DOCTORAL THESIS

# Sustainable Synthesis and Dearomatization of Oxygen-Containing Aromatic Compounds

Anni Kooli

TALLINNA TEHNIKAÜLIKOOL
TALLINN UNIVERSITY OF TECHNOLOGY
TALLINN 2022

TALLINN UNIVERSITY OF TECHNOLOGY
DOCTORAL THESIS
63/2022

# Sustainable Synthesis and Dearomatization of Oxygen-Containing Aromatic Compounds

ANNI KOOLI

TAL TECH PRESS

TALLINN UNIVERSITY OF TECHNOLOGY
School of Science
Department of Chemistry and Biotechnology
This dissertation was accepted for the defence of the degree of Doctor of Philosophy in Chemistry 18/10/2022

**Supervisor**: Prof. Margus Lopp
School of Science
Tallinn University of Technology
Tallinn, Estonia

**Co-supervisor**: Dr. Maksim Ošeka
School of Science
Tallinn University of Technology
Tallinn, Estonia

**Opponents**: Prof. Eugenijus Butkus
Life Sciences Centre
Vilnius University
Vilnius, Lithuania

Assoc. Prof. Uno Mäeorg
Faculty of Science and Technology
Institute of Chemistry
University of Tartu
Tartu, Estonia

**Defence of the thesis**: 25/11/2022, Tallinn

**Declaration:**
Hereby, I declare that this doctoral thesis, my original investigation and achievement, submitted for the doctoral degree at Tallinn University of Technology has not been submitted for any other doctoral or equivalent academic degree.

Anni Kooli

---
signature

European Union
European Regional
Development Fund

Investing
in your future


ISSN 2585-6898 (publication)
ISBN 978-9949-83-915-5 (publication)
ISSN 2585-6901 (PDF)
ISBN 978-9949-83-916-2 (PDF)
Printed by Koopia Niini & Rauam

TALLINNA TEHNIKAÜLIKOOL
DOKTORITÖÖ
63/2022

# Hapnikku sisaldavate aromaatsete ühendite jätkusuutlik süntees ja dearomatiseerimine

ANNI KOOLI

TAL TECH
KIRJASTUS

# Contents

## List of Publications

The list of author's publications, on the basis of which the thesis has been prepared:

I E. Lopušansakaja, A. Kooli, A. Paju, I. Järving, M. Lopp, Towards *ortho*-selective electrophilic substitution/addition to phenolates in anhydrous solvents. *Tetrahedron*, **2021** *83*, 131935.

II A. Kooli, T. Shalima, E. Lopušanskaja, A. Paju, M. Lopp, Selective *C*-alkylation of substituted naphthols under non-aqueous conditions. *Tetrahedron* **2021**, *95*, 132278.

III A. Kooli, L. Wesenberg, M. Beslać, A. Krech, M. Lopp, T. Noël, M. Ošeka, Electrochemical Hydroxylation of Electron-Rich Arenes in Continuous-Flow. *Eur. J. Org. Chem.* **2022**, *e202200011*.

## Author's Contribution to the Publications

Contribution to the papers in this thesis are:

I The author took part in experiment planning and in interpreting the obtained results. The author collaborated in writing the manuscript together with the other co-authors.

II The author played the major role in designing and performing synthetic experiments, as well as in the analysis and characterisation of the obtained products. The author wrote the manuscript with contributions from the co-authors and complied the supporting information.

III The author played the major role in performing the experiments in the scope exploration and characterisation of the obtained products. The author wrote the manuscript with contributions from the co-authors and complied the supporting information.

# Introduction

Phenols and their derivatives can be found in many bioactive compounds and natural products and are common motifs in different synthetic materials, *e.g.* polymers. Electron-rich arenes are also valuable building blocks for the synthesis of useful compounds in both academia and the chemical industry. This makes them an interesting and valuable research topic for an organic chemist. As a result, different methods for the synthesis of aryl oxygen products can be developed.

The hydroxylation of the arenes is a thoroughly investigated area of chemistry, due to the need for new bioactive substances bearing oxygenated phenol units. Methods using transition-metals are still used in combination with rigid experimental conditions, which makes these experimental methods wasteful and inconvenient to use for the chemical industry. A more sustainable, transition-metal-free and industrially friendly approach is to use electricity to perform such reactions. We have studied electrochemical transformations in continuous-flow to synthesise substituted phenols from arenes. The continuous-flow approach eliminates some limitations which exist when using batch electrochemistry. The formed phenols are good starting materials for further derivatisation. Among many prospects, alkylation is a common strategy to modify phenols. Two different methods are used: the alkylation of the hydroxyl group (*O*-alkylation) and the alkylation of the aromatic core (*C*-alkylation). There are different methods known for the selective *C*-alkylation of the aryl oxygen compound, but the majority of them are indirect and require transition-metal catalysis. However, the direct *C*-alkylation of phenols and naphthols, which does not require any transition-metals, is rather unexplored.

This doctoral thesis gives an overview of the synthesis of different phenols and their derivatization by using either traditional synthesis methods or the electrochemical approach. The methods described in the thesis are effective and simple ways to synthesise and dearomatize aryl oxygen compounds (**Publications I-III**). A green and efficient method for the synthesis of electron-rich arenes based on electrochemical oxidation in continuous-flow was explored (**Publication III**). A direct *C*-alkylation reaction was investigated for the selective modification of phenols and their derivatives *via* dearomatization (**Publications I-II**). Along with the mentioned published articles, the results of this research have also been presented at international conferences in Estonia, Thailand and Greece.

## Abbreviations

| | |
|---|---|
| Ac | acetyl |
| aq. | aqueous |
| Ar | aryl |
| BHT | butylated hydroxytoluene (dibutylhydroxytoluene) |
| Bn | benzyl |
| cat | catalyst |
| cod | cyclooctadiene |
| CPME | cyclopentyl methyl ether |
| DBU | 1,8-diazabicyclo[5.4.0]undec-7-ene |
| DCE | 1,2-dichloroethane |
| DCM | dichloromethane |
| DIPEA | *N*,*N*-diisopropylethylamine |
| DIY | do it yourself |
| DMF | dimethylformamide |
| *e.g.* | *exampli gratia* (Latin); for example |
| e.r. | enantiomeric ratio |
| *ee* | enantiomeric excess |
| EM | electron-mediator |
| Et | ethyl |
| *et al.* | *et alia* (Latin); and others |
| EWG | electron withdrawing group |
| GC-FID | gas chromatography-flame ionization detector |
| GC-MS | gas chromatography-mass spectrometry |
| HFIP | hexafluoroisopropanol |
| IBX | *o*-iodoxybenzoic acid |
| *i*-Pr | isopropyl |
| M.S. | molecular sieves |
| Me | methyl |
| Ms | mesyl |
| MTBE | methyl *tert*-butyl ether |
| *n*Bu | normal butyl |
| nd | not determined |
| NMR | nuclear magnetic resonance |
| *n*Pr | normal propyl |
| Ph | phenyl |
| PIDA | (diacetoxyiodo)benzene |
| PIFA | (bis(trifluoroacetoxy)iodo)benzene |
| p$K_a$ | acid dissociation constant at logarithmic scale |
| r.t. | room temperature |
| SCE | saturated calomel electrode (reference electrode) |

| | |
|---|---|
| SET | single electron transfer |
| SIBX | stabilised IBX. SIBX is composed of IBX (49%), benzoic acid (22%) and isophthalic acid (29%) |
| TBS | *tert*-butyldimethylsilyl |
| *t*Bu | *tert*-butyl |
| TEMPO | (2,2,6,6-tetramethylpiperidin-1-yl)oxyl |
| TFA | trifluoroacetic acid |
| TFAA | trifluoroacetic anhydride |
| THF | tetrahydrofuran |
| Ts | tosyl |
| X | halogen |

# 1 Literature Overview

## 1.1 Introduction to Electrochemistry

Everyone understands the word “electrochemistry” differently, but for ordinary chemists it is mainly connected with physical and analytical chemistry rather than with organic chemistry. However, this situation is starting to change. Since the beginning of the last decade, electrochemistry has also gained grater interest among synthetic chemists.[1–9] The reasons for using electrochemistry in organic synthesis vary, but mainly there is a need for sustainable and environmentally friendly synthetic methods. Electrochemical processes are atom-efficient and make it possible to selectively carry out oxidation or reduction reactions under mild reaction conditions. They can replace the use of harsh and toxic chemicals, because the electrons act as traceless and green reactants in such reactions. This makes electrochemical synthesis cleaner and less harmful to the environment.[10–12] In electrochemical transformations, free radicals or radical ions are generated and these reactive species react further, affording new reaction pathways.[2] Despite all of the opportunities it offers, special equipment and know-how is required for electrochemical synthesis.

### 1.1.1 Principles of Electrochemistry

A typical undivided electrochemical setup consists of a reaction vessel and two electrodes (anode and cathode), which are connected to a constant current power supply (Figure 1, **A**). An undivided cell system is easy to set up and operate. It is used when a starting compound or a reaction product does not react on the counter electrode. On the other hand, a divided cell system should be used when the desired and counter reactions are incompatible and must be separated. A divided cell setup consists of two different cell chambers, each containing an electrode that is connected to the power supply. The chambers are connected with each other by a salt bridge or a membrane that is suitable for ion transport (Figure 1, **B**). Because of the salt bridge or the membrane, no substrate or reagent can move between the chambers and the reactions can be carried out separately without problems.[13]

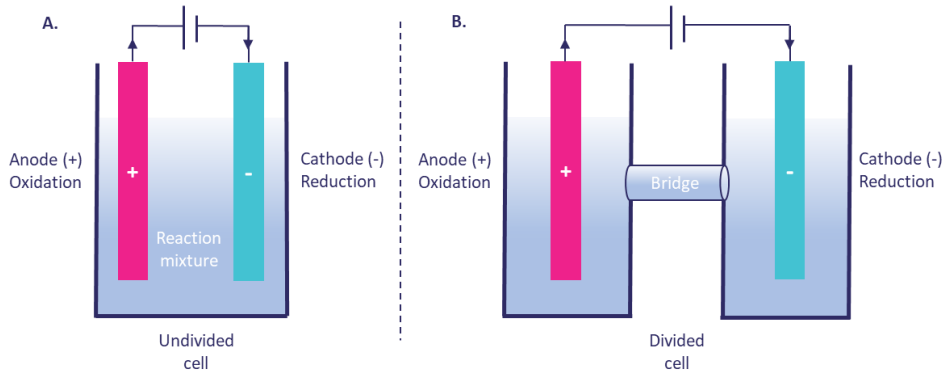



***Figure 1.*** *Electrochemical setups: anode (pink), cathode (blue).* ***A.*** *– undivided cell;* ***B.*** *– divided cell.*

Generally, the targeted reaction takes place only on one electrode: on the anode for oxidation, or on the cathode for reduction. The electrode where the reaction of interest occurs is called “the working electrode”, and the other electrode, used to complete the circuit, is called “the counter electrode”. For the electrochemical reaction to occur, the potential between the anode and the cathode has to be greater than the RedOx potential of a substrate. The potential shows how much energy is required to move electrons from the anode (+) to the cathode (-). When the potential is too low, no reaction occurs, whereas too high a potential causes side reactions, such as overoxidation/reduction, which might lead to polymerisation and deposition of organic material on the electrode surfaces. As two parallel reactions take place on both electrodes, it is important to understand what happens on the counter electrode, because the counter reaction might limit the process.[13] When an anode is the working electrode, solvent degradation with hydrogen gas evolution usually happens at the cathode.[14] Sacrificial metals with low oxidation potential (*e.g.* Mg, Zn or Al) are used as anode material when the reaction of interest occurs at the cathode.[15]

To carry out an electrochemical reaction, we can choose between two approaches, either using constant current (the galvanostatic mode) or constant potential (the potentiostatic mode). In the galvanostatic mode, we know how many electrons are stoichiometrically required by the reaction, and high conversions can be achieved. Furthermore, there is no need for a reference electrode making a reaction setup simpler. On the other hand, we cannot control the potential (voltages), which can lead to undesired products as the potential in a system can rise above the optimum conditions for the designed synthesis. When this happens, it is a good idea to use the constant potential mode as higher selectivity can be achieved, but this requires a reference electrode for accuracy and for reproducibility. However, achieving the full conversion is harder, due to the decreasing amount of the starting material, which will lower the current over time.[6,13]

Besides the mode used in the reaction, the electrochemical reaction type must be determined. There are two types: direct or indirect electrolysis (Figure 2). In direct electrolysis, the reaction takes place on the electrode’s surface, as electrons cannot pass through the reaction mixture. The simplest example of direct electrolysis is solvent degradation at the counter electrode. A new product forms on the working electrode from radicals or reactive intermediates that are produced in the electrochemical reaction.[13,16] In the case of challenging substrates, an electron-mediator can be used for indirect electrolysis, which upon oxidation or reduction on the electrode reacts further with the starting material. This is similar to traditional synthesis methods, where catalysts are used to facilitate reactions.[13,17,18] *N*-oxyl compounds (*e.g.* TEMPO) are the most used electrochemical mediators. They are typically used for hydrogen atom abstraction, such as the oxidation of various alcohols to carbonyl compounds or the oxidation of amines to nitriles.[19,20]

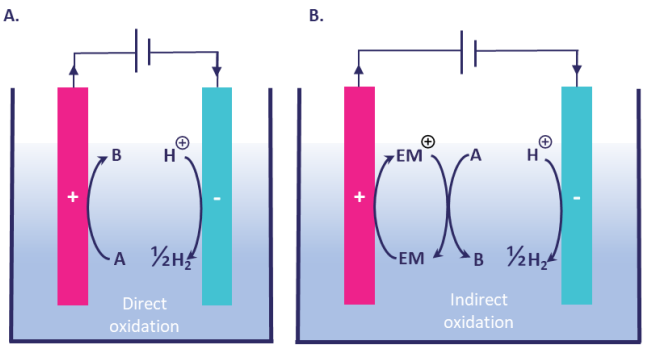



***Figure 2. A.*** *– direct oxidation;* ***B.*** *– indirect oxidation. Anode (+): pink, cathode (-): blue. EM – electron-mediator, EM⁺ – activated electron-mediator, A – reagent, B – product.*

### 1.1.2 Electrochemistry in Continuous-flow

Despite the advantages of electrochemistry, it has some limitations when applied to heterogeneous processes, such as insufficient mixing, hot spot formation and organic matter deposition. All of these problems hinder the use of electrochemical synthesis. To overcome these setbacks, the reactions can be carried out in a continuous-flow setup. In the flow setup, the reactant solution is continuously pumped through a narrow channel between the two electrodes, where the reaction takes place (Figure 3).[21,22]

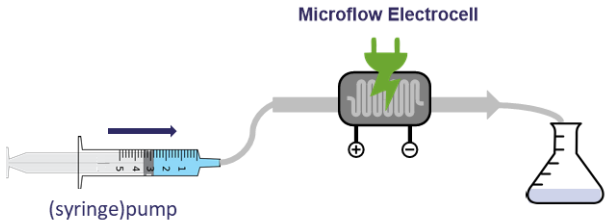
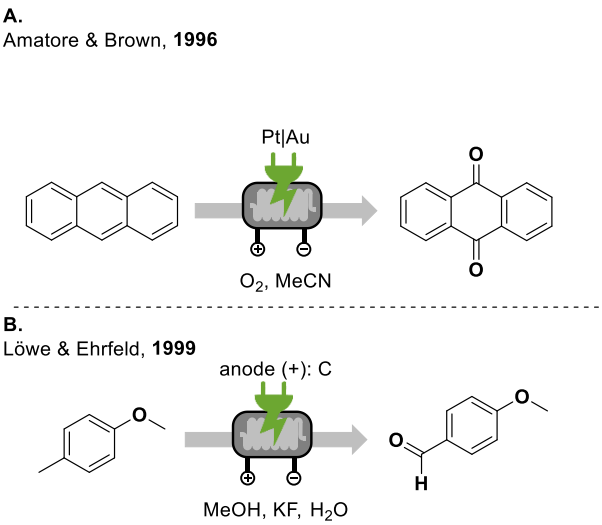



***Figure 3****. Schematic representation of an electrochemical continuous-flow setup.*

Flow microreactors have high surface-to-volume ratios that make it possible to notably reduce the reaction time (from the typical overnight reaction time in batch to 5 minutes in flow). Shorter reaction times help to avoid the degradation of sensitive products and the loss of selectivity. The small interelectrode gap (up to 1 mm) and Taylor flow provide efficient mass and heat transfer.[23,24] Taylor flow is a phenomenon in which gas bubbles form upon hydrogen reduction and liquid segments alternate. This prevents the microchannels from clogging and boosts mixing efficiency. On the other hand, the formed bubbles act as insulators in the channels and prevent the reaction from occurring in the bubble region, requiring more energy for the process.[25] The continuous-flow approach builds a bridge between academia and industry, as it is not feasible to enlarge the electrodes and reaction vessels that batch electrochemical reactions require. That is why continuous-flow reactors are used in industry.[26,27]

The first example of using a microreactor in organic electrolysis was presented by Amatore and Brown in 1996. They investigated the oxidation of anthracene with dioxygen in acetonitrile and obtained anthraquinone with up to 90% yield (Scheme 1A).[28] In 1999, Löwe and Ehrfeld used an undivided cell reactor, where the electrodes were separated

by polyamide foil (75 µm thick) and the reactor was operated in continuous-flow mode. They investigated the anodic oxidation of 4-methoxytoluene in methanol with a supporting electrolyte (potassium fluoride). This resulted in 4-methoxybenzaldehyde with excellent yield (up to 98%) (Scheme 1B).[29] Since these successful examples, the use of flow electroreactors has increased dramatically. But the majority of reactors are still DIY (do-it-yourself) reactors (Figure 4).[30–36]




***Scheme 1**. **A**: Oxidation of anthracene on platinum. **B**: Oxidation of methoxytoluene on glassy carbon.*

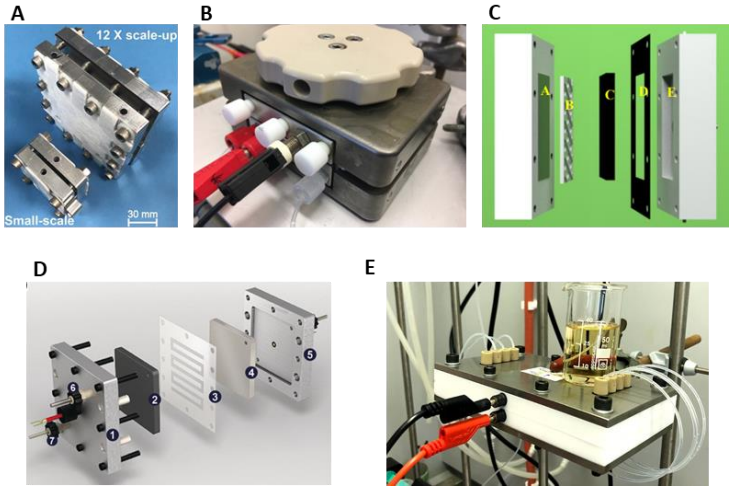
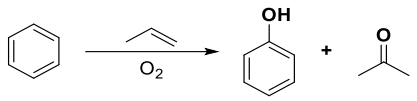



***Figure 4.** Examples of DIY microreactors. **A**: Reprinted from Science, 368, 1352-1357 (2020), with permission from AAAS. **B:** Reprinted from Angew. Chem. Int. Ed. 2019, 58, 9811-9815 with permission from John Wiley and Sons. **C:** Adapted with permission from J. Am. Chem. Soc. 2019, 141, 43, 17198-17206. Copyright (2019) American Chemical Society. **D:** Reprinted from Angew. Chem. Int. Ed. 2019, 58, 6650-6653 with permission from John Wiley and Sons. **E:** our in-house microreactor developed by the Noël group.*

## 1.2 Synthesis of Aryl Oxygen Compounds

Phenol is an aromatic compound, which consists of a phenyl group that is bonded with a hydroxy group. It is a mildly acidic (p$K_a$= 9.95 in water) white crystalline solid first discovered by the German chemist Johan Rudolf Glauber in 1650. However, it took almost two centuries before Friedlieb Ferdinand Runge isolated the impure form of phenol from coal tar, in 1834. Pure phenol was isolated by the French chemist Auguste Laurent in 1841.[37] Since the discovery of phenol, the demand for its production has continued to rise. Two different strategies have been used in industry to obtain phenol: 1) chlorination or sulphonation of benzene, and 2) the oxidation of a cumene intermediate (Hock) process (Scheme 2). Nowadays, the Hock process accounts for more than 90% of total phenol production. Nevertheless, industrial phenol synthesis has several drawbacks, such as high energy consumption, low phenol yield (up to 5% from initial benzene quantity) and dependence on the acetone market.[38,39]

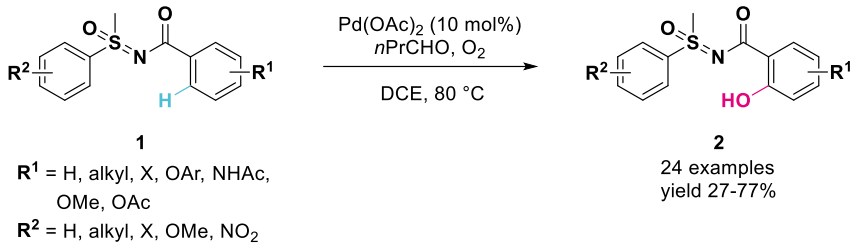



***Scheme 2.*** *Hock process.*

In the last few decades, new environmentally friendly approaches have been proposed using a direct hydroxylation of benzene with oxidizing agents, such as atmospheric or pure oxygen gas, hydrogen peroxide and nitrogen (I) oxide.[40] Hydroxylation of arenes usually proceeds in the presence of a metal catalyst and an oxidant. Palladium is the most common and successful transition-metal catalyst among those used for this transformation.[41] Two approaches are applied for the synthesis: 1) direct hydroxylation with molecular oxygen, hydrogen peroxide and oxone. Phenols or their derivatives are obtained directly from the oxidation reaction; 2) Indirect hydroxylation with trifluoroacetic acid/anhydride. Phenols or their derivatives are obtained through the hydrolysis of TFA ester, which forms in the oxidation step.[42]

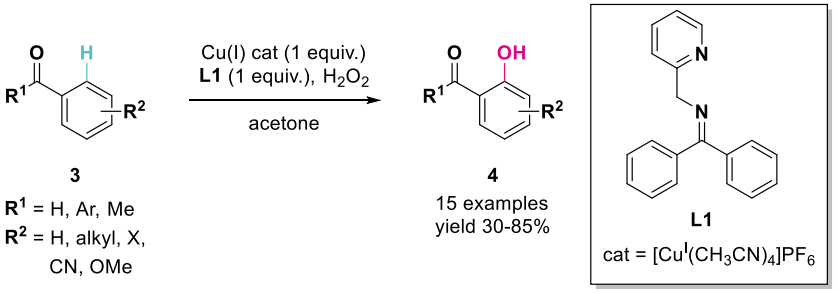
### 1.2.1 Direct Hydroxylation of Arenes

Das and Guin reported a direct hydroxylation of arenes **1** with a palladium catalyst and molecular oxygen in 2018 (Scheme 3).[43] They used molecular oxygen as a green oxidant and as an oxygen source. For the selective reaction, recyclable directing groups, sulfoximines, were used for the selective hydroxylation at the *ortho*-position. They were able to avoid chemical oxidants, such as oxone, peroxides and hypervalent iodine, and directing co-catalysts for the hydroxylation. Electron-rich groups in the phenyl ring gave higher yields, whereas electron-deficient substituent groups, such as halogens, gave lower yields (27%). The best results were achieved when a nitro group was in the directing group structure (77% yield).




***Scheme 3**. Arene hydroxylation with molecular oxygen and a palladium catalyst.*

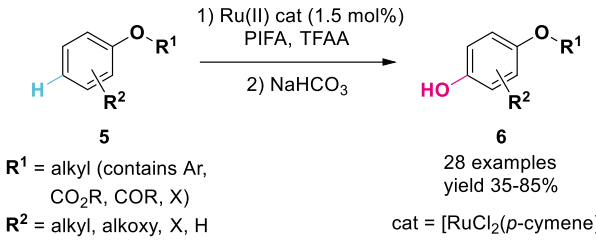
A research group from Spain and the United States demonstrated that, by using hydrogen peroxide with a copper-catalyst/ligand **L1** system, it was possible to hydroxylate benzophenones, acetophenones and benzaldehydes **3** with moderate to good yields (30-85%) (Scheme 4).[44] Different metal catalysts (copper, nickel, iron and manganese) were tested. Of various copper catalysts (*e.g.* copper(I) acetate, copper(II) acetate, copper(II) chloride and copper(II) nitrate), the highest yields were achieved with tetrakis(acetonitrile)copper(I) hexafluorophosphate. Unfortunately, the other metal catalysts produced low or no reaction. Solvents, such as tetrahydrofuran, dichloromethane and acetonitrile, gave moderate yields, while acetone gave high yields. Molecular oxygen, *tert*-butyl hydroperoxide, cumyl hydroperoxide and hydrogen peroxide were tested as oxidants. The molecular oxygen required an elevated temperature (50 °C) to give moderate yields, while the reaction with hydrogen peroxide resulted in high yields at room temperature. *tert*-Butyl and cumyl hydroperoxides did not produce any results. With benzophenone, they were able to carry out a gram-scale reaction with a good overall yield of 64%.




***Scheme 4**. Copper-catalysed hydroxylation with hydrogen peroxide.*

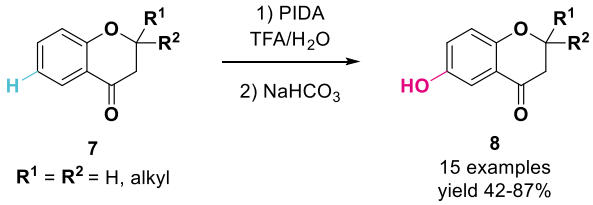
### 1.2.2 Indirect Hydroxylation of Arenes

The Fang research group recently demonstrated the *para*-selective hydroxylation of alkyl aryl ethers **5** in the presence of a ruthenium catalyst. Hypervalent iodine (PIFA) was used as an oxidant and trifluoroacetic anhydride was used as a solvent and an oxygen source (Scheme 5).[45] The solvent was key for the reaction to work efficiently. 1,2-Dichloroethane, trifluoroacetic acid and trifluoroacetic anhydride were used for solvent screening. Dichloroethane gave a low yield (7%) and mixtures of TFA/TFAA resulted in moderate yields (13% and 23%). The best results were achieved with pure trifluoroacetic anhydride. The effectiveness of TFAA might have been due to the relatively low acidity, which stabilises the products, leading to a higher yield. The highest yields were achieved with electron-donating groups (alkyl or alkoxy groups); meanwhile, electron-withdrawing groups gave low or no yield.



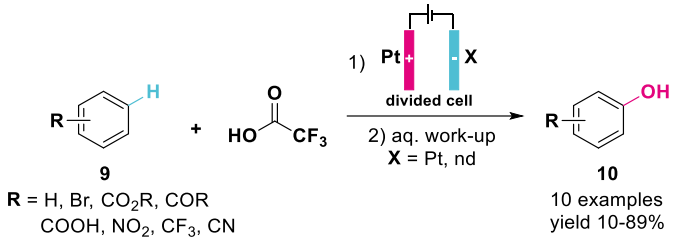

***Scheme 5**. para-Selective hydroxylation of alkyl aryl ethers with ruthenium-catalyst.*

Usually, the hydroxylation of arenes requires a metal catalyst to proceed, but a transition-metal-free hydroxylation of chromones **7** was carried out successfully by the Muthukrishnan group with hypervalent iodine as an oxidant (Scheme 6).[46] A chromone core is a common motif in the structure of natural products that have a wide range of biological activities (*e.g.* antitumor, antibacterial and anti-inflammatory), which makes the synthesis of different chromones valuable. Of different oxidants, such as potassium persulfate, Selectfluor® and di-*tert*-butyl peroxide, the best results were achieved with hypervalent iodine, especially with PIDA. For the solvent system, it was found that a 1:1 TFA/water mixture gave higher yields than pure trifluoroacetic acid (28%) or an acetic acid/water solvent system (< 5%). High temperatures were required (120 °C) for extended periods (up to 12 h) for the reaction to proceed. The reaction conditions were suitable both for short and long alkyl chain and spirochromanone substituents. They also demonstrated the hydroxylation of 2-alkoxy acetophenones, but the yields were low to moderate (15-55%). Unfortunately, reactions with xanthone, coumarin and nitrogen heterocycles did not proceed.



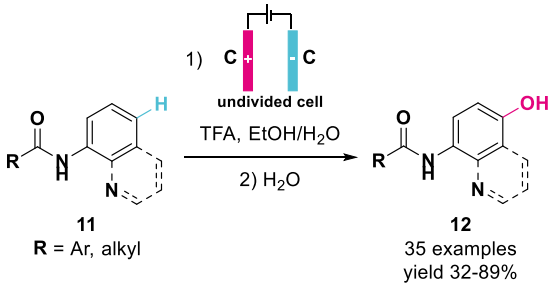

***Scheme 6.** Transition-metal-free indirect arene hydroxylation.*

Many indirect hydroxylation methods are based on the electrochemical oxidation of arenes. In 1975, two different research groups independently reported the electrochemical hydroxylation of arenes with trifluoroacetic acid as an oxygen source. In both cases, the reactions were carried out in divided cell systems and direct electrolysis was applied. The Nyberg group performed the reaction in pure trifluoroacetic acid, while Miller *et al*. used it as a co-solvent, together with dichloromethane. The used starting materials were limited to electron-poor and neutral arenes **9** and only a few examples were established with low to moderate yields **10**.[47,48] Twenty years later similar reactions were carried out by a Japanese group, which resulted in better yields.[49] In all cases, platinum electrodes were used for hydroxylation (Scheme 7).




***Scheme 7**. First examples of electrochemical arene hydroxylation with trifluoroacetic acid.*

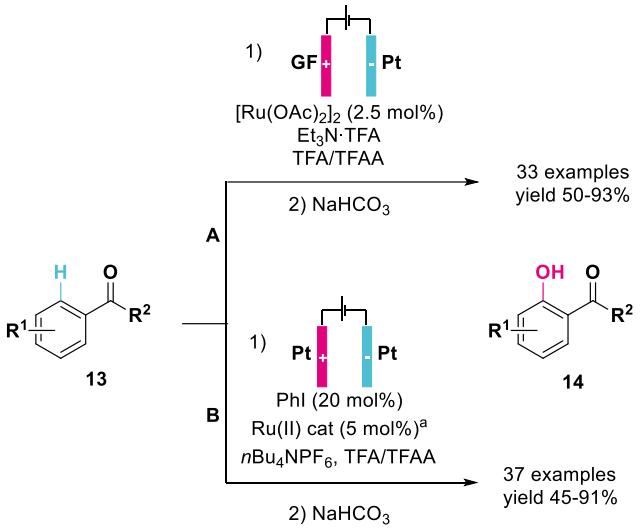
Recently, the Guo group from China demonstrated the *para*-selective hydroxylation of *N*-arylamides under batch and continuous-flow conditions (Scheme 8).[50] The reactions were performed at room temperature and did not require any catalysts, oxidants, acidic solvents or electrolytes. For the electrochemical reaction, combinations of different electrodes (nickel, platinum, carbon rod and reticulated vitreous carbon) were tested. While the nickel and platinum anodes gave moderate yields (51% and 81%), the reticulated vitreous carbon anode did not produce any results. The best results were achieved with the carbon rod electrodes. The solvent system also played an important role. When trifluoroacetic acid was replaced with acetic acid, only traces of product were observed. It turned out that trifluoroacetic acid was indispensable, as the reaction did not proceed without it. Although the best results were obtained with *N*-(quinoline-8-y)arylamides, it did not matter whether the electron-withdrawing or electron-donating groups were applied (yields 61-89%). However, the reactions with *N*-phenylamides gave lower yields (32-60%). The scale-up reactions were completed in continuous-flow and batch setups. In the experiments, it appeared that yields were noticeably higher with the continuous-flow setup (65% vs 88%). Moreover, they were able to reduce trifluoroacetic acid amount from 7 to 3 equivalents and the scaled-up experiments proceeded successfully.




***Scheme 8**. Electrochemical para-selective hydroxylation of N-arylamides.*

In the last few years, two articles on electrochemically indirect arene hydroxylation were published by the Lutz Ackermann group. In both cases, ruthenium-catalysts together with the TFA/TFAA solvent system were used in an undivided cell setup (Scheme 9). Moreover, similar or even the same starting materials were used in both reaction scopes. As the reactions were indirect, additives or electron-mediators were applied. For the reaction **A,** $Et_3N{\cdot}TFA$ salt was used as an electrolyte to conduct the current, and the TFA/TFAA solvent mixture helped solubilise the starting materials.[51] In addition, the reaction was carried out at room temperature. With good to excellent yields (50-93%),

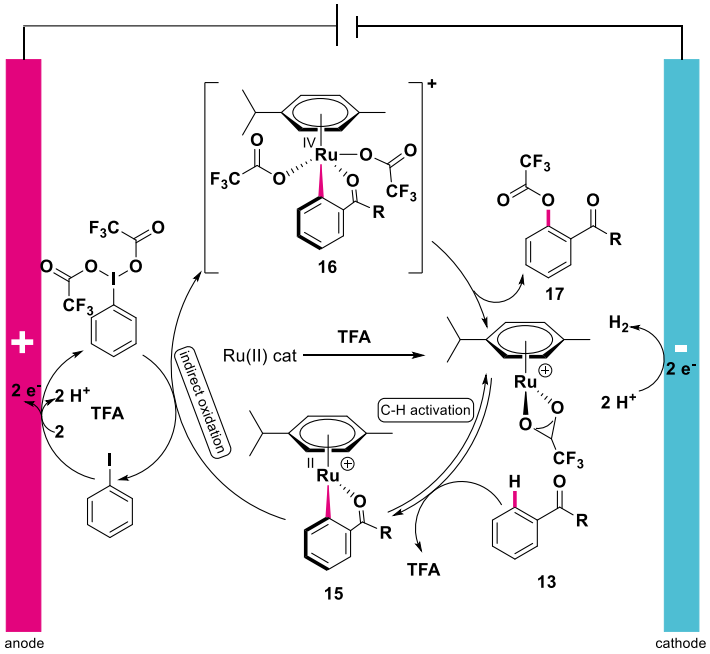
they were able to hydroxylate substituted benzamides and ketones **13**. Additionally, they demonstrated a successful 10 mmol scale-up experiment with lowered catalyst loading and high yield (83%). For reaction **B,** iodobenzene was used as an electron-mediator, as it was the only mediator that provided the desired hydroxylation.[52] As a test, a reticulated vitreous carbon anode was used instead of platinum anode, which resulted in a low yield of 24%. Similarly to reaction **A**, a scale-up reaction was successfully achieved with 84% yield.




**R**$^1$ = H, alkyl, OMe, Ar, X, $CF_3$, $CO_2R$
**R**$^2$ = $NR_2$, alkyl, OMe, Ar
cat = $Ru(OAc)_2$(*p*-cymene) for amides
[$Ru(Cl_2$(*p*-cymene)$]_2$ for ketones
[a] 2.5 mol% for ketones

***Scheme 9.*** *Electrochemical indirect hydroxylation of substituted arenes by the Ackermann group.* ***GF****- graphite felt.*

To understand the ruthenium-catalysed indirect electrochemical transformation, mechanistic studies were carried out. A plausible catalytic cycle is initiated by the C-H activation of amide or ketone by ruthenium(II) carboxylate (Scheme 10). The formed ruthenium(II) complex **15** is mediated for indirect oxidation by the hypervalent iodine(III) reagent, which is formed by anodic oxidation from iodobenzene. The formed intermediate, ruthenium(IV) complex **16**, undergoes rapid reductive elimination to give trifluoroacetic ester **17**. In the last step, the regeneration of the active catalyst takes place. On the counter electrode, hydrogen gas is released. An aqueous workup is required to release free hydroxylated product **14**.




***Scheme 10.*** *Plausible mechanism of indirect electrochemical ruthenium-catalysed hydroxylation of arene.*

## 1.3 Derivatisation and Applications of Phenols and Naphthols

The annual growth of the phenol market has been 5.2% and it will reach €25.8 billion by 2023. Phenol derivatives are required in the manufacturing of pharmaceuticals, dyes, polymers, plastics, agrochemicals and everyday products.[53] Naphthol is a bicyclic aromatic compound that bears a hydroxyl group and is a homologue of phenol. Moreover, they are more reactive than phenols. Naphthols have a wide spectrum of biological activities (*e.g.* antiviral[54], anti-cancer[55], anti-malarial[56] and antibacterial[57]) (Figure 5).[58]

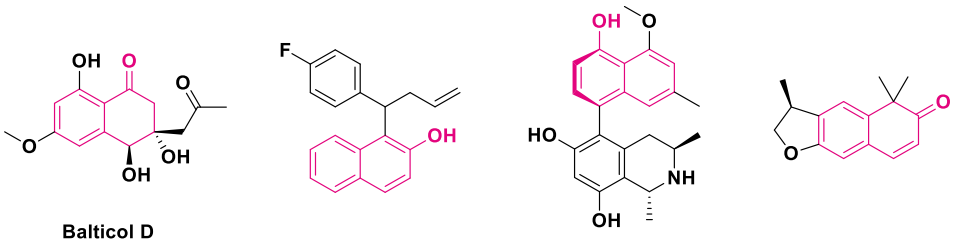
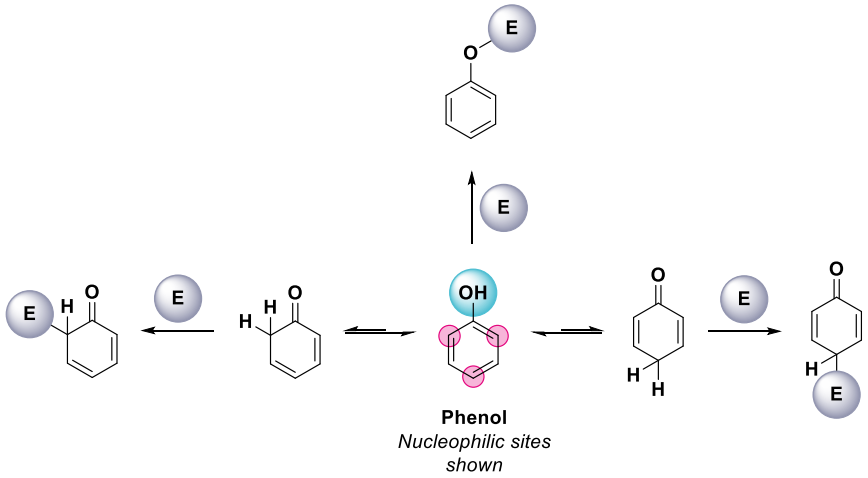



***Figure 5.*** *Biologically active substituted naphthol derivatives.*

This makes the development of new methods for the synthesis of various aryl oxygen substances highly desired. Phenols and naphthols are electron-rich molecules that may be considered nucleophiles. Due to tautomerization, phenols and naphthols have nucleophilic centres located both on oxygen and carbon atoms (Scheme 11).[59]

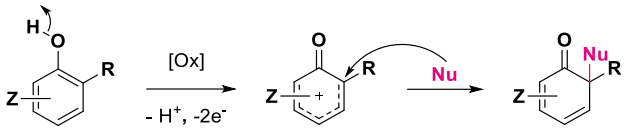



***Scheme 11.*** *Keto-enol tautomerization of phenol and electrophilic substitution. Pink: carbon nucleophilic sites; blue: oxygen nucleophilic site.* ***E*** *– electrophile.*

In reactions with electrophiles, either *O*-alkylated or *C*-alkylated products can potentially form. There is a high probability of the formation of a mixture of alkylated products if a non-selective synthetic approach is applied. Therefore, it is important to develop simple and direct methods to selectively derivatize phenols. The most investigated aryl oxygen derivatisation is *O*-alkylation, Williamson reaction,[60,61] which gives aromatic ethers in excellent yields and selectivity. The aromaticity of phenol makes the enol tautomer of phenol more stable than the keto tautomer. In order to facilitate keto tautomer formation, directing auxiliaries are used (*e.g.* an additional hydroxyl group, arene rings attached to phenol, and the formation of phenolate or substituents in *ortho*- and/or *para*-position).[62] For example, *C*-alkylation occurs under the right reaction conditions with *ortho*-substituted phenols, which leads to the formation of dearomatized product bearing a chiral centre at the carbon atom. Dearomatization is a phenomenon in which an arene ring undergoes a substitution reaction and permanently loses its aromaticity.[63] Investigation of phenol dearomatization is growing and various approaches are being studied (*e.g.* oxygenation, hydrogenation, halogenation, arylation, alkylation and cycloaddition). Different organic, inorganic and enzymatic reagents and catalysts are used to carry out such transformations.[64–69] Furthermore, a dearomative approach provides access to more complex, value-added and synthetically useful intermediates from cheap and readily accessible sources.[64]

### 1.3.1 Dearomatization of Aryl Alcohols by Oxidation

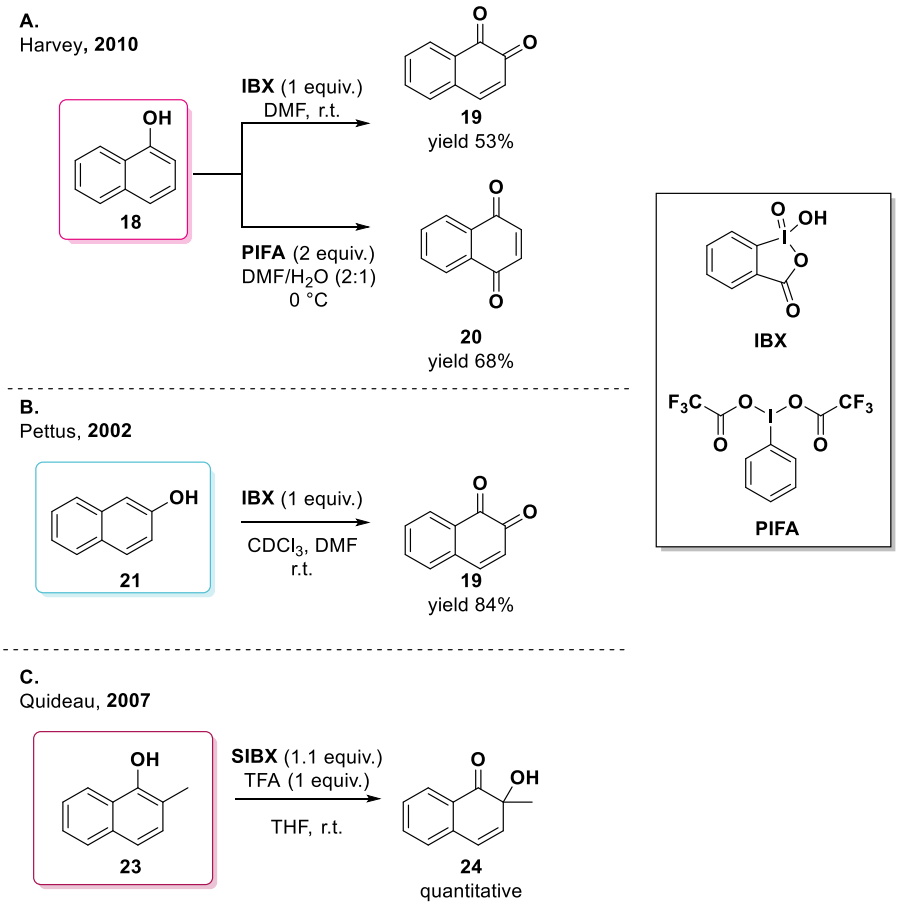
One of the strategies to dearomatize aryl alcohols is oxidation. Oxidative dearomatization of substituted phenols with nucleophilic additives (*e.g.* alcohols) is regioselective and provides cyclohexa-2,4-dienones (Scheme 12).[70,71] The reaction can be viewed as an oxidative nucleophilic substitution, where two electrons are pushed away from the aromatic core (carbocation forms) and are replaced with an oxygen- or carbon-based nucleophilic reaction partner. As a result of this reaction, the substitution takes place at the *ortho*-position and a chiral carbon centre is formed.[72]




**R** = alkyl or alkoxy group
**Nu** = oxygen or carbon-based nucleophile
**Z** = variuous subtituents

***Scheme 12.*** *Oxidative dearomatization of substituted phenol with nucleophile.*

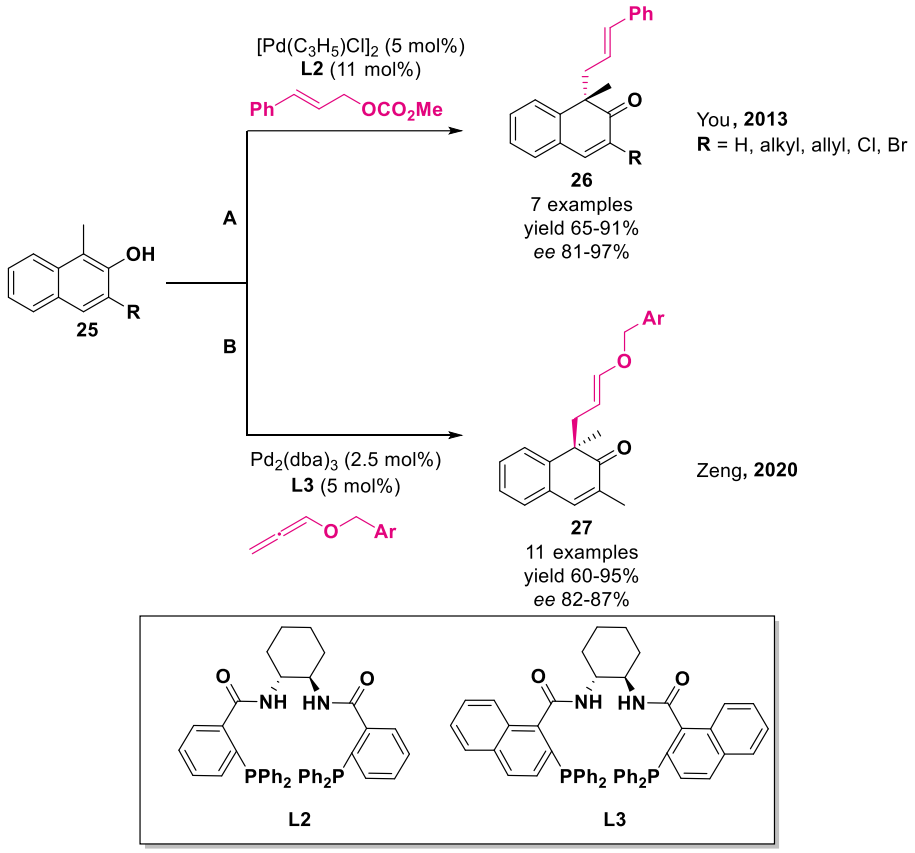
Of the many options, hypervalent iodine compounds are the most frequently used reagents for the oxidation of naphthols to *ortho*- or *para*-naphthoquinones (Scheme 13).[73] The Harvey research group has shown that by using *o*-iodoxybenzoic acid (IBX) and (bis(trifluoroacetoxy)iodo)benzene (PIFA), it was possible to selectively oxidize α-naphthol **18** with good yields (up to 68%), while the IBX gave *ortho*-naphthoquinone **19** and PIFA *para*-naphthoquinone **20** (Scheme 13A).[74] Similarly, Pettus and co-workers obtained *ortho*-naphthoquinone **19** exclusively in good yields while using IBX for the oxidation of β-naphthol **21** (Scheme 13B).[75] With alkylated α-naphthols, the Quideau research group has developed a selective way to dearomatize 2-methyl-1-naphthol **23** using SIBX (a stabilised, non-explosive version of IBX; SIBX is composed of IBX (49%), benzoic acid (22%) and isophthalic acid (29%)) as an oxidant. Methyl-substituted *ortho*-naphthoquinone **24** was produced with a quantitative yield (Scheme 13C).[76]




***Scheme 13**. Hypervalent iodine-mediated oxidative dearomatization of α- and β-naphthols.*

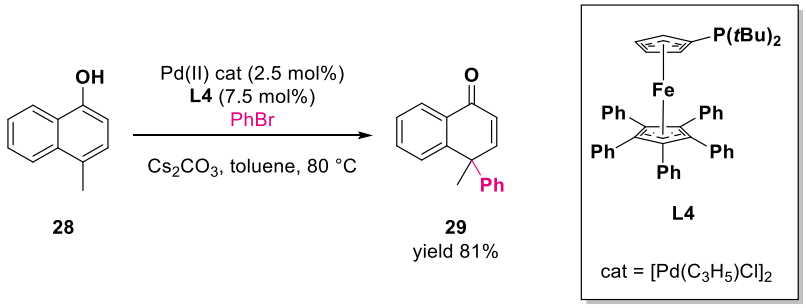
### 1.3.2 Metal-Catalysed Dearomatization of Naphthols

Besides oxidation, transition-metal catalysis is commonly used to dearomatize naphthols. Palladium catalysts are the most popular of the transition metals.[77] In 2013, You *et al.* demonstrated the dearomatization of substituted β-naphthol **25** with cinnamyl carbonate using a palladium catalyst $[Pd(C_3H_5)Cl]_2$ and Trost ligand (**L2**) (Scheme 14A).[78] In high yield and enantioselectivity, β-naphthalenone **26** was obtained. Seven years later, Zeng and co-workers used an approach similar to the You research group's. They used a Trost ligand (**L3**) and palladium catalyst $[Pd_2(dba)_3]$, but alkoxyallenes were used as an alkylating agent (Scheme 14B).[79] They were able to dearomatize β-naphthol **25** with high yields, up to 95%.



