Tampere University

BENEDICTA AKUAMESU ASSOAH

Lewis Base-Catalyzed Modification of Ortho-Substituted Phenols

Tampere University Dissertations 160

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ACADEMIC DISSERTATION
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Dedication

Dedicated to my dad, Mr. Samuel K. Assoah

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stressful times. João R. Vale, thank you for nice friendship and help with HRMS measurements. Thank you Suvi Holmstedt for all the wonderful zumba sessions that helped to sweat off some of the hard times during the research. I really appreciate all the nice conversations we had sharing an office space. I am grateful to Joris Troussier, Aleksi Paakkunainen and Vesa Riihonen for their significant contributions towards my research work. I would also like to thank my former office mates Dr. Ekaterina Lisitsyna and Hanna Manninen for nice conversations.

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Most importantly, this is the doing of the Lord and it is marvelous in my eyes! I will bless the Lord at all times and His praises shall continually be in my mouth.

Tampere, October 2019

Benedicta A. Assoah

ABSTRACT

Lewis base catalysis in chemical transformations has received tremendous recognition in both academic and industrial applications over the years as it offers a convenient alternative to the use of expensive/toxic metal or large enzyme catalysts under mild reaction conditions. In light of this, efforts towards the development of synthetic strategies that employ Lewis base catalysts in mild and selective organic transformations are highly desirable.

In this thesis, we present an efficient Lewis base promoted hydrosilylation protocol with a novel cyclic 5-membered pinacol-derived chlorohydrosilane (PCS). This study provides information on the reactivity of this chlorohydrosilane as a hydride donor in the reduction of carbonyl and C=N moieties. Screening of various Lewis bases led to identification of DMPU as an effective catalyst for the hydrosilylation of salicylaldehydes. The role of the base as a catalyst in the reaction mechanism is further supported by computational studies. Hydroquinone serves as a starting material for the synthesis of formyl-hydroquinone, which was used to test the efficiency of our hydrosilylation protocol. The synthesis of hydroquinone from naturally available quinic acid was also studied. The hydrosilylation method was further developed for the preparation of novel tertiary alkylphenolmethyl amines employing pyridine as an effective Lewis base catalyst.

During the course of the study, the unprecedented preparation of 6, 12-disubstituted methanodibenzo[*b,f*][1,5]dioxocins from pyrrolidine-catalyzed self-condensation of 2'-hydroxyacetophenones was discovered and improved. This fascinating highly bridged polycyclic core is present in numerous biologically active natural products and pharmaceuticals.

The findings presented in this thesis exemplifies the high reactivity of PCS as a new reagent for Lewis base-catalyzed hydrosilylation. It is nevertheless envisioned that this silane finds usefulness in the hydrosilylation of other functional groups besides those employed in this work. In addition, the study provides mild and selective synthetic strategies to access diverse phenolic compounds of potential use by the pharmaceutical industry in the development of new bioactive molecules.

CONTENTS

ABBREVIATIONS

atm	atmosphere
Bn	benzyl
EDDA	ethylenediamine-*N*, *N*'-diacetic acid
DBU	1,8-diazabicyclo(5.4.0)undec-7-ene
DFT	density functional theory
DIPEA	*N*, *N*-di-isopropylethylene amine
DMAP	4-dimethylamino pyridine
DMF	dimethyl formamide
DMSO	dimethyl sulfoxide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
G	Gibbs free energy
Δ*G*	change in Gibbs free energy
GGA	generalized gradient approximation
HMPA	hexamethyl phosphoramide
HMTA	hexamethylenetetramine
HRMS	high-resolution mass spectrometry
LA	Lewis acid
LB	Lewis base
MCR	multicomponent reactions
MFA	*N*-methylformanilide
MS	molecular sieves
MRSA	methicillin-resistant *Staphylococcus aureus*
NMR	nuclear magnetic resonance
o	*ortho*
p	*para*
PBE	Perdew, Burke and Ernzerhof functional
PCM	polarisable continuum model
PCS	pinacol-derived chlorohydrosilane
PFA	paraformaldehyde
PMHS	polymethylhydrosiloxane

Py	pyridine
rt	room temperature
SMD	solvation model based on density
TBAF	tetra-n-butylammonium fluoride
*t*Bu	*tert*-butyl
*t*BuOK	potassium *tert*-butoxide
TES	triethylsilane
THF	tetrahydrofuran
TMEDA	*N*, *N*, *N'*, *N'*-tetramethylethylenediamine
TSAF	tris(dimethylamino)sulfonium difluoridetrimethyl silicate
UV	ultraviolet

ORIGINAL PUBLICATIONS

Publication I Benedicta Assoah, João R. Vale, Elina Kalenius, Luis F. Veiros, and Nuno R. Candeias. Lewis Base Catalyzed Intramolecular Reduction of Salicylaldehydes by Pinacol-Derived Chlorohydrosilane. *Eur. J. Org. Chem.* **2018**, 2910-2917.

Publication II Benedicta Assoah, Luis F. Veiros, Carlos A. M. Afonso, and Nuno R. Candeias. Biomass-Based and Oxidant-Free Preparation of Hydroquinone from Quinic Acid. *Eur. J. Org. Chem.* **2016**, 3856-3861.

Publication III Benedicta Assoah, Luis F. Veiros, and Nuno R. Candeias. Pinacol-Derived Chlorohydrosilane in Metal-Free Reductive Amination for the Preparation of Tertiary Alkylphenolmethyl Amine. *Org. Lett.* **2019**, *21*, 1402-1406.

Publication IV Benedicta Assoah, Vesa Riihonen, João R. Vale, Arto Valkonen, and Nuno R. Candeias. Synthesis of 6, 12-Disubstituted Methanodibenzo[*b,f*][1,5]dioxocins: Pyrrolidine Catalyzed Self-Condensation of 2'-Hydroxyacetophenones. *Molecules*, **2019**, *24*, 2405.

AUTHOR'S CONTRIBUTION

I Benedicta Assoah designed and carried out the synthesis including characterization of the compounds, performed the DFT calculations, interpreted the results and prepared the manuscript. João R. Vale contributed to the synthesis and characterization of some compounds. Elina Kalenius measured the HRMS of PCS. The DFT studies was supervised and results interpreted by Luis F. Veiros. Nuno R. Candeias supervised the work, contributed to the design of experiments, interpretation of the results and revision of the manuscript. All co-authors contributed to the writing of the manuscript.

II Benedicta Assoah contributed to the optimization of the methodology and drafted the manuscript. Nuno R. Candeias conceived and designed the experiments, characterized the compounds, interpreted the results, carried out the computational studies and revised the manuscript with contributions from all co-authors.

III Benedicta Assoah planned, carried out the synthesis and characterization of all compounds, performed the DFT calculations, interpreted the results and prepared the manuscript. Luis F. Veiros supervised the computational studies and contributed to the interpretation of results. Nuno R. Candeias supervised the work and contributed to the experimental design, interpretation of the results and revision of the final manuscript with contributions from all authors.

IV Benedicta Assoah conceived and carried out the synthesis, characterization of the compounds, interpreted the results and drafted the manuscript. Vesa Riihonen and João R. Vale contributed to performing the experiments. Arto Valkonen performed the X-ray crystallographic studies. Nuno R. Candeias supervised the work and contributed to the experimental design and interpretation of the results. The manuscript was written in collaboration with the co-authors.

1 INTRODUCTION

Phenolic compounds are ubiquitous functionalities found in natural products, pharmaceuticals, agrochemicals and synthetic materials. Phenolic compounds exhibit various biological activities such as antioxidant, anti-inflammatory, antimicrobial and antitumor properties providing wide-ranging health benefits [1-3]. These compounds are usually characterized by a simple aromatic ring with one or more hydroxyl groups or exist as a polymerized molecule such as lignin and can be grouped into flavonoids, phenolic acids or tannins. The nature of their molecular structure containing aromatic ring and hydroxyl groups affords them useful bioactivities[4]. Due to the high reactivity of phenols toward electrophilic aromatic substitution and their strong *ortho*/*para* directing ability, various groups can be attached to the aromatic ring [5] via acylation, amination, sulfonation and halogenation among others.

Ortho-substituted phenols are valuable precursors in accessing a wide range of medicinal [6-12] and industrially important compounds [5,13,14]. Thus, a variety of methods for their synthesis and functionalization has been developed over the years. Among these methods are traditional electrophilic and nucleophilic substitution chemistry to more recent protocols such as directed *ortho* metalation and catalytic cross coupling reactions [15,16]. Organosilane chemistry has seen recent expansion into various chemical transformations with synthetic endeavors in silicon based cross-coupling reactions [17-21], reductions [22], oxidations [23] and as directing groups for C-H functionalization [9,10]. These transformations usually require catalysts for which transition-metal catalysts have been exhaustively studied for these processes. However, in recent times, there has been an increased attention to the use of organocatalysts (Lewis acids/bases and Brønsted acids/bases) in modern chemical transformations as they offer the advantage of cost efficiency, enhanced selectivity, mild reaction conditions, functional group tolerance and easy purification of final products devoid of metal contaminants [24,25]. Thus, metal-free catalyzed chemical transformations in accessing substituted phenol derivatives, is an attractive field of study as it provides mild reaction conditions and enhanced selectivity. Lewis bases are seen to effect a much more diverse array of reactivity patterns compared to the

influence of Lewis acids on chemical transformations. In addition, Lewis bases have the ability to enhance both the nucleophilic and electrophilic character of the substrate they are bound to leading to phenomenal versatility for catalysis of reactions by them[26]. This thesis centers on the use of neutral Lewis bases as effective catalysts to effect modifications of *ortho*-substituted phenols.

1.1 Aim and Scope of the thesis

Lewis base catalysis has been widely utilized for various chemical transformations in organic synthesis. One of the essential transformations in synthetic organic chemistry with both academic and industrial applications is the reduction of carbon-heteroatom unsaturated organic compounds. The catalytic reduction of unsaturated carbon-heteroatom compounds has been extensively explored [27,28]. However, Lewis base-catalyzed hydrosilylation reductions provide a more convenient and mild alternative. Although a large number of reduction protocols catalyzed by Lewis bases, which employ silyl hydrides as reducing agents have been reported [29], less attention has been paid to cyclic silyl hydrides as reductants in these methods. The 4 or 5-membered cyclic silyl hydrides have been observed to have increased Lewis acidity compared to their acyclic analogues [30-32]. The hydridic character of hydrosilanes is known to be highly dependent on the silicon's substituents and ring constrain of the silicon atom due to strain release. In addition, the Lewis acidic character of silicon in a cyclic structure is further increased when complexed with a Lewis base due to the formation of a pentavalent silicon complex [33,34].

The ultimate aim of this research work was to synthesize cyclic ring-strained chlorohydrosilanes and assess their usefulness in intramolecular hydride delivery for carbon-heteroatom multiple bond reduction systems based on alkoxysilanes formation and Lewis base activation. Specifically, this study sought to address the following questions:

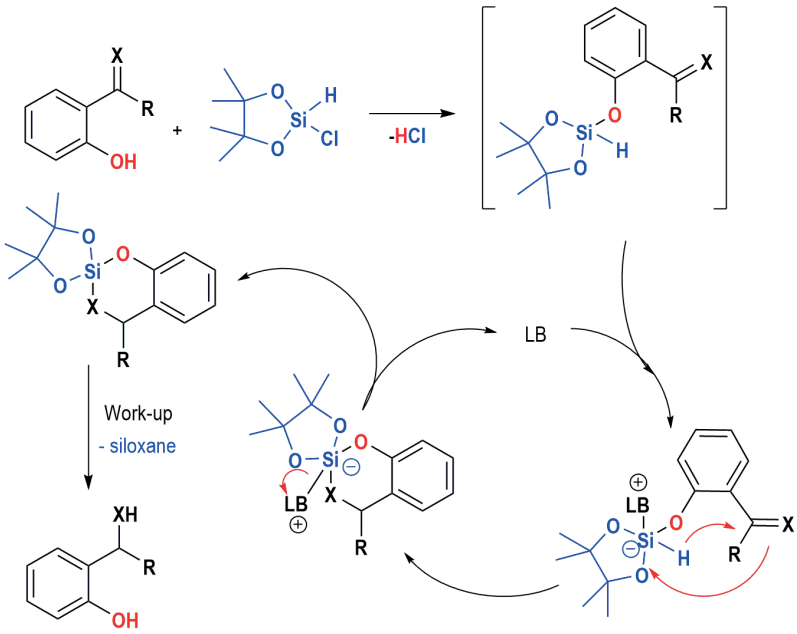
- Would a ring-strained chlorohydrosilane derived from vicinal diols be stable enough to be useful for synthetic purposes?

- Could the hydridic character of such new chlorohydrosilane be increased by activation with a Lewis base? If so, what kind of functional groups should be present in the Lewis base?

- What type of sp^2 carbon-containing functional groups could be hydrosilylated with such new chlorohydrosilanes?

- Could an anchimeric assistance confer regio- and chemoselectivity to the hydrosilylation protocol?

For the purpose of the study in this thesis, we synthetized a novel 5-membered cyclic pinacol-derived chlorohydrosilane (PCS) from pinacol and $HSiCl_3$ (**Publication I**). We selected phenol derivatives with unsaturated carbon-heteroatom substituents at the *ortho* position to be investigated for the Lewis base-catalyzed hydrosilylation reduction with the newly developed pinacol-derived chlorohydrosilane (**Publication I** and **III**). The OH group in phenol would aid in the hydrosilyl ether formation with the chlorohydrosilane and facilitate the concomitant intramolecular hydride delivery at the unsaturated carbon *ortho* to the phenolic OH due to more constrained cyclic transition states (Scheme 1).



Scheme 1. Mechanistic overview of the studied Lewis-base activated hydrosilylation reduction of carbon-heteroatom double bonds via alkoxysilane formation.

In addition, modifications of *ortho*-substituted phenols have the added advantage of providing useful precursors and industrially relevant compounds thereby serving as a suitable substrate for these studies.

From renewable and naturally available quinic acid, we prepared hydroquinone via a simple, one-step and oxidant-free method using Amberlyst-15 (**Publication II**). Readily available formyl-hydroquinone served as one of the salicylaldehyde derivatives, which was employed as substrate in the investigation of PCS as a reductant in the Lewis base (DMPU)-catalyzed preparation of salicyl alcohols. We demonstrated the first Lewis base-catalyzed hydrosilylation of salicylaldehyde with excellent yields, regio- and chemoselectivities (**Publication I**). The same principle of anchimeric-assisted hydrosilylation was explored in the development of a reductive amination protocol for the preparation of an array of novel tertiary aminoalkylphenols using 2'-hydroxy ketones and secondary amines as substrates (**Publication III**). Notwithstanding the similarities of both transformations, pyridine was identified as the best Lewis base to promote the reaction with PCS. The high reactivity of the enamine formed from condensation of 2'-hydroxyacetophenone and pyrrolidine hampered the intended reductive amination. Hence, this phenomena was explored in the development of a Lewis base (pyrrolidine)-catalyzed self-condensation of 2'-hydroxyacetophenone to access the unprecedented structurally robust 6, 12-disubstituted methanodibenzo[*b,f*][1,5]dioxocins, a structural motif found in naturally occurring bioactive compounds (**Publication IV**).

1.2 Thesis Outline

This thesis is structured into five chapters. **Chapter 1** gives a general overview to the aims and scope of the thesis as well as the motivation for this research work.

The background to this work comprising catalytic hydrosilylations of carbonyls, imines and iminiums, Lewis base/acid-catalyzed hydrosilylation of C=O and C=N compounds, and finally modifications of substituted phenols, is discussed in **Chapter 2**.

Chapter 3 describes the materials and methods used in the experimental procedures including the characterization techniques for all new compounds for this thesis work. The computational details for the DFT calculations on studied reaction mechanisms are also outlined in this chapter.

Chapter 4 comprises a summary of the key results and findings from publications **I – IV**, which forms the core of this thesis and is divided into 4 sections. Section 4.1 describes the synthesis of the novel pinacol-derived chlorohydrosilane (PCS) used as a reducing agent in this study and hydroquinone from quinic acid. The reactivity of PCS as a reducing agent in Lewis base-catalyzed hydrosilylation of salicylaldehydes is discussed in section 4.2. Section 4.3 deals with the preparation of novel tertiary alkylphenolmethyl amines. Finally, a pyrrolidine-catalyzed synthesis of 6, 12-disubstituted methanodibenzo[*b,f*][1,5] dioxocin is described in the last section.

In **chapter 5**, a conclusion of the relevant results obtained from this thesis together with additional prospective studies necessary for the full utilization of this work in Lewis base catalysis is presented.

2 BACKGROUND

2.1 Reduction of carbon-heteroatom unsaturated organic compounds

Reductions are among the most versatile and prevailing transformations in organic chemistry. Syntheses of drug candidates in the pharmaceutical industry require functional group manipulations and reductions are preferred for the generation of an array of value-added products [35]. A wide range of reduction protocols for carbon-heteroatom unsaturated compounds have been developed [27,28] however, the reduction of carbonyls, imines and iminiums is the focus of this review. Several reducing systems such as catalytic hydrogenations [36], metal hydrides [37,38] and catalytic hydrosilylations [22,39-41] are used in such transformations. Catalytic hydrogenations often lack selectivity when multiple bonds and reducible groups are present and usually require harsh reaction conditions (e.g. elevated temperatures and pressures). The hazardous reactivity of metal hydrides on the other hand has poor selectivity and lacks tolerance to reducible groups such as halides and nitro groups [38]. In addition, tedious purification procedures accompanied by toxic waste products are associated with reactions involving metal hydrides such as $NaCNBH_3$ and $LiAlH_4$.

Catalytic hydrosilylations in recent years have made significant progress in the reduction of organic substrates as they present a milder, selective, good functional group tolerance and a convenient alternative to the above-mentioned reducing systems [22,42]. Transition metals [41,43-46], Lewis acids [47,48] and Lewis bases [49-51] include the most commonly used catalytic systems in hydrosilylation protocols. Transition metal catalyzed hydrosilylations is a well-established strategy with notable advances in the reduction of carbonyls and C=N bonds [39,52-55]. However, the metal-free versions of such reductions are desirable due to the growing cost and the frequently associated toxicity of metal catalysts as well as the need to obtain pharmaceutical products devoid of metal contaminants [35,56,57].

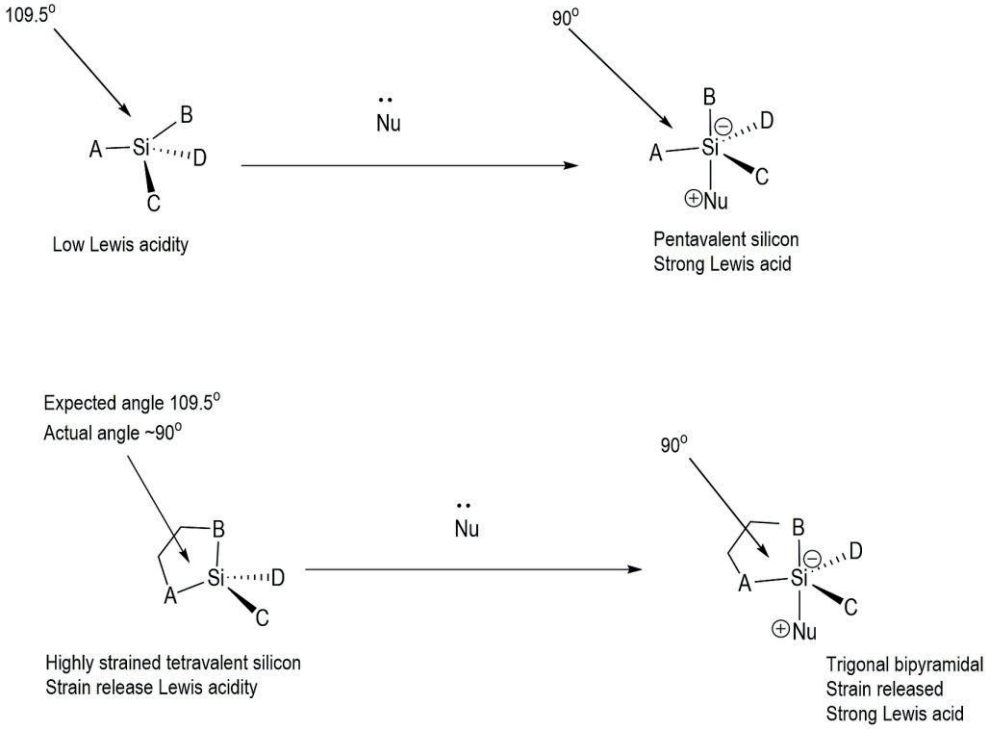
2.2 Metal-free hydrosilylation of carbonyl compounds

Hydrosilanes

Studies on the use of hydrosilanes as mild reducing agents [58] for carbonyl compounds such as aldehydes, ketones and carboxylic acid derivatives have been well documented [52,57,59,60]. The hydrogen in the Si-H bonds present in hydrosilanes is hydridic in nature due to differences in electronegativities between silicon (1.7) and hydrogen (2.1). Due to this hydridic character which makes hydrosilanes susceptible to hydrogen abstraction, they are being used as a major tool in the reduction of organic substrates providing a convenient alternative to the use of metal hydrides and hydrogenation reactions. The reductive abilities of hydrosilanes especially towards carbonyls can be tuned by the nature of substituents attached to the silicon center and usually require activation by catalysts such as transition metal complexes, Brønsted acids [61,62], Lewis acids or Lewis bases [46,51,63]. Depending on the nature of hydrosilanes and reaction conditions employed in the reduction of carbonyls, hydrocarbons or alcohols [47,48,61] can be obtained after desilylation of the silyl ether formed. Triethylsilane [63] and PMHS [64,65] are the most studied hydrosilanes for the hydrosilylation of carbonyls with both acid and base catalysts [29,63,66,67].

Hydrosilanes have typically weak hydride donating abilities compared to other hydride sources. The required carbonyl activation is then accompanied by complexation with Brønsted or Lewis acids in metal-free hydrosilylation of carbonyl groups or activation of the hydrosilane. Undoubtedly, $B(C_6F_5)_3$ is an established versatile catalyst and has been extensively explored [67,68]. Another approach to hydrosilane activation is the expansion of the tetrahedral silicon center with nucleophilic ligands to form pentavalent species [69], which promotes hydride transfer directly from the hydrosilane. Silicon is able to expand its coordination sphere and allow hypervalent bonding due to the ability of the *3p* orbitals of silicon to engage in three-center four-electron bonding. Hypervalency in silicon leads to a redistribution of the electronic density and polarization of the covalent bonds around the silicon atom, which decreases the silicon electron density and increases that of the substituents attached to the silicon [26]. This phenomenon results in increased Lewis acidity of the pentavalent silicon species and higher hydride donating ability compared to its tetravalent congener. [33,34]. The hydridic character of hydrosilanes is further increased when the Si atom is constrained in a ring due to ring strain release as

exemplified by four- and five-membered cyclic hydrosilanes known to exhibit higher Lewis acidity than their acyclic analogues [30-32] (Scheme 2). The more Lewis acidic nature of the hypervalent cyclic hydrosilane is more likely to activate a reducible Lewis basic site such as carbonyls. Nevertheless, phenyl silanes and alkoxysilanes are among the commonly used hydrosilanes in hypervalent silicon intermediate reactions [57,70].



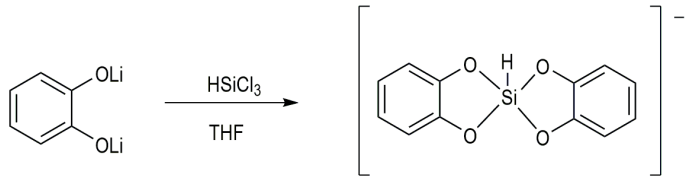
Scheme 2. Effect of cyclic substituents on the structure and Lewis acidity of silanes and corresponding hypervalent silicon species.

Preparation of Silacycles

Silacycles have received tremendous attention in modern organic chemistry and materials chemistry [71]. Traditional synthesis of silacycles is done using halosilanes as starting materials in a Grignard reaction [30,72-74]. Recent strategies for constructing silacycles such as silacyclobutenes, silacyclopentanes, silacyclopentadienes, 6-membered silacycles and their derivatives have been achieved with metal-mediated/catalyzed hydrosilylation of olefinic substrates [75-80]. This

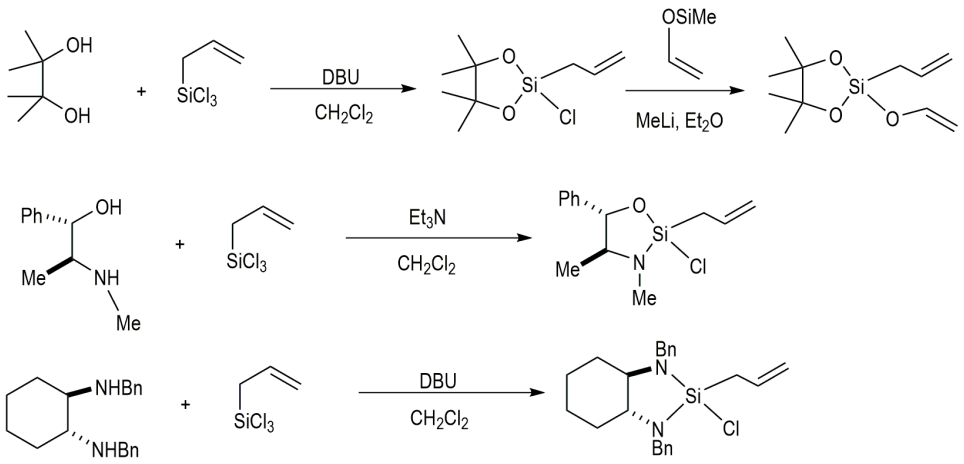
methodology suffers from narrow scope of substrate or silane. Hereafter, more elegant protocols with Lewis acid, for e.g. $B(C_6F_5)_3$, in domino hydrosilylation of unsaturated substrates (dienes, enones, enimines, enynes and ynones) with dihydrosilane have been explored for the preparation of 5-7 membered silacycles which can be further oxidized to 1,n-diols and 1,n-amino alcohols (n= 3-6) of synthetic value [81].

An *in situ* formation of pentacoordinate bis(diolato)hydridosilicates from trichlorosilane and catechol or 2, 2-dihydroxybiphenyl (Scheme 3) can be utilized in the reduction of carbonyl compounds although pentacoordinated hydridosilicates of aliphatic diols for e.g. pinacol and 1, 2-ethanediol are less effective as reducing agents [82].



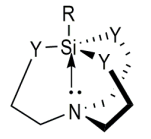
Scheme 3. *In situ* preparation of pentacoordinate bis(1,2-dibenzenediolato)hydridosilicate for the reduction of ketones and aldehydes.

Strained silacycles with the silicon atom constrained in a five-membered ring are prepared with 1, 2-diols, 1, 2-aminoalcohols and 1, 2-diamines with allyltrichlorosilane in the presence of a base (Scheme 4). The substantial Lewis acidity of these strained silacycles have been explored in uncatalyzed allylation of aldehydes. The strain induced in the 1, 2-diols and 1, 2-diamines, for example in a five-membered silacycle presents a reactivity that is absent in the six-membered analogues under similar reaction conditions. This observation in reactivity has limited the syntheses of strained silacycles to the Si atom constrained in five-membered ring systems for increased Lewis acidity. Chiral strained silacycle derivatives, inducing chirality and increasing reactivity, have been obtained from a reaction of chiral, non-racemic 1, 2-aminoalcohols and 1, 2-diamines with allyltrichlorosilane [31,83].



