Synthesis of aryl- and heteroaryl-trifluoroethyl ethers: aims, challenges and new methodologies

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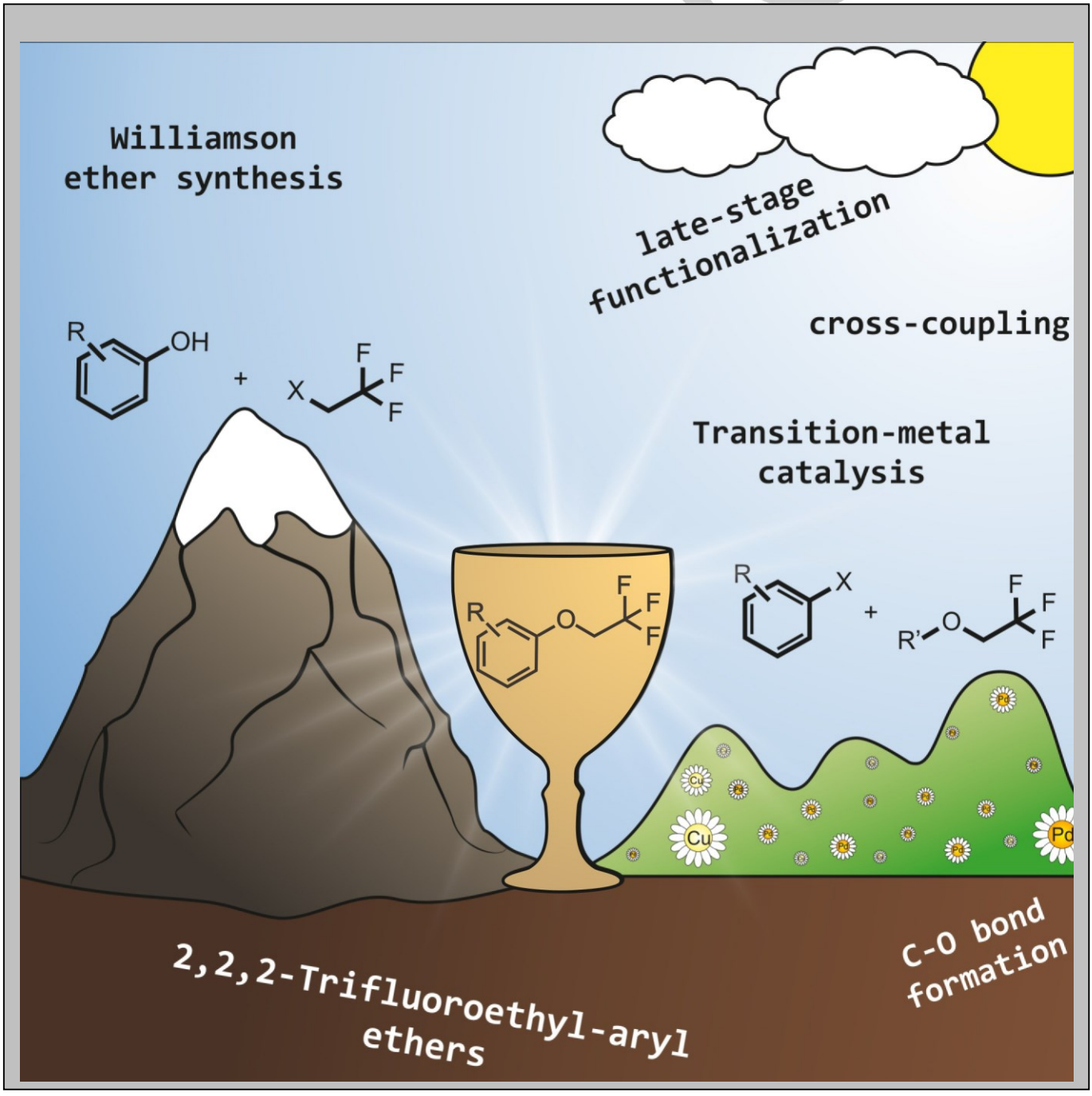
Dedication ((optional))



Abstract: Fluorinated substances have outstanding importance in most fields of the chemical industry, from agrochemicals and material science to pharmaceutical research. Although aryl- and heteroaryl-trifluoroethyl ethers have widespread applications, predominantly as drug molecules, their preparation was limited to classical synthetic methodologies until the last decade. The transition metal catalyzed cross coupling reactions offered novel synthetic approaches for the facile access of trifluoroethoxylated aromatic compounds. The aim of this review is to give a good overview on recent advances in the synthesis of aryl-trifluoroethyl ethers from a practical point of view for synthetic organic chemists working in the field of pharmaceutical industry and academia.

