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Extending the substrate scope of palladium-catalyzed arylfluorination of allylic amine derivatives

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ABSTRACT

Fluorinated molecules often show superior bioactivity or ADME (absorption, distribution, metabolism, and excretion) properties compared to their non-fluorinated analogues. In fact, 20–30 % of newly approved drugs and the majority of recently approved agrochemicals are organofluorine compounds. Unsurprisingly, there is great interest in the development of new and/or improved processes for fluorine incorporation. Pd-catalyzed arylfluorination of alkenes is a novel, emerging fluorination method, which simultaneously introduces a fluorine atom and an aryl group into an alkene framework. The aim of the current work was studying, improving, and extending a literature arylfluorination protocol, which originally utilized *N*-allylated sulfonamide substrates.

1. Introduction

Although organofluorine compounds are very rare in nature, approximately 20–30 % of newly approved drugs and the majority of recently approved agrochemicals are fluorine-containing organic compounds [1–3]. This surprising popularity can be explained by the advantages of fluorination, which is ultimately the consequence of the special properties of fluorine and the C–F bond. First of all, C–F bonds make their molecular environment electron deficient (fluorine is strongly electron-withdrawing), and they are stronger than C–H bonds. As a result, replacement of a hydrogen with fluorine can greatly affect reactivity. This usually leads to improved metabolic or chemical stability, but it can be utilized to create mechanism-based inhibitors or chemically more robust isosteres of certain functional groups as well [1]. Furthermore, the highly polar C–F unit can participate in dipole–dipole interactions, it can strengthen drug–protein binding and enhance potency of the drug [1]. It is also important that the strong electron withdrawal of fluorine decreases pK_a of fluorinated molecules, which – together with the polar hydrophobic nature of the C–F unit – significantly affects lipophilicity and oral bioavailability. Finally, because fluorine is only slightly larger than hydrogen, fluorination usually does not change the steric bulk of a molecule, although the particular stereoelectronic effects of fluorine may have an impact on the conformational landscape. As a result, in many cases, fluorination provides the above-mentioned advantages without negatively affecting bioactivity. Some fluorinated drugs, together with the particular benefits of fluorination, are depicted on Fig. 1 [1,4,5].

Taking into consideration the above-mentioned importance of organofluorine drugs, it is not surprising that the synthesis of fluorine-containing organic compounds has received considerable attention in recent years [6–15]. Numerous syntheses utilize commercially available fluorinated building blocks [16], but more and more new methods are available for the direct introduction of fluorine [6–13], trifluoromethyl groups [11–15], and other small, fluorinated groups [11–13]. The main goals in the development of these methods are increasing yields and selectivity, improving functional group tolerance, achieving enantioselectivity, and discovering useful synthetic pathways.

Pd-catalyzed arylfluorination of alkenes, namely, an olefin difunctionalization process, in which an aryl group and a fluorine atom add simultaneously to an alkene, is one of the most recent methods [10, 17–24]. One of these approaches, 1,1-arylfluorination of *N*-allylated sulfonamides, especially caught our attention [18]. The general reaction

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is depicted on Scheme 1, while the mechanism is shown on Scheme 2. Earlier reports suggest that the role of the sulfonyl group is to stabilize the intermediates by coordination to the palladium center [17].

Organofluorine chemistry is a highlighted research topic of our group [25–28]. Therefore, our goals were further optimization of the 1,1-arylfluorination procedure (Schemes 1 and 2) and its extension to other types of substrates (Fig. 2).

2. Results and discussion

Selectfluor as a bis-quaternary ammonium salt, has good solubility in water and limited solubility in some polar organic solvents (*e.g.* MeOH, MeCN, $MeNO_2$, DMF) [29]. However, it is basically insoluble in other organic solvents [30]. Because of this, the original 1,1-arylfluorination procedure utilized a biphasic system: the aqueous phase (H_2O and some MeCN) dissolved Selectfluor, while the organic phase (CH_2Cl_2 and some MeCN) dissolved the other reactants [18]. Such biphasic systems require intense stirring, and even with that, availability of Selectfluor is still limited. Indeed, Toste and coworkers proposed that palladium migration (see Scheme 2) can take place because the limited access to Selectfluor slows down electrophilic fluorine transfer [18].

The original report carefully investigated the effects of various factors on the process depicted on Schemes 1, 2. The efficiency order of various sulfonyl directing groups was Ns > Ts > Ms > 4-MeO—C_6H_4-SO_2. The reactions were successful with phenylboronic acid and its halogen-, alkyl-, or ester-substituted derivatives. Numerous R^1 substituents [OMe, Cy, Bn, α-(carboethoxy)benzyl, substituted phenyl, and 2-(methoxycarbonyl)thiophen-3-yl group] attached to the nitrogen atom were tolerated. The allyl group was replaceable with a but-3-ene-1-yl group with a slight loss of productivity, but longer ω-alkene-1-yl groups provided much lower yields of < 20 %. The cheap 2,2′-bipyridyl ligand was only slightly inferior to the 4,4′-di-*tert*-butyl-2,2′-bipyridyl ligand [18].

In the case of Cu-catalyzed aryltrifluoromethylation of alkenes, the presence of alcohols was reported to accelerate the transmetalation process [31,32]. Because MeOH dissolves Selectfluor, replacement of H_2O with MeOH in the original ternary solvent system also promised a more homogenous, faster process. With these assumptions in mind, we started our studies by comparing the $CH_2Cl_2/H_2O/MeCN$ and $CH_2Cl_2/MeOH/MeCN$ systems. To be cost-effective, the reactants were *N*-tosylated compound **4** and $PhB(OH)_2$, and 2,2′-bipyridyl was utilized as ligand.

Under conditions described above, the transformation of compound **4** in $CH_2Cl_2/H_2O/MeCN$ 10:2:1 was inefficient. According to TLC, 48 h were needed for complete consumption of the starting compound with a yield of a mere 33 %. The transformation in $CH_2Cl_2/MeOH/MeCN$ 10:2:1, in turn, required only 3.5 h providing 44 % of product (±)−**5** (Scheme 3).

The new system was still heterogeneous (most of Selectfluor was just suspended in the $CH_2Cl_2/MeOH/MeCN$ solvent system), and still required intense stirring. However, the advantages were obvious, and we experimented with the $CH_2Cl_2/MeOH$ ratio (the amount of MeCN and the overall volume were kept unchanged). The results are summarized in Table 1. According to TLC, increasing the amount of MeOH accelerated both product formation and byproduct formation (see the SI for more details). As a result, increasing the amount of MeOH initially improves yield, then an optimum is reached at $CH_2Cl_2/MeOH/MeCN$ 10.6:1.4:1 ratio (Table 1, entry 4), then excessive byproduct formation deteriorates the yield.

With the partially optimized solvent mixture in hand, we briefly investigated the effect of temperature. Performing the reaction under reflux resulted in a slight acceleration at the cost of yield (Scheme 4). Thus, we choose to perform the reactions at RT.

Investigations on variation of the amount of Selecfluor indicated us, that applying higher amount of fluorinating agent (3 equiv) did not affect the yield of the product, however with only 1 equiv Selectfluor at room temperature the isolated yield significantly decreased (from 50 % to 20 %).

Finally, replacing 2,2′-bipyridyl with 4,4′-di-*tert*-butyl-2,2′-bipyridyl enhanced the yield from 50 % to 54 %. As a comparison, phenylfluorination of **4** by the original literature method provided 49 % of product (±)−**5** after 18 h (Scheme 5).

We also compared the original literature conditions and our finalized method utilizing substrate **6** (Scheme 6). Our finalized method provided 54 % yield after 5 h. Using the original literature conditions, complete consumption of **6** required 30 h, and the yield of (±)−**7** was 55 % (if the reaction was worked up after 5 h, the yield was 46 %). According to literature, yield of (±)−**7** can reach 68 % if the reaction is performed on a smaller (0.1 mmol) scale [18].