Scheme 4. Syntheses of silacycles with silicon constrained in a five-membered ring by 1, 2-diol, 1, 2-aminoalcohol and 1, 2-diamine.

Silatranes (Figure 1) are a class of silacycles synthesized from silanes and tertiary amino alcohols with a cage-like structure, where the presence of a lone pair of electrons on the nitrogen atom in their structure renders the silicon atom pentacoordinated. Due to these characteristics, silatranes exhibit diverse reactivity with reported biological and pharmacological activities including antitumor, anticancer, anti-inflammatory, antibacterial and fungicidal activity [84].



Y= O, R= H or Alkyl

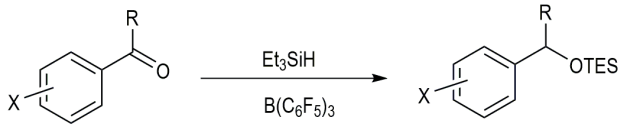
Figure 1. General structure of a silatrane

2.2.1 Acid-catalyzed hydrosilylations

Reduction of carbonyl compounds under hydrosilylation conditions have been extensively studied in Brønsted acidic media as well as carbonyl activation by Lewis acids, of which $B(C_6F_5)_3$ has been comprehensively explored [85-87]. An electron-

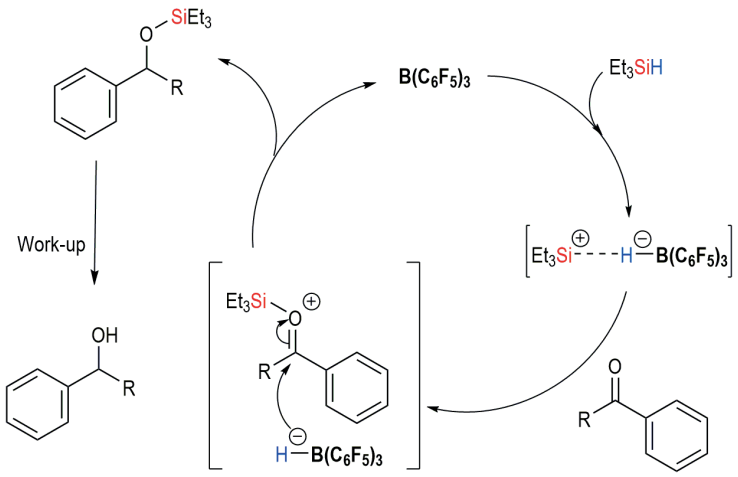
deficient boron atom bonded to highly electron-withdrawing pentafluorophenyl groups gives $B(C_6F_5)_3$ its strong Lewis acidic nature [67]. In a $B(C_6F_5)_3/Et_3SiH$ reduction system, aliphatic aldehydes were exhaustively reduced to hydrocarbons [63] while the hydrosilylation of electron rich and electron deficient substituted aryl aldehydes and acetophenone derivatives led to the isolation of the corresponding silyl ether product with an equimolar amount of the silane (Table 1). The mechanism involved in this hydrosilylation process begins with the complexation of the borane catalyst and hydrosilane. The silylium cation attacks the carbonyl oxygen followed by a nucleophilic attack by the hydridoborate into the carbonyl carbon, which leads to formation of the corresponding silyl ether product. Acidic or basic work up of the silyl ether could provide the corresponding alcohol if desired (Scheme 5). A parallel comparison with metal triflate/Et_3SiH systems exhibited selectivity towards dibenzyl ether formation [88]. Aryl aldehydes and ketones containing electron-donating and withdrawing *p*-substituents have also been selectively reduced to silyl ethers with a $Ph_3SiH/B(C_6F_5)_3$ combination [89]. The polymeric PMHS has also been investigated with $B(C_6F_5)_3$ to promote the reduction of both aliphatic and aromatic aldehydes and ketones to their corresponding alkanes [90].

Table 1. $B(C_6F_5)_3$-catalyzed hydrosilylation of aryl aldehydes and ketones



R= H or methyl

Benzaldehyde Derivatives		Acetophenone Derivatives	
X	Yield (%)	X	Yield (%)
p-Me	87	*p*-Me	85
o-Me	75	*o*-Me	92
p-NO_2	92	*p*-NO_2	89
m-NO_2	95	*p*-Et	71
p-Cl	94	*p*-Cl	96

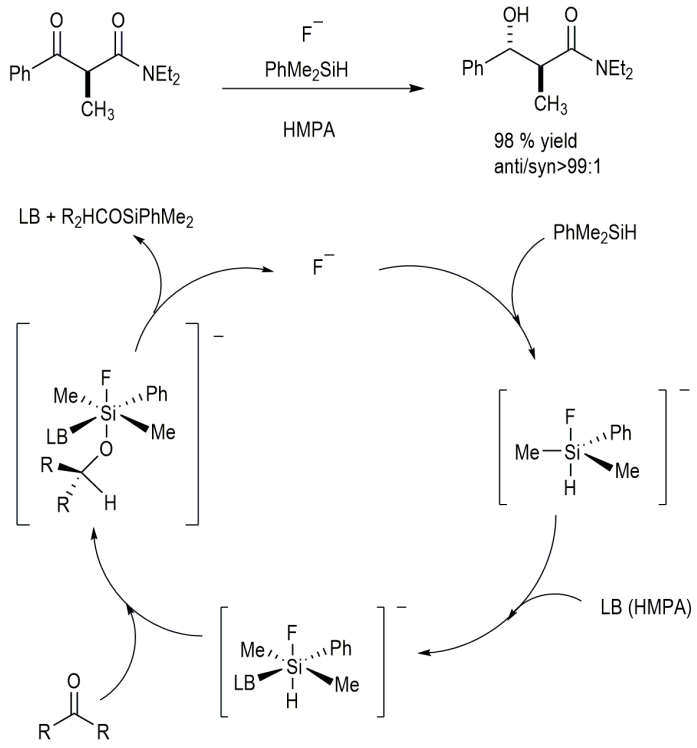


Scheme 5. Mechanism of $B(C_6F_5)_3$-catalyzed hydrosilylation of aryl aldehydes (R=H) and ketones (R=alkyl or aryl)

2.2.2 Base-catalyzed hydrosilylations

Nucleophilic activation of hydrosilanes to furnish hypervalent silicate species is known to act as a powerful strategy to effect hydride donation. The bases usually employed in base-catalyzed hydrosilylations are classified into anionic and neutral bases. Alkali salts containing fluoride ions have made enormous advances in the application of fluoride-catalyzed hydrosilylations for the reduction of carbonyls [26,29]. In these reactions, the fluoride ion interacts with the silicon center of the hydrosilane forming a hypervalent silicate believed to be the active species in the reduction process. The hydride from this hypervalent silicate is then expected to be delivered to the carbonyl center with regeneration of the fluoride ion after formation of the silylated product. Using KF as a nucleophilic promoter in the reduction of carbonyl compounds with PMHS, the hydrosilylation of aldehydes and ketones was achieved with high chemoselectivity, although dependent on the reaction conditions. Other reducible functional groups like amides, acid chlorides, nitriles and imides reacted slowly or were unreactive. Reduction of carboxylic acid esters was attained under $CsF/HSiMe(OEt)_2$ hydrosilylation system [91-93]. The use of TBAF or TSAF as soluble fluoride sources and $PHMe_2SiH$ has been reported to promote the stereoselective reduction of carbonyls. It was demonstrated that the reaction could be

enhanced by the presence of strongly Lewis basic co-solvents such as HMPA, where both the fluoride ion and neutral base are coordinated to the silicon leading to a hexacoordinate silicate formation (Scheme 6) [94-97].



Scheme 6. Mechanism of fluoride ion-catalyzed stereoselective hydrosilylation of β-ketoamides in HMPA as solvent.

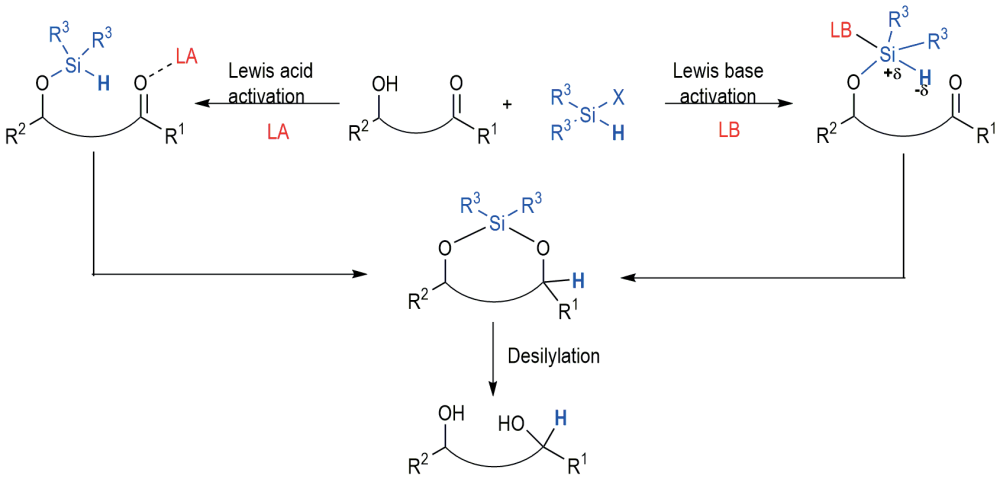
Oxide catalysts are an alternative to fluoride salts in the base-catalyzed hydrosilylations. Recently, a Cs_2CO_3-catalyzed chemoselective hydrosilylation protocol rendered reduction of the ketones in an array of aryl and alkyl α-ketoamides furnishing α-hydroxyamides in moderate to excellent yields using PMHS [57]. Other bases such as K_2CO_3 [66], K_3PO_4 [98], NaOH [99], KOH [100] and *t*-BuOK [64,99,101] have been used as active catalysts or promoters of the chemoselective hydrosilylation of ketones and aldehydes with high functional group tolerance using careful amounts of hydrosilane (PMHS, $PhSiH_3$, $(EtO)_2MeSiH$ and Ph_2SiH_2).

Bassindale and Stout studied the ability of neutral Lewis bases such as DMAP, HMPA, Pyridine-*N*-Oxide, DMPU, DMF, pyridine, triethylamine, etc. to interact with electrophilic silanes. They concluded that for highly electrophilic silanes, activation with strong nucleophiles such as DMAP or HMPA in a polar solvent is ideal for excellent silylation procedures [102]. Benkeser et al demonstrated in the early 70's the ability of simple tertiary amines as neutral bases in combination with $HSiCl_3$ to promote the reduction of organic substrates [103]. DMF as a silane activator was then described by Kobayashi to form a hypervalent Cl_3SiH-DMF silicate, which served as an effective reducing agent for the reductions of aldehydes [104]. After this seminal work, a variety of chiral amines and acid amides with $HSiCl_3$ has been employed in enantioselective reduction of ketones [25,105,106]. In addition, the hydrosilylation of aryl aldehydes and ketones to alcohol products is achievable with hypervalent 1-hydrosilatrane in the presence of a Lewis base [107].

2.2.3 Intramolecular hydrosilylation of hydroxy carbonyl compounds

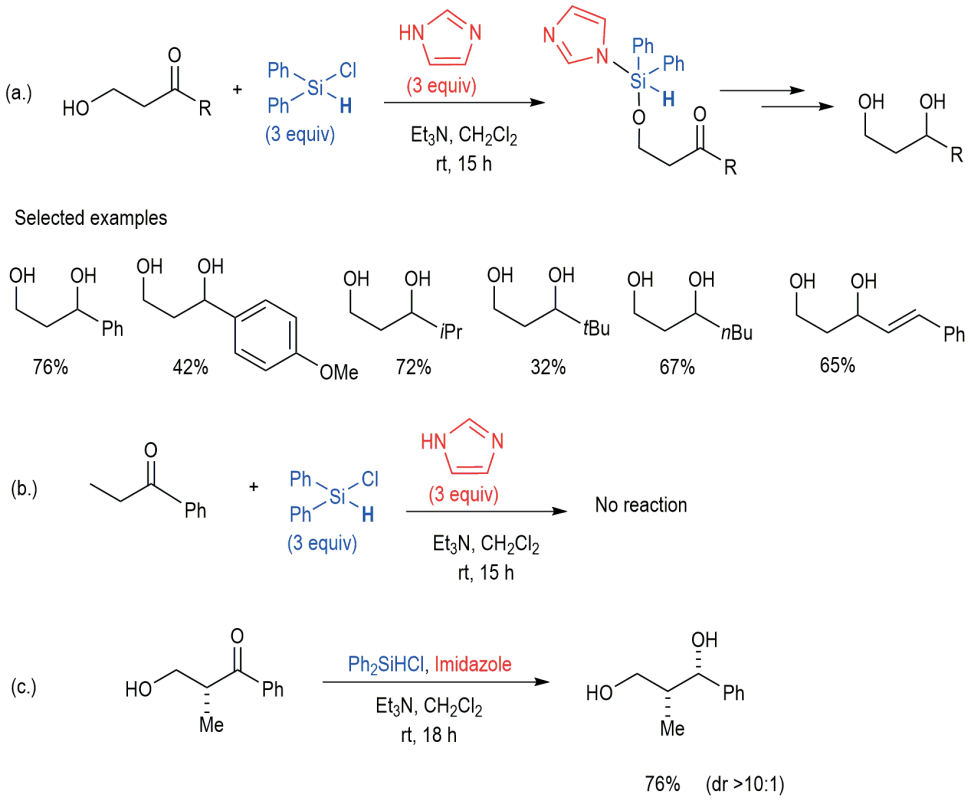
Intramolecular carbonyl hydrosilylation has been utilized in the stereoselective reduction of β-hydroxycarbonyls to access diols or cyclic siloxane intermediates resulting from a more constrained cyclic transition state. These intramolecular hydrosilylation protocols involve the formation of silylether and an intramolecular hydride delivery process, requiring either Lewis acid activation of the carbonyl for enhanced electrophilicity or nucleophilic activation of the silicon center to form a hypervalent hydrosilanide (Scheme 7).

In a $SnCl_4$-catalyzed intramolecular hydrosilylation of β-hydroxyketones using Pr^i_2SiHCl, moderate to excellent stereoselectivities were achieved for the corresponding anti-diols after desilylation [108-110] while the use of catalytic amount of fluoride resulted in the intramolecular hydrosilylation of β-hydroxyesters [111]. Similar transformation was obtained using pentacoordinate hydrosilane activated by an inherent Si-N bond [112].



Scheme 7. General intramolecular hydrosilylation activation modes for hydroxy carbonyl compounds.

Recently, a cooperative Lewis base-mediated intramolecular carbonyl hydrosilylation of β-hydroxyketones has been described (Scheme 8). The intramolecular hydride delivery promoted by imidazole occurred after the formation of the hydrosilyl ether from the reaction of the hydroxyl group and diphenylchlorosilane in the presence of triethylamine. Although the system was not rendered catalytic, as excess amount of the hydrosilane and imidazole was required, no reaction occurred with propiophenone under similar reaction conditions (Scheme 8b). In addition, the intramolecular hydrosilylation exhibited high diastereoselectivity (Scheme 8c) [50,51].



Scheme 8. Imidazole-promoted intramolecular hydrosilylation of β-hydroxyketones (a.) Synthesis of 1, 3-diols (b.) Importance of the hydroxyl group (c.) Diastereoselectivity of the method.

2.3 Metal-free hydrosilylation of carbon – nitrogen unsaturated compounds

The effective synthesis of amines is in high demand due to the ubiquity of this functionality present in biologically active natural products and the numerous applications in pharmaceuticals, agrochemicals and synthetic materials [113]. Reductive amination presents a practical, efficient and fast access to amines among the numerous methods available for the synthesis of amines, thus being widely used [37,114-117]. In the reductive amination process, there is a condensation of a carbonyl compound, preferably an aldehyde or ketone and a primary or secondary amine to form an imine or iminium ion. These intermediates are then reduced either *in situ* in

a one pot reaction, or after isolation by a suitable reductant to give either secondary or tertiary amines.

Metal-free catalytic hydrosilylation in reductive amination methods has been explored with Brønsted acids [118], Lewis acid catalysts especially with $B(C_6F_5)_3$ [119-121] and neutral Lewis bases such DMF [104], acetonitrile, chiral *N*-formamide derivatives, trialkylamines [122], HMPA [123], TMEDA [124], chiral sulfonamide, N-picolinoylpyrrolidine derivatives among others [125]. The "frustrated Lewis pair" (FLP) [126] strategy in catalytic hydrosilylation enables the reduction of imines of which borane-based catalysts have gained increasing attention in recent years [127,128]. Piers and co-workers described the use of $B(C_6F_5)_3$ as an effective catalyst to activate the Si-H bond in hydrosilanes through an FLP mechanism leading to the hydrosilylation of imines in moderate to high yields. The reaction was reported to proceed via a silyliminium cation intermediate with a hydridoborate counterion obtained from the hydride abstracted from the hydrosilane used by the borane catalyst [129]. Hydrosilane activation with Lewis bases in the reductive amination involving ketones and aldehydes has been largely accomplished using the highly reactive trichlorosilane [25,104,125]. More recently, hypervalent 1-hydrosilatrane has been used as a reducing agent in direct reductive amination for the syntheses of secondary and tertiary amines [101].

2.4 Substituted phenols

Phenolic compounds, widespread in nature as flavonoids, phenolic acids or tannins and lignin, have a wide range of biological and pharmaceutical applications as antioxidants, anti-inflammatory, antimicrobial and antitumor compounds [2,4,130]. Simple phenols contain a hydroxyl group attached to an aromatic ring and can have possible substitutions at the *ortho*, *meta* and *para* positions furnishing an array of simple to complex phenolic compounds. The supply of aromatic compounds for e.g. benzene and its derivatives is traditionally obtained from non-renewable fossil feedstock such as coal tar and ring functionalization by nitration, sulfonation, reduction and oxidation reactions. Although there is yet no report of industrial application of the depolymerisation of lignin, it serves as the major renewable source of aromatic compounds [131]. Phenol and its substituted analogues, as for example dihydroxybenzenes are important aromatic compounds in natural product synthesis

and serve as versatile synthetic intermediates for the production of fine chemicals. Thus, new methodologies for their preparation and modification are highly desirable.

2.4.1 Preparation of substituted phenols

Electrophilic and nucleophilic substitution chemistry has served long-standing years in the conventional synthesis of substituted phenols. The *ortho* and *para* directing ability of the phenolic hydroxyl group has been explored in electrophilic aromatic substitution to obtain various *ortho* and *para* substituted phenols in Friedel-Crafts reactions. Due to the lack of regioselectivity of this method, which can restrict functionalization, construction of aromatic rings from substituted linear precursors [132] offered an alternative to avoid a mixture of regioisomeric products. Recent methods for the preparation of phenols include Baeyer-Villager oxidation of aromatic aldehydes [133] , conversion of arylboronic acids to phenols [134,135], Pd-catalyzed C-O bond formation from aryl halides [136], metal-catalyzed ring closing olefin metathesis and catalytic aromatic C-H activation/borylation/oxidation strategy by Maleczka and Smith. The latter protocol by Maleczka and Smith is particularly efficient for the syntheses of mainly *meta* and *para*-substituted phenols [137]. Heterocyclic precursors such as pyrimidines undergo acid-catalyzed condensation with ketones to give phenols via a ring cleavage of the heterocycle and subsequent ring closure [138,139].
Dihydroxybenzenes (catechol, resorcinol and hydroquinone) have useful applications in agriculture, pharmaceuticals and as synthetic intermediates in production of fine chemicals in the chemical industry [5,10]. Preparation of dihydroxybenzenes is well documented in literature for the 1, 3 and 1, 2-dihydroxybenzene isomer (resorcinol and catechol) however, that of 1, 4-dihydroxybenzene isomer (hydroquinone) is very limited. Industrial synthesis of hydroquinone include hydroxylation of phenols [140,141], oxidation of aniline and hydroperoxidation of *p*-diisopropylbenzene. Other synthetic route starting from cyclic non-aromatic compounds for e.g. quinic acid can be obtained from dry distillation [142] and oxidative systems after an enzyme-catalyzed synthesis of quinic acid from glucose [143,144].

2.4.1.1 Synthesis of carbonyl derivatives of phenols

Phenolic carbonyl compounds found in nature are derivatives of phenol and can be grouped into phenolic aldehydes (e.g. salicylaldehyde, vanillin, etc.), phenolic ketones

(raspberry ketone) and phenolic acids (e.g. salicylic acid, hydroxycinnamic acid, gallic acid, etc.). Both naturally occurring and synthetic phenolic carbonyl compounds have usefulness as flavoring agents in food and pharmaceuticals [4].

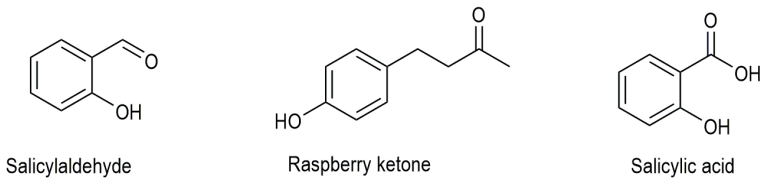
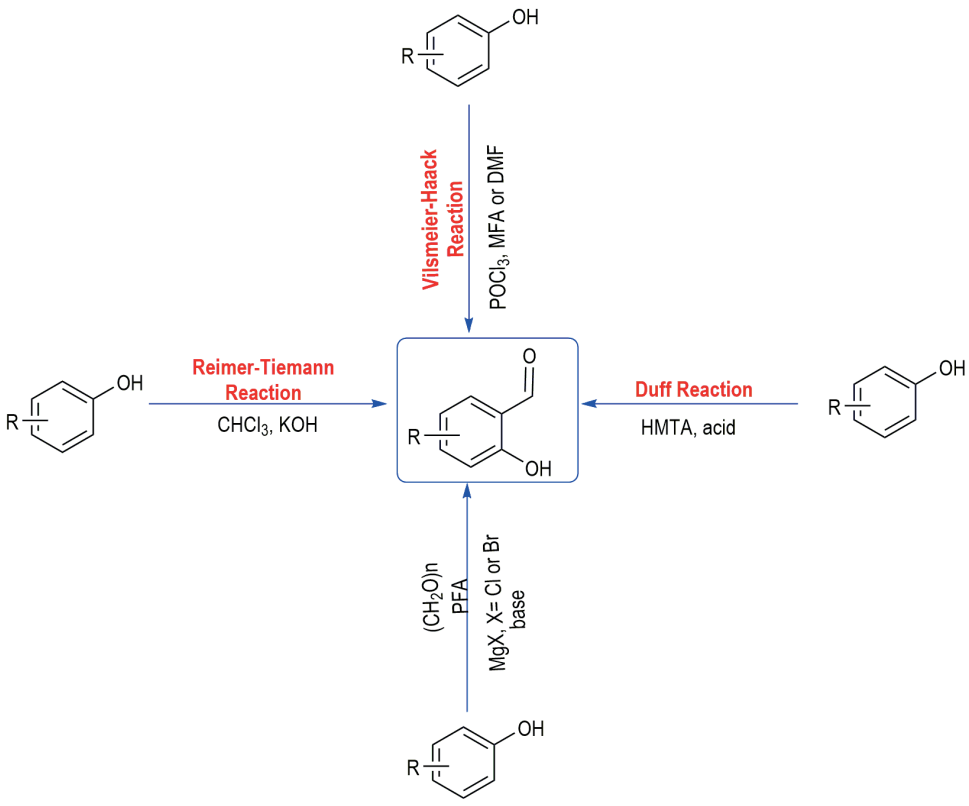


Figure 2. Selected naturally occurring phenolic carbonyl derivatives.

The scanty amount of desired compounds in natural resources put a demand on the need for their syntheses that do not rely solely on nature. Phenolic aldehydes known as hydroxybenzaldehyde, have three isomers (2-hydroxybenzaldehyde, 3-hydroxybenzaldehyde and 4-hydroxybenzaldehyde) and we will focus on the synthesis of 2-hydroxybenzaldehyde (salicylaldehyde) since it has the formyl group *ortho* to the phenol and serves as a precursor to commercially important compounds [145,146]. Salicylaldehyde derivatives synthesis [147,148] usually involves attaching a formyl group *ortho* to phenol. A number of methods for the formylation of phenols [149] to access various salicylaldehyde derivatives are known (Scheme 9). *Ortho*-ketone phenols on the other hand are readily prepared by Friedel-Crafts acylation and Fries rearrangement of aromatic esters where the carbonyl moiety migrates from the phenolic oxygen to the adjacent *ortho* position of the aromatic ring [150]. In addition, 2-hydroxybenzophenones are obtained from the arylation of salicylaldehyde and aryl halides. Salicylic acid is biosynthesized from phenylalanine and commercially produced through Kolbe-Schmitt reaction and acidification to yield the final product. Hydrolysis of its ester derivatives, methyl salicylate (oil of wintergreen) or aspirin (acetylsalicylic acid) provides salicylic acid. Salicylic acid derivatives also have considerable importance in medicinal chemistry. Salicylates are conventionally prepared by esterification of salicylic acid and catalytic cyclization of non-aromatic precursors.



Scheme 9. Most used synthetic methods for the formylation of phenol.

2.4.2 Reactions of *o*-phenolic carbonyl compounds

The chemical modification of the abundantly available secondary metabolites (phenolic aldehydes and acids) useful in natural product syntheses or compounds with potential biological importance has been explored. Due to the polyfunctionality exhibited by the phenolic carbonyl compounds, i.e. the electrophilic nature of the carbonyl and the nucleophilicity of the arene and phenol, a wide range of potential reactivities can be envisioned. Salicylaldehyde and its ketone congener are well known as starting materials in many chemical transformations as they conveniently undergo etherification of the hydroxyl group, reduction or replacement of the carbonyl group and condensation reactions. Salicylaldehyde and 2-hydroxy ketone derivatives are privileged precursors in multicomponent reactions (MCR) affording a plethora of interesting heterocyclic compounds [151,152] and tertiary amines. Petasis borono Mannich reactions have employed salicylaldehydes, organoboronic acids/esters and

amines to prepare alkylaminophenols, which are attractive intermediates for the preparation of pharmaceutical and agrochemical products [153-157].

2.4.3 Preparation of medicinally relevant phenolic derivatives

The synthesis of rare and biologically relevant natural products is a global demand as nature on its own is incapable of supplying the demand placed on these compounds. Synthetic chemists faced with the challenge to produce synthetic bioactive phenolic compounds with pharmaceutical applications have explored the clues nature gives on potential bioactive compounds. As of now, a variety of medicinally relevant heterocycles such as flavonoids and their functionalized derivatives can be readily achieved by small-scale synthesis in the laboratory or by industrial production. Flavonoids consist of phenolic and pyran rings categorized into classes based on structural differences and substitution (Figure 3). They serve as useful synthons or precursors for the synthesis of bioactive natural products and exhibit antibacterial, antioxidant, antifungal, antitumoral, anti-inflammatory and inhibitory activities [158].

