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Exploration of the Scope of Pt-Catalyzed C–F Activation

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We recently reported methods for the catalytic methylation and methoxylation of polyfluoroaryl imines utilizing $[Pt_2Me_4(SMe_2)_2]$ as a precatalyst. These methodologies provide a novel route to partially functionalized aryl fluorides, which have potential utility as building blocks for the synthesis of pharmaceuticals and materials. We report herein efforts to expand the scope of these processes, particularly the choice of directing group. Comparisons to the previously reported scope of Pt^{II}-catalyzed methylation and methoxylation are described.

Introduction

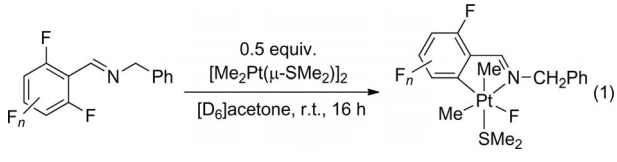
The incorporation of fluorine into chemical structures results in increases in metabolic stability, solubility and lipophilicity.[1] Consequently, fluorine substituents are emerging as common structural motifs in pharmaceuticals and agrochemicals, with approximately half of new drugs containing a fluoroarene.[1,2] Indeed, as of 2009 two of the five top-selling pharmaceuticals in the US (Pfizer's Lipitor and GlaxoSmithKline's Advair) contain an aryl fluoride.[2] Moreover, aryl fluorides are increasingly used in materials and in ligands for transition metals.[3] Because there are no naturally occurring sources of aryl fluorides, these building blocks must be generated through chemical synthesis.[4]

One general strategy for the synthesis of fluoroaromatics has been the selective incorporation of fluorine into a previously non-fluorinated position on an aromatic ring using a transition metal. In this regard, important work on the use of electrophilic fluorinating agents has been developed.[5] Methodologies that utilize nucleophilic fluorine sources in conjunction with transition metal catalysts have also been developed. A significant advance, reported by Buchwald, is the Pd-catalyzed conversion of aryl triflates into aryl fluorides using inexpensive and commercially available fluoride salts.[6]

Hydrodefluorination of perfluoroarenes is another approach to the construction of novel polyfluorinated aromatics.[7] Milstein reported the first example of catalytic defluorination of perfluoroarenes.[7a,7b] More recently, Whittlesey and co-workers disclosed a very effective Ru^{II} system for catalytic defluorination.[7j–7l] The use of early-transition metals[7m–7q] as well as main group elements[7r–7u] in such systems has also been explored. Nevertheless, it would be valuable to replace fluorine with substituents other than hydrogen.

In this regard, stoichiometric C–F activation involving Ni,[8] Pd,[9] Pt[10] and Rh[11] complexes have been extensively explored.[12] Despite various reports of stoichiometric C–F activation, examples of catalytic C–C bond forming reactions are relatively rare.[13] To this end, the Ni^{II}-catalyzed cross-coupling of fluorobenzene with Grignard reagents was the first reported example of a catalytic C–C bond forming reaction involving aryl fluorides.[13a] Methodologies for the catalytic C–F activation of mono and polyfluoroarenes based on group 7[14] and 8[15] metals have been developed but to a much lesser extent. The products of these transformations are partially-functionalized aryl fluorides which have the potential for further use as synthetic building blocks. Of particular interest are late-transition metals capable of C–F activation due to the functional group tolerance of such systems.

With this goal in mind, we have discovered the first examples of Pt-catalyzed methylation and methoxylation of a variety of polyfluoroaryl imines.[16] This methodology is based on the report by Crespo and Martinez that a Pt-dimer, $[Me_2Pt(\mu\text{-}SMe_2)]_2$, effects the stoichiometric C–F activation of a series of polyfluoroaryl imines [Equation (1)].[10a]



(1)

The methylation and methoxylation methodologies provide access to a variety of partially-functionalized aryl fluorides in high yields with high selectivity for *ortho*-functionalization. Furthermore, the majority of these products cannot be obtained from conventional C–Br, –I, or –Cl cross-coupling as the necessary starting materials are not com-

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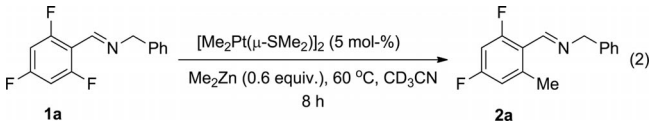
mercially available. Throughout the course of our investigations of Pt^{II}-catalyzed C–F activation we sought to explore and compare the reactivity of different Pt^{II} complexes as well as a variety of polyfluoroarenes. We report herein the results of these investigations.

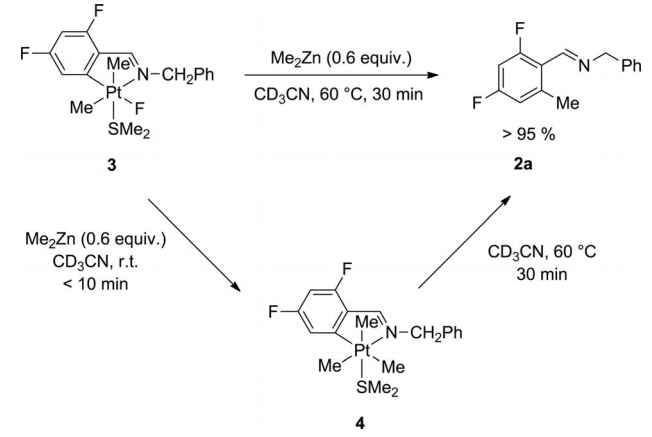
Results and Discussion

Reaction Design

Our investigation of Pt^{II}-catalyzed C–F activation began with the development of a methodology for the methylation of polyfluoroaryl imines. Specifically, use of a catalytic amount (5 mol-%) of the Pt-dimer resulted in complete conversion of *N*-(2,4,6-trifluorobenzylidene)benzylamine (**1a**) to the corresponding methylated imine (**2a**) [Equation (2)].[16a]



