Carbon-Oxygen bond formation in palladium-catalyzed cross-coupling reactions

doctoral thesis

Pethő Bálint

certified chemist, MSc.

Eötvös University, Hevesy György Chemistry Doctoral School,
Program of Synthetic Chemistry, Materials Science and Biomolecular Chemistry

Chair of the doctoral school: Dr. Császár Attila
full professor

Leader of the program: Dr. Perczel András
full professor

Supervisor: Dr. Novák Zoltán
associate proffessor

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1. Introduction

Examining chemical compunds, which have considerable biological effects – especially drug molecules – we can find the aromatic-aliphatic ether structural unit in numerous molecules. According to a recent study, among blockbuster drug molecules, one in five compounds contain alkoxy group attached to an aromatic core.[1]

However, the formation of the aryl-alkyl ether function is mostly carried out by conventional methods, the catalytic methods, that provide milder reaction conditions and better chemoselectivity, are utilized less frequently.

One of the reasons for this, is that the transition metal catalyzed cross-coupling reactions are most effective in carbon-carbon bond formation. Among carbon-heteroatom bond forming reactions, the Buchwald-Hartwig amination is well-known, and frequently used, but requires complex, specific catalysts and ligands. Reactions applicable in forming carbon-oxygen bonds appeared in the early 2000s, however their utility is mostly limited to the alkoxylation of electron-deficient aromatic bromides.

Regarding the above, I appointed in my doctoral research to develop novel, operationally simple cross coupling reactions to form carbon-oxygen bonds, that can supplement the toolkit of synthetic organic chemistry. Specifically, I decided to introduce 2,2,2-trifluoroethoxy- and 2-haloethoxy groups to aromatic and heteroaromatic chlorides, as the former can be found in many bioactive compounds, and the latter might be transformed to numerous valuable compounds by a nucleophilic substitution.

2. Scientific results

2.1 Formation of borate salts and examining their applicability

In our research group a cross coupling reaction applicable to form carbon-oxygen bonds was developed previously, which was applied in the methoxylation of chloroarenes.[2] In this process – the development of which I participated as a student – utilized Pd_2dba_3 (tris(dibenzylideneacetone)dipalladium(0)) as catalyst, and the bulky ^{t}BuXPhos (2-di-*tert*-butylphosphino-2′,4′,6′-triisopropylbiphenyl) as ligand. (**Figure 1.**) The methoxylating agent in our case – unlike in previous literature examples – was not an alcohol, but the sodium

[1] H. Zhang, P. Ruiz-Castillo, S. L. Buchwald, *Org. Lett.* **2018**, *20*, 1580-1583.
[2] G. L. Tolnai, B. Pethő, P. Králl, Z. Novák, *Adv. Synth. Catal.*, **2014**, *356*, 125-129.

tetramethyl-borate ($Na[B(OCH_3)_4]$), a compound that wasn't utilized in coupling reactions previously.

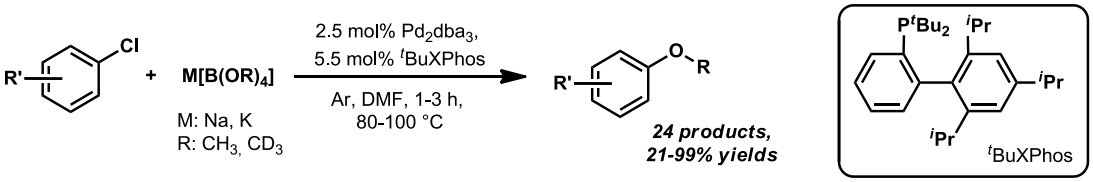


Figure 1. : *Palladium-catalyzed synthesis of aryl-methyl ethers, using borate salts*

With the majority of the examined substrates, full conversion of the starting material was observed, thus we could isolate the desired products with good or excellent yields. As the developed method was convenient and effective, we decided to synthesize more complex aryl-alkyl ethers using boron compounds.

To achieve this goal, we first had to synthesize and examine novel tetravalent borate salts. The preparation of these reagents was carried out similarly to the synthesis of sodium tetramethyl-borate, which was previously applied. This consisted of the reaction of alkaline-borohydrides and the corresponding alcohol, which yielded numerous tetravalent borate compounds. (**Figure 2**.)

