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A novel catalytic process for trifluoromethylation of bromoaromatic compounds†

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The palladium-catalyzed trifluoromethylation of aryl bromides has been achieved in micellar media. The micellar conditions result in enhanced yields and are applicable to bromoaromatics with ketone, aldehyde, hydroxyl and amine functionalities.

The introduction of the strong electron-withdrawing trifluoromethyl group (CF_3) into organic compounds is an important transformation in organic synthesis.[1] Trifluoromethylated organic compounds are often used in pharmaceuticals;[2] because the substitution of CF_3 for a methyl group often alters their bioactivity, biostability, and lipophilicity.[3]

Though efforts to obtain trifluoromethylated aromatic compounds ($ArCF_3$) began in the18th century using fluorine substitution of chlorine in ArCl,[4] few methods are currently available to trifluoromethylate aromatic compounds. The three major approaches employed for trifluoromethylation involve radical, electrophilic, and nucleophilic reactions,[5] in which radical[6] and electrophilic[7] reactions show poor regioselectivity and work only for electron rich aromatic and heteroaromatic compounds. Nucleophilic trifluoromethylation has been used successfully in the last few decades. One important method for converting aryl iodides (ArI) to $ArCF_3$ involves coupling reactions using Cu.[8] However, in most of these Cu coupling trifluoromethylation procedures Cu is used in stoichiometric amounts. An improved catalytic form has been reported;[9] however, substrate specificity is its main limitation. ArI containing electron withdrawing functionalities and some heterocyclic compounds are compatible with the catalytic method. The important applications in medicine and the dearth of catalytic methods to prepare $ArCF_3$ have increased research interest in developing trifluoromethylation methodologies for aromatic compounds containing heavy functionalities and are applicable in later stages of total syntheses.

In the synthesis of medical imaging reagents, the metal catalyzed conversion of ArI to aryl fluorides (ArF) proved very useful;[10] however; it failed to produce $ArCF_3$ in satisfactory yields. The main reason for this failure is a reductive elimination step in the reaction mechanism. Efforts were made to improve yields by changing reaction conditions and the catalyst system; however, no significant advances have been achieved.[11]

An electrophilic fluorine source (CF_3^+) was also used for the conversion of ArX (X = Br or I) to $ArCF_3$,[12] in which the oxidation of Pd(II)–CF_3 complexes with CF_3^+ gave Pd(IV) complexes that yielded $ArCF_3$ after reductive elimination. However, the requirement of specific directing groups in the substrate limits the use of this approach. Recently, a very important mechanistic study was done on the Pd catalyzed trifluoromethylation of ArCl using $(C_2H_5)_3SiCF_3$ and KF as a source of nucleophilic fluorine (CF_3^-).[13] This study demonstrated that trifluoromethylation takes place *via* oxidative addition–transmetallation–reductive elimination from Pd(0) to Pd(II) conversion. However, long reaction times, the use of hygroscopic KF, complex reaction conditions and, most importantly, the necessity of using certain substrates (lower yields with ArBr and substrates with aldehydes, ketones, hydroxyl, and amine functional groups) limit the utility of the method.

Here, we report the use of reverse micelles as reaction media to improve the trifluoromethylation reaction. We previously reported the Pd catalyzed conversion of ArBr (with nucleophilic fluorine sources) to ArF in reverse micellar media.[10a]

The cost effective and eco-friendly use of micellar aggregates as reaction media for reactions in aqueous and organic environment are well known.[14] In the field of radio labelling chemistry (including medical imaging reagents), the use of polymeric micelles, polymeric solid supports, organotrifluoroborate precursors and fluorous-tagged solution-phase analogues of the solid-phase is of growing interest.[15]

Trifluoromethylation of 1-Br-naphthalene was carried out using a biarylphosphine ligand, *i.e.* the cyclohexyl BrettPhos ligand (L), along with $[cinnamylPdCl]_2$, and $(CH_3)_3SiCF_3$; CsF was used as the fluoride source. In the absence of sodium dodecyl sulfate (SDS), the yield of 1-CF_3-naphthalene was very low (Table 1, No. 1 and 3).† On the other hand, when the same reaction was performed in SDS (60 mM), remarkable enhancements in % conversion and isolated yields were observed (Table 1, No. 2 and 4). Thus the presence of reverse micelles in the reaction media enhanced the rate of trifluoromethylation

