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Nucleophilic Trifluoromethylation of Electron-Deficient Arenes

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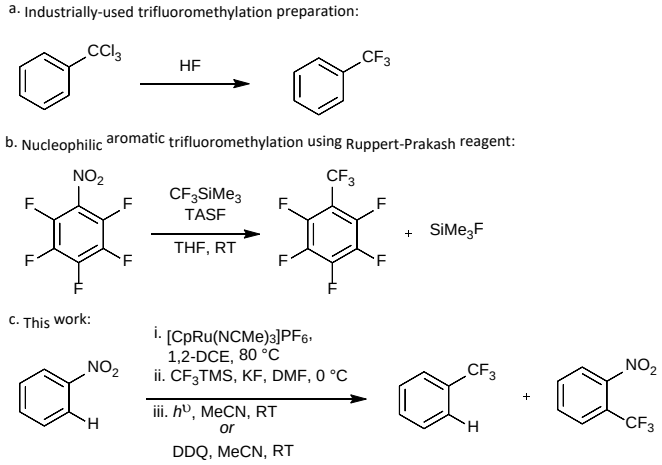
A novel trifluoromethylation of arenes is presented, which proceeds under mild reaction conditions and has the potential for late-stage functionalisation of pharmaceuticals and agrochemicals. The new reaction allows for the regioselective conversion of nitroarenes into 1,2-trifluoromethylated nitroarenes, via a C–H activation pathway. Furthermore, a substitution of nitroarenes to trifluoromethyl arenes is also presented.

The installation of trifluoromethyl moieties into organic compounds is an intense area of research, particularly regarding applications in pharmaceuticals, agrochemicals and materials.[1–12] Currently around 25% of all known pharmaceuticals and 30% of all applied agrochemicals contain at least one fluorine or trifluoromethyl substituent.[13] The industrial preparation of trifluoromethylated arenes relies upon treatment of trichloromethyl arenes with HF (Scheme 1a). This method is inefficient and requires specialised reactors, capable of handling HF. Alternative methods of direct trifluoromethylation have been reported and proceed by one of three mechanisms: nucleophilic,[14] electrophilic[15] and direct free radical trifluoromethylation.[16] Electrophilic and direct free radical trifluoromethylation are often limited by a lack of control over regiochemistry. Previous work from Bardin *et al.* described how electron deficient perfluoronated nitrobenzene undergoes trifluoromethylation with the Ruppert-Prakash reagent, Me_3SiCF_3,[17] via a nucleophilic aromatic substitution (S_NAr) mechanism (Scheme 1b).[14] However, the need for highly-activated pentafluoro-substituted arenes, which is not a common pharmacophore, limits the general applicability of this process.

We recently showed the catalytic S_NAr of unactivated aryl chlorides (i.e. those without electron withdrawing substituents), mediated by transient η^6-coordination to [CpRu]$^+$.[18] The π-complexation of an arene to a transition metal increases its reactivity towards nucleophilic attack,[19–23] resulting in efficient S_NAr. Following the success of this reaction, we hypothesised that the electron-withdrawing effect of π-complexation could allow for trifluoromethylation of arenes with nucleophilic CF_3. This would overcome the limitations of current nucleophilic trifluoromethylations, which require highly electron-deficient perfluorinated arene substrates (e.g. $C_6F_5NO_2$).[14] Herein, we report the successful reaction of the nucleophilic Me_3SiCF_3 reagent towards [(η^6-arene)RuCp]$^+$ π-complexes, producing a single regioisomer of trifluoromethylated products (Scheme 1c). Importantly, we also show the ability to recover the activating transition metal complex, [CpRu(NCMe)$_3$]$^+$, by photolysis. Overall this process allows for the late-stage trifluoromethylation of electron-deficient arenes and could have significant impact upon the pharmaceutical and agrochemicals industry.



Scheme 1

To determine firstly whether trifluoromethylation is feasible, the sandwich complex [(η^6-nitrobenzene)RuCp]PF_6 (**1**) was synthesised. Synthesis was achieved through heating [CpRu(NCMe)$_3$]PF_6 and the corresponding arene at reflux in 1,2-dichloroethane to give the η^6-bound arene complex in high yield (93%, Figure 1). Confirmation of successful complexation to the metal was provided by heteronuclear NMR

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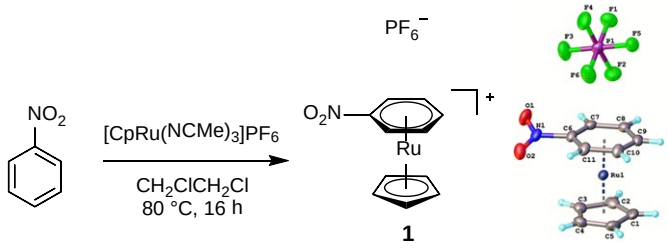
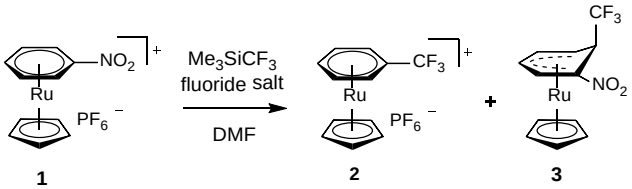