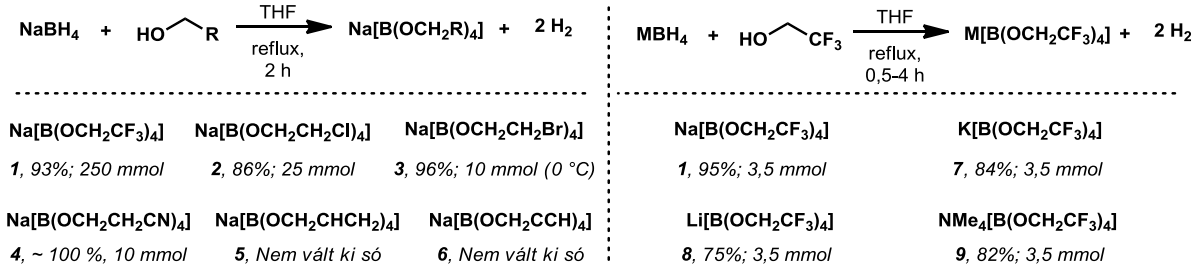
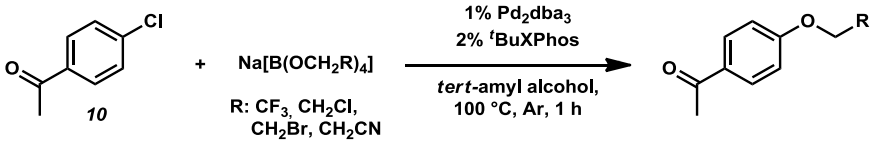


Figure 2.*: Reaction of short chained alcohols with alkaline-borohydride.*

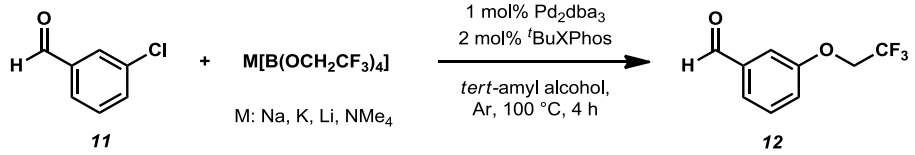
The synthesis of borate salts that contain various alkyl-groups was successful in the cases, where the alcohol reagent was an ethanol derivative containing an electron withdrawing group in position 2 (Compounds **1-4**). In case of alcohols with unsaturated carbon-carbon bonds (allyl-alcohol and propargyl-alcohol) salt formation was not detected. Having performed several test reactions, it became obvious, that selective and efficient can be expected exclusively from the application of the borate salts containing trifluoroethyl (**1**)- and 2-chloroethyl groups (**2**) (**Figure 3**).



Borate salt	1 (R = CF_3)	2 (R = CH_2Cl)	3 (R = CH_2Br)	4 (R = CH_2CN)
Total conversion	100%	100%	59%	62%
Effective conversion	99%	99%	24%	25%

***Figure 3**: Application of borate salts containing various alkoxy groups in cross coupling reactions*

Synthesis of borate salts containing triflouroethyl group, bearing different cations was also carried out (**figure 2**). Potassium- (**7**), lithium- (**8**) and tetramethyl-ammonium-borohydride (**9**) were applied. Examining the activity of these reagents showed, that the compounds containing sodium (**1**) and potassium counterions (**7**) were similarly effective, while the other two salts did not show considerable activity (**Figure 4**).



Borate salt	1 (M = Na)	7 (M = K)	8 (M = Li)	9 (M = $N(CH_3)_4$)
Conversion after 1 hour	37%	45%	3%	6%
Conversion after 4 hours	45%	57%	4%	9%

***Figure 4.**: Reactivity of tetrakis(2,2,2-trifluoroethyl)-borates containing various counterions*

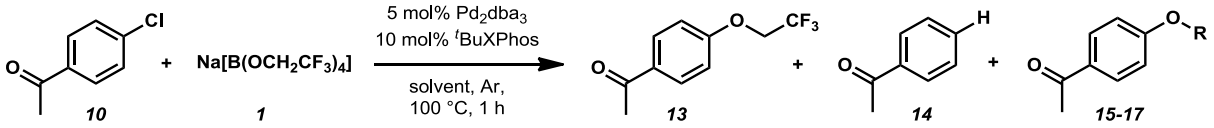
Examination of the properties of novel borate salts showed higher stability than the previous sodium tetramethyl-borate salt. These reagents are completely shelf stable, their melting point is above 350°C, are not hygroscopic, and stored at room temperature, their activity does not decrease within a year.