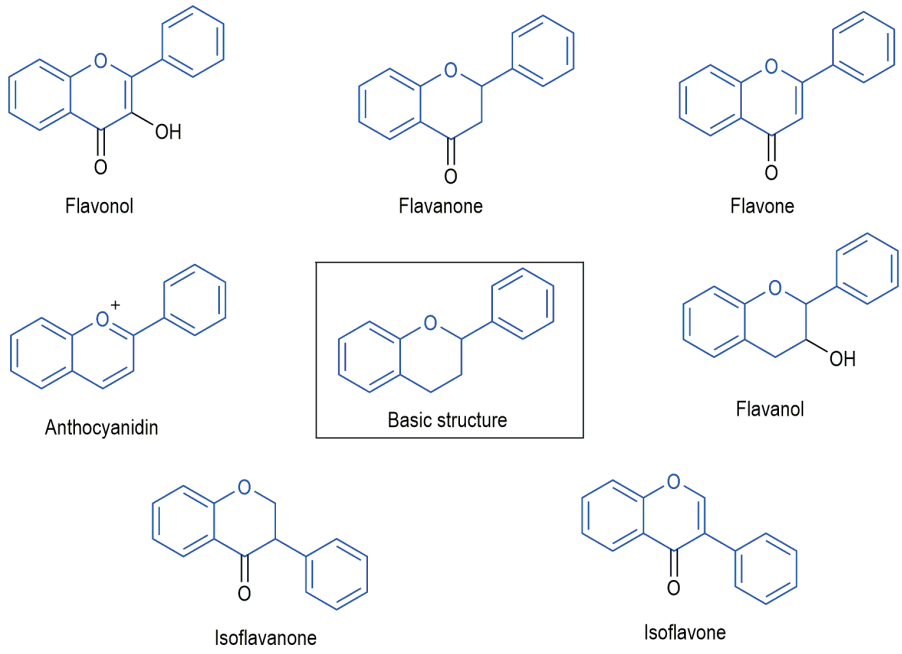


Figure 3. Structural motif of various classes of flavanoids

Ortho phenolic carbonyl compounds such as salicylaldehyde and 2-hydroxyphenones have wide applicability as useful synthetic precursors in the synthesis of biologically useful flavonoids (Figure 4).

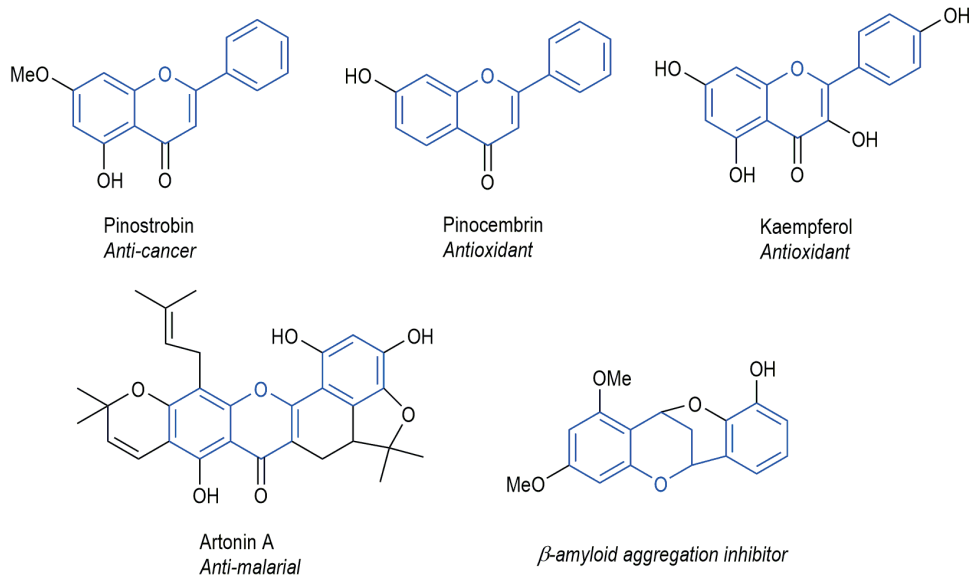
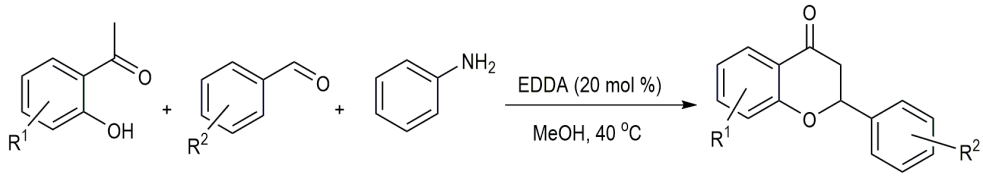


Figure 4. Selected examples of flavonoids with biological activities.

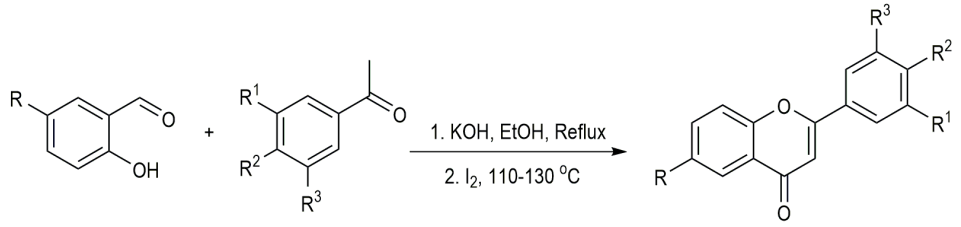
Cyclization of 2'-hydroxychalcones [159] obtained from the condensation of 2-hydroxyacetophenones and aryl aldehydes is the general procedure for the synthesis of flavanones and flavones. The cyclization reaction is usually carried out under acidic, basic, electrochemical or photochemical conditions.

Vuppalapati et al reported an EDDA-catalyzed one-pot synthesis of an array of flavanone derivatives including naturally occurring 7-methoxyflavanone, 4, 7-dimethoxyflavanone and 5, 7-dimethoxyflavanone from 2'-hydroxyacetophenones, aryl aldehydes and aniline via a Mannich-type reaction [152] (Scheme 10).



Scheme 10. EDDA-catalyzed synthesis of flavanones from 2'-hydroxyacetophenone, aromatic aldehydes and aniline.

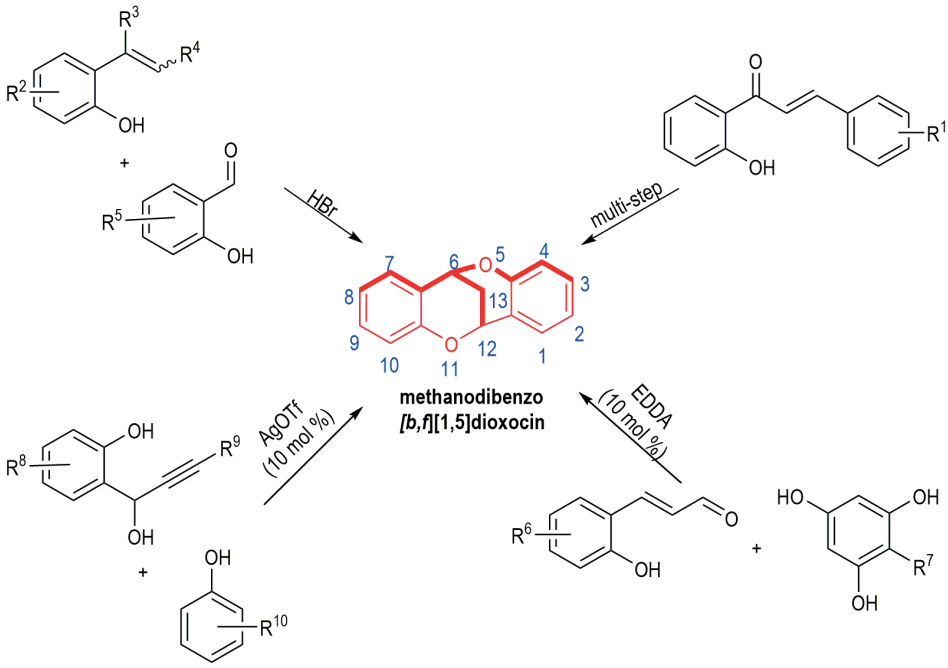
Sashidhara and co-workers reported the use of salicylaldehyde instead of 2'-hydroxyacetophenone [160] in the formation of the 2'-hydroxychalcone. Condensation of acetophenone and salicylaldehyde furnished 2'-hydroxychalcone, which led to the preparation of medicinally relevant flavones after cyclization in the presence of catalytic iodine under neat conditions [161] (Scheme 11) .



Scheme 11. Iodine-catalyzed synthesis of flavones using salicylaldehyde as substrate.

The methanodibenzo[*b*,*f*][1,5]dioxocin structural motif is prevalent in naturally occurring bioactive flavonoids such as cyanomaclurin and pharmaceuticals. Some of these flavonoids are reported to exhibit antibacterial activity, β-amyloid aggregation inhibition, potent anti-MRSA activity etc. [162-172]. Notwithstanding the potential biological usefulness of these flavonoids, literature about synthetic routes towards their construction is very limited (Scheme 12). The construction of this highly bridged polycyclic scaffold is achievable via a multi-step cyclization of chalcone derivatives, however in low yields [172-176]. The neutral 6H, 12H-6, 12-methanodibenzo[*b*,*f*][1,5]dioxocin and its derivatives were reported by Hennis et al. to be prepared from the cyclization of the condensation product from salicylaldehyde and *o*-vinylphenol or *o*-coumaric acid under acidic conditions [177,178]. More recent strategies for the assembling of the methanodibenzo[*b*,*f*][1,5]dioxocin skeleton involve Brønsted and Lewis acids catalysis in cascade reactions. In the Brønsted acid-catalyzed preparation of the dioxocin flavonoid, Liu and co-workers described a bioinspired [3+3] cycloaddition cascade sequence catalyzed by EDDA via an *in situ* generated chromenylium intermediate using 2-hydroxyxcinnamalaldehyde and phloroglucinol as starting materials [179].

Formation of an *in situ* generated *o*-quinone methide from *o*-hydroxybenzyl alcohol and electron-rich phenols triggers a silver triflate-catalyzed 1, 4-conjugate addition/6-endo cyclization/1, 3-aryl shift/1, 4-conjugate addition cascade sequence furnishing 2-substituted methanodibenzo[*b*,*f*][1,5]dioxocins [180].



Scheme 12. Synthetic routes towards the construction of methanodibenzo[*b*,*f*][1,5]dioxocin scaffold.

3 MATERIALS AND METHODS

All syntheses were carried out in oven-dried glassware under Argon atmosphere. Anhydrous dichloromethane, tetrahydrofuran, diethyl ether and triethylamine were obtained using PureSolv Micro multi-unit purification system (passing deoxygenated solvents through activated alumina columns). All other solvents were left standing over 3 Å molecular sieves and used without further purification. Anhydrous pyridine was obtained after pre-drying with KOH and distilling under argon before use. Quinic acid was sieved through a 106 μm sieve prior to use with Retsch ZM200 grinder and AS200 sieve. All reagents were purchased from Sigma Aldrich, TCI Europe or Fluka and used as received without further purification unless otherwise stated. Reactions were monitored through thin layer chromatography (TLC) with commercial silica gel plates (Merck silica gel, 60 F_{254}). Visualization of the developed plates was performed under UV light at 254 nm and by staining with cerium ammonium molybdate and vanillin. Purification of the products was done with flash column chromatography performed on silica gel 60 (40 – 63 μm) as stationary phase.

3.1 Compound characterization

The NMR spectra of all intermediates and final products were recorded with Varian Mercury 300 MHz or JEOL EZCR 500 MHz instruments using $CDCl_3$, DMSO or D_2O as solvent and calibrated using tetramethyl silane as internal standard.

High-resolution mass spectrometry (HRMS) measurements were performed with Waters LCT Premier XE ESI-TOF benchtop mass spectrometer or on ABSciex QSTAR Elite ESI-Q-TOF. Leucine Enkephaline was used as a reference compound for calibration, centering and lock-mass correction.

Crystal data was collected on an Agilent SuperNova single-source diffractometer equipped with an Eos CCD detector at 120(2) K using mirror-monochromated Mo-Kα (λ = 0.71073 Å) radiation. Data collection (ω scans) and reduction was performed using the program *CrysAlisPro* [181]. The analytical face-indexing-based absorption

correction method was applied. The structure was solved by intrinsic phasing methods [182] and refined by full-matrix least squares on F^2 using *SHELXL*-2018/1 [183]. Anisotropic displacement parameters were assigned to non-H atoms. All hydrogen atoms (except O-*H*) were constrained to their idealised positions and refined using riding models with U_{eq}(H) of 1.5U_{eq}(C) for terminal methyl groups and of 1.2U_{eq}(C) for other groups. Hydrogen atom bonded to O atom was found from the electron density maps, restrained to its ideal distance (0.84 Å) from parent atom and refined with U_{eq}(H) of 1.5U_{eq}(O).

3.2 Computational studies

Calculations were performed using the GAUSSIAN 09 software package [184], and the PBE1PBE functional, without symmetry constraints. Such functional uses a hybrid generalized gradient approximation (GGA), including 25 % mixture of Hartree-Fock [185] exchange with DFT [186] exchange-correlation, given by Perdew, Burke and Ernzerhof functional (PBE) [187,188] . The optimized geometries were obtained with a standard 6-31G(d,p) [189-193] basis set. Transition state optimizations were performed with the Synchronous Transit-Guided Quasi-Newton Method (STQN) developed by Schlegel et al [194,195], following extensive searches of the Potential Energy Surface. Frequency calculations were performed to confirm the nature of the stationary points, yielding one imaginary frequency for the transition states and none for the minima. Each transition state was further confirmed by following its vibrational mode downhill on both sides and obtaining the minima presented on the energy profile. The electronic energies (E_{b1}) obtained at the PBE1PBE/6-31G(d, p) level of theory were converted to free energy at 298.15 K and 1 atm (G_{b1}) by using zero point energy and thermal energy corrections based on structural and vibration frequency data calculated at the same level.

Single point energy calculations were performed on the geometries obtained at the PBE1PBE/6-31G(d, p) level using the M06-2X functional and a 6-311++G(d, p) basis set [196-204]. The M06-2X functional is a hybrid meta-GGA functional developed by Truhlar and Zhao [205], and it was shown to perform very well for the kinetics of main group element systems, providing a good description of weak and long range interactions [206,207]. Solvent effects (CH_2Cl_2 or MeCN) were accounted for in all calculations by means of the Polarisable Continuum Model (PCM) initially

devised by Tomasi and co-workers [208-211] with radii and non-electrostatic terms of the SMD solvation model, developed by Truhlar et al [212].

The free energy values presented (G_{b2}^{soln}) were derived from the electronic energy values obtained at the M06-2X/6-311++G(d,p)//PBE1PBE/6-31G(d, p) level, including solvent effects (E_{b2}^{soln}), according to the following expression:

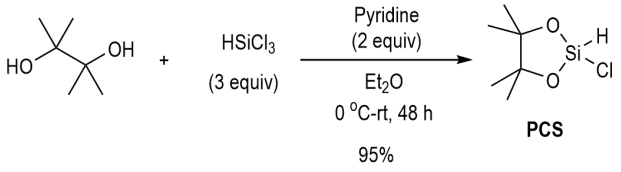
$$G_{b2}^{soln} = E_{b2}^{soln} + G_{b1} - E_{b1}$$

4 RESULTS AND DISCUSSION

4.1 Synthesis of pinacol-derived chlorohydrosilane (PCS)

The hydridic character of hydrosilanes is considered highly dependent on the nature of substituents attached to silicon. Thus, we envisioned that under certain constrains, alkoxy-derived hydrosilanes would be highly reactive. Furthermore, by constraining the silicon atom within a ring, the hydridic character is expected to be further increased as demonstrated by four- and five-membered silacycles that have higher Lewis acidity than their acyclic counterparts due to strain release. Complexation of silacycles with a Lewis base leads to the formation of a pentacoordinate silicon complex, which could consequently further increase its Lewis acidic character and weaken the Si-H bond strength [30,32-34].

Cyclic alkoxy hydrosilanes are traditionally prepared from 1, 2-diols and $HSiCl_3$ in the presence of tertiary amines. Preparation of five-membered chlorohydrosilane in our initial attempts using ethylene glycol and $HSiCl_3$ in the presence of various amine bases resulted in complex mixtures due to disproportionation and silicon-amine adduct formation [103]. We replaced ethylene glycol with pinacol with the aim of increasing the stability of the chlorosilane. This way, we obtained the desired pinacol-derived chlorohydrosilane (PCS) in nearly quantitative yield after treating pinacol with an excess $HSiCl_3$ and pyridine in diethyl ether under inert atmosphere as shown in scheme 13 (Publication I). This pinacol-derived chlorosilane was easily isolated by simple filtration to remove the pyridinium salt and solvent evaporation. PCS is a clear and colorless liquid, which can be stored at -20 °C under Ar without any change in reactivity. Just like many other chlorohydrosilane, PCS is air and moisture sensitive.



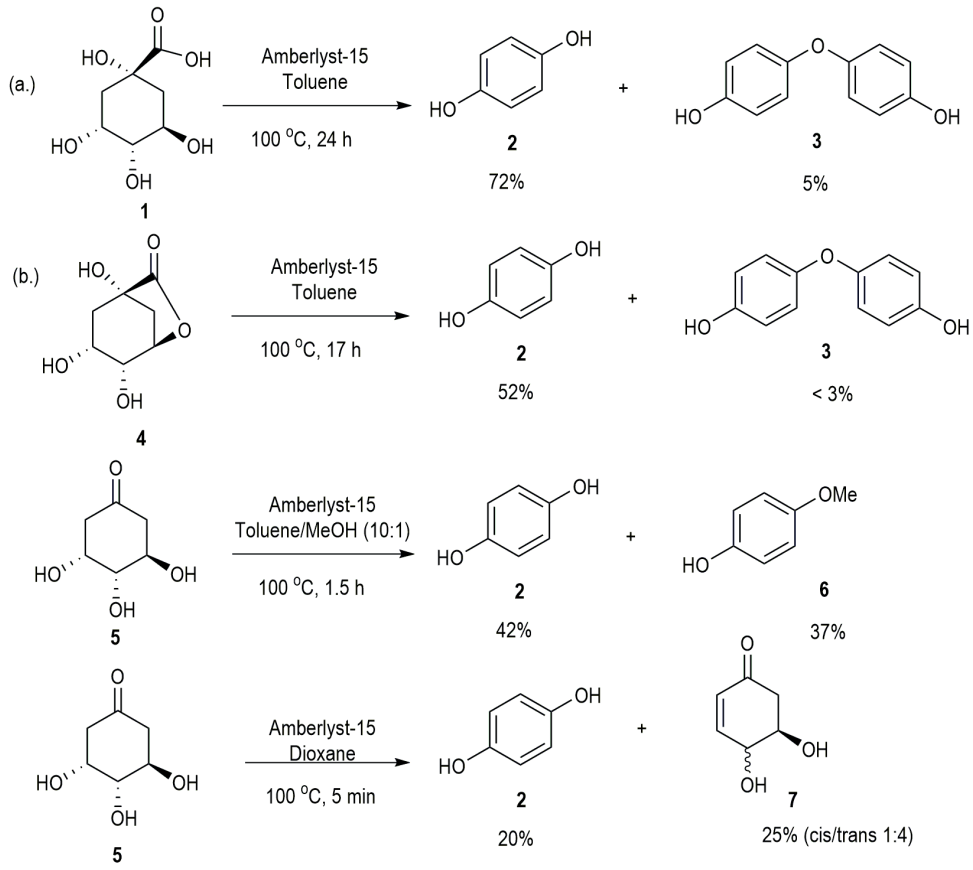
Scheme 13. Preparation of PCS from pinacol and trichlorosilane.

4.2 PCS in Lewis base-catalyzed hydrosilylation of salicylaldehydes.

Reduction of salicylaldehydes to salicyl alcohols [213-218] provides fundamental transformations in organic synthesis. As already stated in chapter 2, metal-free hydrosilylation procedures in the reduction of carbonyl functionalities constitute a mild and selective alternative to the conventional methods for introducing a hydroxyl functionality into a molecule. In this study, we explored the reactivity of PCS as a reducing agent in Lewis base-activated systems for the anchimeric-assisted reduction of salicylaldehydes and its derivatives (Publication I).

4.2.1 Synthesis of hydroquinone from quinic acid under oxidant-free conditions.

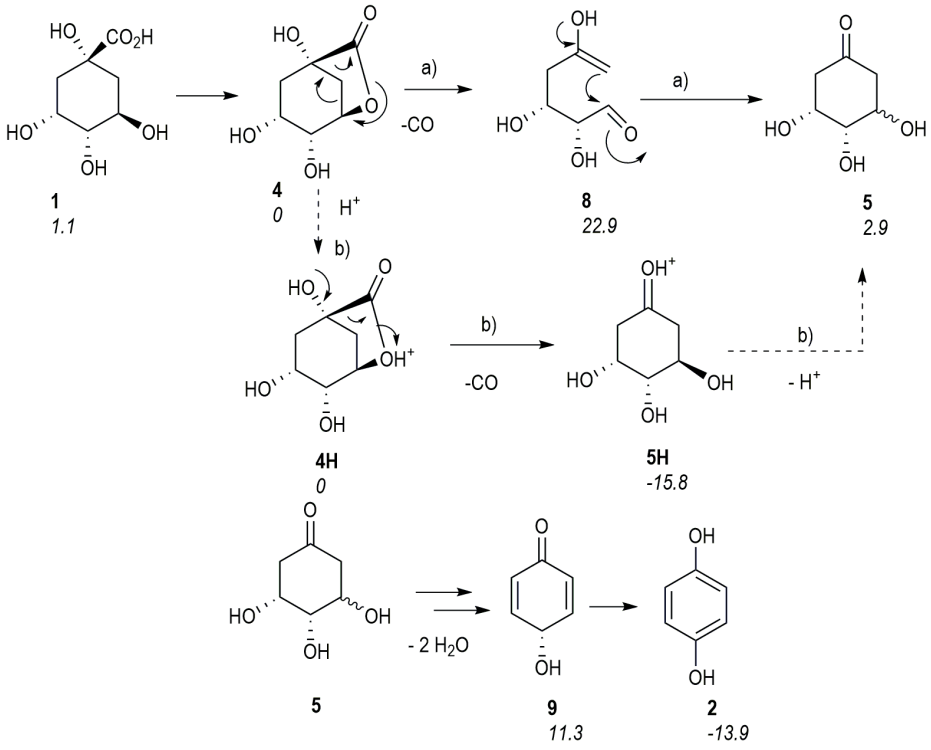
Several methods are available for the synthesis of salicylaldehydes and its derivatives, such as formylation of hydroquinone using Vilsmeier-Haack reagent [219] or paraformaldehyde is a convenient way to access formyl hydroquinone in high yields and selectivity [220]. Hydroquinone is prepared industrially by hydroperoxidation of *p*-diisopropylbenzene, hydroxylation of phenol or oxidation of aniline. Quinic acid, which is the principal constituent of coffee beans and readily available from the bark of cinchona tree, has been used as a non-fossil source in a dry distillation procedure to obtain hydroquinone [142-144]. Based on this transformation, we have successfully synthesized hydroquinone starting from the non-aromatic quinic acid **1** with the use of Amberlyst-15 as an acid promotor in an oxidant-free reaction (Publication II). In the acid-promoted decomposition of quinic acid, other expected products besides hydroquinone includes bicyclic quino-1,5-lactone, benzoic acid and quinone. However, the use of a 1:4 (w/w) ratio of quinic acid/dry Amberlyst-15 was found to be the optimal reaction condition to promote the formation of hydroquinone **2** with only traces of the dimeric side product **3** (Scheme 14a).



Scheme 14. (a.) Synthesis of hydroquinone from Quinic acid (b.) Formation of hydroquinone from putative reaction intermediates

The absence of air or the presence of water had detrimental effect on hydroquinone formation. Putative reaction intermediates **4** and **5** were converted into hydroquinone, while benzoquinone could not be detected in any of the reactions performed (Scheme 14b). Isolation of **7** upon change of the reaction conditions suggest this to be another intermediate when getting hydroquinone from quinic acid. Single-electron-transfer pathways were disregarded after reactions in the presence of (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO), butylated hydroxytoluene (BHT), styrene and azodicarboxylates failed to provide any different outcome. Using lactone **4** as starting point (Scheme 15), two ionic decarbonylation mechanisms can be envisioned i.e. concomitant formation of the enol aldehyde **8** from the pericyclic decarbonylation of the lactone or a ring-opening mechanism of the protonated lactone $\mathbf{4^H}$. The free

energy obtained for intermediate 8 (ΔG = 22.9 kcal/mol) makes this decarbonylation step thermodynamically unfavorable. These findings taken together with identification of carbon monoxide as a side product of the reaction (Scheme 15) and the comparison of ionic and radical mechanisms through DFT optimization of likely intermediates, suggest the ionic decarbonylation of protonated quino-1,5-lactone mechanism as the most reasonable mechanistic route (Figure 5). This method is simple and efficient, as it does not rely on oxidants or elevated temperatures as previously reported ones (Publication II).



Scheme 15. Proposed ionic reaction mechanism. Free energies of intermediates are indicated in italics.

