.
[17] Q. Ding, C. Ye, S. Pu, B. Cao, *Tetrahedron* **2014**, *70*, 409.
[18] a) M. Lafrance, K. Fagnou, *J. Am. Chem. Soc.* **2006**, *128*, 16496; b) D. Garcıa-Cuadrado, P. de Mendoza, A. A. C. Braga, F. Maseras, A. M. Echavarren, *J. Am. Chem. Soc.* **2007**, *129*, 6880.
[19] The Pd(II) complexes formed from a given reactant are denoted by **I-x** (**x**=reactant number) as shown in Scheme 5 with **I-1**.
[20] a) D. C. Powers, T. Ritter, *Nat. Chem.* **2009**, *1*, 302; b) D. C. Powers, M. A. L. Geibel, J. E. M. N. Klein, T. Ritter, *J. Am. Chem. Soc.* **2009**, *131*, 17050; c) D. C. Powers, E. Lee, A. Ariafard, M. S. Sanford, B. F. Yates, A. J. Canty, T. Ritter, *J. Am. Chem. Soc.* **2012**, *134*, 12002; d) D. C. Powers, T. Ritter, *Acc. Chem. Res.* **2012**, *45*, 840, and references cited therein.
[21] a) T. Furuya, D. Benitez, E. Tkatchouk, A. E. Strom, P. Tang, W. A. Goddard, T. Ritter, *J. Am. Chem. Soc.* **2010**, *132*, 3793; b) D.-V. Yandulov, N.-T. Tran, *J. Am. Chem. Soc.* **2007**, *129*, 1342.
[22] L. Cui, M. Saeys, *ChemCatChem* **2011**, *3*, 1060.
[23] An outer-sphere fluorination has been recently proposed for a *nucleophilic* allylic fluorination, see: M. H. Katcher, P.-O. Norrby, A. G. Doyle, *Organometallics* **2014**, *33*, 2121.
[24] a) P. Sehnal, R. J. K. Taylor, I. J. S. Fairlamb, *Chem. Rev.* **2010**, *110*, 824; b) L. Ackermann, R. Vicente, A. R. Kapdi, *Angew. Chem.* **2009**, *121*, 9976; *Angew. Chem. Int. Ed.* **2009**, *48*, 9792; c) K. Muniz, *Angew. Chem.* **2009**, *121*, 9576; *Angew. Chem. Int. Ed.* **2009**, *48*, 9412; d) L. Xue, L. Z. Lin, *Chem. Soc. Rev.* **2010**, *39*, 1692.
[25] E. R. Johnson, S. Keinan, P. Mori-Sánchez, J. Contreras-García, A. J. Cohen, W. Yang, *J. Am. Chem. Soc.* **2010**, *132*, 6498.
[26] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery Jr, J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, N. J. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, *Gaussian 09*, Revision A.02, Gaussian, Inc., Wallingford, CT, **2009**.
[27] J. D. Chai, M. Head-Gordon, *Phys. Chem. Chem. Phys.* **2008**, *10*, 6615.
[28] a) S. Mierts, E. Scrocco, J. Tomasi, *Chem. Phys.* **1981**, *55*, 117; b) M. Cossi, B. Mennucci, J. Tomasi, *Chem. Phys. Lett.* **1994**, *228*, 165–170; c) B. Mennucci, E. Cancès, J. Tomasi, *J. Phys. Chem. B* **1997**, *101*, 10506.
[29] a) E. W. Ren, W. Vanden-Eijnden, *Phys. Rev. B* **2002**, *66*, 052301; b) P. Fleurat-Lessard, P. Dayal, *Opt'n Path v1.50*, freely available at: http://perso.ens-lyon.fr/paul.-fleurat-lessard/ReactionPath.html.
[30] a) P. Hay, W. Wadt, *J. Chem. Phys.* **1985**, *82*, 299; b) A. Ehlers, M. Böhme, S. Dapprich, A. Gobbi, A. Höllwarth, V. Jonas, K. Köhler, R. Stegmann, A. Veldkamp, G. Frenking, *Chem. Phys. Lett.* **1993**, *208*, 111; c) L. Roy, P. Hay, R. Martin, *J. Chem. Theory Comput.* **2008**, *4*, 1029.
[31] a) D. Feller, *J. Comp. Chem.* **1996**, *17*, 1571; b) K. L. Schuchardt, B. T. Didier, T. Elsethagen, L. Sun, V. Gurumoorthi, J. Chase, J. Li, T. L. Windus, *J. Chem. Inf. Model.* **2007**, *47*, 1045.
[32] a) A. E. Reed, L. A. Curtiss, F. Weinhold, *Chem. Rev.* **1988**, *88*, 899, and references cited therein; b) F. Weinhold, J. E. Carpenter, in: *The Structure of Small Molecules and Ions*, (Eds.: R. Naaman, Z. Vager, Plenum Press, **1988**, p 227.