Consequently, sodium tetrakis(2,2,2-trifluoroethyl)borate (**1**) and sodium tetrakis(2,-chloroethyl)borate (**2**) reagents were examined in detail.

2.2 Synthesis of aryl-2,2,2-trifluoroethyl ethers in cross coupling reactions

The introduction of the trifluoroethoxy group into aromatic chlorides was first attempted with the previously described conditions of the methoxylation reaction. Soon it became evident, that the reactivity of the trifluoroethyl-containing borate salt falls far behind the

activity of sodium-tetramethyl-borate, so the reaction had to be optimized thoroughly. During this study we found, that the utilized solvent has an outstanding effect on the efficacy of the transformation. Hence numerous protic and aprotic solvents were examined in the triflorethoxylation reaction of *p*-chloroacetophenone. Several representative examples are shown in **figure 5**.



Solvent	Starting mat. (10)	Product (13)	14	15-17
toluene	97%	3%	-	-
1,4-dioxane	88%	11%	1%	-
dimethyl-formamide	90%	10%	-	-
2,2,2-trifluoroethyl alcohol	99%	<1%	-	-
water	-	32%	-	68% (R: H, **15**)
methanol	-	<1%	-	99% (R: Me, **16**)
iso-propyl alcohol	-	55%	4%	41% (R: ^{i}Pr, **17**)
tert-butyl alcohol	-	100%	-	-
tert-amyl alcohol	-	100%	-	-

***Figure 5.**: Solvent optimization study of the cross coupling reaction*

In case of polar aprotic solvents the conversion was disappointing. When using protic solvents (except 2,2,2-trifluoroethanol) full conversion was always achieved, while in case of water, methanol and *iso*-propyl alcohol, besides the desired product (**13**), a byproduct was also formed containing hydroxy- (**15,** 68%), methoxy- (**16,** 99%), and *iso*-propoxy groups (**17,** 41%) respectively.

We came to the conclusion, that a ligand exchange reaction can take place with the provided reaction conditions. This transforms the tetravalent, symmetric borate anion to a mixed borate reagent, which has improved reactivity in the cross-coupling reaction. When the reaction was performed in tertiary alcohols, the formation of byproducts was not observed and full conversion was achieved. Thus, *tert*-amyl alcohol was selected as the optimal solvent, due to its higher boiling and lower melting points.

After further optimization, the trifluoroethoxylation of numerous aromatic and heteroaromatic chlorides was performed. The reactions were carried out with the application of 0.5 mmol substrate, 1-2 mol% Pd_2dba_3 catalyst and 2-4 mol% ^{t}BuXPhos ligand. Thus 27

different aryl- and heteroaryl-2,2,2-trifluoroethyl-ethers were formed, typically with good or excellent yields (**Figure 6**).