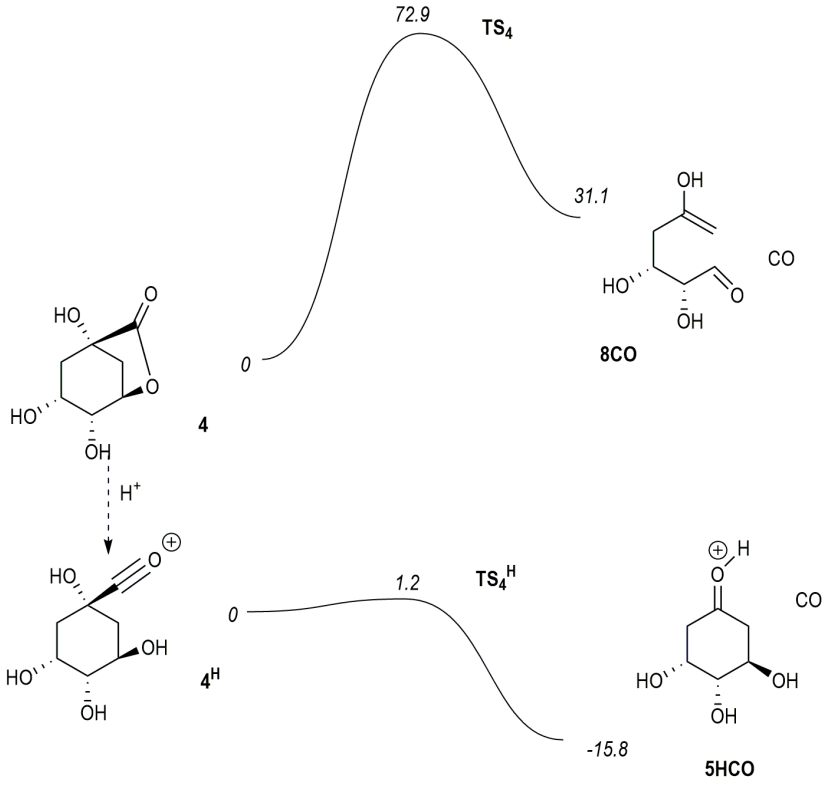


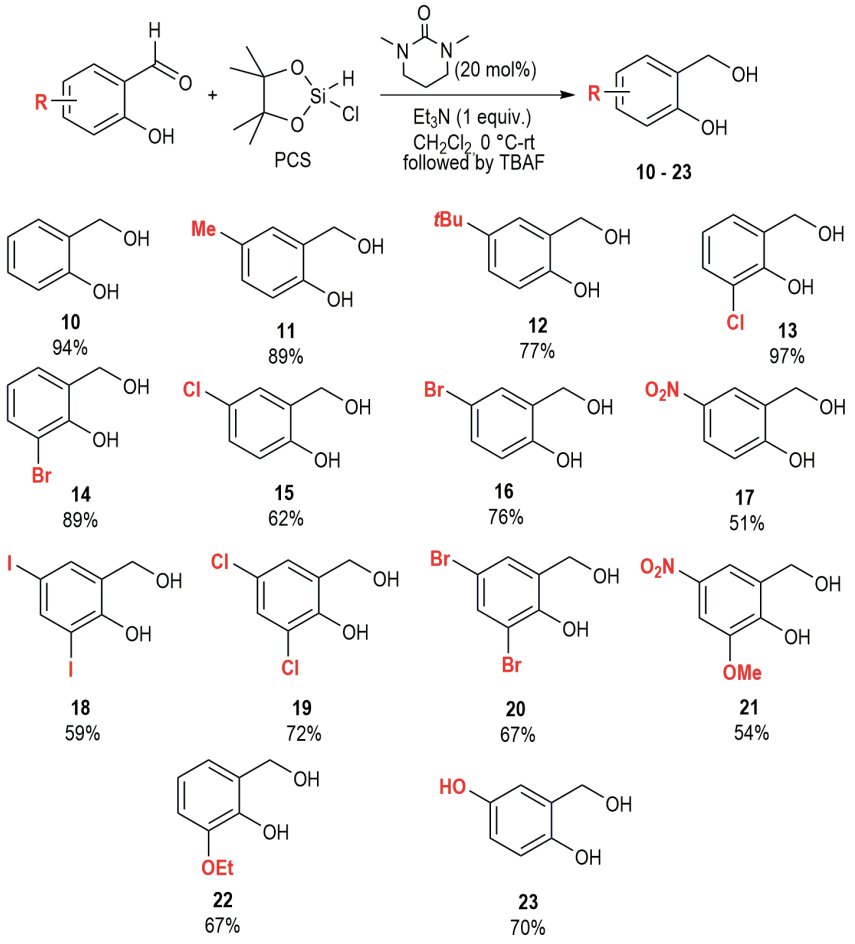
Figure 5. Energy profiles for two alternative decarbonylation steps. Free energies of intermediates and transition states are indicated in italics.

4.2.2 Synthesis of salicyl alcohol derivatives using Lewis base/PCS system

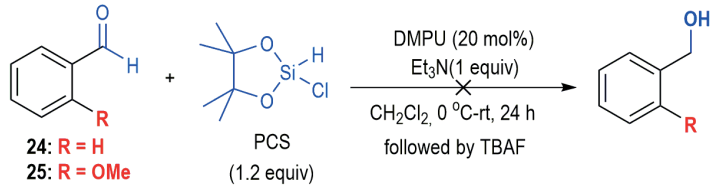
Salicyl alcohol is the precursor in salicylic acid metabolism, which is used in the synthesis of biologically relevant compounds with widespread pharmaceutical applications. It is also employed as starting material in useful heterocyclic compound synthesis [221]. In order to verify the intramolecular hydride delivery ability of PCS, and our hypothesis on effecting such hydride delivery through activation with a Lewis base, we commenced with the screening of several Lewis bases after *in situ* formation of the desired trialkoxyhydrosilane derived from salicylaldehyde. Among several Lewis bases tested (tertiary amines, pyridine, pyridine-*N*-oxide, phosphines, etc), the

use of 20 mol% of DMPU, an environmentally benign alternative to HMPA, was identified as the most suitable to effect the hydrosilylation of salicylaldehydes (Publication I). The DMPU-catalyzed hydrosilylation protocol shown in scheme 16 furnished the corresponding salicyl alcohols in reasonable to excellent yields. 5-Alkyl-substituted salicylaldehydes were efficiently reduced to afford **11** and **12** after desilylation with TBAF. The hydrosilylation protocol tolerated reducible groups such nitro and halogen substituents as only reduction of the carbonyl moiety to yield their corresponding salicyl alcohols was observed. Functional group tolerance of the hydrosilylation protocol is further exemplified by the close proximity of the ether groups to the phenolic OH and yet no reduction of the 3-alkoxy substituents was observed but afforded only the corresponding salicyl alcohols **21** and **22**. Without the need to increase the amount of PCS used in this protocol, the reduction of readily available formyl hydroquinone **23**, which can be prepared from hydroquinone (Publication II), was obtained in 70% yield by changing the reaction solvent from dichloromethane to acetonitrile.

The superiority of PCS as a reducing agent in the reduction of salicylaldehyde was demonstrated by replacing PCS with commercially available chlorohydrosilane in the hydrosilylation protocol. Although diphenylchlorosilane gave the salicyl alcohol **10** in 31% yield after 72 h, chlorodimethylsilane and chlorodiisopropylsilane failed to provide the reduced product under the same reaction conditions.
Attempts to reduce benzaldehyde **24** and *o*-methylsalicylaldehyde **25** with our system proved futile, indicating the required formation of a trialkoxyhydrosilane for the intramolecular reduction process (Scheme 17). The reduction of 2'-hydroxyacetophenone was obtained in only 47% yield in spite of the high reactivity exhibited by PCS in the reduction of salicylaldehydes.



Scheme 16. Scope of DMPU-catalyzed reduction of salicylaldehydes with PCS.

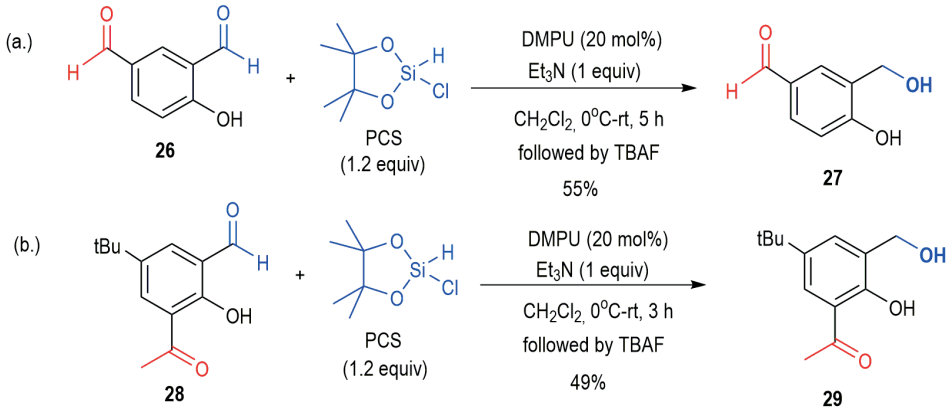


Scheme 17. Importance of phenolic hydroxyl for the DMPU-catalyzed reduction with PCS.

4.2.2.1 Regio- and chemoselective reduction of salicylaldehydes

To evaluate the regioselectivity of the reduction process, commercially available 5-formyl salicylaldehyde **26** was subjected to our reduction system (Scheme 18a). Phenol derivative **27**, derived from the exclusive reduction of the aldehyde group *ortho* to the phenolic OH was obtained in 55% yield, allowing for the regioselectivity of the hydrosilylation protocol.

In order to test the chemoselectivity of the reduction system, we synthesized **28** and applied the same reaction conditions to it (Scheme 18b). The chemoselective reduction of the aldehyde group in compound **28** synthesized from 4-*t*-Bu-2, 6-diformylphenol, yielded exclusively **29** in 49% yield contrasting with the above-mentioned reduction of 2'-hydroxyacetophenone.



Scheme 18. Regio- (a.) and Chemoselectivity (b.) of the PCS/DMPU reduction system.

4.2.2.2 Mechanistic Studies

We proposed an *in situ* trialkoxyhydrosilane formation followed by an intramolecular hydride delivery mechanism promoted by the Lewis base, DMPU for the reduction of salicylaldehyde with PCS. The proposed catalytic mechanism was studied by means of DFT calculations using salicylaldehyde as substrate (Publication I). Trialkoxyhydrosilane obtained from HCl loss from the initial hydrosilane formed the starting point of the calculations. There are three steps associated with the mechanism detailed in the free energy profile in Figure 6.

Step I: Coordination of the base catalyst, DMPU to the Si-atom in the trialkoxyhydrosilane, **A** to **B**.

Step II: Hydride attack into the carbonyl C-atom and the corresponding O-atom's coordination to the Si-atom, **B'** to **C**.

Step III: The final step is the liberation of the DMPU catalyst leading to formation of the final silylated product, **C** to **D**.

Step I is a facile step with a negligible energy barrier to obtain intermediate **B** which leads to rotation of the Si-O_{phenol} bond providing a slightly less stable conformer **B'**. In step II, the new C-H bond formation precedes the C-O counterpart in the transition state $\mathbf{TS_{B'C}}$ in a non-synchronous process. The bond length of the new C-H is only 0.03 Å longer than the one present in **C** while the new Si-O bond is only incipient with a distance of 4.09 Å. This step has the highest barrier of all the paths, $\mathbf{TS_{B'C}}$ being 20.0 kcal/mol less stable than the reactants, although the process is clearly exergonic with ΔG = -32.2 kcal/mol. Release of the base catalyst, DMPU and formation of the final product in the last step has a corresponding transition state $\mathbf{TS_{CD}}$ with a well-advanced Si-O_{DMPU} bond breaking having a bond length already 0.55 Å longer than the one found in intermediate **C**. The overall reaction is thermodynamically favorable with a free energy balance of ΔG = -33.0 kcal/mol.

Investigation into the salicyladehyde reduction mechanism in the absence of a base catalyst by DFT calculations revealed that the role of DMPU as catalyst lowers the total energy barrier of the reaction by 12.9 kcal/mol (Figure 7).

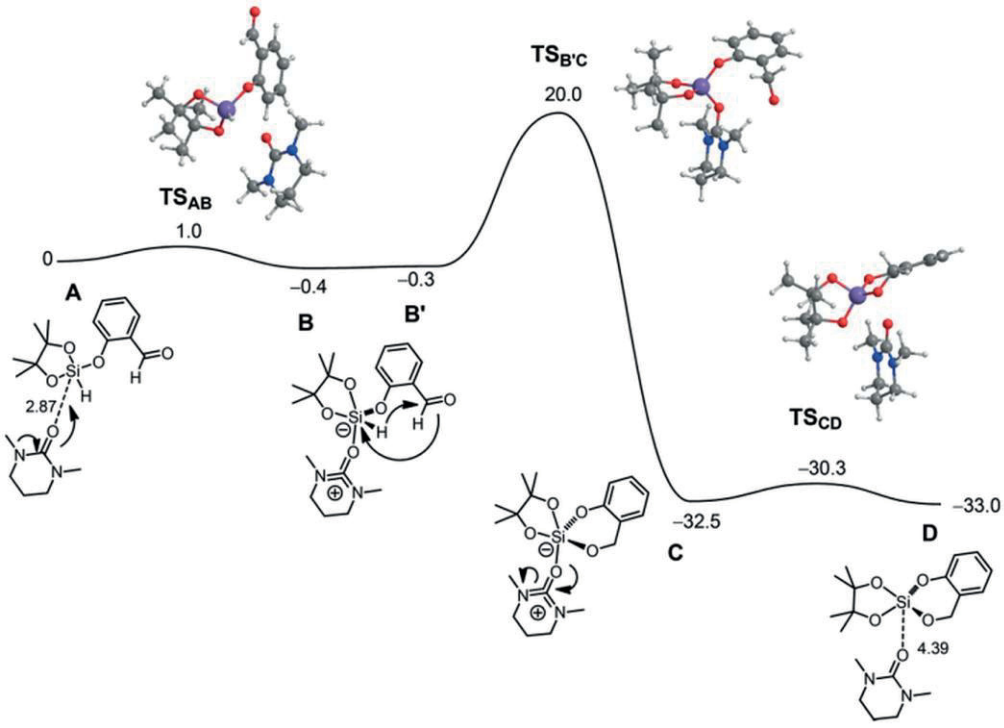


Figure 6. Free energy profile for the reduction of salicylaldehyde with PCS. Free energy values [kcal/mol] relative to the pair of reactants, DMPU plus the trialkoxyhydrosilane **A**. Distance measured in Å.

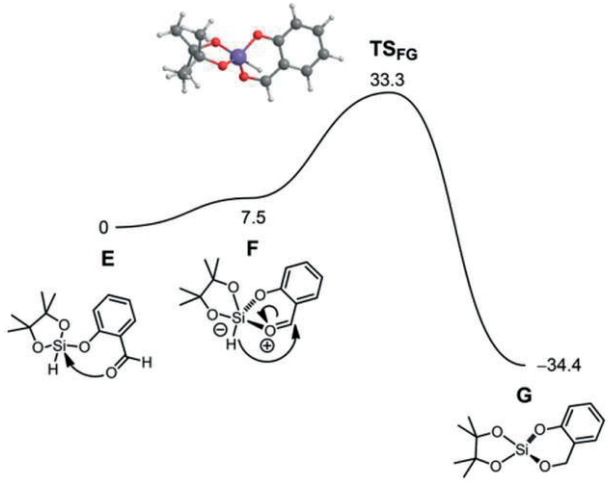
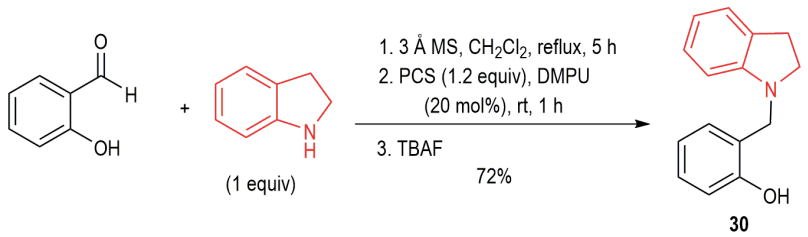


Figure 7. Free energy profile for the uncatalyzed reduction of salicylaldehyde with PCS. Free energy values [kcal/mol] relative to the trialkoxyhydrosilane **E**.

4.2.2.3 Reductive amination of salicylaldehyde-derived iminiums.

After the formation of an *in situ* generated salicylaldehyde-derived iminium from the condensation of salicylaldehyde and indoline, PCS was tested as a reducing agent in a reductive amination method. The corresponding tertiary amine **30** was formed in 72% yield under the established hydrosilylation protocol (Scheme 19) with the use of molecular sieves to trap the water formed in the condensation process (Publication I). The high yield of product in the absence of a base to trap the HCl formed (such as Et_3N) indicates an extensive iminium formation prior to PCS addition.



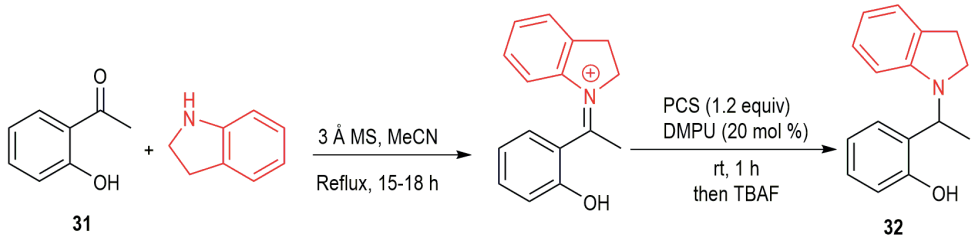
Scheme 19. PCS in a DMPU-catalyzed reductive amination of salicylaldehyde-derived iminium.

4.3 Preparation of Tertiary Alkylphenolmethyl Amines

The conventional synthetic approaches to arylphenolmethyl amines is mainly via Betti [222,223] or Petasis borono-Mannich reactions [224,225]. Notwithstanding the versatility of these synthetic procedures, the use of alkyl aldehydes or alkyl boronic acids or esters in such reactions to access tertiary alkylphenolmethyl amines remain quite challenging due to the lack of reactivity of such species. The suitability of our system, if expandable to the reduction of carbon-heteroatom unsaturated bonds, would provide a new entry to obtain alkylphenolmethyl amines. Following the success in obtaining the reduction of the salicylaldehyde derived-iminium to the tertiary amine **30** with PCS (Publication I), we envisioned that a similar transformation could be used to perform the reductive amination of iminiums derived from alkylphenol ketones and secondary amines. In this study, we employed the one-pot reductive amination method, which is a versatile and fast access to amines with PCS as reducing agent to prepare an array of novel tertiary alkyphenolmethyl amines (Publication III).

Initially, 2'-hydroxyacetophenone **31** and indoline were used as substrates. Similar reaction conditions as in scheme 19 but employing Et_3N (1 equiv) to sequester HCl produced from the silyl ether formation, resulted in formation of the desired tertiary amine **32** in 64% yield. Further optimization of reaction conditions including solvent screening, the amounts of DMPU and indoline revealed that, by increasing the amount of indoline to 2 equivalents, the tertiary amine **32** could be obtained in up to 84% yield with or without the presence of DMPU (Table 2, entries 4 and 5) in acetonitrile (Publication III).

Table 2. Selected entries in initial optimization of reductive amination

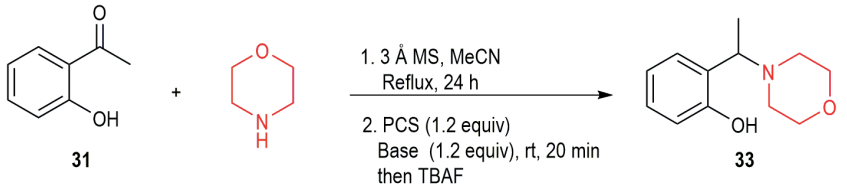


Entry	Deviation from reaction conditions	Isolated yield (%)
1	none	61
2	without DMPU	42
3	1.2 equiv of indoline, without DMPU	63
4	2 equiv of indoline	84
5	2 equiv of indoline, without DMPU	80

We then set out to examine Lewis bases that would allow us keep equimolar amount of the secondary amine and as well catalyze the reaction more effectively than DMPU. Indoline was replaced with morpholine in the subsequent studies due to easier purification of the product. After screening various amount of DMAP as Lewis base and equimolar amounts of amine and ketone, 1.2 equivalents of the base gave the best results with 73% yield of the tertiary amine **33** (Table 3, entry 1). Screening of other Lewis bases (Table 3) resulted in higher yield of 83% of the tertiary alkylphenolmethyl amine **33** with pyridine (Table 3, entry 8) similar to the results with an excess of the secondary amine (Table 2, entry 4). The use of molecular sieves was essential for the reaction conditions in the reductive amination protocol with PCS, as

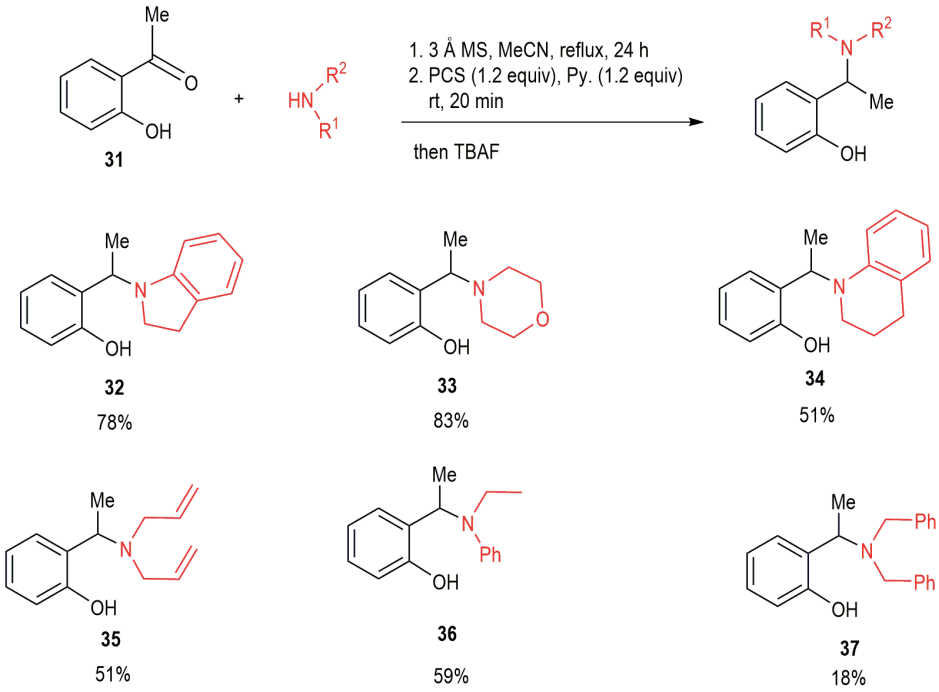
its absence failed to produce the desired reduced product (Publication III). In addition, in the absence of a base promoter, **33** was obtained in only 19% yield (Table 3, entry 9).

Table 3. Screening of Lewis Bases.



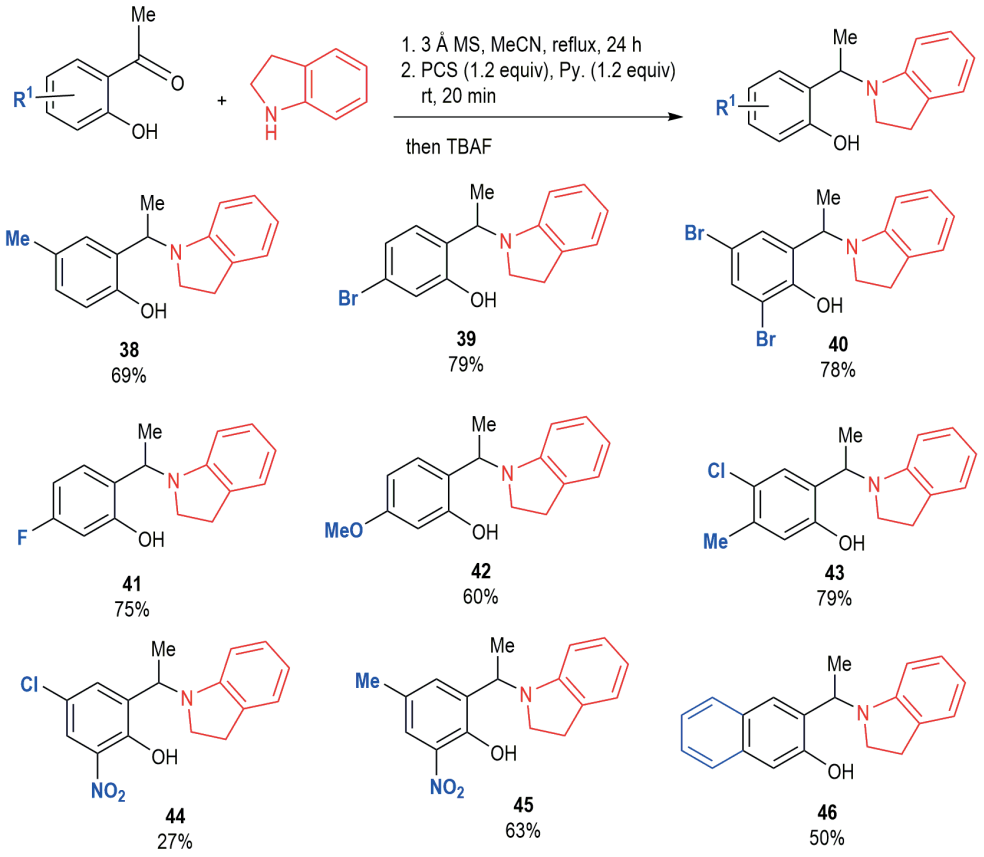
Entry	Base	Isolated yield (%)
1	DMAP	73
2	DIPEA	72
3	DBU	73
4	Et_3N	63
5	Collidine	62
6	Pyridine *N*-oxide	50
7	DMPU	45
8	Pyridine	83
9	none	19

With the optimized conditions in hand (Table 3, entry 8), the amine substrate scope was expanded to other secondary amines with 2'-hydroxyacetophenone. We obtained tertiary alkylphenolmethyl amines **32** – **37** derived from both cyclic and acyclic amines in up to 83% yield with the cyclic ones proving superior (Scheme 20).



Scheme 20. Scope of amines for pyridine-promoted reductive amination with PCS in the preparation of tertiary amines.

The scope of various substituted 2'-hydroxyacetophenones was studied next with indoline providing **38** – **46** (Scheme 21). The method demonstrated good functional group tolerance as nitro and halogen substituted substrates prone to reduction remained intact allowing for the synthesis of their corresponding alkylphenolmethyl amines **39** – **41**, **43** – **45**.

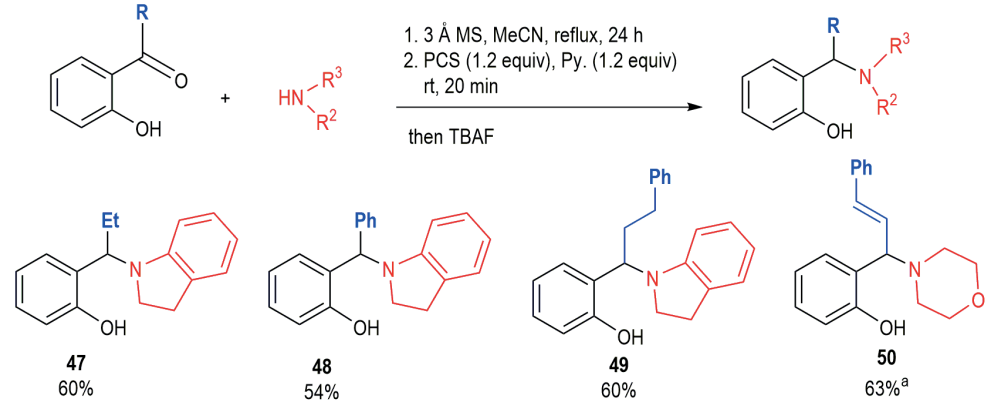


Scheme 21. Scope of substituted 2'-hydroxyacetophenones for the synthesis of alkylphenolmethyl amines.

The utility of this protocol to different alkyl- and phenyl-substituted 2'-hydroxyphenones with indoline or morpholine was examined. Under the standard reaction conditions, compounds **47** – **49** (Scheme 22) and **57** (Scheme 23) were obtained in moderate yields including the efficient reduction of the morpholine-derived eniminium to afford **50** in 63% yield (Scheme 22).

