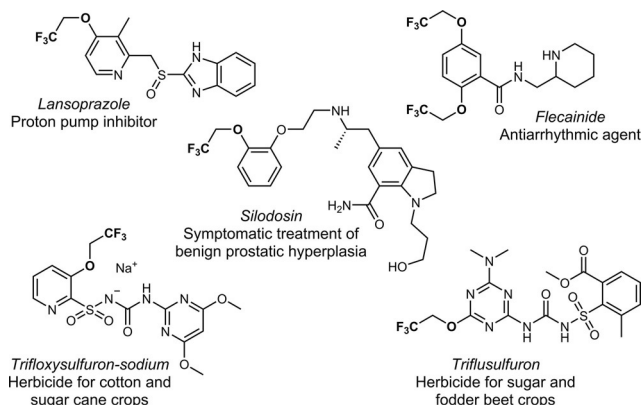


Homogeneous Catalysis

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

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Abstract: A simple and convenient method was developed for the introduction of a 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 fluorinated derivative of Sildenafil.



Scheme 1. Examples for bioactive aryl trifluoroethyl ethers.

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

Modification of current pharmaceuticals^[5] with fluorinated 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 functional-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 Cs₂CO₃ 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 Cs₂CO₃. 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(OCH₂CF₃)₄], its reactivity was studied using 4'-chloroacetophenone as a substrate. To our dis-

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appointment, the reaction gave only 10% conversion after 1 h 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 analogue. We observed that

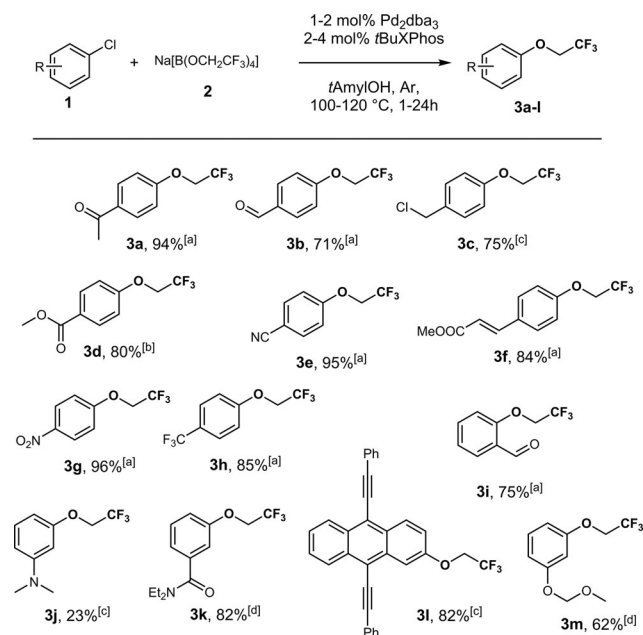
Table 1. Solvent optimization study.^[a]

Entry	Solvent	Conv. [%] ^[b]	Yield [%] ^[b] (3 a)	Yield [%] ^[b] (4)	Yield [%] ^[b] (5)
1	DMF	10	10	–	–
2	dioxane	11	11	–	–
3	acetonitrile	10	10	–	–
4	CF ₃ CH ₂ OH	1 >	1 >	–	–
5	H ₂ O	100	32	–	68 ^[c]
6	MeOH	100	1	–	99 ^[d]
7	<i>i</i> PrOH	100	55	4	41 ^[e]
8	<i>t</i> BuOH	100	100	–	–
9	<i>t</i> AmylOH	100	100	–	–

[a] Reaction conditions: 4'-chloroacetophenone (0.1 mmol), Na[B(OCH₂CF₃)₄] (0.15 mmol; 1.5 equiv.), Pd₂dba₃ (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.

tetraalkoxy-borates readily undergo ligand exchange reactions in various alcohols, and the formed mixed borate salts proved to be more reactive.^[14] Taking advantage of 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 (Table 1, entries 5–9) led to full conversion of the aryl chloride. However, in the case of H₂O, 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 transmetalation 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 expected, in the case of sterically congested tertiary alcohol solvents, the formation of unwanted alkyl-aryl ether was completely suppressed, and the trifluoroethoxylation occurred with 100% conversion in one 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