The most relevant arylfluorinations of substrates **4** and **6** are

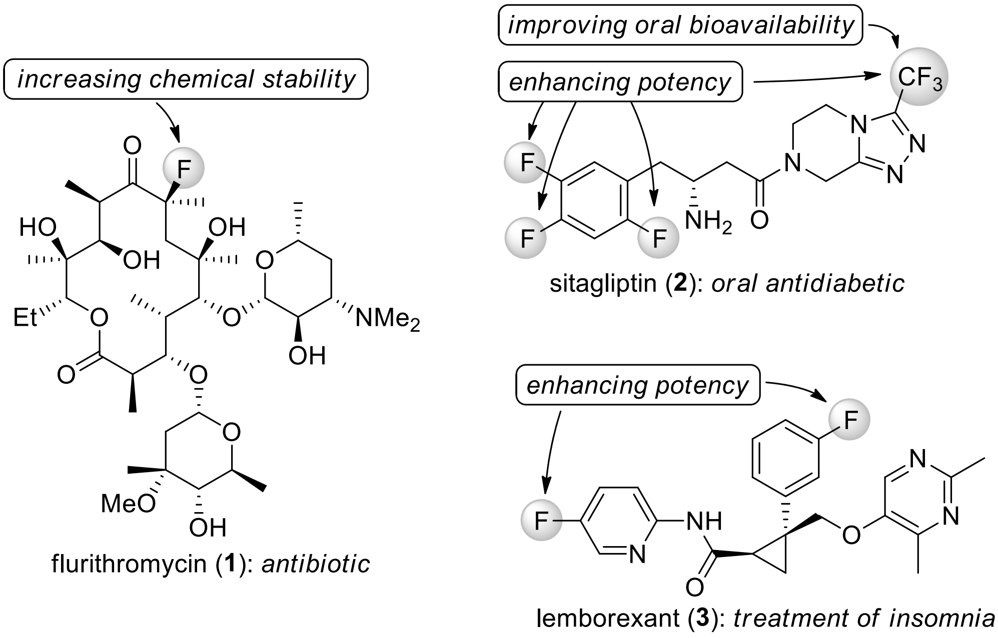
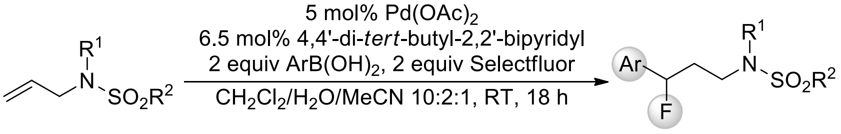
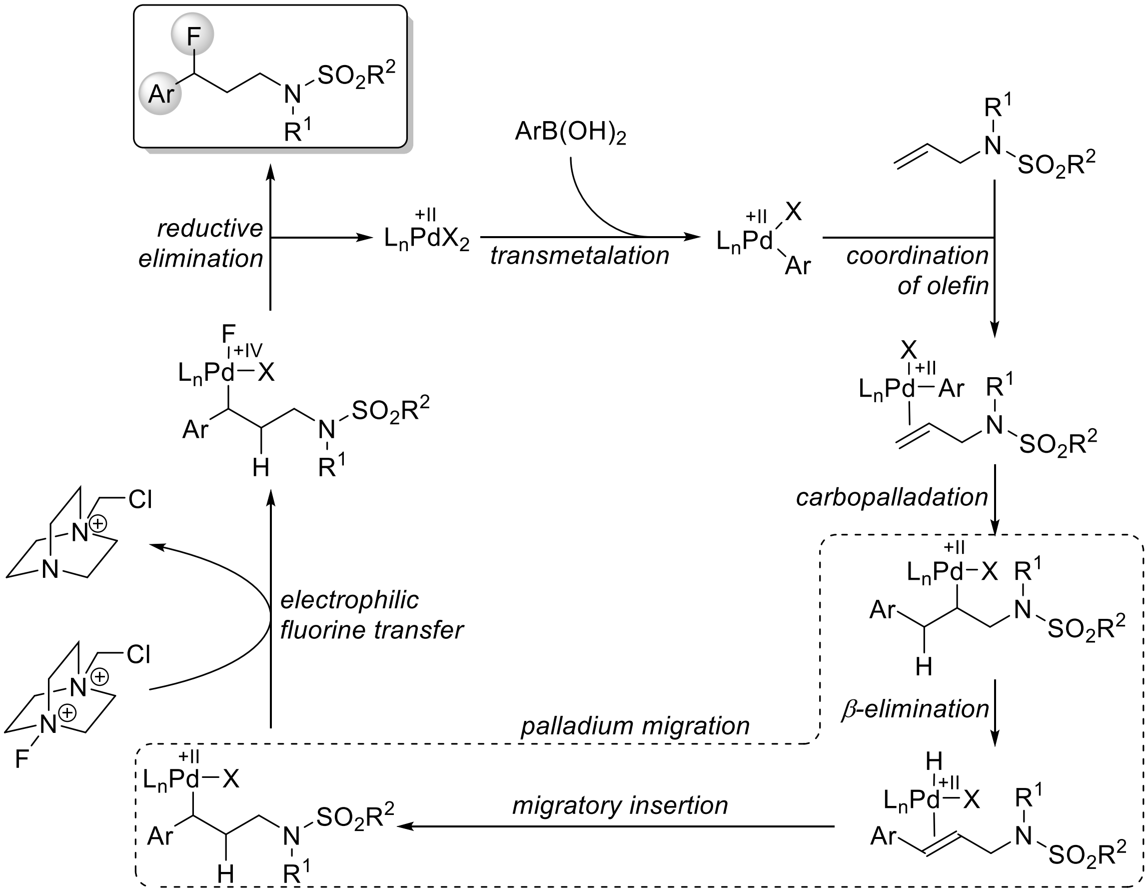


Fig. 1. Examples of the beneficial features of fluorine incorporation into drugs.



Scheme 1. General reaction equation of 1,1-arylfluorination of *N*-allylated sulfonamides.



Scheme 2. Mechanism of 1,1-arylfluorination of *N*-allylated sulfonamides. Coordination of the sulfonyl group to the Pd center is not shown. In the presence of an appropriate chiral ligand, the process is enantioselective.

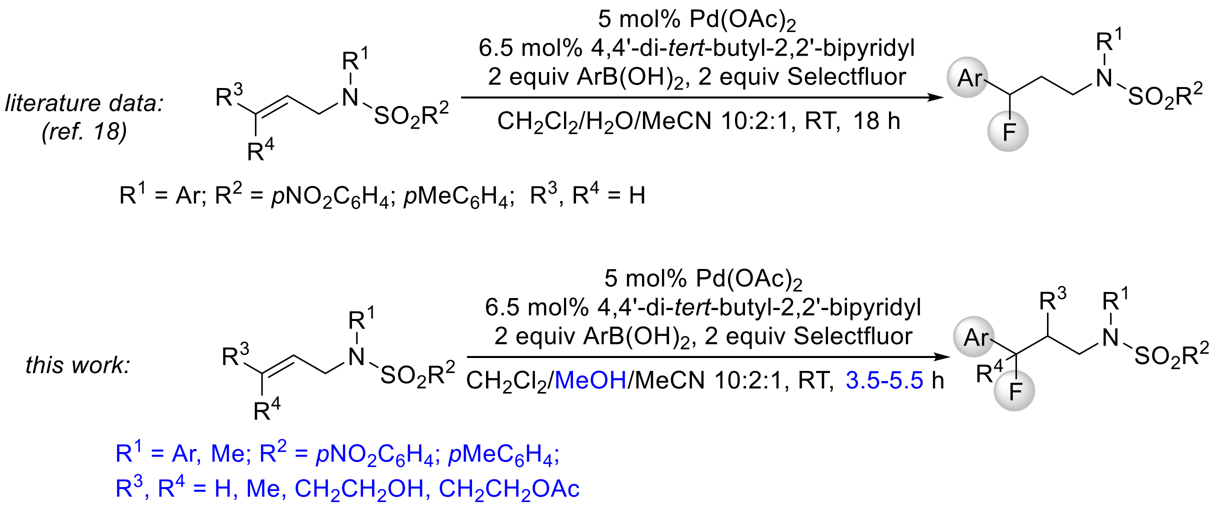
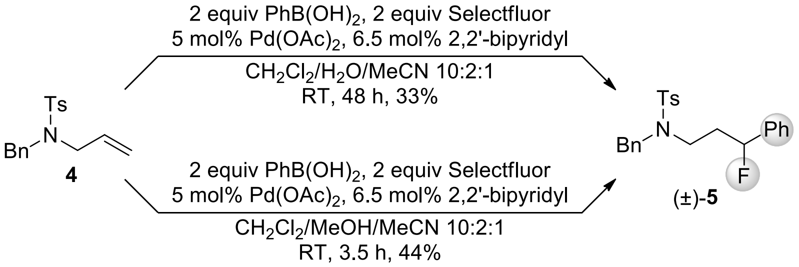


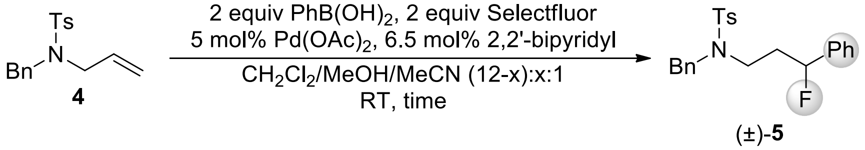
Fig. 2. Literature reaction and its extension during the current work.