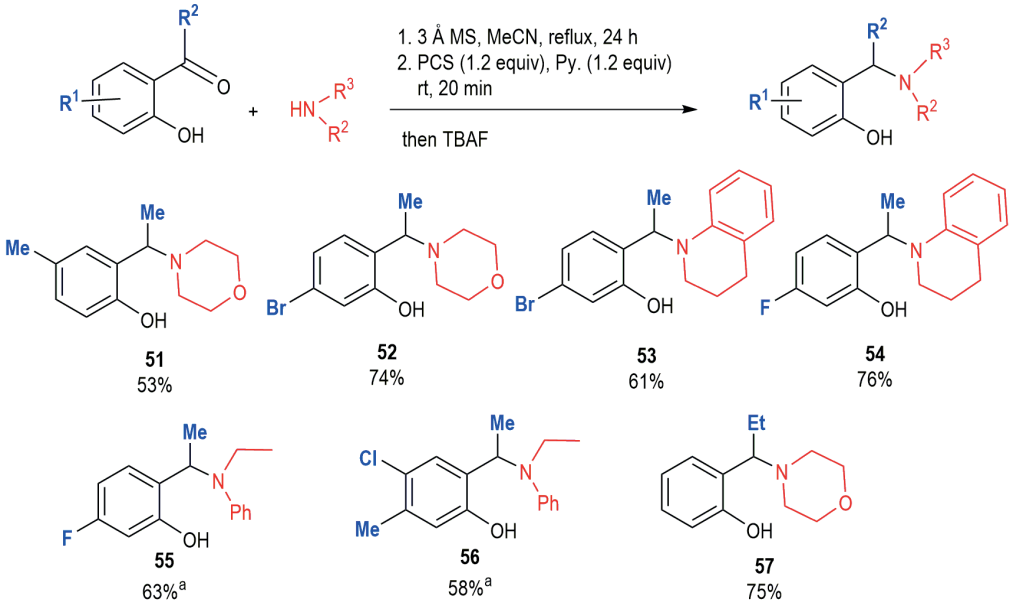
Tertiary amines **51** – **56** of the substituted 2'-hydroxyacetophenone with other amines such as morpholine, ethylaniline and tetrahydroquinoline were also obtained in moderate yields (Scheme 23). Notably, reductions involving ethylaniline as secondary amine and substituted 2'-hydroxyacetophenone generally gave lower yields with the

standard conditions, however moderate yields were obtained for **55** and **56** with the use of 1.8 equivalent of PCS (Scheme 23).



a10 h of reflux

Scheme 22.Scope of α-carbonyl substituted hydroxyphenones in pyridine-promoted reductive amination with PCS.

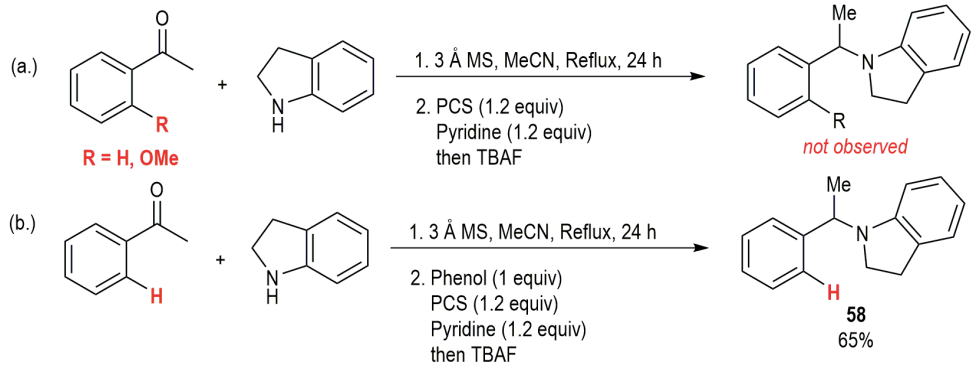


a1.8 equiv. of PCS

Scheme 23. Scope variations in the preparation of alkylphenolmethyl amines.

Commercially available diphenylchlorosilane was tested under the standard conditions in place of PCS and afforded **32** after iminium formation in 66% yield after 2 hours (Publication III).

The reduction of acetophenone- or *o*-methoxyacetophenone-derived iminium failed to occur under the standard reaction protocol (Scheme 24a) exemplifying the importance of the phenolic OH. Interestingly, when phenol was used as an additive under the standard conditions, the acetophenone-derived iminium was smoothly reduced to afford **58** in 65% yield suggesting a possible intermolecular hydride delivery process (Scheme 24b).



Scheme 24. Importance of phenolic hydroxyl moiety in the pyridine-promoted reductive amination method with PCS.

4.3.1 Mechanistic insight

The reductive amination mechanism was studied via DFT calculations using 2'-hydroxyacetophenone and dimethylamine as substrates. The starting point for the calculations is the trialkoxyhydrosilyliminium obtained from HCl loss from the initial hydrosilane. The catalytic cycle proceeds through four steps, which is outlined in the energy profile in figure 8. In the first step, from **A** to **B**, there is coordination of pyridine to the Si-atom in the trialkoxyhydrosilyl iminium. The emergent Si-N bond in the corresponding transition state, $\mathbf{TS_{AB}}$ is 3.30 Å and gradually shortens to 2.07 Å in **B** with intermediate **B** only 1 kcal/mol less stable than the separated reagents. A rotation around the Si-O_{phenol} bond gives conformer **B'** with similar stability. The hydride attack into the iminium C atom from **B'** to **C** has the highest energy barrier

of the entire path with $\mathbf{TS_{B'C}}$ being 16 kcal/mol less stable than intermediate **B'.** A conformer of **C** with similar stability **C'** in a subsequent barrier-less step undergoes *N*-coordination to the silicon atom to produce **D**. This process can be seen as concerted as a prompt Si-N bond formation is observed after the hydride attack. The last step from **D** to **E** proceeds through transition state $\mathbf{TS_{DE}}$ with associated barrier of 12 kcal/mol to liberate pyridine and the final product **E**. A well-advanced Si-$N_{pyridine}$ bond breaking is observed in $\mathbf{TS_{DE}}$ with the Si-$N_{pyridine}$ distance in **D**, 1.89 Å elongated to 2.68 Å. Overall, the reaction is thermodynamically favored with respect to the separated reactants with ΔG = -10 kcal/mol.

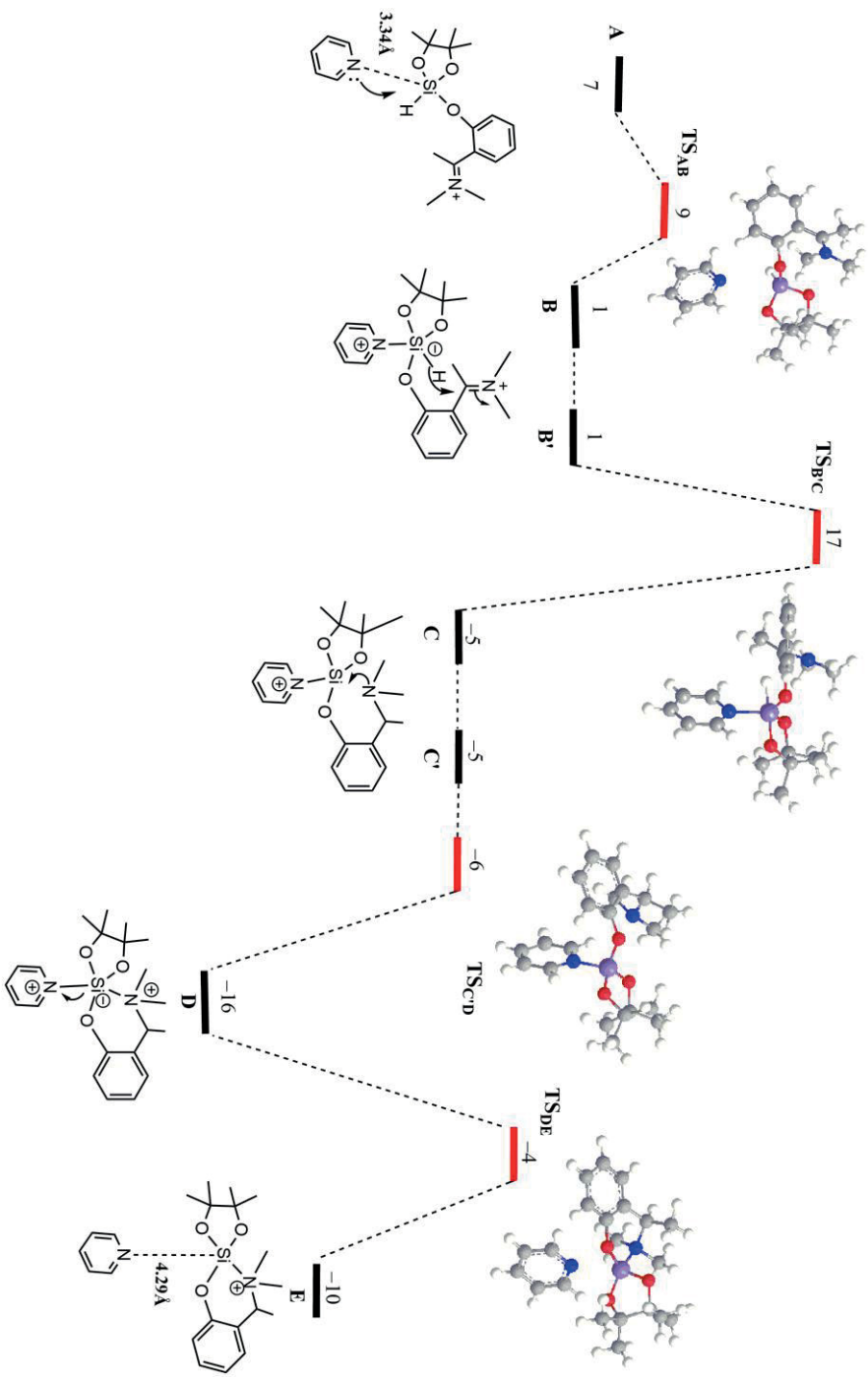


Figure 8. Free energy profile for the pyridine-catalyzed reductive amination. The free energy values [kcal/mol] are relative to the separated reagents: trialkoxysilyliminium plus pyridine

DFT calculations were also performed for the DMPU-catalyzed reductive amination mechanism, for comparison purposes. In fact, lower yields are obtained when DMPU is used as catalyst compared to the pyridine base system (Table 2, entry 1 and Table 3, entry 7) although it functioned as an excellent Lewis base catalyst in the reduction of salicylaldehydes (Publication I). The profile obtained for the DMPU base system is depicted in figure 9. The reaction mechanism calculated for DMPU parallels the one obtained for pyridine described in figure 8.

The catalytic steps are no different from the pyridine-catalyzed mechanism with the first step being the coordination of the O-atom in the base catalyst, DMPU to the Si-atom through transition state $\mathbf{TS_{FG}}$ to give intermediate **G**. Similarly, rotation around the Si_{phenol} bond leads to a less stable conformer, **G'**. In the next step, the hydride attack into the iminium C-atom proceeds through $\mathbf{TS_{G'H}}$ with energy barrier of only 6 kcal/mol, almost 3 times less than the energy required to overcome $\mathbf{TS_{B'C}}$, to give intermediate **H**. **H'** which is a less stable conformer of **H** begins the third step of the N-atom coordination to the Si-atom to form intermediate **I**. In the corresponding transition state, $\mathbf{TS_{H'I}}$ is 3 kcal/mol less stable than **H'**. The last step that involves liberation of the catalyst from **I** to **J** has the highest energy barrier, 26 kcal/mol in the entire reaction paths through the corresponding transition state $\mathbf{TS_{IJ}}$. The $Si\text{-}O_{DMPU}$ bond breaking in $\mathbf{TS_{IJ}}$ is 1.01 Å longer than the distance in **I** with a remaining distance of 1.47 Å to reach its final value in the product **J**.

The major difference between the two reactions is the stability of the base-Si adducts, that is, intermediates **D** and **I**, in the pyridine and DMPU systems, respectively. In fact, **I** is 24 kcal/mol more stable than the separated reagents, thus making DMPU loss the highest barrier step in the path ($\mathbf{TS_{IJ}}$: 26 kcal/mol). Overall, the pyridine mechanism corresponds to a more facile reaction, the highest barrier being associated with hydride attack on $C_{C=N}$ ($\mathbf{TS_{B'C}}$, 17 kcal/mol relative to the separated reagents). These results indicate how strongly an oxygen base such as DMPU binds to the Si-atom and consequently hampers the liberation of the base catalyst and release of the final product. Therefore, the lower yields observed in DMPU catalyzed reductive amination compared to those of the pyridine system are mostly dependent on the stability of base-Si adduct.

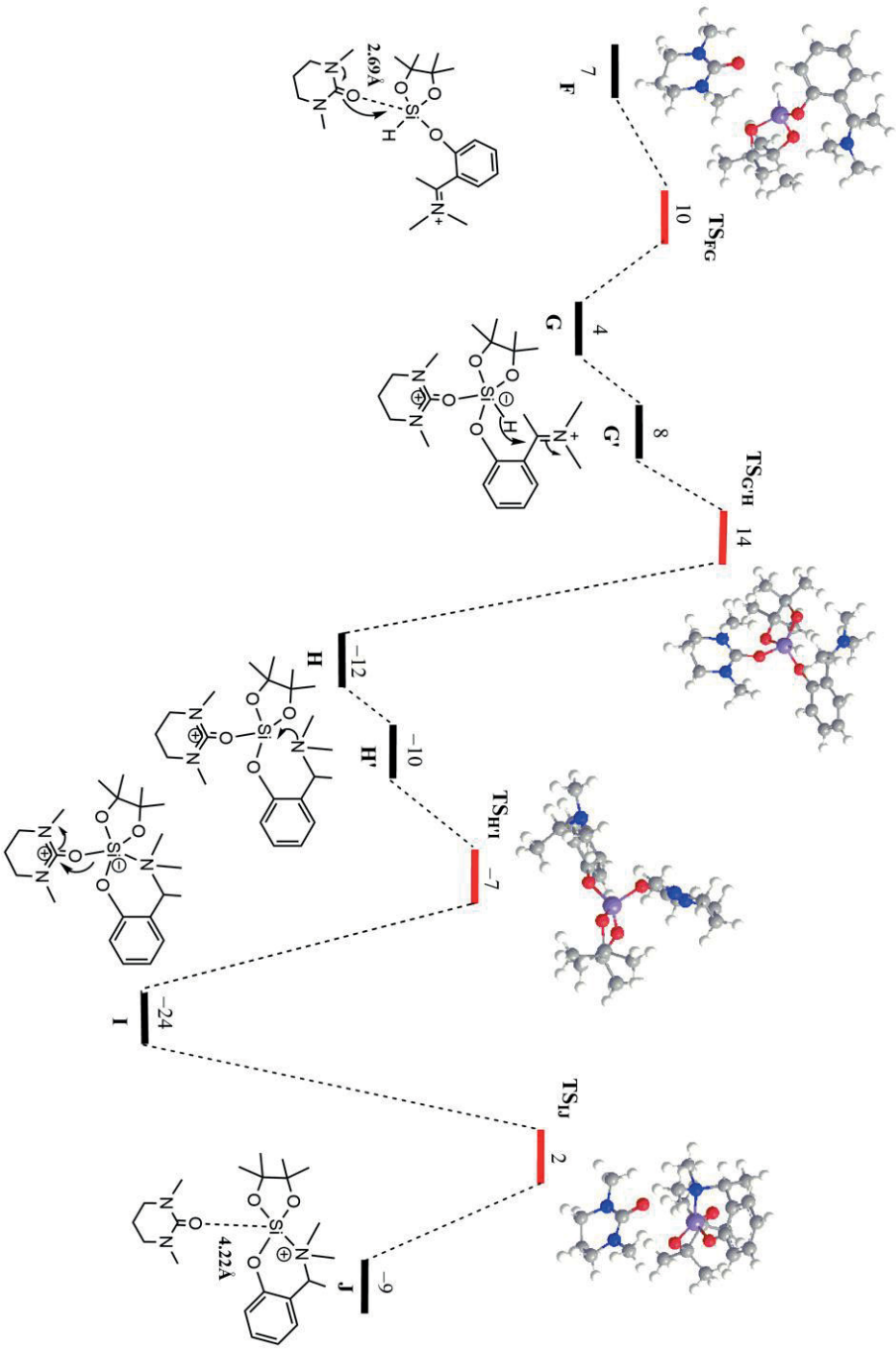


Figure 9. Free energy profile for the reductive amination reaction catalyzed by DMPU. The free energy values [kcal/mol] are relative to the separated reagents: trialkoxyhydrosilyliminium plus DMPU.

The DFT calculations for the reductive amination mechanism without a Lewis base revealed a concerted mechanism with simultaneous hydride transfer and *N*-coordination to Si through a transition state with significant energy barrier of 41 kcal/mol. The reaction is nevertheless exergonic with free energy balance of -15 kcal/mol (Figure 10). A comparison of the barriers calculated for the mechanism with or without Lewis base reveals the active role of either pyridine or DMPU as a promoter.

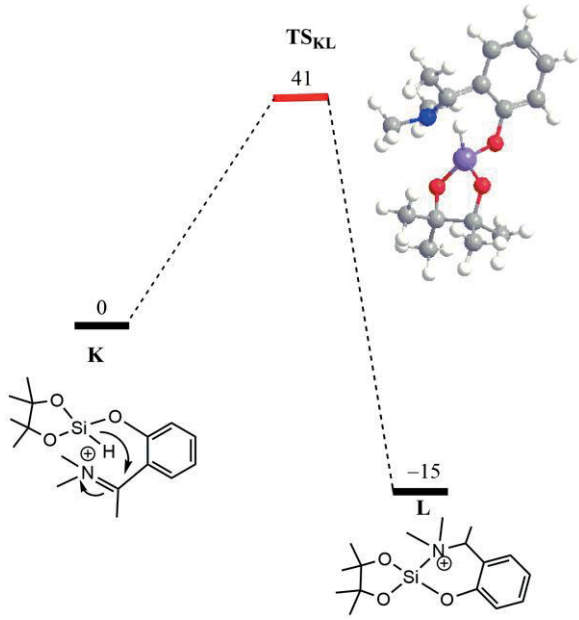


Figure 10. Free energy profile for the uncatalyzed reductive amination reaction. Free energy values [kcal/mol] relative to the trialkoxyhydrosilyliminium (**K**)

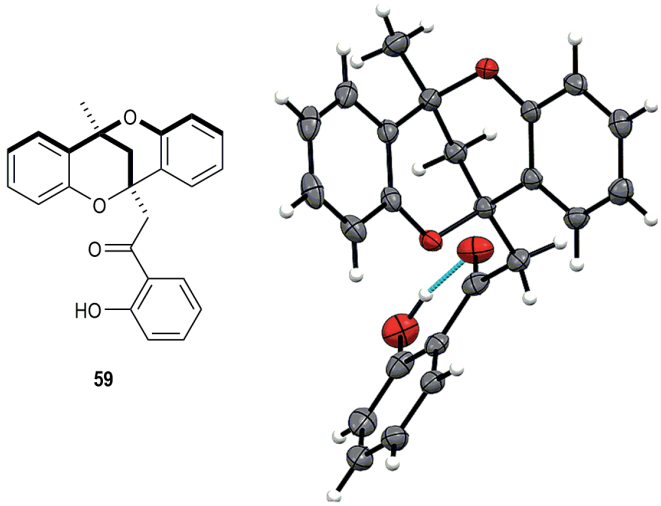
In this study, we concluded that, this protocol is based on the *in situ* formation of a trialkoxyhydrosilane with concomitant hydride delivery promoted by pyridine allowing for the synthesis of a variety of aminoalkylphenols (Publication III).

4.4 Synthesis of 6, 12-disubstituted methanodibenzo[*b,f*][1,5] dioxocins

A growing interest in pharmaceutical research is the quest to develop step-economical synthetic route to new or improved bioactive compounds and novel compounds with

varying structural complexities. The highly bridged polycyclic methanodibenzo[*b,f*][1,5]dioxocin structural motif is prevalent in many bioactive natural products such as cyanomaclurin, its analogues and pharmaceuticals. Synthetic strategies towards the construction of the methanodibenzo[*b,f*][1,5]dioxocin skeleton are very limited in literature [178-180] with less attention paid to this scaffold in drug design.

In the course of investigating the reductive amination protocol with stoichiometric amounts of 2'-hydroxyacetophenone and various secondary amines under our PCS hydrosilylation system (Publication III), we discovered the formation of a 2'-hydroxyacetophenone self-condensation product **59** in 9% yield and the absence of the desired reductive amination product when using pyrrolidine as the secondary amine. The unambiguous characterization of the self-condensation product was done via single crystal X-ray diffraction analysis after crystallization. An intramolecular hydrogen bond and geometric features of the methanodibenzo[*b,f*][1,5]dioxocin core in the crystal structure (Figure 11) of **59** was observed to be similar to that of 7,9-dimethoxy-6H,12H-6,12-methanodibenzo[*b,f*][1,5]dioxocin-4-ol [226], with the exception of the interplanar angle between benzene rings, which was ~88° close to orthogonality. This value is however comparable to the value found in (*E*)-2-(4-((12-methyl-6H,12H-6,12-methanodibenzo[*b,f*][1,5]dioxocin-6-yl)methylene)-4H-chromen-2-yl)phenol [227].



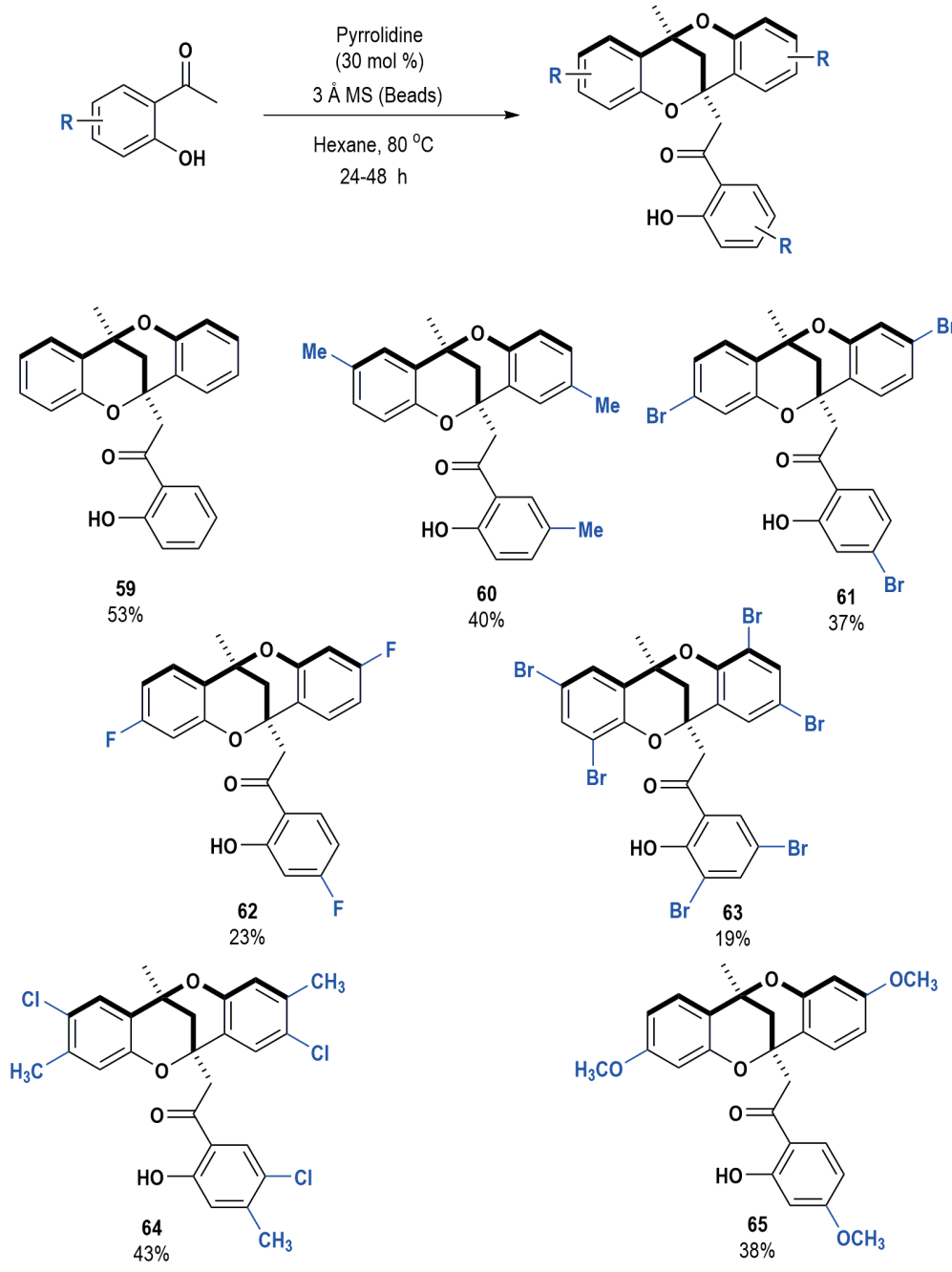
59

Figure 11. Ortep diagram of the molecular structure of **59**

Optimization of the initial reaction conditions led to the synthesis of the unprecedented 6, 12-disubstituted methanodibenzo[*b,f*][1,5]dioxocin in 53% yield using 30 mol% of pyrrolidine as catalyst in refluxing hexane (Scheme 25, Publication IV). Although other synthetic routes for the synthesis of the methanodibenzo[*b,f*][1,5]dioxocin core is reported to be catalyzed by Lewis or Brønsted acids [179,180], all attempts to obtain **59** under acidic conditions failed. Notably, previously reported efforts to dimerize β-hydroxy ketones using acidic/dehydrating conditions proved futile although the dimerization of salicylaldehydes were successful affording 6H, 12H-6,12-epoxydibenzo[*b,f*][1,5]dioxocins [228,229].

The substrate scope for this pyrrolidine-catalyzed self-condensation of 2'-hydroxyacetophenone to afford the unprecedented 6, 12-disubstituted methanodibenzo[*b,f*][1,5]dioxocin was studied with substituted 2'-hydroxyacetophenones (Scheme 25). The protocol demonstrated suitability for accessing alkyl-, halide- and methoxy-substituted methanodibenzo[*b,f*][1,5]dioxocin derivatives **60 – 65**. The application of this methodology to strongly electron donating substituents such as nitro substituted 2'-hydroxyacetophenone failed as observed also for the utilization of the protocol with other 2'-hydroxyketones such as 2'-hydroxpropiophenone or 2'-hydroxy-3-phenylpropiophenone (Publication IV).

The reductive amination of 2'-hydroxyacetophenone and pyrrolidine begins with iminium formation under neat conditions at room temperature [230]. However, the absence of the formation of similar dioxocin products under the PCS hydrosilylation protocol in Publication III with the use of other cyclic secondary amines like morpholine, indoline and tetrahydroquinoline suggests the likelihood of enamine formation in the self-condensation of 2'-hydroxyacetophenone catalyzed by pyrrolidine. Moreover, enamines derived from pyrrolidine are reported to be more reactive than other cyclic amines [231,232]. Nevertheless, the details of the reaction mechanism require full clarification.



Scheme 25. Scope of substituted methanodibenzo[*b,f*][1,5]dioxocin derivatives.

