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Palladium Catalyzed Chloroethoxylation of Aromatic and Heteroaromatic Chlorides: an Orthogonal Functionalization of Chloroethoxy Linker†

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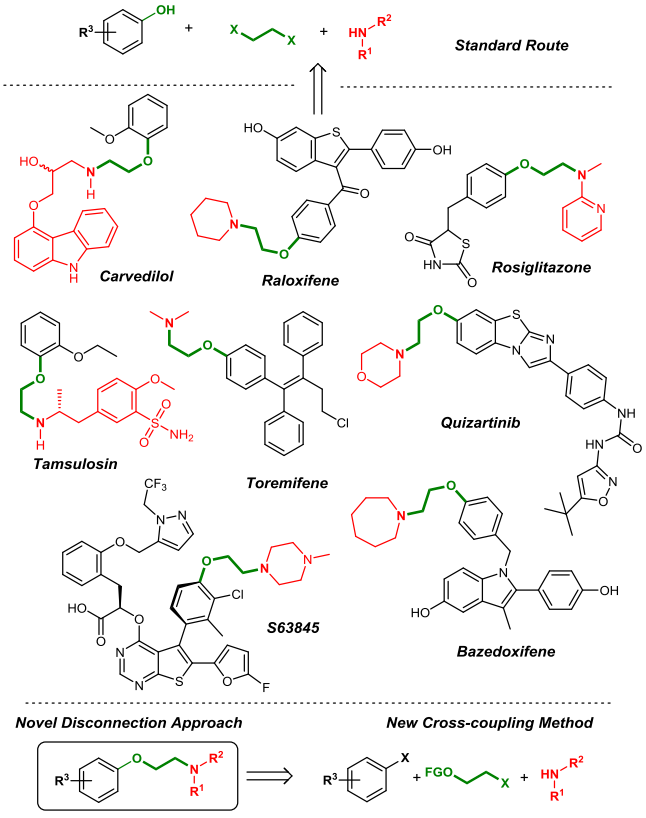
A novel disconnection based on cross-coupling chemistry was designed to access pharmaceutically relevant aryl-aminoethyl ethers. The developed palladium-catalyzed functionalization of aryl- and heteroaryl chlorides with sodium tetrakis-(2-chloroethoxy)-borate salt is orthogonal to the simple nucleophilic replacement of the chloro function of the ethylene linker. The transformation enables efficient 2-chloroethoxylation in the absence of additional external base. Subsequent amine substitution of the alkyl halide affords 2-aminoethoxy arenes. The applicability of this method was demonstrated through the synthesis of various aryl- and heteroaryl-alkyl ethers, including intermediates of marketed drug molecules.

Introduction

Orthogonality is a key aspect of molecular constructions in every branch of synthetic chemistry.[1] Selective functionalization of linkers[2] for the access of crosslinked functional groups is strategically important, but its efficient execution encounters difficulties when reaction centers of the linker have similar properties or could interact under the reactions conditions. To circumvent these synthetic problems, novel orthogonal methods should be developed. Transition metal catalyzed cross-coupling reactions are one of the most powerful tools for the selective functionalization of various molecular scaffolds through the formation of new carbon-carbon and carbon-heteroatom bonds.[3] With the aid of this methodology, a large pool of functional groups can be introduced into aromatic, heteroaromatic and even to acyclic systems with high efficiency. Thus, in pharmaceutical research the transition metal-catalyzed cross-coupling technology has widespread application.[4] However, the functionalization of cheaper and more versatile aromatic chlorides with cross-coupling chemistry[5] often encounters difficulties, and requires special catalyst systems and reaction conditions. On the other hand, introduction of some molecular motifs can also be challenging with the aid of transition metal-catalyzed reactions. One example of this is the 2-haloethoxy group, because the transition metal catalyzed C-O bond formation between 2-haloalcohols and aryl chloride coupling partners is not feasible.