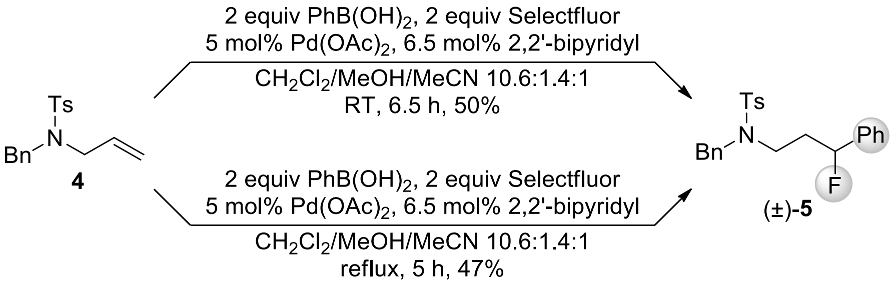
Scheme 3. Arylfluorinations of model compound **4** using 2,2′-bipyridyl ligand. Top arrow: literature solvents, bottom arrow: our first CH_2Cl_2/MeOH/MeCN solvent mixture.

Table 1

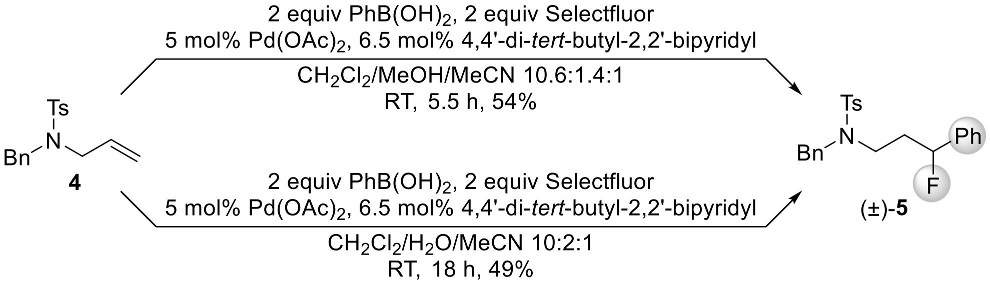
Partial solvent optimization of the CH_2Cl_2/MeOH/MeCN system.



Entry	CH_2Cl_2/MeOH/MeCN ratio	Reaction time	Yield
1	11.4:0.6:1	48 h	42 %
2	11:1:1	18 h	46 %
3	10.8:1.2:1	14 h	46 %
4	10.6:1.4:1	6.5 h	50 %
5	10.4:1.6:1	4 h	45 %
6	10:2:1	3.5 h	44 %
7	9:3:1	3.5 h	35 %
8	8:4:1	2.5 h	34 %

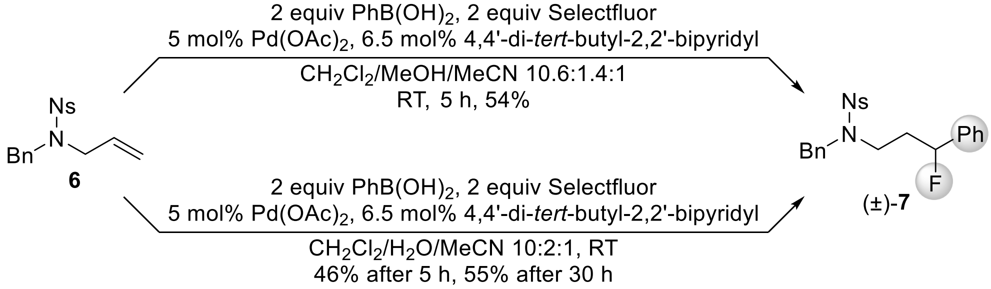


Scheme 4. Investigating the effect of temperature.



Scheme 5. Arylfluorinations of model compound **4** by the finalized method (top) and the literature process (bottom).

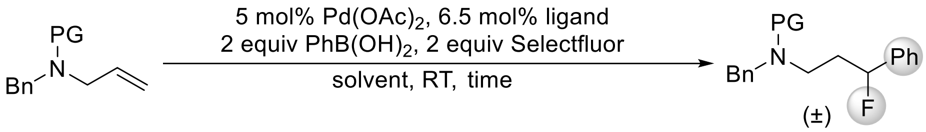
summarized in Table 2. In the case of tosylated substrate **4**, replacing water with methanol always shortened the reaction time and improved the yield (Table 2, entries 1–4). Yield improvement was higher when 2,2′-bipyridyl ligand was used (Table 2, entries 1–2). Our observations suggest that the Pd(II) complex of 2,2′-bipyridyl is prone to precipitation in the apolar CH_2Cl_2 (see *General procedures for arylfluorination* in the SI),



Scheme 6. Arylfluorinations of model compound **6** by the finalized method (top) and the literature method (bottom).

Table 2

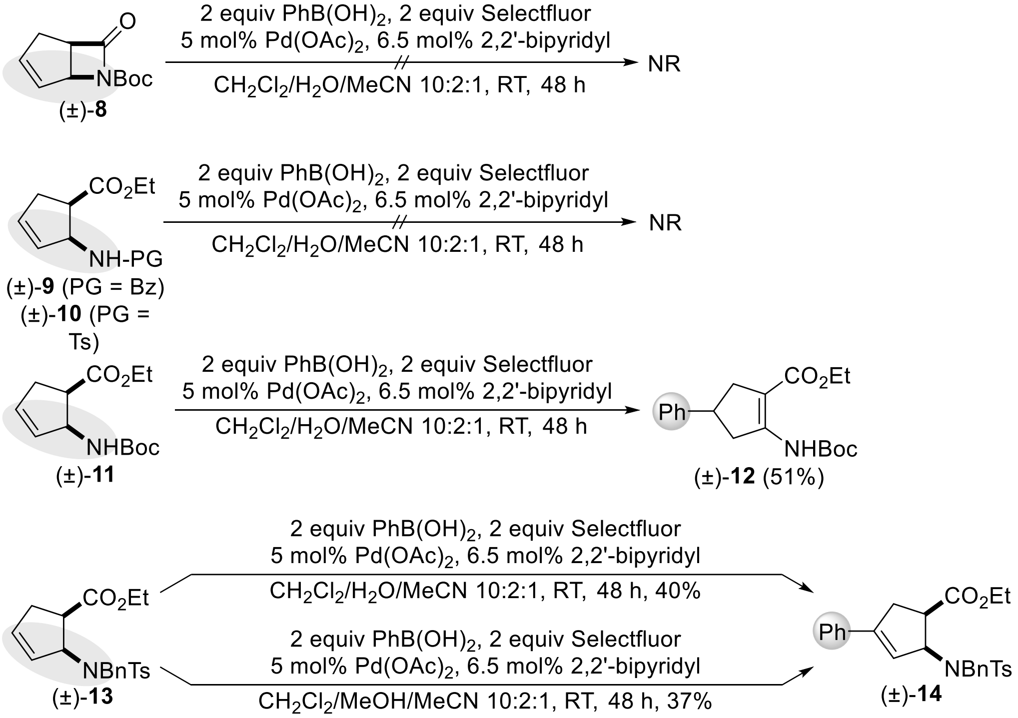
Comparison of arylfluorinations. 'Aqueous' solvent (or literature solvent): $CH_2Cl_2/H_2O/MeCN$ 10:2:1. 'Methanolic' solvent (or our solvent): $CH_2Cl_2/MeOH/MeCN$ 10.6:1.4:1. Ligand **A**: 2,2′-bipyridyl, ligand **B**: 4,4′-di-*tert*-butyl-2,2′-bipyridyl.