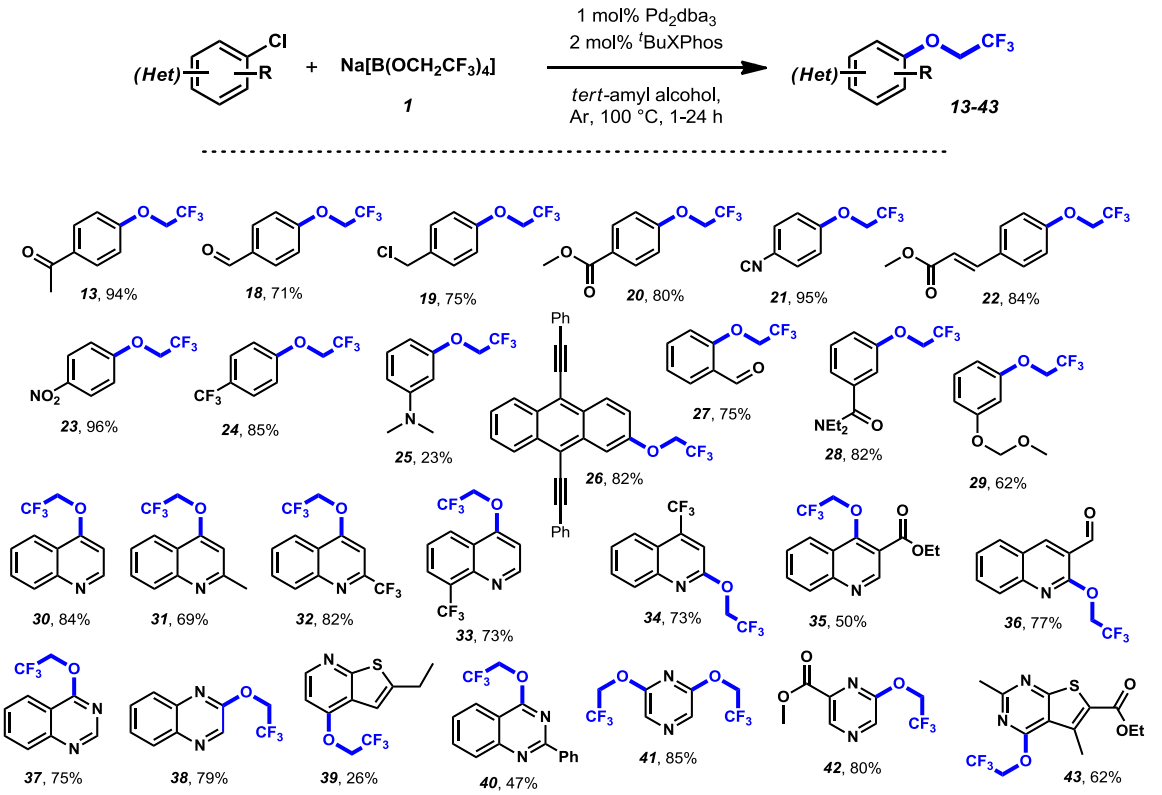


***Figure 6**: Palladium-catalyzed trifluoroethoxylation of aromatic and heteroaromatic chlorides*

Regarding the activity of the chloroarene starting materials it can be generally stated that electron-deficient derivatives yielded full conversion within an hour, meanwhile the transformation of electron rich aryl-chlorides was less effective. Due to the slightly basic conditions, most of the examined functional groups remained intact during the trifluoroethoxylation reaction. Thus aromatic chlorides containing keto- (pl.: **13**, 94%), ester- (pl.: **20**, 80%), cyano- (**21**, 95%), nitro- (**23**, 96%), trifluoromethyl- (**33**, 82%) and aldehyde groups (**18**, 71%) were effectively transformed, as well as numerous substrates with *S*- and *N*-heteroaromatic scaffolds.

2.3 Synthesis of aryl-2-chloroethyl and aryl-2-aminoethyl ethers in coupling reactions

After further examination of the reaction conditions the incorporation of the 2-chloroethoxy group was carried out, utilizing various aryl-chloride substrates (**Figure 7**.). Thus, formally an ethoxy group can be inserted between the aromatic core and the chlorine

atom, which allows a novel transformation, that wasn't viable in synthetic organic chemistry previously.