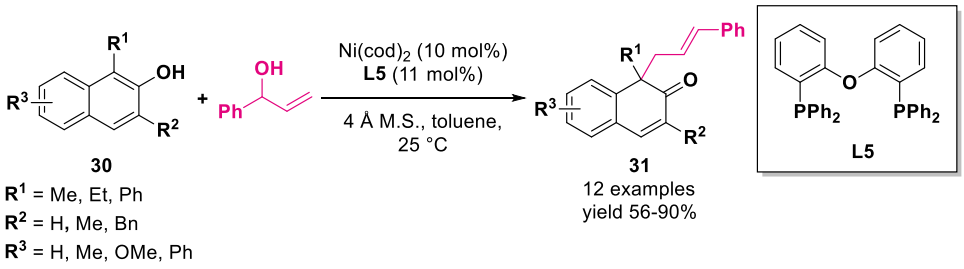

***Scheme 14.*** *Dearomatization of substituted β-naphthols with palladium-catalysts and Trost ligands.*

Dearomatization reactions with α-naphthol are less common than those with other aromatic compounds, such as indoles and β-naphthols.[80] The You research group showed arylative dearomatization with phenyl bromide. As an active complex, a palladium catalyst and Q-Phos ligand (**L4**) were used (Scheme 15).[81] All of the optimization reactions were carried out with substituted β-naphthol. The reaction scope included different substituted β-naphthols and aryl halides. With α-naphthols, two different substrates were tested. With second-position methylated α-naphthol, no dearomatization product was found and only Friedel-Crafts-type products were isolated. However, when fourth-position methylated α-naphthol **28** was tested, the dearomatized product **29** was selectively obtained with good yield (81%).




***Scheme 15**. Selective dearomatization of substituted α-naphthol.*

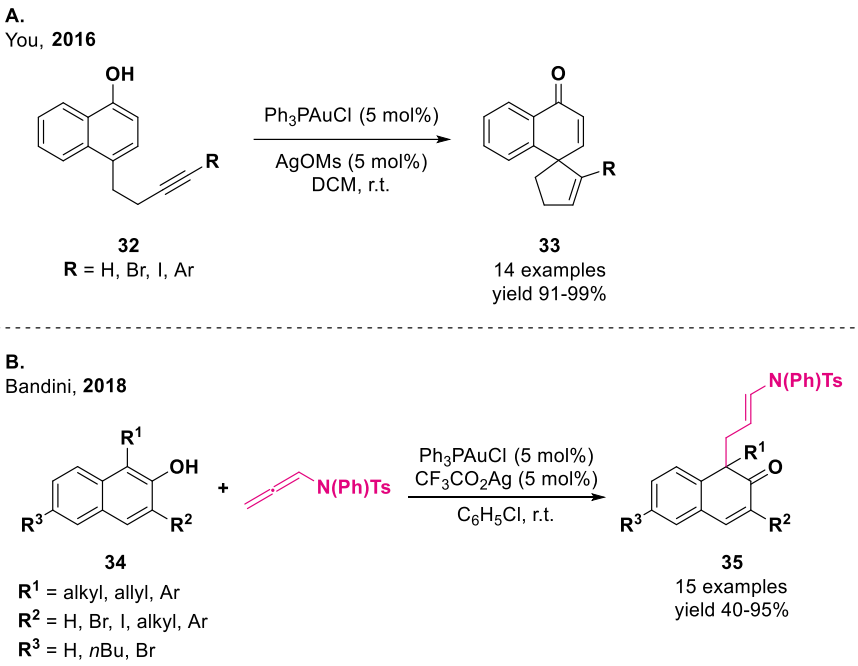
One effective alternative to palladium catalysis is using sustainable and low-cost nickel catalysts. You *et al.* demonstrated in 2020 that by using $Ni(cod)_2$ and commercially available diphosphine ligand **L5**, they were able to dearomatize β-naphthols **30** with allylic alcohol (α-vinylbenzyl alcohol). Different phosphine ligands were tried. 1,4-Bis(diphenylphosphino)butane and 1,1'-bis(diphenylphosphino)ferrocene gave moderate yields (39% and 60% respectively), but diphenylphosphine ether **L5** gave a yield of 82%. Since the yield was not sufficient, different solvents were tested. As diethyl ether, trifluoroacetic acid, 1,4-dioxane and acetonitrile gave moderate or low yields and dichloromethane no yield at all, toluene was tested. Toluene gave high yields and it turned out that the type of molecular sieves had an influence on the yield too. With 3 Å M.S., the yield was lower than with 4 Å M.S. (82% vs 90%). Moreover, they tested different allylic alcohols, but none of the alcohols gave higher yields than α-vinylbenzyl alcohol. Through this reaction, β-naphthalenones **31** were obtained with good yields (Scheme 16). The method also worked excellently with methylated β-naphthol at 5 mmol scale, giving the product in 98% yield.[82]




***Scheme 16.** Dearomatization of β-naphthols with a nickel catalyst and allylic alcohol.*

Gold(I) catalysis is very popular for the dearomatization of naphthols.[83–87] The electrophilic activation of π-systems (*e.g.* alkenes, allenes and alkynes) is easily achieved with gold catalysts.[88–90] Diverse chemical processes are provided by the addition of a nucleophile to a cationic gold complex. Furthermore, gold catalysts are stable and tolerate air and moisture.[91] In 2016, Zhang and You used a commercially available gold(I) catalyst ($Ph_3PAuCl$) to dearomatize α-naphthols **32** intramolecularly. To make the catalyst work, different silver salts as chloride scavengers were tested. The best results were achieved with silver mesylate (5 mol%). The mesylate counter anion eased the 5-*endo-dig* cyclization by deprotonation, which led to the formation of spirocarbocyclic products **33** (Scheme 17A). Moreover, they demonstrated one asymmetric

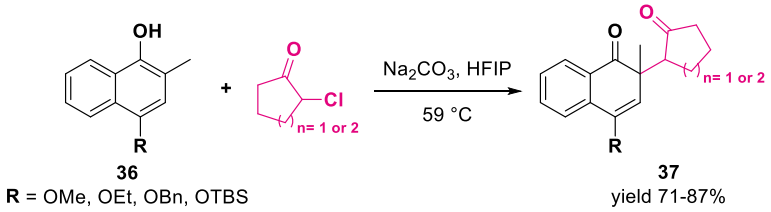
example by using a catalytic amount of $(4\text{-}CF_3C_6H_4)_3PAuCl$ and chiral silver phosphate. A spirocarbocylic product **33** was isolated with 85% of yield and *ee* 90%.[92] A few years later, the Bandini group demonstrated that by using the same catalyst and silver trifluoroacetate they were able to site-selectively synthesise β-naphthalenones **34** with allenamides (yields up to 95%) (Scheme 17B). Anhydrous reaction conditions were required for the reaction to succeed.[93]




***Scheme 17**. Gold(I)-catalysed dearomatization of naphthols.*

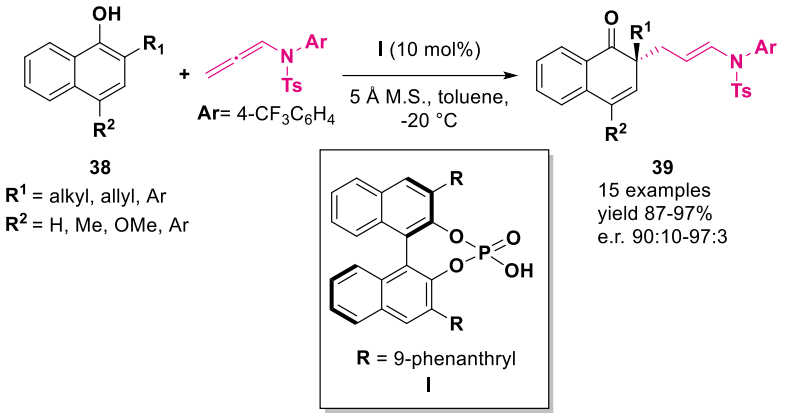
### 1.3.3 Dearomatization of Naphthols by Other Methods

Transition-metal usage for naphthol dearomatization has been thoroughly investigated. However, reactions without any catalyst are unusual. The Shao research group demonstrated that by using oxy-allyl cations as electrophilic reagents they were able to dearomatize substituted α-naphthols **36** with high yields (up to 87%) (Scheme 18). Different bases ($Na_2CO_3$, $K_2CO_3$, $K_2HPO_4$ and $Et_3N$) were screened, and the highest yields were obtained with sodium carbonate. The solvent played an important role in alkylation selectivity and dearomatization so, as non-fluorinated alcohols gave no reaction, fluorinated solvents were tested. Of the fluorinated solvents, the highest yield was achieved with fluorinated isopropanol (HFIP).[94]



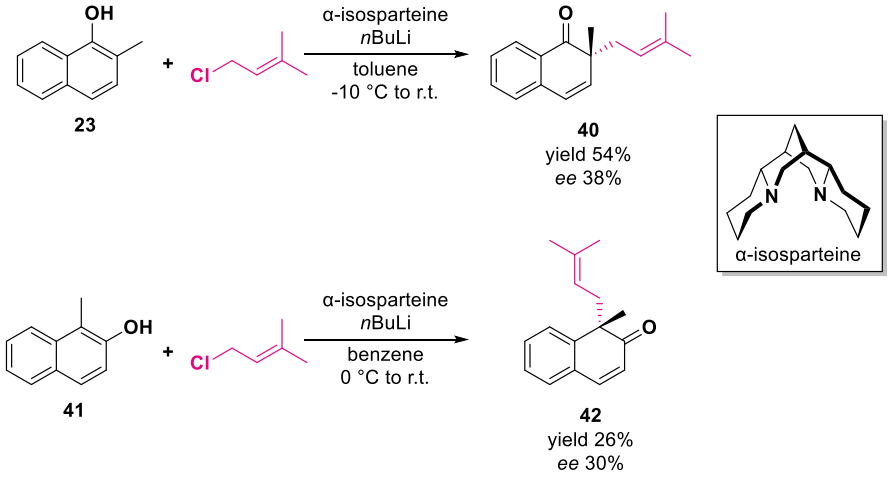

***Scheme 18.** Dearomatization with an oxy-allyl alkylator.*

Later, the same group demonstrated an asymmetric allylic substitution of α-naphthol **38** with an allenamide and chiral phosphoric acid catalyst (**I**) without a transition-metal catalyst. Reactions were carried out at -20 °C in toluene under anhydrous conditions. Fifteen different substituted naphthols **38** underwent dearomatization with high yields (up to 97%) and enantioselectivities (Scheme 19). A gram-scale reaction gave an excellent 97% yield and an e.r. of 95:5.[95]




***Scheme 19**. Substituted α-naphthol dearomatization with chiral phosphoric acid.*

The Fráter group reported a direct asymmetric alkylation of substituted α- and β-naphthol that did not rely on a transition-metal catalyst (Scheme 20). They showed that, by using an alkyl halide (prenyl chloride) as an electrophile and an α-isosparteine as a chiral additive in conjunction with *n*-butyllithium, it was possible to achieve low *ee* (up to 38%) and moderate yield (up to 54%) for dearomatized alkylated naphthols **40** and **42**.[96]




***Scheme 20**. Asymmetric naphthol derivatization with nBuLi and α-isosparteine.*

# 2 Motivation and Aims of the Present Work

The need for new environmentally friendly approaches to obtain appropriately substituted oxygenated aromatic compounds is obvious. Electrochemistry is one of the new promising approaches for that purpose. Performing reactions in continuous-flow mode makes it possible to overcome limitations usually associated with electrochemical transformations, and allows to conveniently scale-up processes, closing the gap between academia and industry. The products obtained electrochemically can be further transformed to the necessary complex compounds. The direct and selective *C*-alkylation of phenols, which does not require transition-metal reagents or catalysts, is one of the possible directions of phenol modification. This approach is at present rather undeveloped and requires new investigations and further study.

**The specific aims of the study were:**

- to explore the conditions for the electrochemical hydroxylation of electron-rich arenes in continuous-flow mode;
- to prove the reliability of the electrochemical continuous-flow approach for the preparative synthesis of oxygenated phenols;
- to develop a direct and selective method for alkylative dearomatization of different substituted phenols and naphthols without using any transition-metal catalysts in aqueous and non-aqueous conditions.

# 3 Results and Discussion

## 3.1 Electrochemical Hydroxylation of Electron-Rich Arenes in Continuous-Flow (Publication III and Unpublished Results)

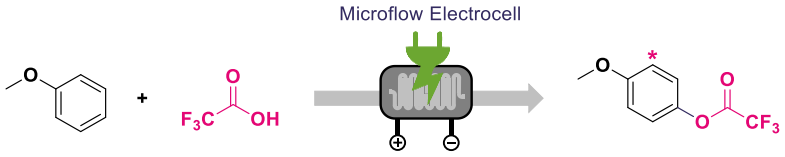
The hydroxylation of arenes is usually achieved with transition-metal catalysts under harsh conditions, which are neither environmentally friendly nor easy to carry out.[97–99] Alternatively, there are some electrochemical examples using trifluoroacetic acid for the indirect hydroxylation of aromatic systems.[47–49] But all of those early examples used trifluoracetic acid as a solvent or co-solvent and the yields were low or not isolated at all. Moreover, they used an unfavourable divided cell system equipped with expensive platinum electrodes for electrolysis, leaving an opportunity for further investigation and improvement.

### 3.1.1 Optimization for Arene Hydroxylation

For the hydroxylation of electron-rich arenes, a reaction setup has to be accessible. We used a DIY undivided-cell microreactor designed by the Noël research group (Figure 4E, page 14).[30] The microreactor was equipped with a graphite anode and a stainless steel cathode. This is different from the previous literature examples, where more complicated systems were used.[47–49] The reactions were performed under galvanostatic conditions, which allowed us to avoid using a reference electrode. Anisole **43** was chosen as the model substrate to carry out indirect hydroxylation. Through thorough research we identified the optimum reaction conditions (Table 1). We chose acetonitrile as our initial solvent, because radical reactions are typically carried out in it. However, in acetonitrile, TFA ester formed with rather low yield (31%), although the conversion was high, which probably indicated the decomposition of the desired product (Table 1, entry 1). Among different solvents (Table 1, entries 1, 7-12) (*e.g.* dichloromethane, hexafluoroisopropanol, dimethylformamide, tetrahydrofuran, methyl *tert*-butyl ether and methanol), the highest GC-FID conversion was achieved with HFIP, but unfortunately no desired product formed. The next best results were achieved with tetrahydrofuran (Table 1, entry 8). However, with THF we saw a moderate deposition of organic material on the electrode surface, which worked as an insulator and hindered the reaction. As the conversion was not complete, we tried to push the reaction by applying higher electrical current, which surprisingly led to decreased yield. This was due to the fact that the desired product was more electron-rich than the starting material, which means that the product tended to overoxidize under the electrochemical conditions, when the concertation of the starting material became low. In some of the cases, overoxidized products were detected along with arene-arene coupling products.[7,100]

Being an oxygen source for the hydroxylation, trifluoroacetic acid also acted as a proton source for the cathodic half-reaction, while amines were needed for the proton transfer (Table 1, entries 1, 3 and 21-22). Acid was used in excess in order to keep the amines protonated. Protonation is required to avoid the oxidation of amine and insure the high conductivity of the system. When we used base in excess compared to acid, the oxidative polymerization of amine took place, which caused deposition on the electrodes and hindered the desired reaction. The optimal ratio of acid to base was two to one (Table 1, entry 22).

***Table 1**. Reaction condition optimisation with anisole.*




| Entry | TFA, (equiv.) | Base, (equiv.) | Solvent | Time (min) | Anode | Cathode | Conv. (%)[b] | Yield (%)[c] |
|---|---|---|---|---|---|---|---|---|
| 1 | 3 | $Bu_3N$ (2 equiv.) | $CH_3CN$ (0.1 M) | 5 | graphite | s. steel | 71 | 31 |
| 2 | 3 | - | $CH_3CN$ (0.1 M) | 5 | graphite | s. steel | 0 | 0 |
| 3 | 3 | collidine (2 equiv.) | $CH_3CN$ (0.1 M) | 5 | graphite | s. steel | 72 | 20 |
| 4 | 1.5 | $Bu_3N$ (2 equiv.) | $CH_3CN$ (0.1 M) | 5 | graphite | s. steel | 0 | 0 |
| 5 | 3 | $Bu_3N$ (1 equiv.) | $CH_3CN$ (0.1 M) | 5 | graphite | s. steel | 78 | 11 |
| 6 | 3 | $Bu_3N$ (4 equiv.) | $CH_3CN$ (0.1 M) | 5 | graphite | s. steel | 0 | 0 |
| 7 | 3 | $Bu_3N$ (2 equiv.) | stab. DCM (0.1 M) | 5 | graphite | s. steel | 72 | 45 |
| 8 | 3 | $Bu_3N$ (2 equiv.) | stab. THF (0.1 M) | 5 | graphite | s. steel | 83 | 68 |
| 9 | 3 | $Bu_3N$ (2 equiv.) | DMF (0.1 M) | 5 | graphite | s. steel | 79 | 45 |
| 10 | 3 | $Bu_3N$ (2 equiv.) | MeOH (0.1 M) | 5 | graphite | s. steel | 74 | 4 |
| 11 | 3 | $Bu_3N$ (2 equiv.) | HFIP (0.1 M) | 5 | graphite | s. steel | 100 | 0 |
| 12 | 3 | $Bu_3N$ (2 equiv.) | MTBE (0.1 M) | 5 | graphite | s. steel | 53 | 44 |
| 13 | 3 | $Bu_3N$ (2 equiv.) | stab. THF (0.1 M) | 5 | s. steel | s. steel | 43 | 12 |
| 14 | 3 | $Bu_3N$ (2 equiv.) | stab. THF (0.1 M) | 5 | graphite | graphite | 85 | 48 |
| 15 | 3 | $Bu_3N$ (2 equiv.) | stab. THF (0.1 M) | 5 | graphite | copper | 83 | 65 |
| 16 | 3 | $Bu_3N$ (2 equiv.) | stab. THF (0.1 M) | 5 | graphite | nickel | 80 | 64 |
| 17 | 3 | $Bu_3N$ (2 equiv.) | stab. THF (0.05 M) | 2.5 | graphite | s. steel | 83 | 68 |
| 18 | 3 | $Bu_3N$ (2 equiv.) | stab. THF (0.025 M) | 1.25 | graphite | s. steel | 90 | 74 |
| 19 | 3 | $Bu_3N$ (2 equiv.) | non-stab. THF (0.025 M) | 1.25 | graphite | s. steel | 85 | 60 |
| 20 | 6 | $Bu_3N$ (3 equiv.) | non-stab. THF (0.025 M) | 1.25 | graphite | s. steel | 78 | 65 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 21 | 6 | $Et_3N$ (3 equiv.) | non-stab. THF (0.025 M) | 1.25 | graphite | s. steel | 70 | 50 |
| 22 | 6 | DIPEA (3 equiv.) | non-stab. THF (0.025 M) | 1.25 | graphite | s. steel | 88 | 71 |
| 23[d] | 6 | DIPEA (3 equiv.) | non-stab. THF (0.025 M) | 1.25 | graphite | s. steel | 0 | 0 |
| 24[e] | 6 | DIPEA (3 equiv.) | non-stab. THF (0.025 M) | 600 | graphite | s. steel | 5[f] | 5 |
| 25[g] | 6 | DIPEA (3 equiv.) | non-stab. THF (0.025 M) | 600 | graphite | s. steel | 33[f] | 29 |

[a]During the screening, the solution was pumped through the undivided-cell microreactor at a fixed flow rate at room temperature. The current varied from 60 to 140 mA, which corresponds to 1.8-5.0 mA $cm^{-2}$. After the reaction had reached steady state (10 minutes), the corresponding potential was noted and a sample (0.1 ml) was collected in a vial, complemented with EtOAc (1 mL) and analysed using GC-FID. The * shows the position(s) of other isomer(s). [b]Conversion determined by GC-FID with decane as an internal standard. [c]Yield determined by GC-FID with decane as an internal standard. [d]No electricity was applied. [e]Batch reaction conditions: 3.3 mA $cm^{-2}$, 3.9 F, 0.25 mmol scale. [f]Conversion determined by $^{19}$F-Q-NMR with benzotrifluoride as an internal standard. [g]Batch reaction conditions: 3.3 mA $cm^{-2}$, 11.8 F, 0.25 mmol scale.

Different electrode combinations were tested to determine the best results (Table 1, entries 8 and 13-16). For example, graphite was tested both as an anode and a cathode (Table 1, entry 14). In theory, that should have allowed us to change the polarity of electrodes back and forth, and therefore eliminate deposited material from the electrode surface.[16,101] Unfortunately, graphite as a cathode was not efficient, giving only a low yield (48%). Moreover, copper and nickel cathodes were tested, but moderate deposition on the surface of the electrodes took place. As different combinations of electrodes did not give better results, other ways to eliminate deposition were investigated. We decided to lower the concentration of solution and increase the flow rate. Those changes helped to flush out any deposition on the electrode surfaces and achieve a steady state, which is required to scale-up the whole reaction. It should be emphasized that the reactor productivity remained the same, because dilution and the faster flow rate were applied simultaneously.

Unfortunately, when we tried to investigate the substrate scope using the established conditions, we discovered that other electron-rich arenes gave rather low yields. Therefore, we went back to the reaction optimization once again. The second time we used stabilizer-free THF (Table 1, entries 19-22). The difference between stabilized and stabilizer-free tetrahydrofuran is butylated hydroxytoluene (BHT). BHT is a stabilizer that is usually used in commercial ether solvents. BHT prevents the radical-mediated oxidation of the solvent and therefore prolongs the solvent shelf life. In our electrochemical reactions, different radicals formed; hence, the inclusion of BHT probably reduced the reaction occurrence. Therefore, we used freshly distilled tetrahydrofuran (distilled with lithium aluminium hydride on the same day) or fresh commercially available stabilizer-free tetrahydrofuran (not opened longer than a few days). The solvent change made the reaction more sensitive to the base, and therefore we had to change it. In our initial trials, tributylamine was used. Since tributylamine gave a moderate yield (65%), two different amines were tested (Table 1, entries 21 and 22). Triethylamine resulted in a lower yield (50%) and the best results were achieved with diisopropylethylamine (DIPEA) (a yield of 71%). For the reaction to be successful,

the DIPEA had to be fresh (it remained fresh up to four months after distillation or after opening a new bottle).

To prove the electrochemical nature of the process, the reaction was carried out without electricity (Table 1, entry 23). As postulated, no reaction took place without electricity. Moreover, to demonstrate the usefulness and reliability of the continuous-flow reaction setup, the batch reactions were carried out with model substrate anisole **43** (Table 1, entries 24 and 25) under similar conditions. The batch electrolysis was conducted at constant current and at room temperature, but a longer reaction time (10 hours in batch vs 1.5 minutes in flow) was required. At first (Table 1, entry 24), the same amount of electricity (3.9 F) was applied as in the continuous-flow setup, but the yield was low (5%). To achieve higher yields, more electricity was applied (11.8 F), but the yield was just 29%. The lower yields can be explained by the prolonged reaction time, as a longer time leads to over-oxidation of electron-rich products and it leads to decomposition on the electrodes. We also calculated the Faraday-efficiency of the reaction and found that in continuous-flow it was much higher ($FE_{flow}$ = 49%) than in the batch reaction ($FE_{batch}$ = 5%), which means that the use of electricity was more sustainable in the continuous-flow setup. The productivity of the continuous-flow setup was 0.64 mmol $h^{-1}$ with 71% yield (0.9 mmol $h^{-1}$ with 100% theoretical yield). This proves that the developed transformation in continuous-flow has many benefits, such as higher efficiency, higher yields and significantly shorter reaction time.

### 3.1.2 Scope of the Reactions

With the optimized reaction conditions in hand, we started testing different electron-rich arenes. Some of them were synthesised *via* esterification, Williamson etherification or by protection reactions (Figure 6), while others were purchased from commercially available sources.

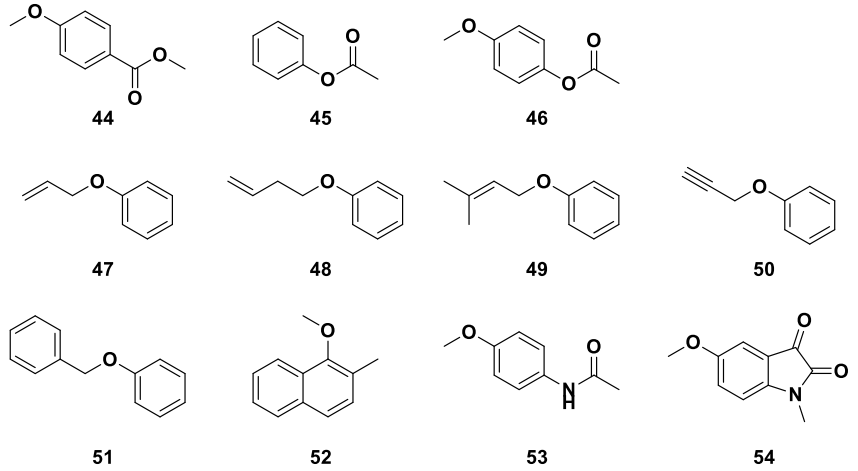
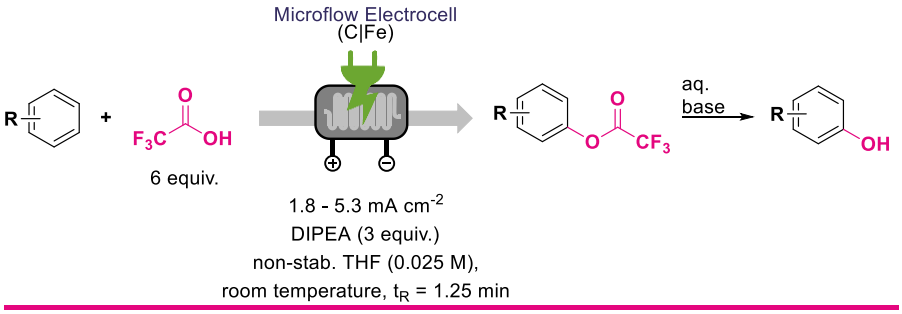
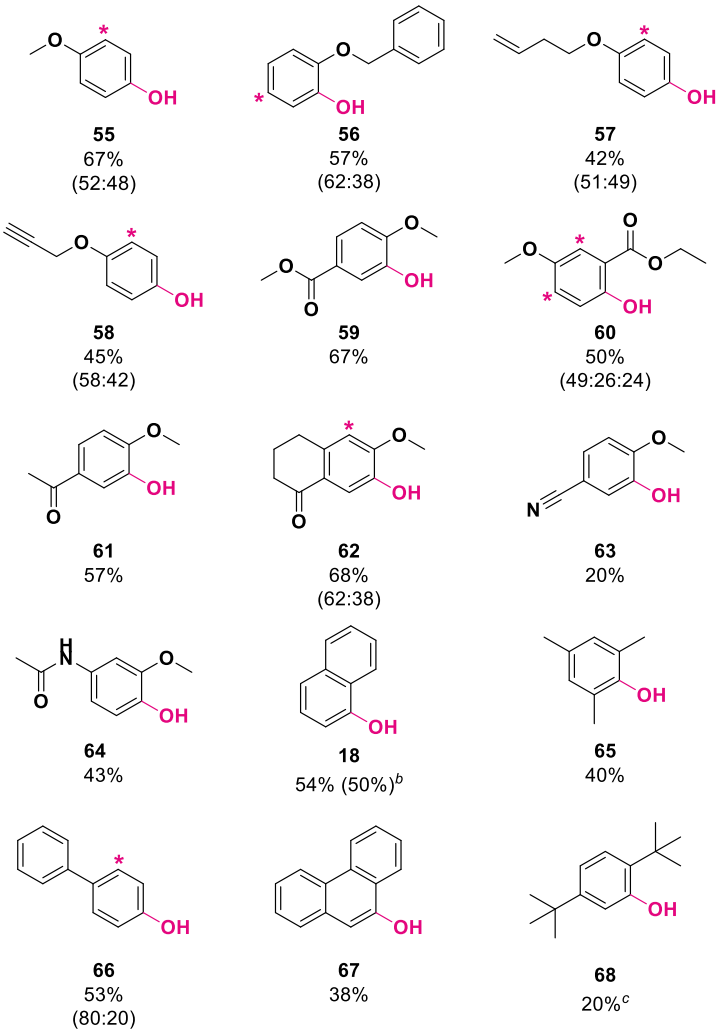



***Figure 6.*** *Synthesised starting materials.*

Successful scope examples are shown in Scheme 21. The reaction sequence consisted of two parts: 1) electrochemical synthesis, which yielded TFA ester, and 2) hydrolysis of TFA ester formed in the previous step to release hydroxylated arene. Usually a mixture of *ortho*- and *para*-isomers of the hydroxylated product was detected. From the successful

reactions, all of the isomers were chromatographically separable. With some products, *e.g.* cresol **55**, it was wise not to separate isomers, as we would have risked losing the product due to the low boiling point. We showed that the functionalities that might be sensitive to side reactions under radical reactions withstood the electrochemical conditions nicely (*e.g.* benzyl **56**, butenyl **57** and propargyl **58**). Besides the *O*-alkylated phenols, different electron-rich arenes containing additional electron-withdrawing groups were tested. The substances containing electron-withdrawing groups (**59**-**62**) required higher currents, but eventually the best results were achieved. Carbonyl and carboxyl groups endured the basic aqueous workup and repelled the hydrolysis and aldol condensation. Sadly, the products containing a nitrogen atom gave low to moderate yields (**63** 20% and **64** 43%). With 4-methoxybenzonitrile **63**, the conversion and yield were low regardless of the applied current. And when protected 4-methoxyaniline was used as a starting material, the isolated hydroxylation product **64** had methyl migrated from the *para*- to the *meta*-position. Most probably, the relocation happened during the basic work-up, when the methyl group from one oxygen atom migrated to another. Besides the above-mentioned, other electron-rich arenes that did not contain alkoxy groups in the structure were tested (**18**, **65**-**68**). The yields were satisfactory (20%-54%). Naphthalene reacted under the standard conditions effortlessly and 1-naphthol **18** was isolated with good yield (54%). Therefore, the naphthalene was chosen for the 10 mmol scale-up reaction to demonstrate the versatility and reliability of the continuous-flow process. The scale-up reaction did not need any additional optimization other than prolonged collection time to work successfully. The yield of 1-naphthol **18** was comparable to the reaction scope result (50% for the scale-up reaction and 54% for the standard conditions). The electrolysis with mesitylene **65** and biphenyl **66** proceeded similarly to other electron-rich arenes and the products were isolated with good yields (40% **65** and 53% **66**). The regioselectivity of biphenyl **66** to the *para*-position was high (80:20). With phenanthrene **67**, multiple problems occurred during the isolation process. At first, the preliminary results were promising. After the first column chromatography, when we checked the thin layer chromatography plate, the product was pure and isolated as a single isomer (only one spot was seen). In the proton NMR of the isolated product, we saw impurities in amounts that made us the question the purity of our isolated product. This made us redo the TLC analysis from the NMR sample and, to our surprise, five other spots occurred. At this point, we thought that the deuterated chloroform had caused the decomposition of the desired product. Because of that we avoided chlorinated solvents in our second attempt. Moreover, as we could not be sure what else might ruin the product, several precautionary measures were implemented: we reduced the contact with visible light by using aluminium foil and darkening the room, and avoided heating, which means the solvent evaporation was done under vacuum at room temperature. Despite all of these measures, the isolated yield was moderate (38%). Finally, we turned our attention to 1,4-di-*tert*-butylbenzene **68**. Under standard conditions, it provided very low yields, but when the reaction was performed at a lower flow rate, we managed to isolate the desired product with 20% yield. Probably the low yield was caused by the steric hindrance from two *tert*-butyl groups.




***Scheme 21.*** *Successful scope results of arene hydroxylation. [a]Reaction conditions: arene (1 mmol), TFA (6 equiv.), DIPEA (3 equiv.), non-stabilized fresh THF (0.025 M), graphite anode/stainless steel cathode, 1.8-5.4 mA cm$^{-2}$, room temperature, residence time 1.25 min, collected for 66.6 min. Workup with saturated $NaHCO_3$. The ratio of different isomers is shown in brackets. The overall isolated yield is given for the chromatographically separated isomers of compounds 2-4, 6 and 8. The * shows the position(s) of other isomer(s). [b]10 mmol scale reaction collected for 66 h 6 min. [c]Residence time 2.5 min, collected for 133.2 min.*

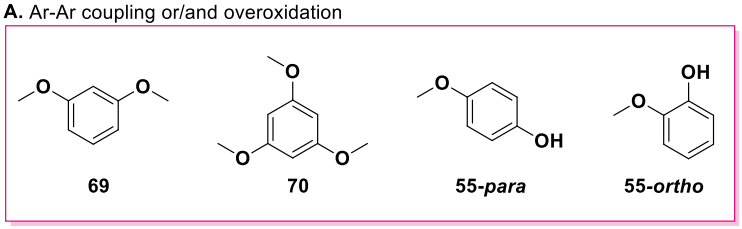
From our experimental results, we found that the working oxidation potential window of the starting material is 1.6 – 2.1 V vs SCE[102] and our model substrate anisole **43** has oxidation potential at 1.8 V vs SCE, which is in the middle of the working window. All of the tested compounds did not work as expected; either they did not fit into the window or for other reasons. Those substances can be divided into four groups (Figure 7). In the first group (Figure 7, **A**), the oxidation potentials of the compounds were low, which led to overoxidation and aryl-aryl coupling in some cases, and resulted in deposition on the electrode surface. Dimethoxybenzene **69** (1.50 V vs SCE) gave coupling products with 15% yield in GS-MS. Trimethoxybenzene **70** acted similarly to dimethoxybenzene **69**. Although, the GS-MS results were promising for 4-methoxyphenol **55-*para*** (1.17 V vs SCE), unfortunately a low yield (20%) was determined by $^{19}$F NMR of the crude mixture and we decided not to proceed with the experiment. We hoped that 2-methoxyphenol **55-*ortho*** would give better results because of its higher oxidation potential (1.41 V vs SCE), but the $^{19}$F NMR yield was even lower.

In the second group (Figure 7, **B**), a mixture of isomers or low GC-MS yields were found. Because many isomers formed with low yields in this group, it was clear that the isolation would be tedious, and therefore reaction mixtures were not hydrolysed. With acetonaphthones (**71** and **72**), different isomers with low yields were detected in GC-MS. Similar results were achieved with substituted naphthalenes (**73** and **74**). The veratraldehyde **75** gave a very low yield in GC-MS and therefore the reaction was not continued. With bromoanisoles (**76** and **77**), one or two isomers were detected, unfortunately with low GC-MS yields. The nitrogen-containing substances **79** and **80** yielded many isomers with low yields.

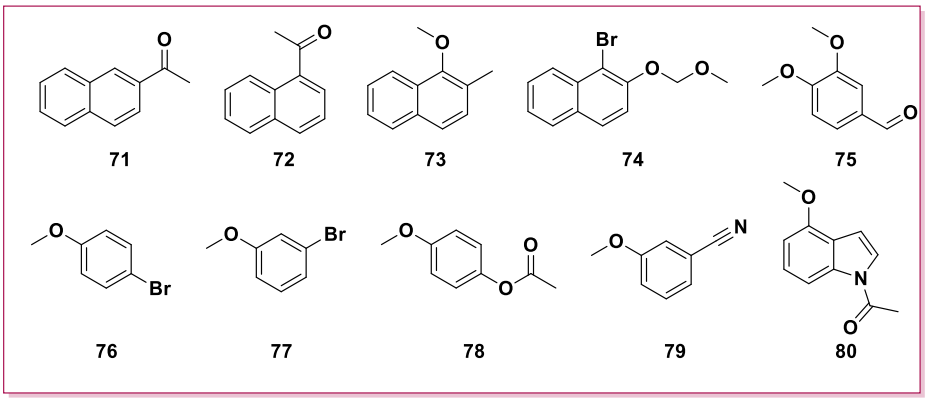
The third group (Figure 7, **C**) of tested starting materials produced side products or deposition on the electrode surfaces. *p*-Xylene **81** and 4-methylanisole **82** had C-H activation, and oxidation took place at the benzylic position. That might be interesting for further investigation. Allyl- and prenyl-substituted oxybenzenes **83** and **84** probably had oxidation on the double bond, which resulted in deposition. Moreover, they did not react like other substituted alkoxybenzenes (Scheme 21, **57** and **58**), which demonstrates how narrow and selective the reaction window is. Xanthene **85** oxidized to ketone and fluorenone **86** was reduced to alcohol. Lastly, some aromatic heterocyclic products were tested. With carbazole **87** and indole **88** (1.16 V vs SCE), the potential rose exponentially over time, which means that deposition took place, and after a few minutes we had to stop the reaction.