1. Introduction

The outstanding importance of fluorine-containing molecules in drug discovery, and other areas of the chemical industry, is a well-known, and frequently cited fact.[1] A large number of recent reviews dissects the special physico-chemical, metabolic and ADME properties attributed to fluorous functional groups and bioisosters.[2] From a medicinal chemist's point of view monofluorinated-, or trifluoromethylated-arenes[3] consist of the most frequently used molecular motifs for the pharmaceutically important compounds. In general, the introduction of these fluorous functional groups into aromatic and heteroaromatic cores can be achieved through well-established synthetic routes and frequent applications.[4] Moreover, the introduction of other biologically relevant promising structural motifs such as fluoroalkoxy groups are more challenging synthetic task.[5] In this review, the synthetic approaches of aryl- and heteroaryl-2,2,2-trifuoroethyl ethers are discussed.

The importance of this fluoroalkylether function in the field of medicinal chemistry can be demonstrated with the large pool of well-known bioactive aryl- or heteroaryl-trifluoroethyl ethers

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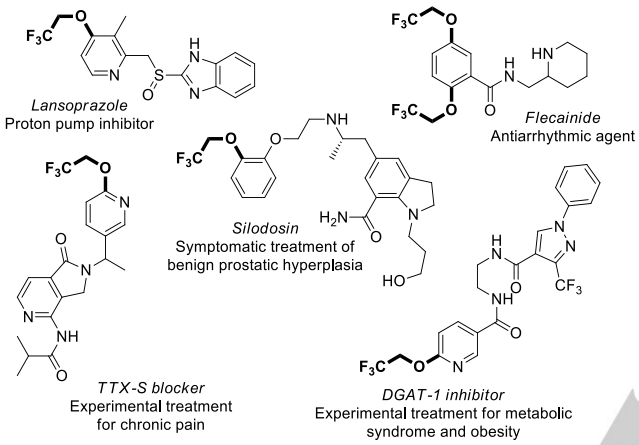
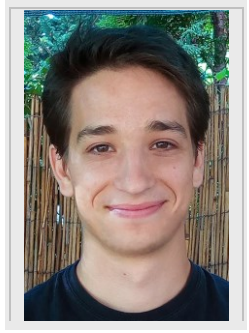
(Scheme 1). Flecainide (antiarrhythmic agent) contains two trifluoroethoxy group on the phenyl ring, while Silodosin (used for treatment of benign prostatic hyperplasia) is equipped one trifluoroethoxy function on the phenyl ring. In the second group of these bioactive molecules the trifluoroethoxy group is attached to pyridine core. Among these heteroaryl trifluoroethyl ethers the most known fluorine containing blockbuster pharmaceuticals is Lansoprazole used as proton pump inhibitor.



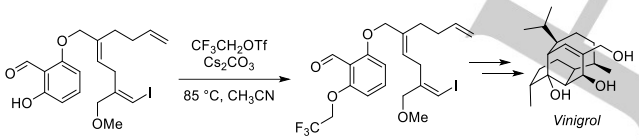


Bálint Pethő was born in 1991, in Budapest, Hungary. He joined the laboratory of Dr. Zoltán Novák in 2010 as an undergraduate researcher, and obtained his BSc. and MSc. degrees in chemistry from Eötvös University

Scheme 1. Illustrious drug molecules, containing aryl-trifluoroethyl ethers.

Besides their widespread industrial applications, trifluoroethoxy-arenes gain more attention recently and have utilizations also in academic research. Njardarson and co-workers demonstrated the applicability of trifluoroethoxy group as a protected phenolic OH function in the total synthesis for vinigrol,[6] a diterpenoid with outstanding structural complexity and biological activity.