Entry	PG	Transformation	Solvent	Ligand	Reaction time	Yield
1	Ts	**4** → (±)–**5**	methanolic	**A**	6.5 h	50 %
2	Ts	**4** → (±)–**5**	aqueous	**A**	48 h	33 %
3	Ts	**4** → (±)–**5**	methanolic	**B**	5.5 h	54 %
4	Ts	**4** → (±)–**5**	aqueous	**B**	18 h	49 %
5	Ns	**6** → (±)–**7**	methanolic	**B**	5 h	54 %
6	Ns	**6** → (±)–**7**	aqueous	**B**	5 h	46 %
7	Ns	**6** → (±)–**7**	aqueous	**B**	30 h	55 %

and dissolution of the precipitate by the polar MeOH could contribute to the large yield enhancement. (The analogous 4,4′-di-*tert*-butyl-2,2′-bipyridyl complex of Pd(II) is not prone to precipitation.)

In the case of nosylated substrate **6**, replacing water with methanol significantly shortened the reaction time (from 30 h to 5 h) at the cost of a small (1 %) yield decrease (Table 2, entries 5 and 7). If the original and



Scheme 7. Attempted arylfluorinations of β-amino ester derivatives with an *N*-protected allylic amine motif (highlighted with grey ellipses) (NR = no reaction).

the improved protocols run for the same time (5 h), the improved protocol provided better yield (Table 2, entries 5–6).

Some cyclic β-amino acids and their derivatives have received high attention over the last two decades. Thus, as relevant examples, natural product cispentacin possesses antifungal properties, while tilidine is a well-known analgetic [25,26]. Therefore, in parallel with studying the reactions of compound **4**, transformation of some cycloalkene β-amino acid derivatives with an *N*-protected allylic amine motif was also attempted. Utilizing 2,2′-bipyridyl ligand and the literature solvent, transformation of *N*-Boc-protected ester (±)−**11** provided arylated compound (±)−**12**, while transformation of substrates (±)−**8**, (±)−**9**, and (±)−**10** failed. The exact reason of this protecting group-dependent (Bz or Ts versus Boc) reactivity is not yet known. Using the same ligand, transformation of ester (±)−**13**, which has more structural similarity to compound **4** (e.g. it lacks the N–H proton), provided arylated product (±)−**14** in both $CH_2Cl_2/H_2O/MeCN$ 10:2:1 and $CH_2Cl_2/MeOH/MeCN$ 10:2:1 (Scheme 7).

Formation of products (±)−**12** and (±)−**14** in our hand can be explained by an oxidative boron Heck reaction (in the case of (±)−**12**, it is followed by C=C bond migration driven by the extension of conjugation). Oxidative Heck reactions are known side reactions of arylfluorinations, their general mechanism is depicted on Scheme 8 [10]. Note that product (±)-**12** was previously synthesized by traditional Heck arylation of β-amino ester (±)−**11** [33].

After we optimized arylfluorination of **4** (see Table 1-2 and Schemes 4-6), one final attempt was made to extend the reaction to cycloalkene β-amino esters. It was assumed that oxidative Heck arylation is preferred because the cyclopentene ring imposes serious conformational restriction to the allylic amine motif. Thus, arylfluorination of cyclooctene β-amino ester (±)-**15**, which contains a more flexible ring system (less conformational restrictions) compared to that of compound (±)−**13**, was attempted with our final optimized system. Unfortunately, even after 2 days, no product was detected, and about 86 % unreacted (±)−**15** was recovered (Scheme 9).

Realizing that we need a deeper understanding of the nature and limitations of arylfluorination, we decided to investigate the substrate scope of the reaction. After realizing that Toste and coworkers did not utilize sulfonamides with a substituted *N*-allyl group [18], we started this work by subjecting such substrates to arylfluorination using our final optimized system.

Arylfluorination of *N*-(2-methylallyl)-substituted substrate **16** was very sluggish, but provided the expected product (±)−**17** in 35 % yield (Scheme 10). Notably, although the reaction generates two chiral centers, the product was obtained as a single diastereoisomer. Unfortunately, the relative configuration of the two chiral centers could not be determined.

N-Prenylated compound **18** was expected to undergo 1,2-arylfluorination (the two methyl groups attached to the olefin bond hinder the usual 1,1-arylfluorination process). Instead, even after 52 h, transformation of compound **18** provided only 17 % acetal **19** (Scheme 10) together with 53 % unreacted starting compound.

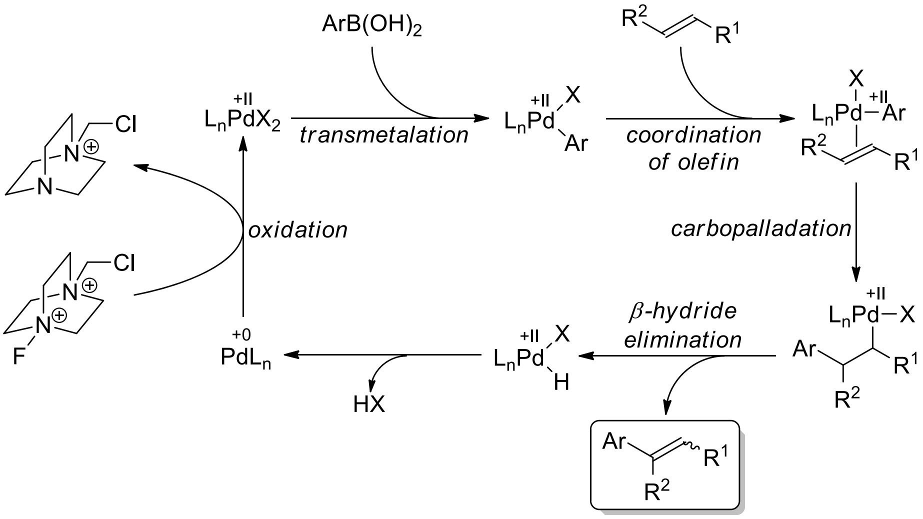
Arylfluorination of *N*-cinnamylated compound **20** yielded mixed results (Scheme 10). On the one hand, NMR of the product mixture indicated the presence of a fluorine-containing product. On the other hand, separation of the products failed.

The proposed mechanism of the formation of acetal **19** is shown on Scheme 11. After carbopalladation, β-hydride elimination, yields an enamine derivative, which is then transformed into a hemiaminal derivative via 2 possible pathways. One pathway involves hydropalladation, coordination of a methanol molecule to the Pd(II) center, then Pd-catalyzed C–O coupling. The other pathway involves direct reaction between methanol and the enamine intermediate. From the formed hemiaminal derivative, the sulfonamide anion, as an acceptable leaving group, is expelled. This generates an oxonium ion, whose reaction with a second molecule of methanol yields product **19**.

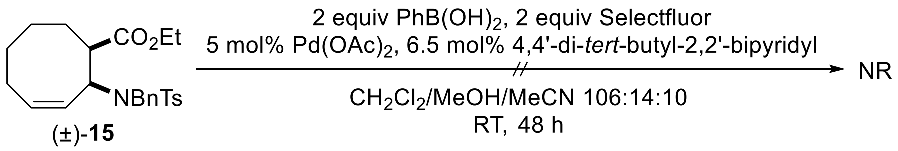
At this stage, we were curious to know if there were any size limitation of the R^1 substituents on nitrogen (see Schemes 1, 2). It was previously demonstrated that R^1 = OMe, which is close in size to the smallest organic group (Me), allows successful arylfluorination [18], but the upper limit of the size of R^1 groups was unknown (groups larger than Bn, 3,4-methylenedioxyphenyl, or 2,4,6-trimethylphenyl were not tested). Considering these, compound **21** (where R^1 is the small Me) and compound **23** (where R^1 is the bulky 9-anthryl group) were subjected to arylfluorination. To our delight, both substrates provided the desired products (Scheme 12).