The last group (Figure 7, **D**) contained substances that had high oxidation potential and did not give any reaction. Benzene **89** and its halogenated derivatives **90** (2.50-2.61V vs SCE) did not react and no phenol was detected. Unfortunately, not all substances containing electron-withdrawing group reacted. No matter what current was applied, phenyl acetate **91** and methyl benzoate **92** (-2.34 V vs SCE) did not give any reaction. For a non-aromatic compound, adamantane **93** was tried, but it also did not react. Moreover, we tried aromatic heterocyclic isatin **94** and its methylated form **95**. As the isatin **94** did not give any product, we thought that by protecting the amide nitrogen with a methyl group, we would see some positive results. Sadly, no hydrogen was formed in the reaction with methylated isatin **95**, and therefore we assumed that an unfavourable reaction had taken place.

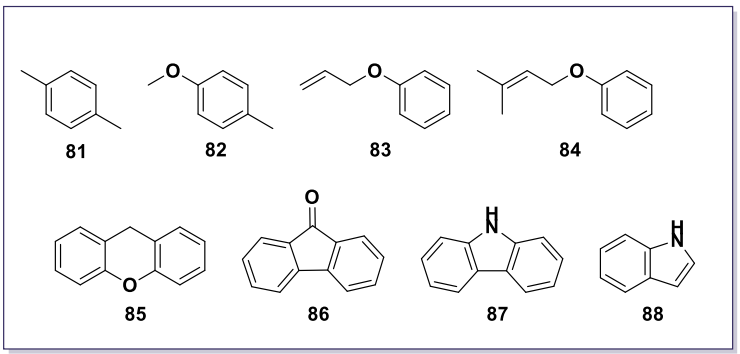
**A.** Ar-Ar coupling or/and overoxidation




**B.** Low reactivity and/or mixture of isomers




**C.** Side reactions




**D.** No reactivity

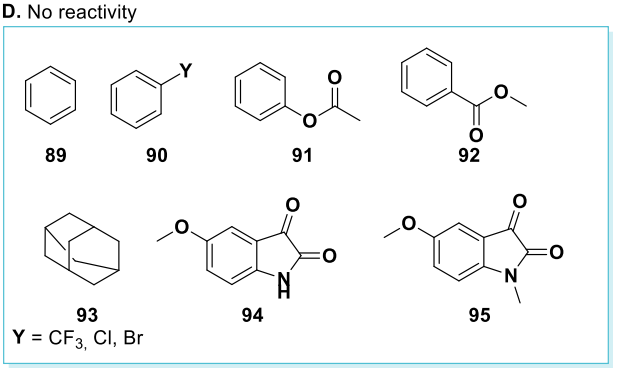
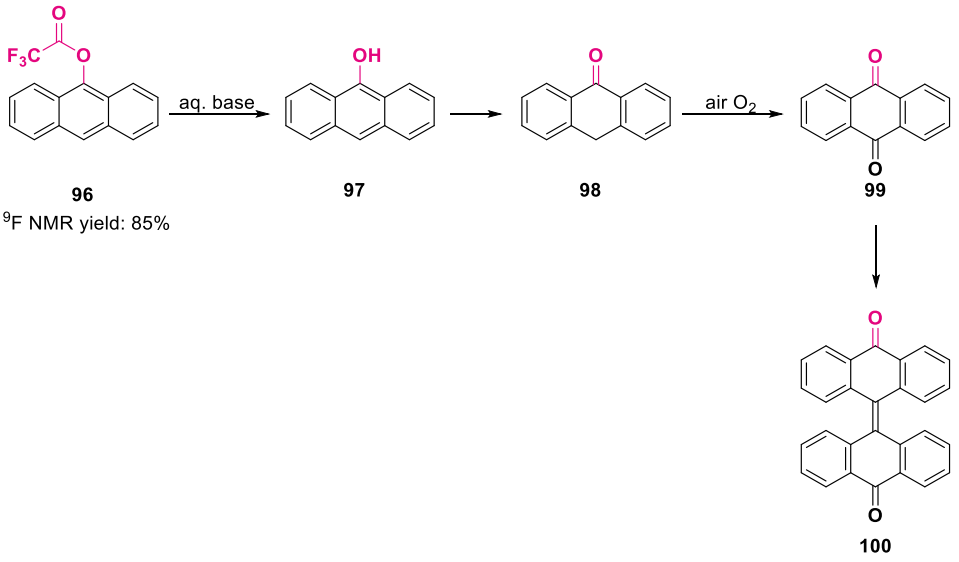


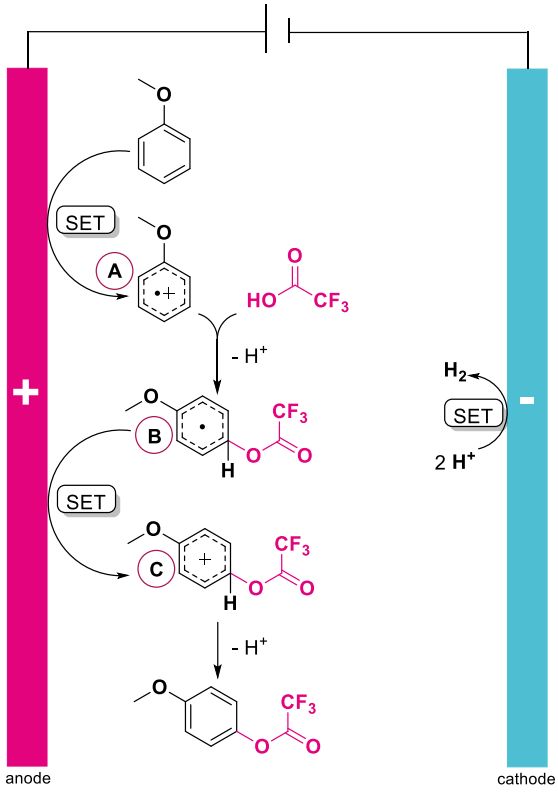

***Figure 7.*** *Starting materials that gave low reactivity, side reactions or did not react at all.*

While the previous examples can be grouped according to similar behaviour, anthracene requires special mention (Scheme 22). The electrochemical oxidation of anthracene provided a corresponding single isomer of TFA ester **96** with the highest recorded $^{19}F$ NMR yield (85%) of the tested starting materials. While the formed TFA ester was stable under the electrochemical conditions, anthrol **97**, which formed upon hydrolysis, tautomerized to a more stable form. Anthrone **98** was partially oxidized by atmospheric oxygen under basic conditions to anthraquinone **99**.[103] Anthrone **98** and anthraquinone **99** reacted further with each other to afford a dimeric product, bianthrone **100**.[104,105] Mixtures of different and inseparable compounds were the results of these transformations. Unfortunately, the isolation attempts did not give any results and we lost our desired product.




***Scheme 22.*** *Oxidative dimerization of anthrone.*

To explain the reaction mechanism, we propose that the electrochemical transformation is initiated by a single electron transfer (SET) oxidation of an electron-rich arene on the surface of the anode, in our case on graphite (Scheme 23). Being a strong electrophile, the formed radical cation **A** is trapped by trifluoroacetic acid, which leads to the formation of neutral radical **B** upon deprotonation. Furthermore, the neutral radical undergoes the second oxidation, giving cation **C**. In the last step, the aromatic system is restored upon deprotonation. Simultaneously with the anodic reaction, a hydrogen reduction takes place on the cathode. Finally, the TFA ester is hydrolysed by an aqueous base during the work-up procedure after the electrochemical transformation, and the corresponding hydroxylated arene is isolated.




***Scheme 23.*** *Proposed mechanism.*

### 3.1.3 Summary of Electrochemical Hydroxylation of Electron-rich Arenes in Continuous-Flow

We demonstrated an easy and convenient way to hydroxylate electron-rich arenes using electrochemical transformation in combination with continuous-flow. We were able to hydroxylate molecules only in 1.25 minute resistance time. The suitable oxidation potential window was 1.6-2.1 V vs SCE. The developed method is also scalable to a synthetically useful range, which helps to bridge the gap between academia and industry. Hydroxylated arenes were obtained with good yields (up to 68%) without the use of toxic oxidants or metal catalysts, demonstrating the sustainability of this method.

## 3.2 Dearomatization of Phenols and Naphthols (Publications I and II, Unpublished Results)

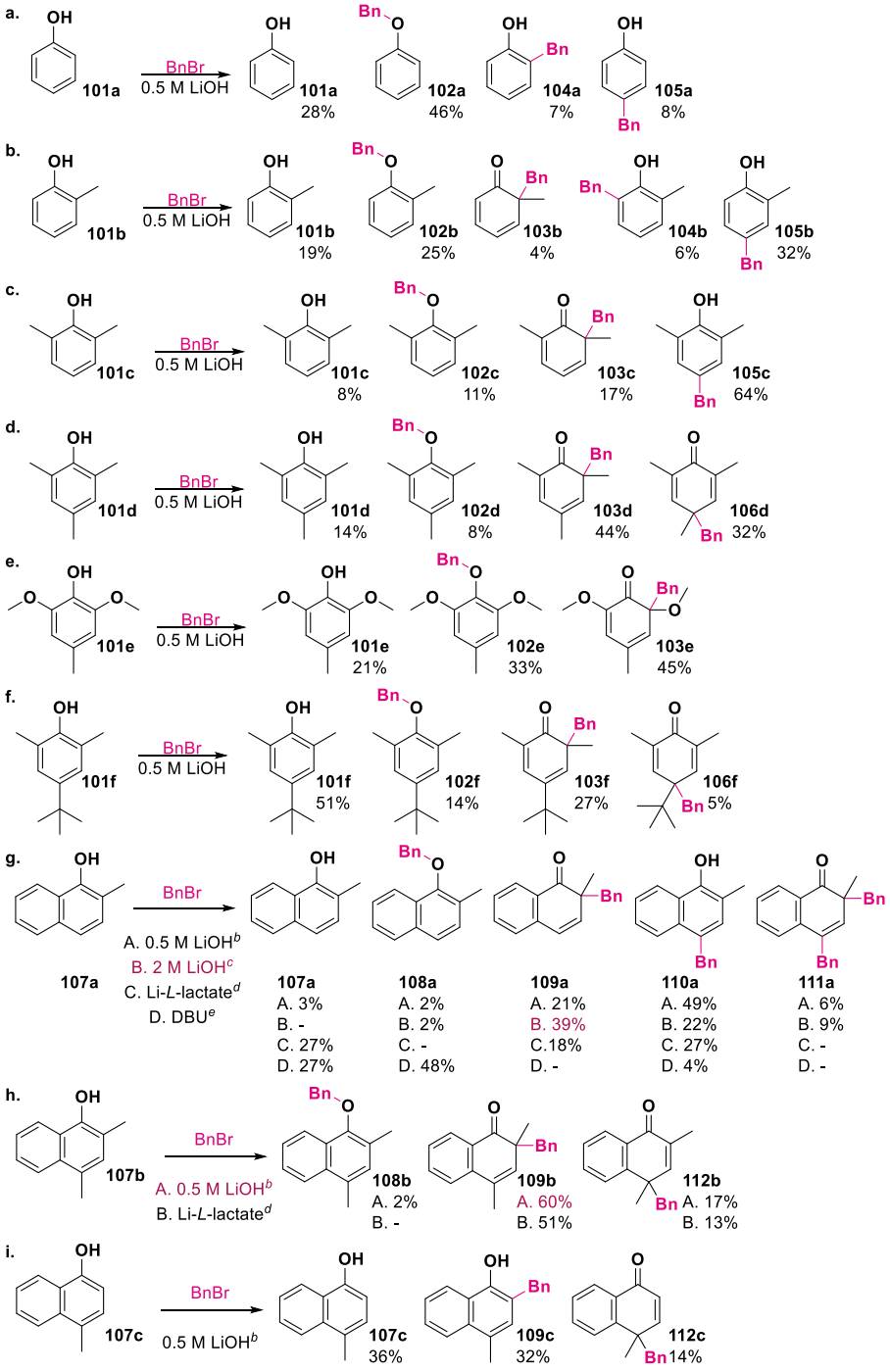
The selective dearomatization of phenols and naphthols in the presence of a transition-metal catalyst is a popular and well investigated area, although dearomatization reactions without a transition-metal catalyst remain rather overlooked. In our group, we investigated dearomatization of phenols and naphthols in aqueous and non-aqueous solutions without any oxidative agents or transition-metal catalysts.

### 3.2.1 Optimization of the Dearomatization Reaction

In 1963, Kornblum, Seltzer and Haberfield investigated the alkylation of naphthoxide with benzyl bromide in aqueous and non-aqueous media. They demonstrated that the solvent played an important role in reaction selectivity. According to their research, *C*-alkylated naphthol was the main formed product when the reaction was carried out under aqueous conditions, with only a low yield of *O*-alkylated naphthol. On the other hand, when the reaction was carried out in a non-aqueous solvent, *O*-alkylated naphthol was obtained as the main product.[106] Therefore, our initial idea was to investigate the selective dearomatization in aqueous conditions with phenols as the starting material (Scheme 24a-f). We chose commercially available benzyl bromide as the alkylating agent and lithium hydroxide was used as a base. First, unsubstituted phenol **101a** was tested (Scheme 24a). Although some starting material was recovered, alkylation proceeded well. More results are presented in Publication I. The reactions with phenols showed us that substituted phenol afforded higher *C*-alkylation yields. The *C*-alkylation took place either at the *ortho*- or *para*-position. As phenols have two *ortho*-positions, the *C*-alkylation selectivity can be lower due to the possibility of either single or double alkylation. All of these results were considered when investigating the alkylation of naphthols. We focused on the alkylation of α-naphthols, because there were no good methods to alkylate these compounds.

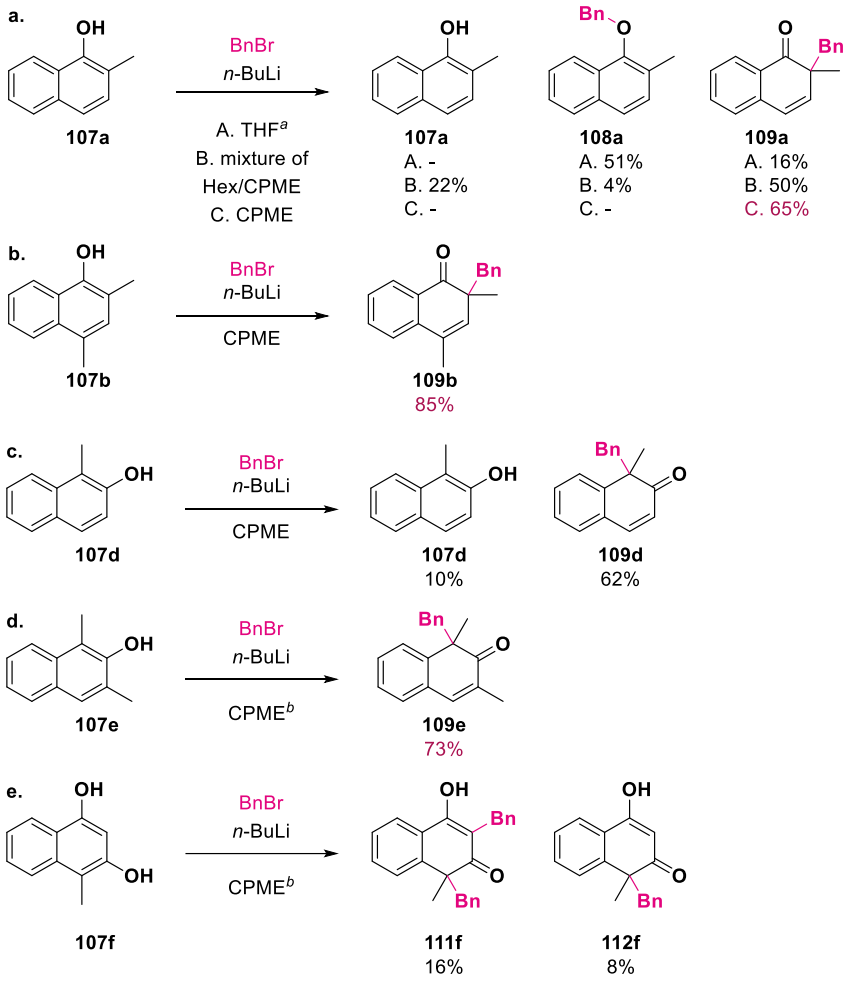
With the established reaction conditions for phenols, we broadened our scope to naphthols (Scheme 24g-i). We started with 2-methyl-1-naphthol **107a** (Scheme 24g, A) and the yield was surprisingly high compared to the previous results with phenols. *C*-Alkylation took place at the second position providing a dearomatized product (**109a**, 21%) and at the fourth position providing alkylated α-naphthol (**110a**, 49%), and some dialkylated product formed (6%), while *O*-alkylation almost did not occur (**108a** 2%). We postulated that the reaction would be regioselective towards the second position, providing dearomatized product, so more optimization reactions were carried out. A more concentrated reaction mixture (Scheme 24g, B) gave higher selectivity towards the second position **109a** (39%), although some alkylation still took place at the fourth position **110a** (22%). Knowing from the reactions with phenols (**Publication I**, Table 1, entry 3 and 5) that a substituent at the fourth position helps direct *C*-alkylation to the second position, disubstituted naphthol **107b** was tested (Scheme 24h, A). The selectivity was higher and the dearomatized product **109b** formed with 60% yield. However, this reaction also yielded the second dearomatized product **112b** (17%). Lastly, when 4-mehtyl-1-naphthol **107c** was tested, dearomatization took place only at the fourth position with low yield (**112c** 14%), and the second position alkylation **109c** was the main product (Scheme 24i). These observations demonstrated that the reaction conditions were regioselective towards the second position regardless of whether there was substituent at the second position or not. Moreover, at the same conditions used for phenols, the *O*-alkylation of naphthols was suppressed. Besides lithium hydroxide, lithium-*L*-lactate was tested as a base (Scheme 24g, C; Scheme 24h, B). Unfortunately, the dearomatization yields were lower (18% vs 39% and 51% vs 60%). Moreover, we tested organic base DBU in aqueous conditions (Scheme 24g, D), but mainly *O*-alkylation took place (**108a** 48%), and quite a significant amount of the starting material (27%) was recovered.

We found that by using lithium hydroxide as a base and benzyl bromide as an alkylating agent it was possible to regioselectively alkylate α-naphthols (**107a**-**107c**) in aqueous conditions. As the yields were not satisfactory, we turned our attention to the reactions in non-aqueous media (Scheme 25).




***Scheme 24.*** *Dearomatization of phenols and naphthols in aqueous conditions. Reaction conditions for phenols: phenol (1 mmol), BnBr (1.2 mmol, 1.2 equiv.), 0.5 M LiOH in water (2 mL), room temperature, 20 h. Reaction conditions for naphthols: naphthol (0.5 mmol), BnBr (0.6 mmol, 1.2 equiv.), base, room temperature, 20 h.* [b]*0.5 M LiOH (1 mL).* [c]*2 M LiOH (0.5 mL).* [d]*$H_2O$ (1 mL), HFIP (0.3 mL), lithium-L-lactate (1 equiv).* [e]*$H_2O$ (1 mL), DBU (1.1 equiv). The yields are given for the chromatographically isolated products.*

For the base we chose commercially available *n*-butyllithium, as it contains lithium cation, which is important for lithium naphtholate formation. First, we tried tetrahydrofuran as a solvent, together with α-naphthol **107a** (Scheme 25a, A). Unfortunately, mainly *O*-alkylation product **108a** formed (51%) with some dearomatized *C*-alkylation product **109a** (16%). In the next step, we tried cyclopentyl methyl ether, which is a greener alternative to THF.[107] We tested two approaches with 2-methyl-1-naphthol **107a** (Scheme 25a, B and C). We started the reaction in hexane, because *n*-BuLi is sold as a hexane solution, but we had problems with solubility, as our naphthol **107a** was not fully soluble in hexane (Scheme 25a, B). Before adding the alkylating agent to the reaction mixture, CPME was added. Dearomatized product **109a** formed with good yield (50%), but still quite a big amount of the starting material remained unreacted (22%) and ether **108a** was isolated with low yield (4%). In order to improve the selectivity and the yield, a second attempt was carried out with a solvent exchange (Scheme 25a, C). The reaction mixture was mixed together similarly to the first attempt but, before adding CPME, the hexane was evaporated away with argon. This inconvenient method provided dearomatized product **109a** selectively with higher yield (65%). Since more substituted α-naphthol **107b** gave high yields in an aqueous solution, it was also tested in a non-aqueous solution with CPME (Scheme 25b). Dearomatized product **109b** was received with a high yield (85%). To broaden the scope, β-naphthols **107d** and **107e** were tested (Scheme 25c-d). Similarly to α-naphthols, the more substituted β-naphthol was more reactive, as the *C*-alkylation yields were 62% for **109d** and 73% for **109e**. To our surprise, the yields were lower with β-naphthols than with α-naphthols. The trend is the opposite of the previous literature examples.[79,81] Lastly, one resorcinol **107f** was tested (Scheme 25e). Although *C*-alkylation took place and dearomatization products **111f** and **112f** formed, the yields were much lower (16% and 8%, respectively) compared to other naphthols. Therefore, we did not proceed with any extra reactions. As the yields of dearomatization with butyllithium in non-aqueous conditions were high, but the procedure was inconvenient, we started using *n*-BuLi in toluene. Using toluene helped with two problems: solubility, as our starting materials were soluble in toluene, and it allowed us to avoid blowing the solvent away before adding cyclopentyl methyl ether. As the reaction was now carried out in toluene and not in pure cyclopentyl methyl ether, we had to optimize the reaction conditions once again (Table 2). First, we did not add any additive, hoping that *n*-BuLi in toluene itself would be efficient for our transformation (Table 2, entry 1). However, no desired product formed, while some starting material was recovered (10%) along with different aromatic compounds. It became clear that some additive was needed. As the CPME previously worked, we added two equivalents of it to the reaction mixture (Table 2, entry 2). The reaction results were very good, and we obtained the dearomatization product **109a** with the highest yield so far (73%). Then, we switched to the more substituted α-naphthol **107b**, but surprisingly it gave a slightly lower yield (68%) (Table 2, entry 4). Previously, when the reaction was carried out with a solvent switch, the yield of **109b** was 85% and it was higher than with less substituted α-naphthol **109a** (65%) (Scheme 24g, C). We hoped to see a similar trend with the new conditions, but sadly that was not the case. An even bigger surprise was that β-naphthol **107d** gave a low yield of 37% (Table 2, entry 5), and the yield drop was drastic compared to the reactions in hexane (from 73% to 37%). As the yield of β-naphthol **107d** was low, we tested a higher reaction concentration, which was beneficial for the reactions in water (Scheme 24g, B).



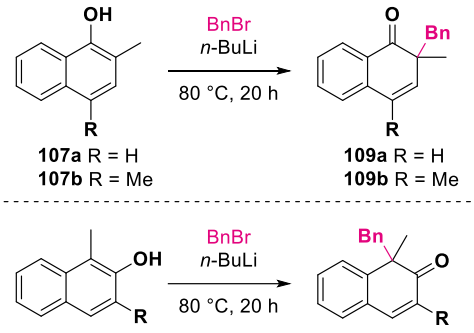

***Scheme 25.*** *Substituted naphthol alkylation with benzyl bromide in non-aqueous media. Reaction conditions: naphthol (0.5 mmol) in hexane, n-BuLi in hexane (2 equiv.), solvent exchange, BnBr (0.6 mmol, 1.2 equiv.), 80 °C, 20 h. [a]Temperature 70 °C. [b]Naphthol (0.5 mmol) in diethyl ether. All yields were isolated chromatographically.*

We added more benzyl bromide and less butyllithium and the improvement was remarkable. The desired product **109d** was isolated in 90% yield (Table 2, entry 6). As the results with β-naphthol **107d** were excellent, we tried more concentrated conditions with α-naphthol **107a** (Table 2, entry 3). Unfortunately, this did not provide any advantage, but lowered the alkylation product **109a** yield (54%) instead. Moreover, the yield was slightly higher (45%) with more substituted β-naphthol **107e** than with less substituted β-naphthol **107d** (37%) (Table 2, entry 7) in the same conditions, but still much lower than in the reaction in hexane (73%) (Scheme 25d).

Besides cyclopentyl methyl ether, another ether was tested as an additive: methyl *tert*-butyl ether (Table 2, entries 8-9). The reactions with MTBE were successful in that they gave only *C*-alkylated products. Alternative reaction conditions were examined because of the low boiling temperature of MTBE (65 °C). With less substituted α-naphthol **107a**, the yield of dearomatized product **109a** was 76% (Table 2, entry 8), which was

slightly higher than with the CPME (73%, Table 2, entry 2). Similarly to CPME, more substituted α-naphthol **107b** gave a lower yield (56%) than the less substituted compound **107a** (Table 2, entry 9). Furthermore, different alcohols were tested as additives (Table 2, entries 10-15). Methanol gave the lowest yield (37%), while isopropanol and (*S*)-butanol gave higher yields (57% and 56%, respectively). Thus, it seemed that the bigger the alcohol molecule the higher the yield of *C*-alkylation product, but unfortunately *tert*-butanol gave a lower yield (44%). We also tried chiral *L*-menthol as an additive (Table 2, entries 14-15) and the dearomatized product yields were high: 70% for **107a** and 76% for **107b**. In the case of α-naphthol **107b**, it was the highest recorded yield with toluene.

***Table 2.*** *The effect of different additives on C-alkylation.*




| Entry[a] | Temp. (°C) | Naphthol | BnBr (equiv.) | Additive (equiv.) | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 | 80 | **107a** | 1.2 | - | - |
| 2 | 80 | **107a** | 1.2 | CPME (2) | 73 |
| 3[c] | 90 | **107a** | 2 | CPME (2) | 54 |
| 4 | 80 | **107b** | 1.2 | CPME (2) | 68 |
| 5 | 80 | **107d** | 1.2 | CPME (2) | 37 |
| 6[c] | 90 | **107d** | 2 | CPME (2) | 90 |
| 7 | 80 | **107e** | 1.2 | CPME (2) | 45 |
| 8 | 65 | **107a** | 1.2 | MTBE (4) | 76 |
| 9 | 65 | **107b** | 1.2 | MTBE (4) | 56 |
| 10 | 80 | **107a** | 1.2 | methanol (1) | 37 |
| 11[d] | 80 | **107a** | 1.2 | *i*-propanol (1) | 57 |
| 12[e] | 80 | **107a** | 1.2 | (*S*)-butanol (2) | 56 |
| 13 | 80 | **107a** | 1.2 | *t*-butanol (2) | 44 |
| 14 | 80 | **107a** | 1.2 | *L*-menthol (2) | 70 |
| 15 | 80 | **107b** | 1.2 | *L*-menthol (2) | 76 |

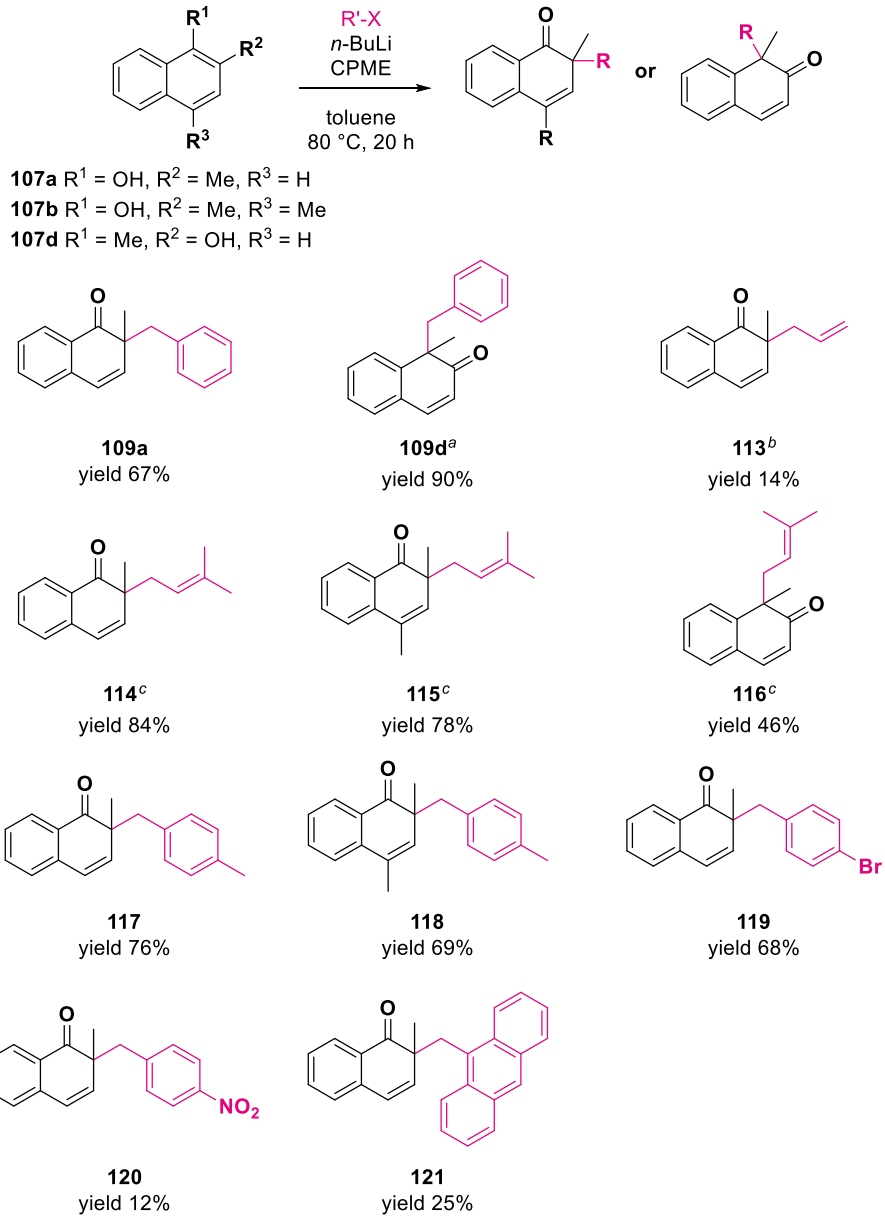
[a]Reaction conditions: naphthol (0.5 mmol) in toluene (0.6 mL), *n*-BuLi in toluene (2 equiv.), additive and BnBr were added, 80 °C, 20 h. [b]Isolated yield. [c]in toluene (0.3 mL), *n*-BuLi in toluene (1.1 equiv.). [d]toluene (1 mL). [e]toluene (0.4 mL).

Unfortunately, we did not find any enantiomeric excess of the chiral dearomatized product when *L*-menthol was used as an additive. From the optimization, we saw that the reaction was sensitive to the substrate structure, as well as to additives.

The amount of alkylating halide also played an important role, as when in an alkylating agent was used in great excess the yield of α-naphthol decreased (Table 2, entry 3), whereas the outcome was the opposite with β-naphthol, yielding 90% of the dearomatized product (Table 2, entry 6). Moreover, the bulkiness of an additive was important, as a small molecule, such as methanol, gave a lower yield than bulkier *L*-menthol.

### 3.2.2 Scope of the Reactions

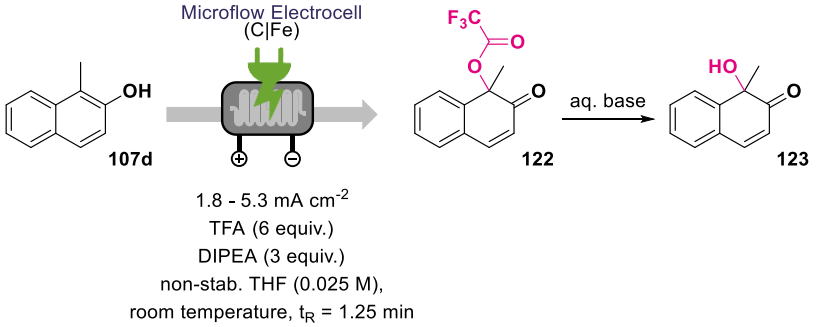
With the optimal conditions in hand, we broadened our scope by using other alkylic halides (Scheme 26). From Lovchik *et al.* we knew that it was possible to selectively *C*-alkylate naphthols with prenyl chloride.[96] However, in the preliminary experiments with prenyl bromide under the established conditions, the yield of *C*-alkylated product **114** was only 4%. As we had an excess amount of *n*-BuLi in our mixture, we assumed it had reacted with the alkyl halide and therefore the yield of dearomatized product decreased. Next, we lowered the *n*-BuLi amount from 2 to 1.2 equivalents and the temperature (to room temperature), because prenyl bromide is more reactive than benzyl bromide. The dearomatized product **114** was obtained with a high yield (84%). Unfortunately, lowering the *n*-BuLi amount also lowered the yield of the dearomatized product **109a** in the reaction of **107a** with benzyl bromide from 73% to 67% (Scheme 26; Table 2, entry 2). We also carried out reactions with more substituted α-naphthol **107b** and β-naphthol **107d** using prenyl bromide and, in both cases, the yields were lower than with less substituted α-naphthol **107a** (78% for **115** and 46% for **116**). Then, we turned our attention to different substituted benzyl bromides. The reaction yields with α-naphthol **107a** and 4-methylbenzyl bromide were higher than with benzyl bromide, rising from 67% to 76%. And similarly to the previous results, the more substituted α-naphthol **107b** gave a slightly lower yield (**118**, 69%). We also tried 4-bromobenzyl bromide with **107a** and the yield (68%) was comparable to another substituted benzyl bromide. The lowest yields were obtained with 4-nitrobenzyl bromide (**120**, 12%) and 9-(chloromethyl)anthracene (**121**, 25%). Unfortunately, other commonly used electrophiles, such as methyl iodide and methyl tosylate, gave no *C*-alkylation products. With methyl tosylate, *O*-alkylation took place with 52% yield.




***Scheme 26.*** *Dearomatization of naphthols* ***107a***, ***107b*** *and* ***107d*** *with different active halides. Reaction conditions: naphthol (0.5 mmol) in toluene (0.6 mL), n-BuLi in toluene (1.2 equiv.), CPME (2 equiv.), alkyl halide (1.2 equiv.), 80 °C, 20 h. [a]BnBr (2 equiv.), 90 °C. [b]40 °C. [c]r.t.*

We tried other approaches to dearomatize naphthols, such as the electrochemical oxidation of β-naphthol **107d** in continuous-flow (Scheme 27). With the conditions established for hydroxylate electron-rich arenes in Chapter 3.1.2 (Scope of the Reactions), we were able to dearomatize β-naphthol by hydroxylating it at the first position, with the low yield (**123**, 11%). To the best of our knowledge, this is the first example of such a transformation and it is a subject for future investigation. We have also tried to achieve asymmetric induction in dearomatization reactions with alkylating agents. For this purpose,

several salts, *e.g.* $LaCl_3$, La(*i*-PrO)$_3$ and $CeCl_3$, together with chiral additives, *e.g.* *L*-menthol and (*S*)-butanol, were tested. To our disappointment, all of the products were racemic, and the lanthanide salts offered a lower yield for *C*-alkylation.




***Scheme 27.*** *Electrochemical dearomatization of β-naphthol* ***107d****.*

### 3.2.3 Summary of Dearomatization of Naphthols

α- And β-naphthols dearomatize without any transition-metal catalyst with high yields (up to 90%). Under the obtained optimized reaction conditions, *C*-alkylation takes place exclusively with high selectivity at position 2. We determined that some additives may improve yields, but they were case specific rather than general. The best additives were ethers, such as cyclopentyl methyl ether and methyl *tert*-butyl ether. Bulky alcohols, such as *L*-menthol, were also good additives.

# 4 Conclusions

We developed an environmentally friendly method for the synthesis of oxygen-containing aromatic compounds and easy approaches to dearomatize them.

- A sustainable electrochemical method to synthesise hydroxylated arenes was developed. The reactions were carried out in at DIY continuous-flow reactor. Synthesised electron-rich hydroxylated arenes were isolated with yields up to 68%.

- A preparative scale synthesis of α-naphthol **18** in a 50% yield from naphthalene was carried out in 10 mmol scale. This result was comparable with that obtained in 1 mmol scale (yields of 50 vs 54%). This experiment showed us that the continuous-flow approach can be used for the reaction at a bigger scale, which makes it attractive for industry.

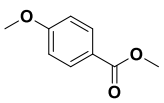
- The oxidation potential window for the developed electrochemical reaction is 1.6-2.1 V vs SCE.

- We demonstrated an easy and efficient method for a selective *C*-alkylation of phenols and α- and β-naphthols without any transition-metal catalysts. The dearomatized products were isolated with high yields (up to 90%).

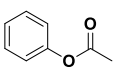
- The importance of different donating additives for alkylation reactions was demonstrated.

# 5 Experimental

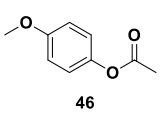
**Methyl 4-methoxybenzoate 44.**[108] *p*-Anisic acid (2 g, 13.15 mmol, 1 equiv.) was dissolved in methanol (66 mL) and $H_2SO_4$ (0.70 mL). The mixture was refluxed for 4 hours and then cooled down to room temperature. The reaction mixture was concentrated *in vacuo* and saturated $NaHCO_3$ (aq.) (10 mL) was added to the flask. Then the reaction mixture was extracted with dichloromethane (4x10 mL). Organic layers were washed with brine (10 mL). The crude mixture was dried over $Na_2SO_4$ overnight and filtrated. Solvents were evaporated *in vacuo* to give **44** (2.11 g, 96.7%) as a white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.01 – 7.97 (m, 2H), 6.93 – 6.89 (m, 2H), 3.88 (s, 3H), 3.85 (s, 3H). The NMR data were in agreement with the literature data.[109]


44

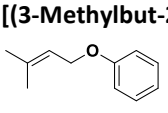
**Phenyl acetate 45.** To phenol (2 g, 21.25 mmol, 1 equiv.), dichloromethane (100 mL), $K_2CO_3$ (5.9 g, 42.50 mmol, 2 equiv.) and acetic anhydride (2.5 mL) were added. The reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was washed with water (3x50 mL) and dried over $MgSO_4$ and filtrated. The solvents were evaporated *in vacuo* to give **45** (2.65 g, 92%) as a colourless liquid. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.34 (m, 2H), 7.26 – 7.19 (m, 1H), 7.10 – 7.06 (m, 2H), 2.29 (s, 3H). The NMR data were in agreement with the literature data.[110]


45

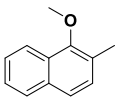
**4-Methoxyphenyl acetate 46.** To 4-methoxyphenol (2 g, 16.11 mmol, 1 equiv.), dichloromethane (100 mL), $K_2CO_3$ (4.45 g, 32.22 mmol, 2 equiv.) and acetic anhydride (1.83 mL) were added. The reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was washed with water (3x50 mL), dried over $MgSO_4$ and filtrated. The solvents were evaporated *in vacuo* to give **46** (2.66 g, 99%) as a colourless liquid. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.04 – 6.98 (m, 2H), 6.92 – 6.86 (m, 2H), 3.77 (s, 3H), 2.26 (s, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ = 169.8, 157.2, 144.1, 122.3, 114.3, 55.4, 20.9.


46

**[(3-Methylbut-2-en-1-yl)oxy]benzene 49.** A mixture of phenol (1 g, 10.63 mmol, 1.5 equiv.), prenyl bromide (819 µL, 7.08 mmol, 1 equiv.) and $K_2CO_3$ (1.96 g, 14.17 mmol, 2 equiv.) in acetone (30 mL) was heated to reflux. Upon completion, stirring for 12 hours, the reaction mixture was cooled to room temperature, filtered and the solvent was removed *in vacuo*. The crude product was purified by column chromatography on silica gel (10-25% of DCM in PE) to give **49** (919 mg, 80%) as a pale yellow oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.25 (m, 2H), 6.99 – 6.90 (m, 3H), 5.52 (ddt, *J* = 6.7, 5.3, 1.4 Hz, 1H), 4.52 (d, *J* = 6.8 Hz, 2H), 1.81 (d, *J* = 1.5 Hz, 3H), 1.76 (d, *J* = 1.3 Hz, 3H). The NMR data were in agreement with the literature data.[111]

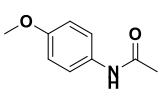

49

**1-Methoxy-2-methylnaphthalene 52.** A mixture of 2-methyl-1-naphthol (1 g, 6.32 mmol, 1.5 equiv.), methyl iodide (537 µL, 8.63 mmol, 2 equiv.) and $K_2CO_3$ (1.16 g, 8.43 mmol, 2 equiv.) in acetone (30 mL) was heated to reflux. Upon completion, stirring for 12 hours, the reaction mixture was cooled to room temperature, filtered and the solvent was removed *in vacuo*. The crude product was purified by column chromatography on silica gel (10-25% of


52

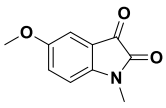
DCM in PE) to give **52** (919 mg, 80%) as a pale yellow oil. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 7.7 Hz, 1H), 7.82 (d, *J* = 8.1 Hz, 1H), 7.59 – 7.40 (m, 3H), 7.32 (d, *J* = 8.4 Hz, 1H), 3.93 (s, 3H), 2.48 (s, 3H). The NMR data were in agreement with the literature data.[112]

***N*-(4-methoxyphenyl)acetamide 53.** To methoxy aniline (2 g, 16.24 mmol, 1 equiv.), dichloromethane (100 mL) and acetic anhydride (2 mL) were added. The reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was washed with saturated $NaHCO_3$ (aq.) (3x20 mL). The organic layer was dried with a phase separator and the solvents were evaporated *in vacuo*. The crude product was purified by column chromatography on silica gel (5-30% of DCM in EtOAc) to give **53** (1.39 g, 52%) as a white solid. $^{1}$H NMR (400 MHz, MeOD) δ 7.44 – 7.39 (m, 2H), 6.88 – 6.84 (m, 2H), 3.76 (s, 3H), 2.09 (s, 3H). $^{13}$C NMR (101 MHz, MeOD) δ = 171.4, 157.9, 132.8, 123.0, 114.9, 55.8, 23.5.



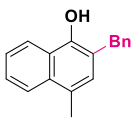
53

**5-Methoxy-1-methylindoline-2,3-dione 54.** To isatin (2 g, 11.29 mmol, 1 equiv.) a solution in DMF (55 mL) NaH (352 mg, 14.7 mmol, 1.3 equiv.) (60% dispersion in mineral oil) was added at 0 °C under argon. The mixture was stirred at 0 °C for 20 minutes, then methyl iodide (2.28 mL, 13.55 mmol, 1.2 equiv.) was added and the reaction mixture was further stirred for 2 hours at room temperature. The reaction was quenched with water (1 mL) and the solvent was evaporated *in vacuo*. The reaction mixture was then suspended with a saturated $NH_4Cl$ solution (10 mL), extracted with EtOAc (3x25 mL) and dried over $MgSO_4$. The mixture was filtrated and the solvent was removed *in vacuo*. The crude product was purified by column chromatography on silica gel (2-5% of MeOH in DCM) to give **54** as a red solid (600 mg, 28%). $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.16 (d, *J* = 2.7 Hz, 1H), 7.14 (d, *J* = 1.7 Hz, 1H), 6.82 – 6.79 (m, 1H), 3.80 (s, 3H), 3.22 (s, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ = 183.9, 158.5, 156.7, 145.5, 124.8, 118.0, 111.0, 109.7, 56.1, 26.4.