During their synthesis, they used trifluoroethyl group as a very stable protecting group for alcohols, which can be cleaved with strong bases.[7] (Scheme 2)



Scheme 2. Further applications of trifluoroethoxy-arenes.

2. Classical synthetic routes

Considering the huge economic driving force behind blockbuster pharmaceuticals like Lansoprazole, it is quite reasonable, that several methods have been developed for large-scale synthesis of trifluoroethoxy-arenes.

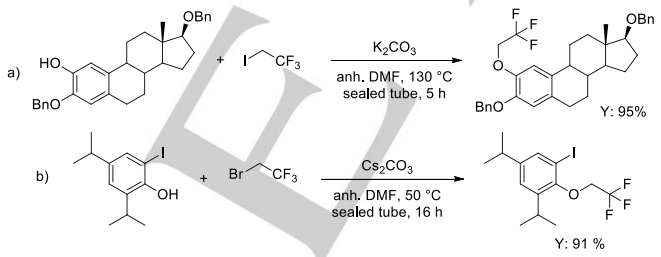
in 2012 and 2014 respectively. He started his PhD studies in 2014 in the same research group. In 2016, he joined L'Oreál R&D department for a 6 months internship with the supervision of Dr. Zhibo Liu. Currently, he is working at Egis Pharmaceuticals Plc. as research and development chemist, on the field of synthetic chemistry.

Zoltán Novák performed his M.Sc. and PhD studies at Eötvös University, Budapest with Professor András Kotschy and obtained his MSc. degree in 1999, and received his Ph.D. in 2004. In 2004, he joined the group of Professor Brian M. Stoltz at the California Institute of Technology as a postdoctoral researcher. After returning to Hungary in 2005, he continued his research at Eötvös University, again in the group of Professor Kotschy. In September 2007, he started his independent research career at the Department of Organic Chemistry, Institute of Chemistry at Eötvös University, where he is the leader of ELTE "Lendület" Catalysis and Organic Research Group as an associate professor.

Two major retrosynthetic paths are used for the synthesis of the aryl fluoroalkyl ethers. In the first approach, C-O bond formation occurs between a phenolic species and a trifluoroethyl electrophile synthon, while the other a synthetic option for the formation of C-O bond is the reaction of trifluoroalkoxyde synthons with activated aryl species.

2.1. Reaction of phenols and trifluoroethyl-electrophiles

An obvious choice for the production of aryl-alkylethers is the Williamson-type synthesis, utilizing phenolates and alkyl-electrophiles. Considering the broad availability of hydroxy-arenes and heteroarenes this synthetic approach has obvious advantages. However, due to the special reactivity and physical properties of fluoroalkyl compounds equipped with any type of leaving group, unexpected difficulties may occur during nucleophilic substitutions. For instance, trifluoroethyl-halides are highly volatile compounds (the boiling point of 1,1,1-trifluoro-2-iodoethane is 54.8 °C), which considerably limits their use at elevated temperatures. Additionally, these compounds have typically low reactivity as electrophiles,[8] which is attributed to the strong electron withdrawing effect of the CF_3-group.

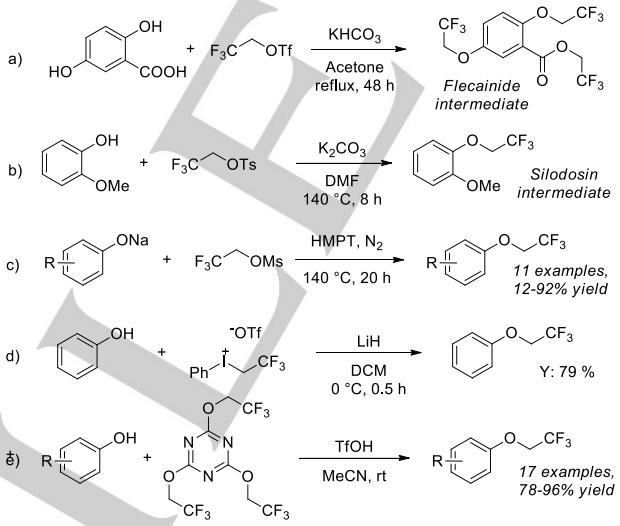


Scheme 3. Trifluoroethylation of phenols utilizing trifluoroethyl-halides.