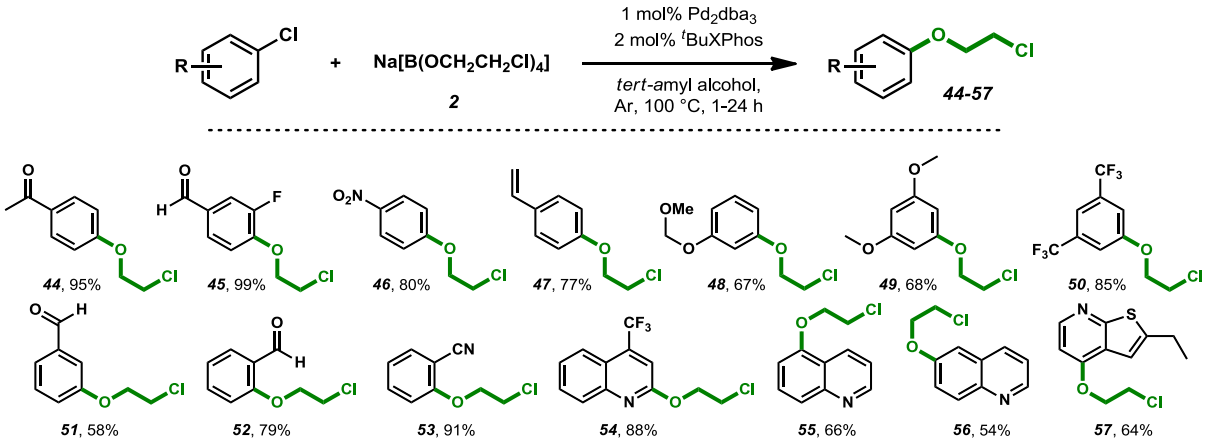


***Figure 7**: Direct 2-chloroethoxylation of aromatic and heteroaromatic chlorides*

The coupling reaction took place with an effectivity similar to the trifluoroethoxylation reaction. Aryl-chlorides that contained electron-withdrawing groups in *para*- or *ortho*-positions could be transformed with excellent yields, while utilizing electron rich aromatic and heteroaromatic chlorides, the yields were less consistent. The reactions performed using the same substrate demonstrated, that the introduction of the 2-chloroethoxy group is significantly more effective than the trifluoroethoxylation reaction (see: compound **39**, 26% yield and compound **57**, 64% yield).

The previously synthesized aryl-2-chloroethyl ethers can easily be transformed in nucleophilic substitution reaction. Thus, a *one pot* reaction was developed to convert aromatic chlorides to aryl-2-aminoethyl ethers (**Figure 8**).

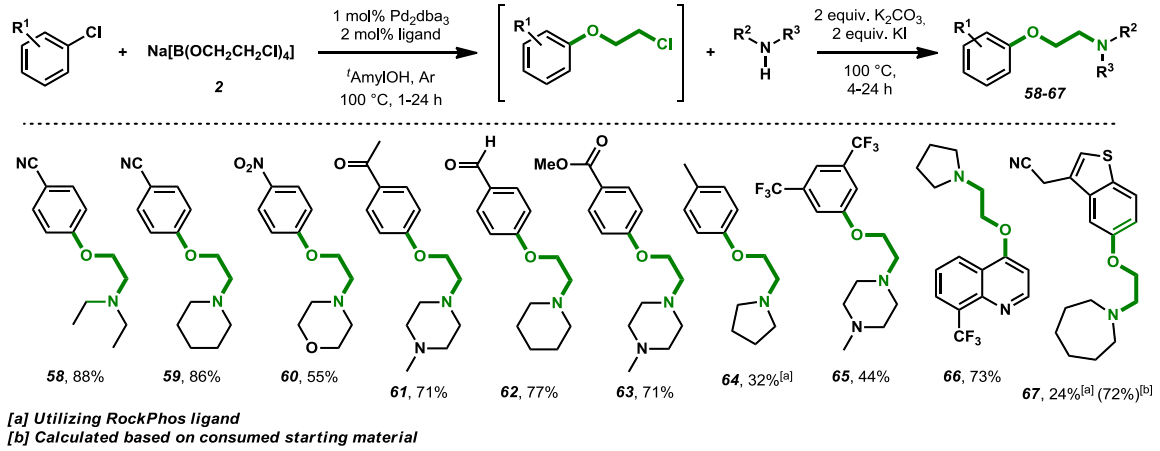


***Figure 8**: Collocation of various 2-aminoethoxy group to aryl-chlorides with „one pot" reaction*

This was carried out by the addition of potassium carbonate, potassium iodide and the nucleophile (secondary amine) to the reaction mixtures after the cross-coupling step. Thus, we successfully incorporated piperidine (pl.: **59**, 80%), 1-methyl-piperazine (pl.: **61**, 70%), morpholine (**60,** 55%), diethyl-amino (**58**, 88%), pyrrolidine (pl.: **66**, 73%) and azepane (**67**, 24%) structural motifs in the second step of the method. The intermediate was fully converted in every case.

2.4 Synthesis of bioactive aryl-alkyl ethers

Since most applications of palladium-catalyzed cross coupling reactions were developed in the pharmaceutical industry, our determined aim was to demonstrate the utility of the elaborated methods through the synthesis of bioactive compounds and their derivatives.

The trifluoroethoxylating cross-coupling reaction was successfully utilized in the total synthesis of the fluorinated analogue of Sildenafil (**Figure 9**).