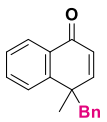


54

**2-Benzyl-4-methylnaphthalen-1-ol 109c** and **4-benzyl-4-methylnaphthalen-1(4*H*)-one 112c.** To naphthol **107c** (0.5 mmol, 124 mg, 1 equiv.), 0.5 M LiOH (1 mL) was added at 0°C. The reaction mixture was stirred for 15 minutes. Then BnBr (0.6 mmol, 72 µL, 1.2 equiv) was added. The reaction mixture was allowed to warm up to room temperature and was stirred for 20 hours. The reaction mixture was extracted with EtOAc (3x7 mL) and the organic layers were washed with brine (10 mL). The reaction mixture was dried over $MgSO_4$ and filtrated. The crude product was purified by column chromatography on silica gel (5-25% of EtOAc in PE) to give **109c** as a colourless oil (39 mg, 32%) and **112c** (17 mg, 14%). $^{1}$H NMR of **109c** (400 MHz, $CDCl_3$) δ 8.30 – 8.25 (m, 1H), 8.09 – 8.04 (m, 1H), 7.67 – 7.59 (m, 2H), 7.48 – 7.41 (m, 2H), 7.41 – 7.34 (m, 3H), 5.15 (s, 1H), 4.26 (s, 2H), 2.75 (d, *J* = 1.0 Hz, 3H). $^{13}$C NMR of **109c** (101 MHz, $CDCl_3$) δ = 147.5, 139.6, 132.7, 129.5, 129.0, 128.7, 126.8, 126.7, 125.7, 125.3, 125.2, 124.3, 121.8, 119.6, 36.8, 18.9. $^{1}$H NMR of **112c** (400 MHz, $CDCl_3$) δ 8.15 – 8.11 (m, 1H), 7.67 – 7.63 (m, 2H), 7.44 – 7.38 (m, 1H), 7.12 – 7.05 (m, 3H), 6.91 (d, *J* = 10.2 Hz, 1H), 6.40 (d, *J* = 10.2 Hz, 1H), 4.16 (q, *J* = 7.2 Hz, 1H), 3.25 – 3.05 (m, 2H), 2.62 (s, 3H).

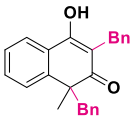


109c

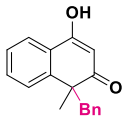


112c

**1,3-Dibenzyl-4-hydroxy-1-methylnaphthalen-2(1*H*)-one 111f** and **1-benzyl-4-hydroxy-1-methylnaphthalen-2(1*H*)-one 112f.** To naphthol **107f** (174 mg, 0.5 mmol, 1 equiv.), diethyl ether (3 mL) under argon *n*BuLi in hexane (0.4 mL, 2 equiv.) was added. The solvents were evaporated with an argon flow. CPME (1 mL) was added and the reaction mixture was stirred for 10 minutes. BnBr (72 µL, 0.6 mmol, 1.2 equiv.) was added. The reaction mixture was stirred at 80 °C for 20 hours. The reaction mixture was cooled down to room temperature and was extracted with EtOAc (3x7 mL) and dried over $MgSO_4$. The reaction mixture was filtrated and the solvents were evaporated *in vacuo*. The crude product was purified by column chromatography on silica gel (5-25% of EtOAc in PE) to give **111f** (29 mg, 16%) as a yellow oil and **112f** (11 mg, 8%) as a yellow oil.$^1$H NMR of **111f** (400 MHz, $CDCl_3$) δ 9.23 (s, 1H), 7.73 (dd, *J* = 4.1, 1.5 Hz, 1H), 7.18 – 7.10 (m, 14H), 3.78 (s, 1H), 3.04 (s, 2H), 1.96 (s, 3H). $^{13}$C NMR of **111f** (101 MHz, $CDCl_3$) δ = 209.0, 196.2, 143.2, 137.1, 134.7, 131.8, 130.8, 130.3, 130.0, 128.2, 127.8, 127.7, 127.2, 126.7, 96.5, 86.8, 55.0, 53.7, 51.8, 50.4, 45.3, 44.2, 42.5, 34.0, 25.7.$^1$H NMR of **112f** (400 MHz, $CDCl_3$) δ 8.05 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.70 – 7.62 (m, 2H), 7.51 – 7.46 (m, 4H), 7.40 (ddd, *J* = 8.4, 6.9, 1.6 Hz, 1H), 5.75 (s, 1H), 4.99 (d, *J* = 7.1 Hz, 2H), 3.44 (d, *J* = 13.2 Hz, 1H), 3.24 (d, *J* = 13.2 Hz, 1H), 1.77 (s, 3H). $^{13}$C NMR of **112f** (101 MHz, $CDCl_3$) δ = 185.5, 176.5, 145.9, 136.5, 132.3, 129.1, 129.0, 127.9, 127.8, 126.9, 126.8, 126.4, 126.2, 104.3, 70.5, 47.8, 46.4, 27.8.

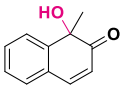


111f



112f

**1-Hydroxy-1-methylnaphthalen-2(1*H*)-one 123.** Naphthol **1d** (198 mg, 1.25 mmol, 1 equiv.) together with trifluoroacetic acid (0.57 mL, 7.50 mmol, 6 equiv.) and DIPEA (0.65 mL, 3.75 mmol, 3 equiv.) were charged in a 50 mL volumetric flask, which was filled with freshly distilled THF (0.025 M) up to the bar. The mixture was swirled until homogeneous and taken up into a 50 mL disposable syringe. The solution was pumped through an electrochemical setup at a fixed flow rate of 0.6 mL/min to 1.25 min in the active part of a reactor equipped with a graphite anode and a stainless steel cathode divided by a 0.25 mm thick Teflon gasket. A constant current of 80 mA was applied and the system was stabilized for 10 minutes. After a steady state was reached, the reaction mixture was collected in a 100 mL round-bottom flask for 66.6 min, which corresponds to 10 mmol scale. The cure mixture was concentrated *in vacuo* and saturated $NaHCO_3$ (aq.) (25 mL) was added to the flask. The reaction mixture was vigorously stirred overnight at room temperature to achieve full hydrolysis of the TFA ester. Next the reaction mixture was extracted with DCM (4x15 mL) first from a $NaHCO_3$ solution and then from a 1 M HCl solution (25 mL). The organic layers were combined, dried using a phase separator and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (2-10% of $Et_2O$ in DCM) to give **123** (24 mg, 11 %) as a yellow solid. $^1$H NMR (400 MHz, MeOD) δ 7.71 (ddt, *J* = 7.8, 1.3, 0.7 Hz, 1H), 7.56 (d, *J* = 9.9 Hz, 1H), 7.45 (td, *J* = 7.5, 1.6 Hz, 1H), 7.41 – 7.38 (m, 1H), 7.37 – 7.31 (m, 1H), 6.13 (d, *J* = 9.9 Hz, 1H), 1.49 (s, 3H). $^{13}$C NMR (101 MHz, MeOD) δ = 206.5, 147.6, 146.7, 131.5, 130.6, 130.3, 129.0, 126.7, 124.3, 77.8, 32.2.



123

***Table 3.*** *Supporting information concerning compounds discussed in the thesis but not presented in the Experimental section can be found in the corresponding publications.*

| Entry | Compound number in thesis | Compound number in publication | | |
|---|---|---|---|---|
| | | **I** | **II** | **III** |
| 1 | **47** | | | **S-4** |
| 2 | **48** | | | **S-2** |
| 3 | **50** | | | **S-3** |
| 4 | **51** | | | **S-1** |
| 5 | **55** | | | **1** |
| 6 | **56** | | | **2** |
| 7 | **57** | | | **3** |
| 8 | **58** | | | **4** |
| 9 | **59** | | | **5** |
| 10 | **60** | | | **6** |
| 11 | **61** | | | **7** |
| 12 | **62** | | | **8** |
| 13 | **63** | | | **9** |
| 14 | **64** | | | **10** |
| 15 | **18** | | | **11** |
| 16 | **65** | | | **12** |
| 17 | **66** | | | **13** |
| 18 | **67** | | | **14** |
| 19 | **68** | | | **15** |
| 20 | **101a** | **1a** | | |
| 21 | **102a** | **2a** | | |
| 22 | **104a** | **3a** | | |
| 23 | **105a** | **4a** | | |
| 24 | **107a** | **1a** | | |
| 25 | **101b** | **1b** | | |
| 26 | **102b** | **2b** | | |
| 27 | **103b** | **3´b** | | |
| 28 | **104b** | **3b** | | |
| 29 | **105b** | **4b** | | |
| 30 | **101c** | **1f** | | |
| 31 | **102c** | **2f** | | |
| 32 | **103c** | **3´f** | | |
| 33 | **105c** | **4f** | | |
| 34 | **101d** | **1h** | | |
| 35 | **102d** | **2h** | | |
| 36 | **103d** | **3'h** | | |
| 37 | **106d** | **4´h** | | |
| 38 | **101e** | **1i** | | |

| | | | | |
|---|---|---|---|---|
| 39 | **102e** | **2i** | | |
| 40 | **103e** | **3´i** | | |
| 41 | **101f** | **1k** | | |
| 42 | **102f** | **2k** | | |
| 43 | **103f** | **3´k** | | |
| 44 | **106f** | **4´k** | | |
| 45 | **108a** | | **3a** | |
| 46 | **109a** | | **4a** | |
| 47 | **110a** | | **5a** | |
| 48 | **111a** | | **6a** | |
| 49 | **107b** | | **1b** | |
| 50 | **108b** | | **3b** | |
| 51 | **109b** | | **4b** | |
| 52 | **112b** | | **5b** | |
| 53 | **109d** | | **4c** | |
| 54 | **107e** | | **1d** | |
| 55 | **109e** | | **4d** | |
| 56 | **113** | | **4ab** | |
| 57 | **114** | | **4ac** | |
| 58 | **115** | | **4bc** | |
| 59 | **116** | | **4cc** | |
| 60 | **117** | | **4ad** | |
| 61 | **118** | | **4bd** | |
| 62 | **119** | | **4af** | |
| 63 | **120** | | **4ae** | |
| 64 | **121** | | **4ag** | |

## References


[1] J. B. Sperr, D. L. Wright, *Chem. Soc. Rev.* **2006**, *35*, 605–621.
[2] J. I. Yoshida, K. Kataoka, R. Horcajada, A. Nagaki, *Chem. Rev.* **2008**, *108*, 2265–2299.
[3] S. R. Waldvogel, B. Janza, *Angew. Chem. Int. Ed.* **2014**, *53*, 7122–7123.
[4] M. Yan, Y. Kawamata, P. S. Baran, *Chem. Rev.* **2017**, *117*, 13230–13319.
[5] R. D. Little, K. D. Moeller, *Chem. Rev.* **2018**, *118*, 4483–4484.
[6] A. Wiebe, T. Gieshoff, S. Möhle, E. Rodrigo, M. Zirbes, S. R. Waldvogel, *Angew. Chem. Int. Ed.* **2018**, *57*, 5594–5619.
[7] S. R. Waldvogel, S. Lips, M. Selt, B. Riehl, C. J. Kampf, *Chem. Rev.* **2018**, *118*, 6706–6765.
[8] D. Pollok, S. R. Waldvogel, *Chem. Sci.* **2020**, *11*, 12386–12400.
[9] D. Cantillo, *Chem. Commun.* **2022**, *58*, 619–628.
[10] B. A. Frontana-Uribe, R. D. Little, J. G. Ibanez, A. Palma, R. Vasquez-Medrano, *Green Chem.* **2010**, *12*, 2099–2119.
[11] Y. Yuan, A. Lei, *Nat. Commun.* **2020**, *11*, 2018–2020.
[12] S. B. Beil, D. Pollok, S. R. Waldvogel, *Angew. Chem. Int. Ed.* **2021**, *60*, 14750–14759.
[13] C. Schotten, T. P. Nicholls, R. A. Bourne, N. Kapur, B. N. Nguyen, C. E. Willans, *Green Chem.* **2020**, *22*, 3358–3375.
[14] S. Tang, Y. Liu, A. Lei, *Chem* **2018**, *4*, 27–45.
[15] D. M. Heard, A. J. J. Lennox, *Angew. Chem. Int. Ed.* **2020**, *59*, 18866–18884.
[16] C. Kingston, M. D. Palkowitz, Y. Takahira, J. C. Vantourout, B. K. Peters, Y. Kawamata, P. S. Baran, *Acc. Chem. Res.* **2020**, *53*, 72–83.
[17] R. Francke, R. D. Little, *Chem. Soc. Rev.* **2014**, *43*, 2492–2521.
[18] L. F. T. Novaes, J. Liu, Y. Shen, L. Lu, J. M. Meinhardt, S. Lin, *Chem. Soc. Rev.* **2021**, *50*, 7941–8002.
[19] J. E. Nutting, M. Rafiee, S. S. Stahl, *Chem. Rev.* **2018**, *118*, 4834–4885.
[20] N. Prakash, R. Rajeev, A. John, A. Vijayan, L. George, A. Varghese, *ChemistrySelect* **2021**, *6*, 7691–7710.
[21] M. Atobe, H. Tateno, Y. Matsumura, *Chem. Rev.* **2018**, *118*, 4541–4572.
[22] S. Zheng, J. Yan, K. Wang, *Engineering* **2021**, *7*, 22–32.
[23] M. B. Plutschack, B. Pieber, K. Gilmore, P. H. Seeberger, *Chem. Rev.* **2017**, *117*, 11796–11893.
[24] M. Elsherbini, T. Wirth, *Acc. Chem. Res.* **2019**, *52*, 3287–3296.
[25] Y. Cao, C. Soares, N. Padoin, T. Noël, *Chem. Eng. J.* **2021**, *406*, 126811.
[26] T. Noël, Y. Cao, G. Laudadio, *Acc. Chem. Res.* **2019**, *52*, 2858–2869.
[27] N. Tanbouza, T. Ollevier, K. Lam, *iScience* **2020**, *23*, 101720.
[28] C. Amatore, A. R. Brown, *J. Am. Chem. Soc.* **1996**, *118*, 1482–1486.
[29] H. Löwe, W. Ehrfeld, *Electrochim. Acta* **1999**, *44*, 3679–3689.
[30] G. Laudadio, W. de Smet, L. Struik, Y. Cao, T. Noël, *J. Flow Chem.* **2018**, *8*, 157–165.
[31] C. Huang, X. Y. Qian, H. C. Xu, *Angew. Chem. Int. Ed.* **2019**, *58*, 6650–6653.
[32] W. J. Kong, L. H. Finger, A. M. Messinis, R. Kuniyil, J. C. A. Oliveira, L. Ackermann, *J. Am. Chem. Soc.* **2019**, *141*, 17198–17206.
[33] M. Elsherbini, B. Winterson, H. Alharbi, A. A. Folgueiras-Amador, C. Génot, T. Wirth, *Angew. Chem. Int. Ed.* **2019**, *58*, 9811–9815.
[34] T. P. Nicholls, C. Schotten, C. E. Willans, *Curr. Opin. Green Sustain. Chem.* **2020**, *26*, 100355.

[35] Y. Mo, Z. Lu, G. Rughoobur, P. Patil, N. Gershenfeld, A. I. Akinwande, S. L. Buchwald, K. F. Jensen, *Science* **2020**, *368*, 1352–1357.
[36] N. Shida, Y. Nakamura, M. Atobe, *Chem. Rec.* **2021**, *21*, 2164–2177.
[37] M. T. Nguyen, E. S. Kryachko, L. G. Vanquickenborne, in *PATAI'S Chem. Funct. Groups*, John Wiley & Sons, Inc., **2009**, pp. 1–179.
[38] R. J. Schmidt, *Appl. Catal. A Gen.* **2005**, *280*, 89–103.
[39] M. Weber, M. Weber, V. Weber, in *Ullmann's Encycl. Ind. Chem.*, **2020**, pp. 1–20.
[40] S. Fukuzumi, K. Ohkubo, *Asian J. Org. Chem.* **2015**, *4*, 836–845.
[41] Z. Iqbal, A. Joshi, S. Ranjan De, *Adv. Synth. Catal.* **2020**, *362*, 5301–5351.
[42] D. Saha, P. Das, P. Biswas, J. Guin, *Chem. Asian J.* **2019**, *14*, 4534–4548.
[43] P. Das, J. Guin, *ChemCatChem* **2018**, *10*, 2370–2373.
[44] R. Trammell, L. D'Amore, A. Cordova, P. Polunin, N. Xie, M. A. Siegler, P. Belanzoni, M. Swart, I. Garcia-Bosch, *Inorg. Chem.* **2019**, *58*, 7584–7592.
[45] R. Zhu, Q. Sun, J. Li, L. Li, Q. Gao, Y. Wang, L. Fang, *Chem. Commun.* **2021**, *57*, 13190–13193.
[46] N. Viswanadh, G. S. Ghotekar, M. B. Thoke, R. Velayudham, A. C. Shaikh, M. Karthikeyan, M. Muthukrishnan, *Chem. Commun.* **2018**, *54*, 2252–2255.
[47] Y. H. So, J. Y. Becker, L. L. Miller, *J. Chem. Soc. Chem. Commun.* **1975**, 262–263.
[48] Z. Blum, L. Cedheim, K. Nyberg, *Acta Chem. Scand. Ser. B* **1975**, *29*, 715–718.
[49] K. Fujimoto, H. Maekawa, Y. Tokuda, Y. Matsubara, T. Mizuno, I. Nishiguchi, *Synlett* **1995**, 661–662.
[50] C. K. Liu, M. Y. Chen, X. X. Lin, Z. Fang, K. Guo, *Green Chem.* **2020**, *22*, 6437–6443.
[51] X. Tan, L. Massignan, X. Hou, J. Frey, J. C. A. Oliveira, M. N. Hussain, L. Ackermann, *Angew. Chem. Int. Ed.* **2021**, *60*, 13264–13270.
[52] L. Massignan, X. Tan, T. H. Meyer, R. Kuniyil, A. M. Messinis, L. Ackermann, *Angew. Chem. Int. Ed.* **2020**, *59*, 3184–3189.
[53] L. Wood, "Phenol Market: Global Industry Trends, Share, Size, Growth, Opportunity and Forecast (2019-2024)," can be found under https://www.businesswire.com/news/home/20190228005516/en, **2019**.
[54] M. A. M. Shushni, R. Mentel, U. Lindequist, R. Jansen, *Chem. Biodivers.* **2009**, *6*, 127–137.
[55] B. Das, C. R. Reddy, J. Kashanna, S. K. Mamidyala, C. G. Kumar, *Med. Chem. Res.* **2012**, *21*, 3321–3325.
[56] Y. F. Hallock, K. P. Manfredi, J. W. Blunt, J. H. Cardellina, M. Schäffer, K. P. Gulden, G. Bringmann, A. Y. Lee, J. Clardy, G. François, M. R. Boyd, *J. Org. Chem.* **1994**, *59*, 6349–6355.
[57] S. Amand, M. Vallet, L. Guedon, G. Genta-Jouve, F. Wien, S. Mann, J. Dupont, S. Prado, B. Nay, *Org. Lett.* **2017**, *19*, 4038–4041.
[58] J. A. M. Vargas, D. P. Day, A. C. B. Burtoloso, *Eur. J. Org. Chem.* **2021**, *2021*, 741–756.
[59] R. J. Mayer, M. Breugst, N. Hampel, A. R. Ofial, H. Mayr, *J. Org. Chem.* **2019**, *84*, 8837–8858.
[60] E. Fuhrmann, J. Talbiersky, *Org. Process Res. Dev.* **2005**, *9*, 206–211.
[61] A. R. Massah, M. Mosharafian, A. R. Momeni, H. Aliyan, H. J. Naghash, M. Adibnejad, *Synth. Commun.* **2007**, *37*, 1807–1815.
[62] W. T. Wu, L. Zhang, S. L. You, *Chem. Soc. Rev.* **2016**, *45*, 1570–1580.
[63] F. C. Pigge, *Chem. Int.* **2018**, *40*, 42–45.
[64] S. P. Roche, J. A. Porco, *Angew. Chem. Int. Ed.* **2011**, *50*, 4068–4093.

[65] C. X. Zhuo, W. Zhang, S. L. You, *Angew. Chem. Int. Ed.* **2012**, *51*, 12662–12686.
[66] Q. Ding, Y. Ye, R. Fan, *Synth.* **2013**, *45*, 1–16.
[67] S. E. Lewis, in *Asymmetric Dearomatization React.*, **2016**, pp. 279–346.
[68] W. Sun, G. Li, L. Hong, R. Wang, *Org. Biomol. Chem.* **2016**, *14*, 2164–2176.
[69] R. Kumar, F. V. Singh, N. Takenaga, T. Dohi, *Chem. Asian J.* **2022**, *17*, e202101115.
[70] D. Magdziak, S. J. Meek, T. R. R. Pettus, *Chem. Rev.* **2004**, *104*, 1383–1429.
[71] B. Chen, C. Y. He, W. D. Chu, Q. Z. Liu, *Org. Chem. Front.* **2021**, *8*, 825–843.
[72] S. Quideau, L. Pouységu, D. Deffieux, *Synlett* **2008**, 467–495.
[73] S. Quideau, L. Pouységu, P. A. Peixoto, D. Deffieux, in *Hypervalent Iodine Chem.* (Ed.: T. Wirth), Springer, Cham, **2016**, pp. 25–74.
[74] A. Wu, Y. Duan, D. Xu, T. M. Penning, R. G. Harvey, *Tetrahedron* **2010**, *66*, 2111–2118.
[75] D. Magdziak, A. A. Rodriguez, R. W. Van De Water, T. R. R. Pettus, *Org. Lett.* **2002**, *4*, 285–288.
[76] N. Lebrasseur, J. Gagnepain, A. Ozanne-Beaudenon, J. M. Léger, S. Quideau, *J. Org. Chem.* **2007**, *72*, 6280–6283.
[77] J. An, M. Bandini, *Eur. J. Org. Chem.* **2020**, 4087–4097.
[78] C.-X. Zhuo, S.-L. You, *Angew. Chemie* **2013**, *125*, 10240–10243.
[79] J. Hu, S. Pan, S. Zhu, P. Yu, R. Xu, G. Zhong, X. Zeng, *J. Org. Chem.* **2020**, *85*, 7896–7904.
[80] C. Zheng, S. L. You, *Chem* **2016**, *1*, 830–857.
[81] R.-Q. Xu, P. Yang, H.-F. Tu, S.-G. Wang, S.-L. You, *Angew. Chemie* **2016**, *128*, 15361–15365.
[82] H.-J. Zhang, Q. Gu, S. L. You, *Org. Lett.* **2020**, *22*, 3297−3301.
[83] M. T. Peruzzi, S. J. Lee, M. R. Gagné, *Org. Lett.* **2017**, *19*, 6256–6259.
[84] J. An, A. Parodi, M. Monari, M. C. Reis, C. S. Lopez, M. Bandini, *Chem. Eur. J.* **2017**, *23*, 17473–17477.
[85] L. Ding, W. T. Wu, L. Zhang, S. L. You, *Org. Lett.* **2020**, *22*, 5861–5865.
[86] Y. Li, Z. Tang, J. Zhang, L. Liu, *Chem. Commun.* **2020**, *56*, 8202–8205.
[87] Y. Yu, Z. Zhang, A. Voituriez, N. Rabasso, G. Frison, A. Marinetti, X. Guinchard, *Chem. Commun.* **2021**, *57*, 10779–10782.
[88] D. J. Gorin, F. D. Toste, *Nature* **2007**, *446*, 395–403.
[89] M. Pernpointner, A. S. K. Hashmi, *J. Chem. Theory Comput.* **2009**, *5*, 2717–2725.
[90] Z. Lu, T. Li, S. R. Mudshinge, B. Xu, G. B. Hammond, *Chem. Rev.* **2021**, *121*, 8452–8477.
[91] K. Hashmi, A. Stephen, *Chem. Rev.* **2007**, *107*, 3180–3211.
[92] W. T. Wu, R. Q. Xu, L. Zhang, S. L. You, *Chem. Sci.* **2016**, *7*, 3427–3431.
[93] J. An, L. Lombardi, S. Grilli, M. Bandini, *Org. Lett.* **2018**, *20*, 7380–7383.
[94] B. Yang, X. Zhai, S. Feng, Z. Shao, *Org. Chem. Front.* **2018**, *5*, 2794–2798.
[95] B. Yang, X. Zhai, S. Feng, D. Hu, Y. Deng, Z. Shao, *Org. Lett.* **2019**, *21*, 330–334.
[96] M. A. Lovchik, A. Goeke, G. Frater, *Tetrahedron Asymmetry* **2006**, *17*, 1693–1699.
[97] S. Enthaler, A. Company, *Chem. Soc. Rev.* **2011**, *40*, 4912–4924.
[98] T. Yamaguchi, E. Yamaguchi, N. Tada, A. Itoh, *Adv. Synth. Catal.* **2015**, *357*, 2017–2021.
[99] N. Tezuka, K. Shimojo, K. Hirano, S. Komagawa, K. Yoshida, C. Wang, K. Miyamoto, T. Saito, R. Takita, M. Uchiyama, *J. Am. Chem. Soc.* **2016**, *138*, 9166–9171.
[100] J. L. Röckl, D. Pollok, R. Franke, S. R. Waldvogel, *Acc. Chem. Res.* **2020**, *53*, 45–61.

[101] Y. Takahira, M. Chen, Y. Kawamata, P. Mykhailiuk, H. Nakamura, B. K. Peters, S. H. Reisberg, C. Li, L. Chen, T. Hoshikawa, T. Shibuguchi, P. S. Baran, *Synlett* **2019**, *30*, 1178–1182.
[102] H. G. Roth, N. A. Romero, D. A. Nicewicz, *Synlett* **2016**, *27*, 714–723.
[103] A. A. Serdyuk, M. G. Kasianchuk, I. A. Opeida, *Russ. J. Phys. Chem. A* **2010**, *84*, 391–394.
[104] D. Villemin, M. Hachémi, M. Hammadi, *J. Chem. Res. - Part S* **2003**, 260–261.
[105] A. A. Serdyuk, A. A. Abakumov, I. V. Kapitanov, M. G. Kasianczuk, I. A. Opeida, *Russ. J. Phys. Chem. A* **2013**, *87*, 1470–1473.
[106] N. Kornblum, R. Seltzer, P. Haberfield, *J. Am. Chem. Soc.* **1963**, *85*, 1148–1154.
[107] K. Watanabe, N. Yamagiwa, Y. Torisawa, *Org. Process Res. Dev.* **2007**, *11*, 251–258.
[108] O. O. Kovalenko, H. Adolfsson, *Chem. - A Eur. J.* **2015**, *21*, 2785–2788.
[109] S. Omar, R. Abu-Reziq, *J. Phys. Chem. C* **2014**, *118*, 30045–30056.
[110] R. J. Abraham, B. Bardsley, M. Mobli, R. J. Smith, *Magn. Reson. Chem.* **2005**, *43*, 3–15.
[111] F. R. Wuest, M. Berndt, *J. Label. Compd. Radiopharm.* **2006**, *49*, 91–100.
[112] J. Betz, W. Bauer, *J. Am. Chem. Soc.* **2002**, *124*, 8699–8706.

# Acknowledgements

This work was conducted in the Department of Chemistry and Biotechnology of the School of Science at Tallinn University of Technology with collaborators from the Van't Hoff Institute for Molecular Sciences (HIMS) at the University of Amsterdam and from Micro Flow Chemistry & Synthetic Methodology at the Eindhoven University of Technology. This work was financially supported by the European Regional Development Fund and the programme Mobilitas Pluss (Grant No MOBTP180), the Estonian Ministry of Education and Research (Grant No's PRG 1031, PRG657, IUT19-32, SSGF22006) and the Centre of Excellence in Molecular Cell Engineering (2014-2020.4.01.15-0013). This work was partially supported by the ASTRA "TUT Institutional Development Programme for 2016-2022" Graduate School of Functional Materials and Technologies (2014-2020.4.01.16-0032).

I thank my supervisor, Prof. Margus Lopp for giving me an opportunity to do research in his lab. I thank Karolin and Anne for teaching me the basics of working in an organic chemistry lab. I am very grateful to my co-supervisor, Dr. Maksim Ošeka. You understood my background and took me under your supervision. You showed me how cool electro- and flow chemistry can be and believed in me even when I did not believe in myself. I am thankful that you gave me an opportunity and put up with my questions and Yoda-like writing style. I am also grateful to Prof. Tõnis Kanger for his support. I would like to thank Dr. Kadri Kriis for reviewing my thesis and giving very useful feedback.

I would like to thank all of my present and former co-workers from the third and fourth floors. I would especially like to thank the library gang: Kristin for always listening, understanding and giving me ideas; Aleksandra for being my desk mate, giving me chocolates and candies, and explaining organic chemistry to me; Nastja for helping me with article revision; Estelle for having the patience to listen to all of my funny and sad stories; and Harry for being curious about my experiments and hobbies. I also have to mention our former gang members: Dmitri for generating new ideas and always providing nice compliments, and Mariliis for being compassionate and knowing what it meant to lose at Ligretto. Also, I would like to thank Kaarel for all his weird jokes and for explaining sugars to me, and Nele for being the coolest travel buddy and a good friend.

I am grateful to my friends and course mates from my bachelor studies: Silja, Annela and Monika. I am the first to complete my PhD studies but I would not be the last. I believe in you girls and in a few years, we can call ourselves the "doktoriplixid". I am very grateful to my best friend Marit for always listening and all the time we spent together. Our husbands will soon have to call us Doctor, because we are almighty.

I am thankful to my parents and sister, who have supported me in my studies even though they probably still do not understand much about my profession. You were there for me during the darkest times, when it felt like everything was falling apart. I have now shown that all of your support was not wasted and if you are still trying to figure out what I am, the short answer is: a chemist.

I am most grateful to my husband Renee, who has been there for me through all the years of my studies from the beginning of my bachelor days to the end of my doctoral studies. The things I have had to do, to reach this point were beyond my imagination and you were there for me. From now on, you can call me Doctor Kooli.

# Abstract
# Sustainable Synthesis and Dearomatization of Oxygen-containing Aromatic Compounds

Oxygen-containing aromatic motifs are found in various bioactive compounds and natural products. Moreover, they are common structural units in different synthetic polymers, and are valuable building blocks for synthesis both in academia and industry. The synthesis of hydroxylated arenes often requires either toxic oxidants or transition-metal catalysts, which makes it generally unsustainable. Therefore, there is a need for more environmentally friendly methods. Electrochemistry is one of the highly attractive alternatives. Electricity from sustainable sources (solar, wind and hydro power) can be used as a traceless and non-toxic reagent, which makes synthesis more sustainable and suitable for future needs. Electrochemistry combined with continuous-flow technology allows to scale-up reactions easily, which closes the gap between academia and industry.

The hydroxylation of arenes with TFA under electrochemical conditions has been studied before, but the studies were limited to electron-poor and neutral molecules and the yields were low or not isolated at all. Herein, we report the hydroxylation of various electron-rich arenes using an electrochemical approach combined with the continuous-flow technique. The used electrodes are readily available and inexpensive (graphite and stainless steel). Hydroxylated arenes were isolated with yields up to 68% and without the use of any toxic additives or transition-metal catalysts.

Hydroxylated arenes can be further modified to produce more valuable products. One of the derivatization possibilities is to dearomatize phenols and naphthols in alkylation. Usually, transition-metal catalysts are required for dearomatization reactions. Thus, the transition-metal-free dearomatization of oxygen-containing aromatic compounds remains rather unexplored.

We developed a simple method to dearomatize phenols and naphthols in the course of *C*-alkylation with various alkyl halides in high yields (up to 90%). The alkylation reaction was regioselective and proceeded mostly to the second position. We discovered that usually additives (ether or alcohol) supported the reaction. The best results were achieved when cyclopentyl methyl ether or *L*-menthol was used as an additive.

The results of the work open up new opportunities for the electrochemical hydroxylation of electron-rich arenes in the continuous-flow mode. Also the selective derivatization of phenols and naphthols by dearomative alkylation in good yields is possible in many cases. All of these reactions were carried out without any transition-metal catalysts.

# Lühikokkuvõte
# Hapnikku sisaldavate aromaatsete ühendite jätkusuutlik süntees ja dearomatiseerimine

Paljudes bioaktiivsetes ning looduslikes ühendites leidub hapnikku sisaldavaid aromaatsete ühendite fragmente. Veelgi enam, need struktuuriühikud esinevad ka erinevates sünteetilistes polümeerides. Fenoolid ja naftoolid on samuti väga laialt kasutatavad väärtuslikud lähteained keemilises sünteesiks nii akadeemilises uurimises kui ka tööstuses. Selleks, et sünteesida hüdroksüleeritud areene, kasutatakse tihti mürgiseid oksüdeerijaid või siirdemetallilisi katalüsaatoreid, mis muudab sellised reaktsioonid toime tõttu keskkonnale jätkusuutmatuks. Seetõttu on roheliste ja keskkonnasõbralike meetodite järele suur nõudlus. Elektrokeemia on üheks selliseks suurepäraseks alternatiiviks. Elektrit, mis pärineb jätkusuutlikest allikatest (päikese-, tuule- ja hüdroenergia) on võimalik kasutada jääkideta mitte toksilise reagendina, mis muudab sünteesi jätkusuutlikumaks ning sobivaks meie tuleviku vajadustele. Elektrokeemia kombineeritult läbivoolu tehnoloogiaga lubab meil läbi viia reaktsioone suurtes kogustes ning see omakorda aitab lähendada akadeemilisi teadusuuringuid tööstusele.

Elektrokeemilist areenide hüdroksüleerimist trifluoroäädikhappega on uuritud juba varem, kuid siiski on reaktsiooni ulatus olnud piiratud kas elektronvaeste või neutraalsete molekulidega ning saagised on olnud väikesed või pole neid üldse näidatud. Elektrokeemilisel hüdroksüleerimisel on aga elektronrikkad areenid jäänud vaeslapse rolli. Selles töös me näitame kuidas on võimalik, kasutades elektrokeemilist lähenemist koos läbivoolu tehnikaga, hüdroksüleerida erinevaid elektronrikkaid areene. Elektrokeemiliseks reaktsiooniks kasutati lihtsasti kättesaadavaid ning mõistliku hinnaga elektroode (grafiit ja roostevaba teras). Hüdroksüleeritud areenid isoleeriti heade saagistega (kuni 68%), kusjuures ei kasutatud ühtegi toksilist lisandit ega siirdemetallilist katalüsaatorit.

Selleks, et saada vajalikke ühendid saab hüdroksüleeritud areene edasi modifitseerida. Üks muundamise võimalustest on fenoolide ja naftoolide dearomatiseerimine. Tavaliselt kasutatakse dearomatiseerimise reaktsioonides siirdemetallilist katalüsaatorit. Samas on hapnikku sisaldavate aromaatsete ühendite dearomatiseerimine ilma siirdemetallilise katalüsaatori kasutamiseta jäänud uurimata.

Me oleme välja töötanud lihtsa meetodi fenoolide ja naftoolide *C*-alküleerimiseks erinevate alküülhaliididega, saades heade kuni kõrge saagisega (kuni 90%) alküleeritud dearomatiseerituid ühendeid. Alküleerimisereaktsioonid on regioselektiivsed andes eelistatult reaktsiooni teise positsiooni süsinikuga. Samuti leidsime, et reaktsiooni toetavad donoorsed lisandid (eetrid või alkoholid), tõstes reaktsiooni saagiseid. Parimad tulemused saadi tsüklopentüülmetüüleetrit või *L*-mentooli kasutamisel lisandina.

Saadud tulemused avavad uusi võimalusi elektronrikaste areenide hüdroksüleerimiseks elektrokeemiliselt läbivoolu reaktorites ning fenoolide ja naftoolide alküleerivaks dearomatiseemiseks nende derivaatide saamisel. Üheski läbiviidud reaktsioonis ei kasutatud siirdemetallilisi katalüsaatoreid.

# Appendix 1

**Publication I**

E. Lopušansakaja, A. Kooli, A. Paju, I. Järving, M. Lopp, Towards *ortho*-selective electrophilic substitution/addition to phenolates in anhydrous solvents. *Tetrahedron* **2021**, *83*, 131935

Tetrahedron 83 (2021) 131935

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

# Towards *ortho*-selective electrophilic substitution/addition to phenolates in anhydrous solvents

Eleana Lopušanskaja, Anni Kooli, Anne Paju, Ivar Järving, Margus Lopp*

*Department of Chemistry and Biotechnology, School of Science, Tallinn University of Technology, Akadeemia Tee 15, 12618, Tallinn, Estonia*

ARTICLE INFO

*Article history:*
Received 13 November 2020
Received in revised form
5 January 2021
Accepted 7 January 2021
Available online 30 January 2021

*Keywords:*
Li-phenolates
Electrophilic addition/substitution
ortho-Selective alkylation

ABSTRACT

Alkyl-substituted Li-phenolates with BnBr in water solution lead to a mixture of *o*- and *p*-Bn-substituted phenols together with a substantial amount of phenol Bn ether. In CPME, and especially in toluene with 1−2 equivalents of ether or alcohol additives, *ortho*-selective alkylation is achieved. In the case of *o,o,p*-tri- and *o,o*-di-substituted phenols dearomatization occurs affording *o*-Bn-substituted alkyl cyclohexadienones with yields up to 92% with an *o*/*p* ratio up to 90/1.



## 1. Introduction

Phenols are known electron-rich aromatic compounds with nucleophilicity at *C*- and *O*-nucleophilic sites, giving in the reaction with electrophiles both, *C*- and *O*-alkylated products. Phenolates are more reactive with increased reactivity towards electrophiles in *C*- and *O*-alkylation reactions [1]. With unsubstituted phenolates the electrophilic reactions proceed in a common way leading to the aromatic substitution and Williamson products [2]. With substituted phenolates the electrophilic addition reactions may lead to dearomatization, resulting in cyclic dienones [3]. These structures are of great synthetic interest being intermediates for the synthesis of various bioactive and natural products [4].

The dearomatization of phenols has been well studied using oxidative strategies with hypervalent iodine(III) [5] and with Rh and Ru catalysts under oxidative conditions [6]. However, simple electrophilic alkylation reactions have been almost neglected because of low *C*-/*O*-alkylation selectivity, with *O*-alkylation dominating [7]. Selective *O*-alkylations have been achieved by using quaternary ammonium salts [8] while selective mono-*p*- and *o*-alkylation has been achieved only in rare cases [9]. According to early studies by Kornblum et al., in strong hydrogen-bonding solvents such as water, phenol and fluorinated alcohols substantial amounts of C-alkylated products can form [10]. So, usually alkylations have been performed with Na- and K-phenolates in water solution affording alkylphenols and cyclohexadienones in moderate yields [11]. There are only a few examples of using, Li, Mg or Ti phenolates [12].

In the present study we tried to expand borders of electrophilic *C*-alkylation of phenolates and find ways for chemo- and regioselective substitution/addition in phenolates.

## 2. Results/discussion

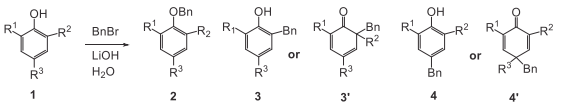
In order to obtain comparable data, we started with the alkylation of various unsubstituted and substituted Li-phenolates with benzyl bromide (BnBr) in a water solution of LiOH. The obtained results are presented in Table 1.

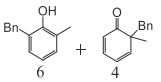
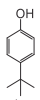
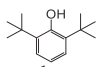
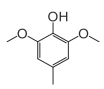
Unsubstituted phenol (**1a**) shows moderate reactivity in aqueous LiOH solution, giving predominantly *O*-alkylated product (46%), and almost equally low amount of *o*- and *p*-substituted products. At used reaction conditions 28% of unreacted starting phenol **1a** was recovered after the reaction (Table 1, entry 1). Mono-substituted phenols show different activity and regioselectivity, depending on the substituents and their bulkiness. Introduction of an *ortho*-substituent, even not a bulky one, such as methyl, substantially reduces a relative amount of *O*-alkylated product. So, the amount of *O*-alkylation decreased from 46% for unsubstituted **1a** (Table 1, entry 1; **2a**) to 25% for *o*-Me phenol **1b** (Table 1, entry 2; **2b**) and to 16% for *tert*-butyl phenol **1d** (**2d**, Table 1, entry 4). Thus, *o*-Me phenol afforded mostly *C*-alkylation with *C*/*O*-alkylation ratio 1.7/1 (sum of **3b** + **3b'**+ **4b** to **2b**), while *o*/*p* ratio (**3b** + **3b'** to **4b**)

* Corresponding author.
*E-mail address:* margus.lopp@taltech.ee (M. Lopp).

https://doi.org/10.1016/j.tet.2021.131935
0040-4020/

**Table 1**
Alkylation of phenols with benzyl bromide in aqueous LiOH solution[a].




| Entry | Phenol No | Recovered 1 (%) | Yield of 2 (%) | Yield of *o*-product, % | Yield of *p*-product, % |
|---|---|---|---|---|---|
| | | | | 3 | 4 |
| 1 |  **1a** | 28 | 46 | 7 | 8 |
| 2 |  **1b** | 19 | 25 |  6 + 4 | 32 |
| 3 |  **1c** | 32 | 35 | 13 | – |
| 4 |  **1d** | 41 | 16 |  6 | 19 |
| 5 |  **1e** | 38 | 58 | 4 | – |
| 6 |  **1f** | 8 | 11 | 17 | 64 |
| 7 |  **1g** | 100 | – | – | – |
| 8 |  **1h** | 14 | 8 | 44 | 32 |
| 9 |  **1i** | 21 | 33 | 45 | – |
| 10 |  **1j** | 86 | – |  6 | – |
| 11 |  **1k** | 51 | 14 | 27 | 5 |
| 12[b] | **1k** | 19 | 15 | 44 | 4 |
| 13[c] | **1k** | 51 | 15 | 28 | 4 |
| 14[d] | **1k** | 37 | 21 | 32 | 5 |
| 15[e] | **1k** | 71 | 9 | 17 | 1 |

[a] Reaction conditions: Phenol (1 mmol), BnBr (1.2 mmol), 1 M LiOH (1 mL), water (1 mL), room temperature, overnight; yields of isolated products are presented.
[b] No additional water added.
[c] NaOH as an alkali, no additional water added.
[d] 0.2 mL MeOH added. [e]No additional water added, 1 mL of $CF_3CH_2OH$ added.

was 1/3.2 in favour to *p*-product. It is interesting to note that a quaternary *o*-substitution at Me group **3b'** was almost equal to that of substitution to a free *o*-position **3b** (4 and 6%, respectively).

Substituents in the *para*-position (Table 1, entries 3 and 5) did not support *C*-alkylation affording *O*-alkylation product predominantly with a **3c/2c** ratio of 1/2.7 for phenol **1c** and 1/14.5 for phenol **1e**.

Of the *o*-disubstituted phenols **1f** and **1g**, only *o*-di-Me phenol **1f** reacted with BnBr, showing a good *C*/*O* selectivity (Table 1, entries 6 and 7). With *o*-di-Me phenol **1f** the *o*-addition reaction with dearomatization occurred, affording quaternary *o*-Bn-alkylated product **3f** in considerable yield (17%). The *para*-product was dominant with 64% yield. The yield of the *O*-alkylation product **2f** was only 11% which was only half of that for *o*-Me phenol **2b**.

The tri-Me-substituted phenol **1h** revealed a good reactivity but low regioselectivity affording dearomatized quaternary products **3h** (a chiral structure) and **4h** in 44% and 32% yield respectively. Also, with phenol **1h** a good ratio of *C*-and *O*-alkylation with only 8% of ether **2h** was observed. Trisubstituted *o*-dimethoxy-*p*-Me phenol **1i** also reacted smoothly, affording exclusively *ortho*-*C*-alkylation product **3i** in 45% yield, although together with 33% of the *O*-alkylation product **2i**.