Also for this reason, trifluoroethyl-electrophiles may show unsatisfactory chemoselectivity in substitutions, thus elimination by-products or even reversed selectivity can be observed, which means that the leaving group may act as an electrophile. [8a] Thus, besides several applications of trifluoroethyliodide,[9] only few examples can be found for other halides such as trilfuoroethylbromide [10] (Scheme 3). Both alkylating agent were used for the *O*-alkylation of phenolic derivatives in polar aprotic solvent at elevated temperature in a sealed reaction vessel under basic reaction conditions.

To overcome the technical difficulties of the *O*-alkylation with trifluoroethyl halides, several other methods were developed for the 2,2,2-trifluoroethylation of phenol derivatives with the use of alternative trifluoroethylating agents (Scheme 4). The most common class of these reagents are sulfonates, that possess overall acceptable reactivity with decreased volatility (trifluoroethyl-triflate, the most reactive and volatile reagent of this group boils at 91 °C). Large-scale, industrial applications, as well as small-scale, exploratory research examples exist for the utilization of trifluoroethyl-mesylate, -tosylate and -triflate in the synthesis aryl trifluoroethyl ethers.[11] According to the reactivity of these trifluoroethyl synthons trifluoroethyl-triflate can be used for the alkylation of phenols below 100 °C, other sulfonates usually require much higher temperatures, which could limit the functional group tolerance of a transformation in case of sensitive compounds.

Hypervalent iodonium salts can also serve as trifluoroethyl-electrophiles, as shown by Umemoto et al.[12] The iodonium super leaving group attached to the trifluoroethyl group makes this species highly reactive towards heteroatom nucleophiles even at low temperature, and ensures shorter reaction times compared to the former reagents.



Scheme 4. Trifluoroethylation of phenols with various electrophiles.

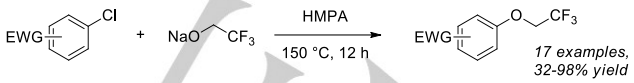
Although economic considerations might not make aryl-trifluoroethyl iodonium triflates the best option, selective transformation of sensitive molecules can justify their application.

Similarly, recent studies show, that 2,4,6-tris-(2,2,2-trifluoroethoxy)-[1,3,5] triazene, or PhenoFluor reagent can also be applied for the trifluoroethylation of phenol derivatives, and provide the desired trifluoroethylethers in good yield under ambient reaction conditions.[13]

2.2. Aromatic nucleophilic substitutions

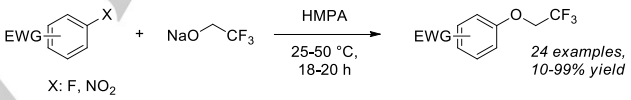
In spite of the reduced nucleophilic character of trifluoroethanol,[14] the aromatic nucleophilic substitution approach for the synthesis of trifluoroethoxylated pharmaceuticals is quite common and have remarkable industrial background. Considering the nature of aromatic nucleophilic substitution, the substrate scope of S_NAr reactions are rather limited to electron poor aromatic compounds. Fluorine, chlorine or nitro group are applicable as leaving group and generally elevated temperature is required to the achievement of the transformation.

An early example of trifluoroethoxylation through nucleophilic substitution of chloroarenes well represents the characteristics of this type of reaction (Scheme 5).[15] Electron deficient aromatic chlorides underwent substitution in HMPA at elevated temperature with sodium salt of trifluoroethanol providing the desired ethers in good yields.



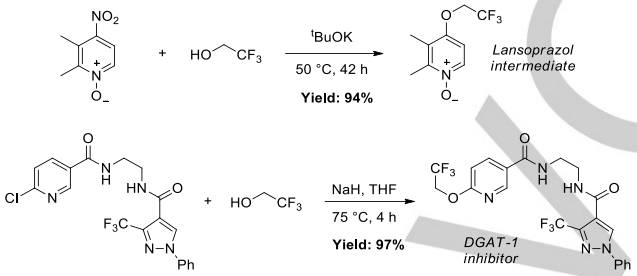
Scheme 5. Transformation of electron deficient chloroarenes to trifluoroethyl-ethers in S_NAr reaction

Switching to more reactive starting materials, fluoro- and nitroarenes, the reaction temperature could be drastically reduced (Scheme 6).[16] However, the efficient procedure still requires the presence of the strong electron withdrawing groups in *orto*- and *para*-positions to the leaving group.