It was previously demonstrated that this arylfluorination reaction tolerates aryl halides, alkoxy groups, the methylenedioxy group, and ester groups [18]. However, there was no information, whether the reaction tolerates hydroxylated substrates. Therefore, we subjected alcohol **25** to arylfluorination. To our delight, the desired arylfluorinated product (±)−**26** was formed in 51 % yield (Scheme 13). Less surprisingly, transformation of the *O*-acetyl protected derivative of **25** was also successful (Scheme 13). Apparently, direct arylfluorination of alcohol-containing substrates seems to give better yield than an *O*-protection/arylfluorination/*O*-deprotection sequence.

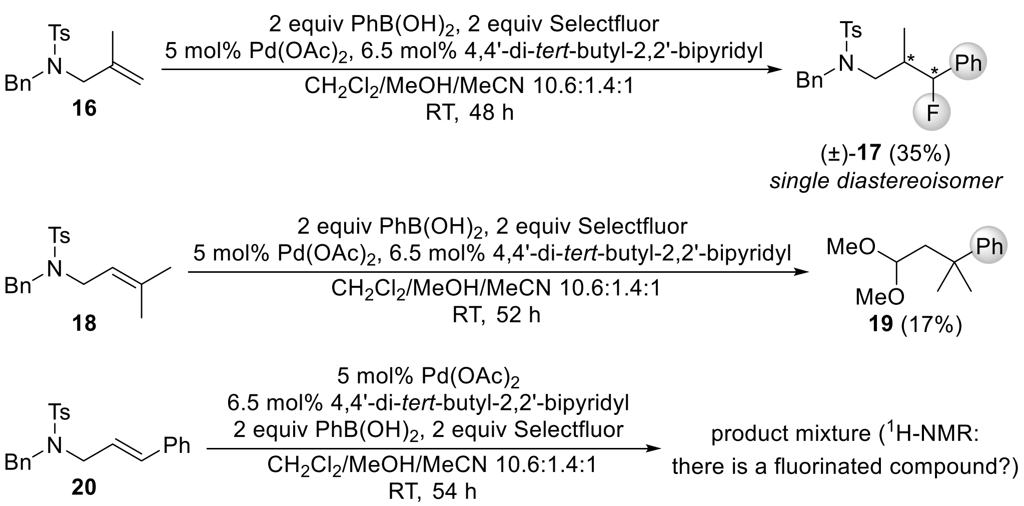
Arylfluorination of *N*-(3-hydroxyphenyl) substituted compound **29** was also investigated, but all attempts resulted in a mixture of unidentifiable products. Because the analogous *N*-phenyl substituted



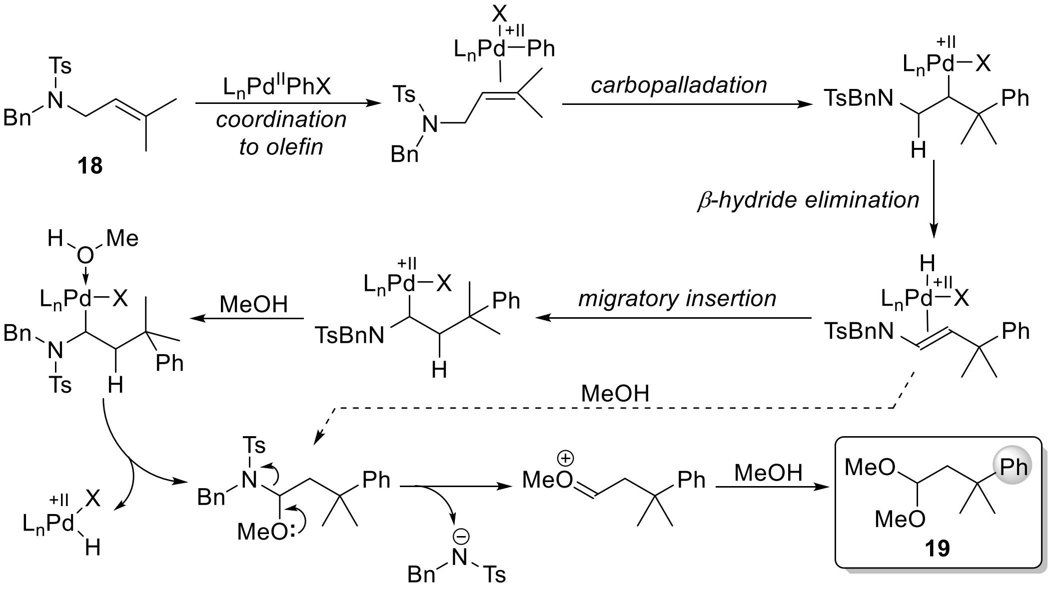
Scheme 8. Mechanism of oxidative boron Heck arylation under arylfluorination conditions.



Scheme 9. Attempted arylfluorination of β-amino ester (±)−**15**.



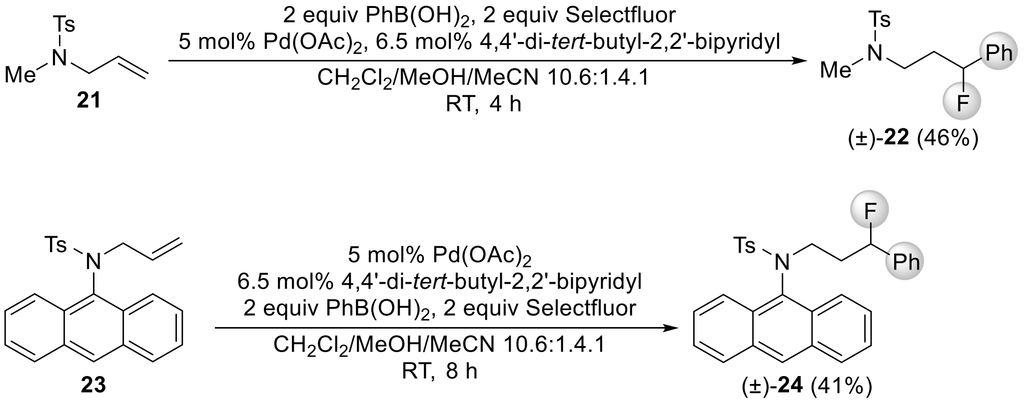
Scheme 10. Arylfluorination analogues of compound **4** with substituted allyl groups. Product (±)−**17** was isolated as a single diastereoisomer, but the relative configuration of the two chiral centers was not determined.



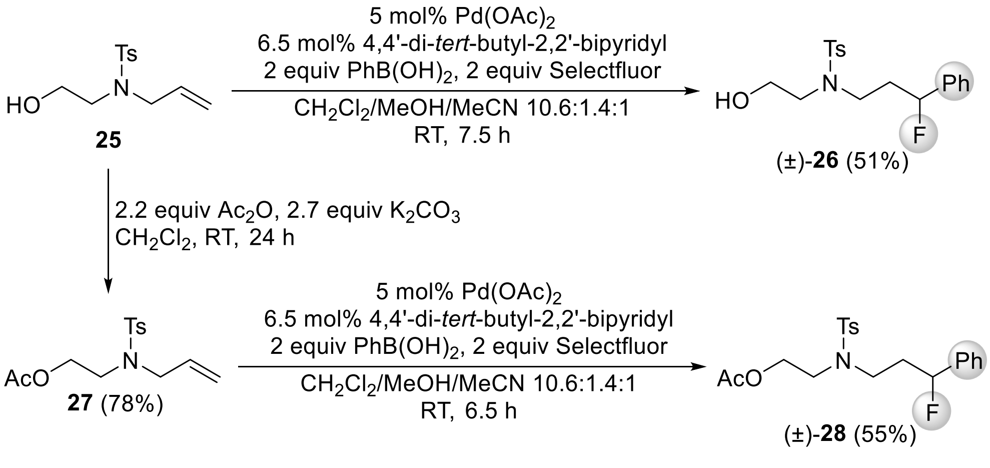
Scheme 11. Formation mechanism of acetal **19**.

compound can be arylfluorinated [18], the problem was clearly the presence of the phenolic hydroxy group. Therefore, we attempted to arylfluorinate acetate **30** (the *O*-protected derivative of phenol **29**). Although the arylfluorination reaction should tolerate ester groups [18], compound **30** yielded only oxidative Heck product **31** in a low yield. The *E* geometry of **31** was deduced from the large coupling constant between the olefin proton ($3\,J \approx 15.80$ Hz). Finally, transformation of compound **32**, a side product of the synthesis of phenol **29**, was also attempted. We were curious to know, whether the second C=C bond (the *O*-allyl group) interferes with arylfluorination. Unfortunately, all attempts resulted in a mixture of unidentifiable products. These results are summarized on Scheme 14.