The development of this methodology was based on previous work by Crespo and Martinez regarding stoichiometric C–F activation with the Pt-dimer $[Me_2Pt(\mu\text{-}SMe_2)]_2$.[10a] On the basis of this result, we proposed that the resulting Pt–F species could undergo transmetalation with a suitable organometallic reagent; subsequent reductive elimination would lead to C–C bond formation. To this end, treatment of the Pt^{IV}–F complex **3** with dimethylzinc resulted in successful transmetalation to give the Me_3Pt^{IV} complex **4** (Scheme 1). Upon heating, complex **4** underwent clean reductive elimination to give the methylated imine product **2a**.

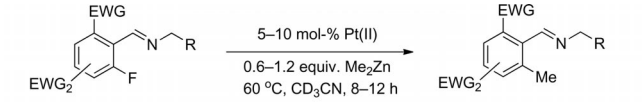


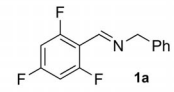
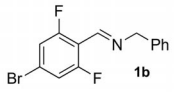
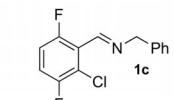
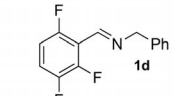
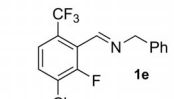
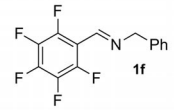
Scheme 1. Transmetalation and reductive elimination of Pt^{IV} complexes.

Methylation of Fluoroarylimines – Scope

Having demonstrated the feasibility of this process, we then explored the substrate scope. The reaction was quite successful for a series of polyfluoroaryl imines (Table 1). The reaction was selective for functionalization in the *ortho* position. Importantly, a significantly weaker carbon–bromine bond was left untouched (entry 2). Substrates **1d** and **1e** (entries 3 and 4, respectively) reacted exclusively at the *ortho* site with an adjacent fluoride, consistent with the selectivity observed in stoichiometric C–F activation.[10a] A variety of substitution patterns can also be tolerated (entries 3–6). In general, the reaction was selective for monomethylation because the methylated products were less-susceptible to oxidative addition than the starting materials. If the initially formed methylated product had a sufficient number of fluorine substituents, di-methylation could be achieved (entry 6).

Table 1. Imine scope of Pt^{II}-catalyzed methylation.



Entry	Imine	$[Me_2Pt(\mu\text{-}SMe_2)]$[a,b]	$PtCl_2(SMe_2)_2$[a,c]	$PtCl_2(DMSO)_2$[a,d]
1	 **1a**	95 %	60 %	95 %
2	 **1b**	85 %	63 %	85 %
3	 **1c**	95 %	30 %	95 %
4	 **1d**	92 %	50 %	90 %
5	 **1e**	95 %[d]	60 %[d]	95 %
6	 **1f**	74 %[e]	20 %	70 %

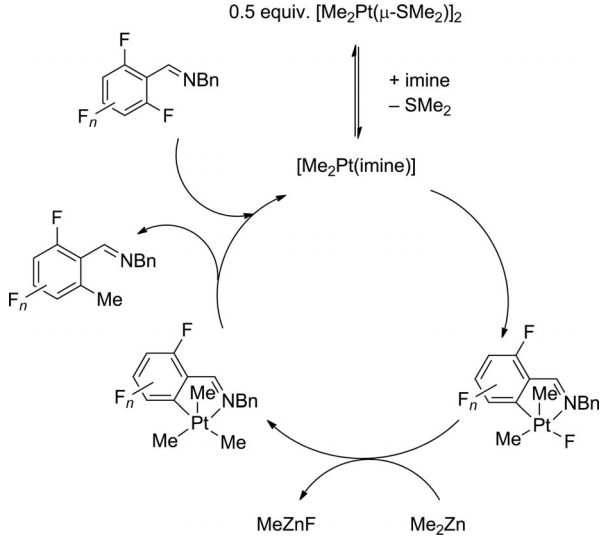
[a] Yield based on ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. [b] Taken from ref.[16a]; conditions: 0.6 equiv. Me_2Zn, 8 h. [c] Taken from ref.[16b]; conditions: 1.2 equiv. Me_2Zn, 12 h. [d] Taken from ref.[16c]; conditions: 1.2 equiv. Me_2Zn, 12 h. [e] Addition of a second equivalent of Me_2Zn after 12 h resulted in dimethylation.

Based on the reactivity of the Pt-dimer $[Me_2Pt(\mu\text{-}SMe_2)]_2$, we were interested in exploring the potential of other related Pt^{II} complexes to promote this reactivity. We discovered two additional Pt^{II} complexes {$[PtCl_2(SMe_2)_2]$[16b] and $[PtCl_2(DMSO)_2]$[16c]} that catalyzed the methylation of the same series of polyfluoroaryl imines. The yields with all three catalysts are included for comparative purposes in Table 1. Preliminary mechanistic investigations revealed that all three likely generate the same active cata-

lyst in the presence of Me_2Zn. Of the Pt^{II} complexes we investigated, $[Me_2Pt(\mu\text{-}SMe_2)]$ remains the most active catalyst over a range of polyfluoroaryl imine substrates.