Scheme 6. Trifluoroethoxylation of electron poor nitro- and fluoroarenes in S_NAr reactions

Regarding to pharmaceutical applications, introduction of the 2,2,2-trifluoroethoxy-moiety takes place through the replacement of a nitro-group or a halogen in several notable examples (Scheme 7).[17] Despite the simplicity and effectiveness, the known safety risks related to this reaction route is also worth to mention and take into account during the plan and design of synthetic sequence, especially on industrial scale.[18]



Scheme 7. Applications of aromatic nucleophilic substitution in medicinal chemistry.

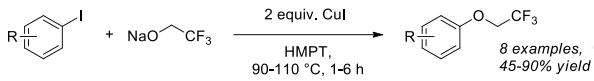
3. Transition-metal mediated trifluoroethoxylations

Although procedures mentioned in previous section represent well-established synthetic methodologies for certain challenges, universally applicable reactions for the preparation of trifluoroethoxy-arenes were absent until the last decade. In the last few years, transition metal catalyzed C-O bond forming reactions underwent rapid and efficient developments,[19] and several new transformations became available for the efficient synthesis of the desired ether species. Thus, with novel, efficient and selective catalytic systems, most of the challenges in the field of fluoroalkoxylation of aryl-halides were addressed.

3.1. Transformations of aryl-iodides

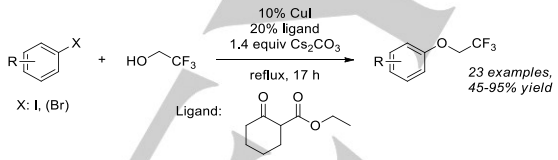
Considering the existing C-O bond forming cross-coupling reactions, it can be concluded, that replacement of an iodine atom by an alkoxide is best supported by copper catalysis. The first example for copper-mediated displacement of iodine to form aryl-trifluoroethyl ethers was described in 1985, by A. Osuka and co-workers.[20] With the applied conditions, unactivated iodobenzenes bearing electron donating groups, such as methyl and methoxy, were converted to trifluoroethyl ethers. Moderate to good yields were achieved, applying 2 equivalents of copper-iodide (Scheme 8). While chloroarenes remained completely inactive, aryl bromides

reacted sluggishly (less, than 30 % conversion after 12 hours) under these reaction conditions, making iodoarenes the only viable option as substrates.



Scheme 8. Copper-catalyzed trifluoroethoxylation of aryl-iodides.

While several attempts were made in the meantime, it was more than two decades later, when Vuluga and co-workers published the first, widely applicable catalytic system for the trifluoroethoxylation of aryl iodides (Scheme 9).[21] In this reaction, iodoarene starting materials are reacted with large excess of 2,2,2-trifluoroethanol (used as solvent) in the presence of Cs_2CO_3 base, catalytic CuI and an inexpensive keto-ester ligand. Similarly to previous findings, aryl bromides reacted less readily (when both halogens were present, iodine was displaced first), and chlorides were completely inactive with the given conditions.



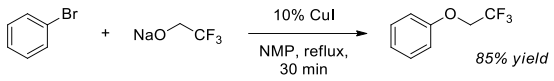
Scheme 9. Copper-catalyzed trifluoroethoxylation of aryl-iodides and bromides.

3.2. Transformations of aryl bromides

While aryl iodides are predominantly converted to the desired ethers by copper catalysis, transformation of bromoarenes can be achieved by copper and palladium catalysis as well. Usually, the former being a more economic, while the latter catalytic method provides a more specific and selective choice. Transformation of aryl bromides are more challenging, but also more advantageous than aryl iodides, since their price and availability makes them the preferred starting material.