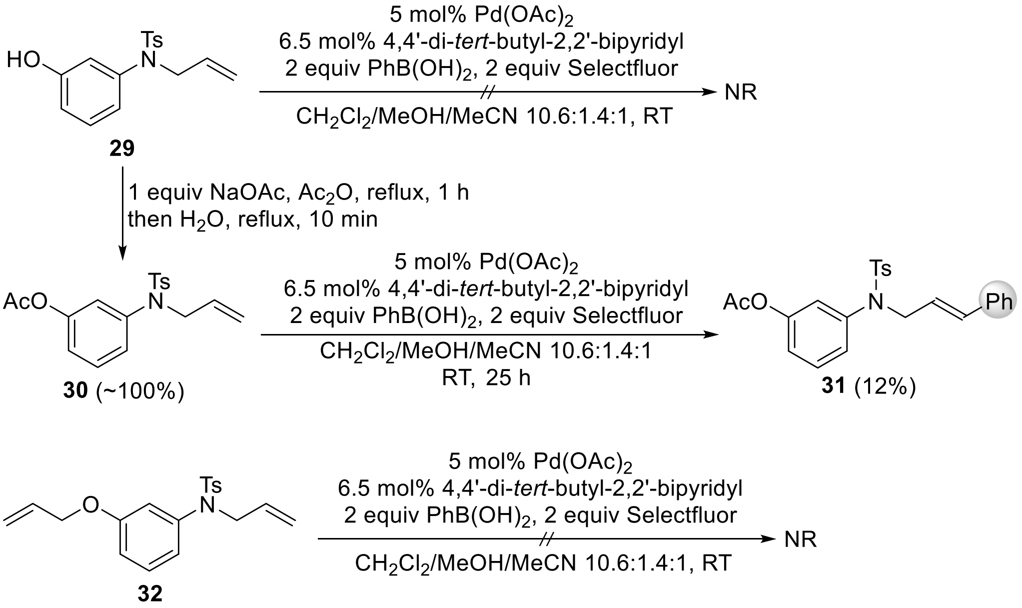
Although the transformation of compound **32** failed, arylfluorination of dienes was still a promising goal. We assumed that if the olefin bonds are close enough to each other, the initially formed alkylpalladium(II) intermediate might undergo carbopalladation on the second olefin bond before any palladium migration or electrophilic fluorination could occur. Such a chain of events may result in a completely new



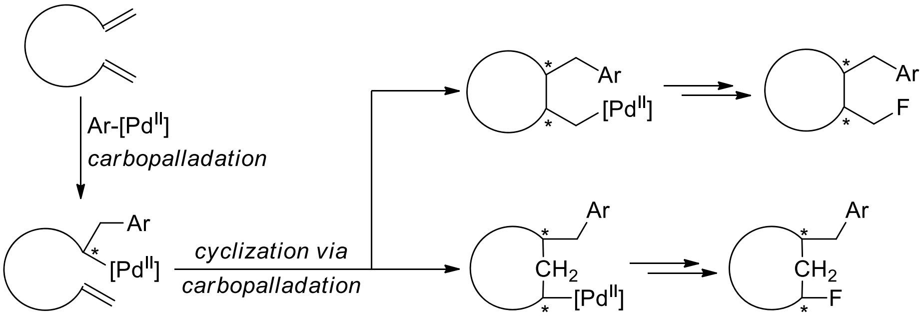
Scheme 12. Investigating size constraints of the unchanged non-sulfonyl *N*-substituent (the R[1] group on Schemes 1, 2).



Scheme 13. Investigating functional group tolerance: transformation of alcohol **25** and its *O*-protected derivative **27**.



Scheme 14. Attempted arylfluorination of phenol **29** and its *O*-allylated and *O*-acetylated derivatives.



Scheme 15. Planned arylfluorinative cyclization of dienes.

arylfluorinative cyclization process (Scheme 15).

To test this hypothesis, *N,N*-diallylated sulfonamide **33** was synthesized. Arylfluorination of compound **33** yielded a complex product mixture. With difficulties, two products – olefin (±)−**34** and arylfluorinated product (±)−**35** – were isolated in very low yields (Scheme 16). Although the structure of **33** should enable both pyrrolidine and piperidine ring formation (see Scheme 15), both products contained a pyrrolidine ring. Notably, although product (±)−**35** possesses three chiral centers, it was isolated as a single diastereoisomer. Unfortunately, our attempts to grow single crystals suitable for X-ray crystallography failed. NOESY suggests that a *trans* disubstituted pyrrolidine ring is more likely than a *cis* disubstituted one, but the evidence is inconclusive. Therefore, the relative configurations of the chiral centers have not yet been determined.

The mechanism proposed for the formation of the two products is depicted on Scheme 17. The initial steps – intermolecular carbopalladation, then pyrrolidine ring formation via a second (intramolecular) carbopalladation – are identical. The formed intermediate can undergo either β-elimination to yield olefin (±)−**34**, or three consecutive palladium migrations followed by electrophilic fluorine transfer and reductive elimination to yield product (±)−**35**. However, the low yields of these two products strongly suggest that the described processes are accompanied with a number of side reactions.

Up to this point, almost all substrates, which were successfully arylfluorinated by us (or the authors of the original report), were sulfonamides without N–H protons [18], where the electronic structure of the sulfonamide group should favor coordination to palladium via the oxygen atom. This suggests that mainly the sulfonyl part of the directing group is important. Therefore, the sulfonamide nitrogen may be replaced with other atoms and the reaction can be extended to other types of substrates as well. To test this hypothesis, allyl tosylate **36** and sulfone **37** were prepared and subjected to arylfluorination. In the case of allyl tosylate **36**, the reaction resulted only in decomposition of the starting compound (Scheme 18). This can be accounted for by the good leaving group nature of the tosylate anion, which enables formation of allyl cations and possibly (η^3-allyl)Pd(II) complexes during the reaction, opening alternative reaction pathways. In contrast, transformation of sulfone **37**, where the leaving group problem is absent, was successful, although the process is not as effective as the transformation of sulfonamides (Scheme 18). It is worth to note that successful arylfluorination of *N*-methyl-2-vinylbenzenesulfonamide, which has some structural similarity to **37**, was already reported in the literature [17].

Recently, arylfluorination of *N*-(alk-1-ene-1-yl) substituted cyclic carbamates, amides, thiocarbamates, and carbamides was reported [21]. This prompted us to investigate arylfluorination of readily available *N*-allylated cyclic imides. Toste and coworkers briefly investigated transformation of *N*-allylphthalimide **39**, and obtained 28 % yield under unoptimized conditions [18]. Under our conditions, the yield of arylfluorinated product (±)−**40** increased to 40 % (0.5 mmol scale) or 51 % (3.5 mmol scale). Interestingly, transformation of *N*-allylsuccinimide **41** was much less efficient. It provided only 9 % arylfluorinated product (±)−**42** along with 6 % oxidative Heck product **43**. The reason behind this striking difference is currently unclear. These results are summarized on Scheme 19.