The *t*-butyl group in the *ortho*-position (*o*-Me-*o*-*t*Bu-phenol **1j**) considerably reduced the reactivity, affording the addition to *ortho*-carbon at the Me group (ketone **3j**) only in 6% yield, while the initial phenol **1j** remained mostly unreacted (Table 1, entry 10). The trisubstituted *o*,*o*-diMe-*p*-*t*Bu-phenol **1k** was more reactive affording the *ortho*-addition product **3k** in 27% yield and surprisingly, also quaternary *p*-product **4k** in 5% yield (Table 1, entry 11). *O*-alkylation product ether **2k** was formed in 14% yield.

We observed that phenols with large *t*-Bu-substituents **1d, 1e**, **1j** and **1k** were less reactive, leaving a considerable amount of substrate unreacted (Table 1, entries 4, 5 and 10–15). 2,6-Di *t*-Bu phenol **1g** did not react at all (Table 1, entry 7). We believe that the low reactivity in the case of phenol **1k** in water solution was also caused by the low solubility of that Li-phenolate in alkaline water. So, we carried out some additional experiments with **1k** to clarify the matter.

First, we increased the concentration of Li-phenolate **1k** in the reaction mixture by reducing the water content (Table 1, entry 12). Only 19% of **1k** remained unreacted because of the increased solubility of phenolate. The sum of the alkylated products increased from 46% to 63% (calculated from Table 1, entries 11 and 12). Under these reaction conditions, the *o*/*p* ratio of alkylation increased considerably from 5.4/1 to 11/1. Also, the ratio of *C*/*O*-alkylation increased from 2.3/1 to 3.2/1.

Using NaOH instead of LiOH slightly improved the solubility of **1k** but resulted in low reactivity (51% of **1k** remained unreacted), and a low *C*/*O*-alkylation ratio (only 2.1/1). However, a good *o*/*p* ratio was observed (7/1; Table 1, entry 13).

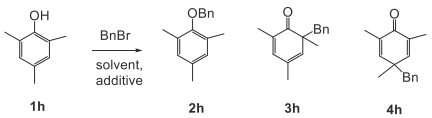
To further increase the homogeneity of the reaction medium, 0.2 mL MeOH (~10% from solvent) was added and the reaction was performed according to the usual conditions (footnote[d] in Table 1). We observed that MeOH had no positive effect on the *C*/*O*-alkylation, nor on the *o*/*p* ratio (Table 1, entry 14).

When fluorinated alcohol $CF_3CH_2OH$ was used as an additive, the reaction selectivity changed. Thus, *ortho*-selectivity increased drastically to *o*/*p* > 17/1, together with moderate *C*/*O*-alkylation selectivity. However, the reactivity of phenol **1k** remained low, with 71% of the starting phenol **1k** recovered (Table 1, entry 15). The negative effect the additive was the reactivity of $CF_3CH_2OH$ itself in the Williamson reaction towards BnBr consuming the reagent.

The main conclusion from the obtained results was that the reaction is very sensitive to phenol substitutes and the low solubility of some alkyl phenolates in water solution is a serious problem, causing low yield and selectivity. So, we turned to non-aqueous solutions using *n*-BuLi to generate the phenolate. Trimethyl phenol **1h** was selected as a model structure in the reaction with BnBr.

First, *n*-BuLi was used in hexane. To ensure the solubility of the

**Table 2**
Addition of BnBr to 2,4,6-trimethylphenol **1h** in non-aqueous conditions[a].




| Entry | n-BuLi (equiv) | Solvent | Additive (equiv) | Temperature (°C) | Yield, 3(%) | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | 1 h | 2 h | 3 h | 4 h |
| 1[b] | 1 | CPME | – | r.t. | 85 | 0.2 | 5 | |
| 2[b] | 2 | CPME | – | r.t. | 51 | 1 | 13 | 1 |
| 3[b] | 2.2 | CPME | – | 50 | 27 | 2 | 44 | 1 |
| 4[b] | 2.2 | CPME | – | 80 | | 10 | 84 | 2 |
| 5 | 2.2 | toluene | – | 80 | 57 | 1 | 38 | 3 |
| 6 | 2.2 | toluene | CPME; 1 | 80 | 19 | 2 | 71 | 3 |
| 7 | 1.1 | toluene | CPME; 2 | 80 | 25 | 3 | 66 | 2 |
| 8 | 2.2 | toluene | CPME; 2 | 80 | 9 | 3 | 79 | 3 |
| 9 | 2.2 | toluene | CPME; 4 | 80 | 45 | 2 | 43 | 1 |
| 10 | 2.2 | toluene | MTBE; 1 | 80 | 33 | 2 | 62 | 2 |
| 11 | 2.2 | toluene | anisole; 2 | 80 | 21 | 1 | 63 | 3 |
| 12 | 1.1 | toluene | *t*-BuOH; 1 | 80 | – | 15 | 83 | 1 |
| 13 | 2.2 | toluene | (R)-*s*-BuOH; 1 | 80 | – | 8 | 90 | 1 |
| 14 | 1.3 | toluene | (R)-*s*-BuOH; 0.2 | 80 | 15 | 4 | 63 | 2 |
| 15 | 2.2 | toluene | *n*-BuOH; 1 | 80 | 7 | 3 | 87 | 2 |
| 16 | 2.2 | toluene | *L*-Menthol; 1 | 80 | – | 5 | 82 | 12 |
| 17 | 2.2 | toluene | *i*-PrOH; 1 | 60 | – | 5 | 92 | 2 |
| 18 | 2.2 | toluene | MeOH; 1 | 60 | 10 | 1 | 86 | 2 |

[a] Conditions: 1 mmol phenol **1h**, solvent, n-BuLi, additive, overnight at given temperatures.
[b] Hexane changed to CPME after *n*-BuLi was added to phenol; yields are determined by $^1$H NMR analysis of the crude reaction mixture.

phenolates in the reaction medium hexane was replaced by cyclopentyl methyl ether (CPME) which was used earlier in the case of naphthols [13].

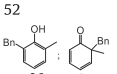
The obtained results are presented in Table 2 (entries 1–4). By using 1 equivalent of *n*-BuLi at room temperature the reaction was very slow, resulting predominantly in quaternary *ortho*-product **3h** in 5% yield, with 85% of unreacted substrate **1h** left. A higher yield of the addition product **3h** was obtained with 2 equivalents of *n*-BuLi (Table 2, entry 2). Higher temperature substantially increased the yield of the product **3h**, from 13% at r.t., to 44% at 50 °C, and finally, to 84% at 80 °C. The increase in temperature slightly reduced the *C*/*O*-alkylation selectivity from 20/1 at 50 °C to 8.4/1 at 80 °C. Still, the *C*/*O*-selectivity was acceptable. The *o*/*p* selectivity remained excellent at all temperatures (*o*/*p* ratio at 80 °C > 40/1) (Table 2, entries 2–4).

In order to simplify the experimental procedure and avoid solvent change, toluene as a solvent was introduced together with the use of *n*-BuLi solution in toluene. The first attempt in neat toluene affording good *C*/*O*-alkylation selectivity but moderate reactivity encouraged us to continue in this direction. (Table 2, No 5). To improve the solubility of the Li-phenolate in the reaction medium, different additives to the toluene were tested. First, CMPE, which was a good solvent for alkylation was used as a toluene additive. With 1 equivalent of CMPE to phenolate, an almost selective *ortho*-addition reaction was observed with high *C*/*O*-alkylation ratio (35/1), and with only 19% of the starting compound **1h** recovered (Table 2, entry 6). To find the optimal amount of the additive, experiments with 2 and 4 equivalents of CMPE were performed. The best result was achieved by using 2.2 equivalents of *n*-BuLi in toluene with 2 equivalents of CPME additive, after the overnight reaction at 80 °C, with only 9% of substrate **1h** unreacted and with 79% of *ortho*-benzyl dearomatized product **3h** formed. The ether **2h** and *para*-addition product **4h** were observed in minor amounts (Table 2, entry 8). The reaction was quite sensitive to the reagents' ratio: reducing the amount of *n*-BuLi to 1.1 equivalents in respect to phenol caused a considerable drop in both, reactivity and selectivity; increasing the amount of CPME additive to 4 equivalents reduced the reactivity of phenolate and increasing the amount of unreacted **1h** to 45% (Table 2, entry 9).

We also checked the effect of methyl *tert*-butyl ether (MTBE) and anisole additives to the alkylation. We found that they both also acted as selective catalysts in the electrophilic addition of BnBr to phenolate, being slightly less active than CPME (Table 2, entries 10 and 11).

To our surprise, different alcohol additives also had a positive effect on BnBr addition to Li-phenolate in toluene. All of the used alcohols, primary, secondary and tertiary butanols in 1 equivalent quantity, revealed similar high activity and selectivity to the reaction, affording *ortho*-addition product in >80% yield. Of them, *n*-BuOH was the most selective and *s*-BuOH the most active (Table 2,

**Table 3**
Electrophilic reaction of various phenolates in non-aqueous conditions [a].

| Entry | Phenol | *n*-BuLi (eq) | BnBr (eq) | 2 (%) | 3 (%) | 4 (%) | 5 (%) |
|---|---|---|---|---|---|---|---|
| 1 |  **1a** | 2 | 2 | 5 | 39 | 2 |  5 |
| 2[b] | **1a** | 1.2 | 2 | 10 | 52 | 3 | 8 |
| 3[b] |  **1b** | 1.5 | 2 | 4 |  25 ; 5 | 3 | – |
| 4 |  **1c** | 1.5 | 2 | 2 | 50 | – |  5 |
| 5 |  **1j** | 2.2 | 1.2 | 1 | 20 | – | – |
| 6[c] | **1f** | 2.2 | 1.2 | 27 | 56 | 1 | |
| 7 |  **1h** | 2.2 | 1.2 | 3 | 79 | 3 | – |
| 8 |  **1i** | 2.2 | 1.2 | 42 | – | – | – |
| 9 |  **1j** | 2.2 | 1.2 | – |  35 | – | – |
| 10 |  **1k** | 2.2 | 1.2 | 3 | 45 | – | – |

[a] Conditions: CPME 2 eq, temperature 80 °C; yields of isolated compounds are presented.
[b] temperature 90 °C.
[c] Reaction conditions: CPME as that for Table 2, entry 4.

entries 12–15). The chiral ligands (*R*)-*sec*-butanol and *L*-menthol both afforded chiral quaternary addition product **3h** in high yields (90 and 88% respectively; Table 2, entries 13, 16). However, to our disappointment, these were in a racemic form. Even methanol and isopropanol in 1 equivalent amounts revealed high activity and selectivity as catalysts in a phenolate alkylation reaction (Table 2, entries 17 and 18).

With 2 equivalents of *n*-BuLi, the phenol **1h** turned to Li-phenolate anion with one equivalent of *n*-BuLi, and the second equivalent turned the alcohol additive to an alcoholate. The alcoholates catalyse the selective electrophilic *C*-addition on BnBr to the phenolate.

We re-investigated the electrophilic substitution/additions of BnBr to various phenolates in non-aqueous conditions with CPME additive. The obtained results are presented in Table 3. The reaction conditions for individual phenolates were not optimized.

As expected, less substituted phenol derivatives revealed lower reactivity. So, to overcome this, more BnBr was added to those phenols.

The unsubstituted phenol **1a**, which in a LiOH solution with BnBr led to only 7% of *ortho*-substitution and mainly the *O*-alkylation with formation of **2a** in 46% yield (Table 1, entry 1), in a non-aqueous medium resulted mainly in *ortho*-substitution product **3a** in 39% yield at 80 °C, and in 52% yield at 90 °C, with the formation of ether **2a** in ~10%. The regioselectivity of the substitution was also satisfactory, with *p*- and *o*,*o*-disubstitution products observed only in ~10% yield in total (Table 3, entries 1 and 2).

The *o*-Me phenol **1b** resulted in 25% of the *ortho*-substitution product **3b** at 90 °C. It is interesting to note that the yield of the quaternary *ortho*-addition product **3b'** was higher than that of the *para*-substitution product **4b** (5 vs 3%; Table 3, entry 3). This was different from that observed in water solution, where the *para*-substitution product **4b** together with *O*-alkylation product **2b**, dominated (Table 1, entry 2).

*p*-Me phenol **1c** afforded almost exclusively the *ortho*-substituted product **3c** with a small amount of ether **2c.** No quantity of the quaternary *para*-product **4c** was observed. (Table 3, entry 4).

Disubstituted 2,6-diMe-phenol **1f** which reacts quite smoothly in water solution affording mainly *para*-product **4f** in 64% yield (Table 1, entry 6), in the non-aqueous conditions afforded only quaternary *ortho*-product **3f** in 20% yield, with only a very small amount of ether **2f** (Table 3, entry 5). At the same time, in CPME the **3f** was formed in 56% yield, with a substantial amount of ether **2f** (27%; Table 3, entry 6).

Comparing the benzylation of Li-phenolate of 2,4,6-tri-Me phenol **1h** in a non-aqueous environment and in a water solution, we observed almost exclusive *ortho*-addition affording quaternary dearomatized **3h** in good yield (79%; Table 3, entry 7), while in water-LiOH solution *ortho*- and *para*-addition products were formed in almost equal amounts, in 44% and 32%, respectively (Table 1, entry 8). A remarkable difference in reactivities was also observed for 2,6-dimehoxy-4-mehyl phenol **1i**: in the LiOH water solution the *ortho*-product **3i** in 45% yield was formed, together with ether **2i** in 33% yield, while in the toluene solution with a CPME additive only ether **2i** was observed in a 42% yield, without any traces of other products (Table 3, entry 8). Phenol **1j** with a bulky *t*-Bu group in *ortho*-position almost failed to react in an alkali water solution because of solubility problems. In non-aqueous conditions, **1j** afforded mainly the quaternary *ortho*-product with Bn addition to Me-carbon **3j** in 35% yield, with only a trace amount of *p*-quaternary product **4j** (Table 3, entry 9). When the bulky *t*-Bu group was in *para*-position, the *ortho*-addition occurred in both media. In water solution the solubility of the substrate was a problem, and the yield was only 27% (Table 1, entry 11), while in the toluene solution the *ortho*-addition product **3k** was formed in 45% yield (Table 3, entry 10). In both cases the formation of ether was insignificant.

## 3. Conclusion

The alkylation of phenolates in non-aqueous conditions offers mainly *C*-alkylation, with the *C*/*O*-alkylation ratio usually >10/1. The *C*-alkylation is *ortho*-selective in up to 92% yield. Even in the case of unsubstituted phenol **1** the yield of *o*-Bn-phenol exceeded 50%. In the case of *o*,*o*,*p*-tri- and *o*,*o*-substituted phenols dearomatization occurs affording *o*-Bn-substituted alkyl cyclohexadienones with yields up to 92%, with an *o*/*p* ratio up to 90/1. The method is sensitive to phenol structure, therefore, optimal conditions separately for every phenolate may be needed. The substitution reaction is catalysed by ethers and by alcohols. The possibility of introducing asymmetric induction to the dearomatization reaction is currently under study.

## 4. Experimental section

$^{1}$H and $^{13}$C NMR spectra were recorded in deuterated solvents on a Bruker Avance USLA 400 spectrometer. Deuterated solvent peaks were used as references. 2D FT methods were used for the full assignment of $^{1}$H and $^{13}$C chemical shifts. High-resolution mass spectra were recorded with an Agilent Technologies 6540 UHD Accurate-Mass Q-TOF LC/MS spectrometer by using AJ-ESI ionization. IR spectra were recorded on a Bruker PMA 50 spectrometer. Precoated Merck silica gel 60 $F_{254}$ plates were used for TLC. Column chromatography was performed with 40–63 μm silica gel. The measured melting points obtained on a Boëtius (Nagema) instrument and are uncorrected. All reactions sensitive to oxygen or moisture were conducted under argon atmosphere in oven-dried glassware. Purchased chemicals and solvents were used as received. The petroleum ether fraction b.p. 40–60 °C was used. The yields of isolated compounds are presented; in Table 2 the yields were determined from $^{1}$H NMR analysis of the crude mixture.

### 4.1. General procedure A (GPA) for the dearomatization reaction in aqueous conditions

To an aqueous solution of 1 M LiOH (1 mL) on an ice bath phenol (1 mmol) was added and the mixture stirred for 15 min. Then water (1 mL) and BnBr (1.2 mmol) was added, the reaction mixture warmed up to room temperature and stirred overnight. To the reaction mixture water (5 mL) was added, pH adjusted to ~7 and the mixture was extracted with EtOAc. The combined organic layers were washed with brine and dried with phase separator or on $MgSO_4$ and filtered if necessary. Then solvent was removed with rotary evaporator and the products were obtained after flash chromatography on silica gel (petroleum ether/EtOAc).

### 4.2. General procedure B (GPB) for the dearomatization reaction in non-aqueous conditions

To solution of phenol (1 mmol) in a solvent under argon atmosphere n-BuLi (2.7 M in toluene; 0.82 mL; 2.2 mmol) was added dropwise. After addition of the additives BnBr (1.2 mmol) was applied. The reaction mixture was warmed up to 80 °C and stirred at this temperature overnight. After cooling water was added and the reaction mixture was extracted with EtOAc. The combined organic layers were washed with brine and dried with phase separator or on $MgSO_4$. The crude product solution was filtered if necessary, and then solvent was removed with rotary evaporator. The products were separated by flash chromatography on silica gel (petroleum ether/EtOAc).

### 4.3. General procedure C (GPC) for the dearomatization reaction in non-aqueous conditions

Phenol (1 mmol) was dissolved in hexane (3 mL) and n-BuLi (2.5 M in toluene; 0.88 mL; 2.2 mmol) was added dropwise under argon atmosphere and stirred for 15 min. Then hexane was removed with argon flow and CPME (1 mL) was added. To the obtained clear solution BnBr (1.2 mmol) was added, the reaction mixture warmed up to 80 °C and stirred overnight at this temperature. After cooling water was added and the reaction mixture was extracted with EtOAc. The combined organic layers were washed with brine and dried with phase separator or on $MgSO_4$. The crude solution was filtered if necessary and the solvent was removed with rotary evaporator. The products were separated by flash chromatography on silica gel (petroleum ether/EtOAc).

### 4.4. Characterisation of compounds

#### 4.4.1. Benzyloxybenzene (**2a**)

Following GPA gave **2a** (84 mg, 46%) after purification as a white solid; mp 36–37 °C; IR (KBr) $\nu_{max}$: 3035, 2907 2867 1599, 1586, 1498, 1468, 1455, 1378, 1300, 1247, 1171, 1079, 1030, 1013, 991, 916, 858, 745, 696 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.49–7.44 (m, 2H), 7.44–7.37 (m, 2H), 7.37–7.28 (m, 3H), 7.03–6.96 (m, 3H), 5.09 (s, 2H); $^{13}C$ NMR (101 MHz, $CDCl_3$) δ 158.9, 137.2, 129.6, 128.7, 128.1, 127.6, 121.1, 115.0, 70.0; HRMS (ESI): *m/z* $[M+Na]^+$ calculated for $C_{13}H_{12}O$ 207.0780, found 207.0776.

#### 4.4.2. 2-Benzylphenol (**3a**)

Following GPB product **3a** (96 mg, 52%) was obtained as a colourless oil; IR (neat) $\nu_{max}$: 3535, 3028, 2920, 1593, 1494, 1454, 1329, 1213, 1169, 1094, 1040, 936, 851, 754, 731, 698 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.31–7.27 (m. 2H), 7.23–7.18 (m, 3H), 7.14–7.10 (m, 2H), 6.89 (td, $J$ = 1.21, 7.49 Hz, 1H), 6.77 (d, $J$ = 8.27 Hz, 1H), 4.66 (s, 1H), 3.99 (s, 2H); $^{13}C$ NMR (101 MHz, $CDCl_3$): $\delta$ = 153.8, 140.0, 131.2, 128.81, 128.76, 128.0, 127.1, 126.5, 121.1, 115.8, 36.5; HRMS (ESI): *m/z* $[M-H]^-$ calculated for $C_{13}H_{12}O$ 183.0815, found 183.0816.

#### 4.4.3. 4-Benzylphenol (**4a**)

Following GPA **1p** (15 mg, 8%) was obtained after purification as a white solid; mp 77–79 °C; IR (KBr) $\nu_{max}$: 3223, 3021, 1600, 1511, 1493, 1454, 1379, 1243, 1175, 1102, 843, 785, 731, 698, 595 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.35–7.25 (m, 2H), 7.26–7.15 (m, 3H), 7.11–7.03 (m, 2H), 6.80–6.72 (m, 2H), 4.66 (s, 1H), 3.93 (s, 2H); $^{13}C$ NMR (101 MHz, $CDCl_3$) δ 153.9, 141.6, 133.6, 130.2, 129.0, 128.6, 126.1, 115.4, 41.1; HRMS (ESI): *m/z* $[M-H]^-$ calculated for $C_{13}H_{12}O$ 183.0815, found 183.0818.

#### 4.4.4. 2,6-Dibenzylphenol (**5a**)

Following GPB **5a** (21 mg, 8%) as a white solid was obtained; mp 28–29 °C; IR (KBr) $\nu_{max}$: 3559, 3062, 3027, 2924, 1602, 1494, 1452, 1252, 1186, 1079, 1030, 840, 735, 698 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.30–7.27 (m. 4H), 7.22–7.19 (m, 6H), 7.03 (d, $J$ = 7.52 Hz, 2H), 6.85 (dd, $J$ = 7.15, 7.89 Hz, 1H), 4.60 (s, 1H), 3.97 (s, 4H); $^{13}C$ NMR (101 MHz, $CDCl_3$): $\delta$ = 152.3, 139.8, 129.5, 128.82, 128.77, 127.3, 126.6, 120.8, 36.8; HRMS (ESI): *m/z* $[M-H]^-$ calculated for $C_{20}H_{18}O$: 273.1285, found 273.1300.

#### 4.4.5. 1-(Benzyloxy)-2-methylbenzene (**2b**)

Following GPA **2b** (49 mg, 25%) after purification as a colourless oil was obtained; IR (neat) $\nu_{max}$: 3031, 2927, 1602, 1495, 1454, 1380, 1312, 1289, 1243, 1191, 1122, 1051, 1026, 855, 750, 713, 696, 624, 441 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.50–7.45 (m, 2H), 7.43–7.38 (m, 2H), 7.37–7.30 (m, 1H), 7.21–7.15 (m, 2H), 6.90 (d, $J$ = 7.7 Hz, 2H), 5.10 (s, 2H), 2.31 (s, 3H); $^{13}C$ NMR (101 MHz, $CDCl_3$) δ 157.0, 137.7, 130.9, 128.6, 127.9, 127.2, 126.9, 120.7, 111.6, 70.0, 16.6; HRMS (ESI): *m/z* $[M+Na]^+$ calculated for $C_{14}H_{14}O$ 221.0937, found 221.0927.

#### 4.4.6. 2-Benzyl-6-methylphenol (**3b**)

Following GPB **3b** (50 mg, 25%) as a white solid was obtained; mp 46–47 °C; IR (KBr) $\nu_{max}$: 3565, 3026, 2920, 1594, 1494, 1470, 1453, 1324, 1263, 1197, 1084, 1030, 946, 833, 767,734, 699 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.30–7.26 (m. 2H), 7.23–7.18 (m, 3H), 7.02 (d, $J$ = 7.60 Hz, 1H), 6.98 (d, $J$ = 7.28 Hz, 1H), 6.80 (t, $J$ = 7.48 Hz, 1H), 4.60 (s, 1H), 3.98 (s, 2H), 2.21 (s, 3H); $^{13}C$ NMR (101 MHz, $CDCl_3$): $\delta$ = 152.3, 139.9, 129.4, 128.81, 128.78, 126.55, 126.49, 123.9, 120.5, 36.8, 16.0; HRMS (ESI): *m/z* $[M+H]^+[-H_2O]$ calculated for $C_{14}H_{14}O$ 181.1012, found 181.1008.

#### 4.4.7. 6-Benzyl-6-methylcyclohexa-2,4-dien-1-one (**3b'**)

Following GPA **3b'** (8 mg, 4%) after purification as a green oil was obtained; IR (neat) $\nu_{max}$: 3030, 2925, 2854, 1721, 1662, 1631, 1559, 1495, 1453, 1417, 1379, 1141, 761, 705, 496 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.18 (td, $J$ = 5.1, 2.4 Hz, 3H), 7.05 (dd, $J$ = 7.5, 2.0 Hz, 2H), 6.86 (ddd, $J$ = 9.8, 5.8, 1.8 Hz, 1H), 6.35 (ddd, $J$ = 9.4, 1.8, 0.9 Hz, 1H), 6.14 (ddd, $J$ = 9.5, 5.8, 0.9 Hz, 1H), 5.95 (dt, $J$ = 9.7, 0.9 Hz, 1H), 3.22 (d, $J$ = 13.2 Hz, 1H), 2.75 (d, $J$ = 13.2 Hz, 1H), 1.26 (s, 3H); $^{13}C$ NMR (101 MHz, $CDCl_3$) δ 205.5, 147.3, 141.8, 137.1, 130.0, 128.0, 126.7, 126.1, 120.6, 52.7, 46.2, 24.8; HRMS (ESI): *m/z* $[M+Na]^+$ calculated for $C_{14}H_{14}O$ 221.0937, found 221.0925.

#### 4.4.8. 4-Benzyl-2-methylphenol (**4b**)

Following GPA **4b** (63 mg, 32%) as a yellow oil was obtained after purification; IR (neat) $\nu_{max}$: 3418, 3026, 2921, 1602, 1507, 1494, 1453, 1327, 1260, 1204, 1115, 1074, 1030, 781, 724, 698, 621, 524, 443 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.35–7.25 (m, 2H), 7.25–7.16 (m, 3H), 6.96 (d, $J$ = 2.1 Hz, 1H), 6.91 (dd, $J$ = 8.1, 2.2 Hz, 1H), 6.70 (d, $J$ = 8.1 Hz, 1H), 4.60 (s, 1H), 3.89 (s, 2H), 2.22 (s, 3H); $^{13}C$ NMR (101 MHz, $CDCl_3$) δ 152.2, 141.8, 133.5, 131.7, 128.9, 128.6, 127.6, 126.1, 123.8, 115.0, 41.2, 15.9; HRMS (ESI): *m/z* $[M-H]^-$ calculated for $C_{14}H_{14}O$ 197.0972, found 197.0973.

#### 4.4.9. 1-(Benzyloxy)-4-methylbenzene (**2c**)

Following GPA **2c** (89 mg, 45%) as a white solid was obtained after purification; mp 33–35 °C; IR (KBr) $\nu_{max}$: 3032, 2922, 1613, 1585, 1511, 1454, 1381, 1291, 1239, 1175, 1110, 1026, 861, 817, 734, 696, 604, 512 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.51 (d, $J$ = 7.3 Hz, 2H), 7.46 (t, $J$ = 7.3 Hz, 2H), 7.40 (d, $J$ = 7.0 Hz, 1H), 7.17 (d, $J$ = 8.0 Hz, 2H), 6.97 (d, $J$ = 8.6 Hz, 2H), 5.11 (s, 2H), 2.37 (s, 3H); $^{13}C$ NMR (101 MHz, $CDCl_3$) δ 156.8, 137.4, 130.2, 130.0, 128.6, 128.0, 127.6, 114.8, 70.1, 20.6; HRMS (ESI): *m/z* $[M+Na]^+$ calculated for $C_{14}H_{14}O$ 221.0937, found 221.0931.

#### 4.4.10. 2-Benzyl-4-methylphenol (**3c**)

Following GPB **3c** (99 mg, 50%) as a colourless oil was obtained; IR (neat) $\nu_{max}$: 3536, 3026, 2922, 2859, 1602, 1506, 1495, 1325, 1259, 1188, 1104, 1030, 935, 812, 751, 728, 697 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.29–7.25 (m. 2H), 7.22–7.17 (m, 3H), 6.91–6.89 (m, 2H), 6.65 (d, $J$ = 8.26 Hz, 1H), 4.60 (s, 1H), 3.94 (s, 2H), 2.24 (s, 3H); $^{13}C$ NMR (101 MHz, $CDCl_3$): $\delta$ = 151.6, 140.2, 131.7, 130.3, 128.78, 128.75, 128.3, 126.8, 126.4, 115.7, 36.5, 20.7; HRMS (ESI): *m/z* $[M-H]^-$ calculated for $C_{14}H_{14}O$: 197.0972, found 197.0978.

#### 4.4.11. 2,6-Dibenzyl-4-methylphenol (**5c**)

Following GPB gave product **5c** (14 mg, 5%) as a colourless oil; IR (neat) $\nu_{max}$: 3556, 3026, 2920, 1602, 1494, 1479, 1245, 1198, 1075, 1030, 863, 731, 699 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.30–7.26 (m. 4H), 7.21–7.18 (m, 6H), 6.84 (s, 2H), 4.42 (s, 1H), 3.93 (s, 4H),

2.23 (s, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta$ = 150.0, 140.0, 130.0, 129.9, 128.8, 128.7, 127.1, 126.5, 36.8, 20.7; HRMS (ESI): *m/z* $[M-H]^-$ calculated for $C_{21}H_{20}O$ 287.1441, found 287.1459.

*4.4.12. 1-(Benzyloxy)-2-(tert-butyl)-benzene (**2d**)*

Following GPA **2d** (39 mg, 16%) as a colourless oil was obtained after purification; IR (neat) $\nu_{max}$: 2961, 1744, 1608, 1513, 1455, 1364, 1295, 1244, 1182, 1025, 828, 735, 697, 553 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.3 Hz, 2H), 7.46–7.40 (m, 2H), 7.40–7.33 (m, 2H), 7.21 (ddd, *J* = 8.2, 7.3, 1.7 Hz, 1H), 7.00–6.92 (m, 2H), 5.16 (s, 2H), 1.46 (s, 9H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 157.7, 138.5, 137.6, 128.7, 127.8, 127.4, 127.2, 126.9, 120.7, 112.6, 70.2, 35.0, 30.0; HRMS (ESI): *m/z* $[M+H]^+$ calculated for $C_{17}H_{20}O$ 241.1587, found 241.1576.

*4.4.13. 2-Benzyl-6-(tert-butyl)-phenol (**3d**)*

Following GPA **3d** (15 mg, 6%) after purification as a green oil was obtained; IR (neat) $\nu_{max}$: 3560, 3062, 3028, 2958, 1603, 1494, 1437, 1391, 1361, 1247, 1206, 1134, 1088, 1029, 887, 844, 797, 776, 747, 699, 532, 458 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.33 (t, *J* = 7.2 Hz, 2H), 7.29–7.25 (m, 1H), 7.23 (d, *J* = 7.7 Hz, 3H), 7.03 (dd, *J* = 7.4, 1.6 Hz, 1H), 6.87 (t, *J* = 7.6 Hz, 1H), 4.77 (s, 1H), 4.01 (s, 2H), 1.40 (s, 9H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 153.1, 139.0, 136.8, 129.1, 129.0, 128.7, 127.0, 126.8, 125.8, 120.3, 37.3, 34.7, 30.0; HRMS (ESI): *m/z* $[M-H]^-$ calculated for $C_{17}H_{20}O$ 239.1441, found 239.1448.

*4.4.14. 4-Benzyl-2-(tert-butyl)-phenol (**4d**)*

Following GPA **4d** (46 mg, 19%) as a brown oil was obtained after purification; IR (neat) $\nu_{max}$: cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.35–7.27 (m, 2H), 7.24–7.18 (m, 3H), 7.13 (d, *J* = 2.2 Hz, 1H), 6.86 (dd, *J* = 8.0, 2.2 Hz, 1H), 6.59 (d, *J* = 8.0 Hz, 1H), 4.71 (s, 1H), 3.93 (s, 2H), 1.41 (s, 9H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 152.6, 141.8, 136.1, 133.1, 129.0, 128.5, 127.9, 127.3, 126.0, 116.7, 41.5, 34.6, 29.7; HRMS (ESI): *m/z* $[M-H]^-$ calculated for $C_{17}H_{20}O$ 239.1441, found 239.1443.

*4.4.15. 1-(Benzyloxy)-4-(tert-butyl)-benzene (**2e**)*

Following GPA **2e** (139 mg, 58%) as a white solid was obtained after purification; mp 61–63 °C; IR (KBr) $\nu_{max}$: 2952, 2931, 2866, 1608, 1514, 1454, 1363, 1299, 1243, 1187, 1125, 914, 837, 811, 750, 701, 555, 514 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.48–7.43 (m, 2H), 7.43–7.37 (m, 2H), 7.36–7.29 (m, 3H), 6.99–6.89 (m, 2H), 5.06 (s, 2H), 1.32 (s, 9H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 156.7, 143.7, 137.4, 128.7, 128.0, 127.6, 126.4, 114.4, 70.2, 34.2, 31.7; HRMS (ESI): *m/z* $[M+Na]^+$ calculated for $C_{17}H_{20}O$ 263.1406, found 263.1393.

*4.4.16. 2-Benzyl-4-(tert-butyl)-phenol (**3e**)*

Following GPA **3e** (10 mg, 4%) after purification as a white solid was obtained; mp 48–50 °C; IR (KBr) $\nu_{max}$: 3346, 2962, 1637, 1551, 1509, 1469, 1429, 1385, 1365, 1318, 1270, 1220, 1175, 1124, 1093, 1031, 953, 816, 770, 730, 698, 605 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.43–7.36 (m, 2H), 7.36–7.28 (m, 3H), 7.28–7.21 (m, 2H), 6.86–6.77 (m, 1H), 4.63 (s, 1H), 4.10 (s, 2H), 1.39 (d, *J* = 0.5 Hz, 9H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 151.6, 143.8, 140.2, 128.8, 128.7, 128.2, 126.4, 126.2, 124.7, 115.4, 37.0, 34.2, 31.7; HRMS (ESI): *m/z* $[M+Na]^+$ calculated for $C_{17}H_{20}O$ 263.1406, found 263.1402.

*4.4.17. 2-(Benzyloxy)-1,3-dimethylbenzene (**2f**)*

Following GPA **2f** (23 mg, 11%) after purification as a colorless oil was obtained; IR (neat) $\nu_{max}$: 3031, 2922. 2860, 1591, 1496, 1476, 1454, 1373, 1263, 1198, 1091, 1013, 915, 859, 769, 734, 698, 562, 462 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.56–7.49 (m, 2H), 7.48–7.36 (m, 3H), 7.11–7.04 (m, 2H), 6.99 (dd, *J* = 8.2, 6.6 Hz, 1H), 4.85 (s, 2H), 2.35 (s, 6H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 155.9, 137.9, 131.3, 129.0, 128.7, 128.1, 127.9, 124.1, 74.0, 16.5; HRMS (ESI): *m/z* $[M+H]^+$ calculated for $C_{15}H_{16}O$ 213.1274, found 213.1262.

*4.4.18. 6-Benzyl-2,6-dimethylcyclohexa-2,4-dien-1-one (**3f**)*

Following GPB **3f** (119 mg, 56%) as a green viscous oil was obtained after purification; IR (neat) $\nu_{max}$: 3029, 2974, 2922, 1715, 1677, 1655, 1639, 1582, 1495, 1452, 1376, 1072, 1019, 738, 702, 512 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, *J* = 7.2 Hz, 3H), 7.02 (dd, *J* = 7.5, 2.0 Hz, 2H), 6.63 (dt, *J* = 6.0, 1.6 Hz, 1H), 6.22 (ddd, *J* = 9.5, 1.8, 0.9 Hz, 1H), 6.05 (dd, *J* = 9.5, 6.0 Hz, 1H), 3.17 (d, *J* = 13.0 Hz, 1H), 2.74 (d, *J* = 13.0 Hz, 1H), 1.79 (s, 3H), 1.25 (s, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 205.6, 144.6, 138.2, 137.2, 133.3, 129.8, 127.8, 126.5, 120.6, 52.0, 46.7, 24.9, 15.5; HRMS (ESI): *m/z* $[M+Na]^+$ calculated for $C_{15}H_{16}O$ 235.1093, found 235.1086.

*4.4.19. 4-Benzyl-2,6-dimethylphenol (**4f**)*

Following GPA **4f** (136 mg, 64%) as a yellow solid was obtained after purification; mp 62–64 °C; IR (KBr) $\nu_{max}$: 3395, 3026, 2915, 1603, 1490, 1452, 1385, 1348, 1303, 1212, 1147, 1030, 960, 879, 780, 726, 695, 657, 589, 494, 449 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.45–7.25 (m, 2H), 7.21 (ddt, *J* = 7.4, 3.0, 1.8 Hz, 3H), 6.83 (s, 2H), 4.52 (s, 1H), 3.87 (s, 2H), 2.22 (s, 6H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 150.6, 141.9, 132.9, 129.2, 128.9, 128.5, 126.0, 123.1, 41.2, 16.0; HRMS (ESI): *m/z* $[M-H]^-$ calculated for $C_{15}H_{16}O$ 211.1128, found 211.1124.

*4.4.20. 2-(Benzyloxy)-1,3,5-trimethylbenzene (**2h**)*

Following GPB **2h** (22 mg (10%) as a colorless oil was obtained after purification; IR (neat) $\nu_{max}$: 2920, 1483, 1454, 1373, 1307, 1213, 1147, 1020, 857, 727, 696, 573 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.57–7.51 (m, 2H), 7.48–7.42 (m, 2H), 7.42–7.36 (m, 1H), 6.90 (s, 2H), 4.84 (s, 2H), 2.33 (s, 6H), 2.31 (s, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 153.7, 137.9, 133.4, 130.8, 129.6, 128.6, 128.0, 127.9, 74.2, 20.8, 16.4; HRMS (ESI): *m/z* $[M+Na]^+$ calculated for $C_{16}H_{18}O$ 249.1250, found 249.1253.

*4.4.21. 6-Benzyl-2,4,6-trimethylcyclohexa-2,4-dien-1-one (**3h**)*

Following GPB **3h** (190 mg, 84%) as a white solid was obtained after purification; mp 43–45 °C; IR (KBr) $\nu_{max}$: 3449, 3060, 3027, 2977, 2918, 2862, 1667, 1638, 1585, 1495, 1449, 1383, 1237, 1190, 1074, 1018, 983, 949, 855, 772, 746, 703, 603, 565, 503, 424 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.23–7.09 (m, 3H), 7.00 (dd, *J* = 7.5, 2.1 Hz, 2H), 6.46 (dq, *J* = 2.8, 1.5 Hz, 1H), 5.87 (s, 1H), 3.08 (d, *J* = 12.8 Hz, 1H), 2.70 (d, *J* = 12.9 Hz, 1H), 1.82 (d, *J* = 1.6 Hz, 3H), 1.76 (s, 3H), 1.21 (s, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 205.7, 142.5, 138.9, 137.4, 132.8, 129.9, 128.0, 127.6, 126.4, 51.1, 47.2, 25.0, 21.2, 15.4; HRMS (ESI): *m/z* $[M+Na]^+$ calculated for $C_{16}H_{18}O$ 249.1250, found 249.1250.

*4.4.22. 4-Benzyl-2,4,6-trimethylcyclohexa-2,5-dien-1-one (**4h**)*

Following GPA **4h** (73 mg, 32%) as a colourless oil was obtained after purification; IR (neat) $\nu_{max}$: 3028, 2963, 2923, 1669, 1635, 1495, 1452, 1400, 1374, 1217, 1039, 1015, 916, 776, 740, 702, 478 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.27–7.16 (m, 3H), 7.09–6.96 (m, 2H), 6.59 (s, 2H), 2.79 (s, 2H), 1.83 (s, 6H), 1.22 (s, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 187.3, 150.5, 136.7, 134.2, 130.2, 127.9, 126.8, 47.3, 41.7, 25.3, 16.2; HRMS (ESI): *m/z* $[M+Na]^+$ calculated for $C_{16}H_{18}O$ 249.1250, found 249.1251.

*4.4.23. 2-(Benzyloxy)-1,3-dimethoxy-5-methylbenzene (**2i**)*

Following GPA **2i** (85 mg, 33%) as a yellow oil was obtained after purification; IR (neat) $\nu_{max}$: 2938, 1591, 1505, 1464, 1415, 1374, 1332, 1238, 1129, 1011, 969, 914, 814, 734, 698, 585, 528 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.60–7.44 (m, 2H), 7.42–7.27 (m, 3H), 6.39 (s,

2H), 4.98 (s, 2H), 3.81 (s, 6H), 2.32 (s, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 153.4, 138.1, 134.9, 133.8, 128.6, 128.2, 127.8, 106.2, 75.2, 56.2, 22.0; HRMS (ESI): *m/z* $[M+H]^+$ calculated for $C_{16}H_{18}O_3$ 259.1329, found 259.1325.

#### 4.4.24. 6-Benzyl-2,6-dimethoxy-4-methylcyclohexa-2,4-dien-1-one (**3i**)

Following GPA **3i** (117 mg, 45%) as a yellow oil was obtained after purification; IR (neat) $\nu_{max}$: 2927, 1684, 1659, 1584, 1496, 1454, 1376, 1342, 1248, 1111, 1083, 1033, 953, 817, 771, 746, 701, 526 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.26–7.13 (m, 3H), 7.09 (dq, *J* = 4.5, 3.3, 2.5 Hz, 2H), 5.62–5.47 (m, 2H), 3.54 (s, 3H), 3.13 (s, 3H), 2.93 (q, *J* = 12.6 Hz, 2H), 1.90 (d, *J* = 1.5 Hz, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 199.2, 151.5, 134.6, 132.5, 130.6, 128.0, 127.6, 126.9, 115.1, 84.6, 55.4, 54.0, 47.2, 22.1; HRMS (ESI): *m/z* $[M+H]^+$ calculated for $C_{16}H_{18}O_3$ 259.1329, found 259.1320.

#### 4.4.25. 6-Benzyl-2-(tert-butyl)-4,6-dimethylcyclohexa-2,4-dien-1-one (**3j**)

Following GPC **3j** (94 mg, 35%) as a yellow solid was obtained after purification; mp 82–85 °C; IR (KBr) $\nu_{max}$: 3026, 2949, 2917, 2866, 1640, 1576, 1492, 1450, 1364, 1266, 1201, 1072, 1030, 921, 842, 792, 748, 701, 601, 571, 521, 432 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.21–7.10 (m, 3H), 7.07–6.98 (m, 2H), 6.50 (d, *J* = 2.3 Hz, 1H), 5.88 (dd, *J* = 2.3, 1.5 Hz, 1H), 3.13 (d, *J* = 13.0 Hz, 1H), 2.67 (d, *J* = 12.9 Hz, 1H), 1.86 (d, *J* = 1.5 Hz, 3H), 1.18 (s, 3H), 1.16 (s, 9H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 204.7, 143.4, 140.0, 139.2, 137.6, 130.1, 127.8, 127.7, 126.3, 52.0, 46.7, 34.2, 29.3, 25.1, 22.0; HRMS (ESI): *m/z* $[M+Na]^+$ calculated for $C_{19}H_{24}O$ 291.1719, found 291.1720.