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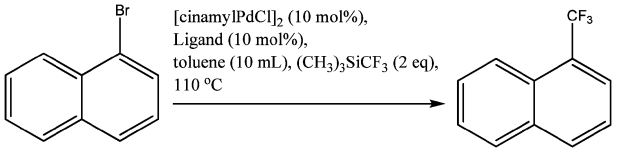
Table 1 Optimization of 1-Br-naphthalene trifluoromethylation



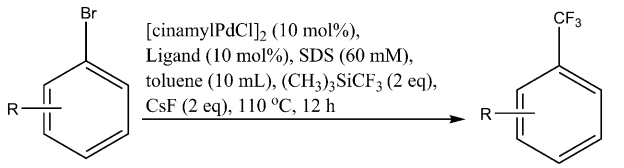
No.	Reaction conditions	Conversion[a] (%)	Yield[b] (%)
1	KF (2 eq.), 20 h	48	32
2	KF (2 eq.), SDS (60 mM), 20 h	87	84
3	CsF (2 eq.), 24 h	30	21
4	CsF (2 eq.), SDS (60 mM), 12 h	90	88

[a] Determined by gas chromatography. [b] Isolated yield.

of the ArBr. We also studied a polar solvent (1,4-dioxane) for the trifluoromethylation of naphthalene in micellar media. However, the improvement in the conversion (with or without SDS surfactant) was minimal; in polar solvents the spatial orientation of aromatic compounds in the micelles is different from the orientation in nonpolar solvents such as toluene. Another factor influencing the yield of CF_3-naphthalene in polar solvent is the stability of the moisture sensitive KF, CsF and $(CH_3)_3SiCF_3$. Hence, we used toluene in this method.

Application of the micellar trifluoromethylation reaction to various ArBr is shown in Table 2; in which aromatic compounds with electron withdrawing functionalities (Table 2, No. 1) as well as electron donating functionalities (Table 2, No. 2–7) have been converted into the corresponding $ArCF_3$ in excellent yield. An important finding of this study is the successful trifluoromethylation of aromatic compounds containing aldehyde (Table 2, No. 4) and unprotected hydrogen containing functional groups including both hydroxyl (Table 2, No. 2–4) and amine (Table 2, No. 5–7) groups. It was ascertained by ^{1}H NMR spectroscopy study that aromatic compounds like phenols, naphthalene, *etc*. exist in a preferred average orientation in the domain of the surfactant micelle.[16] The anisotropic palisade layer appears to be a useful reaction site for the oxidative addition of ArBr and LPd(0) to form an ArLPdBr complex.

Table 2 Trifluoromethylation of various ArBr



No.	Substrate	Product (% Conversion[a], % Yield[b])
1	1-Br-3-Me-4-NO_2-benzene	2-Me-1-NO_2-4-CF_3-benzene (80%, 77%)
2	*p*-Br-phenol	4-CF_3-phenol (75%, 70%)
3	*o*-Br-phenol	2-CF_3-phenol (77%, 74%)
4	2-Br-5-OH-benzaldehyde	2-OH-5-CF_3-benzaldehyde (71%, 68%)
5	*o*-Br-aniline	2-CF_3-aniline (72%, 70%)
6	*p*-Br-aniline	4-CF_3-aniline (74%, 71%)
7	5-Br-biPh-2-amine	2-Ph-4-CF_3-aniline (75%, 72%)
8	9-Br-anthracene	9-CF_3-anthracene (85%, 80%)

[a] Determined by gas chromatography. [b] Isolated yield.

Thus, oxidative addition in the micellar palisade layer overcomes the necessity of using ArCl as a starting material in this process. The use of ArBr (instead of ArCl) in oxidative addition is an advantage since ArBr is a thermodynamically favoured substrate for this reaction.

To learn more about the trifluoromethylation reaction in micellar media, we synthesized two intermediates of the reaction (ArLPdBr and $ArLPdCF_3$; where Ar = naphthalene) by applying the procedure described previously.[13] After isolation of these intermediate complexes, a solubilisation study in toluene-d_8 and SDS + toluene-d_8 medium using ^{1}H NMR spectroscopy was carried out. The complete proton resonance spectra of complex shifted to lower δ values in the presence of SDS (Fig. S1 and S2, ESI†). The change in the chemical shifts of the proton resonance due to the addition of SDS indicates that both of these complexes are solubilised inside the palisade layer of SDS reverse micelles.