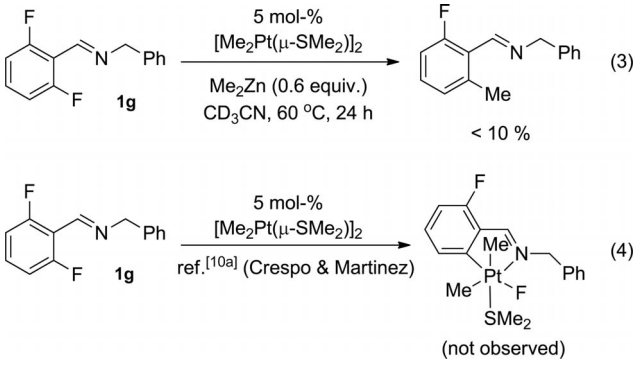
Methylation of Fluoroarylimines – Mechanism

Mechanistic analysis of Pt^{II}-catalyzed methylation indicated that the reaction proceeds through a standard cross-coupling mechanism involving oxidative addition, transmetalation and reductive elimination (Scheme 2).[17] Of note is that the reaction requires a directing group to promote intramolecular C–F activation, providing high selectivity for the *ortho* position. Furthermore, mechanistic investigations found C–F activation to occur on a different timescale compared to either transmetalation or reductive elimination, but on a similar timescale as the overall catalytic reaction.[18] These results indicate that C–F activation is rate-determining (at least for most substrates).



Scheme 2. Mechanism of Pt^{II}-catalyzed methylation of polyfluoroaryl imines.

Importantly, during the course of establishing the substrate scope of this methodology we noticed similarities between the catalytic reactivity of a given imine and its ability to undergo stoichiometric C–F activation. Specifically, 2,6-difluoroimine substrate **1g** was found to have limited catalytic reactivity[16a] [see Equation (3)] and also failed to undergo stoichiometric C–F activation [see Equation (4)].[10a] In addition, the requirement of at least three electron-withdrawing groups in addition to the imine functionality for significant catalytic reactivity was demonstrated by this substrate. A similar dependence was reported by Crespo and Martinez.[10a]



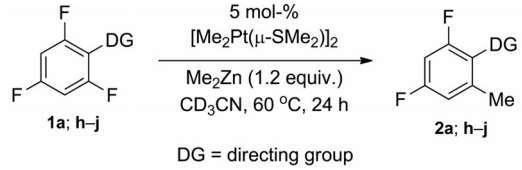
Methylation with Other Directing Groups

The wide range of applications for aryl fluorides necessitates development of a methodology with a broad substrate scope. Unfortunately, attempts to expand the nucleophile scope of Pt^{II}-catalyzed C–F activation beyond that of methylation and methoxylation (vide infra) have been largely unsuccessful. Instead, we sought to explore the potential for a variety of *ortho*-directing groups to undergo catalytic C–F activation utilizing the platinum dimer, given the important role that directing group plays in reaction mechanism.

We began our investigations by preparing a series of 2,4,6-trifluoro-substrates with a series of different directing groups that have literature precedent for directed carbon-atom bond activations.[19] The 2,4,6-trifluoro substitution pattern was selected based on its excellent performance in both Pt^{II}-catalyzed methylation and methoxylation (see Tables 1 and 4).[16a,16d]

Investigations of the reactivity of all substrates towards catalytic methylation were performed at 60 °C in $[D_3]$acetonitrile using 1.2 equiv. of dimethylzinc and 5 mol-% of the Pt-dimer (Table 2). These conditions were selected based on previous optimization studies for methylation of polyfluoroaryl imines (Table 1).[16a] Under these conditions the ox-

Table 2. Directing group scope of Pt^{II}-catalyzed methylation.



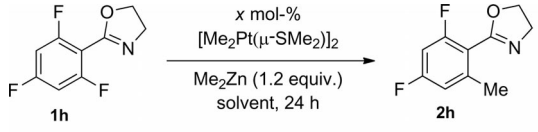
Entry	Directing group	Conversion (%)[a]
1	 **1a**	95
2	 **1h**	52
3	 **1i**	0[b]
4	 **1j**	0[b]

[a] Conversion was determined based on ^1H NMR spectroscopy. In cases that resulted in product formation, the conversions are the average of three independent experiments. [b] Unidentified precipitate formed.

azoline substrate **1h** was converted into the corresponding *ortho*-methylated product in 52% conversion (entry 2; Table 2). Importantly, there was no reactivity in the absence of Pt-catalyst for either imine-based (**1a**, given in entry 1 for comparison) or oxazoline-based substrates **1h**. Neither imidazole nor pyridine directing groups provided the desired product (entries 3 and 4, respectively), although the substrates did undergo reaction (vide infra). A variety of other nitrogen and/or oxygen-based directing groups were explored but were found to be unreactive towards catalytic methylation. Examples include aldehyde, amide and ester functionalities as well as stronger directing groups such as methoxymethyl ether as well as N and O-carbamates. Given that C–F activation is the rate-determining step for the catalytic methylation of 2,4,6-trifluoroarenes, failure of a given substrate to promote catalytic methylation could be the result of an ability of the same substrate to achieve C–F activation and, thus, gain entry into the catalytic cycle.

Attempts were made to further optimize the methylation of the oxazoline substrate by varying temperature, solvent and catalyst loading (Table 3). We anticipated that other polar, coordinating solvents such as [D_6]acetone and [D_6]-DMSO would be successful; however, these resulted in little or no reactivity (entries 1 and 2, Table 3). Non-polar solvents also resulted in negligible conversion to product (entries 3–5; Table 3). In addition, neither increased temperature nor increased catalyst loading led to increased conversion to product (entries 8–9; Table 3). Lower overall conversion at increased temperature is likely the result of catalyst decomposition upon several hours of heating at elevated temperatures.[20] Furthermore, the addition of a second equivalent of dimethylzinc with, or without, catalyst also failed to increase conversion to product.

