Palladium Catalyzed 2,2,2-Trifluoroethoxylation of Aromatic and Heteroaromatic Chlorides Utilizing Borate Salt and the Synthesis of Trifluoro Analog of Sildenafil

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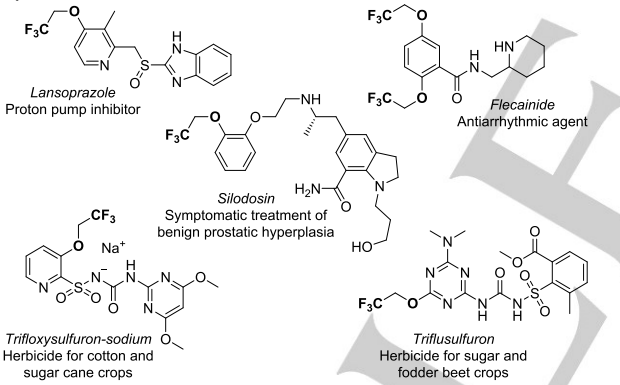
Abstract: A simple and convenient method was developed for the introduction of 2,2,2-trifluoroethoxy group to various aromatic and heteroaromatic systems. The novel process utilizes aromatic chlorides as substrates, and tetrakis(2,2,2-trifluoroethoxy) borate salt as an inexpensive and readily available fluoroalkoxy source in a palladium-catalyzed cross coupling reaction. The power of the developed methodology was demonstrated in the synthesis of a fluorous derivative of Sildenafil.

In the last few decades, the synthesis of organic molecules having fluoroalkyl groups becomes one of the most intensively developed fields of the organic chemistry,[1] due to the high interest of chemical industry.[2] Besides the wide application of trifluoromethylated organic compounds,[3] other small fluoroalkyl groups such as the 2,2,2-trifluoroethyl, can be found in numerous drug molecules, and agrochemicals [Scheme 1]. Trifluoroethyl group attached to oxygen atom can have beneficial effect on the metabolic stability and lipophilicity of biologically active aryl-alkyl ethers. Furthermore, trifluoroethyl group can also be considered as a relatively stable protecting group for alcohols[4].



Scheme 1. Examples for bioactive aryl trifluoroethyl ethers

Modification of current pharmaceuticals[5] with fluorous functional groups can develop better ADME (Absorption, Distribution, Metabolism and Excretion) properties,[6] thus this strategy is frequently used in medicinal chemistry. This applied strategy explains the increasing interest for direct C-, O- and N-fluoroalkylation, and fluoroalkoxylation reactions.[7]

To overcome the difficulties of classical ether syntheses,[8] many efforts have been made recently towards the 2,2,2-trifluoroethoxylation of aryl-halides by copper-catalyzed reactions,[9] granting a new approach to trifluoroethyl-aryl ethers. Weng and co-workers[10] developed a copper-mediated procedure for the transformation of various (hetero)aryl bromides to the corresponding trifluoroethyl ether, with good function group tolerance. However the reaction requires stoichiometric amounts of a copper-organic reagent and the addition of strong base. The palladium-catalyzed cross-coupling reaction between aryl halides and 2,2,2-trifluoroethanol (TFE) in the presence of Cs_2CO_3 base were also developed, but in general electron-deficient, highly activated aryl-halides (mostly bromides) are the applicable substrates for the coupling.[11]

Nevertheless, the facile trifluoroethoxylation of versatile (hetero)aryl-chlorides, the most economic, and easily available group of haloarenes, remains challenging. Therefore, our objective was to develop an operationally simple, reliable and scalable catalytic method for the 2,2,2-trifluoroethoxylation of chloroarenes, without external base, and thus eliminating the necessity of genotoxic Cs_2CO_3. The applicability of tetravalent fluoroalkoxy-borate salts[12] could offer a solution for this approach, considering that the palladium catalyzed C-O bond forming reactions of aryl chlorides is possible with borate salts.[13]