5 CONCLUSIONS

A novel 5-membered cyclic chlorohydrosilane has been designed and synthesized conveniently from pinacol and trichlorosilane with easy isolation by simple filtration to remove the pyridinium chloride salt. The reactivity of this novel pinacol-derived chlorohydrosilane has been explored in the formation of trialkoxyhydrosilanes and in subsequent Lewis base activation for the reduction of phenolic compounds with carbon-heteroatom substituents at the *ortho* position.

To investigate the Lewis base-catalyzed reduction of salicylaldehydes with pinacol-derived chlorohydrosilane, various substituted salicylaldehydes including formyl-hydroquinone were employed. The ability of the pinacol-derived chlorohydrosilane to react as an effective reducing agent was increased upon the *in situ* formation of a trialkoxyhydrosilane and activation with a Lewis base. DMPU emerged as the best Lewis base activator in the metal-free reduction of salicylaldehydes to obtain several substituted salicyl alcohols in moderate to excellent yields and good functional group tolerance. The catalytic role of DMPU in promoting the intramolecular hydride delivery was further verified by DFT studies. We have demonstrated that notwithstanding the high reactivity of this metal-free protocol, it allows for regio- and chemoselective reductions of aldehydes in *ortho* positions to phenols even in the presence of vicinal ketones. This study forms the first reported Lewis-base catalyzed hydrosilylation of salicylaldehydes.

Industrially relevant hydroquinone, from which formyl-hydroquinone can be prepared, has been synthesized using a biomass-based route starting from naturally available quinic acid. The mild and efficient oxidant-free method for the conversion of quinic acid to hydroquinone employs Amberlyst-15 in its dry form as an acid promoter to access hydroquinone in up to 72% yield with little contamination by the dimeric ether. Experimental and computational calculations supported a proposed ionic decarbonylation mechanism for the hydroquinone formation.

Synthesis of tertiary alkylphenolmethyl amines from a metal-free reductive amination protocol using pinacol-derived chlorohydrosilane/pyridine system was developed. This method based on the *in situ* formation of a trialkoxyhydrosilane with concomitant intramolecular hydride delivery through Lewis base activation as further indicated by computational studies is selective towards iminiums derived from alkylphenol ketones. Under this protocol, an array of aminoalkylphenols was obtained in reasonable to high yields with equimolar amounts of reactants and a wide substrate scope, allowing for high functional group tolerance. In addition, the scope of the method could be expanded by using phenol as an additive in an intermolecular hydride delivery fashion.

A pyrrolidine-catalyzed metal-free and simple synthetic route to the preparation of 6, 12-disubstituted methanodibenzo[*b*,*f*][1,5] dioxocin has been developed. These structurally robust unprecedented derivatives with potential usefulness in medicinal chemistry could be obtained from the self-condensation of 2'-hydroxyacetophenones. This protocol provides in a single step the construction of two C–O bonds, two C–C bonds, a methylene bridge and two quaternary centers. In spite of the narrow scope of the transformation, the observed formation of the methanodibenzo[*b*,*f*][1,5]dioxocin scaffold without the need to use any metals or strongly acidic conditions is a clear advantage over other reported methods.

Notwithstanding the superior performance of PCS in the intramolecular hydride delivery, the initial studies on the reactivity of the PCS-derived trialkoxyhydrosilanes presented here might serve as the starting point for the development of more complex systems. The herein reported reduction of prochiral sp^2-carbons together with the ability to effect the intermolecular hydride delivery from PCS, using phenol as additive, present opportunities for the development of asymmetric hydrosilylation procedures based on PCS.

Finally, the scope of this thesis did not cover any biological activity studies of the novel 6, 12-disubstituted methanodibenzo[*b*,*f*][1,5]dioxocin derivatives. As some natural products possessing the same structural core have exhibited antibacterial activity, antidipogenic properties and inhibitory activities against β-amyloid aggregation and tyrosinase, the comprehensive biological activity studies of these new derivatives are encouraged.

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PUBLICATIONS

Publication I Benedicta Assoah, João R. Vale, Elina Kalenius, Luis F. Veiros, and Nuno R. Candeias. Lewis Base Catalyzed Intramolecular Reduction of Salicylaldehydes by Pinacol-Derived Chlorohydrosilane. *Eur. J. Org. Chem.* **2018**, 2910-2917.

Publication II Benedicta Assoah, Luis F. Veiros, Carlos A. M. Afonso, and Nuno R. Candeias. Biomass-Based and Oxidant-Free Preparation of Hydroquinone from Quinic Acid. *Eur. J. Org. Chem.* **2016**, 3856-3861.

Publication III Benedicta Assoah, Luis F. Veiros, and Nuno R. Candeias. Pinacol-Derived Chlorohydrosilane in Metal-Free Reductive Amination for the Preparation of Tertiary Alkylphenolmethyl Amine. *Org. Lett.* **2019**, *21*, 1402-1406.

Publication IV Benedicta Assoah, Vesa Riihonen, João R. Vale, Arto Valkonen, and Nuno R. Candeias. Synthesis of 6, 12-Disubstituted Methanodibenzo[*b,f*][1,5]dioxocins: Pyrrolidine Catalyzed Self-Condensation of 2'-Hydroxyacetophenones. *Molecules*, **2019**, *24*, 2405.

PUBLICATION I

Lewis base catalysed intramolecular reduction of salicylaldehydes by pinacol-derived chlorohydrosilane.

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Selective Reduction

Lewis Base Catalyzed Intramolecular Reduction of Salicylaldehydes by Pinacol-Derived Chlorohydrosilane

Benedicta Assoah,*[a] João R. Vale,[a,b] Elina Kalenius,[c] Luis F. Veiros,[d] and Nuno R. Candeias*[a]

Abstract: A newly developed stable chlorohydrosilane derived from pinacol is herein described. This was successfully used in the reduction of salicylaldehydes in reasonable to excellent yields (51–97 %). The ability of the hydrosilane to react as a reducing agent is increased upon the in situ formation of a trialkoxyhydrosilane and activation with a Lewis base, as further indicated by density functional theory studies. 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) was identified to be a suitable catalyst for this metal-free reduction, promoting the regio- and chemoselective reduction of aldehydes in *ortho*-position to phenols, despite the presence of vicinal ketones. The performance of pinacol-derived chlorohydrosilane in the reduction of salicylaldehydes was further observed to be superior to that of well-established commercially available chlorohydrosilanes.

Introduction

The reduction of carbon-heteroatom unsaturated organic compounds remains one of the most essential transformations in synthetic organic chemistry for both academic and industrial applications. An array of catalytic protocols such as hydrogenation reactions, electron transfer and hydride transfer reductions have been explored extensively with carbon-heteroatom multiple bond reductions.[1]

In recent years, catalytic hydrosilylation has made significant progress and is being used as a major tool in the reduction of organic substrates, serving as a convenient alternative to the use of hydrogenation and metal hydrides.[2] Since the electronic and steric properties of hydrosilanes can be tuned by interaction with unreactive functional groups in the substrate or with external chemical agents, these reagents have found their way in the reduction toolbox of synthetic chemists, as they can be used to perform a large variety of chemoselective reductions under mild conditions.[3] Specifically, their reducing properties towards carbonyl can be controlled by the silicon substituents along with catalysts[2a,4] such as Lewis acids,[5] Lewis bases[6] or transition metal complexes.[7] Despite the notable progresses made in transition metal catalyzed hydrosilylations,[3c,8] the metal-free version of such reductions has received tremendous importance in recent research endeavors;[3a] as they benefit from the absence of costly and often toxic metal catalysts and the need to remove any metal impurities particularly relevant for pharmaceutical products.[9]

Mild reductions of carbonyl groups to the corresponding alcohol functionality by metal-free hydrosilylation methods have been largely accomplished through use of acid and bases as catalysts.[2a,6b] Despite the rather low Si–H bond energy of hydrosilanes when compared with C–H bond, employing hydrosilanes in metal-free carbonyl reduction requires either carbonyl activation by complexation with Brønsted or Lewis acids or activation of the hydrosilane, in which $B(C_6F_5)_3$ has been extensively explored.[10] Both alcohols or hydrocarbons[5,11] can be obtained, depending on the reaction conditions and the hydrosilane used. One of the approaches explored in the activation of hydrosilanes has been the expansion of tetrahedral silicon to a pentavalent anion intermediate upon complexation with nucleophilic species.[12] Silicon valence expansion leads to a redistribution of the electronic density, polarizing the covalent bonds around silicon, decreasing silicon electron density and increasing the electron density of the silicon substituents. Overall, these results in a higher hydride donating ability of the pentavalent complex when compared with its tetracoordinate counterpart.[13] Mitsuo and co-workers reported an in situ formation of pentacoordinate bis(diolato)hydridosilicates from trichlorosilane and catechol or 2,2′-dihydroxybiphenyl for the reduction of carbonyl compounds. However, pentacoordinate hydridosilicates from aliphatic diols such as 1,2-ethanediol and pinacol proved to be less effective as reducing agents.[14] Cs_2CO_3,[3a,15] TBAF,[16] *t*BuOK,[17] CsF, and KF[6a] have been re-

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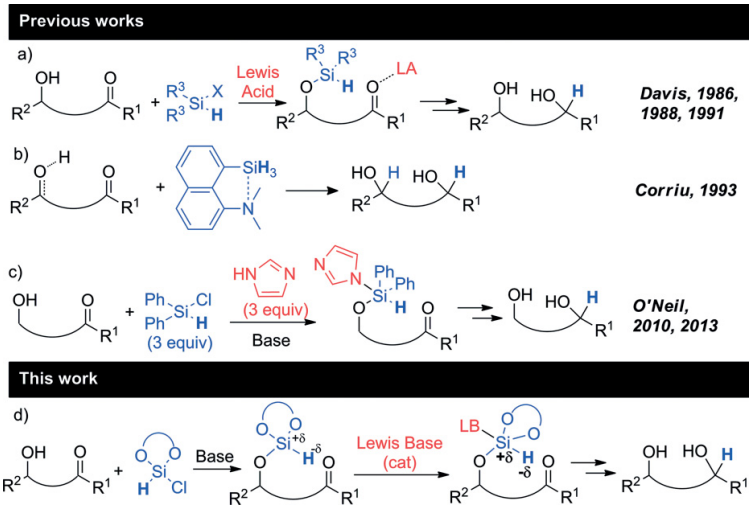


Scheme 1. Intramolecular hydrosilylation of hydroxy carbonyl compounds.

ported as active catalysts or activators in the chemoselective hydrosilylation of aldehydes and ketones, while being tolerant to other functional groups. Hypervalent Cl_3SiH-DMF silicate was described by Kobayashi et al. to be an effective reducing agent in the reduction of aldehydes, imines and in the reductive amination of aldehydes.[18]

The intramolecular hydrosilylation of carbonyl compounds has been explored as a way to achieve stereoselective reductions due to more constrained cyclic transition states (Scheme 1). Davis and co-workers achieved moderate to excellent stereoselectivities on the intramolecular hydrosilylation of β-hydroxyketones using Lewis acid catalysis (Scheme 1a),[19] while intramolecular hydrosilylation of β-hydroxyesters was better accomplished with catalytic amounts of fluoride.[20] Pentacoordinate hydrosilanes, activated by an internal N–Si bond have been successfully used in the same kind of transformation (Scheme 1b).[21] More recently, O'Neil and co-workers[6b,6c] reported a cooperative Lewis base-mediated intramolecular carbonyl hydrosilylation of β-hydroxyketones (Scheme 1c). The hydrosilyl ether formed upon reaction of the hydroxyl group with diphenylchlorosilane, in presence of a tertiary base, could undergo an intramolecular hydride delivery promoted by imidazole. However, the system was not rendered catalytic and the use of superstoichiometric amounts of imidazole and diphenylchlorosilane were required.

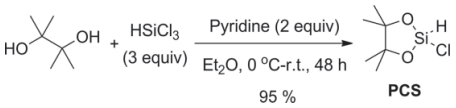
Considering that the hydride character of hydrosilanes is highly dependent on the silicon substituents, we envisioned that alkoxy derived hydrosilanes would be highly reactive under certain constrains (Scheme 1d). The hydride character would be further increased by constraining the silicon atom within a ring, as known that 4- and five-membered silacycles have higher Lewis acid character than their acyclic counterparts, due to strain release.[22] Cyclic structures derived from silicon could have their Lewis acid character further increased upon complexation with a Lewis base, as a pentavalent silicon complex would form.[23] Such an event would activate a Lewis basic site such as oxygen of a carbonyl, and simultaneously decrease the Si–H bond strength.

In order to verify these assumptions a novel chlorohydrosilane was prepared and its reactivity tested in the Lewis base catalyzed hydrosilylation of salicylaldehyde derivatives, which we used in several instances in multicomponent Petasis borono-Mannich reaction.[24] Notably, despite the widely available methods for reduction of salicylaldehyde,[25] as far as our knowledge goes its Lewis base-catalyzed hydrosilylation has never been reported.

Results and Discussion

Our initial attempts on the preparation of five-membered chlorohydrosilane derived from ethylene glycol with $HSiCl_3$ in presence of different amines resulted in complex mixtures due to disproportionation and formation of silicon-amine adducts.[26] Questioning the putative high reactivity of the five-membered chlorohydrosilane formed under such conditions, the ethylene glycol was replaced by pinacol aiming at increasing the stability of the chlorohydrosilane. Gladly, treatment of pinacol with an excess amount of trichlorosilane and pyridine in diethyl ether under inert atmosphere yielded the desired pinacol-derived chlorohydrosilane (PCS) in nearly quantitative yield after filtration and solvent removal (Scheme 2). Just as many chlorosilanes, PCS is an air and moisture sensitive clear colorless liquid that can be stored for at least 6 months at −20 °C under inert atmosphere without any change in reactivity.

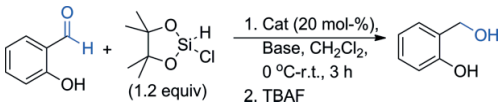
The ability of PCS to serve as a reducing agent was tested in the hydrosilylation of salicylaldehyde in dichloromethane (Table 1), for which the corresponding salicyl alcohol was obtained in 24 % yield after 72 h in dichloromethane in absence of base (entry 1). Gratifyingly, the same alcohol was obtained



Scheme 2. Preparation of pinacol-derived chlorohydrosilane (PCS).

in 70 % after 3 h when using triethylamine as a hydrochloric acid sequester (entry 2). When diminishing the amount of base to 20 mol-%, reduction was rather incomplete as judged by TLC, and the product was formed in only 29 %, indicating the dual role of the amine as a catalyst and HCl sequester (entry 3). Screening of other bases prone for HCl sequestering and Lewis base catalysis, such as pyridine and Hünig's base, led to product formation in lower yields (entries 4 and 5). Use of DMF as reaction solvent, in absence of any additive, resulted in salicyl alcohol formation in 68 % likely due to the Lewis base character of DMF.[27] Although the promoter role of triethylamine was notoriously visible, a more effective Lewis base was searched to be used in combination with the amine HCl sequester. Moderate yields were observed when using PPh_3, pyridine *N*-oxide and HMPA, for which presence of triethylamine had a negligible effect (entries 7–9). Gladly, when using 20 mol-% of DMPU, an environmentally benign substitute to HMPA,[28] the desired product was obtained in excellent 94 % yield after 3 h (entry 10), for which the presence of triethylamine showed a negligible effect other than HCl trapping.

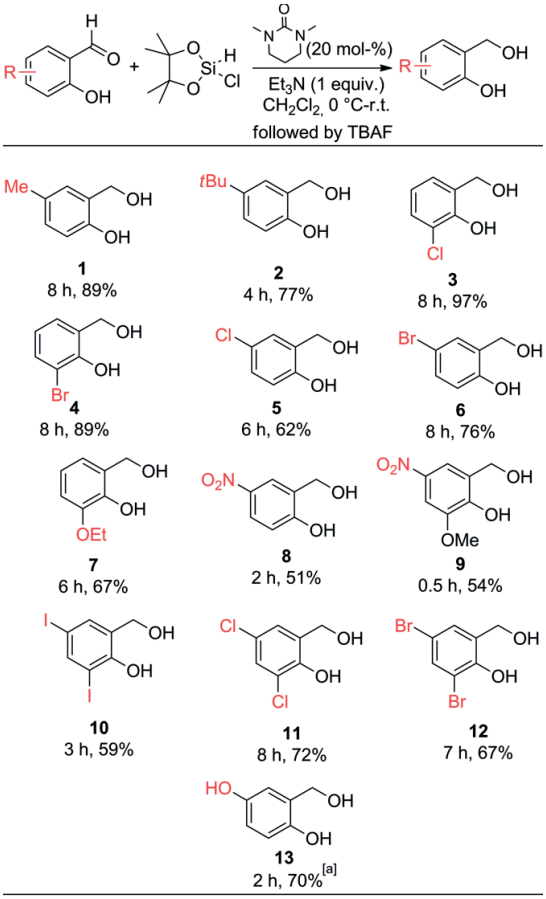
Table 1. Lewis base-catalyzed reduction of salicylaldehyde with PCS.



Entry[a]	Base [equiv.]	Cat.	Yield [%][b]
1	–	–	24[c]
2	Et_3N (1.2)	–	70
3	–	Et_3N	29
4	DIPEA (1.2)	–	51
5	pyridine (1.2)	–	58
6	DMF[d]	–	68
7	Et_3N (1.0)	PPh_3	58 (57)[e]
8	Et_3N (1.0)	pyridine *N*-oxide	70 (56)[e]
9	Et_3N (1.0)	HMPA	64 (64)[e]
10	Et_3N (1.0)	DMPU	94 (97)[e]

[a] PCS (0.65 mmol) in DCM (1 mL) was added over 5 min to a mixture of salicylaldehyde (0.54 mmol), base and catalyst in DCM (1.5 mL) at 0 °C. After 20 min, mixture was left reacting at room temperature for 3 h and then treated with TBAF (1 M in THF, 0.75 mmol). [b] Isolated yield. [c] Reaction conducted for 72 h. [d] DMF used as solvent. [e] Reaction yield in absence of TEA in parenthesis.

After optimization of the reaction conditions, the reduction of different substituted salicylaldehydes was performed (Scheme 3). Reaction times varied between 0.5 h and 8 h, affording the desired salicyl alcohols in reasonable to excellent yields (51–97 %). 5-Alkyl-substituted salicylaldehydes were promptly reduced to afford **1** and **2** after desilylation with TBAF. Despite the presence of nitro and halogen substituents susceptible to reduction, the salicylaldehydes efficiently undergo reduction of the carbonyl group. 3-Halogen substituted salicylaldehydes were generally reduced more efficiently affording **3** and **4** in excellent yields, while 5-halogen derivatives were obtained in slightly lower yields as for **5** and **6**. 5-Nitrosalicylaldehydes could be efficiently reduced in less than 2 h, affording **8** and **9** in up to 54 % yield. Notably, despite the vicinity of ether groups to the hydroxyl substituent of salicylaldehyde, no reduction of 3-alkoxy substituents was observed, as only the corresponding salicyl alcohols **7** and **9** were obtained. The procedure was further expanded to the reduction of 3,5-dihalogens resulting in formation of **10**–**12** in up to 72 % yield. As a continuation of our work on preparation of hydroquinone from quinic acid,[29] we also performed the reduction of readily available formyl-hydroquinone.[30] The reduced product **13** was obtained in 70 % yield by changing the solvent from dichloromethane to acetonitrile without increasing the amount of PCS.

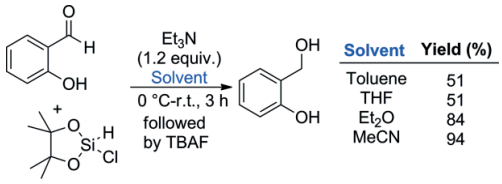


[a] Acetonitrile used as solvent.

Scheme 3. Scope of Lewis base-promoted reduction of salicylaldehydes with PCS.

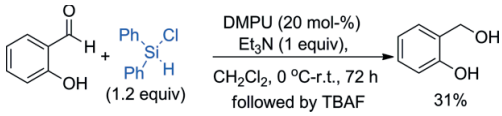
Considering the observed dual role of triethylamine in the reduction of salicylaldehyde, as the use of 1.2 equiv. allowed formation of the desired product in 70 % yield (Table 1, entry 2), we have optimized the reaction conditions as this could ren-

der a more practical use of PCS as reducing agent. Gratefully, salicyl alcohol could be obtained in 94 % isolated yield in acetonitrile after 3 h and further treatment with TBAF (Scheme 4). Nevertheless, a superior catalytic role of DMPU was observed, as the use of 20 mol-% in DCM led to formation of salicyl alcohol in 97 % yield in the absence of any HCl sequester (Table 1, entry 10).



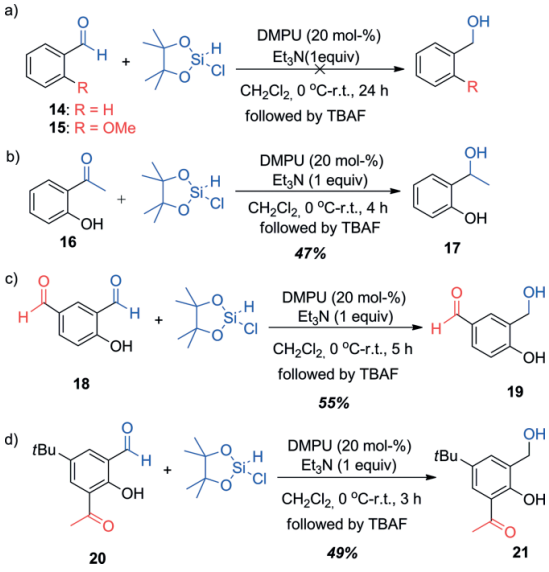
Scheme 4. Optimization for dual use of Et_3N in reduction of salicylaldehyde with PCS.

In order to attest the superiority of PCS for salicylaldehyde reduction, commercially available chlorohydrosilanes were tested using the optimized procedures. When using diphenylchlorosilane with dichloromethane as solvent and DMPU as catalyst in presence of stoichiometric amount of triethylamine, salicylic alcohol was obtained in only 31 % yield after 72 h (Scheme 5). Chlorodimethylsilane and chlorodiisopropylsilane failed in providing the reduced product under the same conditions.



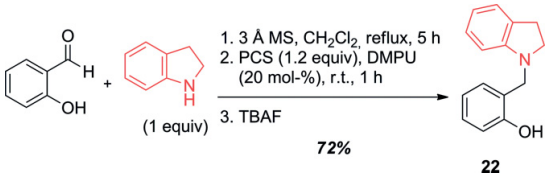
Scheme 5. Reduction of salicylaldehyde with diphenylchlorosilane.

The several attempts to reduce benzaldehyde with PCS using the optimized protocol proved futile, even when increasing the reaction time to 24 h or the reaction temperature. The lack of reactivity of benzaldehyde towards PCS indicate the required formation of a trialkoxyhydrosilane as well as the intramolecular reduction process. Furthermore, the reduction of *O*-methyl salicylaldehyde **15** was not accomplished with the reaction conditions as only starting material was visible after 24 h (Scheme 6a). Despite the rather high reactivity of PCS, its ability to reduce aryl ketones is notoriously low, as confirmed by formation of **17** in only 47 % yield after 4 h (Scheme 6b). With such information in hand, we also examined the chemo- and regioselectivity of the reduction process (Scheme 6c and d). Gratifyingly, our system allowed the regioselective reduction of 5-formyl salicylaldehyde **18**, resulting in exclusive reduction of the aldehyde group in the *ortho*-phenol position in 55 % yield. In order to test the chemoselectivity of the system, **20** was synthesized and submitted to the same reduction conditions. Despite the previously observed reduction of the ketone in **16**, the chemoselective reduction of the aldehyde functionality of **20** was observed, rendering product **21** exclusively in 49 % yield after 3 h.



Scheme 6. Regioselective and chemoselective DMPU-catalyzed reduction of salicylaldehydes with PCS.

In order to expand the suitability of this system to the reduction of carbon-heteroatom unsaturated bonds, PCS was tested as a reducing agent in the reductive amination of a salicylaldehyde-derived iminium (Scheme 7). After condensation of salicylaldehyde and indoline for 6 h in refluxing dichloromethane, the in situ formed iminium was reduced by PCS, affording the corresponding tertiary amine **22** in 72 % yield. Delightfully, despite the high propensity of PCS towards hydrolysis, the use of molecular sieves was enough to trap the water formed in the condensation process. Optimization of this process and its expansion to other amines is under way and will be reported in due course.



Scheme 7. DMPU-catalyzed reductive amination of salicylaldehyde-derived iminium with PCS.

The mechanism of aldehyde reduction with PCS was studied by means of DFT calculations[31] using salicylaldehyde as substrate. The calculations starting point is the trialkoxyhydrosilane that results from HCl loss from the initial hydrosilane, and the free energy profile obtained is depicted in Figure 1.

In the first step of the mechanism, from **A** to **B**, there is coordination of the base, DMPU, to the Si-atom in the trialkoxyhydrosilane. In the corresponding transition state, $\mathbf{TS_{AB}}$, the new Si–O bond is only incipient with a distance of 2.56 Å, still 0.58 Å longer than its final value, in **B**. This is a very facile step

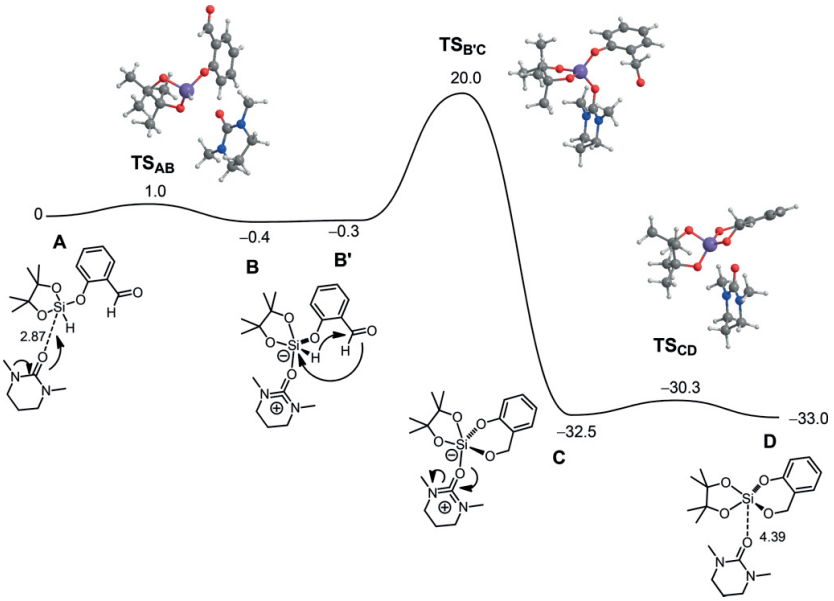


Figure 1. Free energy profile for the reduction of salicylaldehyde with PCS catalyzed by DMPU. Free energy values [kcal/mol] relative to the pair of reactants, DMPU plus the trialkoxyhydrosilane (**A**). Distances in Å.

with a negligible barrier of only 1.0 kcal/mol and the resulting intermediate (**B**) is only 0.4 kcal/mol more stable than the reagents. From **B**, there is rotation around the Si–O_{phenol} bond that leads to another conformer, **B′**. In the following step, from **B′** to **C**, there is hydride attack into the carbonyl C-atom and coordination of the corresponding O-atom to silicon. In the transition state, **TS$_{B'C}$**, formation of the new C–H bond is practically accomplished with a bond length only 0.03 Å longer than the one existing in **C**, while the Si–O bond is only beginning to form with a distance of 4.09 Å, indicating a non-synchronous process in which C–H bond formation precedes the C–O counterpart. The barrier associated with this step is the highest of all path, **TS$_{B'C}$** being 20.0 kcal/mol less stable than the reactants, but the process is clearly exergonic with ΔG = −32.2 kcal/mol. In the last step of the mechanism, there is liberation of the catalyst, DMPU, and formation of the final product, salicyl alcohol. In the corresponding transition state, **TS$_{CD}$**, the process of Si–O_{DMPU} bond breaking is well advanced, with distance of 2.37 Å, already 0.55 Å longer than the one present in intermediate **C**. This is a fairly easy step with a barrier of only 2.2 kcal/mol, and overall the reaction is thermodynamically favorable, with a free energy balance of ΔG = −33.0 kcal/mol.