The spatial orientation of ArLPdBr in the palisade layer appears to be responsible for the selectivity in the trifluoromethylation reaction, which orients the bromine toward the hydrophilic core (*i.e*. toward the $(CH_3)_3SiCF_3$–CsF fluorine source) to form $ArLPdCF_3$. The transmetallation reaction is the independent step of this mechanism; which is initiated due to bond formation between silicon and fluorine. This involves the reaction of $(CH_3)_3SiCF_3$ and CsF to form CF_3^- and $(CH_3)_3SF$. The use of micelles in the reaction prevents the decomposition of $(CH_3)_3SiCF_3$; hence, formation of $(CH_3)_3SiF$ and CF_2^- as side products is avoided.

The reductive elimination of the ArLPdF complex is the most important step in trifluoromethylation reaction. The $ArLPdCF_3$ complex is made up of the hydrophilic CF_3 and a hydrophobic ligand. The attractive force on the hydrophobic ligand towards the surface of reverse micelle and the Ar towards the CF_3 group may reduce the Ar–Pd–CF_3 angle. Also, the stability of ArLPdF complex may be reduced due to the hydrophobic and hydrophilic balance contained in it. Either or both of these effects lead to a rapid reductive elimination of $ArCF_3$. Similar effects of preferred average spatial orientation in the palisade layer of the micelle have been observed for the fluorination of ArBr.[10a]

In the absence of sodium dodecyl sulfate (SDS), the yield of 4-CF_3-phenol from *p*-Br phenol is very low. This is due to the proton transfer between the unprotected phenolic OH and CF_3^- to give fluoroform (CHF_3). The higher yield in the presence of SDS may be a consequence of the fact that $(CH_3)_3SiCF_3$–CsF is present in the hydrophilic core and ArBr is in the palisade layer. This separation of reagents leads to transmetallation reactions in the hydrophilic core and oxidative addition reactions in the palisade layer. The direct contact of unprotected phenolic OH with $(CH_3)_3SiCF_3$ might be minimized due to micellar phenomena (Fig. 1).

The successful trifluoromethylation of naphthalene and anthracene (Table 2, No. 8) in high yields demonstrates the importance of this process in the synthesis of $ArCF_3$ containing more than one ring. All products obtained by this approach (Table 2) have an important role in the total synthesis of pharmaceutically important organic compounds; this includes the use of, OH-CF_3-benzaldehydes in the synthesis of pyrrole EP_1,[17] and hH_3,[18] receptor antagonists; CF_3-anilines in the

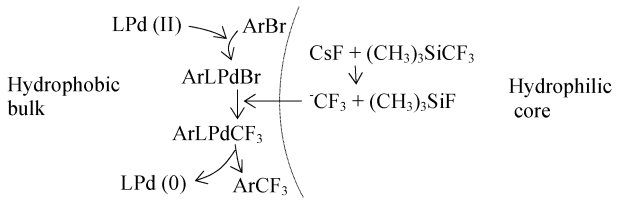


Fig. 1 Proposed mechanism of aryl trifluoromethylation in micellar medium.

synthesis of HCT-116 tumour xenograft for tumour growth inhibition;[19] CF_3-phenols in the synthesis of anti-measles compounds,[20] antihypertensive agents,[21] and inhibitors of multi-drug resistance of vincristine pre-treated HeLa-MDR1;[22] *etc.* The use of ArBr as starting compounds with no restriction on the functionality of substrates is especially significant.

To understand the effect of micellar head group charges, the study was conducted using two types of ionic surfactants: an anionic SDS, linear alkyl benzene sulfonate (LABS) and a cationic cetyltrimethylammonium bromide (CTAB). However, little difference was observed on the reaction rates or yields when using either of these surfactants (Fig. S3, ESI†).

In conclusion, an improved method for converting ArBr into their corresponding $ArCF_3$ has been developed using reverse micellar media. The anisotropic palisade layer of SDS reverse micelles provided an effective oxidative addition reaction site for LPd and ArBr to form ArLPdBr. The prevention of $(CH_3)_3SiCF_3$ decomposition in the transmetallation reaction and the spatial orientation of the $ArLPdCF_3$ during the reductive elimination reaction appear to positively affect the yield of the desired $ArCF_3$ products. Overall, the scope of this trifluoromethylation pathway is wide in that the reaction is successful for various aromatic compounds containing OH, –CO, –CHO and $–NH_2$ functionalities.

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