Table 3. Optimization of conditions for oxazoline directed cross-coupling.



Entry	mol-% Pt-dimer	Solvent	Temp. (°C)	Conv. (%)[a]
1	5	[D_6]acetone	60	10
2	5	[D_6]DMSO	60	0
3	5	C_6D_6	60	0[b]
4	5	[D_8]toluene	60	0[b]
5	5	CD_2Cl_2	35	0
6	5	CD_3CN	35	15
7	5	CD_3CN	60	52
8	10	CD_3CN	60	50
9	5	CD_3CN	80	44

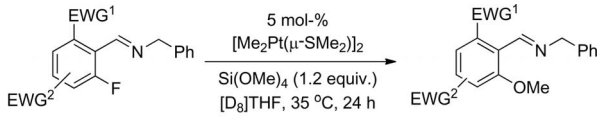
[a] Conversion based on ^{19}F NMR spectroscopy and are the result of a single experiment. [b] Compound was only partially soluble.

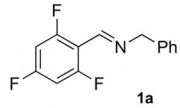
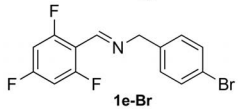
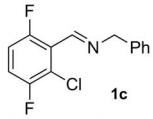
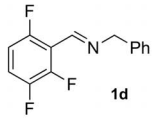
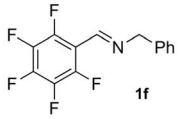
Interestingly, other heterocyclic directing groups such as pyridine or imidazole rings displayed unusual reactivity. More specifically, addition of dimethylzinc to a solution of imidazole substrate (**1i**) or pyridine substrate (**1j**) resulted in immediate formation of intractable precipitates. The lack of solubility of both precipitates has prevented their definitive identification and characterization. For the imidazole substrate, the precipitate presumably results from deprotonation of the imidazole ring. Consistent with this assumption, addition of dimethylzinc resulted in the formation of bubbles. Formation of a precipitate from the pyridine substrate is unlikely a result of deprotonation. Instead, we postulate that nucleophilic addition of a methyl group from dimethylzinc to the pyridine ring generates a Meisenheimer complex.[21]

Methoxylation of Fluoroarylimines – Scope

On the other hand, preliminary investigations have indicated the mechanism of Pt^{II}-catalyzed methoxylation to be a Pt^{II}-catalyzed process mechanistically distinct from the analogous methylation reaction.[22] Of particular significance is that a different catalytic cycle is indicative of cataly-

Table 4. Imine scope of Pt^{II}-catalyzed methoxylation.



Entry	Imine	Conversion (%)[a,b]
1	 **1a**	> 95
2	 **1e-Br**	76
3	 **1b**	71
4	 **1c**	ca. 15
5	 **1d**	< 5
6	 **1f**	< 5

[a] Yield based on ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. [b] As reported in ref.[15d]

sis proceeding via a different Pt^{IV} species. Therefore, substrates which were not found capable of stoichiometric C–F activation may still be active in catalytic methoxylation.

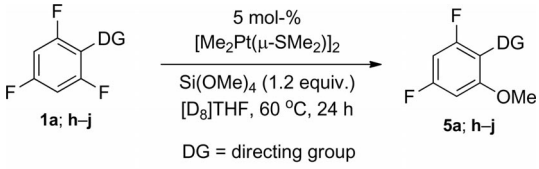
Initial substrate scope investigations made use of the same series of polyfluoroaryl imine substrate as were utilized in the analogous methylation reaction.[16d] Similar reactivity towards Pt^{II}-catalyzed methoxylation was obtained for several imines (entries 1–3; Table 4). However, several important differences in reactivity were noted. Substrates which deviated from the 2,4,6-trifluorosubstitution pattern (entries 3–6; Table 4) displayed significantly lower catalytic activity compared to what was observed with catalytic methylation (entries 3–6; Table 1). This result is of particular significance as it seems to suggest that an alternate mechanism may be operable.

Methoxylation with Other Directing Groups

On the basis of these reactivity differences, we were prompted to investigate the scope of Pt^{II}-catalyzed methoxylation with the same series of non-imine based substrates. As before, the conditions utilized for screening substrates for catalytic reactivity were the conditions previously optimized for the imine-based substrates –35 °C, [D_8]THF, 1.2 equiv. of $Si(OMe)_4$.[16d]

Once again, oxazoline substrate **1h** was found capable of directing catalytic methoxylation resulting in 80% conversion to the methoxylated product under the optimized conditions (entry 2; Table 5). However, the oxazoline ring is the only directing group in addition to imine that is capable of directing both catalytic methylation and methoxylation. Interestingly, the imidazole substrate **1i** displayed reasonable reactivity towards catalytic methoxylation resulting in 69% conversion to the methoxylated product (entry 3; Table 5). As before, other substrates containing both nitrogen and oxygen-based directing groups were found to be catalytically inactive. Control experiments showed no reactivity in the absence of Pt-catalyst for all substrates.

Table 5. Directing group scope of Pt^{II}-catalyzed methoxylation.