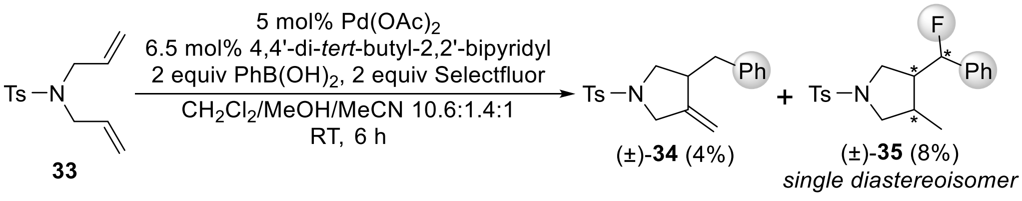
3. Conclusions

Our investigation of Pd-catalyzed 1,1-arylfluorination of *N*-allylated sulfonamides resulted in an improved method, a better understanding of the substrate scope of the process, and the extension of the method to some other compound classes. First of all, it was discovered that this arylfluorination reaction can be greatly accelerated by replacing water with methanol in the solvent mixture. Importantly, rate enhancement was achieved without compromising the yield.

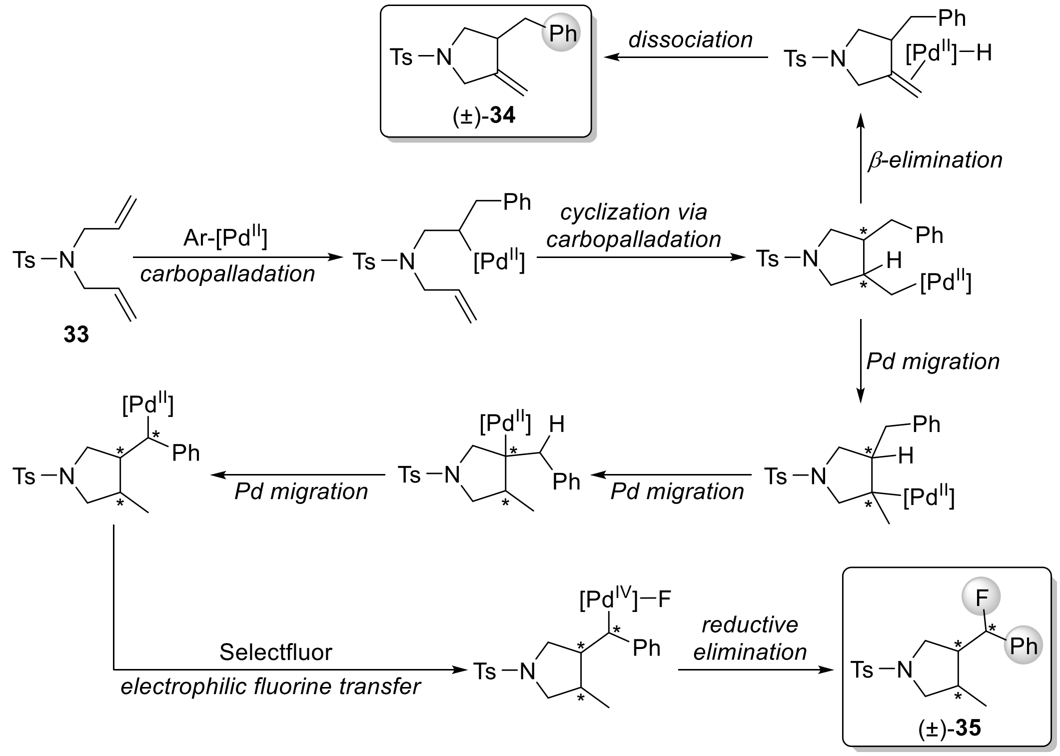
The substrate scope of this 1,1-arylfluorination process was studied previously [18], but the present report provides some important new information. Successful transformation of an *N*-(2-methylallyl)-substituted sulfonamide proved that a limited amount of substituents on the *N*-allyl group is tolerated (although it negatively affects the rate and the yield of the reaction). It was also demonstrated that sulfonamides with a bulky *N*-substituent (*e.g.* a 9-anthryl group) can be transformed fairly normally (only a slightly increased reaction time was necessary). Finally, it was found that the reaction tolerates alcoholic hydroxy groups, but not phenolic hydroxy groups.

Furthermore, the 1,1-arylfluorination process was successfully extended to a sulfone and an *N*-allylphthalimide. However, transformation of cyclic β-amino esters and allyl tosylate failed.

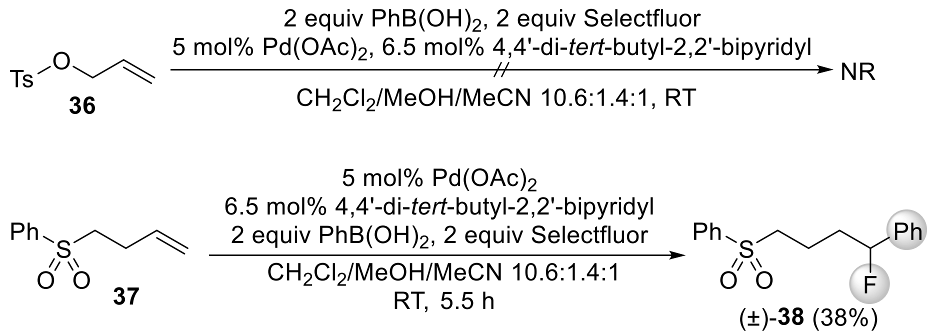
It was demonstrated that arylfluorination of dienes can result in



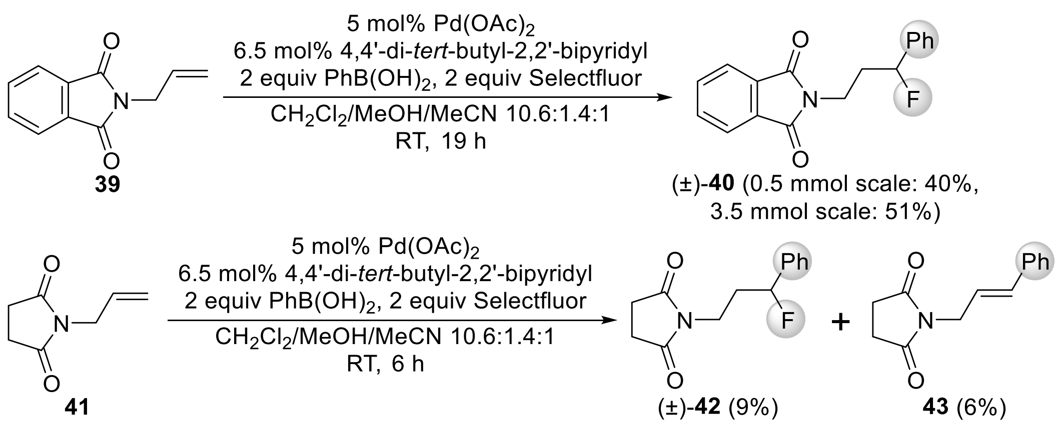
Scheme 16. Arylfluorination of *N,N*-diallyl sulfonamide **33**. Product (±)−**35** was isolated as a single diastereoisomer, but relative configuration of the three chiral centers was not determined.



Scheme 17. Formation mechanisms of compounds (±)−**34** and (±)−**35**.



Scheme 18. Attempted arylfluorination of sulfonate **36** and sulfone **37**.



Scheme 19. Arylfluorination of cyclic imides **39** and **41**.

arylfluorinative cyclization. However, because of the wide variety of the accompanying side reactions, the yield is rather low. To sum up, this cyclization process will require further development and optimization to become synthetically useful.

To sum up our intention in this paper was to give a preliminary insight into the arylfluorination of various sulfonamide derivatives with structural and functional diversity complemented with other classes of unsaturated compounds (amino esters, sulfones, sulfonates, imides). As the arylfluorination protocol has been found to be a highly substrate dependent and functional group directed processes, further extensions and studies on this methodology are currently underway in our laboratory.