Scheme 1. Examples of drug molecules having aminoalkoxy function

In spite of the significant developments in the field of C-O bond forming cross-coupling reactions for the synthesis of aryl-alkyl ethers,[6] this approach remained an elusive transformation due to the presence of a nucleophilic oxygen

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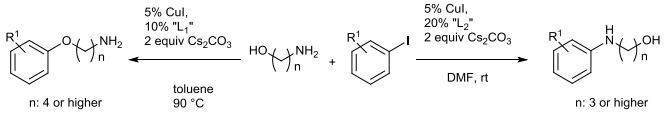
atom and a sensitive alkyl halide moiety in the same coupling partner. Thus, the necessity of rather strong external bases in the aforementioned C-O bond forming coupling reactions lead to the formation of different side products. Successful formation of aryl-alkyl ethers bearing halide leaving groups attached to the alkyl chain offers versatile transformation possibilities. The halogen can be readily replaced with heteroatom nucleophiles, such as amines to provide the 2-aminoethoxy group, which can be found in many drug molecules and other bioactive compounds (Scheme 1).[7]

The construction of 2-aminoethoxy arenes is mostly based on the *O*-alkylation of phenol derivatives with the utilization of alkylene synthons with appropriate leaving groups.[8] In case of sensitive and complex substrates, the Mitsunobu reaction of 2-aminoalcohols and phenols is a viable option,[9] and in special cases, addition reactions,[10] or nucleophilic aromatic substitutions could also be applied.[11] A successful example of the synthesis of aryl-aminoalkyl ethers through cross-coupling reactions was described by Buchwald and co-workers (Scheme 2).[6g] Although there are numerous remarkable aspects of this transformation, two important features remained unsolved. First, aryl-iodides were used as substrates, while the corresponding bromides or chlorides were inactive, and selective C-O bond forming reaction could only be achieved by longer alkyl linkers.



Scheme 2. Cu-catalyzed aminoalkoxylation of aryl-iodides

Thus, the objective of our research was the development of an efficient and selective catalytic method for the 2-chloroethoxylation of aryl chlorides. With a subsequent substitution reaction, a wide variety of nucleophiles can be introduced to the aryl-chloroethyl ethers, granting a modular synthetic route to 2-aminoethoxy-arenes, which are precious targets of pharmaceutical research. With respect to this goal, the application of borate salt-based catalytic methods for the synthesis of aryl-alkyl ethers developed in our laboratory could provide solution to the difficulties of the desired cross-coupling.[12]

The development of a new cross-coupling approach to 2-chloroethoxylation offers an alternative disconnection and provides a new synthetic tool beyond the existing phenol-based transformations to construct C-O bonds. This can be useful, when instability issues, tautomerism or economic reasons make the phenol-type starting material unavailable.

Results and discussion, Experimental

For the examination of the applicability of the palladium-catalyzed C-O bond forming reaction between aryl chlorides and borate reagents, first we prepared a novel tetrakis(2-chloroethoxy) borate salt from inexpensive starting materials: 2-chloroethanol and $NaBH_4$. The coupling of the borate salt with *p*-chloroacetophenone was then examined in *tert*-amyl alcohol at 100°C in the presence of Pd_2dba_3 catalyst with different phosphine ligands (Table 1). The study of the ligand effect revealed that bulky, dialkyl-biphenyl phosphines were generally appropriate ligands for the efficient coupling.

Table 1. Study of ligand effect on the coupling reaction[a]

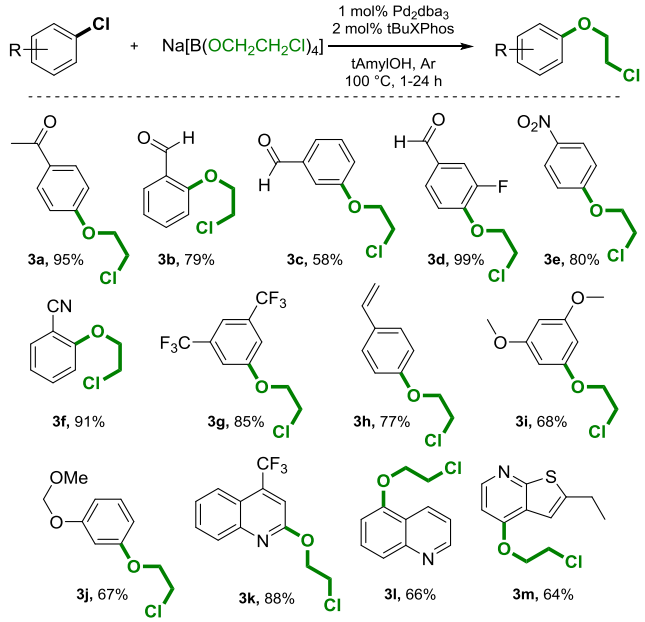
Entry	Reagent	Ligand	**3H** (%) [b]	**3a,** (%)[b]
1	**2a**	CyJohnPhos	1	1
2	**2a**	JohnPhos	24	63
3	**2a**	BrettPhos	1	92
4	**2a**	XPhos	13	54
5	**2a**	Me_4^{t}BuXPhos	0	86
6	**2a**	RockPhos	0	99
7	**2a**	^{t}BuXPhos	0	100(95)[c]
8	**2b**	^{t}BuXPhos	complex mixture	45[c, d]