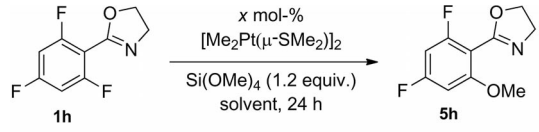


Entry	Directing group	Conversion (%)[a]
1	 **1a**	95[b,c]
2	 **1h**	80 (40[d,e])
3	 **1i**	69 (31[d,e])
4	 **1j**	0

[a] Conversion was determined based on ^{1}H NMR spectroscopy. In cases that resulted in product formation, the conversions are the average of three independent experiments. [b] Conversion at 35 °C. [c] Conversion of imine substrate at 60 °C was 61%. [d] Isolated yield. [e] Compound volatility resulted in a low yield of isolated product; see Supporting Information for details.

Efforts to optimize the reactivity of oxazoline **1h** and imidazole **1i** substrates were based on varying solvent, temperature and catalyst loading. Initial screening revealed the ability of an oxazoline ring to direct catalytic methoxylation achieving 76% conversion to the corresponding methoxylated product (entry 1; Table 6). Increasing the temperature from 35–60 °C resulted in an increased conversion to product (entry 2; Table 6). However, increasing catalyst loading (5–10 mol-%) had a negligible effect (entry 3; Table 6). [D_2]Dichloromethane and [D_3]acetonitrile were also capable of promoting this reaction giving similar results to THF (entries 4 and 5; Table 6). [D_6]Acetone and [D_6]DMSO proved to be poor solvents for this reaction (entries 6 and 7; Table 6). Interestingly, dichloromethane and acetonitrile were identified as reasonable solvents during the previous optimization of the methoxylation of polyfluoroaryl imines.[16d]

Table 6. Optimization of conditions for oxazoline directed cross-coupling.



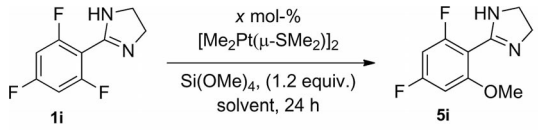
Entry	mol-% Pt-dimer	Solvent	Temp. (°C)	Conv. (%)[a]
1	5	[D_8]THF	35	76
2	5	[D_8]THF	60	80
3	10	[D_8]THF	60	83
4	5	CD_2Cl_2	35	83
5	5	CD_3CN	80	84
6	10	[D_6]acetone	35	44
7	5	[D_6]DMSO	35	0

[a] Conversion based on ^{19}F NMR spectroscopy and are the result of a single experiment.

For the imidazole substrate, the optimized conditions were found to be THF, 60 °C and 10 mol-% Pt-catalyst (entry 1; Table 7). Notably, increasing the catalyst loading from 5–10 mol-% did result in a significant increase in conversion to product (entries 1–2; 3–4; Table 7). All other solvents were unable to promote this reactivity.

The reactivity of the imidazole substrate **1i** in catalytic methoxylation is a particularly interesting result as this substrate was not capable of stoichiometric C–F activation; yet was found to have reasonable reactivity in catalytic meth-

Table 7. Optimization of conditions for imidazole directed cross-coupling.



Entry	mol-% Pt-dimer	Solvent	Temp. (°C)	Conv. (%)[a]
1	10	[D8]THF	60	80
2	5	[D8]THF	60	69
3	5	[D8]THF	35	53
4	10	[D8]THF	35	66
5	5	CD_3CN	60	0
6	5	[D6]acetone	60	0
7	5	C_6D_6	35	0[b]
8	5	[D8]toluene	60	0[b]
9	5	[D6]DMSO	35	0
10	5	CD_2Cl_2	35	0

[a] Conversion based on ^{19}F NMR spectroscopy and are the result of a single experiment. [b] Compound was only partially soluble.

oxylation (entry 3; Table 5). Clearly, the reactivity of a given substrate in catalytic methylation does not, necessarily, imply that the same reactivity will be observed in the analogous catalytic methoxylation reaction. As such, a mechanism for Pt^{II}-catalyzed methoxylation which does not invoke C–F activation as the entrance into the catalytic cycle would explain these results.

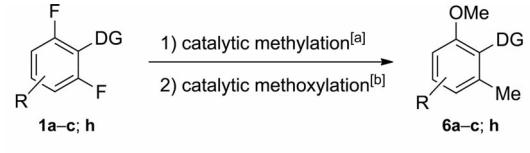
Sequential Methylation/Methoxylation – Scope

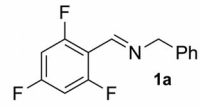
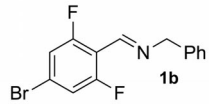
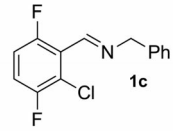
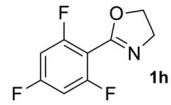
Having established the scope of Pt^{II}-catalyzed methylation and methoxylation reactions, it was of interest to explore the potential for sequential methylation/methoxylation. The substrates chosen were those which displayed relatively high reactivity in either the methylation and/or methoxylation reactions (see Tables 1 and 4; respectively).

The catalytic reactions were performed using the optimized conditions for each respective reaction. Due to the differences in the solvents required for these conditions (acetonitrile and THF for methylation and methoxylation; respectively), the acetonitrile was removed after completion of the methylation reaction and replaced with THF for the subsequent methoxylation reaction.

The results clearly indicate that substrates which show high reactivity in both catalytic reactions are able to undergo sequential methylation/methoxylation (entries 1 and 2; Table 8). Of note is that the reverse process (sequential methoxylation/methylation) failed to provide the desired difunctionalized products in all cases. This is postulated to be the result of two mechanistically distinct catalytic processes.

Table 8. Sequential methylation/methoxylation.