#### 4.4.26. 2-(Benzyloxy)-5-(tert-butyl)-1,3-dimethylbenzene (**2k**)

Following GPA **2k** (37 mg, 14%) as a yellow oil was obtained after purification; IR (neat) $\nu_{max}$: 3032, 2962, 2867, 1486, 1455, 1363, 1310, 1243, 1196, 1123, 1020, 911, 872, 754, 726, 695, 645 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.57–7.50 (m, 2H), 7.48–7.40 (m, 2H), 7.40–7.33 (m, 1H), 7.07 (s, 2H), 4.83 (s, 2H), 2.35 (s, 6H), 1.34 (s, 9H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 153.6, 146.7, 138.1, 130.3, 128.6, 128.0, 127.8, 125.9, 74.0, 34.3, 31.7, 16.8; HRMS (ESI): *m/z* $[M+Na]^+$ calculated for $C_{19}H_{24}O$ 291.1719, found 291.1721.

#### 4.4.27. 6-Benzyl-4-(tert-butyl)-2,6-dimethylcyclohexa-2,4-dien-1-one (**3k**)

Following GPB **3k** (120 mg, 45%) as a yellow oil was obtained after purification; IR (neat) $\nu_{max}$: 3029, 2964, 2869, 1644, 1585, 1494, 1451, 1364, 1264, 1019, 852, 773, 745, 700, 616, 522 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.18–7.07 (m, 3H), 7.02–6.92 (m, 2H), 6.70 (dq, *J* = 2.8, 1.4 Hz, 1H), 5.90 (dd, *J* = 2.4, 0.8 Hz, 1H), 3.12 (d, *J* = 12.7 Hz, 1H), 2.70 (d, *J* = 12.8 Hz, 1H), 1.78 (dd, *J* = 1.4, 0.6 Hz, 3H), 1.24 (s, 3H), 1.04 (s, 9H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 205.9, 140.1, 139.5, 137.2, 135.3, 132.7, 129.8, 127.5, 126.4, 50.5, 47.8, 33.9, 29.0, 24.9, 15.8; HRMS (ESI): *m/z* $[M+Na]^+$ calculated for $C_{19}H_{24}O$ 291.1719, found 291.1718.

#### 4.4.28. 4-Benzyl-4-(tert-butyl)-2,6-dimethylcyclohexa-2,5-dien-1-one (**4k**)

Following GPA a mixture of **4k** (14 mg, 5%) and **11** (11 mg, 6%) as a yellow oil was obtained after purification; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.17–7.04 (m, 3H), 6.96–6.85 (m, 2H), 6.79 (s, 2H), 3.00 (s, 2H), 1.78 (s, 6H), 1.09 (s, 9H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 187.0, 148.1, 137.3, 136.5, 129.9, 127.3, 126.4, 51.4, 40.2, 38.0, 26.7, 16.2; HRMS (ESI): *m/z* $[M+Na]^+$ calculated for $C_{19}H_{24}O$ 291.1719, found 291.1721.


## Funding information

We thank Dr. Aleksander-Mati Müürisepp for performing IR spectra. We also thank Estonian Ministry of Education and Research grant no. PRG657 and the Centre of Excellence in Molecular Cell Engineering grant no. 2014-2020.4.01.15-0013 for financial support.


## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2021.131935.

## References


[1] R. Mayer, M. Breugst, N. Hampel, A.R. Ofial, H.J. Mayr, J. Org. Chem. 84 (2019) 8837–8858, https://doi.org/10.1021/acs.joc.9b01485, and references cited therein.

[2] A.R. Massah, M. Mosharafian, A.R. Momeni, H. Aliyan, H.J. Naghash, M. Adibnejad, Synth. Commun. 37 (2007) 1807–1815, https://doi.org/10.1080/00397910701316268.

[3] (a) F.Y. Curtin, R.R.J. Fraser, J. Am. Chem. Soc. 80 (1958) 6016–6020, https://doi.org/10.1021/ja01555a033;
(b) R.S. Topgi, J. Org. Chem. 54 (1989) 6125–6127, https://doi.org/10.1021/jo00287a030;
(c) A. Ozanne-Beaudenon, S. Quideau, Angew. Chem. Int. Ed. 44 (2005) 7065–7069, https://doi.org/10.1002/anie.200501638.

[4] (a) K.C. Nicolaou, A. Li, D.J. Edmonds, G.S. Tria, S.P. Ellery, J. Am. Chem. Soc. 131 (2009) 16905–16918, https://doi.org/10.1021/ja9068003;
(b) E.J. Corey, L.I. Wu, J. Am. Chem. Soc. 115 (1993) 9327–9328, https://doi.org/10.1021/ja00073a074;
(c) S.A. Snyder, T.C. Sherwood, A.G. Ross, Angew. Chem. Int. Ed. 49 (2010) 5146–5150, https://doi.org/10.1002/anie.201002264.

[5] (a) S. Quideau, L. Pouységu, D. Deffieux, Synlett (2008) 467–495, https://doi.org/10.1055/s-2008-1032094;
(b) Q. Ding, Y. Ye, R. Fan, Synthesis 45 (2013) 1–16, https://doi.org/10.1055/s-0032-1317575;
(c) A. Parra, S. Reboredo, Chem. Eur J. 19 (2013) 17244–17260, https://doi.org/10.1002/chem.201302220.

[6] (a) J. Zheng, S.B. Wang, C. Zheng, S.L. You, J. Am. Chem. Soc. 137 (2015) 4880–4883, https://doi.org/10.1021/jacs.5b01707;
(b) A. Seoane, N. Casanova, N. Quiñones, J.L. Mascareñas, M. Gulías, J. Am. Chem. Soc. 136 (2014) 7607–7610, https://doi.org/10.1021/ja5034952;
(c) J. Nan, Zh Zuo, L. Luo, L. Bai, H. Zheng, Y. Yuan, J. Liu, X. Luan, Y. Wang, J. Am. Chem. Soc. 135 (2013) 17306–17309, https://doi.org/10.1021/ja410060e;
(d) Zh Zuo, X. Yang, J. Liu, J. Nan, L. Bai, Y. Wang, X. Luan, J. Org. Chem. 80 (2015) 3349–3356, https://doi.org/10.1021/acs.joc.5b00316.

[7] (a) K. Wilson, D.J. Adams, G. Rothenberg, J.H. Clark, J. Mol. Catal. A Chem. 159 (2000) 309–314, https://doi.org/10.1016/S1381-1169(00)00185-0;
(b) G. Keglevich, E. Balint, E. Karsai, J. Varga, A. Grün, M. Balint, I. Greiner, Lett. Org. Chem. 6 (2009) 535–539, https://doi.org/10.2174/157017809789869500.

[8] (a) E. Reinholz, A. Becker, B. Hagenbruch, S. Schäfer, A. Schmitt, Synthesis (1990) 1069–1071, https://doi.org/10.1055/s-1990-27096;
(b) J.J.V. Eynde, I. Mailleux, Synth. Commun. 31 (2001) 1–7, https://doi.org/10.1081/SCC-100000172;
(c) M.T. Coleman, G. Leblanc, Org. Process Res. Dev. 14 (2010) 732–736, https://doi.org/10.1021/op900324p;
(d) S.E. Denmark, R.C. Weintraub, N.D. Gould, J. Am. Chem. Soc. 134 (2012) 13415–13429, https://doi.org/10.1021/ja304808u.

[9] (a) J.L. Zhao, L. Liu, C.L. Gu, D. Wang, Y.J. Chen, Tetrahedron Lett. 49 (2008) 1476–1479, https://doi.org/10.1016/j.tetlet.2007.12.129;
(b) H. Naeimi, A. Amini, M. Moradian, Org. Chem. Front. 1 (2014) 415–421, https://doi.org/10.1039/c4qo00031e;
(c) D.H. Lee, K.H. Kwon, C.S. Yi, J. Am. Chem. Soc. 134 (2012) 7325–7328, https://doi.org/10.1021/ja302710v.

[10] (a) N. Kornblum, R. Seltzer, P.J. Haberfield, J. Am. Chem. Soc. 85 (1963) 1148–1154, https://doi.org/10.1021/ja00891a025;
(b) N. Kornblum, P.-J. Berrigan, W.J. Noble, J. Am. Chem. Soc. 85 (1963) 1141–1147, https://doi.org/10.1021/ja00891a024;
(c) N. Kornblum, P.J. Berrigan, W.J. Noble, J. Am. Chem. Soc. 82 (1960) 1257–1258, https://doi.org/10.1021/ja01490a063.

[11] (a) K. Damodar, J.-K. Kim, J.-G. Jun, Chin. Chem. Lett. 27 (2016) 698–702, https://doi.org/10.1016/j.cclet.2016.01.043;

(b) A.J. McCarroll, J.A. Crayston, J.C. Walton, Tetrahedron 59 (2003) 4275–4280, https://doi.org/10.1016/S0040-4020(03)00632-X;
(c) Y.-L. Yang, H. Zhou, G. Du, K.-N. Feng, T. Feng, X.-L. Fu, J.-K. Liu, Y. Zeng, Angew. Chem. Int. Ed. 55 (2016) 5463–5466, https://doi.org/10.1002/anie.201510928;
(d) G.V. Rao, B.N. Swamy, V. Chandregowda, G.C. Reddy, Eur. J. Med. Chem. 44 (2009) 2239–2245, https://doi.org/10.1016/j.ejmech.2008.05.032.
[12] G. Sartori, R. Maggi, F. Bigi, G. Casnati, J. Chem. Soc. Perkin Trans. I (1991) 3059–3063, https://doi.org/10.1039/P19910003059.
[13] D. Yang, L. Wang, M. Kai, D. Li, X. Yao, R. Wang, Angew. Chem. Int. Ed. 54 (2015) 9523–9527, https://doi.org/10.1002/anie.201503056.

# Appendix 2

**Publication II**

A. Kooli, T. Shalima, E. Lopušanskaja, A. Paju, M. Lopp, Selective C-alkylation of substituted naphthols under non-aqueous conditions. *Tetrahedron* **2021**, *95*, 132278

Tetrahedron 95 (2021) 132278

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

# Selective *C*-alkylation of substituted naphthols under non-aqueous conditions

Anni Kooli, Tatsiana Shalima, Eleana Lopušanskaja, Anne Paju, Margus Lopp*

*Department of Chemistry and Biotechnology, Faculty of Science, Tallinn University of Technology, Akadeemia Tee 15, 12618, Tallinn, Estonia*

ARTICLE INFO

*Article history:*
Received 19 April 2021
Received in revised form
31 May 2021
Accepted 3 June 2021
Available online 23 July 2021

*Keywords:*
1-naphthol
Dearomatization
*C*-alkylation
Naphthalenones

ABSTRACT

A simple and selective *C*-alkylation of 1- and 2-naphthols with benzylic and allylic halides was developed. In an organic solvent, like cyclopentyl methyl ether, or toluene in the presence of the ether or alcohol additives, a selective *ortho*-addition leading to substituted naphthalenones up to 90 % was achieved.



## 1. Introduction

Phenols and phenolates belong to a group of electron-rich aromatic compounds which bear nucleophilic sites at *C*- and *O*-atoms, giving rise to both, *C*- and *O*-alkylating products with electrophilic reagents [1,2]. In the case of substituted phenolates *C*-alkylation leads to dearomatization, resulting in cyclic keto dienones [3,4]. We recently developed a regioselective method for the *C*-alkylation of substituted phenols in anhydrous conditions [5]. Naphthols behave similarly to phenols. The *O*-alkylation with electrophiles is a typical $S_N2$ reaction (Williamson reaction [6,7]), affording in excellent yield naphthol ethers, particularly in the presence of phase-transfer catalysts [8,9]. *C*-alkylation results in substitution in the naphthol ring. Usually a mixture of *O*-alkylation and isomeric *C*-alkylation products is obtained [8,10–12]. Common alkylating agents are alkyl halides, alcohols and alkenes [13–15]. With substituted naphthols *C*-alkylation leads to dearomatization, affording chiral substituted naphthalenones [16,17], which are useful starting compounds for the synthesis of various natural products and bioactive compounds [18–20]. Usually, transition metal-catalysed reactions are applied [21]. One example of a successful non-catalytic alkylation with an oxy-allyl cation precursor from 2-chlorocyclopentanone, was recently described by Yang et al., demonstrating a successful dearomatization of both, 1- and 2-naphthols with yields up to 99 % [22]. However, the possibilities of the direct selective *C*-alkylation of naphthols, especially of 1-naphthols, with common alkyl halides, remains undeveloped [23–25]. To the best of our knowledge, there have been no systematic studies in this field.

In the present study, we tried to apply the anhydrous alkylation conditions developed for phenols to naphthols in order to achieve a method for selective *C*-alkylation of naphthols with halides. The model naphthols **1a**, **1b**, **1c** and **1d** were alkylated with allylic and benzylic halides **2**, without a use of the transition metal catalyst. These results may serve as a good basis for further developing an asymmetric version of alkylation for obtaining enantiomeric substituted naphthalenones.

## 2. Results and discussion

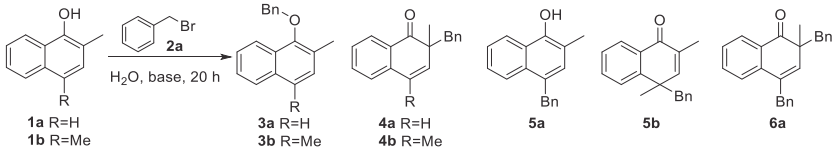
The common alkylation of naphthols is performed in water solution. In order to obtain comparable reference data, we first studied the reaction of 2-methyl-1-naphthol **1a** with benzyl bromide **2a** using a water solution. LiOH, lithium *l*-lactate and DBU were used as the bases to generate naphtholate anion. The obtained results are presented in Table 1.

With naphthol **1a** in LiOH water solution, *C*-alkylation with the formation of a mixture of *o*- and *p*-alkylated products **4a** and **5a** occurred, with only traces of naphthol ether **3a**. The regioselectivity of alkylation was poor and depended on the concentration of LiOH: in a 0.5 M LiOH solution, a mixture with an *o*/*p* ratio of ~0.47/1 was

* Corresponding author.
*E-mail address:* margus.lopp@taltech.ee (M. Lopp).

https://doi.org/10.1016/j.tet.2021.132278
0040-4020/

**Table 1**
Alkylation of 2-methyl- and 2,4-dimethyl-1-naphthols with benzyl bromide in water[a].




| Entry | Naphthol | Base | Isolated yield % | | | | |
|---|---|---|---|---|---|---|---|
| | | | 1 | 3 | 4 | 5 | 6 |
| 1[b] | **1a** | 0.5 M LiOH | 3 | 2 | 23 | 49 | 6 |
| 2[c] | **1a** | 2 M LiOH | – | 2 | 39 | 22 | 9 |
| 3[b] | **1b** | 0.5 M LiOH | – | – | 60 | 17 | – |
| 4[d] | **1a** | Li-*l*-lactate | 27 | – | 18 | 27 | 5 |
| 5[d] | **1b** | Li-*l*-lactate | – | – | 51 | 13 | – |
| 6[e] | **1a** | DBU | 27 | 48 | 5 | 4 | – |

[a] Reaction conditions: base, **1a** or **1b** (0.5 mmol), **2a** (0.6 mmol, 1.2 equiv), room temperature, 20 h.
[b] $H_2O$ (0.5 mL), 1 M LiOH (0.5 mL).
[c] 2 M LiOH (0.5 mL).
[d] $H_2O$ (1 mL), HFIP (300 μL), lithium *l*-lactate (1 equiv).
[e] $H_2O$ (1 mL), DBU (1.1 equiv).

obtained; in 2 M LiOH solution, the yield of *C*-alkylated products was higher, and the *o*/*p* selectivity also increased to 1.8/1. The *C*/*O* selectivity remained high (Table 1, entries 1 and 2). The use of lithium *l*-lactate as a base reduced the yield of alkylation of the naphthol **1a** with only 18 % of **4a** formed, together with a substantial amount of isomeric **5a**, with a ratio of **4a**/**5a** 0.7/1 in favour of the *p*-product **5a**. A considerable amount of the substrate **1a** remained unreacted (27 %; Table 1, entry 4).

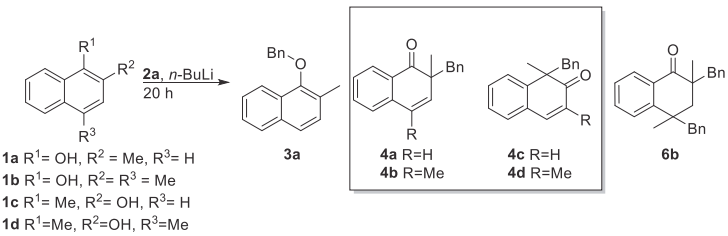
2,4-Dimethyl-1-naphthol **1b** was more reactive and regioselective, mainly yielding the *ortho*-product **4b** in 60 % yield and the ratio of **4b**/**5b**—3.5/1. Similarly, with lithium *l*-lactate the yield of **4b** was 51 %, with 13 % of the *para*-product **5b** formed (a ratio of **4b**/**5b**—4/1; Table 1, entries 3 and 5). It was also observed that formation of the dialkylation product **6a** in up to 10 % yield was observed only in the case of 2-methyl-1-naphthol **1a** (Table 1, entries 1, 2 and 4).

Using the organic base DBU led predominately to *O*-alkylation with the formation of **3a** in 48 % yield and leaving of 27 % of the substrate unreacted under the used reaction conditions (Table 1, entry 6).

We have previously observed increase in alkylation yield and selectivity in phenol alkylations in anhydrous condition [5], so the *n*-BuLi generated Li-enolate of 2-methyl-1-naphthol **1a** was allowed to react in ether solvents with benzyl bromide **2a**. The obtained results are presented in Table 2.

The reaction in tetrahydrofuran (THF) proceeded smoothly,

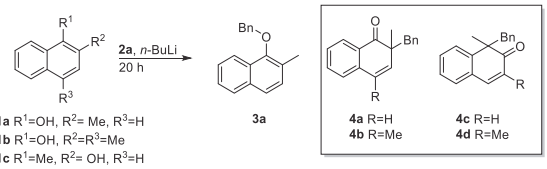
**Table 2**
Alkylation of substituted 1-naphthols with benzyl bromide in ether solvents[a].




| Entry | Naphthol | Solvent | 4[b] yield % |
|---|---|---|---|
| 1[c] | **1a** | THF | 16 |
| 2 | **1a** | CPME | 65 |
| 3[d] | **1b** | CPME | 85 |
| 4 | **1c** | CPME | 62 |
| 5[e] | **1d** | CPME | 73 |
| 6[f] | **1a** | CPME | 50 |

[a] Reaction conditions: **1a**-**1d** (0.5 mmol) in hexane, *n*-BuLi in hexane (2 equiv), solvent exchange, **2a** (1.2 equiv), 80 °C for 20 h.
[b] Isolated yield.
[c] Temperature 70 °C for 20 h, **3a** 51 %.
[d] **5b** 4 % and **6b** 4 %. **1d** 22 %.
[e] **1d** in $Et_2O$.
[f] *n*-BuLi in hexane was added to **1a** in CPME.

**Table 3**
Alkylation of substituted 1-naphthols in toluene with ether and alcohol additives[a].




**1a** $R^1$=OH, $R^2$= Me, $R^3$=H
**1b** $R^1$=OH, $R^2$=$R^3$=Me
**1c** $R^1$=Me, $R^2$= OH, $R^3$=H
**1d** $R^1$=Me, $R^2$=OH, $R^3$=Me

| Entry | Temperature, °C | Naphthol | BnBr; equiv. | Additive; equiv. | Isolated yield % | |
|---|---|---|---|---|---|---|
| | | | | | 3 | 4 |
| 1 | 80 | **1a** | 1.2 | – | – | – |
| 2 | 80 | **1a** | 1.2 | CPME; 2 | 3 | 73 |
| 3[b] | 90 | **1a** | 2 | CPME; 2 | 5 | 54 |
| 4 | 80 | **1b** | 1.2 | CPME; 2 | – | 68 |
| 5 | 80 | **1c** | 1.2 | CPME; 2 | – | 37 |
| 6[b] | 90 | **1c** | 2 | CPME; 2 | – | 90 |
| 7 | 80 | **1d** | 1.2 | CPME; 2 | – | 45 |
| 8 | 65 | **1a** | 1.2 | MTBE; 4 | – | 76 |
| 9 | 65 | **1b** | 1.2 | MTBE; 4 | – | 56 |
| 10 | 80 | **1a** | 1.2 | Anisole; 2 | – | 40 |
| 11 | 80 | **1a** | 1.2 | *i*-PrOH; 1 | – | 57 |
| 12 | 80 | **1a** | 1.2 | *t*-BuOH; 2 | – | 44 |
| 13 | 80 | **1a** | 1.2 | *l*-menthol; 2 | 5 | 70 |
| 14 | 80 | **1b** | 1.2 | *l*-menthol; 2 | – | 76 |
| 15[c] | 80 | **1a** | 1.2 | – | 6 | 54 |

[c]PhMe (1 mL).
[d]PhMe (0.4 mL).
[a] Reaction conditions: **1a**-**1d** (0.5 mmol) in PhMe (0.6 mL), *n*-BuLi in PhMe (2 equiv), additive and **2a** were added, the mixture was stirred for 20 h.
[b] **1a** or **1c** (0.5 mmol) in PhMe (0.3 mL), *n*-BuLi in PhMe (1.2 equiv).
[c] *t*-BuOLi (2 equiv) was used instead *n*-BuLi, *t*-BuOH from the transmetallation of naphthol.

although mainly an *O*-alkylation reaction occurred, resulting in ether **3a** in 51 % yield, together with only 16 % of the ring addition product **4a** (Table 2, entry 1). Knowing from the literature [26] and from our previous study [5] that cyclopentyl methyl ether (CPME) is a good alternative to THF, we turned to that solvent. Indeed, in CPME a selective *C*-alkylation reaction proceeded, affording the *ortho*-addition product **4a** in 65 % yield (Table 2, entry 2). As expected, 2,4-dimethyl-1-naphthol **1b** was again more reactive, resulting predominantly in the *ortho*-product **4b** in 85 % yield, together with only a trace amount of the *para*-addition product **5b** and the dialkylated product **6b** (4 % each; Table 2, entry 3).

1-Methyl-2-naphthol **1c** and 1,3-dimethyl-2-naphthol **1d** also reacted easily with **2a**, affording mainly the 1-Bn-substituted products **4c** and **4d** in 62 % and 73 % yield, respectively (Table 2, entries 4 and 5).

To simplify the procedure, Li-naphtholate generation *n*-BuLi in hexane solution was replaced by a toluene solution, affording a better solubility of naphthols in the reaction medium. The alkylation results with different additives in toluene are presented in Table 3.

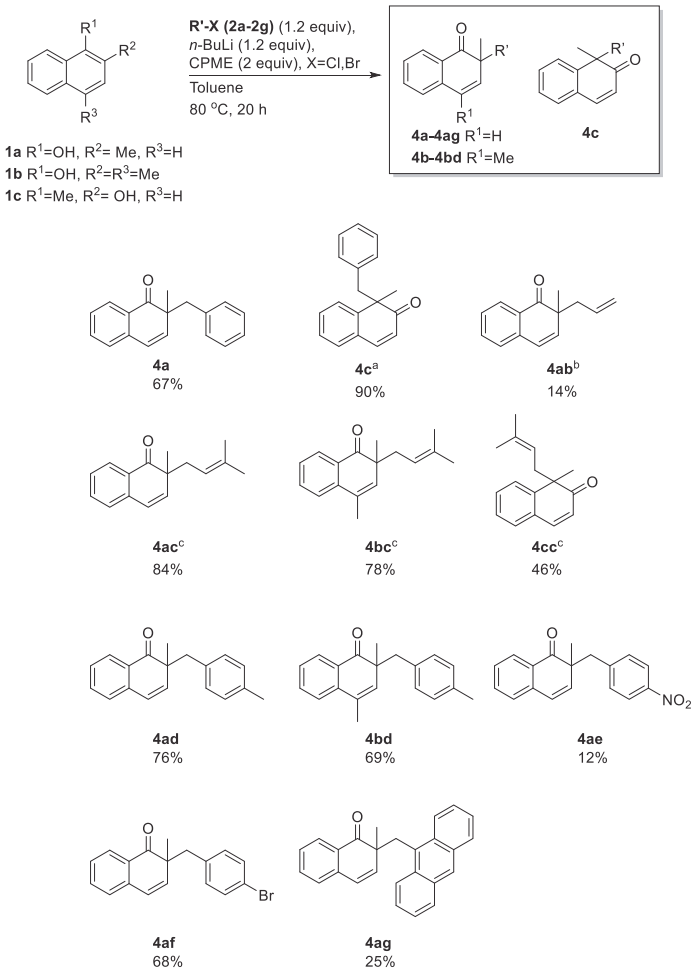
When performing the reaction of 2-Me-1-naphthol **1a** with benzyl bromide **2a** in toluene as a solvent without additives, only an inseparable mixture of different aromatic products was formed, with only 10 % of the substrate **1a** recovered (Table 3, entry 1).

The alkylation reaction proceeded well when additives were applied to the reaction medium. So, when 2 equivalents of CPME was added to toluene and the reaction was carried out at 80 °C a selective *ortho*-addition of benzyl bromide to **1a** occurred, affording naphthalenone **4a** in 73 % isolated yield (Table 3, entry 2). 2,4-Di-Me-1-naphthol **1b** also reacted well with CPME additive, resulting only in the *ortho*-*C*-alkylated product **4b**, in 68 % yield (Table 3, entry 4). Quite surprisingly, the 2-naphthol **1c** afforded with **2a** addition to carbon C1, resulting in **4c** only in a 37 % yield. The naphthol **1d** gave a slightly higher yield of dearomatized product **4d** (Table 3, entry 7), than the less substituted naphthol **1c**. Using more concentrated solution, i.e. adding less *n*-BuLi and more BnBr, the yield of **4c** raised to 90 % (Table 3, entries 5 and 6). Under these conditions, 1-naphthol **1a** afforded a 54 % yield of **4a** (Table 3, entry 3). Therefore, it is seen that the reaction is quite sensitive to the substrate structure.

In order to elucidate the scope of possible additives to toluene, different ethers and alcohols were tested. We found that other ethers are also suitable as additives. Thus, methyl *tert*-butyl ether (MTBE) with **1a** afforded a selective *C*2-alkylated product **4a** in 76 % yield. With **1b**, the *C*2-alkylated product **4b** was obtained in 56 % yield (Table 3, entries 8 and 9). A slightly bigger amount of MTBE (4 equivalents) and a lower temperature (65 °C) to avoid the loss of during the reaction because of its low boiling point, was needed with MTBE. The methyl phenyl ether (anisole) additive gave a relatively low yield (40 %) of the addition. (Table 3, entry 10).

Alcohols which are weaker acids then phenols, were also tested as additives to toluene. The 1-naphthol **1a** with alcoholic additives *i*-PrOH and *t*-BuOH afforded a selective *ortho*-addition, forming **4a** with moderate yield (57 % and 44 %, respectively; Table 3, entries 11 and 12). *l*-menthol, which is a more sterically hindered secondary alcohol afforded the highest yield with both substrates **1a** and **1b** (Table 3, entries 13 and 14). In some cases, the formation of a small amount of *O*-alkylation product **3** was also observed (Table 3, entries 2, 3, 13 and 15).

These results forced us to check Li alcoholates as the bases for generating naphtholates. With 2 equivalents of *t*-BuOLi naphthol **1a** together with **2a** afforded the alkylated product **4a** in 54 % yield, which was similar to that obtained with *n*-BuLi (Table 3, entry 12 and entry 15). This means that alcoholates may be an alternative




**Scheme 1.** *C*-alkylation of substituted naphthols with active halides in toluene with CPME additive. Isolated yields are shown.

when selecting a suitable base for the alkylation of naphthols.

To broaden the choice of possible halides different allylic and benzylic halides were used. The obtained results are presented in Scheme 1.

We found that prenyl bromide **2c**, together with 2 equivalents of *n*-BuLi in the presence of CPME at room temperature yielded a *C*-alkylation of only 4 %. We assumed that the active electrophiles might react with the excess of *n*-BuLi, consuming the reagent and so reducing the yield of alkylation. Indeed, when a reduced amount of *n*-BuLi (1.2 equivalents) was used, the best alkylation yield was obtained (84 %; Scheme 1, **4ac**). At the same time, with benzyl bromide **2a** a reduced amount of *n*-BuLi (1.2 equivalents) caused a slight decrease in yield of **4a**, from 73 % to 67 % (Table 3, entry 2; Scheme 1, **4a**).

These results are in good accordance with the Lovchik et al. report, demonstrating that prenyl chloride alkylates **1a** when using an α-isosparteine additive in 54 % yield with *ee* 34 % [25]. With naphthols **1b** and **1c**, alkylation with **2a** and **2c** afforded lower yields than that for **1a** (Scheme 1, 78 % for **4bc** and 46 % for **4 cc**).

Additionally, the different substituted benzyl bromides 4-Me-benzyl bromide (**2d**), 4-Br-benzyl bromide (**2f**) and 4-$NO_2$-benzyl bromide (**2e**) were applied for alkylation of naphthols. The substituted benzyl bromides **2d** and **2f** afforded a yield comparable with that of **2a**, while *p*-nitrobenzyl bromide **2e** gave lower yield of the alkylation (Scheme 1, **4ad**, **4af** and **4ae**). Even a bulky benzyl derivative 9-(chloromethyl)anthracene **2g** with **1a** gave a moderate yield of the alkylation (Scheme 1, **4 ag**). To our disappointment, other common electrophiles, such as iodomethane and methyl tosylate, did not give any *C*-alkylation product. With methyl tosylate only *O*-alkylation with the formation of *O*—Me naphthol in 52 % yield was obtained.

## 3. Conclusion

The separation of isomeric naphthols is a complicated task, especially in a preparative scale. The alkylation of 1- and 2-naphthols in anhydrous condition offers a selective way to get only one of the possible isomers. Moderate to good yields with high selectivity make the method competitive for the synthesis of substituted naphthalenones. Especially suitable is the approach for 1-naphthols, giving a lower yield for direct *ortho* alkylation in water. The obtained results provide a good basis for further developing an asymmetric alkylation of naphthols.

## 4. Experimental section

All reactions were carried out under argon atmosphere with oven-dried glassware. All reagents were used as received unless noted otherwise. CPME, $Et_2O$ and toluene for reaction were dried with 4 Å molecular sieves. **1a**, **1b**, **1c**, **1d** [27] were vacuum dried for 15 min before reaction.

PE refers to petroleum ether b.p 40–60 °C, EtOAc refers to ethyl acetate, CPME refers to cyclopentyl methyl ether, BnBr refers to benzyl bromide, and MTBE refers to methyl *tert*-butyl ether. $^1$H and $^{13}$C NMR spectra were recorded on a Bruker Avance III instrument at 400 MHz for $^1$H and 100 MHz for $^{13}$C. HRMS were recorded by using an Agilent Technologies 6540 UHD Accurate-Mass Q-TOF LC/MS spectrometer by using ESI ionization. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrophotometer. Precoated silica gel plates (Merck 60 F254) were used for TLC. Column chromatography was performed on a Biotage Isolera Prime preparative purification system with silica gel Kieselgel 63–200 μm.

### 4.1. 2,4-dimethylnaphthalen-1-ol (*1b*)

#### 4.1.1. 4-Hydroxy-3-methyl-1-naphthaldehyde

At −20 °C to **1a** (2 g, 12.7 mmol) in $CH_2Cl_2$ (130 mL) 1 M $TiCl_4$ in toluene (38 mL, 38 mmol) was added dropwise. To mixture dichloro(methoxy)methane (1.8 mL, 19 mmol) was added dropwise. Mixture was stirred for 30 min. Reaction mixture was allowed to warm up to room temperature and was stirred other 30 min. Mixture was cooled down to 0 °C and ice-cold water (100 mL) was added. After 10 min of vigorous stirring 1 M HCl (200 mL) was added. Mixture was stirred until all salts were dissolved. Reaction was extracted with $CH_2Cl_2$ and extracts were washed with brine, dried over $Na_2SO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography ($CH_2Cl_2$/EtOAc, 2–20 %). To give 4-hydroxy-3-methyl-1-naphthaldehyde (1.65 g, 70 %) as a yellow oil. PE/EtOAc = 10:1, $R_f$ = 0.43.$^1$H NMR (400 MHz, MeOD) δ 10.04 (s, 1H), 9.24–9.13 (m, 1H), 8.35–8.23 (m, 1H), 7.80 (s, 1H), 7.63–7.44 (m, 2H), 2.42 (s, 3H). $^{13}$C NMR (101 MHz, MeOD) δ 194.14, 158.49, 144.26, 132.43, 129.33, 126.88, 126.45, 125.58, 124.89, 123.34, 118.08, 16.16.

#### 4.1.2. 2,4-dimethylnaphthalen-1-ol (*1b*)

To 4-hydroxy-3-methyl-1-naphthaldehyde (1.65 g, 8.9 mmol) in *p*-xylene (40 mL) 3.5 M Red-Al in toluene (3.9 mL, 13.3 mmol) was added dropwise. Reaction mixture was refluxed for 1 h. After 1 h reaction mixture was allowed cool down to room temperature and $Et_2O$ (15 mL) was added. Reaction mixture was cooled to 0 °C and 10 % KOH (20 mL) was added. Two little pieces of dry ice ($CO_2$) were added carefully to neutralise mixture. Reaction was extracted with $Et_2O$ (4x50 mL), extracts were washed with brine and dried over $Na_2SO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (PE/EtOAc, 1–15 %). To give 2,4-dimethylnaphthalen-1-ol **1b** as a white pinkish solid (1.18 g, 77 %). PE/EtOAc = 10:1, $R_f$ = 0.30.$^1$H NMR (400 MHz, $CDCl_3$) δ 8.19–8.13 (m, 1H), 7.95–7.88 (m, 1H), 7.53–7.45 (m, 2H), 7.09 (s, 1H), 4.92 (s, 1H), 2.60 (d, $J$ = 0.9 Hz, 3H), 2.39 (s, 3H). Analytical data are in agreement with the literature data [28].

### 4.2. General method A

To the corresponding naphthol (**1a**-**1c**) (0.5 mmol) solution in toluene (0.6 mL) at 0 °C *n*-BuLi 2.7 M in toluene (0.22 mL, 0.6 mmol) was added dropwise. The reaction mixture was stirred for 15 min and then at room temperature until precipitation occurred or 20 min. As an additive CPME (116 μL, 1 mmol) was added dropwise and stirred for 5 min. Alkylating agent **2a**-**2g** (1.2 equiv) was added dropwise/portion wise and the reaction mixture was stirred at 80 °C for 20 h. The reaction mixture was diluted with water and extracted with EtOAc (3x7 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (PE/EtOAc).

#### 4.2.1. 2-benzyl-2-methyl-1-naphthalenone (*4a*)

Compound **4a** was prepared using method A. To a **1a** in reaction as an alkylating agent benzyl bromide **2a** (71.5 μL, 0.6 mmol) was used. Column chromatography PE/EtOAc 1–20 %. Gave 2-benzyl-2-methyl-1-naphthalenone **4a** as a yellow oil (91 mg, 73 %). PE/EtOAc = 10:1, $R_f$ = 0.53. IR (neat): 3028.85, 1672.52, 1644.10, 1598.26, 1451.11, 1285.90, 982.64, 792.66 cm−1$^1$H NMR (400 MHz, $CDCl_3$) δ 8.08–7.98 (m, 1H), 7.55–7.44 (m, 1H), 7.31 (td, $J$ = 7.6, 1.2 Hz, 1H), 7.20–7.04 (m, 6H), 6.51 (d, $J$ = 9.8 Hz, 1H), 6.09 (d, $J$ = 9.8 Hz, 1H), 3.25 (d, $J$ = 13.2 Hz, 1H), 2.83 (d, $J$ = 13.2 Hz, 1H), 1.32 (s, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 203.15, 139.32, 138.35, 137.16, 134.39, 130.23, 129.24, 127.91, 127.86, 127.34, 127.10, 126.54, 123.92, 50.32, 45.97, 24.97. HRMS (ESI) *m/z* calculated for $C_{18}H_{16}ONa$ $[M+Na]^+$ 271.1093, found 271.1087.

#### 4.2.2. 2-allyl-2-methylnaphthalen-1(2H)-one (*4 ab*)

Compound **4 ab** was prepared using method A. To **1a** in reaction as an alkylating agent allyl bromide **2b** (52 μL, 0.6 mmol) was used. Reaction mixture was stirred at 40 °C for 20 h. Column chromatography PE/EtOAc 1–20 %. To give 2-allyl-2-methylnaphthalen-1(2*H*)-one **4 ab** as a yellow oil (14 mg, 14 %). PE/EtOAc = 10:1, $R_f$ = 0.49. IR (neat): 2976.62, 1674.39, 1643.25, 1598.40, 1483.15, 1319.85, 985.48, 729.16, 693.65 cm−1$^1$H NMR (400 MHz, $CDCl_3$) δ 8.08–8.02 (m, 1H), 7.55 (td, $J$ = 7.5, 1.4 Hz, 1H), 7.34 (td, $J$ = 7.6, 1.2 Hz, 1H), 7.26–7.19 (m, 1H), 6.59 (d, $J$ = 9.7 Hz, 1H), 6.10 (d, $J$ = 9.8 Hz, 1H), 5.66–5.49 (m, 1H), 5.06–4.88 (m, 2H), 2.73–2.63 (m, 1H), 2.34–2.25 (m, 1H), 1.27 (s, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 203.09, 139.61, 138.47, 134.45, 133.47, 129.32, 127.94, 127.41, 127.08, 124.00, 118.14, 49.28, 44.62, 24.77. HRMS (ESI) *m/z* calculated for $C_{14}H_{14}ONa$ $[M+Na]^+$ 221.0937, found 221.0936.

#### 4.2.3. 2-methyl-2-(3-methylbut-2-en-1-yl)naphthalen-1(2H)-one (*4ac*)

Compound **4ac** was prepared using method A. To a **1a** in reaction as an alkylating agent prenyl bromide **2c** (69.5 μL, 0.6 mmol) was used. Reaction mixture was stirred at room temperature for 20 h. Column chromatography PE/EtOAc 1–20 %. To give 2–methyl-2-(3-methylbut-2-en-1-yl)naphthalen-1(2*H*)-one **4ac** as a yellow oil (95 mg, 84 %). PE/EtOAc = 10:1, $R_f$ = 0.56. IR (neat): 3028.95, 1775.82, 1598.41, 1482.51, 1449.03, 981.49, 792.47, 692.00 cm−1$^1$H NMR (400 MHz, $CDCl_3$) δ 8.05–8.01 (m, 1H), 7.54 (td, $J$ = 7.5, 1.4 Hz, 1H), 7.33 (td, $J$ = 7.6, 1.2 Hz, 1H), 7.24–7.19 (m, 1H), 6.60–6.54 (m, 1H), 6.10 (d, $J$ = 9.8 Hz, 1H), 4.99–4.91 (m, 1H), 2.65–2.56 (m, 1H), 2.28–2.19 (m, 1H), 1.61–1.52 (m, 6H), 1.26 (s, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 203.60, 140.12, 138.55, 134.72, 134.27, 129.39, 127.75, 127.28, 126.94, 123.77, 119.06, 49.73, 38.82, 25.90, 24.38, 18.11. HRMS (ESI) *m/z* calculated for $C_{16}H_{18}ONa$ $[M+Na]^+$ 249.1250,

found 249.1243.

*4.2.4. 2-methyl-2-(4-methylbenzyl)naphthalen-1(2H)-one (**4ad**)*

Compound **4ad** was prepared using method A. To a **1a** in reaction as an alkylating agent 4-methylbenzyl bromide **2d** (111 mg, 0.6 mmol) was used. Column chromatography PE/EtOAc 1–15 %. To give 2-methyl-2-(4-methylbenzyl)naphthalen-1(2*H*)-one **4ad** as an orange oil (100 mg, 76 %). PE/EtOAc = 10:1, $R_f$ = 0.55. IR (neat): 3029.15, 1672.83, 1597.74, 1482.89, 1448.80, 981.83, 791.53, 691.20 cm−1$^1$H NMR (400 MHz, $CDCl_3$) δ 8.10–8.05 (m, 1H), 7.50 (td, *J* = 7.5, 1.4 Hz, 1H), 7.32 (td, *J* = 7.6, 1.2 Hz, 1H), 7.18–7.13 (m, 1H), 7.05–6.95 (m, 4H), 6.53 (d, *J* = 9.8 Hz, 1H), 6.11 (d, *J* = 9.8 Hz, 1H), 3.23 (d, *J* = 13.2 Hz, 1H), 2.82 (d, *J* = 13.2 Hz, 1H), 2.25 (s, 3H), 1.33 (s, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 203.13, 139.46, 138.31, 135.93, 134.29, 134.01, 130.05, 129.14, 128.59, 127.76, 127.29, 127.03, 123.73, 50.28, 45.39, 24.82, 21.07. HRMS (ESI) *m/z* calculated for $C_{19}H_{18}ONa$ $[M+Na]^+$ 285.1250, found 285.1246.

*4.2.5. 2-methyl-2-(4-nitrobenzyl)naphthalen-1(2H)-one (**4ae**)*

Compound **4ae** was prepared using method A. To a **1a** in reaction as an alkylating agent 4-nitrobenzyl bromide **2e** (130 mg, 0.6 mmol) was used. Column chromatography PE/EtOAc 1–20 %. To give 2-methyl-2-(4-nitrobenzyl)naphthalen-1(2*H*)-one **4ae** as an orange oil (17 mg, 12 % yield). PE/EtOAc = 10:1, $R_f$ = 0.14. IR (neat): 2925.50, 1673.28, 1597.95, 1518.65, 1345.13, 794.76, 772.70 cm−1$^1$H NMR (400 MHz, $CDCl_3$) δ 8.02–7.99 (m, 1H), 7.98–7.94 (m, 2H), 7.50 (td, *J* = 7.5, 1.4 Hz, 1H), 7.31 (td, *J* = 7.6, 1.2 Hz, 1H), 7.24–7.18 (m, 2H), 7.15–7.10 (m, 1H), 6.53 (d, *J* = 9.6 Hz, 1H), 6.10 (d, *J* = 9.8 Hz, 1H), 3.45 (d, *J* = 13.1 Hz, 1H), 2.87 (d, *J* = 13.1 Hz, 1H), 1.37 (s, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 202.27, 146.77, 145.13, 138.11, 137.99, 134.79, 130.76, 129.05, 128.24, 127.55, 127.07, 124.88, 123.11, 50.52, 45.61, 25.81. HRMS (ESI) *m/z* calculated for $C_{18}H_{15}NO_3Na$ $[M+Na]^+$ 316.0944, found 316.0941.