Figure 1. Synthesis and molecular structure of complex **1**; thermal ellipsoids are drawn at 50% probability level.

spectroscopy, mass spectrometry and elemental analysis. In addition, it was possible to obtain single crystals of a suitable quality for X-ray diffraction studies for compound **1** by layering a concentrated acetone solution with diethyl ether (Figure 1, CCDC 1546706). Complex **1** displays the expected pseudo-linear geometry about the Ru centre. The Ru-C_6(plane) distance (1.711 Å) and Ru-C_5(plane) distance (1.819 Å) are in agreement with structures of other similar sandwich complexes.[24] For crystal and structural refinement data, see Table S1.

In an attempt to achieve aryl trifluoromethylation, complex **1** was treated with Me_3SiCF_3 under similar conditions to those used previously for the substitution of pentafluoro-nitrobenzene[14] (Table 1). In order to activate Me_3SiCF_3 as a nucleophilic source of CF_3, a stoichiometric amount of F^- is required. Initial investigations using tetrabutylammonium fluoride (TBAF) as the source of F^- and anhydrous DMF as solvent resulted in low reaction conversions. When anhydrous KF was employed as the fluoride salt, however, the trifluoromethylation proceeded smoothly. Monitoring the reaction *in situ* by mass spectrometry showed complete consumption of starting material after 12 hours. ^{1}H- and ^{19}F-NMR spectroscopy of the reaction mixture prior to purification showed a mixture of two compounds. The two species were isolated by column chromatography on silica and fully characterised. One of these species was confirmed to be the complex [(η^6-α,α,α-trifluorotoluene)RuCp]PF_6 (**2**), the product of nitro substitution by CF_3, via an S_NAr mechanism. To validate the formation of this complex, spectral comparison was

Table 1 Trifluoromethylation of complex **1** with Me_3SiCF_3. Conditions: starting complex (0.2 mmol), Me_3SiCF_3 (1.1 equiv.), fluoride salt (1.1 equiv.). Conversions determined by ^{1}H-NMR, using an internal standard.



Entry	Fluoride Source	T (°C)	Time (h)	Conv. (%)	Product Ratio (2:3)
1	TBAF	25	8	0	–
2	KF	25	8	28	50:50
3	KF	0	8	64	50:50
4	KF	40	8	19	50:50

carried out with a sample of [(η^6-α,α,α-trifluorotoluene)RuCp]PF_6 prepared by reaction between trifluoromethylbenzene and [(MeCN)$_3$CpRu]PF_6.

The second species obtained from the crude reaction mixture was the Meisenheimer complex [Ru(η^5-1-nitro-2-trifluoromethylcyclohexadienyl)(η^5-cyclopentadienyl)] (**3**). This species is formed by the nucleophilic addition of "CF_3^-" to the carbon *ortho* to the aryl nitro group. Similar nucleophilic addition reactions have been observed for related η^6-arene transition metal complexes.[21,25–27] Heteronuclear NMR and IR spectroscopy data were used to assign the Meisenheimer intermediate and confirmed the intact nitro group in the complex. Based on the ^{1}H-NMR coupling constants, the product of the *exo*-addition of CF_3 moiety is exclusively observed. This is likely due to the steric bulk of the ruthenium metal centre and Cp ring restricting the *endo* attack of "CF_3^-". Figure 2 shows the shift assignment for the protons within the 6 membered ring. It is evident from the significant lower chemical shifts of the peaks that the aromaticity has been broken, and the introduction of fluorine brings about increased complexity in splitting patterns. It is also worth considering that the sample of this complex collected would be a racemic mixture of two enantiomeric complexes, where the