Entry	Substrate	Conversion (%)[c]
1	 1a	75
2	 1b	58
3	 1c	< 5
4	 1h	19

[a] Conditions: Me_2Zn (1.2 equiv.), CD_3CN, 60 °C, 24 h. [b] Conditions: $Si(OMe)_4$ (1.2 equiv.), [D8]THF, 35 °C. [c] Conversion based on ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. [d] Methoxylation was performed at 60 °C.

More specifically, catalytic methylation requires a certain minimum number of electron-withdrawing functionalities on the aromatic ring in order to ensure reasonable reactivity [see Equation (4)]. However, substrate reactivity is seemingly not dependent on the substitution pattern of the electron-withdrawing groups. To this end, imine substrates with 2,5,6-trifluoro (**1d** and **1e**) as well as pentafluoro substitution patterns display excellent reactivity (entries 4–6; Table 1). On the other hand, the opposite trend was observed for catalytic methoxylation. Indeed, it was observed that a 2,4,6-substitution pattern on the aromatic ring was a requirement for substrate reactivity (Table 4).

On the basis of the observed constraints for each catalytic system, only methylation/methoxylation would be expected to result in successful di-functionalization. Methoxylation of the 2,4,6-trifluoro-substituted substrates, though successful, would reduce the number of electron-withdrawing groups below the minimum requirement for catalytic methylation. As a result, methylation of such substrates proved to be unsuccessful. Conversely, catalytic methoxylation of mono-methylated products was found to be reasonably successful (Table 8). This can be rationalized on the basis that the *ortho*-methylated products still maintain the 2,4,6-substitution pattern required for catalytic methoxylation.

Of the substrates examined, 4-bromo-2,6-difluoroimine substrate **1b** is particularly interesting as the product of these sequential reactions has only a *para*-bromo substituent as the only halogen remaining on the aryl ring. This

could serve as a versatile synthetic handle due to the number of Pd and Ni-catalyzed cross-coupling reactions which utilize aryl bromides. The low reactivity of 6-chloro-2,5-difluoroimine substrate **1c** (entry 3; Table 8) can be rationalized on the basis that this substrate was highly active in catalytic methylation (95% conversion) but demonstrated limited reactivity in the methoxylation reaction (ca. 15% conversion). Non-imine-based oxazoline substrate **1h** (entry 4; Table 8) was also capable of sequential catalysis giving a 19% overall conversion to the di-functionalized product (entry 4; Table 8). These results are noteworthy as the potential for a substrate to undergo sequential catalytic reactions results in di-functionalized products which could be difficult to obtain via other synthetic methodologies.

Conclusions

The reactivity of a series of 2,4,6-trifluoroarenes containing a variety of *ortho*-directing functionalities has been examined. The ability of an oxazoline ring to direct both catalytic reactions has been demonstrated. In addition, the analogous imidazole functionality was found to have reactivity exclusive to catalytic methoxylation. Polyfluoroaryl imines remain the optimal substrates for both methylation and methoxylation, with reactions proceeding to greater than 95% conversion to product in both cases. However, the dependence on an imine-directing motif is not necessarily a significant limitation as these functionalities are versatile synthetic intermediates. In addition to their biological relevance, a variety of C–O and C–N containing functionalities, such as aldehydes, alcohols and imines, can be readily accessed via the imine functionality. Finally, throughout the course of these investigations differences in substrate reactivity in Pt^{II}-catalyzed methylation from that of Pt^{II}-catalyzed methoxylation were uncovered. Specifically, the imidazole-based substrate which did not undergo stoichiometric C–F activation was found to promote Pt^{II}-catalyzed methoxylation. These results imply distinct mechanisms for these two processes. In addition, we have determined that sequential methylation and methoxylation can be achieved. Detailed mechanistic analysis of Pt^{II}-catalyzed methoxylation is underway.

Experimental Section

General Procedures: Manipulation of organometallic compounds was performed using standard Schlenk techniques under an atmosphere of dry nitrogen or in a nitrogen-filled Vacuum Atmospheres drybox ($O_2 < 2$ ppm). NMR spectra were recorded on Bruker Avance 300, Bruker Avance 400 or Bruker Avance 600 spectrometers. ^1H, ^{19}F and $^{13}C\{^1H\}$ chemical shifts are reported in parts per million (ppm) and referenced to residual solvent when applicable. Coupling constant values were extracted assuming first-order coupling. The multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, m = multiplet. All spectra were obtained at 25 °C. Mass spectra were recorded on Kratos MS-50 and Waters/Micromass LCT mass spectrometers. Elemental analyses were performed using a Carlo–Erba Elemental Analyzer EA 1108.

Materials and Methods: Deuterated solvents were purchased from Cambridge Isotopes Inc. and degassed prior to use. Acetonitrile was dried by refluxing over calcium hydride, stored over molecular sieves and degassed prior to use. Tetrahydrofuran was dried on molecular sieves and degassed prior to use. All organic reagents were obtained from commercial sources and used as received. 1,3,5-trimethoxybenzene was sublimed prior to use. $K_2PtCl_4$was purchased from Strem Chemicals and was used without further purification. $[PtCl_2(SMe_2)_2]$,[23] and $Pd(PPh_3)_4$[24] were prepared by previously reported procedures. $[Me_2Pt(\mu\text{-}SMe_2)]$ was prepared based on a modification of a previously reported procedure[23] as described in the Supporting Information. All substrates were prepared based on previously reported procedures as indicated below. Dimethylzinc (1.2 M solution in toluene) was purchased from Aldrich and titrated with LiCl and I_2 before use.[25] $Si(OMe)_4$ was purchased from Alfa Aesar and degassed prior to use.