After the synthesis of $Na[B(OCH_2CF_3)_4]$, its reactivity was studied using 4'-chloroacetophenone as a substrate. To our disappointment, the reaction gave only 10 % conversion after 1h in DMF, dioxane and acetonitrile (Table 1, entries 1-3) supposedly due to the higher stability of the trifluoroethoxy borate salts compared to the methoxy analog. We observed that tetraalkoxy-borates readily undergo ligand exchange reactions in various alcohols, and the formed mixed borate salts proved to be more reactive.[14] Taken advantage on the ligand exchange around the boron center, we supplemented the solvent optimization study with polar, protic solvents. Although trifluoroethanol as solvent did not enhance the reaction, to our great delight, applying water or other alcohols (entries 5-9) led to full conversion of the aryl chloride. However in case of H_2O, MeOH and IPA, besides the desired product [**3a**] hydroxyl-, methoxy and *iso*-propoxy-acetophenone [**5**] was also formed in significant amounts (entries 5-7). We thought that steric effects might play an important role in the transmetallation step, therefore we intended to use bulky alcohols such as *tert*-butanol (^{t}BuOH) and *tert*-amylalcohol (^{t}AmOH) to facilitate the coupling reaction and keep the reaction performing with high selectivity. As it was expected, in case of sterically congested tertiary alcohol solvents, the formation of unwanted alkyl-aryl ether was completely suppressed, and the trifluoroethoxylation occurred

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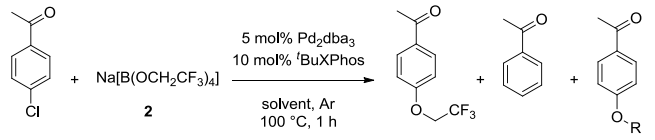
Table 1. Solvent optimization study[a]



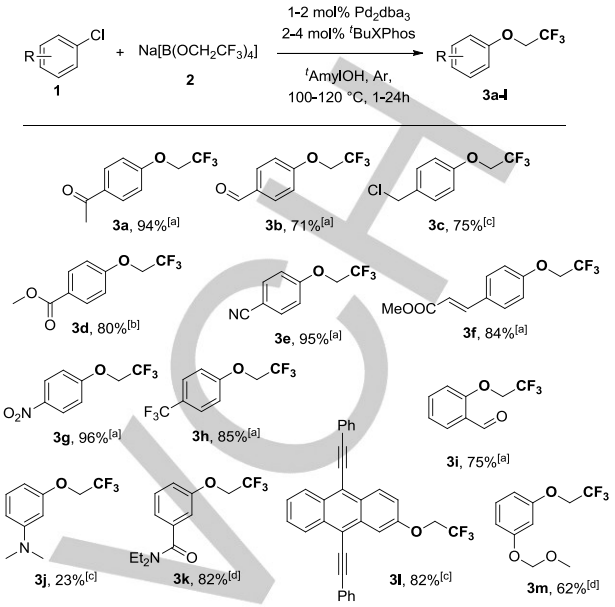
Entry	Solvent	Conv. [%][b]	Yield[%][b] (**3a**)	Yield[%][b] (**4**)	Yield[%][b] (**5**)
1	DMF	10	10	-	-
2	dioxane	11	11	-	-
3	acetonitrile	10	10	-	-
4	CF_3CH_2OH	1>	1>	-	-
5	H_2O	100	32	-	68 [c]
6	MeOH	100	1	-	99 [d]
7	^{i}PrOH	100	55	4	41 [e]
8	^{t}BuOH	100	100	-	-
9	^{t}AmylOH	100	100	-	-

[a] Reaction conditions: 4'-chloroacetophenone (0.1 mmol), $Na[B(OCH_2CF_3)_4]$ (0.15 mmol; 1.5 eq.), Pd_2dba_3 (1 mol%), ^{t}BuXPhos (2 mol%), Solvent (0.1 ml), 100 °C, 1 h. [b] Determined by GC analysis [c] R = OH [d] R = OMe [e] R = O^{i}Pr

with 100% conversion in 1 hour under the developed reaction conditions (entries 8 and 9).