The mechanism of salicylaldehyde reduction in the absence of catalyst was also investigated by DFT calculations, for comparison purposes. The free energy profile obtained is represented in Figure 2.

The reaction starts with coordination of the carbonyl O-atom to silicon, from **E** to **F**. From **F**, there is hydride transfer from silicon to the $C_{C=O}$-atom, through transition state **TS$_{FG}$**. In the transition state the process of Si–H bond breaking and C–H bond formation is halfway through with distances of 1.61 and

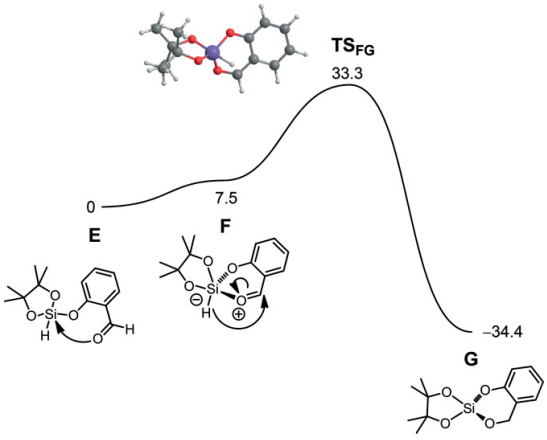


Figure 2. Free energy profile for the reduction of salicylaldehyde with PCS in the absence of catalyst. Free energy values [kcal/mol] relative to the trialkoxyhydrosilane (**E**).

1.87 Å, respectively. Significantly, the reaction has an associated barrier of 33.3 kcal/mol, and the overall process is very favorable with ΔG = −34.4 kcal/mol. The comparison of the two mechanism shows the role of DMPU as catalyst, lowering 12.9 kcal/mol the total barrier of the reaction.

Conclusions

Herein we report the easy preparation of a novel chlorohydrosilane derived from pinacol that can be easily isolated by simple

filtration to remove the pyridinium chloride salt. Its Lewis base promoted and metal-free reduction of salicylaldehydes enables the preparation of several substituted salicyl alcohols in reasonable to excellent yields. Despite the high reactivity of the developed system, we demonstrated its ability to perform the desired reductions in a regio- and chemoselective manner due to the in situ formation of a trialkoxyhydrosilane followed by intramolecular hydride delivery promoted by a Lewis base. From screening of several Lewis bases, DMPU was identified as the best base in promoting the intramolecular hydride delivery, and its catalytic role was further verified by DFT calculations. Nevertheless, a more practical procedure using small excess of common triethylamine is also reported. The potential use of pinacol-derived chlorohydrosilane has been preliminarily demonstrated through its ability to perform the reductive amination of a salicylaldehyde-derived iminium.

Experimental Section

All syntheses were carried out in oven-dried glassware under inert atmosphere. Dichloromethane was dried by distillation under argon with calcium hydride. Triethylamine, pyridine and DMF were purified and dried before use. Reactions were monitored through thin-layer chromatography (TLC) with commercial silica gel plates (Merck silica gel, 60 F254). Visualization of the developed plates was performed under UV lights at 254 nm and by staining with cerium ammonium molybdate. Flash column chromatography was performed on silica gel 60 (40–63 μm) as stationary phase. ^{1}H NMR spectra were recorded at 300 MHz, and ^{13}C NMR spectra were recorded at 75 MHz in a 300 MHz Varian Mercury spectrometer, using $CDCl_3$ as solvent. ^{29}Si NMR was recorded at 99 MHz in a Jeol ECZR 500. Chemical shifts (δ) are reported in ppm referenced to the $CDCl_3$ residual peak (δ = 7.26 ppm) or TMS peak (δ = 0.00 ppm) for ^{1}H NMR, to $CDCl_3$ (δ = 77.16 ppm) for ^{13}C NMR and to TMS for ^{29}Si NMR (δ = 0.00 ppm). The following abbreviations were used to describe peak splitting patterns: s = singlet, d = doublet, t = triplet, m = multiplet. Coupling constants, *J*, were reported in Hertz [Hz]. High-resolution mass spectra were recorded on a Waters ESI-TOF MS spectrometer or on ABSciex QSTAR Elite ESI-Q-TOF.

Synthesis of the Pinacol-Derived Chlorohydrosilane (PCS): A solution of trichlorosilane (22.3 g, 166 mmol) in diethyl ether (150 mL) in a round-bottomed flask fitted with a dropping funnel under argon was cooled to 0 °C in an ice bath. A mixture of pinacol (6.5 g, 55 mmol) and pyridine (9 mL, 111 mmol) in diethyl ether (100 mL) was transferred to the dropping funnel via a syringe and added slowly to the reaction mixture for about an hour. After complete addition, the mixture was warmed up to room temperature and stirred for 48 h. The pyridinium chloride salt was then filtered out and the solvents evaporated under reduced pressure affording PCS in 95 % yield (9.8 g, 54.5 mmol), that was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.45 (s, 12 H, CH_3) 5.69 (s, 1 H, SiH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.9, 84.6 ppm. ^{29}Si NMR (99 MHz, $CDCl_3$, 25 °C, TMS): δ = –37.5 (d, J_{Si-H} = 354 Hz) ppm. HR-MS (ESI$^+$): calculated for $C_6H_{15}O_3Si^+$ [M – Cl + H_2O]$^+$ 163.0785, found 163.0786. For [$C_6H_{13}O^+$] calculated 101.0961, found 101.0961.

General Procedure for DMPU-Catalyzed Hydrosilylation of Salicylaldehyde: DMPU (14 mg, 0.11 mmol) followed by triethylamine (66 mg, 0.54 mmol) were added to a stirred solution of salicylaldehyde (0.54 mmol) in dichloromethane (1.5 mL) at 0 °C. A solution of PCS (0.65 mmol) in dichloromethane (1 mL) was added dropwise via syringe pump to the reaction mixture over 5 min and the resulting solution stirred at this temperature for 20 min and then warmed to room temperature. After consumption of salicylaldehyde, as judged by TLC, the reaction was treated with a solution of TBAF in 1 M THF (0.75 mL, 0.75 mmol) and stirred for 30 min. The mixture was then quenched with saturated NH_4Cl (15 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was dried with $MgSO_4$, filtered out and solvent removed under reduced pressure. The crude product obtained was purified by flash column chromatography. NMR spectra of compounds **1**–**2**, **4**–**9**, **11**–**13**, **17**, **19** and **22** are consistent with previously reported.[32]

3: Yield 97 % (83 mg, 0.52 mmol). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 2.45 (br. s., 1 H; CH_2OH) 4.79 (s, 2 H, $ArCH_2$) 6.71 (br. s., 1 H; ArOH) 6.82 (t, *J* = 8.2 Hz, 1 H; ArH) 7.09 (d, *J* = 8.2 Hz, 1 H; ArH) 7.28 (dd, *J* = 6.4, 1.8 Hz, 1 H; ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 62.7, 120.4, 120.8, 127.0, 127.4, 128.8, 150.2 ppm. MS (ESI) *m/z* calculated for $C_7H_7ClO_2Na^+$ [M + Na]$^+$ 181.0027, found 181.0034.

10: Yield 59 % (119 mg, 0.32 mmol). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 2.28–2.56 (br.s., 1 H; CH_2OH) 4.76 (s, 2 H, $ArCH_2$) 7.27–7.33 (br.s., 1 H; ArOH) 7.36–7.41 (m, 1 H, ArH) 7.91 (d, *J* = 1.8 Hz, 1 H; ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = ppm, 63.1, 82.5, 86.9, 127.7, 136.8, 145.3, 154.2 ppm. MS (ESI) *m/z* calculated for $C_7H_6I_2O_2^+$ [M]$^+$ 376.8452, found 376.8455.

Preparation of 3-Acetyl-5-(*tert*-butyl)salicylaldehyde (20) and Reduction by PCS: 4-*tert*-Butyl-2,6-diformylphenol (300 mg, 1.45 mmol, 1 equiv.) was dissolved in 5 mL of dry DCM in a round-bottomed flask under Argon. Triethylamine (252 μL, 1.81 mmol, 1.25 equiv.) and DMAP were added (18 mg, 0.15 mmol, 0.1 equiv.). Then, *tert*-butyldimethylsilyl chloride (264 mg, 1.75 mmol, 1.2 equiv.) was added. The solution was stirred at room temperature for three hours. The reaction was quenched with 5 mL of saturated aqueous NH_4Cl solution and the layers separated. The organic phase was collected and the aqueous phase extracted with DCM (2 × 5 mL). The organic phases were combined, dried with $MgSO_4$, filtered, and the solvent evaporated under vacuum. Purification by flash chromatography (Hex/DCM, 1:1) gave **20a** in 75 % yield (349 mg, 1.09 mmol) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = ppm 0.17 [s, 6 H, $Si(CH_3)_2$] 1.09 (s, 9 H, *t*Bu) 1.34 (s, 9 H, *t*Bu) 8.10 (s, 2 H, ArH) 10.35 (s, 2 H, CHO) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = ppm –4.4, 18.6, 25.8, 31.2, 34.8, 128.8, 131.8, 145.9, 158.9, 189.0 ppm.

20a: (376 mg, 1.17 mmol, 1 equiv.) was dissolved in 13 mL of dry THF in a round-bottomed flask under argon. The solution was cooled to –78 °C and MeLi (1.17 mL of 1.6 M solution, 1.17 mmol, 1 equiv.) was added dropwise. After addition, the solution was warmed to room temperature for 10 min. The reaction was quenched with 15 mL of saturated aqueous NH_4Cl solution and the layers separated. The organic phase was collected and the aqueous phase extracted with Et_2O (2 × 15 mL). The organic phases were combined, dried with $MgSO_4$, filtered, and the solvent evaporated under reduced pressure. Purification by flash chromatography (Hex/DCM, 4:1) gave **20b** in 61 % yield (241 mg, 0.72 mmol) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = –0.01 (s, 3 H, $SiCH_3$) 0.07 (s, 3 H, $SiCH_3$) 0.92 (s, 9 H, *t*Bu) 1.33 (s, 9 H, *t*Bu) 1.41 (d, *J* = 6.4 Hz, 3 H; CH_3CH) 5.23 (q, *J* = 6.1 Hz, 1 H; CHOTBDMS) 7.40 (d, *J* = 2.3 Hz, 1 H; ArH) 7.90 (d, *J* = 2.3 Hz, 1 H; ArH) 9.89 (s, 1 H, CHO) 11.08 (s, 1 H, ArOH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.8, –4.8, 18.4, 25.3, 26.0, 31.4, 34.4, 65.0, 128.1, 131.7, 135.0, 142.6, 155.6, 197.1 ppm.

20b: (201 mg, 0.6 mmol, 1 equiv.) was dissolved in 5 mL of THF. The solution was cooled to 0 °C and TBAF (1.2 mL of 1 M solution,

1.2 mmol, 2 equiv.) was added. The reaction was then warmed to room temperature for 30 min. The solution was diluted with 15 mL of Et_2O and washed with saturated $NaHCO_3$ aqueous solution (3 × 15 mL). The organic layer was collected, dried with $MgSO_4$, filtered and the solvent evaporated to give **20c** as a colorless oil in quantitative yield (0.6 mmol, 137 mg), which was used directly in the next step. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.33 (s, 9 H, *t*Bu) 1.55 (d, *J* = 6.4 Hz, 3 H; CH_3CH) 5.17 (q, *J* = 6.8 Hz, 1 H; CHOH) 7.44 (d, *J* = 2.9 Hz, 1 H; ArH) 7.69 (d, *J* = 2.3 Hz, 1 H; ArH) 9.90 (s, 1 H, CHO) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.1, 31.4, 34.4, 66.3, 120.0, 128.8, 131.4, 133.3, 142.9, 156.7, 197.2 ppm.

20c: Was dissolved in 24 mL of dry DCM in a round-bottomed flask under Argon. $NaHCO_3$ (126 mg, 1.5 mmol, 2.5 equiv.) was added and the solution cooled to 0 °C. Dess–Martin periodinane (306 mg, 0.72 mmol, 1.2 equiv.) was added and the reaction warmed to room temperature for 30 min. The reaction was then quenched with 2 % $Na_2S_2O_3$ aqueous solution (25 mL) and the layers were separated. The organic phase was collected and the aqueous phase extracted with DCM (2 × 25 mL). The organic phases were combined and the solvent dried with $MgSO_4$, filtered and the solvents evaporated. Purification by flash chromatography (DCM) gave 3-acetyl-5-(*tert*-butyl)salicylaldehyde **20** in 50 % yield (66 mg, 0.30 mmol) as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.34 (s, 9 H, *t*Bu) 2.69 (s, 3 H, CH_3CO) 7.90–8.13 (m, 2 H, ArH) 10.44 (s, 1 H, CHO) 12.66 (s, 1 H, ArOH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.8, 31.3, 34.4, 121.4, 124.1, 132.8, 133.9, 142.0, 162.4, 190.2, 203.9 ppm. MS (ESI^+) *m/z* calculated for $C_{13}H_{17}O_3^+$ $[M + H]^+$ 221.1172, found 221.1161.

21: 49 % yield (20 mg), following general procedure, starting from 0.182 mmol (40 mg) of **20**. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.32 (s, 12 H, *t*Bu) 2.51–2.56 (br.s., 1 H, CH_2OH) 2.66 (s, 3 H, CH_3) 4.74 (s, 2 H, $ArCH_2$) 7.56 (d, *J* = 2.3 Hz, 1 H; ArH) 7.64 (d, *J* = 2.3 Hz, 1 H; ArH) 12.57 (s, 1 H, ArOH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.8, 34.2, 61.8, 110.0, 118.8, 125.8, 129.2, 133.2, 141.4, 158.4, 204.97 ppm. MS (ESI) *m/z* calculated for $C_{13}H_{19}O_3^+$ $[M + H]^+$ 223.1329, found 223.1329.

Reductive Amination of Salicylaldehyde and Indoline-Derived Iminium: A mixture of salicylaldehyde (0.54 mmol), indoline (64.4 mg, 0.54 mmol) and molecular sieves (3 Å, 255 mg) in dichloromethane (1 mL) was refluxed for 5 h under argon. The mixture was then cooled to room temp. and DMPU (0.11 mmol, 14 mg) added in one portion followed by dropwise addition of a solution of PCS (0.65 mmol) in dichloromethane (1 mL) via a syringe pump over 5 min. The resulting mixture was stirred for 1 h, treated with a solution of TBAF in 1 M THF (0.75 mL, 0.75 mmol) and stirred for additional 10 min. The mixture was quenched with saturated NH_4Cl (15 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried with $MgSO_4$, filtered out and solvent removed under reduced pressure. The crude product obtained was purified by flash column chromatography to afford **22** in 72 % yield (87 mg, 0.39 mmol), with similar spectral characterization as described previously.[32l]

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Keywords: Hydrosilylation · Aldehydes · Alcohols · Lewis bases · Homogeneous catalysis

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PUBLICATION II

Biomass-based and oxidant-free preparation of hydroquinone from quinic acid.

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Hydroquinone Synthesis

Biomass-Based and Oxidant-Free Preparation of Hydroquinone from Quinic Acid

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Abstract: A biomass-based route to the preparation of hydroquinone starting from the renewable starting material quinic acid is described. Amberlyst-15 in the dry form promoted the one-step formation of hydroquinone from quinic acid in toluene without any oxidants or metal catalysts in 72 % yield. Several acidic polymer-based resins and organic acids as promoters as well as a variety of reaction conditions were screened including temperature, concentration and low- and high-boiling-point solvents. A 1:4 (w/w) ratio of quinic acid/Amberlyst-15 was determined to be optimal to promote hydroquinone formation with only traces of a dimeric side-product. A mechanism has been proposed based on the decarbonylation of protonated quino-1,5-lactone that is supported by experimental and computational calculation data.

Introduction

The chemical industry has made enormous efforts in the last decades to minimise waste and use less toxic and/or hazardous reagents to develop safer and greener processes. However, most of the raw materials used in the chemical industry are generally obtained from fossil resources totalling 10 % of the crude oil consumption.[1] To accomplish sustainable methods for the production of commodity chemicals and liquid fuels, non-renewable fossil resources (crude oil, coal and natural gas) should be replaced by sustainable feedstocks. Despite the intense interest and the methods developed for the large-scale industrial conversion of biomass into chemicals and materials in the second half of the 19th century, such investments declined in the 20th century due to the much cheaper products synthesised by the now conventional routes from abundantly available fossil resources.[2] Fossil raw materials are irrevocably decreasing and the environmental consciousness of the chemical industry and the regulatory authorities has led to enormous research activity in the last decade to progressively shift to renewable feedstocks.[3] The selective defunctionalisation of highly functionalised molecules derived from renewable feedstocks is probably the biggest challenge in such a shift, considering that sugars and polyol platforms can be highly exploited.[4] However, the production of aromatic compounds continues to be highly dependent on non-renewable fossil feedstocks. Despite the enormous achievements in the depolymerisation of lignin, the only renewable source of high-volume aromatic compounds,[5] the industrial application of any of the reported methods has not yet been achieved.

Hydroquinone is prepared industrially by the hydroperoxidation of *p*-diisopropylbenzene, the hydroxylation of phenol and the oxidation of aniline. The world production of hydroquinone is 40000–50000 tons a year and it is mainly used in the rubber industry, as monomer inhibitors, dyes and pigments and antioxidants as well as in agricultural and photographic applications.[6] It is mostly used as a water-soluble reducing agent in photography film development and in the rubber industry for the production of anti-oxidants and anti-ozonants. It is also used as an inhibitor of acrylic acid, methyl methacrylate, cyanoacrylate and other monomers commonly used in adhesives, glue and other types of bonding applications and in cosmetic applications in skin-whitening compositions.

The preparation of hydroquinone from non-fossil sources has been reported by Frost and co-workers since the seminal work of Woskresensky[7] on the isolation of hydroquinone by the dry distillation of quinic acid (**1**, Scheme 1). Frost reported the preparation of hydroquinone from glucose in two enzyme-catalysed steps and two chemical steps via 2-deoxy-*scyllo*-inosose synthase.[8] The construction of a transgenic *Escherichia coli* strain able to synthesise quinic acid from glucose under shake-flask conditions was coupled with the oxidation of the obtained quinic acid with stoichiometric amounts of MnO_2 to hydroquinone.[9] Other oxidative systems such as NaOCl, $(NH_4)_2Ce_2(SO_4)_3$, V_2O_5 and $K_2S_2O_8$ in the presence of catalytic amounts of Ag_3PO_4 have been reported to induce the same transformation in up to 91 % yield.[10] Quinic acid[11] is readily available from the bark of the cinchona tree[12] as a side-product during the extraction

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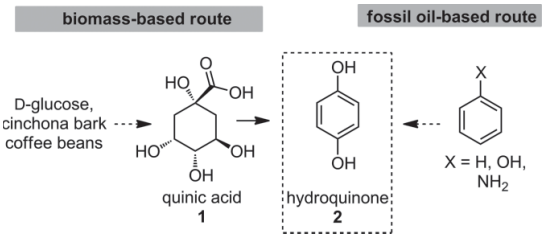
of cinchona alkaloids and is the principal constituent in coffee beans and other plant products.[13]



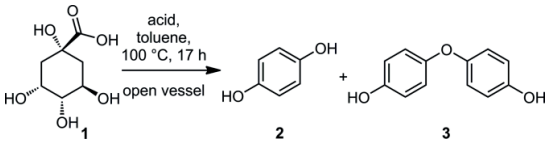
Scheme 1. Fossil-based route and the alternative biomass-based route to hydroquinone.

Taking the dry distillation of quinic acid for the preparation of hydroquinone,[7] it was hypothesised that the same transformation could be achieved under aerobic, strongly acidic conditions. Besides the formation of hydroquinone, other products expected in the acid-promoted decomposition of quinic acid are bicyclic quino-1,5-lactone,[14] benzoic acid[15] and quinone.[10]

Results and Discussion

Versatile and robust polymer-based resins were screened as promoters for the conversion of quinic acid (**1**) into hydroquinone (**2**).[16] Preliminary reactions of quinic acid were carried out with different forms of polystyrene macro-reticular Amberlyst resins: Amberlyst-15 (dry and wet), Amberlyst-16 and Amberlyst-36 in toluene at 100 °C (Table 1). Amberlyst-15 in the dry form resulted in the formation of hydroquinone (**2**) in 62 % yield accompanied by ether **3**, which results from the condensation of hydroquinone (entry 1). Despite the presence of quino-1,5-lactone in the reaction mixture, a likely reaction intermediate, benzoquinone formation was not observed. Amberlyst-15 has been reported in many instances as a mild and selective heterogeneous polymeric material for routine acid-catalysed transformations in organic synthesis.[17] Other Amberlyst resins tested showed inferior activity, leading to only traces of the desired hydroquinone (entries 2–4). Acidic ion-exchange resins Amberlite IRC86, IR120/H and Dowex 50WX4 also failed to provide hydroquinone (**2**) in decent yields (entries 5–7). Despite the high moisture content (64–72 %), Dowex 50WX4 proved to be superior to the other ion-exchange resins, providing 12 % of hydroquinone after 17 h (entry 7). After identification of Amberlyst-15 in the dry form as the best reaction promoter amongst those tested, and being a polymer-supported sulfonic acid resin, we tested *p*-toluenesulfonic acid (*p*TSA, entries 8 and 9) and sulfuric acid (entry 10) as reaction promoters. Although sulfuric acid and monohydrate *p*TSA resulted in traces of hydroquinone (entries 8 and 10), use of molecular sieves and anhydrous *p*TSA resulted in recovery of the starting materials after 17 h (entry 9). Better conversions of the starting quinic acid were achieved by employing ground Amberlyst-15, sieved through a 106 μm sieve. Previous studies on the acid-site accessibility of Amberlyst-15 showed similar strengths of acid sites for both the bead and powder forms of Amberlyst-15 and the higher activity of the powder resin should be associated with the exposed external surface of the resin.[18] Despite the 71 % yield of hydroquinone (**2**), use of the ground Amberlyst led to considerable formation of the ether side-product **3** (entry 13).

Table 1. Screening of acid promoters for the formation of hydroquinone from quinic acid.[a]



Entry	Acid	Yield [%][b]	
		2	**3**
1	Amberlyst-15 (dry)	62	3
2	Amberlyst-15 (wet)	6	n.d.[c]
3	Amberlyst-16 (wet)	4	n.d.
4	Amberlyst-36 (wet)	5	n.d.
5	Amberlite IRC86	n.d.	n.d.
6	Amberlite IR120/H	6	n.d.
7	Dowex 50WX4	12	<3
8	*p*TSA•H_2O[d]	<3	n.d.
9	*p*TSA, 4 Å MS[d]	n.r.[e]	
10	H_2SO_4[f]	<3	n.d.
11	Acetic acid[g]	n.d.	n.d.
12	none	n.r.	
13	Amberlyst-15 (dry), ground	71	7

[a] Reagents and conditions: Unless otherwise stated, the reaction was carried out with quinic acid (0.5 mmol), resin (0.3 g), and toluene (15 mL) at 100 °C for 17 h in an open vessel. [b] Determined by analysis of the ^{1}H NMR spectra of the reaction mixtures using bromobenzene as internal standard. [c] n.d.: not detected. [d] 0.5 mmol of *p*TSA in 7 mL of toluene heated for 24 h. [e] n.r.: no reaction. [f] 1.5 mL of H_2SO_4 in 15 mL of toluene. [g] 3 mL of AcOH as solvent.

In an attempt to optimise the reaction conditions and to allow the dissolution of quinic acid into the reaction solvent, other solvents were screened. Using Amberlyst-15 as the reaction promoter in THF, 1,4-dioxane, CH_2Cl_2, 1,2-dichloroethane, CCl_4, chlorobenzene and methanol at reflux temperature or in glycerol, sulfolane and poly(ethylene glycol) at 125 °C for 24 h did not improve the selectivity towards hydroquinone formation. Besides toluene, hydroquinone (**2**) was detected in the crude reaction mixtures of only chlorinated solvents. Of the above-mentioned solvents, chlorobenzene gave the highest formation of hydroquinone when the reaction was performed in a sealed tube, with **2** and **3** obtained in a 4:3 ratio (68 % conversion).

Taking toluene as the reaction solvent for this two-phase reaction, the influence of temperature on the reaction outcome was assessed (Figure 1). Very low conversions were achieved below 100 °C, hydroquinone was formed in higher yields in the range 100–110 °C, and higher temperatures induced the dimerisation of **2** into ether **3**. This process was verified by the exclusive formation of **3** in 48 % isolated yield after heating hydroquinone **2** in toluene in the presence of Amberlyst-15 for 6 days.

With these optimised conditions, we shifted our attention to the effect of the Amberlyst/quinic acid ratio on the reaction (Table 2). It was observed that the yield of hydroquinone

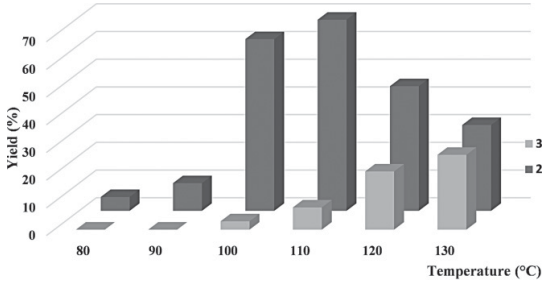
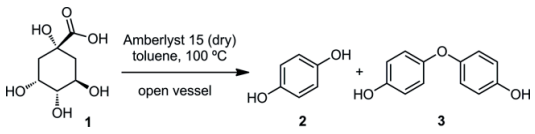


Figure 1. Effect of temperature on hydroquinone formation. Reagents and conditions: Quinic acid (0.5 mmol), Amberlyst-15 (0.3 g), toluene (15 mL), 100 °C, 17 h.

increased with only trace formation of ether **3**, or none at all, as the Amberlyst/quinic acid ratio (w/w) was increased from 0.5 to 4 (entries 1–7). Further increasing the amount of Amberlyst did not show any considerable improvement when performing the reaction at 100 °C for 17 h (entries 7–9). Tuning the reaction conditions further, namely the amount of solvent and reaction time (see the Supporting Information), resulted in the formation of the desired hydroquinone in a yield of 71 % together with 5 % of ether **3** after 25 h (entry 10) and isolation by chromatography. Extension of the reaction time to 48 h proved beneficial for ether **3** formation, but the yield of hydroquinone remained the same (entry 11).