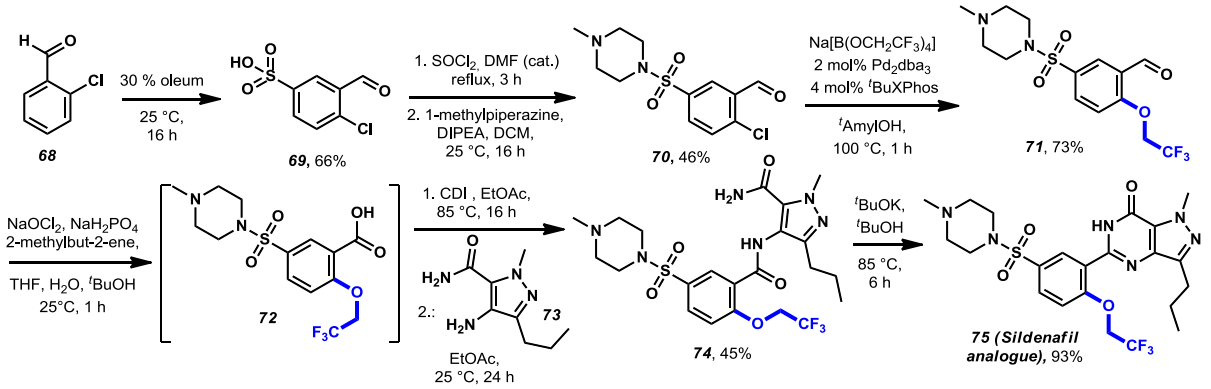


Figure 9: Synthesis of the fluorinated analogue of Sildenafil

The starting material of the synthesis was 2-chlorobenzaldehyde (**68**), which was sulphonated in the first step, to give an aromatic sulphonic acid product (**69)**. This compound – after activated by thionyl chloride – was transformed in a substitution reaction with *N*-methyl-piperazine to the sulphonamide **70**. This compound is a suitable starting material for the trifluoroethoxylation reaction. It was converted to the aryl-2,2,2-trifluoroethyl ether **71** with 73% yield, in the cross-coupling reaction developed by our research group. This product was transformed to carboxylic acid (**72**) in a Pinnick-oxidation reaction. This intermediate was converted to the amide compound **74** using a commercially available amino-pyrazol derivative (**73**). In the last step it was transformed to the fluorinated analogue of Sildenafil (**75**) by a base-mediated ring closure.

The introduction of the 2-chloroethoxy group could be a key step in the synthesis of numerous well-known drug molecules, thus the chloroethoxylation reaction was first used in the alternative synthetic route of Raloxifene (**Figure 10**).

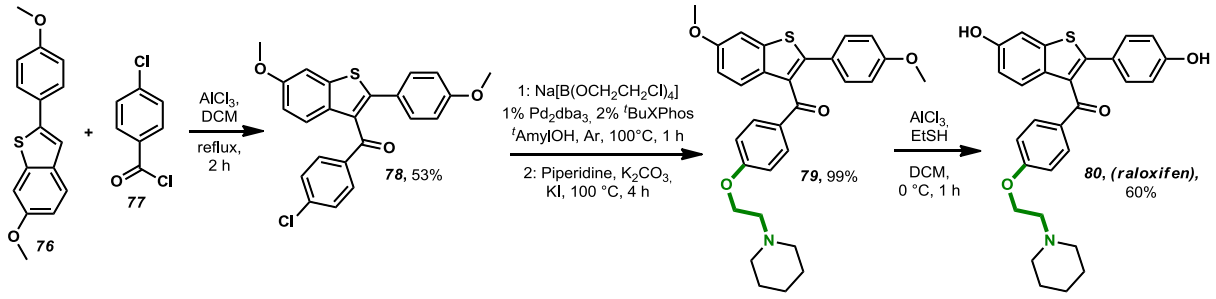


Figure 10: *Alternative synthetic route of Raloxifene*

In the first step the compound number **78** was synthesized by the Friedel-Crafts acylation of the commercially available 6-methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophene (**76**). This product was converted to the aminoethoxy-derivative (**79**) with excellent yield in the *one pot* aminoethoxylation described above. The dimethyl-raloxifene (**79**) we obtained, is an intermedier of the original synthetic route as well, thus the last, demethylation step was carried out according to a literature example. Raloxifen (**80**) was prepared with 60 % yield.

Along with this, a simplified derivative of Bazedoxifene (**84**) was produced (**Figure 11**). In contrary to the original drug substance, our target molecule didn't contain *p*-hydroxyphenyl group at position 2, methyl-group in position 3 and hydroxy group in position 5.