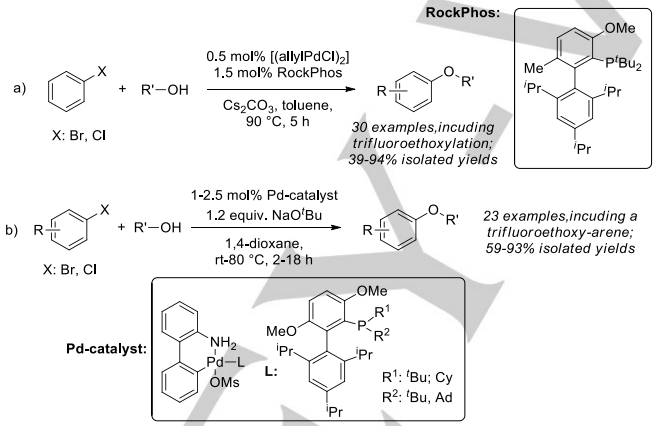
The first example for catalytic displacement of bromine to form aryl-trifluoroethyl ether was described in 1992, by M. A. Keegstra and co-workers. (Scheme 10).[22] In the early and simple protocol, NMP ensures good reaction medium for the CuI-catalyzed alkoxylation of

bromobenzene. However, harsh conditions did not allow the transformation of flexibly functionalized haloarenes.



Scheme 10. Copper-catalyzed trifluoroethoxylation of bromobenzene.

In 2011, almost 20 years later, S. L. Buchwald and co-workers developed an efficient, palladium catalyzed etherification reaction.[23]

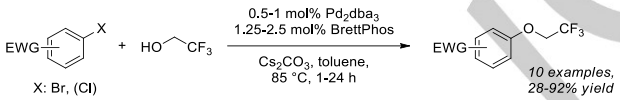


Scheme 11. Cross-coupling reaction of aryl-halides and primary alcohols mediated by palladacycle catalyst.

This publication describes the functionalization of variously substituted aryl- and heteroaryl bromides and chlorides with different primary and secondary alcohols. The coupling reaction was achieved by a special, bulky and electron rich phosphine ligand, RockPhos. Among many examples for alkoxylations with different aliphatic alcohols, the trifluoroethoxylation of a substrate was also described as the part of the substrate scope of the developed methodology (Scheme 11, a).

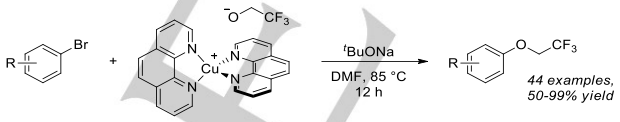
In 2018, the same research group disclosed the further study on efficient ligands for palladium catalyzed ether synthesis.[24] In this work, extensive examination and optimization of catalysts was carried out, in order to find an efficient and selective method for functionalization of diverse, sometimes unactivated aryl-bromides and chlorides with primary alcohols (Scheme 11, b).

Prasad and co-workers described the transformation of electron-poor aryl halides to fluoroalkylethers, mainly trifluoroethoxides in 2014. This method features an established catalytic system, consisting of a stable Pd(0)-source and a bulky, dialkyl-biphenyl phosphine ligand, BrettPhos, which was developed by the laboratory of S. L. Buchwald. In this study, conversion of highly activated bromoarenes was straightforward, however less electron poor bromides performed poorly, while aryl chlorides only underwent trifluoroethoxylation when strong electron-withdrawing groups were present in *para*- or *orto*-position. (Scheme 12). [25]



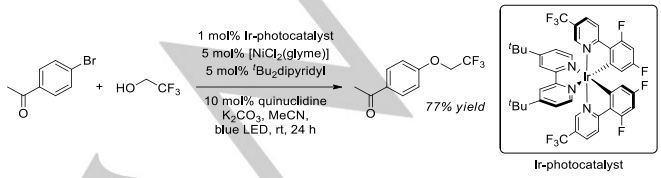
Scheme 12. Palladium catalyzed trifluoroethoxylation of electron deficient aryl bromides.