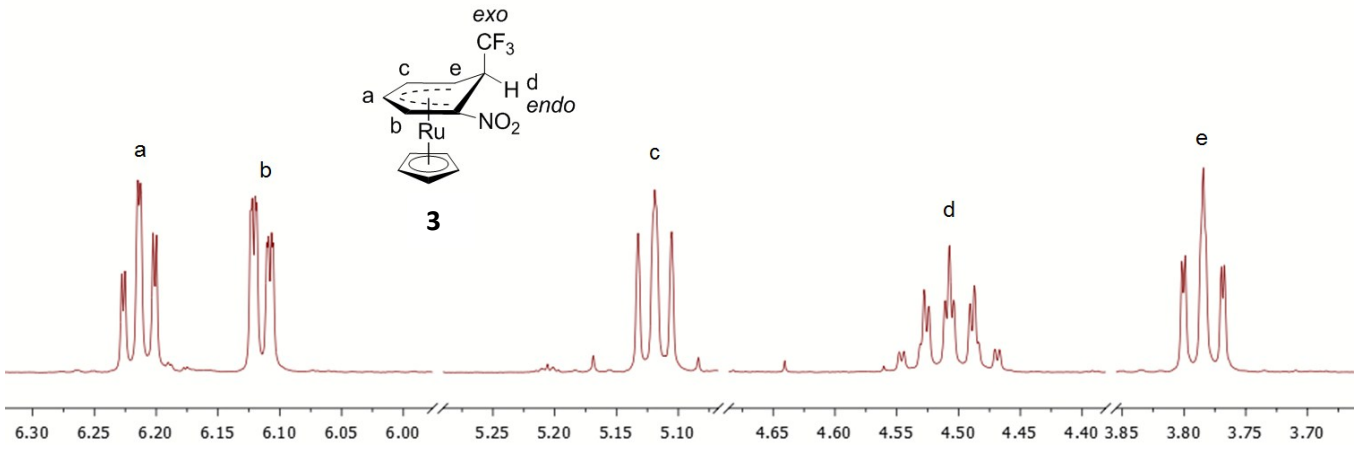


Figure 2. ^{1}H-NMR spectrum of Meisenheimer complex **3**. ($CO(CD_3)_2$, 298 K, 400 MHz)

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exo-addition occurs at the *ortho* carbon either side of the nitro group.

Under the initial conditions described above, analysis of the ^{1}H- and ^{19}F-NMR suggests an approximate 50:50 ratio between complexes **2** and **3**. In an attempt to shift the ratio in which the two complexes are produced and probe if any thermodynamic or kinetic preference exists for either complex, the reaction was repeated using similar conditions at a variety of temperatures (Table 1, entries 2-4). While the product ratio was unaffected by the change in reaction temperature, it was found that lower temperatures increased the overall reaction yield, suggesting decreased complex decomposition at lower temperature.

Next, we investigated the potential to liberate the functionalised arenes from their Ru complexes. Complex **2** was dissolved in deuterated acetonitrile and subjected to ultraviolet irradiation (Scheme 2a). Photolysis was monitored by ^{1}H-NMR and revealed 90% decomplexation of trifluoromethylbenzene after 8 h irradiation (365 nm), along with an equimolar quantity of $[CpRu(NCCD_3)_3]^+$. This Ru species is the MeCN-d_3 analogue of the Ru complex used to synthesise complex **1**, highlighting the ability to fully recycle the activating Ru complex. After 27 h, quantitative conversion had been achieved (Figure 3).

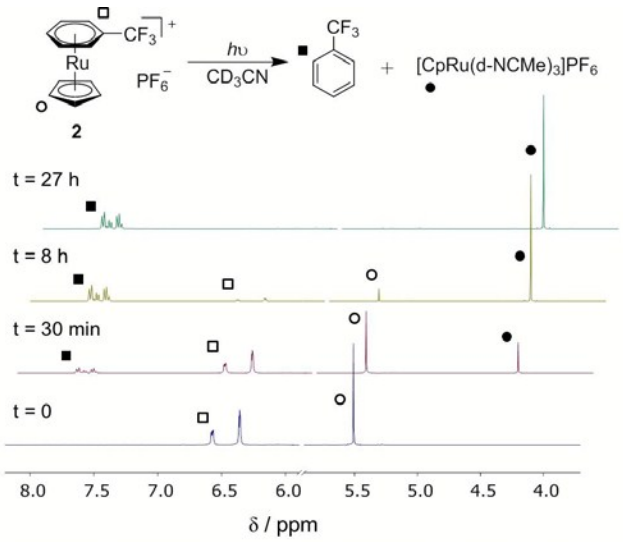
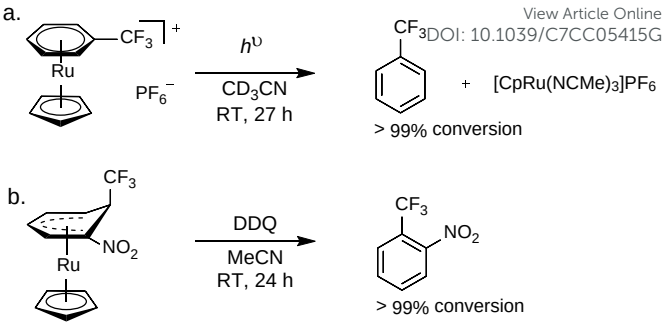


Figure 3. Photolysis (365 nm, 9 W, d_3-MeCN, 298 K) of complex **2**, showing full conversion over 27 h.