*4.2.6. 2-(4-bromobenzyl)-2-methylnaphthalen-1(2H)-one (**4af**)*

Compound **4af** was prepared using method A. To a **1a** in reaction as an alkylating agent 4-bromobenzyl bromide **2f** (150 mg, 0.6 mmol) was used. Column chromatography PE/EtOAc 1–15 %. To give 2-(4-bromobenzyl)-2-methylnaphthalen-1(2*H*)-one **4af** as an orange oil (111 mg, 68 %). PE/EtOAc = 10:1, $R_f$ = 0.45. IR (neat): 2923.62,1673.37, 1597.47, 1487.57, 1448.63, 1072.18, 1011.69, 792.83, 691.83 cm−1$^1$H NMR (400 MHz, $CDCl_3$) δ 8.04–7.98 (m, 1H), 7.48 (td, *J* = 7.5, 1.4 Hz, 1H), 7.29 (td, *J* = 7.6, 1.2 Hz, 1H), 7.27–7.21 (m, 2H), 7.14–7.09 (m, 1H), 6.96–6.91 (m, 2H), 6.50 (d, *J* = 9.8 Hz, 1H), 6.06 (d, *J* = 9.8 Hz, 1H), 3.23 (d, *J* = 13.2 Hz, 1H), 2.74 (d, *J* = 13.2 Hz, 1H), 1.30 (s, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 202.70, 138.76, 138.14, 136.18, 134.50, 131.74, 130.94, 129.05, 127.95, 127.40, 127.00, 124.27, 120.49, 50.24, 45.19, 25.23. HRMS (ESI) *m/z* calculated for $C_{18}H_{15}BrONa$ $[M+Na]^+$ 349.0198, found 349.0194.

*4.2.7. 2-(anthracen-9-ylmethyl)-2-methylnaphthalen-1(2H)-one (**4 ag**)*

Compound **4 ag** was prepared using method A. To a **1a** in reaction as an alkylating agent 9-(Chloromethyl)anthracene **2g** (136.2 mg, 0.6 mmol) was used. Column chromatography PE/EtOAc 1–20 %. To give 2-(anthracen-9-ylmethyl)-2-methylnaphthalen-1(2*H*)-one **4 ag** as a yellow oil (45 mg, 26 %). PE/EtOAc = 10:1, $R_f$ = 0.33. IR (neat): 3051.83, 1670.00, 1596.91, 1446.50, 983.50, 796.96, 734.80, 689.04 cm−1$^1$H NMR (400 MHz, $CDCl_3$) δ 8.39–8.30 (m, 3H), 8.13–8.08 (m, 1H), 8.00–7.95 (m, 2H), 7.57–7.38 (m, 6H), 7.34 (td, *J* = 7.6, 1.2 Hz, 1H), 7.15–7.09 (m, 1H), 6.30 (d, *J* = 9.8 Hz, 1H), 5.82 (d, *J* = 9.9 Hz, 1H), 4.29 (d, *J* = 14.6 Hz, 1H), 4.00 (d, *J* = 14.6 Hz, 1H), 1.31 (s, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 203.92, 139.98, 138.24, 134.52, 131.63, 131.56, 129.52, 129.11, 129.02, 127.83, 127.33, 127.21, 127.19, 126.01, 125.36, 124.88, 122.69, 50.98, 34.98, 24.99. HRMS (ESI) *m/z* calculated for $C_{26}H_{20}ONa$ $[M+Na]^+$ 371.1406, found 371.1407.

*4.2.8. 2-benzyl-2,4-dimethylnaphthalen-1(2H)-one (**4b**)*

To **1b** (86 mg, 0.5 mmol) solution in hexane (3 mL) at 0 °C *n*-BuLi 2.5 M in hexane (0.4 mL, 1 mmol) was added dropwise. Reaction mixture was allowed rise to room temperature and all solvents were removed with argon. CPME (1 mL) was added dropwise and stirred for 10 min **2a** (71.5 μL, 0.6 mmol) was added dropwise and reaction mixture was stirred at 80 °C for 20 h. Reaction was diluted with water and extracted with EtOAc (3x7 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography PE/EtOAc (1–18 %). To give 2- benzyl-2,4-dimethylnaphthalen-1(2*H*)-one **4b** as a light yellow oil (111 mg, 85 %). PE/EtOAc = 10:1, $R_f$ = 0.70. IR (neat): 3028.87, 1672.48, 1597.39, 1483.79, 1451.23, 1220.73, 983.78, 764.52 cm−1$^1$H NMR (400 MHz, $CDCl_3$) δ 8.12–8.07 (m, 1H), 7.55 (td, *J* = 7.6, 1.5 Hz, 1H), 7.37–7.27 (m, 2H), 7.20–7.05 (m, 5H), 5.94–5.88 (m, 1H), 3.21 (d, *J* = 13.1 Hz, 1H), 2.83 (d, *J* = 13.1 Hz, 1H), 2.13 (d, *J* = 1.4 Hz, 3H), 1.33 (s, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 203.45, 139.20, 137.11, 136.03, 134.20, 130.20, 129.21, 127.97, 127.71, 127.44, 127.16, 126.37, 124.13, 49.84, 46.26, 24.76, 19.29. HRMS (ESI) *m/z* calculated for $C_{19}H_{18}ONa$ $[M+Na]^+$ 285.1250, found 285.1252.

*4.2.9. 2,4-dimethyl-2-(3-methylbut-2-en-1-yl)naphthalen-1(2H)-one (**4bc**)*

Compound **4bc** was prepared using method A. To a **1b** in reaction as an alkylating agent prenyl bromide **2c** (69.5 μL, 0.6 mmol) was used. Reaction mixture was stirred at room temperature for 20 h. Column chromatography PE/EtOAc 1–20 %. To give 2,4-dimethyl-2-(3-methylbut-2-en-1-yl)naphthalen-1(2*H*)-one **4bc** as a pale yellow oil (94 mg, 78 %). PE/EtOAc = 10:1, $R_f$ = 0.70. IR (neat): 2925.29, 1673.89, 1597.51, 1448.72, 1377.60, 1219.94, 982.07, 763.67, 698.39 cm−1$^1$H NMR (400 MHz, $CDCl_3$) δ 8.11–8.01 (m, 1H), 7.60 (td, *J* = 7.6, 1.5 Hz, 1H), 7.41–7.33 (m, 2H), 5.94–5.84 (m, 1H), 5.01–4.86 (m, 1H), 2.62–2.50 (m, 1H), 2.27–2.17 (m, 1H), 2.16 (d, *J* = 1.4 Hz, 3H), 1.59–1.53 (m, 6H), 1.24 (s, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 204.08, 139.50, 136.96, 134.61, 134.19, 129.41, 127.75, 127.44, 127.15, 124.18, 119.25, 49.43, 38.97, 25.92, 24.36, 19.46, 18.08. HRMS (ESI) *m/z* calculated for $C_{17}H_{20}ONa$ $[M+Na]^+$ 263.1406, found 263.1402.

*4.2.10. 2,4-dimethyl-2-(4-methylbenzyl)naphthalen-1(2H)-one (**4bd**)*

Compound **4bd** was prepared using method A. To a **1b** in reaction as an alkylating agent 4-methylbenzyl bromide **2d** (111 mg, 0.6 mmol) was used. Column chromatography PE/EtOAc 1–15 %. To give 2,4-dimethyl-2-(4-methylbenzyl)naphthalen-1(2*H*)-one **4bd** as a pale yellow oil (95 mg, 69 %). PE/EtOAc = 10:1, $R_f$ = 0.66. IR (neat): 2922.91, 1672.22, 1596.99, 1514.40, 1447.75, 1220.64, 983.30, 793.31, 701.53 cm−1$^1$H NMR (400 MHz, $CDCl_3$) δ 8.10 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.56 (td, *J* = 7.6, 1.5 Hz, 1H), 7.39–7.27 (m, 2H), 6.99 (s, 4H), 5.94–5.84 (m, 1H), 3.15 (d, *J* = 13.1 Hz, 1H), 2.80 (d, *J* = 13.1 Hz, 1H), 2.25 (s, 3H), 2.13 (d, *J* = 1.5 Hz, 3H), 1.31 (s, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 203.55, 139.24, 136.25, 135.80, 134.17, 134.00, 130.12, 129.15, 128.46, 127.78, 127.42, 127.19, 124.14, 49.86, 45.68, 24.61, 21.06, 19.30. HRMS (ESI) *m/z* calculated for $C_{20}H_{20}ONa$ $[M+Na]^+$ 299.1406, found 299.1405.

*4.2.11. 1-benzyl-1-methylnaphthalen-2(1H)-one (**4c**)*

To **1c** (79 mg, 0.5 mmol) solution in CPME (116 μL) at 0 °C *n*-BuLi 2.7 M in toluene (0.17 mL, 0.45 mmol) was added dropwise. Then toluene was added (0.3 mL). The reaction mixture was stirred for 15 min and then at room temperature for 20 min **2a** (171 μL, 1 mmol) was added dropwise and reaction mixture was stirred at

90 °C for 20 h. Reaction was diluted with water and extracted with EtOAc (3x7 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography PE/EtOAc (1–20 %). To give 1-benzyl-1-methylnaphthalen-2(1*H*)-one **4c** as a yellow oil (111 mg, 90 %). PE/EtOAc = 10:1, $R_f$ = 0.35. IR (neat): 3028.60, 1656.05, 1452.90, 835.56, 759.04, 700.87 cm−1$^1$H NMR (400 MHz, $CDCl_3$) δ 7.48–7.38 (m, 2H), 7.29–7.22 (m, 1H), 7.20–7.10 (m, 2H), 7.07–6.94 (m, 3H), 6.65–6.56 (m, 2H), 5.98 (d, *J* = 9.8 Hz, 1H), 3.37 (d, *J* = 13.0 Hz, 1H), 3.05 (d, *J* = 13.0 Hz, 1H), 1.59 (s, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 204.00, 145.41, 145.03, 136.60, 130.06, 129.77, 129.66, 129.42, 127.61, 127.30, 126.94, 126.40, 125.48, 52.81, 49.75, 26.37. HRMS (ESI) *m/z* calculated for $C_{18}H_{16}ONa$ $[M+Na]^+$ 271.1093, found 271.1091.

#### 4.2.12. 1-methyl-1-(3-methylbut-2-en-1-yl)naphthalen-2(1H)-one (**4 cc**)

Compound **4 cc** was prepared using method A. To a **1c** in reaction as an alkylating agent prenyl bromide **2c** (69.5 μL, 0.6 mmol) was used. Reaction mixture was stirred at room temperature for 20 h. Column chromatography PE/EtOAc 1–15 %. To give 1- methyl-1-(3-methylbut-2-en-1-yl)naphthalen-2(1*H*)-one **4 cc** as a yellow oil (52 mg, 46 %). PE/EtOAc = 10:1, $R_f$ = 0.40. IR (neat): 2969.11, 2928.57, 1659.22, 1565.34, 1449.85, 1396.83, 1376.22, 1299.64, 1239.70, 1207.78, 836.17, 756.15 cm−1$^1$H NMR (400 MHz, $CDCl_3$) δ 7.44–7.36 (m, 3H), 7.33–7.24 (m, 2H), 6.14 (d, *J* = 9.9 Hz, 1H), 4.70–4.60 (m, 1H), 2.82–2.74 (m, 1H), 2.50–2.41 (m, 1H), 1.50–1.48 (m, 3H), 1.47 (s, 3H), 1.42–1.39 (m, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 204.42, 146.21, 144.97, 134.63, 129.90, 129.83, 129.40, 126.87, 126.68, 125.36, 118.76, 51.99, 41.77, 25.86, 25.80, 17.86. HRMS (ESI) *m/z* calculated for $C_{16}H_{18}ONa$ $[M+Na]^+$ 249.1250, found 249.1246.

#### 4.2.13. 1-benzyl-1,3-dimethylnaphthalen-2(1H)-one (**4d**)

Compound **4d** was prepared using same method as for **4b**. **1d** solution in $Et_2O$ (1.5 mL). To a **1d** in reaction as an alkylating agent benzyl bromide **2a** (71.5 μL, 0.6 mmol) was used. Column chromatography PE/EtOAc 1–20 %. To give 1-benzyl-1,3-dimethylnaphthalen-2(1H)-one **4d** as a yellow oil (96 mg, 73 %). PE/EtOAc = 10:1, $R_f$ = 0.55. IR (neat): 3443.05, 2924.14, 1640.45,1493.26, 1451.54, 1373.16, 1273.43, 1029.31, 765.90, 698.80.$^1$H NMR (400 MHz, $CDCl_3$) δ 7.44–7.39 (m, 1H), 7.34 (td, *J* = 7.6, 1.4 Hz, 1H), 7.21 (td, *J* = 7.4, 1.3 Hz, 1H), 7.09–7.03 (m, 1H), 7.02–6.99 (m, 1H), 6.98–6.92 (m, 2H), 6.92–6.87 (m, 1H), 6.59–6.52 (m, 2H), 3.31 (d, *J* = 12.8 Hz, 1H), 3.00 (d, *J* = 12.8 Hz, 1H), 1.82 (d, *J* = 1.4 Hz, 3H), 1.58 (s, 4H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 203.96, 144.71, 141.54, 136.68, 132.70, 130.66, 129.39, 128.59, 128.40, 127.44, 126.93, 126.82, 126.35, 52.37, 50.55, 26.08, 15.78.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgments

We would like to thank Aleksander-Mati Müürisepp for IR analysis.

We thank for supporting this work Estonian Ministry of Education and Research grant no. PRG657 and PRG1031; the Centre of Excellence in Molecular Cell Engineering grant no. 2014-2020.4.01.15–0013 and European Regional Development fund grant no. 2014-2020.4.02.16-0050.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2021.132278.

## References

[1] R.J. Mayer, M. Breugst, N. Hampel, A.R. Ofial, H. Mayr, Ambident reactivity of phenolate anions revisited: a quantitative approach to phenolate reactivities, J. Org. Chem. 84 (2019) 8837–8858, https://doi.org/10.1021/acs.joc.9b01485.
[2] G. Keglevich, E. Bálint, É. Karsai, A. Grün, M. Bálint, I. Greiner, Chemoselectivity in the microwave-assisted solvent-free solid-liquid phase benzylation of phenols: O- versus C-alkylation, Tetrahedron Lett. 49 (2008) 5039–5042, https://doi.org/10.1016/j.tetlet.2008.06.051.
[3] D.Y. Curtin, R.R. Fraser, formation of cyclohexadienones by direct alkylation of phenols with saturated alkyl derivatives, J. Am. Chem. Soc. 80 (1958) 6016–6020, https://doi.org/10.1021/ja01555a033.
[4] R.S. Topgi, Novel synthesis of cyclohexa-2,4-dien-l-ones. Its use in a partial synthesis of the chromophore portion of phomenoic acid, J. Org. Chem. 54 (1989) 6125–6127, https://doi.org/10.1021/jo00287a030.
[5] E. Lopušanskaja, A. Kooli, A. Paju, I. Järving, M. Lopp, Towards ortho-selective electrophilic substitution/addition to phenolates in anhydrous solvents, Tetrahedron (2021), https://doi.org/10.1016/j.tet.2021.131935.
[6] A. Williamson, On etherification, Q. J. Chem. Soc. 4 (1852) 229–239. https://doi.org/doi:10.1039/QJ8520400229.
[7] A.R. Massah, M. Mosharafian, A.R. Momeni, H. Aliyan, H.J. Naghash, M. Adibnejad, Solvent-free Williamson synthesis: an efficient, simple, and convenient method for chemoselective etherification of phenols and bisphenols, Synth. Commun. 37 (2007) 1807–1815, https://doi.org/10.1080/00397910701316268.
[8] E. Balint, O. Kovacs, L. Drahos, G. Keglevich, Microwave-Assisted solid-liquid phase Alkylation of naphthols, Lett. Org. Chem. 10 (2013) 330–336, https://doi.org/10.2174/1570178611310050005.
[9] E. V Dehmlow, Influence of phase transfer catalyst structure on selectivity, Russ. Chem. Bull. 44 (1995) 1998–2005, https://doi.org/10.1007/BF00696697.
[10] N. Kornblum, R. Seltzer, P. Haberfield, Solvation as a factor in the alkylation of ambident anions: the importance of the dielectric factor, J. Am. Chem. Soc. 85 (1963) 1148–1154, https://doi.org/10.1021/ja00891a025.
[11] C. Li, B. Breit, Rhodium-Catalyzed dynamic kinetic asymmetric allylation of phenols and 2-hydroxypyridines, Chem. Eur J. 22 (2016) 14655–14663, https://doi.org/10.1002/chem.201603532.
[12] B.C. Gagea, A.N. Parvulescu, V.I. Parvulescu, A. Auroux, P. Grange, G. Poncelet, Alkylation of phenols and naphthols on silica-immobilized triflate derivatives, Catal. Lett. 91 (2003) 141–144, https://doi.org/10.1023/B:CATL.0000006330.84737.fb.
[13] G.A. Olah, R. Krishnamurti, G.K.S. Prakash, Friedel–crafts alkylations, in: Compr. Org. Synth., Elsevier, 1991, pp. 293–339, https://doi.org/10.1016/B978-0-08-052349-1.00065-2.
[14] A.Z. Halimehjani, F. Aryanasab, M.R. Saidi, Catalyst-free Friedel-Crafts alkylation of naphthols with nitrostyrenes in the presence of water, Tetrahedron Lett. 50 (2009) 1441–1443, https://doi.org/10.1016/j.tetlet.2009.01.067.
[15] C. Zhang, Y. Cheng, F. Li, Y. Luan, P. Li, W. Li, Organocatalytic enantioselective regiodivergent C–H bond functionalization of 1-naphthols with 1-azadienes, Adv. Synth. Catal. 362 (2020) 1286–1291, https://doi.org/10.1002/adsc.201901608.
[16] C.X. Zhuo, W. Zhang, S.L. You, Catalytic asymmetric dearomatization reactions, Angew. Chem. Int. Ed. 51 (2012) 12662–12686, https://doi.org/10.1002/anie.201204822.
[17] B. Yang, X. Zhai, S. Feng, D. Hu, Y. Deng, Z. Shao, Organocatalyzed intermolecular asymmetric allylic dearomatization of both α- and β-naphthols, Org. Lett. 21 (2019) 330–334, https://doi.org/10.1021/acs.orglett.8b03934.
[18] R.C. Neugebauer, U. Uchiechowska, R. Meier, H. Hruby, V. Valkov, E. Verdin, W. Sippl, M. Jung, Structure-activity studies on splitomicin derivatives as sirtuin inhibitors and computational prediction of binding mode, J. Med. Chem. 51 (2008) 1203–1213, https://doi.org/10.1021/jm700972e.
[19] G. Chen, X.M. Pi, C.Y. Yu, A new naphthalenone isolated from the green walnut husks of Juglans mandshurica Maxim, Nat. Prod. Res. 29 (2015) 174–179, https://doi.org/10.1080/14786419.2014.971789.
[20] D.L. Zhao, C.L. Shao, C.Y. Wang, M. Wang, L.J. Yang, C.Y. Wang, Naphthalenones and depsidones from a sponge-derived strain of the fungus Corynespora cassiicola, Molecules 21 (2016) 160, https://doi.org/10.3390/molecules21020160.
[21] J. An, M. Bandini, Recent advances in the catalytic dearomatization of naphthols, Eur. J. Org Chem. (2020) 4087–4097, https://doi.org/10.1002/ejoc.202000107.
[22] B. Yang, X. Zhai, S. Feng, Z. Shao, Dearomatization of naphthols using oxy-allyl cations: efficient construction of α-all-carbon quaternary center-containing 2-(2-oxocycloalkyl)cycloalkyl diketones, Org. Chem. Front. 5 (2018) 2794–2798, https://doi.org/10.1039/c8qo00783g.
[23] B. Miller, M.R. Saidi, Allyl and benzyl migrations in the rearrangements of naphthalenones, J. Am. Chem. Soc. 98 (1976) 2227–2238, https://doi.org/10.1021/ja00424a036.
[24] S. Yamada, T. Takeshita, J. Tanaka, Selective allylation of sodium naphtholate,

Bull. Chem. Soc. Jpn. 59 (1986) 2901–2902, https://doi.org/10.1246/bcsj.59.2901.
[25] M.A. Lovchik, A. Goeke, G. Frater, Stereoselective synthesis of cyclohexa-2,4-dien-1-ones and cyclohex-2-en-1-ones from phenols, Tetrahedron Asymmetry 17 (2006) 1693–1699, https://doi.org/10.1016/j.tetasy.2006.06.017.
[26] K. Watanabe, N. Yamagiwa, Y. Torisawa, Cyclopentyl methyl ether as a new and alternative process solvent, Org. Process Res. Dev. 11 (2007) 251–258, https://doi.org/10.1021/op0680136.
[27] T. Oguma, T. Katsuki, Iron-catalyzed dioxygen-driven C-C bond formation: oxidative dearomatization of 2-naphthols with construction of a chiral quaternary stereocenter, J. Am. Chem. Soc. 134 (2012), https://doi.org/10.1021/ja310203c, 20017–20020.
[28] Y. Terao, T. Satoh, M. Miura, M. Nomura, Palladium-catalyzed annulation reaction of o-bromobenzaldehydes with carbonyl compounds to produce naphthol and/or naphthalene derivatives, Tetrahedron 56 (2001) 1315–1320, https://doi.org/10.1016/S0040-4020(00)00043-0.

# Appendix 3

**Publication III**

A. Kooli, L. Wesenberg, M. Beslać, A. Krech, M. Lopp, T. Noël, M. Ošeka, Electrochemical Hydroxylation of Electron-Rich Arenes in Continuous-Flow. *Eur. J. Org. Chem.* **2022**, *e202200011*

EurJOC
European Journal of Organic Chemistry

Research Article
doi.org/10.1002/ejoc.202200011

Chemistry Europe
European Chemical Societies Publishing

www.eurjoc.org

# Electrochemical Hydroxylation of Electron-Rich Arenes in Continuous Flow

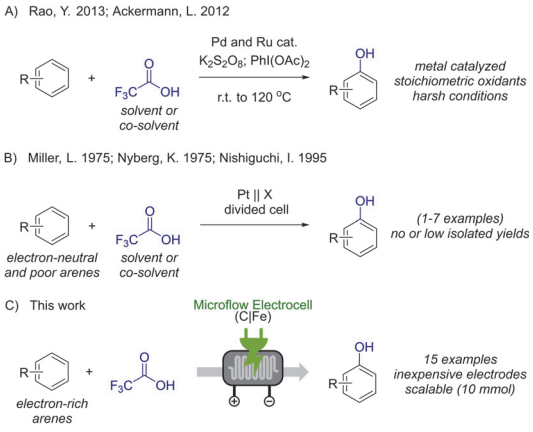
Anni Kooli,[a] Lars Wesenberg,[b] Marko Beslać,[c] Anastasiya Krech,[a] Margus Lopp,[a] Timothy Noël,[b] and Maksim Ošeka*[a]

*Dedicated to Laura Ošeka, who was born during the preparation of the manuscript for this article and helped to write it.*

Electrochemical hydroxylation of arenes by trifluoroacetic acid provides a straightforward access to aryl oxygen compounds under the mild and environmental benign reaction conditions. Harmful and pollutant stoichiometric amounts of oxidation reagents and the use of metal-catalysts can be avoided. Herein, we present a novel method for the synthesis of hydroxylated products from electron-rich arenes that was achieved by the implementation of a continuous-flow setup. The continuous nature of the process allowed to fine-tune the reactions conditions in order to prevent the decomposition of the sensitive products expanding the reaction scope beyond electron-poor and neutral arenes that were previously reported in the batch processes. Thus, synthetically valuable hydroxylated arenes were obtained in good yields with the residence time just over a minute. In order to demonstrate the reliability and the efficiency of the electrochemical flow setup, a scale up experiment was also performed.

## Introduction

Aryl oxygen compounds are important precursors for synthesis of valuable polymers, complex bioactive compounds, and are common structural motifs in many natural products.[1–3] Direct synthesis of phenols by oxidative hydroxylation of arenes is the most straightforward yet challenging approach as the products of such transformation are more electron-rich than substrates and are prone to be overoxidized. The traditional methods for arene hydroxylation rely on transition-metal catalysis and often require harsh reaction conditions.[4–6] Out of different possible options to hydroxylate arenes,[7,8] oxygen[9,10] and $H_2O_2$[11–13] are the most frequently used oxidative hydroxylation agents. Lutz Ackerman and Yu Rao have demonstrated methods in which trifluoroacetic acid was used as a hydroxyl group source in transition-metal catalyzed oxidation of arenes in the presence of stoichiometric oxidants (Scheme 1A).[14,15] Synthetic electrochemistry gathered a significant attention over the last decade since it is a great alternative to the traditional methods that require stoichiometric amounts of toxic and wasteful oxidants and metal catalysts.[16,17] In electrochemical transformations, electrons are used as safe and clean reactants to generate highly reactive radical intermediates under the mild reaction conditions providing access to the previously unapproachable reaction pathways.[18] Therefore, electrochemistry satisfies the principles of green chemistry in many aspects and can be considered sustainable.[19] In the early reported examples of electrochemical hydroxylation of arenes, trifluoroacetic acid was used in high excess, either as a solvent or co-solvent. Additionally, these transformations were carried out in an unfavorable divided electrochemical cell equipped mostly with costly platinum electrodes (Scheme 1B).[20–22] Moreover, these methodologies are limited in their broad reaction applicability with respect to electronic properties of arene substrates. Only seven




**Scheme 1.** Hydroxylation of arenes using TFA.

[a] A. Kooli, A. Krech, Prof. M. Lopp, Dr. M. Ošeka
Department of Chemistry and Biotechnology
Tallinn University of Technology
Akadeemia tee 15, 12618, Tallinn, Estonia
E-mail: maksim.oseka@taltech.ee
[b] Dr. L. Wesenberg, Prof. T. Noël
Van't Hoff Institute for Molecular Sciences (HIMS)
University of Amsterdam,
Science Park 904, 1098 XH Amsterdam, The Netherlands
[c] M. Beslać
Department of Chemical Engineering and Chemistry,
Micro Flow Chemistry & Synthetic Methodology
Eindhoven University of Technology
5612 AZ Eindhoven, The Netherlands

Supporting information for this article is available on the WWW under https://doi.org/10.1002/ejoc.202200011

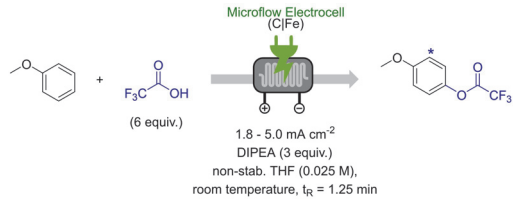
Research Article
doi.org/10.1002/ejoc.202200011



examples in total on the oxidation of electron-poor or neutral arenes with moderate yields are accessible. The more recent work by Nakajama et al. describes electrochemical esterification with TFA in a more feasible undivided cell setup, but this approach is limited only to one aromatic compound, benzene, leaving the scope of electron-rich arenes unexplored.[23] In the transformations described above, the substrate is directly oxidized on the electrode surface. Alternatively, the Ackerman group has recently demonstrated the indirect electrochemical hydroxylation of arenes catalyzed by transition-metals.[24,25]

Selective direct electrochemical hydroxylation of electron-rich arenes is still a difficult task. The desired hydroxylated product is much easier to oxidize than the starting compound, thus overoxidation and polymerization can easily occur leading to deposition on the electrode surface.[26,27] Fouling of electrodes is a common problem for electrochemical batch processes.[18,28] Moreover, such processes can also suffer from emerging local hot-spots and insufficient mixing. However, limitations of the batch-conditions can be overcome by transferring the reaction into a continuous-flow setup. In flow microreactors, the reaction mixture is continuously pumped through narrow channels between the two isolated electrodes (average 250 μm interelectrode gap), which ensures a very efficient mass and heat transfer by diffusion. High electrode surface-to-volume ratio and effective mixing significantly reduce the reaction time (typically 5 min in flow vs. overnight in batch), which helps to prevent degradation of sensitive products under electrochemical conditions and increases the reaction selectivity.[29–31] This knowledge and the previous experience helped us to develop a convenient continuous-flow methodology for the electrochemical hydroxylation of electron-rich aromatic compounds by the use of trifluoroacetic acid as the oxygen source.[32–35] With this procedure we successfully demonstrate a scale-up experiment as well (Scheme 1, C).

**Table 1.** Reaction Optimization.[a]




| Entry | Variation from the standard conditions | Conversion [%][b] | Yield [%][c] |
|---|---|---|---|
| 1 | TFA (3 equiv.), $Bu_3N$ (2 equiv.), $CH_3CN$ (0.1 M), $t_R = 5$ min | 71 | 31 |
| 2 | TFA (3 equiv.), $Bu_3N$ (2 equiv.), stab. THF (0.1 M), $t_R = 5$ min | 83 | 68 |
| 3 | TFA (3 equiv.), $Bu_3N$ (2 equiv.), stab. THF (0.1 M), $t_R = 5$ min graphite anode | 85 | 48 |
| 4 | TFA (3 equiv.), $Bu_3N$ (2 equiv.), stab. THF | 90 | 74 |
| 5 | none | 88 | 71 |
| 6 | no electricity | 0 | 0 |
| 7 | batch[d] | 5 | 5 |
| 8 | batch[e] | 33 | 29 |

[a] Reaction conditions: anisole (1.25 mmol), TFA (6 equiv.), DIPEA (3 equiv.), non-stabilized fresh THF (0.025 M), graphite anode/stainless steel cathode, 1.8–5.0 mA $cm^{-2}$, room temperature, residence time 1.25 min. [b] Conversion determined by GC-FID with decane as an internal standard. [c] Yield determined by GC-FID with decane as an internal standard. [d] Batch reaction conditions: 0.25 mmol scale, 3.3 mA $cm^{-2}$, 3.9 F, graphite anode/stainless steel cathode. [e] Batch reaction conditions: 3.3 mA $cm^{-2}$, 11.8 F, graphite anode/stainless steel cathode, 0.25 mmol scale.

## Results and Discussion

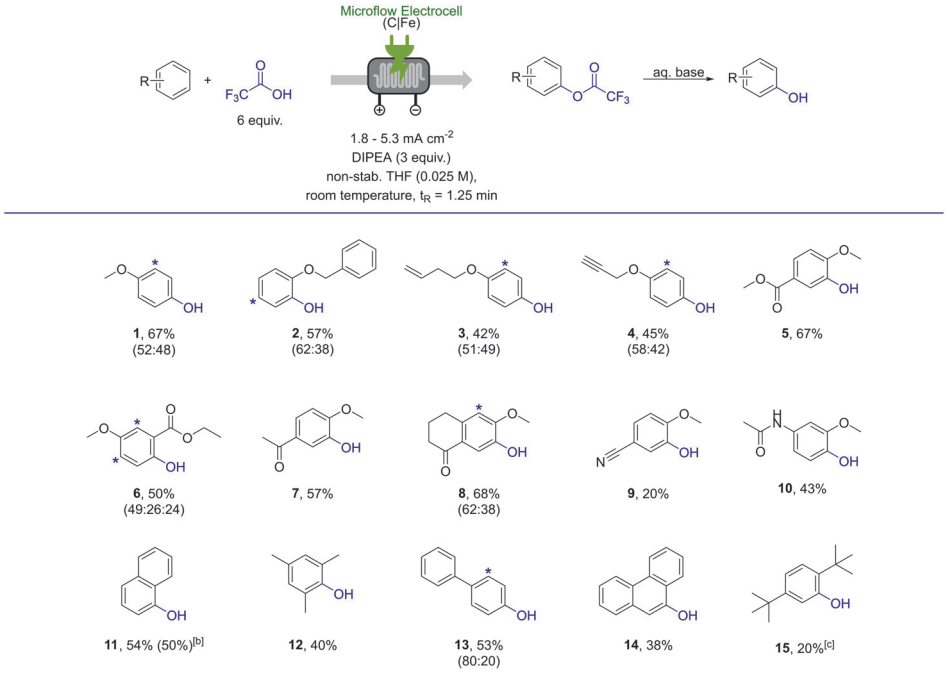
We started our investigation of the electrochemical hydroxylation of electron-rich arenes by performing the reaction under the galvanostatic conditions with anisole, as a model substrate, in an electrochemical microflow reactor.[36] In order to keep the reaction setup simple and inexpensive, an undivided-cell reactor equipped with the carbon based anode (graphite) and stainless steel cathode was used alternatively to the previously described methods.[20–22] We have performed an intensive screening for the optimal reaction conditions and the highlights are represented in Table 1 (see *Supporting Information* for the complete screening). First, the preliminary results revealed that TFA ester of cresol **1** forms in low yield, when the reaction is performed in acetonitrile, a typical first-choice solvent for radical transformation (Table 1, entry 1). The optimization experiments showed that the highest yields were achieved with incomplete conversions. Pushing the reactions to the full conversion by increasing the electric current resulted in the degradation of the desired product, as it is more reactive than the starting material. The main detected side products were overoxidized compounds and some arene–arene coupling products.[37,38] Trifluoroacetic acid has to be used in excess in comparison to the amine base to keep it protonated. First, this ensures enough conductivity by forming a salt and second its oxidation potential is thereby substantially elevated. Hence, oxidative deposition/degradation of the amine base can be avoided on the electrode surface, which could subsequently inhibit the electrochemical process. The yield of the reaction increased significantly after the solvent was changed to THF (Table 1, entry 2). Potentially, TFA ester is more stable in THF, while in acetonitrile it undergoes hydrolysis leading to the formation of cresol **1**, which is further overoxidized under the electrochemical conditions. Unfortunately, with the increased yield we have also faced some deposition of the side products on the electrodes over the operation time. To overcome this issue, different electrode combinations were tested. Particularly, we aimed to use graphite for the both electrodes, which would allow to slowly alter the polarity and suppress deposition.[39] However, the graphite cathode proved to be inefficient for the described transformation (Table 1, entry 3). The simultaneous dilution of the reaction mixture and the increase of the flow

Research Article
doi.org/10.1002/ejoc.202200011



rate enabled stable steady state with high yields while the process productivity remained at the same level. Any deposited materials could thus be flushed out of the active zone of the reactor, while the process remained performing constantly and efficiently. TFA ester of cresol **1** was obtained in 74% yield with the residence time only 1.25 minutes (Table 1, entry 4). To our surprise, these conditions appeared to be completely unproductive when other electron-rich arenes were tested. Further investigation revealed that BHT, used for THF stabilization, also inhibits oxidation of less electron-rich arenes. After reoptimization of the reaction conditions, we have achieved similar to previous results while using an increased amount of TFA and diisopropylethylamine instead of tributylamine and distilled or freshly opened non-stabilized THF (Table 1, entry 5). The newly established conditions were later successfully applied for other substrates in the series. It should be mentioned that the reaction became sensitive to the quality of solvent and amine after BHT was removed. Next, no conversion was observed without electricity confirming the electrochemical nature of the process (Table 1, entry 6). Finally, the reaction performed under the batch conditions provided the product with considerably lower yield comparing to flow (Table 1, entry 7 and 8). High electrode surface-to-volume ratio of the flow microreactor, short interelectrode gap and effective mixing allowed to obtain the product just in 1.25 minutes, whereas the batch process required 10 hours to reach only 33% conversion. Prolonged reaction time causes the decomposition of electron-rich compounds by overoxidation under the electrochemical conditions. Moreover, the Faraday-efficiency of the reaction performed in flow is much higher comparing to that of the batch process ($FE_{flow}$ 49% vs $FE_{batch}$ 5%), making the transformation more sustainable. The productivity of the flow process is 0.64 mmol $h^{-1}$ with 71% yield (0.9 mmol $h^{-1}$ with 100% theoretical yield).

With the optimal reaction conditions in hand, the scope of electrochemical hydroxylation of different electron-rich arenes was investigated (Scheme 2). After completion of the electrochemical reaction, the crude mixture was treated with an aqueous base to yield the hydroxylated product upon TFA ester hydrolysis. Anisole and its derivatives provided a mixture of *ortho*- and *para*-isomers, which are chromatographically separable (Scheme 2, compounds **1**–**4**). However, we kept isomers of cresol **1** unseparated to avoid evaporation of the volatile *ortho*-isomer. Functional groups that might be sensitive towards radical reactions, such as benzyl, propargyl and terminal double bond, stayed intact under our electrochemical conditions. Next, we studied the influence of electron-withdrawing groups on the reactivity of the substrates. Even though these compounds required higher current densities to reach useful conversion rates, the corresponding products were isolated in the highest yields (Scheme 2, compounds **5**–**8**). Both carboxyl and carbonyl groups tolerated the work-up procedure well and did not

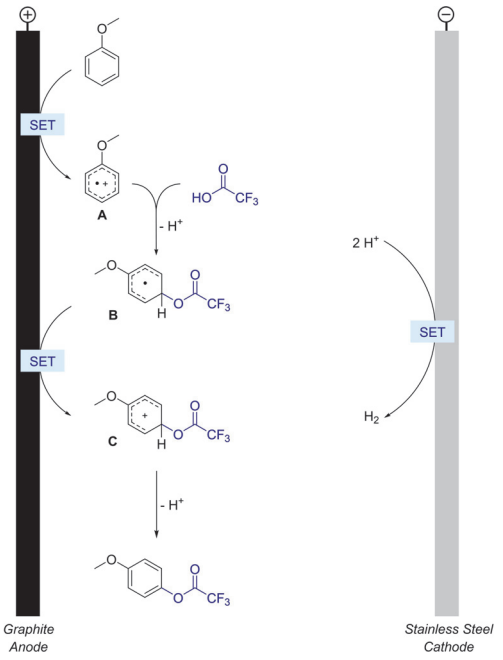



**Scheme 2.** Scope of hydroxylation of electron-rich arenes. [a] Reaction conditions: arene (1 mmol), TFA (6 equiv.), DIPEA (3 equiv.), non-stabilized fresh THF (0.025 M), graphite anode/stainless steel cathode, 1.8–5.3 mA $cm^{-2}$, room temperature, residence time 1.25 min, collected for 66.6 min. Work-up with saturated $NaHCO_3$. In brackets the ratio of different isomers is shown. The overall isolated yield is given for the chromatographically separated isomers of compounds **2**–**4**, **6** and **8**. [b] 10 mmol scale reaction collected for 66 h 6 min. [c] Residence time 2.5 min, collected for 133.2 min.

Research Article
doi.org/10.1002/ejoc.202200011


undergo hydrolysis nor aldol reaction. Unfortunately, 4-methoxybenzonitrile showed low conversion even at high current giving the product in rather low yield (Scheme 2, compound **9**). When acetyl protected 4-methoxyaniline was submitted to the electrochemical reaction, the obtained hydroxylated product contained methoxy group at the *meta*-position (Scheme 2, compound **10**). Potentially, the methyl group migrated from one oxygen-atom to another during the basic work-up procedure. Finally, we have turned our attention to other electron-rich arenes that do not contain methoxy group in the structure (Scheme 2, compounds **11**–**15**). Naphthalene reacted smoothly under the standard reaction conditions and 1-naphthol **11** was obtained exclusively in good yield. In order to demonstrate the usefulness of the developed method and the reliability of the flow process, we performed the scale up experiment (10 mmol) without any additional optimization by pumping the reaction mixture for a prolonged time.[30,31,40] Further, the electrochemical hydroxylation of mesitylene and biphenyl proceeded similarly to other electron-rich arenes and products were isolated in good yields and high regioselectivity for the latter (Scheme 2, compounds **12** and **13**). Although in the reaction with phenanthrene the preliminary experiments demonstrated very promising results, isolation of phenanthrol **14** proved challenging, as it was prone to the partial decomposition during the work-up. Moreover, electrochemical oxidation of anthracene in the presence of trifluoroacetic acid proceeded very efficiently providing the corresponding ester as a single isomer with the highest NMR yield (85 %) in the series. However, despite the stability of the corresponding TFA ester under the electrochemical conditions, 9-anthracenol was oxidized by atmospheric oxygen and formed dimeric compound upon the work-up leading to the complete loss of the desired product (for more information see *Supporting Information*). An attempt to isolate TFA ester of anthracenol resulted in sluggish yield, as it readily hydrolyzed on silica gel and decomposed. On the contrary, 1,4-di-*tert*-butylbenzene stayed almost unreactive under the standard reaction condition, probably due to the steric hindrance from two *tert*-butyl groups, and only a small amount of compound **15** was obtained, when the reaction was performed at lower flow rate. Finally, it is worth mentioning that the highest possible yields for all the substrates were obtained without reaching the full conversion making it possible to recover unreacted starting material.

We propose that the electrochemical transformation is initiated by a single electron transfer (SET) oxidation of an electron-rich arene on the surface of anode (Scheme 3). Being a strong electrophile, radical cation **A** is trapped by trifluoroacetic acid leading to the formation of the neutral radical **B**, which further undergoes second oxidation event. Finally, the aromatic system is restored upon deprotonation of cation **C** by the base. Simultaneously with oxidative processes, hydrogen reduction occurs as a cathodic half-reaction. After completion of the electrochemical part of the reaction sequence, TFA ester is hydrolyzed by aqueous base during the work-up procedure to yield the corresponding hydroxylated product. Comparing our experimental results to the previously published data,[41,42] it can be assumed that the working oxidation potential window for




**Scheme 3.** Proposed mechanism.

the developed method is approximately 1.6–2.1 V *vs* SCE with anisole in the middle. For the substrates with higher $E_{OX}$ only traces of products were observed, while solvent oxidation was prevalent. On the contrary, it was challenging to perform mono hydroxylation of very electron-rich arenes with $E_{OX}$ lower than 1.6 volts, as they tend to be overoxidized or/and form arene–arene coupling products.[26,27]

## Conclusion

In conclusion, we have reported the electrochemical hydroxylation of electron-rich arenes. The developed transformation is performed under the continuous-flow conditions that allowed to obtain sensitive products in only 1.25 minutes residence time. The method can be straightforwardly scaled up to the synthetically useful scale. Valuable hydroxylated arenes were obtained in good yields without the use of harmful stoichiometric oxidants or metal-catalysts, demonstrating the sustainability of this presented electrochemical procedure.

## Experimental Section

**General information**. All capillary tubing and microfluidic fittings were purchased from IDEX Health & Science. Disposable syringes were from BD Discardit II®, NORM-JECT® purchased from VWR Scientific. Syringe pumps used: Chemix Inc. Fusion 200 Touch and KD Scientific Inc. KDS-200-CE. Reagents and dry solvents were

bought from Sigma Aldrich, TCI, Honeywell and Fluorochem and are used as received. Technical solvents were bought from VWR International, Keemiakaubandus AS and Biosolve, and are used as received. THF refers to tetrahydrofuran, when needed THF was distilled over $LiAlH_4$, PE refers to petroleum ether b.p 40–60 °C, EtOAc refers to ethyl acetate, DCM refers to dichloromethane. $^1$H, $^{19}$F and $^{13}$C NMR spectra were recorded on a Bruker Avance III instrument or Bruker-Avance 400 at 400 MHz for $^1$H, 377 MHz for $^{19}$F and 100 MHz for $^{13}$C. $^1$H NMR spectra are reported in parts per million (ppm) downfield relative to $CD_3OD$ (3.31 ppm), DMSO-$d_6$ (2.50 ppm) or $CDCl_3$ (7.26 ppm) and $^{13}$C NMR spectra are reported in ppm relative to $CD_3OD$ (49.00 ppm), DMSO-$d_6$ (39.52 ppm) or $CDCl_3$ (77.16 ppm) unless stated otherwise. GC analyses were performed on a GC-MS combination (Shimadzu GC-2010 Plus coupled to a Mass Spectrometer; Shimadzu GCMS-QP 2010 Ultra) with an auto sampler unit (AOC-20i, Shimadzu) and GC-FID (Shimadzu GC-2010) with an auto sampler unit (AOC-20i, Shimadzu). Precoated silica gel plates (Merck 60 F254 or F254, Supelco Sigma-Aldrich™) were used for TLC. Flash column chromatography was performed on a Biotage® Isolera Prime with silica gel Kieselgel 63–200 μm.