[a] 0.1 mmol aryl chloride, 0.15 mmol $Na[B(OCH_2CH_2Cl)_4]$, 200 µL ^{t}Amyl-alcohol. [b] Determined by GC analysis after 1 h; numbers in parenthesis indicate conversions after 24 h. [c] Isolated yield. [d] 1.5 equiv of Cs_2CO_3 was used as base.

Comparing the alkyl-substituents, ligands bearing *tert*-butyl groups were more active, than their cyclohexyl-substituted derivatives (entries 1 vs 2 and 4 vs. 7). Among the tested ligands ^{t}BuXPhos proved to be the best choice with respect to both activity and economy. With its application, 100% conversion was reached in 1h, and after the workup the chloroethoxylated product **3a** was isolated in 95% yield. To demonstrate the beneficial effect of borate coupling partners over simple alcohols, the preparation of the same product was attempted using the well-established reaction of chloroacetophenone and 2-chloroethanol in the presence of Cs_2CO_3. [13] This reaction gave a complex product mixture after complete consumption of the substrate, and the desired coupled product **3a** was isolated only in 45% yield (entry 8).

With the optimized reaction conditions in hand, we turned our attention to the applicability of the method in the synthesis of various aromatic and heteroaromatic 2-chloroethoxy derivatives (Scheme 3). The formyl group was tolerated well and coupling reaction through the chloro function in *ortho*-, *meta*-, and *para*-position to the aldehyde group was successful under the optimized reaction conditions, affording products **3b-d** in 79, 58 and 99% yield respectively. The coupling reaction took place smoothly in the presence of electron withdrawing groups such as nitro, cyano and trifluoromethyl, providing products **3e-g** in 80-91% yield. 4-Chloro-vinylbenzene was also chloroethoxylated, providing **3h** in 77% yield. Electron donating groups such as methoxy- or MOM-protected phenolic OH also enabled the cross-coupling on the chloride, however, the electron rich nature of the substrates resulted in lower reactivity. Products **3i** and **3j** were isolated in 68% and 67% yield after the workup of the reaction mixture. A

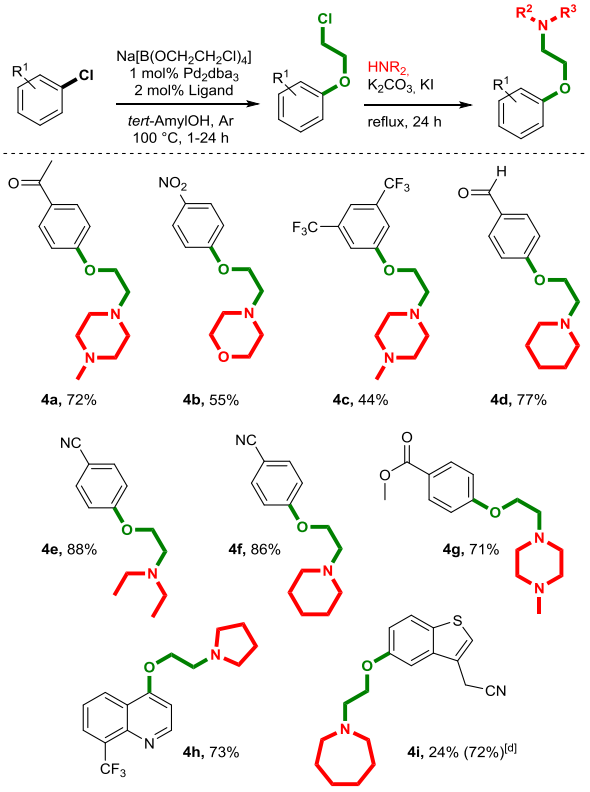
notable limitation of the transformation occurred when the methoxy group was *para* to the chloro function; the conversion of the reaction reached only 10% (not shown), indicating that the electronic factors play a key role in the transformation.