With an optimized[15], reliable and reproducible method in hand, we turned our attention to the substrate scope of the reaction, first examining various substituted aromatic chlorides under the optimized reaction conditions [Scheme 2]. The functional group tolerance, due to the slightly basic and relatively mild conditions, was found to be excellent, as ketone- [**3a**], aldehyde- [**3b**, **3i**], benzyl chloride moiety [**3c**], ester- [**3d**, **3f**], cyano- [**3e**], nitro- [**3g**], amide- [**3k**] , alkyne [**3l**] and protected alcohol- [**3m**] remained intact, showing a broad spectrum of applicability and high efficiency (62-95% yield). Only the very electron rich *N,N*-dimethylamino derivative **3j** was obtained in lower, 23% yield even after 24 hours. We also examined the scalability of the reaction, with the lowest possible catalyst loading. In case of 4'-chloroacetophenone the reaction was carried out on 10 mmol (2 g) scale without loss of efficiency, in the presence of 0.2 mol% Pd_2dba_3 catalyst and 0.4 mol% ^{t}BuXPhos ligand the product **3a** was obtained in 96% yield.

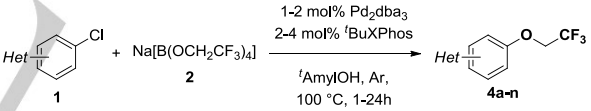
Next, we demonstrated the synthetic applicability of the transformation with the functionalization of versatile biologically relevant, heteroaromatic scaffolds [Scheme 3]. Unsubstituted 4-chloroquinoline [**4a**] was converted with excellent efficiency (84%), likewise other substituted quinolines [**4b-g**] also provided good yields (69-82% yields), while the relatively moderate result (50%) of [**4e**] can be explained partly by steric hindrance. Quinazoline [**4h**, **4i**] and quinoxaline [**4j**] derivatives, as well as substituted pyrazine [**4k**] were also transformed effectively. Bis-trifluoroethoxylation of the dichloropyrazine [**4l**] was also performed with excellent yield (85%). In addition to the studied *N*-heterocycles, the functionalization of other heterocyclic systems containing nitrogen and sulfur heteroatoms such as thienopyridine and thienopyrimidine were also carried out, and

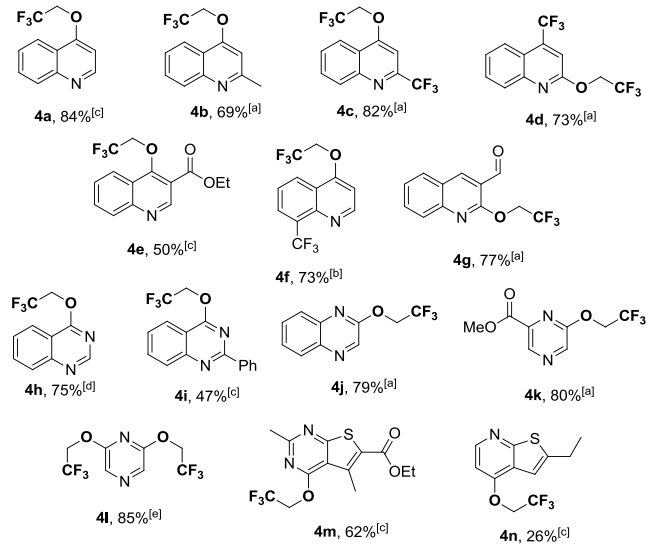


Scheme 2. Preparation of carboaromatic trifluoroethyl-aryl ethers. [a] 1h. [b] 4h. [c] 24h. [d] Pd_2dba_3 (2 mol%), ^{t}BuXPhos (4 mol%) at 120 °C, 4h.

the corresponding products [**4m**] and [**4n**] were isolated in 26% and 62% respectively.