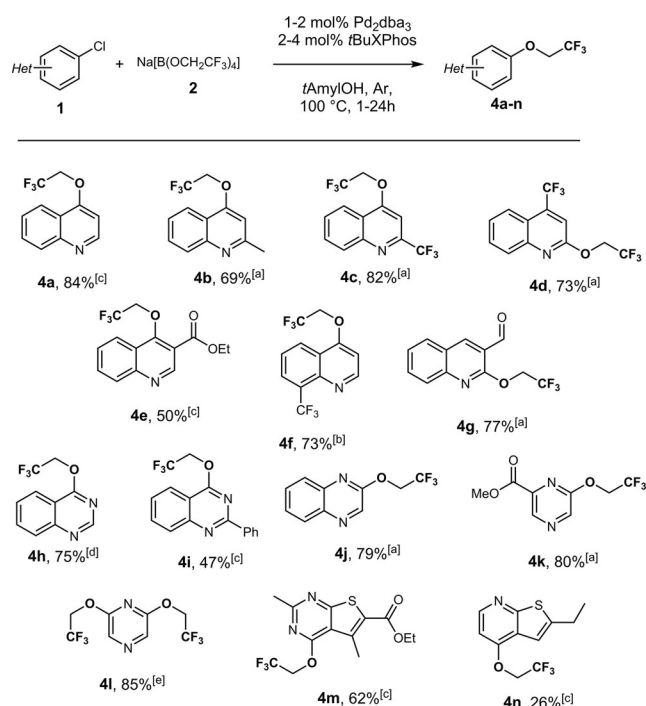
Scheme 2. Preparation of carboaromatic trifluoroethyl-aryl ethers. [a] 1 h. [b] 4 h. [c] 24 h. [d] Pd₂dba₃ (2 mol %), *t*BuXPhos (4 mol %) at 120 °C, 4 h.

applicability and high efficiency (62–95% yield). Only the very electron rich *N,N*-dimethylamino derivative 3j was obtained in lower (23%) yield after 24 hours. We also examined the scalability of the reaction, with the lowest possible catalyst loading. In the 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 % Pd₂dba₃ catalyst (dba: dibenzylideneacetone) and 0.4 mol % *t*BuXPhos ligand (2-Di-*tert*-butylphosphino-2',4',6'-triisopropylbiphenyl) 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), whereas 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 the corresponding products [4m] and [4n] were isolated in 26 and 62% yield, respectively.

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

To reach our goal, first, the sulfonation of 2-chlorobenzaldehyde was carried out, leading to sulfonic acid 5 in 66% yield.



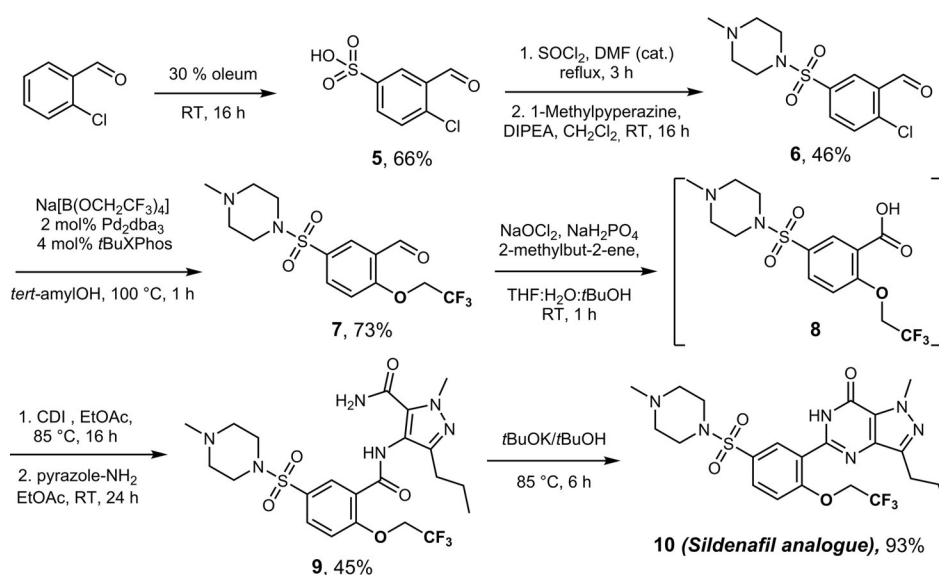
Scheme 3. 2,2,2-Trifluoroethoxylation of heteroaromatic chlorides. [a] 1 h. [b] 4 h. [c] 24 h. [d] Pd₂dba₃ (2.7 mol%), tBuXPhos (5.4 mol%), 24 h. [e] Na[B(OCH₂CF₃)₄] (1.5 mmol; 3.0 equiv), Pd₂dba₃ (2 mol%, dba: dibenzylideneacetone), tBuXPhos (4 mol%, 2-Di-*tert*-butylphosphino-2',4',6'-triisopropylbiphenyl), 1 h.