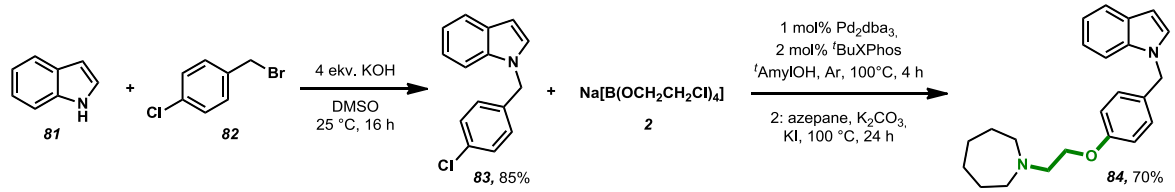


Figure 11*:Synthesis of a simplified derivative of Bazedoxifene*

First, the substitution of indol (**81**) in position 1 was performed with *p*-chlorobenzyl-bromide (**82**), thus compound number **83** was formed. This aryl-chloride was a suitable substrate of the cross-coupling reaction, so the *one pot* aminoethoxylation reaction was applied. The chlorethoxylation step was conducted in 4 hours, after what we gave potassium carbonate and potassium iodide and azepane to the reaction mixture. The mixture was stirred at 100 °C for further 24 hours. The desired product (**84**) was isolated with 70 % yield.

Synthesis and examination of numerous novel borate salts was carried out, that can be used in coupling reactions. Thus the functionalization of aromatic chlorides with motifs that were considerably challenging (2,2,2-trifluoroethoxy-group) or even impossible previously (2-chloroethoxy group), became viable.

Applying the developed methods, 27 variously substituted aryl- and heteroaryl-2,2,2-trifluoroethyl ethers, 14 aryl-2-chloroethyl ethers and 10 aryl-2-aminoethyl-ethers were formed. The total synthesis of complex, bioactive molecules was accomplished, using the C-O bond forming cross-coupling methodologies.

3. Publications related to the doctoral thesis

1. „*Palladium-Catalyzed 2,2,2-Trifluoroethoxylation of Aromatic and Heteroaromatic Chlorides Utilizing Borate Salt and the Synthesis of a Trifluoro Analogue of Sildenafil*" Bálint Pethő, Márton Zwillinger, János T. Csenki, Anna E. Káncz, Balázs Krámos, Judit Müller, György T. Balogh, Zoltán Novák, *Chem. Eur. J.* **2017**, *23*, 15628-15632.
2. „*Palladium catalyzed chloroethoxylation of aromatic and heteroaromatic chlorides: an orthogonal functionalization of a chloroethoxy linker*" Bálint Pethő, Dóra Vangel, János T. Csenki, Márton Zwillinger, Zoltán Novák, *Org. Biomol. Chem.*, **2018**, *16*, 4895-4899.
3. „*Synthesis of Aryl- and Heteroaryl-trifluoroethyl Ethers: Aims, Challenges and New Methodologies*" Bálint Pethő, Zoltán Novák, *Asian J. Org. Chem.*, **2018**, DOI: 10.1002/ajoc.201800414

4. Further publications

1. „*Iron-surfactant nanocomposit-catalyzed benzylic oxidation in water*" Fruzsina Szabó, Bálint Pethő, Zsombor Gonda, Zoltán Novák, *RSC Advances*, **2013**, *3*, 4903-4908.
2. „*Palladium-Catalyzed Methoxylation of Aromatic Chlorides with Borate Salts*" Gergely L. Tolnai, Bálint Pethő, Péter Králl, Zoltán Novák, *Adv. Synth. Catal.*, **2014**, *356*, 125-129.

5. Oral presentations

1. „*Palládiumkatalizált alkoxilezési reakciók vizsgálata, és gyógyszerkémiai alkalmazásuk*" Pethő Bálint**,** Zwillinger Márton, Csenki János, Vangel Dóra, Balogh György, Novák Zoltán, *MTA Heterociklusos és Elemorganikus Kémiai Munkabizottsági ülés*, Balatonszemes, 2018. june 6-8.
2. „*Palladium-catalyzed C-O bond forming reactions in the service of medicinal chemistry*" Bálint Pethő, Dóra Vangel, Márton Zwillinger, János T. Csenki, Zoltán Novák, *XLIII "A. Corbella" International Summer School on Organic Synthesis*, Gargnano (Italy), 2018. june 10-14.