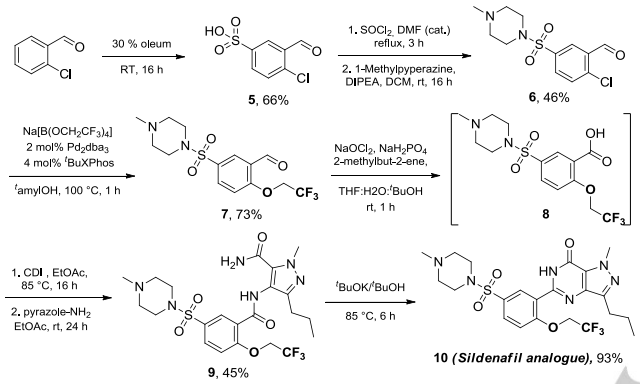
Providing a further evidence of the method's utility, we elaborated the synthesis of the trifluoroethoxy-analogue of the blockbuster drug, Sildenafil (Viagra). Our aim was to replace the ethoxy group of the original compound with the trifluoroethoxy moiety [Scheme 4].





Scheme 3. 2,2,2-Trifluoroethoxylation of heteroaromatic chlorides. [a] 1h. [b] 4h. [c] 24h. [d] Pd_2dba_3 (2.7 mol%), ^{t}BuXPhos (5.4 mol%), 24h. [e] $Na[B(OCH_2CF_3)_4]$ (1.5 mmol; 3.0 equiv.), Pd_2dba_3 (2 mol%), ^{t}BuXPhos (4 mol%), 1h.

To reach our goal, first, the sulfonation of 2-chlorobenzaldehyde was carried out, leading to sulfonic acid **5** in 66% yield. This product was transformed to the corresponding sulfonyl chloride with $SOCl_2$, then the latter was amidated with the methylpiperazine, to give 2-chloro-5-((4-methylpiperazin-1-yl)sulfonyl)benzaldehyde **6** in 46% yield. On this aromatic chloride the developed palladium-catalyzed methodology was applied using the borate salt to obtain the desired aryl-trifluoroethyl ether **7** in 73% yield. Following the key coupling, the aldehyde was transformed by a Pinnick-oxidation to a carboxylic acid intermediate **8**. This compound underwent a CDI-mediated amidation[16] to give **9**, and a base-catalyzed cyclization step to give the desired Sildenafil-analog, **10**.



Scheme 4. Synthesis of a Sildenafil analogue.

Physicochemical and in vitro ADME characterization of Sildenafil and **10** were also investigated [Table 2]. In case of Sildenafil pK_a, log*P/D* values (entries 1-5) were in strong correlation with previously determined parameters[17]. In the comparison study, physicochemical properties showed significant differences in pK_a values of acidic pyrazolo-pyrimidine-NH function (entry 2) and in $\Delta\log P_{OCT\text{-}DCE}$ values (entry 6). The lower $pK_{a,\text{pyrazolo-pyrimidine-NH}}$ and $\Delta\log P_{OCT\text{-}DCE}$ values of **10** suggest weaker intramolecular H-bond between the H-atom of the acidic NH at pyrazolo-pyrimidine and the O-atom of the $–OCH_2CF_3$ group. QM and MM calculations indicate that the formation of intramolecular $NH\cdots OCH_2CF_3$ H-bond is preferred both in Sildenafil and in **10** analogue. However, in accordance with the reported experimental physicochemical parameters, this interaction is slightly weaker in the **10** compound. Proton affinity calculations also support the increased acidic character of pyrazolo-pyrimidine-NH moiety in **10** [18].

Although, **10** is slightly more lipophilic than Sildenafil, in the in vitro gastrointestinal- and blood-brain barrier-specific permeability studies, (entries 7 and 8) the two compounds showed the same behaviour. Regarding microsome-derived intrinsic clearance values, **10** showed greater metabolic rate in human species (entry 9), while there were no significant difference in the metabolic clearance, in rat species (entry 11). Based on earlier study[19] for metabolic pathway indentification of Sildenafil, [20] major microsomal dependent metabolic routes of **10** was also investigated by LC-MS/MS analytical method. Similar to Sildenafil microsomal metabolism, *N*-demethylated (piperazine, M10), *N,N*-deethylated (piperazine, M9), hydroxylated (aliphatic, M6) and M9-demethylated derivatives (piperazine, M8A) of **10** were indentificated as major metabolites by similarity to MS-derived m/z and elution time of Sildenafil [20]. The results justify the differences between HLM- and RLM-related intrinsic clearance values of the two related compounds.