We hypothesised that oxidation of the Meisenheimer complex **3** would lead to a disubstitued η^6-coordinated aromatic complex. A range of oxidising agents showed no reactivity with **3**, including trityl chloride (Ph_3CCl), trityl tetrafluoroborate (Ph_3CBF_4) and pentachlorophosphate (PCl_5), while reaction with nitrosyl tetrafluoroborate ($NOBF_4$) gave a mixture of unassignable products. Treatment of **3** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), however, led to successful oxidation and decomplexation to give quantitative conversion to the unbound arene, 1-nitro-2-trifluoromethylbenzene (Scheme 2b). Overall this reaction is a regioselective mild C–H activation and trifluoromethylation of nitrobenzene. Importantly, when unbound nitrobenzene is

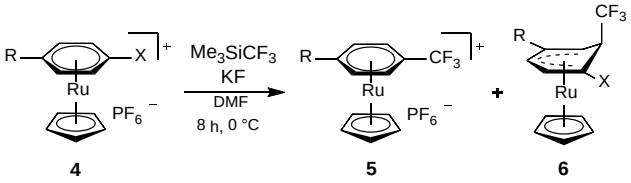


Scheme 2

treated under the same trifluoromethylation conditions, no reaction is observed, confirming the importance of the $[CpRu]^+$ fragment, which is essential to facilitate both the S_NAr reaction and the *ortho* addition reaction.

To determine the versatility of our trifluoromethylation method, a selection of alternative arenes was investigated under the optimised reaction conditions (Table 2). Several Ru complexes were synthesised, incorporating η^6-bound substituted arenes, including nitrotoluene, cyanobenzene, benzoic acid, chlorotoluene, fluorobenzene and trifluoromethylbenzene. Each new complex was subjected to the trifluoromethylation conditions. Reaction of $[(\eta^6$-4-nitrotoluene)RuCp$]PF_6$ gave a 1:1 mixture of substitution product (**5**, R = Me) and Meisenheimer complex (**6**, R = CH_3, X = NO_2) (Table 2, entry 1). The observation that the substitution product is a single regioisomer provides confirmation of an S_NAr mechanism, in which initial attack of the CF_3 moiety occurs at the nitro-bound carbon. Reaction with the cyanobenzene complex (Table 2, entry 2) gave exclusively the Meisenheimer complex (**6**, R = H, X = CN). The absence of any substitution product is consistent with the poorer leaving group ability of the cyano group. This highlights the potential

Table 2 Trifluoromethylation of various Ru complexes, with Me_3SiCF_3. Conditions: starting complex (0.2 mmol), Me_3SiCF_3 (1.1 equiv.), KF (1.1 equiv.). Conversions determined by ^{1}H-NMR, using an internal standard. [a]Carried out at 40 °C. [b]Reaction with the fluorobenzene complex resulted in slow hydrolysis and formation of the bound phenol complex.



Entry	R	X	Conversion (%)	Product Ratio (5:6)
1	CH_3	NO_2	61	50:50
2	H	CN	26	0:100
3	CH_3	Cl	12	0:100
4	H	CH_3	10	0:100
5	H	CF_3	0	–
6	H	CO_2H	0	–
7	H	H	22[a]	0:100
8	H	F	0[b]	–

for a selective C–H activation and trifluoromethylation and also demonstrates the versatility of the mild activation protocol. Exclusive formation of the Meisenheimer intermediate was also observed for 4-chlorotoluene- and toluene-bound complexes, albeit in low conversion (Table 2, entries 3 and 4). The benzene complex reacted to give 22% conversion to the Meiesenheimer complex, but required heating at 40 °C to ensure solubility of the starting complex. No reaction was observed with the other arene complexes tested, with the exception of the fluorobenzene complex, which undergoes slow hydrolysis to the phenol complex.

In summary, we present the trifluoromethylation of nitro- and cyanobenzene using Me_3SiCF_3, facilitated by η^6-coordination to $[CpRu]^+$. Under the optimised reaction conditions, nitrobenzene is converted in a 1:1 ratio of two products. The substitution product, trifluoromethylbenzene, is isolated by photolysis, with recovery of the $[RuCp]^+$ activating group. The C–H activation product, trifluoromethyl-nitrobenzene, can also be isolated following oxidation of the Meisenheimer intermediate with DDQ. The trifluoromethylation proceeds under very mild conditions and liberation of the unbound arene from the complex is high yielding. To our knowledge, this method of trifluoromethylation of arenes using Me_3SiCF_3 facilitated by the η^6-binding to a Ru metal fragment is the first of its kind and could be applied to the late-stage functionalisation of pharmaceuticals and agrochemicals. Furthermore, the ability to produce 1,2-substituted trifluoro-nitroarenes may lead to compounds with enhanced efficacy.

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A new trifluoromethylation of arenes is presented, which proceeds via a Ru(II) π-arene complex and is carried out under mild reaction conditions.