In 2015, Weng and co-workers described a copper-mediated trifluoroethoxylation with excellent functional group tolerance, and good selectivity (Scheme 13).[26] Electron-rich and –poor substrates, as well as sterically-hindered and heteroaromatic bromides were transformed in good or excellent yields utilizing a novel, copper-containing trifluoroethoxy-source.



Scheme 13. Stoichiometric copper-mediated trifluoroethoxylation of bromoarenes.

In 2015, MacMillan et al. described a mechanistically fascinating, photocatalytic method for C-O bond formation (Scheme 14).[27] In this study, substrates were mostly activated aryl bromides, which were converted with good or excellent yields to the corresponding alkoxy arenes with the aid of five different catalysts and additives, and the presence of blue light.

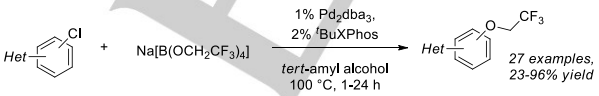


Scheme 14. Photocatalyzed trifluoroethoxylation of aryl-bromides.

3.3. Transformations of aryl chlorides

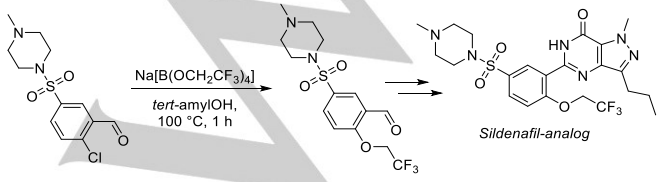
The cross-coupling etherification of aryl chlorides is even less frequent, than the transformation of bromides, and contains exclusively palladium catalyzed reactions. As mentioned above, trifluoroethoxylation of certain chloroarenes is possible in palladium catalyzed reactions described by the Buchwald group.[22,23] Also, it was shown that electron deficient aryl-chlorides underwent trifluoroethoxylation in similar conditions, with less specialized catalytic system.[25]

However, a widely applicable process deliberately for transforming aryl chlorides to the corresponding trifluoroethyl ethers was absent until 2017, when it was developed by our research group (Scheme 15).[28] Similarly to other C-O bond forming cross-coupling reactions, 1 mol% Pd_2dba_3, a dialkyl-biphenyl phosphine ligand, ^{t}BuXPhos was necessary for efficient reaction. The alkoxy-source in this method is not the alcohol itself, but a tetravalent borate salt, containing trifluoroethoxy groups. The utilization of borate salts in C-O bond forming coupling reactions was developed previously by our research group, and it makes the utilization of an external base unnecessary. [29] As a consequence of this feature, base sensitive molecular motifs were well tolerated during the reaction, and several aryl and heteroaryl trifluoroethyl ethers were isolated after the coupling reactions.



Scheme 15. Trifluoroethoxylation of aryl-chlorides utilizing a borate salt.

As the demonstration of the synthetic power of the borate based palladium catalyzed trifluoroethoxylation reaction, the synthesis of a fluorous analog of Sildenafil was carried out also. During the synthetic route, it was shown that the cross coupling can be achieved on an aryl chloride bearing aldehyde- sulfonamide- and tertiary amine functions as well.

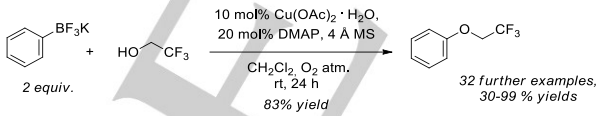


Scheme 16. Utilization of the borate based, palladium catalyzed trifluoroethoxylation for the synthesis of the fluorous analog of Sildenafil

Completion of the synthetic sequence provided the fluorous analog of Silednafil which was ready for in vitro evaluation. The comparison of physico-chemical and ADME properties of the original drug substance and the fluorinated derivative showed the expected differences which are usually attributed to fluorinated pharmaceuticals.