Scheme 3. Chloroethoxylation of aromatic chlorides

To expand further the substrate scope of the coupling reaction we examined 2-chloro- and 5-chloroquinolines. These experiments showed that both the heterocyclic and the carbocyclic part of the ring could be functionalized in the palladium catalyzed reaction, and product **3k** and **3l** were isolated in 88% and 66% yields. Thienopyridines are important heterocyclic scaffolds in medicinal chemistry, therefore we examined the chloroethoxylation of the chloro derivative of this heterocycle. To our delight this special heterocyclic building block underwent smooth transformation and the target product **3m** was isolated in 64% yield.

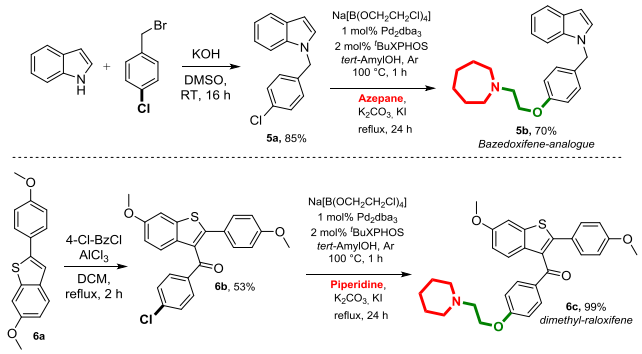
After demonstrating of the applicability of the developed coupling for the synthesis of 2-chloroethoxylated building blocks, we extended the coupling with a subsequent substitution step to prepare aminoethoxy derivatives in a one-pot manner (Scheme 4). Among the several well-known methods for this purpose, our choice was to keep it simple, utilizing the Finkelstein halogen exchange reaction followed by nucleophilic substitution with secondary amines in the presence of potassium iodide and potassium carbonate base. For the examination of the two step one-pot functionalization method we performed the palladium-catalyzed step on three different aryl chlorides previously chloroethoxylated. Then intermediates **3a**, **3e** and **3g** were subjected to nucleophilic replacement of the chloro group with *N*-methylpiperazine and morpholine affording the aminoethoxylated products **4a-c** in 44-72% yield. For the further studies we used different aryl chlorides to expand the substrate scope of both the cross-coupling step and the one-pot aminoalkoxylation strategy. Chlorobenzenes bearing formyl, nitro or ester group in the *para*-position were straightforwardly chloroethoxylated in the palladium-catalyzed transformation and then substituted with piperidine, diethylamine and *N*-methylmorpholine, affording products **4d-g** in 71-88% yield. Compound **4h** was obtained in 73% yield in the two step procedure starting from 4-chloro-8-trifluoromethyl-quinoline, with pyrrolidine being used as the



Scheme 4. One-pot aminoethoxylation of chloroarenes

amine nucleophile after the palladium-catalyzed chloroethoxylation step. The same strategy was used to prepare a highly electron-rich benzothiophene substrate, though a large amount of unreacted starting material was recovered beside the isolation of compound **4i** as the desired aminoethoxylated product.

To illustrate the applicability of this method, we carried out the synthesis of an analog and an intermediate of active pharmaceutical ingredients (Scheme 5) containing condensed heterocyclic cores such as indoles and benzothiophenes. First, we prepared the aryl-chloride substrate **5a** through the *N*-benzylation of indole with 4-chlorobenzyl-bromide,[14] for the key aminoalkoxylation step. Then the palladium-catalyzed coupling reaction with $Na[B(OCH_2CH_2Cl)_4]$ and subsequent amination under the developed reaction conditions led to a 70% yield of the desired product **5b**, which contains the core of the selective estrogen receptor modulator (SERM) drug,



Scheme 5. Synthesis of Bazedoxifene-analogue and the intermediate of Raloxifene

Bazedoxifene. Another example to illustrate the applicability of our aminoalkoxylation method was the design of an alternative synthetic route to Raloxifene intermediate **6c**. First, the Friedel-Crafts acylation of a commercially available benzothiophene-derivative (**6a)** was achieved,[15] leading to the starting material (**6b)** equipped with chloro function necessary for the cross-coupling reaction. The 2-chloroethoxylation with the borate salt under the catalytic conditions and subsequent substitution step with piperidine afforded the desired Raloxifene intermediate (**6c**) in almost quantitative yield.