This product was transformed to the corresponding sulfonyl chloride with SOCl₂, 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 (CDI = 1,1'-carbonyldiimidazole) amidation^[16] to give **9**, and a base-catalyzed cyclization step to give the desired Sildenafil analogue **10**.

Physicochemical and in vitro ADME characterization of Sildenafil and **10** were also investigated (Table 2). In the case of Sildenafil, pK_a and log *P*/*D* values (Table 2, 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 Δlog *P*_{OCT-DCE} values (entry 6). The lower pK_{a,pyrazolo-pyrimidine-NH} and Δlog *P*_{OCT-DCE} values of **10** suggest weaker intramolecular hydrogen bonds between the hydrogen atom of the acidic NH at pyrazolo-pyrimidine and the oxygen atom of the -OCH₂CF₃ group. QM (quantum mechanics) and MM (molecular mechanics) calculations indicate that the formation of an intramolecular NH...OCH₂CF₃ hydrogen 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, (Table 2, entries 7 and 8) the two compounds showed the same behaviour. Regarding microsome-derived intrinsic clearance values, **10** showed a greater metabolic rate in human species (entry 9), whereas there were no significant differences in the metabolic clearance rates in rat species (entry 11). Based on an earlier study^[19] for metabolic pathway identification of Sildenafil,^[20] major microsomal-dependent metabolic routes of **10** were also investigated by LC-MS/MS analysis. 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 identified as major metabolites



Scheme 4. Synthesis of a Sildenafil analogue.

Table 2. Physicochemical 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	Δlog P _{OCT-DCE}	−0.94 (−0.57) ^[17]	−0.36
7	P _{e(cm/s)} (PAMPA-Gl _{pH6.5})/HIA _{class}	9.2 × 10 ^{−16} /high	5.5 × 10 ^{−6} /high
8	log P _e (PAMPA-BBB)/est.logBB	−4.77/0.29	−4.74/0.34
9	HLM Cl _{int} (mL min ^{−1} kg ^{−1})	7.7/low	14.6/moderate
10	in vivo human Cl _{plasma}	6 (mL min ^{−1} kg ^{−1}) ^[19]	–
11	RLM Cl _{int} (mL min ^{−1} kg ^{−1})	172.9/high	125.6/high
12	in vivo male rat Cl _{plasma}	48 (mL min ^{−1} kg ^{−1}) ^[19]	–

[a] log P_{OCT/w} and log P_{DCE/w} are partition coefficient in octanol–water and dichloroethane–water systems, respectively. Δlog P_{OCT-DCE} is a difference between log P_{OCT/w} and log P_{DCE/w}. PAMPA-Gl_{pH6.5} and PAMPA-BBB are in vitro non-cell permeability study for gastrointestinal (GI)- and blood–brain barrier (BBB)-specific permeation, respectively. HLM and RLM Cl_{int} are human and rat microsome-derived intrinsic clearances (see the Supporting Information).

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.

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 analogue of Sildenafil. The physicochemical properties of **10** showed slight differences with Sildenafil, including a weaker affinity towards intramolecular hydrogen-bond formation. The fluorinated analogue showed enhanced metabolism too, which might not be disadvantageous, considering the therapeutic field of Sildenafil.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: borates • cross-coupling • heterocycles • homogeneous catalysis • palladium • trifluoroethoxylation

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