***N*-(2,4,6-Trifluorobenzylidene)benzylamine (1a):** As described in the literature procedure.[16a] Pale yellow oil, 1.03 g, 85% yield. Characterization data matches previously reported data.[15a] See Supporting Information for details.

***N*-(4-Bromo-2,6-difluorobenzylidene)benzylamine (1b):** As described in the literature procedure.[16a] Light yellow solid, 1.89 g, 90% yield. Characterization data matches previously reported data.[15a] See supplementary data for details.

***N*-(2-Chloro-3,6-difluorobenzylidene)benzylamine (1c):** As described in the literature procedure.[16a] Yellow oil, 0.88 g, 78% yield. Characterization data matches previously reported data.[15a] See Supporting Information for details.

2-(2,4,6-Trifluorophenyl)oxazoline (1h): As described in the literature procedure.[26] White solid, 1.54 g, 54% yield. Characterization data matches previously reported data.[26] See Supporting Information for details.

2-(2,4,6-Trifluorophenyl)-4,5-dihydro-1*H*-imidazole (1i): As described in the literature procedure.[27] Yellow solid, 0.52 g, 84% yield. ^1H NMR ([D$_3$]acetonitrile, 300 MHz): δ = 6.91 (t, J = 8.1 Hz, 2 H, 2-H), 3.66 (s, 4 H, -CH_2CH_2-) ppm. ^{19}F NMR ([D$_3$]acetonitrile, 282 MHz): δ = –107.9 (q, J = 7.5 Hz, 1 F, 1-F), –109.8 (t, J = 7.2 Hz, 2 F, 3-F) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 163.3 (dt, J = 252.0, J = 16.5 Hz, 1-C), 161.4 (ddd, J = 252.0, 15.0, 9.0 Hz, 3-C), 155.6 (t, J = 2.4 Hz, 5-C), 106.0 (dt, J = 16.5, J = 6.0 Hz, 4-C), 101.0 (dt, J = 25.5, 3.0 Hz, 2-C) ppm. HRMS (ESI positive ion mode): m/z calcd. for $C_9H_8F_3N_2$: 201.0640; found 201.0636.

2-(2,4,6-Trifluorophenyl)pyridine (1j): As described in the literature procedure.[28] The amount of $Pd(PPh_3)_4$ was increased from 5–10 mol-% to obtain comparable yields; yellow solid, 0.80 g, 40% yield. Characterization data matches previously reported data. See Supporting Information for details.

General Procedure for Catalytic Reactions

NMR Scale Reactions: In the glovebox, a 20 mL glass vial was charged with 0.034 mmol substrate, 0.034 mmol (0.0059 mg) 1,3,5-trimethoxybenzene and dissolved in 1.0 mL of degassed, deuterated solvent. In a separate 20 mL vial was weighed 0.017 mmol of $[Me_2Pt(\mu\text{-}SMe_2)]_2$ which was subsequently dissolved in 1.0 mL of degassed, deuterated solvent; 100 μL of the resulting Pt solution was added to the vial containing substrate. The resulting solution was transferred to an NMR tube with a screw-cap containing a septum. Me_2Zn (0.041 mmol, 37 μL of ≈ 1.2 M solution in toluene; titrated according to literature procedure; 1.2 equiv.) or $Si(OMe)_4$ (6.2 μL, 0.040 mmol, 1.2 equiv.) was added via microsyringe. The

NMR tube was sealed, removed from the glovebox and placed in an oil bath at the indicated temperature (see text). Reaction progress was monitored over time via ^1H and ^{19}F NMR spectroscopy.

Preparative Scale Reactions: In a 20 mL vial, substrate (0.4 mmol) and $[Me_2Pt(\mu\text{-}SMe_2)]_2$ (11.5 mg, 0.02 mmol, 0.05 equiv.) were dissolved in CH_3CN (4–5 mL). The resulting solution was transferred into a test tube fitted with a screw cap containing a septum. Me_2Zn (0.480 mmol, 433 μL of ca. 1.2 M solution in toluene) or $Si(OMe)_4$ (0.480 mmol, 73 μL) was then added by microsyringe. The resulting solution was heated at the indicated temperature for 8–24 h (see text). The solution was cooled to room temperature and the solvent was removed by rotary evaporation. The residue was extracted with petroleum ether (3 × 20 mL). The combined organic extracts were filtered through Celite. The filtrate was concentrated by rotary evaporation to provide the crude product. Further column chromatography (details included in Supporting Information) provides clean products. Functionalized products were found to be particularly volatile making purification difficult and low yielding. The methoxylated oxazoline **5h** and imidazole **5i** compounds were isolated by combining and leaving the relevant column fractions to evaporate in air.

Analytical Data for 2-(2,4-Difluoro-6-methylphenyl)oxazoline (2h): Based on in-situ NMR spectroscopic characterization. 52% yield based on integration of ^1H NMR spectrum relative to an internal standard (1,3,5-trimethoxybenzene). ^1H NMR ([D$_3$]acetonitrile, 300 MHz): δ = 6.77–6.67 (m, aryl-H), 4.43 (t, 2 H, J = 8.7 Hz, -OCH_2CH$_2$N-), 4.10 (t, 2 H, J = 8.7 Hz, -OCH$_2$CH_2N-), 2.40 (s, CH$_3$). ^{19}F NMR ([D$_3$]acetonitrile, 282 MHz): δ = –108.1 (q, J = 9.0 Hz, 1 F), –109.4 (t, J = 9.0 Hz, 1 F) ppm.