Conclusions

In conclusion, we have developed an alternative, simple and convenient synthetic route to the access of 2-chloroethoxy-arenes using palladium-catalyzed cross-coupling reaction of aryl chlorides and tetraethoxyborates. This methodology is orthogonal to nucleophilic substitution and enables the modular synthesis of various molecules containing ethoxy linkers between nucleophilic centers (eg. amines) and aromatic cores. The utilization of a novel borate salt ensures efficient transformation with good functional group tolerance due to the absence of external base, and eliminates synthetic difficulties of the traditional alkoxylation with haloalcohols. This special feature of the transformation provides a new synthesis concept in the field of C-O bond forming reactions. With a subsequent simple nucleophilic substitution reaction step, wide variety of 2-aminoethoxy-arenes can be prepared in a one-pot manner. Beyond several aminoalkoxylated model compounds, the applicability of the two step one-pot reaction was demonstrated with the synthesis of a Bazedoxifene-analogue and the final intermediate of Raloxifene. Thus, previously unavailable synthetic routes to bioactive molecules can be performed with the application of this method, which can be an alternative, efficient tool for generic and original pharmaceutical research. The new methodology paves the way for versatile alkoxylation reactions to the direct access of aryl-haloalkyl ethers which are susceptible for further transformations with various nucleophiles.

Experimental

General procedure for the 2-chloroethoxylation of chloroarenes: A 4 ml screw cap vial was charged with Pd_2dba_3 (4.6 mg, 5,0 µmol, 1 mol%), 2-di-*tert*-butylphosphino-2',4',6'-triisopropylbiphenyl (^{t}BuXphos, 4.2 mg, 10.0 µmol, 2 mol%), the aryl chloride substrate (0.5 mmol, 1 equiv) and 100 µl *tert*-amyl alcohol. The atmosphere was changed to argon, then the suspension of sodium tetrakis(2-chloroethoxy) borate in 900 µl *tert*-amyl alcohol was added via syringe, and stirring started at 100 °C, usually for one hour. When the reaction was complete, the mixture was diluted with brine (10 ml) and extracted with EtOAc (3*15 ml). The combined organic layers were evaporated and purified by column chromatography.

General procedure for the one-pot synthesis of 2-aminoethoxy arenes: A 4 ml screw-cap vial equipped with a stirring bar was charged with Pd_2dba_3 (4.6 mg, 5 µmol, 1.0 mol%), ^{t}BuXPhos (4.2 mg, 10 µmol, 2.0 mol%) the substrate if solid (0.5 mmol, 1 equiv), and *tert*-amyl alcohol (100 µl). The atmosphere was changed to argon, and the solution was stirred at RT for 5 minutes. The suspension of $Na[B(OCH_2CH_2Cl)_4]$ (263.9 mg, 0.75 mmol, 1.5 equiv) in *tert*-amyl alcohol (900 µl), and the substrate (0.5 mmol) if liquid was added and the mixture was stirred at 100 °C for 1-24 hours. The mixture was allowed to cool down to room temperature, KI (166 mg, 1 mmol, 2 equiv), K_2CO_3 (138 mg, 1 mmol, 2 equiv) and secondary amine (eg.: piperidine, 2 ml) was added to the solution, then stirred at 100 °C for further 4-24 hours. The mixture was cooled down to room temperature, diluted with water (10 ml), and extracted with EtOAc (3X15 ml). The combined organic layers were evaporated under reduced pressure, and purified by column chromatography (silica gel, DCM:MeOH eluent mixture).

Conflicts of interest

There are no conflicts to declare"

Acknowledgements

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