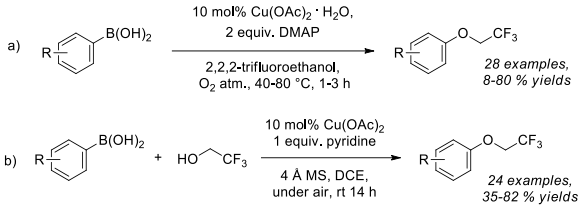
3.4. Trifluoroethoxylation through oxidative processes

Besides aryl halides, several different starting materials have also emerged for the preparation of aryl trifluoroethyl ethers. In 2003, a Chan-Evans-Lam type transformation of aryl-trifluoroborate salts and aliphatic alcohols to the corresponding ethers was described.[30] The reaction proceeds at room temperature, under O_2 atmosphere, in the presence of 4 Å molecular sieves, $Cu(OAc)_2$ catalyst and 4-(dimethylamino)pyridine ligand. In the substrate scope, among the introduction of many different alkoxy-groups, one example for trifluoroethoxylation was reported with good yield (Scheme 17).



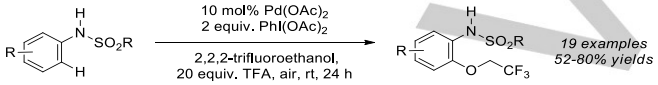
Scheme 17. Copper-catalyzed oxidative alkoxylation of organotrifluoroborates.

On the other hand, later developments by Wu[31] and Qing et al.[32] described very similar reaction conditions to previous methods for the facile synthesis of aryl trifluoroethylethers. Their methodologies are based on the use of $Cu(OAc)_2$ catalyst, pyridine-type base and oxidative atmosphere. (Scheme 18 a and b respectively). Under these circumstances, a large variety of aryl- and heteroarylboronic acids were trifluoroethoxylated, and the target products were isolated in 50-60% yield range.



Scheme 18. Trifluoroethoxylation of arylboronic acids in Chan-Evans-Lam type reactions.

In 2017, a palladium-catalyzed trifluoroethoxylation through C-H activation of *N*-Sulfonylbenzamides was published by Li and co-workers (Scheme 19).[33]



Scheme 19. Palladium catalyzed trifluoroethoxylation through C-H activation.

The *ortho*-selective transformation requires 10% $Pd(OAc)_2$ catalyst, large excess of trifluoroacetic acid and trifluoroethanol and stoichiometric amount of oxidant, $PhI(OAc)_2$, and provided the trifluoroethoxy-substituted *N*-sulphonylbenzamides in 50-60% yields.

An oxidative trifluoroethoxylation of acetanilides was reported this year by Mal et al.[34] In this process, trifluoroethoxy group is introduced in the *para*-position by an S_EAr-type oxidative functionalization of C-H bonds. The reaction setup is quite simple, does not require transition-metal catalysts, and several derivatives were prepared under mild reaction conditions in the range of 25-77% yield (Scheme 20).

Scheme 20. Oxidative C-H bond trifluoroethoxylation of anilides

4. Summary and outlook

In summary, synthetic tools based on transition metal catalyzed trifluoroethoxylation of aromatic and heteroaromatic molecules provide novel approach to trifluoroethyl arylethers. The

existing and discussed C-O bond formations through cross coupling or C-H activation ensure efficient syntheses for the target compounds, which generally have importance from the aspects of medicinal chemistry. These methodologies could have widespread application in the synthesis of biologically active molecules having trifluoroethoxy group, and further developments in the future.

Acknowledgements

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Keywords: Palladium • Copper • Cross coupling • C-H activation • Trifluoroethyoxylation

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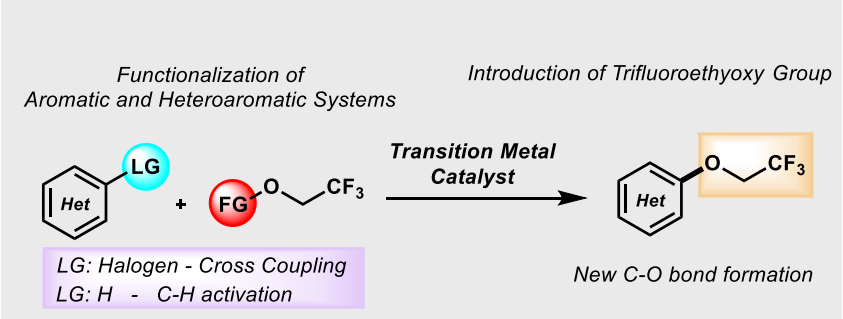

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