4. Experimental section

4.1. General information

Chemicals were purchased from Sigma–Aldrich, TCI, Apollo Scientific, and Thermo Fischer Scientific. Solvents were used as received from the suppliers. Melting points were determined with a Kofler apparatus. TLC plates (TLC Silica gel 60 F_{254}) and silica gel for column chromatography (technical grade, pore size 60 Å, 70–230 mesh) were purchased from Merck. NMR spectra were acquired at room temperature on a Bruker Avance Neo 500 spectrometer with 11.75 T magnetic field strength (^1H frequency 500.20 MHz, ^{19}F frequency 470.66 MHz, ^{13}C frequency 125.78 MHz) in $CDCl_3$, D_6-DMSO, or D_6-benzene solution, using the deuterium signal of the solvent to lock the field. The ^1H and ^{13}C chemical shifts are given relative to TMS and ^{19}F to $CFCl_3$ (0.00 ppm). HRMS were acquired on either a Thermo Scientific Q-Exactive Plus Orbitrap mass spectrometer (Thermo Fisher Scientific Inc., Budapest, Hungary) equipped with an electrospray ionization ion source in the positive ionization mode, or a Q-TOF Premier mass spectrometer (Waters Corporation, Milford, MA, USA) in positive electrospray ionization mode.

4.2. Experimental procedures

Details of the experimental procedures, characterization of the compounds, ^1H and ^{13}C NMR spectra of new compounds, some preliminary results, and additional references [34–62] can be found in the supplementary material associated with this article.

4.2.1. General procedure for N-sulfonylation of amines

To a solution of 7.70 mmol amine in 30 ml CH_2Cl_2, 1.5 equiv Et_3N ($\rho = 0.726$ g/ml → 1.61 ml) was added, followed by 1 equiv sulfonyl chloride (TsCl or NsCl) in small portions. The reaction mixture was stirred at room temperature for the indicated time (generally 1–2 h). Then, 25 ml water was added, and the aqueous phase was extracted with 3 × 15 ml CH_2Cl_2. The combined organic phase was dried on Na_2SO_4. The pure product was obtained via crystallization or column chromatography.

4.2.2. General procedure for sulfonamide N-alkylation

7.16 mmol sulfonamide was dissolved in 50 ml THF, followed by the addition of 1.2–1.8 equiv alkyl halide, 0.2 equiv $n\mathrm{Bu_4NBr}$ (0.46 g), 0.1 equiv KI (0.12 g), and 2.1 equiv freshly powdered KOH (0.84 g). The reaction mixture was stirred vigorously at room temperature for the time indicated in the *Supporting Information* (1.5–22 h). Then, the reaction was quenched with 50 ml saturated aqueous NH_4Cl solution, and the reaction mixture was extracted with 3 × 50 ml EtOAc. The organic phase was dried on Na_2SO_4. After the drying agent was filtered out, the resulting filtrate was evaporated to silica gel and purified by column chromatography.

4.2.3. Synthesis of 2-(N-allyl-4-methylphenylsulfonamido)ethyl acetate (27)

To a solution of *N*-allyl-*N*-(2-hydroxyethyl)−4-methylbenzenesulfonamide **25** (255 mg, 1.00 mmol) in 5 ml CH_2Cl_2, 2.2 equiv Ac_2O ($\rho = 1.082$ g/ml → 0.21 ml) and 2.7 equiv K_2CO_3 (373 mg) were added, and the resulting suspension was stirred vigorously at RT for 24 h. After that, the reaction mixture was washed with 6 ml saturated aqueous $NaHCO_3$ solution, and the organic phase was dried on Na_2SO_4. After the drying agent was filtered out, the filtrate was evaporated to silica gel and purified by column chromatography. The product was 231 mg colorless oil (78 %).

4.2.4. Synthesis of 3-(N-allyl-4-methylphenylsulfonamido)phenyl acetate (30)

To the solution of *N*-allyl-*N*-(3-hydroxyphenyl)−4-methylbenzenesulfonamide **29** (0.51 g, 1.68 mmol) in 5 ml Ac_2O, 1 equiv NaOAc (0.14 g) was added, and the mixture was refluxed for 1 h. Then, 5 ml water was added, and the reaction mixture was refluxed for an additional 10 min. The hot reaction mixture was poured into 50 ml water. The resulting aqueous phase was extracted with 3 × 10 ml CH_2Cl_2. The organic phase was dried on Na_2SO_4. After the drying agent was filtered out, the filtrate was evaporated to silica gel and purified by column chromatography. The product was 0.58 g pale brown oil (yield: quantitative).

4.2.5. Synthesis of allyl 4-methylbenzenesulfonate (36)

A mixture of 10 ml diethyl ether, 0.58 g (10.00 mmol) allyl alcohol, and 1 equiv tosyl chloride (1.91 g) was cooled to 0 °C. Then, 2.77 equiv powdered NaOH (1.11 g) was added. The mixture was stirred vigorously for 6 h and slowly warmed up to RT. Then the precipitates were filtered out, the filtrate was evaporated to silica gel, and purified by column chromatography. The product was 426 mg colorless oil (20 %).

4.2.6. Synthesis of (but-3-en-1-ylsulfonyl)benzene (37)

To the suspension of 0.15 g (6.17 mmol) magnesium turnings according to Grignard for synthesis in 3 ml anhydrous THF, 0.51 ml EtBr ($\rho = 1.460$ g/ml → 6.88 mmol) was added. After formation of the ~2 M EtMgBr solution was complete, it was cooled to RT, and a solution of 0.78 g (5.00 mmol) methyl phenyl sulfone in 5 ml anhydrous toluene was added quickly via dropping funnel. After stirring at RT for 10 min, the reaction mixture was brought rapidly to boiling with a preheated oil bath, maintained for 3 min at reflux, then cooled back to room temperature. To the resulting $PhSO_2CH_2MgBr$ solution, the mixture of 0.39 ml allyl bromide ($\rho = 1.398$ g/ml → 4.50 mmol) and 0.4 ml anhydrous toluene was added, followed by 25 mg (0.25 mmol) CuCl. The reaction mixture was stirred at 50–60 °C for 2 h, then poured to a mixture of 10 ml 5 % aqueous HCl and 10 g crushed ice. The phases were separated, and the aqueous phase was extracted with 2 × 10 ml diethyl ether. The combined organic phase was dried on Na_2SO_4. After the drying agent was filtered out, the filtrate was evaporated to silica gel and purified by column chromatography. The product was 579 mg colorless oil (66 %).

4.2.7. Synthesis of cyclic N-allylated imides

To a mixture of 5 ml toluene and 5.06 mmol cyclic anhydride, 1 equiv allylamine ($\rho = 0.761$ g/ml → 0.38 ml) was added. The reaction mixture was stirred at RT for overnight then it was refluxed for 12 h. After cooling down to RT, the mixture was washed with 5 ml water and the organic phase was dried on Na_2SO_4. After the drying agent was filtered out, the filtrate was evaporated to silica gel and purified by column chromatography.

4.2.8. Final procedure for arylfluorination

First, the catalyst solution was prepared. ~5 mol% $Pd(OAc)_2$ (6 mg) and ~6.5 mol% 4,4′-di-*tert*-butyl-2,2′-bipyridyl (9 mg) were dissolved in 1.0 ml CH_2Cl_2, and the resulting mixture was stirred at room temperature for 15–20 min. During this time, the reactant solution was prepared by adding 4.3 ml CH_2Cl_2, 0.7 ml MeOH and 0.5 ml acetonitrile to the mixture of 0.50 mmol starting compound, 2 equiv $PhB(OH)_2$, and 2 equiv Selectfluor powder. Argon gas was bubbled through the reactant solution at room temperature for some minutes (degassing/Ar atmosphere), then the catalyst solution was added. The resulting reaction mixture was stirred vigorously at room temperature for the indicated time. Then, the reaction mixture was diluted with 20 ml CH_2Cl_2, and washed with 4 × 20 ml water (in the case of emulsion formation, some solid NaCl was added to the contents of the separatory funnel). The organic phase was dried on Na_2SO_4. After the drying agent was filtered out, the resulting filtrate was evaporated to silica gel and purified by column chromatography.

Author contribution statement

A. M. R. and L. K. conceived and designed the experiments. T. T. N., T. C. T. N., and A. M. R. performed the experiments. A. M. R., G. H., and L. K. analyzed the data. Á. G. contributed with high-resolution mass spectrometric analysis. A. M. R. and L. K. wrote the paper.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jfluchem.2023.110239.

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