For all electrochemical continuous-flow reactions, a homemade flow cell was used, together with a Velleman LABPS3005D power supply (for more information see *Supporting information*). The cell consists of a working electrode and a counter electrode, with a PTFE (polytetrafluoroethylene) gasket containing micro-channels in between. The material used for the electrodes were stainless steel electrode (316 L) and Graphite AC-K800 premium Grade (purchased by AgieCharmilles). The active reactor volume is 700 μL. This results in an undivided electrochemical cell. In the cell, direct contact between the electrode surface and the reaction mixture is established. The reaction mixture is pumped through the system via syringe pump, and is collected in a glass vial. All the technical data of the electrochemical microreactor are reported elsewhere.[36]

**Voltammograms**. Arene (1.0 equiv., 1.25 mmol) together with trifluoroacetic acid (6 equiv., 7.50 mmol, 0.57 mL) and *N*,*N*-diisopropylethylamine (DIPEA, 3.0 equiv., 3.75 mmol, 0.65 mL) were charged to 50 mL volumetric flask and filled with freshly distilled THF (0.025 M) until the bar. The mixture was swirled until homogeneous and taken up into a 50 mL disposable syringe. The solution was pumped through the electrochemical setup with a fixed flowrate of 0.6 mL/min to give a residence time of 1.25 minutes in the active part of the reactor, equipped with a graphite anode, steel cathode divided by a 0.25 mm thick Teflon gasket. Next, the current was increased from 50 mA to 150 mA with increments of 10 mA. After steady reaction state was reached (10 minutes at 0.6 mL/min), the corresponding potential was noted and a sample (0.1 mL) was collected in a vial for each data point. The samples were diluted with DCM and analyzed using GC-MS with decane or dodecane as an internal standard.

**General procedure**. Arene (1.0 equiv., 1.25 mmol) together with trifluoroacetic acid (6 equiv., 7.50 mmol, 0.57 mL) and *N*,*N*-diisopropylethylamine (DIPEA, 3.0 equiv., 3.75 mmol, 0.65 mL) were charged to 50 mL volumetric flask and filled with freshly distilled THF (0.025 M) until the bar. The mixture was swirled until homogeneous and taken up into a 50 mL disposable syringe. The solution was pumped through the electrochemical setup with a fixed flowrate of 0.6 mL/min to give a residence time of 1.25 minutes in the active part of the reactor, equipped with a graphite anode, steel cathode divided by a 0.25 mm thick Teflon gasket. Next, the constant current (selected on the basis of the voltammograms recorded) was applied and the system was stabilized for 10minutes. After steady state was reached, the reaction mixture was collected to a 100 mL round-bottom flask for 66.6 min, which corresponds to 1.0 mmol scale. The crude mixture was concentrated under vacuum and saturated aq. $NaHCO_3$ (25 mL) was added to the flask. The reaction mixture was vigorously stirred overnight at room temperature to achieve full hydrolysis of TFA ester. Next, the reaction mixture was extracted with DCM (4×15 mL) first from $NaHCO_3$ solution and then from 1 M HCl solution (25 mL). The organic layers were combined, dried using a phase separator and concentrated under vacuum. The crude product was purified by flash column chromatography on silica gel and analyzed by TLC, GS-MS, $^{19}$F-NMR, $^1$H-NMR and $^{13}$C-NMR.

**4-Methoxyphenol (1 a) and 2-methoxyphenol (1 b).**[43] Reaction was performed following the general procedure at 70 mA for 66.6 minutes. Purified by flash column chromatography on silica gel (5–50 % of $Et_2O$ in pentane) to give mixture of isomers **1 a** and **1 b** as a colorless oil in 67 % yield (83 mg, 0.67 mmol) and isomer ratio 52 : 48. $^1$H NMR of **1 a** (399 MHz, MeOD) δ 6.75 (d, *J* = 9.1 Hz, 2H, Ar–H), 6.70 (d, *J* = 9.0 Hz, 2H, Ar–H), 3.71 (s, 3H, $OCH_3$). $^{13}$C NMR of **1 a** (100 MHz, MeOD) δ = 154.5, 149.0, 116.8, 115.7, 56.2. MS of **1 a** (70 eV) *m/z*: 124 (96) $[M]^+$, 109 (100), 81 (48). $^1$H NMR of **1 b** (399 MHz, MeOD) δ 6.95–6.85 (m, 1H, Ar–H), 6.81–6.75 (m, 3H, Ar–H), 3.83 (s, 3H, $OCH_3$). $^{13}$C NMR of **1 b** (100 MHz, MeOD) δ = 152.2, 147.6, 122.2, 120.8, 116.3, 112.8, 56.3. MS of **1 b** (70 eV) *m/z*: 124 (89) $[M]^+$, 109 (100), 81 (58).

**2-(Benzyloxy)phenol (2 a)**[44] **and 4-(benzyloxy)phenol (2 b).**[45] Reaction was performed following the general procedure at 70 mA for 66.6 minutes. Purified by flash column chromatography on silica (5–50 % of $Et_2O$ in PE) to give **2 a** as a yellow oil and **2 b** as a white solid in 57 % combined yield (113 mg, 0.56 mmol) and isomer ratio 62 : 38. $^1$H NMR of **2 a** (400 MHz, $CDCl_3$) δ 7.48–7.35 (m, 5H, Ar–H), 7.01–6.82 (m, 4H, Ar–H), 5.72 (s, 1H, OH), 5.12 (s, 2H, $OCH_2$). $^{13}$C NMR of **2 a** (101 MHz, $CDCl_3$) δ = 146.1, 145.9, 136.5, 128.8, 128.5, 127.9, 122.0, 120.2, 114.9, 112.4, 71.2. 2-orto MS of **2 a** (70 eV) *m/z*: 200 (6) $[M]^+$, 92 (9), 91 (100). $^1$H NMR of 2b (400 MHz, $CDCl_3$) δ 7.46–7.35 (m, 4H, Ar–H), 7.35–7.29 (m, 1H, Ar–H), 6.86 (d, *J* = 9.0 Hz, 2H, Ar–H), 6.76 (d, *J* = 9.0 Hz, 2H, Ar–H), 5.01 (s, 2H, $OCH_2$), 4.51 (s, 1H, OH). $^{13}$C NMR of **2 b** (101 MHz, $CDCl_3$) δ = 153.2, 149.8, 137.4, 128.7, 128.0, 127.6, 116.20, 116.18, 70.9. MS of **2 b** (70 eV) *m/z*: 200 (11) $[M]^+$, 92 (8), 91 (100).

**4-(But-3-en-1-yloxy)phenol (3 a)**[46] **and 2-(but-3-en-1-yloxy)phenol (3 b).**[47] Reaction was performed following the general procedure at 50 mA for 66.6 minutes. Purified by flash column chromatography on silica gel (5–30 % of $Et_2O$ in PE) to give **3 a** as a yellow solid and **3 b** as a yellow oil in 42 % combined yield (69 mg, 0.42 mmol) and isomer ratio 51 : 49. $^1$H NMR of **3 a** (400 MHz, $CDCl_3$) δ 6.80 (d, *J* = 9.4 Hz, 2H, Ar–H), 6.75 (d, *J* = 9.4 Hz, 2H, Ar–H), 5.90 (ddt, *J* = 17.1, 10.3, 6.7 Hz, 1H, *CH*=$CH_2$), 5.16 (dq, *J* = 17.2, 1.6 Hz, 1H, =$CH_2$), 5.10 (dq, *J* = 10.3, 1.3 Hz, 1H, =$CH_2$), 4.91 (s, 1H, OH), 3.96 (t, *J* = 6.7 Hz, 2H, $OCH_2$), 2.52 (qt, *J* = 6.8, 1.4 Hz, 2H, CH–*$CH_2$*–$CH_2$). $^{13}$C NMR of **3 a** (101 MHz, $CDCl_3$) δ = 153.1, 149.7, 134.7, 117.1, 116.2, 116.0, 68.2, 33.9. MS of **3 a** (70 eV) *m/z*: 164 (25) $[M]^+$, 110 (100), 55 (40). $^1$H NMR of **3 b** (400 MHz, $CDCl_3$) δ 6.97–6.92 (m, 1H, Ar–H), 6.91–6.80 (m, 3H, Ar–H), 5.90 (ddt, *J* = 17.1, 10.3, 6.7 Hz, 1H, *CH*=$CH_2$), 5.69 (s, 1H, OH), 5.20 (dq, *J* = 17.2, 1.6 Hz, 1H, =$CH_2$), 5.15 (dq, *J* = 10.2, 1.4 Hz, 1H, =$CH_2$), 4.11 (t, *J* = 6.5 Hz, 2H, $OCH_2$), 2.57 (qt, *J* = 6.6, 1.4 Hz, 2H, CH–*$CH_2$*–$CH_2$). $^{13}$C NMR of **3 b** (101 MHz, $CDCl_3$) δ = 146.1, 145.9, 134.3, 121.8, 120.2, 117.6, 114.7, 112.2, 68.2, 33.8. MS of **3 b** (70 eV) *m/z*: 164 (31) $[M]^+$, 110 (78), 55 (100).

**4-(Prop-2-yn-1-yloxy)phenol (4 a)**[48] **and 2-(prop-2-yn-1-yloxy)phenol (4 b).**[49] Reaction was performed following the general procedure at 70 mA for 66.6 minutes. Purified by flash column chromatography on silica gel (5–50 % of $Et_2O$ in PE) to give **4 a** as a yellow oil and **4 b** as a yellow oil in 45 % combined yield (67 mg, 0.45 mmol) and isomer ratio 58 : 42. $^1$H NMR of **4 a** (400 MHz, $CDCl_3$) δ 6.90–6.84 (m, 2H, Ar–H), 6.80–6.75 (m, 2H, Ar–H), 4.76 (s, 1H, OH), 4.63 (d, *J* = 2.4 Hz, 2H, $OCH_2$), 2.51 (t, *J* = 2.4 Hz, 1H, ≡CH). $^{13}$C NMR of **4 a** (101 MHz, $CDCl_3$) δ = 151.9, 150.4,

116.5, 116.2, 79.0, 75.5, 56.8. MS of **4a** (70 eV) *m/z*: 148 (31) $[M]^+$, 109 (100). $^1$H NMR of **4b** (400 MHz, $CDCl_3$) δ 7.01–6.90 (m, 3H, Ar–H), 6.88–6.83 (m, 1H, Ar–H), 5.63 (s, 1H, OH), 4.76 (d, *J* = 2.4 Hz, 2H, $OCH_2$), 2.56 (t, *J* = 2.4 Hz, 1H, ≡CH). $^{13}$C NMR of **4b** (101 MHz, $CDCl_3$) δ = 146.3, 144.8, 122.9, 120.3, 115.3, 113.0, 78.2, 76.3, 57.2. MS of **4b** (70 eV) *m/z*: 148 (40) $[M]^+$, 109 (100).

**Methyl 3-hydroxy-4-methoxybenzoate (5).**[50] Reaction was performed following the general procedure at 130 mA for 66.6 minutes. Purified by flash column chromatography on silica gel (5–35% of EtOAc in PE) to give **5** as a colorless oil in 67% yield (122 mg, 0.67 mmol). $^1$H NMR of **5** (400 MHz, MeOD) δ 7.53 (dd, J = 8.5, 2.1 Hz, 1H, Ar–H), 7.42 (d, J = 2.1 Hz, 1H, Ar–H), 6.98 (d, J = 8.5 Hz, 1H, Ar–H), 3.91 (s, 3H, $OCH_3$), 3.85 (s, 3H, OCH3). $^{13}$C NMR of **5** (101 MHz, MeOD) δ = 168.6, 153.4, 147.5, 123.9, 123.4, 117.0, 111.8, 56.4, 52.4. MS of **5** (70 eV) *m/z*: 182 (51) $[M]^+$, 167 (4), 151 (100), 123 (24), 108 (10).

**Ethyl 2-hydroxy-5-methoxybenzoate (6a),**[51] **ethyl 4-hydroxy-3-methoxybenzoate (6b),**[52] **and ethyl 2-hydroxy-3-methoxybenzoate (6c).**[51] Reaction was performed following the general procedure at 90 mA for 66.6 minutes. Purified by flash column chromatography on silica gel (10–30% of $Et_2O$ in PE) to give **6a** as a colorless oil, **6b** as a beige solid and **6c** as a colorless oil in 50% combined yield (99 mg, 0.5 mmol) and isomer ratio 49:26:24. $^1$H NMR of **6a** (400 MHz, $CDCl_3$) δ 10.45 (s, 1H, OH), 7.29 (d, *J* = 3.2 Hz, 1H, Ar–H), 7.07 (dd, *J* = 9.1, 3.2 Hz, 1H, Ar–H), 6.90 (d, *J* = 9.0 Hz, 1H, Ar–H), 4.41 (q, *J* = 7.1 Hz, 2H, $OCH_2$), 3.78 (s, 3H, $OCH_3$), 1.41 (t, *J* = 7.1 Hz, 3H, $CH_2$–$CH_3$). $^{13}$C NMR of **6a** (101 MHz, $CDCl_3$) δ = 170.0, 156.2, 152.1, 123.8, 118.6, 112.3, 112.2, 61.6, 56.0, 14.3. MS of **6a** (70 eV) *m/z*: 196 (36) $[M]^+$, 150 (57), 122 (100), 107 (17), 92 (10). $^1$H NMR of **6b** (400 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 8.3, 1.9 Hz, 1H, Ar–H), 7.55 (d, *J* = 2.0 Hz, 1H, Ar–H), 6.94 (d, *J* = 8.3 Hz, 1H, Ar–H), 5.98 (s, 1H, OH), 4.35 (q, *J* = 7.1 Hz, 2H, $OCH_2$), 3.95 (s, 3H, $OCH_3$), 1.38 (t, *J* = 7.1 Hz, 3H, $CH_2$–$CH_3$). $^{13}$C NMR of **6b** (101 MHz, $CDCl_3$) δ = 166.6, 150.0, 146.3, 124.3, 122.8, 114.1, 111.8, 60.9, 56.3, 14.5. MS of **6b** (70 eV) *m/z*: 196 (28) $[M]^+$, 150 (100), 122 (17), 107 (25). $^1$H NMR of **6c** (400 MHz, $CDCl_3$) δ 11.09 (bs, 1H, OH), 7.44 (dd, *J* = 8.1, 1.5 Hz, 1H, Ar–H), 7.03 (dd, *J* = 7.9, 1.5 Hz, 1H, Ar–H), 6.81 (t, *J* = 8.0 Hz, 1H, Ar–H), 4.40 (q, *J* = 7.1 Hz, 2H, $OCH_2$), 3.89 (s, 3H, $OCH_3$), 1.41 (t, *J* = 7.1 Hz, 3H, $CH_2$–$CH_3$). $^{13}$C NMR of **6c** (101 MHz, $CDCl_3$) δ = 170.6, 152.2, 148.6, 121.2, 118.5, 116.5, 112.9, 61.7, 56.3, 14.3. MS of **6c** (70 eV) *m/z*: 196 (44) $[M]^+$, 151 (100), 123 (22), 108 (8).

**1-(3-Hydroxy-4-methoxyphenyl)ethan-1-one (7).**[53] Reaction was performed following the general procedure at 100 mA for 66.6 minutes. Purified by flash column chromatography on silica gel (2–10% of $Et_2O$ in DCM) to give **7** as a yellowish solid in 57% yield (94 mg, 0.56 mmol). $^1$H NMR of **7** (400 MHz, MeOD) δ 7.54 (dd, *J* = 8.4, 2.2 Hz, 1H, Ar–H), 7.41 (d, *J* = 2.2 Hz, 1H, Ar–H), 6.99 (d, *J* = 8.5 Hz, 1H, Ar–H), 3.92 (s, 3H, $OCH_3$), 2.52 (s, 3H, C=$OCH_3$). $^{13}$C NMR of **7** (101 MHz, MeOD) δ = 199.6, 153.8, 147.6, 131.7, 123.1, 115.7, 111.7, 56.4, 26.3. MS of **7** (70 eV) *m/z*: 166 (47) $[M]^+$, 151 (100), 123 (33), 108 (11).

**7-Hydroxy-6-methoxy-3,4-dihydronaphthalen-1(2*H*)-one (8a) and 5-hydroxy-6-methoxy-3,4-dihydronaphthalen-1(2*H*)-one (8b).**[54–56] Reaction was performed following the general procedure at 100 mA for 66.6 minutes. Purified by flash column chromatography on silica gel (1–30% of EtOAc in PE) to give **8a** as a white and **8b** as an orange solid in 67% combined yield (129 mg, 0.67 mmol) and isomer ratio 62:38. $^1$H NMR of **8a** (400 MHz, MeOD) δ = 7.34 (s, 1H, Ar–H), 6.80 (s, 1H, Ar–H), 3.91 (s, 3H, $OCH_3$), 2.89 (t, *J* = 6.1, 2H, Ar–$CH_2$), 2.54 (dd, *J* = 7.2, 5.8, 2H, C=$OCH_2$), 2.07 (p, *J* = 6.5, 2H, $CH_2$–$CH_2$–$CH_2$). $^{13}$C NMR of **8a** (101 MHz, MeOD) δ = 200.1, 154.4, 146.5, 140.4, 126.9, 113.3, 111.6, 56.4, 39.5, 30.3, 24.9. MS of **8a** (70 eV) *m/z*: 192 (81) $[M]^+$, 177 (12), 164 (47), 136 (100). $^1$H NMR of **8b** (400 MHz, MeOD) δ 7.55 (d, *J* = 8.7 Hz, 1H, Ar–H), 6.93 (d, *J* = 8.6 Hz, 1H, Ar–H), 3.93 (s, 3H, $OCH_3$), 2.91 (t, *J* = 6.2 Hz, 2H, Ar–$CH_2$), 2.56 (dd, *J* = 7.3, 5.7 Hz, 2H, C=$OCH_2$), 2.07 (p, *J* = 6.6 Hz, 2H, $CH_2$–$CH_2$–$CH_2$). $^{13}$C NMR of **8b** (101 MHz, MeOD) δ = 200.7, 153.0, 144.1, 132.9, 127.4, 120.5, 109.9, 56.4, 39.7, 24.00, 23.97. MS of **8b** (70 eV) *m/z*: 192 (100) $[M]^+$, 177 (28), 164 (86), 136 (76).

**3-Hydroxy-4-methoxybenzonitrile (9).**[57] Reaction was performed following the general procedure at 150 mA for 66.6 minutes. Purified by flash column chromatography on silica gel (2–15% of EtOAc in 1:1 PE:DCM) to give **9** as a white solid in 20% yield (30 mg, 0.2 mmol). $^1$H NMR of **9** (400 MHz, MeOD) δ 7.17 (dd, *J* = 8.3, 2.1 Hz, 1H, Ar–H), 7.05 (d, *J* = 2.1 Hz, 1H, Ar–H), 7.01 (d, *J* = 8.4 Hz, 1H, Ar–H), 3.90 (s, 3H, $OCH_3$). $^{13}$C NMR of **9** (101 MHz, MeOD) δ = 153.3, 148.4, 126.1, 120.2, 119.0, 112.9, 104.7, 56.5. MS of **9** (70 eV) *m/z*: 149 (71) $[M]^+$, 134 (100), 106 (66).

***N*-(4-Hydroxy-3-methoxyphenyl)acetamide (10).**[58] Reaction was performed following the general procedure at 50 mA for 66.6 minutes. Purified by flash column chromatography on silica gel (5–45% of EtOAc in DCM) to give **10** as an orange solid in 43% yield (77 mg, 0.42 mmol). $^1$H NMR of **10** (400 MHz, DMSO) δ 9.77 (s, 1H, NH), 9.27 (s, 1H, OH), 7.39 (d, *J* = 8.8 Hz, 1H, Ar–H), 6.42 (d, *J* = 2.8 Hz, 1H, Ar–H), 6.35 (dd, *J* = 8.8, 2.8 Hz, 1H, Ar–H), 3.67 (s, 3H, $OCH_3$), 2.04 (s, 3H, C=$OCH_3$). $^{13}$C NMR of **10** (101 MHz, DMSO) δ = 168.8, 156.9, 149.7, 123.9, 119.6, 104.2, 102.1, 55.0, 23.3. MS of **10** (70 eV) *m/z*: 181 (25) $[M]^+$, 139 (79), 124 (100).

**1-Naphthol (11).**[59] Reaction was performed following the general procedure at 75 mA for 66.6 minutes. Purified by flash column chromatography on silica gel (2–10% of EtOAc in PE) to give **11** as a pale pink solid in 54% yield (78 mg, 0.54 mmol). $^1$H NMR of **11** (400 MHz, $CDCl_3$) δ 8.21–8.16 (m, 1H, Ar–H), 7.86–7.78 (m, 1H, Ar–H), 7.53–7.47 (m, 2H, Ar–H), 7.45 (d, *J* = 8.3 Hz, 1H, Ar–H), 7.31 (dd, *J* = 8.3, 7.4 Hz, 1H, Ar–H), 6.82 (dd, *J* = 7.5, 1.0 Hz, 1H, Ar–H), 5.28 (s, 1H, OH). $^{13}$C NMR of **11** (101 MHz, $CDCl_3$) δ = 151.5, 134.9, 127.8, 126.6, 126.0, 125.4, 124.5, 121.7, 120.8, 108.7. MS of **11** (70 eV) *m/z*: 144 (95) $[M]^+$, 115 (100).

**2,4,6-Trimethylphenol (12).**[60] Reaction was performed following the general procedure at 100 mA for 66.6 minutes. Purified by flash column chromatography on silica gel (2–10% of EtOAc in hexane) to give **12** as a light-yellow solid in 40% yield (55 mg, 0.4 mmol). $^1$H NMR of **12** δ 6.80 (s, 2H, Ar–H), 4.38 (bs, 1H, OH), 2.22 (s, 9H, 3x$CH_3$). $^{13}$C NMR of **12** (100 MHz, $CDCl_3$) δ = 150.0, 129.4, 129.2, 122.9, 20.5, 16.0. MS of **12** (70 eV) *m/z*: 136 (71) $[M]^+$, 121 (100), 91 (29).

**[1,1′-Biphenyl]-4-ol (13).**[61] Reaction was performed following the general procedure at 70 mA for 66.6 minutes. Purified by flash column chromatography on silica gel (5–20% of EtOAc in hexane) to give **13** as a mixture of isomers (80:20) in 53% yield (91 mg, 0.53 mmol). $^1$H NMR of **13** the main *para*-isomer (400 MHz, MeOD) δ 7.59–7.48 (m, 2H, Ar–H), 7.44 (d, *J* = 8.6 Hz, 2H, Ar–H), 7.40–7.33 (m, 2H, Ar–H), 7.27–7.20 (m, 1H, Ar–H), 6.85 (d, *J* = 8.6 Hz, 2H, Ar–H). $^{13}$C NMR of **13** the main *para*-isomer (101 MHz, MeOD) δ = 158.2, 142.4, 133.9, 129.7, 129.0, 127.4, 127.4, 116.6. MS of **13** (70 eV) *m/z*: 170 (100) $[M]^+$, 141 (24).

**Phenanthren-9-ol (14).**[62] Reaction was performed following the general procedure at 50 mA for 66.6 minutes. Purified by flash column chromatography on silica gel (2–10% of EtOAc in PE) to give **14** as a yellow oil in 38% yield (74 mg, 0.38 mmol). $^1$H NMR of **14** (400 MHz, MeOD) δ 8.68 (d, *J* = 8.3 Hz, 1H, Ar–H), 8.59 (d, *J* = 8.1 Hz, 1H, Ar–H), 8.32 (dd, *J* = 8.1, 1.6 Hz, 1H, Ar–H), 7.69–7.55 (m, 3H, Ar–H), 7.49–7.38 (m, 2H, Ar–H), 7.01 (s, 1H, Ar–H). $^{13}$C NMR of **14** (101 MHz, MeOD) δ = 152.5, 134.9, 132.8, 127.9, 127.77, 127.75, 127.6, 127.4, 127.0, 124.6, 123.8, 123.6, 123.5, 105.9. MS of **14** (70 eV) *m/z*: 194 (100) $[M]^+$, 165 (89).

**2,5-Di-*tert*-butylphenol (15).**[63] Reaction was performed following the general procedure at 90 mA and 0.3 mL/min flowrate for 133.2 minutes. Purified by flash column chromatography on silica gel (2–10% of EtOAc in cyclohexane) to give **15** as a light-yellow solid in 20% yield (42 mg, 0.2 mmol). $^1$H NMR of **15** (399 MHz, MeOD) δ 7.07 (d, $J$ = 8.1 Hz, 1H, Ar–H), 6.77 (d, $J$ = 1.9 Hz, 1H, Ar–H), 6.74 (dd, $J$ = 8.1, 2.0 Hz, 1H, Ar–H), 1.36 (s, 9H, 3x$CH_3$), 1.27 (s, 9H, 3x$CH_3$). $^{13}$C NMR of **15** (100 MHz, MeOD) δ = 156.8, 150.9, 134.0, 127.0, 116.8, 114.3, 35.1, 34.9, 31.8, 30.1. MS of **15** (70 eV) *m/z*: 206 (18) $[M]^+$, 191 (100).

**Procedure for scale-up experiment**. Naphthalene (1.0 equiv., 12.5 mmol, 1.6 g) together with trifluoroacetic acid (6 equiv., 75.5 mmol, 5.74 mL) and *N*,*N*-diisopropylethylamine (DIPEA, 3.0 equiv., 37.5 mmol, 6.73 mL) were charged to 500 mL volumetric flask and filled with fresh non-stabilized HPLC-grade THF (0.025 M) until the bar. The mixture was stirred until the solution was homogeneous and placed into a 500 mL round-bottom flask. The solution was pumped using ThalesNano Micro HPLC pump through the electrochemical setup with a fixed flowrate of 0.6 mL/min to give a residence time of 1.25 minutes in the active part of the reactor, equipped with a graphite anode, steel cathode divided by a 0.25 mm thick Teflon gasket. Next, the constant current of 80 mA was applied and the system was stabilized for 10minutes. After steady state was reached, the reaction mixture was collected to a 500 mL round-bottom flask for 666 min, which corresponds to 10 mmol scale. The crude mixture was concentrated under vacuum and saturated aq. $NaHCO_3$ (100 mL) was added to the flask. The reaction mixture was vigorously stirred overnight at room temperature to achieve full hydrolysis of TFA ester. Next, the reaction mixture was extracted with DCM (4×150 mL) first from $NaHCO_3$ solution and then from 1 M HCl solution (100 mL). The organic layers were combined, dried over $Na_2SO_4$ and concentrated under vacuum. The crude product was purified by flash column chromatography on silica gel (5–20% of $Et_2O$ in PE) to give **1-naphthol (11)** as a pinkish solid in 50% yield (720 mg, 5.0 mmol).

## Acknowledgements

*The authors acknowledge financial support from the European Regional Development Fund and the programme Mobilitas Pluss (Grant No MOBTP180), the Estonian Ministry of Education and Research (Grant No PRG1031), the Centre of Excellence in Molecular Cell Engineering (2014-2020.4.01.15-0013) and Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) – 465153121. We also would like to thank Aleksander-Mati Müürisepp for GC-MS analysis of crude mixtures.*

## Conflict of Interest

The authors declare no conflict of interest.

## Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

**Keywords:** Aromatic substitution · Electrolysis · Flow chemistry · Hydroxylation

[1] M. Yamaguchi, in *PATAI'S Chem. Funct. Groups* (Ed.: Z. Rappoport), John Wiley & Sons, Inc., **2009**, pp. 1–52.
[2] M. T. Nguyen, E. S. Kryachko, L. G. Vanquickenborne, in *Chem. Phenols* (Ed.: Z. Rappoport), John Wiley & Sons, Inc., **2003**, pp. 1–189.
[3] D. Lin, M. Xiao, J. Zhao, Z. Li, B. Xing, X. Li, M. Kong, L. Li, Q. Zhang, Y. Liu, H. Chen, W. Qin, H. Wu, S. Chen, *Molecules* **2016**, *21*, 1374.
[4] S. Enthaler, A. Company, *Chem. Soc. Rev.* **2011**, *40*, 4912–4924.
[5] T. Yamaguchi, E. Yamaguchi, N. Tada, A. Itoh, *Adv. Synth. Catal.* **2015**, *357*, 2017–2021.
[6] N. Tezuka, K. Shimojo, K. Hirano, S. Komagawa, K. Yoshida, C. Wang, K. Miyamoto, T. Saito, R. Takita, M. Uchiyama, *J. Am. Chem. Soc.* **2016**, *138*, 9166–9171.
[7] D. Saha, P. Das, P. Biswas, J. Guin, *Chem. Asian J.* **2019**, *14*, 4534–4548.
[8] Z. Iqbal, A. Joshi, S. Ranjan De, *Adv. Synth. Catal.* **2020**, *362*, 5301–5351.
[9] Y. Yan, P. Feng, Q. Z. Zheng, Y. F. Liang, J. F. Lu, Y. Cui, N. Jiao, *Angew. Chem. Int. Ed.* **2013**, *52*, 5827–5831; *Angew. Chem.* **2013**, *125*, 5939–5943.
[10] P. Das, D. Saha, D. Saha, J. Guin, *ACS Catal.* **2016**, *6*, 6050–6054.
[11] J. F. Bartoli, V. Mouries-Mansuy, K. Le Barch-Ozette, M. Palacio, P. Battioni, D. Mansuy, *Chem. Commun.* **2000**, 827–828.
[12] O. V. Makhlynets, P. Das, S. Taktak, M. Flook, R. Mas-Ballesté, E. V. Rybak-Akimova, L. Que, *Chem. Eur. J.* **2009**, *15*, 13171–13180.
[13] M. M. Khodaei, A. Alizadeh, H. A. Hezarkhani, *Lett. Org. Chem.* **2018**, *15*, 878–882.
[14] V. S. Thirunavukkarasu, J. Hubrich, L. Ackermann, *Org. Lett.* **2012**, *14*, 4210–4213.
[15] Y. Rao, *Synlett* **2013**, *24*, 2472–2476.
[16] M. Yan, Y. Kawamata, P. S. Baran, *Chem. Rev.* **2017**, *117*, 13230–13319.
[17] C. Schotten, T. P. Nicholls, R. A. Bourne, N. Kapur, B. N. Nguyen, C. E. Willans, *Green Chem.* **2020**, *22*, 3358–3375.
[18] A. Wiebe, T. Gieshoff, S. Möhle, E. Rodrigo, M. Zirbes, S. R. Waldvogel, *Angew. Chem. Int. Ed.* **2018**, *57*, 5594–5619; *Angew. Chem.* **2018**, *130*, 5694–5721.
[19] B. A. Frontana-Uribe, R. D. Little, J. G. Ibanez, A. Palma, R. Vasquez-Medrano, *Green Chem.* **2010**, *12*, 2099–2119.
[20] Y. H. So, J. Y. Becker, L. L. Miller, *J. Chem. Soc. Chem. Commun.* **1975**, 262–263.
[21] Z. Blum, L. Cedheim, K. Nyberg, *Acta Chem. Scand. Ser. B* **1975**, *29*, 715–718.
[22] K. Fujimoto, H. Maekawa, Y. Tokuda, Y. Matsubara, T. Mizuno, I. Nishiguchi, *Synlett* **1995**, 661–662.
[23] T. Tajima, Y. Kishi, A. Nakajima, *Electrochim. Acta* **2009**, *54*, 5959–5963.
[24] L. Massignan, X. Tan, T. H. Meyer, R. Kuniyil, A. M. Messinis, L. Ackermann, *Angew. Chem. Int. Ed.* **2020**, *59*, 3184–3189; *Angew. Chem.* **2020**, *132*, 3210–3215.
[25] X. Tan, L. Massignan, X. Hou, J. Frey, J. C. A. Oliveira, M. N. Hussain, L. Ackermann, *Angew. Chem. Int. Ed.* **2021**, *60*, 13264–13270; *Angew. Chem.* **2021**, *133*, 13373–13379.
[26] S. R. Waldvogel, S. Lips, M. Selt, B. Riehl, C. J. Kampf, *Chem. Rev.* **2018**, *118*, 6706–6765.
[27] J. L. Röckl, D. Pollok, R. Franke, S. R. Waldvogel, *Acc. Chem. Res.* **2020**, *53*, 45–61.
[28] R. Francke, R. D. Little, *Chem. Soc. Rev.* **2014**, *43*, 2492–2521.
[29] M. B. Plutschack, B. Pieber, K. Gilmore, P. H. Seeberger, *Chem. Rev.* **2017**, *117*, 11796–11893.
[30] T. Noël, Y. Cao, G. Laudadio, *Acc. Chem. Res.* **2019**, *52*, 2858–2869.
[31] M. Elsherbini, T. Wirth, *Acc. Chem. Res.* **2019**, *52*, 3287–3296.
[32] G. Laudadio, E. Barmpoutsis, C. Schotten, L. Struik, S. Govaerts, D. L. Browne, T. Noël, *J. Am. Chem. Soc.* **2019**, *141*, 5664–5668.
[33] Y. Cao, B. Adriaenssens, A. de A. Bartolomeu, G. Laudadio, K. T. de Oliveira, T. Noël, *J. Flow Chem.* **2020**, *10*, 191–197.
[34] M. Ošeka, G. Laudadio, N. P. van Leest, M. Dyga, A. de A. Bartolomeu, L. J. Gooßen, B. de Bruin, K. T. de Oliveira, T. Noël, *Chem* **2021**, *7*, 255–266.
[35] L. Buglioni, M. Beslać, T. Noël, *J. Org. Chem.* **2021**, *86*, 16195–16203.
[36] G. Laudadio, W. de Smet, L. Struik, Y. Cao, T. Noël, *J. Flow Chem.* **2018**, *8*, 157–165.
[37] I. M. Malkowsky, C. E. Rommel, K. Wedeking, R. Fröhlich, K. Bergander, M. Nieger, C. Quaiser, U. Griesbach, H. Pütter, S. R. Waldvogel, *Eur. J. Org. Chem.* **2006**, 241–245.

[38] S. R. Waldvogel, *Pure Appl. Chem.* **2010**, *82*, 1055–1063.
[39] C. Kingston, M. D. Palkowitz, Y. Takahira, J. C. Vantourout, B. K. Peters, Y. Kawamata, P. S. Baran, *Acc. Chem. Res.* **2020**, *53*, 72–83.
[40] D. Pletcher, R. A. Green, R. C. D. Brown, *Chem. Rev.* **2018**, *118*, 4573–4591.
[41] P. B. Merkel, P. Luo, J. P. Dinnocenzo, S. Farid, *J. Org. Chem.* **2009**, *74*, 5163–5173.
[42] H. G. Roth, N. A. Romero, D. A. Nicewicz, *Synlett* **2016**, *27*, 714–723.
[43] R. Bernini, A. Coratti, G. Provenzano, G. Fabrizi, D. Tofani, *Tetrahedron* **2005**, *61*, 1821–1825.
[44] M. A. Brimble, Y. C. Liu, M. Trzoss, *Synthesis.* **2007**, *9*, 1392–1402.
[45] N. Shohji, T. Kawaji, S. Okamoto, *Org. Lett.* **2011**, *13*, 2626–2629.
[46] C. Martín-Santos, C. Jarava-Barrera, S. Del Pozo, A. Parra, S. Díaz-Tendero, R. Mas-Ballesté, S. Cabrera, J. Alemán, *Angew. Chem. Int. Ed.* **2014**, *53*, 8184–8189; *Angew. Chem.* **2014**, *126*, 8323–8328.
[47] D. J. Miller, B. U. Surfraz, M. Akhtar, D. Gani, R. K. Allemann, *Org. Biomol. Chem.* **2004**, *2*, 671–688.
[48] S. Punna, S. Meunier, M. G. Finn, *Org. Lett.* **2004**, *6*, 2777–2779.
[49] P. R. Loaiza, S. Löber, H. Hübner, P. Gmeiner, *Bioorg. Med. Chem.* **2009**, *17*, 5482–5487.
[50] R. J. Payne, E. M. M. Bulloch, A. D. Abell, C. Abell, *Org. Biomol. Chem.* **2005**, *3*, 3629–3635.
[51] Y. Yang, Y. Lin, Y. Rao, *Org. Lett.* **2012**, *14*, 2874–2877.
[52] V. V. Gaikwad, B. M. Bhanage, *Eur. J. Org. Chem.* **2018**, *2018*, 2877–2881.
[53] Y. Kong, K. Wang, M. C. Edler, E. Hamel, S. L. Mooberry, M. A. Paige, M. L. Brown, *Bioorg. Med. Chem.* **2010**, *18*, 971–977.
[54] F. D. Ramdayal, D. J. Kiemle, R. T. LaLonde, *J. Org. Chem.* **1999**, *64*, 4607–4609.
[55] A. M. Camelio, Y. Liang, A. M. Eliasen, T. C. Johnson, C. Yuan, A. W. Schuppe, K. N. Houk, D. Siegel, *J. Org. Chem.* **2015**, *80*, 8084–8095.
[56] A. Ghatak, J. M. Dorsey, C. M. Garner, K. G. Pinney, *Tetrahedron Lett.* **2003**, *44*, 4145–4148.
[57] J. R. Hwu, C. H. Hsu, F. F. Wong, C. S. Chung, G. H. Hakimelahi, *Synthesis.* **1998**, 329–332.
[58] D. Yan, G. Wang, F. Xiong, W. Y. Sun, Z. Shi, Y. Lu, S. Li, J. Zhao, *Nat. Commun.* **2018**, *9*, 1–9.
[59] T. Schulz, C. Torborg, B. Schäffner, J. Huang, A. Zapf, R. Kadyrov, A. Börner, M. Beller, *Angew. Chem. Int. Ed.* **2009**, *48*, 918–921; *Angew. Chem.* **2009**, *121*, 936–939.
[60] M. Jiang, H. J. Yang, Y. Li, Z. Y. Jia, H. Fu, *Chin. Chem. Lett.* **2014**, *25*, 715–719.
[61] S. Ishikawa, K. Manabe, *Angew. Chem. Int. Ed.* **2010**, *49*, 772–775; *Angew. Chem.* **2010**, *122*, 784–787.
[62] S. Lin, T. You, *Tetrahedron* **2008**, *64*, 9906–9910.
[63] H. Künzer, S. Berger, *J. Org. Chem.* **1985**, *50*, 3222–3223.

Manuscript received: January 6, 2022
Revised manuscript received: February 8, 2022
Accepted manuscript online: March 9, 2022

# Author's Other Publications, Conference Presentations

**Other publications:**

1. "Ettevaatust lõhnaõli!" *Tiiu*, April **2022**, p. 68. Interview about allergens found in perfumes with the Tiiu journal. https://tiiu-digi.ohtuleht.ee/1059374/ettevaatust-lohnaoli-imeline-parfuum-voib-tekitada-hoopis-allergia

**Television appearances:**

1. Interview about scented candles with Estonian Public Broadcasting (Eesti Rahvusringhääling) at "Terevisioon" 22.12.2021. https://novaator.err.ee/1608443813/keemik-tanaval-kondida-on-lohnakuunla-poletamisest-ohtlikum

2. Interview about the dangers of chemicals that nail technicians use for their work with TV3 at "Laser" 22.02.2022. https://laser.ee/tervis/karm-tode-geelkuuntest-akki-ilu-ei-peaks-siiski-nii-palju-ohvreid-noudma/

**Conference Presentations:**

1. A. Larin, A. Paju, M. Lopp, Synthesis of Different α-Naphthols and Dearomatization. 20$^{th}$ Tetrahedron Symposium, **2019**, Bangkok, Thailand (Poster).
2. A. Larin, A. Paju, M. Lopp, Erinevate α-naftoolide süntees ja dearomatiseerimine. XXXIV Estonian Chemistry Days: 100th Anniversary Scientific Conference, **2019**, Tallinn, Estonia (Poster).
3. A. Larin, M. Lopp, Dearomatization of Naphthols *via* Alkylation. GSFMT Scientific Conference, **2020**, Tallinn, Estonia (Poster).
4. A. Kooli, M. Ošeka, Electrochemical Synthesis of Aryl Alcohols in Continuous-Flow. 9$^{th}$ IUPAC International Conference on Green Chemistry, **2022**, Athens, Greece (Poster).

# Curriculum Vitae

**Personal data**

| | |
|---|---|
| Name: | Anni Kooli (née Larin) |
| Date of birth: | 16.06.1994 |
| Place of birth: | Tallinn, Estonia |
| Citizenship: | Estonian |

**Contact data**

| | |
|---|---|
| E-mail: | anni@kooli.org |

**Education**

| | |
|---|---|
| 2018–2022 | Tallinn University of Technology, Chemistry and Biotechnology – PhD |
| 2016–2018 | Tallinn University of Technology, Applied Chemistry and Biotechnology – MSc |
| 2013–2016 | Tallinn University of Technology, Applied Chemistry and Biotechnology – BSc |
| 2001–2013 | Tallinn Laagna High School |

**Language competence**

| | |
|---|---|
| Estonian | Native |
| English | Fluent |

**Professional employment**

| | |
|---|---|
| 2018– | Tallinn University of Technology, Department of Chemistry and Biotechnology, Early-stage researcher/PhD student |

**Professional associations**

| | |
|---|---|
| 2018– | The Estonian Chemical Society, member |

**Honours and awards**

| | |
|---|---|
| 2022 | Dora Plus Short study visit scholarship (T1.1) (The Archimedes Foundation, Estonia) |
| 2019 | Dora Plus Short study visit scholarship (T1.1) (The Archimedes Foundation, Estonia) |

**Teaching experience**

| | |
|---|---|
| Autumn 2019 | Organic chemistry I, exercise tutorials (undergraduate course) |

# Elulookirjeldus

**Isikuandmed**

| | |
|---|---|
| Nimi: | Anni Kooli (Larin) |
| Sünniaeg: | 16.06.1994 |
| Sünnikoht: | Tallinn, Eesti |
| Kodakondsus: | eesti |

**Kontaktandmed**

| | |
|---|---|
| E-post: | anni@kooli.org |

**Hariduskäik**

| | |
|---|---|
| 2018–2022 | Tallinna Tehnikaülikool, Keemia ja Biotehnoloogia – PhD |
| 2016–2018 | Tallinna Tehnikaülikool, Rakenduskeemia ja biotehnoloogia – MSc |
| 2013–2016 | Tallinna Tehnikaülikool, Rakenduskeemia ja biotehnoloogia – BSc |
| 2001–2013 | Tallinna Laagna Gümnaasium – Keskharidus |

**Keelteoskus**

| | |
|---|---|
| Eesti keel | Emakeel |
| Inglise keel | Kõrgtase |

**Teenistuskäik**

| | |
|---|---|
| 2018– | Tallinna Tehnikaülikool, Keemia ja biotehnoloogia instituut, Nooremteadur/doktorant |

**Kuuluvus erialaühingutesse**

| | |
|---|---|
| 2018– | Eesti keemiaselts, liige |

**Teaduspreemiad ja tunnustused**

| | |
|---|---|
| 2022 | Dora Pluss Lühiajalise õpirände stipendium (T1.1) (SA Archimedes, Eesti) |
| 2019 | Dora Pluss Lühiajalise õpirände stipendium (T1.1) (SA Archimedes, Eesti) |

**Õpetamiskogemus**

| | |
|---|---|
| Sügis 2019 | Orgaaniline keemia I, harjutustunnid (bakalaureuseõpe) |

ISSN 2585-6901 (PDF)
ISBN 978-9949-83-916-2 (PDF)