Table 2. Physico-chemical and in vitro ADME properties of Sildenafil and **10**

Entry	Physico-chemical and in vitro ADME parameters [a]	Sildenafil-citrate	Sildenafil-CF_3 (**10**) (in citrate form)
1	pK_a,(piperazine-N)	6.65 (6.78)[17]	6.43
2	pK_a,(pyrazolo-pyrimidin-NH)	9.15 (9.12)[17]	8.58
3	log$P_{OCT/w}$	3.07 (3.18)[17]	3.40
4	log$D_{7.4/6.5}$	2.99 / 2.69	3.34 / 3.13
5	log$P_{DCE/w}$	4.01 (3.75)[17]	3.76
6	$\Delta\log P_{OCT\text{-}DCE}$	-0.94 (-0.57)[17]	-0.36
7	$P_{e(cm/s)}$(PAMPA-$GI_{pH6.5}$) / HIA_{class}	$9.2*10^{-6}$ / high	$5.5*10^{-6}$ / high
8	logP_e (PAMPA-BBB) / est.logBB	-4.77 / 0.29	-4.74 / 0.34
9	HLM Cl_{int} (mL/min/kg)	7.7 / low	14.6 / moderate
10	in vivo human Cl_{plasma}	6 (ml/min/kg)[19]	-
11	RLM Cl_{int} (mL/min/kg)	172.9 / high	125.6 / high
12	in vivo male rat Cl_{plasma}	48 (ml/min/kg)[19]	-

[a] logPOCT/w and logPDCE/w are partition coefficient in octanol-water and dichloroethane-water systems, respectively. ΔlogPOCT-DCE is a difference between logPOCT/w and logPDCE/w. PAMPA-GIpH6.5 and PAMPA-BBB are in vitro non-cell permeability study for gastrointestinal (GI)- and blood-brain barrier (BBB)-specific permeation, respectively. HLM and RLM Clint are human and rat microsome-derived intrinsic clearances (see in SI)

In conclusion, we developed an operationally simple palladium-catalyzed transformation for the trifluoroethoxylation of aryl- and heteroaryl utilizing novel, bench stable, tetravalent alkoxy borate salt without the use of external base. The applicability of the developed procedure was demonstrated with the synthesis of variously substituted aryl- and heteroaryl-2,2,2-trifluoroethyl ethers, as well as the total synthesis of a fluorinated analog of Sildenafil. The physico-chemical properties of **10** showed slight differences with Sildenafil, including a weaker affinity towards intramolecular H-bond formation. The fluorinated analog showed enhanced metabolism too, which might not be disadvantageous, considering the therapeutic field of Sildenafil.

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Keywords: Cross-Coupling • Borates • Heterocycles • Palladium • Homogeneous Catalysis • Trifluoroethoxylation

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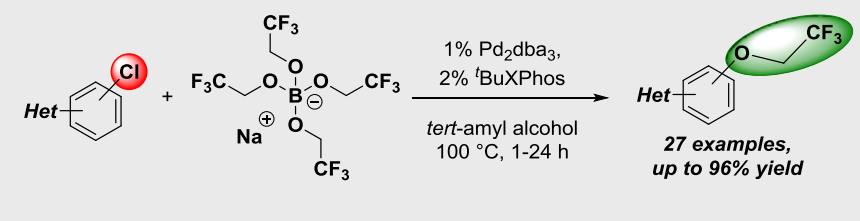

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Palladium-catalyzed 2,2,2-Trifluoroethoxylation of aromatic and heteroaromatic chlorides utilizing borate-salts

A novel palladium catalyzed trifluorethyoxylation of aryl chlorides was developed with the aid of new type of borate based trifluoroethoxylating reagent. Beyond the functionalization of various aromatic and heteroaromatic systems, the synthesis of the trifluoro analog of Sidenafil (Viagra) was achieved together with the determination of its physicochemical properties.