Analytical Data for 2-(2,4-Difluoro-6-methoxyphenyl)oxazoline (5h): White solid, 0.020 g, 40% yield. ^1H NMR (CDCl$_3$, 300 MHz): δ = 6.49 (t, J = 9.0 Hz, 2 H, 2-H, 9-H), 4.43 (t, J = 9.0 Hz, 2 H, 6-H), 4.09 (t, J = 9.0 Hz, 2 H, 7-H), 3.85 (s, 3 H, OCH$_3$) ppm. ^{19}F NMR (CDCl$_3$, 282 MHz): δ = –105.3 (q, J = 8.5 Hz, 1 F, 1-F), –109.0 (t, J = 8.5 Hz, 1 F, 8-F) ppm. $^{13}C\{^1H\}$ NMR (CDCl$_3$, 100 MHz): δ = 164.0 (dd, J = 397.5, J = 16.1 Hz, 1-C), 162.5 (dd, J = 436.5, J = 14.9 Hz, 8-C), 160.3 (dd, J = 51.0, J = 9.2 Hz, 3-C), 158.3 (s, 5-C), 103.7 (d, J = 4.7 Hz, 4-C), 96.7 (t, J = 26.3 Hz, 9-C), 95.6 (dd, J = 25.1, J = 3.5 Hz, 2-C), 67.5 (s, 6-C), 56.7 (s, OCH$_3$), 55.1 (s, 7-C) ppm. HRMS (ESI positive ion mode) m/z calcd. for $C_{10}H_9F_2NO_2$: 214.0680; found 214.0683. $C_{10}H_9F_2NO_2$: C 56.34, H 4.20, N 6.57; found C 56.32, H 4.20, N 6.52.

Analytical Data for 2-(2,4-Difluoro-6-methoxyphenyl)-4,5-dihydro-1*H*-imidazole (5i): Yellow solid, 0.012 g, 31% yield. ^1H NMR (CDCl$_3$, 300 MHz): δ = 6.58–6.47 (m, 2 H, H-2, H-9), 3.90 (s, 3 H, H-6, H-7), 3.84 (s, 4 H, OCH$_3$) ppm. ^{19}F NMR (CDCl$_3$, 282 MHz): δ = –104.0 (m, 1 F, 1-F), –107.1 (d, J = 11.6 Hz, 1 F, 8-F) ppm. $^{13}C\{^1H\}$ NMR (CDCl$_3$, 150 MHz): δ = 181.3 (dd, J = 385.5, J = 15.2 Hz, 1-C), 178.2 (dd, J = 397.4, J = 15.7 Hz, 8-C), 170.3 (dd, J = 50.0, J = 9.8 Hz, 3-C), 160.4 (s, 5-C), 104.4 (d, J = 5.7 Hz, 4-C), 97.5 (t, J = 27.3 Hz, 9-C), 96.0 (dd, J = 19.5, J = 3.3 Hz, 2-C), 56.9 (s, OCH$_3$), 41.1 (s, 6-C, 7-C) ppm. HRMS (ESI positive ion mode) m/z calcd. for $C_{10}H_{11}N_2OF_2$: 213.0839; found 213.0843.

Analytical Data for *N*-(4-Fluoro-6-methoxy-2-methylbenzylidene) benzylamine (6a): Based on in-situ NMR spectroscopic characterization. 75% yield based on integration of ^1H NMR spectrum relative to an internal standard (1,3,5-trimethoxybenzene). ^1H NMR ([D$_3$]acetonitrile, 300 MHz): δ = 8.79 (s, 1 H), 7.37–7.20 (overlapping peaks, aryl-H), 6.33–6.29 (d, J = 12.0 Hz, 2 H), 4.75 (s, 2 H, -CH$_2$-), 3.78 (s, 3 H, OCH$_3$), 2.42 (s, 3 H, CH$_3$) ppm. ^{19}F NMR ([D$_3$]acetonitrile, 282 MHz): δ = –110.1 (m, 1 F) ppm.

Analytical Data for *N*-(4-Bromo-6-methoxy-2-methylbenzylidene)-benzylamine (6b): Based on in-situ NMR spectroscopic characterization. 58% yield based on integration of the ^1H NMR spectrum relative to an internal standard (1,3,5-trimethoxybenzene). ^1H NMR ([D$_3$]acetonitrile, 300 MHz): δ = 8.75 (s, 1 H), 7.38–7.22 (overlapping peaks, aryl-H), 4.64 (s, 2 H, -CH$_2$-), 3.65 (s, 3 H, OCH$_3$), 2.49 (s, 3 H, CH$_3$) ppm. ^{19}F NMR ([D$_3$]acetonitrile, 282 MHz): δ = –119.6 (q, J = 7.9 Hz, 1 F) ppm.

Analytical Data for *N*-(4-Fluoro-6-methoxy-2-methylphenyl)-2-oxazoline (6c): Based on in-situ NMR spectroscopic characterization. 19% yield based on integration of the ^1H NMR spectrum relative to an internal standard (1,3,5-trimethoxybenzene). ^1H NMR ([D$_3$]-acetonitrile, 300 MHz): δ = 6.49–6.46 (overlapping peaks, aryl H), 4.45–4.40 (overlapping peaks, -OCH_2CH$_2$N-), 4.10–4.07 (overlapping peaks, -OCH$_2$CH_2N-), 3.81 (s, OCH$_3$), 2.23 (s, CH$_3$) ppm. ^{19}F NMR ([D$_3$]acetonitrile, 282 MHz): δ = –112.7 (q, J = 6.9 Hz, 1 F) ppm.

Supporting Information (see footnote on the first page of this article): Complete experimental details and spectra of all isolated compounds.

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