Table 2. Effect of amberlyst/quinic acid ratio on reaction.[a]

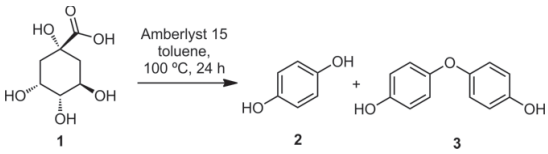


Entry	Amberlyst-15/**1** ratio (w/w)	Time [h]	Yield [%][b] **2**	**3**
1	0.5	17	9	n.d.[c]
2	1	17	17	n.d.
3	2	17	29	n.d.
4	3	17	43	<3
5	3.125	17	48	<3
6	3.5	17	56	<3
7	4	17	55	<3
8	5	17	55	<3
9	10	17	59	<3
10[d]	4	25	72 (71)[e]	5
11[d]	4	48	72	9

[a] Reagents and conditions: Unless otherwise stated, the reaction was carried out with quinic acid (0.5 mmol), Amberlyst-15 (dry) in toluene (15 mL) at 100 °C in an open vessel. [b] Yield calculated from the ^{1}H NMR spectra of reaction mixtures using bromobenzene as internal standard. [c] n.d.: not detected. [d] 10 mL of toluene as solvent. [e] Isolated yield after flash chromatography.

Being a formal oxidation, the influence of oxygen and other oxidative conditions were also investigated (Table 3). The absence of air or the presence of water had a detrimental effect on hydroquinone formation and neither oxygen nor copper salts[19] were effective catalysts in the putative aerobic oxidation process.

Table 3. Effect of oxidation conditions on the reaction.[a]



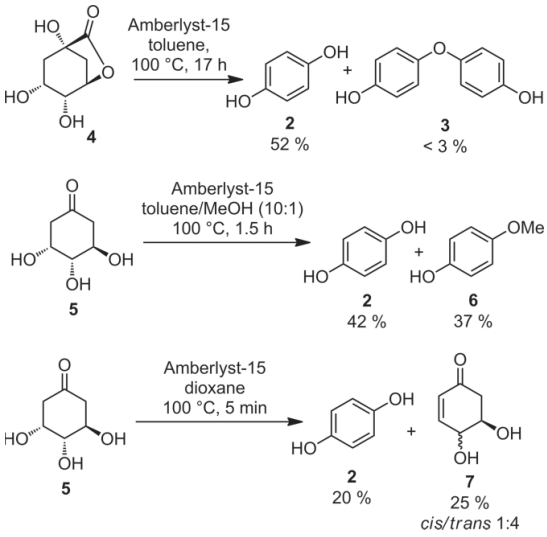
Entry	Reaction conditions	Yield [%][b] **2**	**3**
1	open vessel	72	5
2	O_2 atmosphere	64	6
3	argon atmosphere	46	<3
4	1.5 equiv. of H_2O	62	3
5	5 mol-% CuBr	58	4
6	5 mol-% CuI	51	4
7	5 mol-% $CuBr_2$	43	3
8	5 mol-% $CuCl_2{\cdot}H_2O$	47	4

[a] Reagents and conditions: Quinic acid (0.5 mmol), Amberlyst-15 (1:4 ratio, w/w) in toluene (10 mL) at 100 °C for 24 h in an open vessel, except entries 2 and 3. [b] Determined by analysis of ^{1}H NMR spectra of the reaction mixtures using bromobenzene as internal standard.

To gain further insight into the reaction mechanism, two possible reaction intermediates, **4** and **5**, were prepared and allowed to react under similar reaction conditions (Scheme 2). Lactone **4** was converted into hydroquinone (**2**) in 52 % yield, as observed for the reaction of quinic acid. As previously demonstrated by Frost and co-workers,[10] ketone **5** was converted into the hydroquinone via the two possible enone intermediates. In such a strongly acidic medium, the dehydration of **5** is a very fast process and such intermediates are not visible in the NMR spectrum of the quinic acid dehydration reaction mixture. It was nevertheless possible to detect and isolate a mixture of the enones **7** in 25 % yield when the reaction was performed in dioxane.

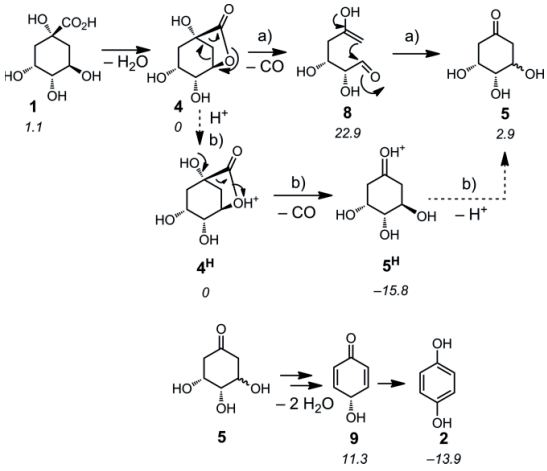
Adding (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO), butylated hydroxytoluene (BHT), styrene and azodicarboxylates to the reaction mixture did not allow the isolation of any intermediates derived from a single-electron-transfer pathway. Curiously, TEMPO inhibited the formation of the hydroquinone (**2**) and only starting material and lactone **4** were detected. Additionally, the use of *tert*-butyl peroxide as radical initiator did not improve hydroquinone formation or reduce the reaction rate. The carbon atom lost in the conversion of quinic acid (**1**) into hydroquinone (**2**) occurs through the liberation of carbon monoxide. Such an event was confirmed by the reduction of palladium chloride to palladium when a filter paper soaked in $PdCl_2$ aqueous solution (1:500, w/v) was placed on the top of the reaction condenser (see the Supporting Information).[20]

DFT calculations[21] were performed to compare ionic and radical mechanisms through the optimisation of likely intermediates. The free-energy values obtained for the diradical intermediates considered in single-electron-transfer processes clearly preclude a radical pathway for the reaction (ΔG = 80–84 kcal/mol, see the Supporting Information for details). Furthermore, the high acidity of Amberlyst should favour an ionic

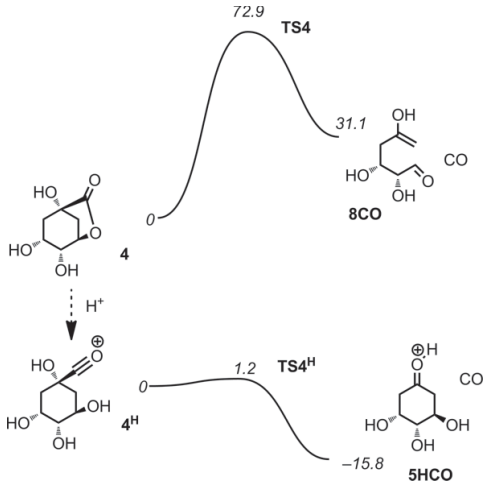


Scheme 2. Reactivity of reaction intermediates **4** and **5**.

mechanism by the favourable protonation of the starting material and reaction intermediates. Two ionic mechanisms were considered for the decarbonylation step, both having lactone **4** as the starting point: 1) Pericyclic decarbonylation of the lactone with concomitant formation of the enol aldehyde **8** and b) ring-opening of protonated lactone $\mathbf{4^H}$ (Scheme 3). From a thermodynamic point of view, the formation of enol aldehyde **8** seems to be unlikely due to its high free energy (ΔG = 22.9 kcal/mol) whereas the decarbonylation of protonated lactone $\mathbf{4^H}$ should be a spontaneous process towards the formation of protonated ketone $\mathbf{5^H}$ (ΔG = −15.8 kcal/mol). This is further confirmed by the energy barriers calculated for both processes, which clearly indicate a preference for the ring-opening of the protonated lactone over the pericyclic process (Scheme 4): A large energy barrier of 72.9 kcal/mol needs to be overcome for the pericyclic process, whereas the energy barrier for the decarbonylation of $\mathbf{4^H}$ is only 1.2 kcal/mol. Under the highly acidic reaction conditions, **9** should be formed after the double protonation and dehydration of **5** to form the more stable hydroquinone. The overall reaction from quinic acid (**1**) to hydroquinone (**2**) is a thermodynamically favourable process with ΔG = −15 kcal/mol.



Scheme 3. Proposed ionic reaction mechanisms. Calculated free energies of the intermediates are indicated in italics [kcal/mol].



Scheme 4. Energy profiles calculated for two alternative decarbonylation steps. The free energies of the intermediates and transition states are indicated in italics [kcal/mol].

Conclusions

A mild and efficient method for the conversion of naturally available quinic acid (**1**) into hydroquinone (**2**) has been disclosed herein. By using Amberlyst-15 in its dry form as an acid promoter it is possible to obtain the hydroquinone in up to 72 % yield with only small amounts of the dimeric ether compound formed after 24 h. This method does not rely on the use of any oxidants or high temperatures unlike the previously reported methods. An ionic decarbonylation mechanism has been proposed, supported by experimental and computational calculation data.

Experimental Section

General Methods: Polymer-based resins were used as received from suppliers: Amberlyst-15 (dry), 20–50 mesh from Fluka (06423) and Aldrich (216380), Amberlyst-15 (wet) from Aldrich (216399), Amberlyst-16 (wet) from Aldrich (86317), Amberlyst-36 (wet) from Fluka (06455), Amberlite IRC86 from Aldrich (10322), Amberlite IR120/H from Aldrich (216534) and Dowex 50WX4 from Aldrich (422096). Quinic acid was obtained from Sigma–Aldrich and sieved through a 106 μm sieve prior to use. Retsch ZM200 and Retsch AS200 were used as grinder and sieve, respectively. Other reagents were used as obtained from the suppliers (Sigma–Aldrich and

Fluka). The reactions were monitored by TLC carried out on precoated (Merck TLC silica gel 60 F254) aluminium plates by using UV light as visualising agent and cerium molybdate solution as developing agent. Flash column chromatography was performed on silica gel 60 (Merck, 0.040–0.063 mm). NMR spectra were recorded with a Varian Mercury 300 MHz spectrometer using $CDCl_3$, [D_6]DMSO or D_2O as solvent and calibrated by using tetramethylsilane as internal standard. Chemical shifts are reported in ppm relative to TMS and coupling constants are reported in Hz. ^1H NMR yields were determined by adding a known amount of bromobenzene to the reaction mixture after work-up.

Hydroquinone (2): Quinic acid (0.5 mmol) was added to a suspension of Amberlyst-15 (dry, 0.38 g) in toluene (10 mL) in a round-bottomed flask equipped with a magnetic stirrer bar and condenser open to the air. The mixture was heated at 100 °C for 24 h. After cooling to room temperature methanol (5 mL) was added and the mixture stirred vigorously for 5 min. The mixture was filtered and the solid residue re-suspended in methanol (20 mL) and stirred for an additional 5 min. After filtration and washing with more methanol (10 mL), the solvents were removed under reduced pressure. The residue was either dissolved in [D_6]DMSO for ^1H NMR yield determination (72 %) or purified by flash chromatography with toluene/ethyl acetate (3:1) to afford pure hydroquinone (39 mg, 71 % yield) with similar spectroscopic data as commercial samples. ^1H NMR ([D_6]DMSO, 300 MHz): δ = 8.64 (s, 2 H), 6.55 (s, 4 H) ppm. ^{13}C NMR ([D_6]DMSO, 75 MHz): δ = 149.8, 115.8 ppm.

Bis(4-hydroxyphenyl) Ether (3): Hydroquinone (1.0 mmol) was added to a suspension of Amberlyst-15 (dry, 0.77 g) in toluene (20 mL) in a round-bottomed flask equipped with a magnetic stirrer bar and condenser. The mixture was heated at 100 °C for 6 d. After cooling to room temperature, methanol (10 mL) was added and the mixture stirred vigorously for 5 min. The mixture was filtered and the solid residue re-suspended in methanol (40 mL) and stirred for an additional 5 min. After filtration and washing with more methanol (20 mL), the solvents were removed under reduced pressure. The residue was purified by preparative TLC with toluene/ethyl acetate (3:1) to afford pure **3** (49 mg, 48 %) with similar spectroscopic data as previously reported.[22] ^1H NMR ($CDCl_3$, 300 MHz): δ = 6.70–6.83 (m, 8 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 151.9, 150.8, 120.1, 119.4, 115.9 ppm.

Quino-1,5-lactone (4): Amberlyst-15 (dry, 0.69 g) was added to a suspension of quinic acid (3 mmol) in acetonitrile (150 mL) and the mixture stirred at 50 °C for 24 h. After cooling, the reaction mixture was filtered through Celite and washed with methanol. Solvent removal under reduced pressure yielded the desired lactone **4** in quantitative yield (0.52 g) with similar spectroscopic data as previously reported.[23] ^1H NMR ([D_6]DMSO, 300 MHz): δ = 5.90 (s, 1 H), 5.24 (d, J = 3.8 Hz, 1 H), 4.84 (d, J = 6.7 Hz, 1 H), 4.61 (t, J = 5.3 Hz, 1 H), 3.81 (d, J = 4.1 Hz, 1 H), 3.49 (dd, J = 11.0, 4.8 Hz, 1 H), 2.27–2.24 (m, 1 H), 2.13–2.07 (m, 1 H), 1.87–1.82 (m, 1 H), 1.75–1.66 (m, 1 H) ppm. ^{13}C NMR ([D_6]DMSO, 75 MHz): δ = 177.8, 76.0, 71.6, 65.6, 65.3, 39.4, 36.8 ppm.

(3*R*,5*R*)-3,4,5-Trihydroxycyclohexanone (5): Prepared according to a previously reported procedure.[10] A 14 % aqueous NaOCl solution (30 mmol) and H_2SO_4 (8 mmol) were added dropwise to a stirred solution of quinic acid (10 mmol) in water (7 mL) over 30 min. The reaction was stirred at room temperature for 2.5 h. The reaction was then quenched with isopropanol (30 mmol) and stirred for 30 min. After pH neutralisation with an aqueous saturated solution of Na_2CO_3, the solvent was removed under reduced pressure. The obtained residue was re-suspended in acetone (55 mL) and left to stir overnight at room temperature. After filtration and solvent removal under reduced pressure, the residue obtained was purified by flash chromatography with an eluent gradient from ethyl acetate/hexane (9:1) to methanol/ethyl acetate (1:9). The desired ketone **5** was obtained in 75 % yield (1.03 g) with similar spectroscopic data as previously reported.[10] ^1H NMR (D_2O, 300 MHz): δ = 4.83 (s, 3 H), 4.29 (ddd, J = 6.3, 3.7, 2.9 Hz, 1 H), 4.15 (td, J = 8.2, 5.3 Hz, 1 H), 3.97 (dd, J = 7.8, 2.8 Hz, 1 H), 2.83–2.80 (m, 1 H), 2.78–2.75 (m, 1 H), 2.65–2.50 (m, 2 H) ppm. ^{13}C NMR (D_2O, 75 MHz): δ = 212.8, 73.0, 68.7, 45.7 ppm.

4-Methoxyphenol (6): Ketone **5** (0.5 mmol) was dissolved in methanol (1 mL) and dispersed in toluene (10 mL) in a round-bottomed flask equipped with a magnetic stirrer bar. Amberlyst 15 (dry, 384 mg) was added and the mixture stirred at 100 °C until disappearance of the starting material, as judged by TLC (1.5 h). After cooling to room temperature, methanol (5 mL) was added, the mixture filtered and the solvent removed under reduced pressure. The residue was purified by flash chromatography with gradient elution with ethyl acetate/hexane (1:9 to 1:1), to afford 42 % (23 mg) of hydroquinone (**2**) and 37 % (23 mg) of **6** with similar spectroscopic data as previously reported.[24] ^1H NMR ($CDCl_3$, 300 MHz): δ = 6.78 (d, J = 1.8 Hz, 4 H), 4.93 (br. s., 1 H), 3.77 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 153.6, 149.4, 116.0, 114.8, 55.8 ppm.

4,5-Dihydroxycyclohex-2-en-1-one (7): Amberlyst-15 (dry, 0.38 g) was added to a solution of ketone **5** (1 mmol) in 1,4-dioxane (10 mL) and the mixture stirred at 100 °C for 5 min. After cooling to room temperature the mixture was filtered and the solvent removed under reduced pressure. The residue was purified by flash chromatography with eluent gradient from ethyl acetate/hexane (4:1) to methanol/ethyl acetate (1:9) to afford 20 % (20 mg) of hydroquinone (**2**) and 25 % (31 mg) of **7** in a *cis/trans* ratio of 1:4, as determined by ^1H NMR spectroscopy and comparison with previous reports.[10] ^1H NMR (D_2O, 300 MHz): δ = 6.96 (dd, J = 10.1, 2.2 Hz, 1 H), 6.92–6.87 (m, 0.2 H), 6.73–6.72 (m, 0.2 H), 6.06 (dd, J = 2.2, 1.0 Hz, 0.2 H), 6.03–5.98 (m, 1 H), 4.64–4.61 (m, 0.2 H), 4.39–4.30 (m, 1.2 H), 3.99–3.91 (m, 1 H), 2.78–2.76 (m, 0.5 H), 2.73–2.71 (m, 1 H), 2.68 (dd, J = 5.1, 1.0 Hz, 0.2 H), 2.55–2.46 (m, 1.3 H) ppm. ^{13}C NMR (D_2O, 75 MHz): δ = 204.8, 204.4, 156.2, 154.2, 151.8, 131.6, 131.5, 119.2, 74.4, 74.3, 72.5, 70.3, 68.8, 63.3, 57.8, 46.5, 45.7 ppm.

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Keywords: Sustainable chemistry · Heterogeneous catalysis · Natural products · Cyclitols

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PUBLICATION III

Pinacol-derived chlorohydrosilane in metal-free reductive amination for the preparation of tertiary alkylphenolmethyl amines.

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Pinacol-Derived Chlorohydrosilane in Metal-Free Reductive Amination for the Preparation of Tertiary Alkylphenolmethyl Amines

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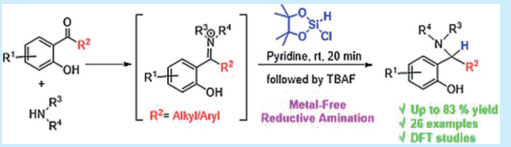
Supporting Information

ABSTRACT: A new metal-free reductive amination protocol using a pinacol-derived chlorohydrosilane/pyridine system for the preparation of aminoalkylphenols is described. This method is selective toward iminiums derived from alkylphenol ketones under an in situ formation of a trialkoxyhydrosilane and activation with a Lewis base, as further indicated by computational studies. This method demonstrated high functional group tolerance affording an array of novel aminoalkylphenols in moderate to high yields with equimolar amounts of reactants and a wide substrate scope.



Amines are ubiquitous functionalities present in natural products, pharmaceuticals, agrochemicals, and synthetic materials.[1] Among the numerous methods available for the synthesis of amines, the one-pot reductive amination method[2−5] presents a versatile and preferable option considering efficiency and fast access to amines. Several reducing systems including metal hydrides[2] and catalytic hydrogenation methods[6] are employed for such transformations.[7] Nonetheless, poor selectivity and functional group tolerance (e.g., halogens and nitro groups) are some of the challenges associated with the hazardous reactivity of metal hydrides.[8] Catalytic hydrogenations also are often incompatible with compounds containing multiple bonds and reducible groups. They usually require harsh reaction conditions such as elevated temperatures and pressures. Reductive hydrosilylations present a milder, selective, good functional group tolerance and convenient alternative to these conventional methods, which have been widely explored in metal-catalyzed reduction systems for the reduction of imines,[9,10] iminiums,[11] and amides.[12−17]

Hydrosilanes require activation by either a Lewis acid[18] or a Lewis base[19] with a high affinity for silicon due to their typically weak hydride donating ability compared to other hydride sources. The metal-free catalytic hydrosilylation of amides[20,21] and reductive aminations with "frustrated Lewis pairs" of which $B(C_5F_5)_3$ has been established as a versatile catalyst[22,23] are some examples of hydrosilanes' activation by Lewis acids.

Hypervalency in silicon where its valence is expanded after complexation with a nucleophilic species leads to a higher hydride donating ability compared to its tetracoordinate counterpart,[24−26] and a variety of methods based on hydrosilane/Lewis acid combination have been explored for reductive amination.[3,27] On the other hand, reductive amination protocols which exploit activation of trichlorosilane as a reductant by various Lewis bases including DMF,[28] trialkylamines, acetonitrile, chiral *N*-formamide derivatives,[24] chiral sulfonamide, and *N*-picolinoylpyrrolidine derivatives, among others,[29] have been reported. Recently, HMPA and TMEDA have been shown to be suitable activators of highly reactive trichlorosilane in the reductive amination involving aldehydes and ketones with secondary amines.[30,31] Secondary and tertiary amines are achievable through hydrosilylation of C═N bonds using hypervalent hydrosilatrane.[32]

Tertiary diarylmethylamines (**I**) where one of the aryl substituents is a 2-phenol are typically prepared in good yields through Betti[33,34] or multicomponent Petasis borono-Mannich (PBM) reactions.[35,36] While these procedures are somewhat general for diarylmethyl moieties, tertiary alkylphenolmethyl amines (**II**) are more difficult to access this way, as less reactive alkyl aldehydes or alkyl boronic acids or esters are required. A few examples can nevertheless be found.[37−40]

In our previous work,[41] a novel 5-membered cyclic pinacol-derived chlorohydrosilane (PCS) was demonstrated to reduce salicylaldehydes catalyzed by a Lewis base (DMPU) in high yields and good chemo- and regioselectivity (Scheme 1). After reporting in the same work the ability of PCS to perform the reductive amination of a salicylaldehyde-derived iminium, we hypothesized that a similar transformation could be used in the reductive amination of iminiums derived from alkylphenol ketones and secondary amines. Herein, we report the first one-pot, metal- and protective-group-free reductive amination

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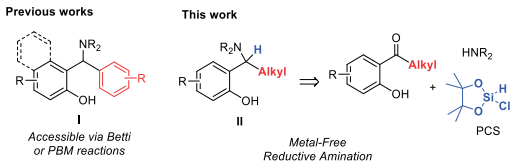
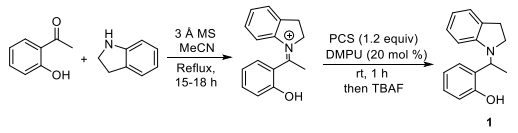
Scheme 1. Approaches to Alkylphenolmethyl Amines



method for preparation of tertiary alkylphenolmethyl amines. This reductive amination procedure is superior to the use of $NaCNBH_3$ since only equimolar amounts of amine are required and it is not susceptible to cyanide contamination. Moreover, the reduction of aromatic and unsaturated ketones by other borohydrides such as $Na(OAc)_3BH$ suffers from lack of reactivity.[4]

Optimization of the reaction conditions was initially examined with 2′-hydroxyacetophenone and indoline as substrates, affording the corresponding aminoalkylphenol **1**. Further screening of the reaction conditions regarding solvent, reaction times, and amounts of DMPU and indoline was performed (see the SI for complete screening). After identification of MeCN as the most promising solvent, we focused on the amount of Lewis base (Table 1). The desired

Table 1. Selected Entries in Optimization of Reductive Amination



1

entry[a]	deviation from reaction conditions	yield[b] (%)
1	none	61
2	without DMPU	42
3	1.2 equiv of indoline, without DMPU	63
4	2 equiv of indoline	84
5	2 equiv of indoline, without DMPU	80

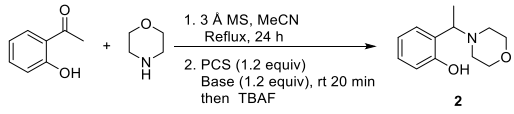
[a]Unless otherwise stated, condensation of 2′-hydroxyacetophenone (0.54 mmol) and indoline (0.54 mmol) in refluxing MeCN (1 mL). PCS (0.65 mmol) in MeCN (1 mL) is added over 5 min to the cooled mixture in the presence of DMPU (0.11 mmol) at rt. After 1 h, the mixture is treated with TBAF (1 M in THF, 0.75 mmol). [b]Isolated yields.

amine **1** was obtained in 61% yield with stoichiometric amounts of the ketone and indoline and 20 mol % of DMPU (entry 1). The absence of DMPU had a detrimental effect on the yield, which could be restored upon increasing the amount of indoline to 1.2 equiv (entries 2 and 3). Increasing the amount of indoline to 2 equiv provided the tertiary amine in up to 84% yield, regardless the presence of DMPU (entries 4 and 5).

In the subsequent studies, indoline was replaced by morpholine due to the easier purification of the product. Based on the above observations, we set out to investigate a Lewis base that would catalyze the reaction more effectively than DMPU, thus allowing us to keep an equimolar amount of secondary amine.

With equimolar amounts of amine and ketone, satisfactory yields of the product could only be obtained by increasing the amount of Lewis base. After various amounts of DMAP were screened (see the SI), 1.2 equiv of the base emerged the best result with 73% yield of the aminoalkylphenol (Table 2, entry

Table 2. Lewis Base Screening



2

entry[a]	base	yield[b] (%)
1	DMAP	73
2	DIPEA	72
3	DBU	73
4	Et_3N	63
5	collidine	62
6	pyridine *N*-oxide	50
7	DMPU	45
8	pyridine	83[c]
9	none	19

[a]Condensation of 2′-hydroxyacetophenone (0.54 mmol) and morpholine (0.54 mmol) in refluxing MeCN (1 mL). PCS (0.65 mmol) in MeCN (1 mL) is added over 5 min to the cooled mixture in the presence of the Lewis base (0.65 mmol) at rt. After 20 min, the mixture is treated with TBAF (1 M in THF, 0.75 mmol). [b]Isolated yields. [c]No product detected without MS.

1). Screening other Lewis bases such as DBU and Hünig's base gave the aminoalkylphenol **2** in yields comparable to that using DMAP (Table 2, entries 2 and 3). Moderate yields were observed for triethylamine, collidine, and pyridine *N*-oxide (Table 2, entries 4–6). A rather low yield of **2** (45%, Table 2, entry 7) was observed with 1.2 equiv of DMPU. Gratifyingly, the desired product was obtained in 83% yield with pyridine (Table 2, entry 8), matching the previous result with an excess of the secondary amine (Table 1, entry 5). Without a base promoter, **2** was obtained in only 19% yield (Table 2, entry 9). The use of molecular sieves was vital for the reaction, as no reduced products were obtained in their absence.

The substrate scope for different secondary amines with 2′-hydroxyacetophenone (Scheme 2) was examined. Tertiary amines **1**–**6** derived from cyclic and acyclic secondary amines were obtained in up to 83% yield, with the former proving superior. Next we expanded the substrate scope to various substituted 2′-hydroxyacetophenones, providing **7**–**15**. 5-Methyl-substituted 2′-hydroxyacetophenone-derived iminiums with either indoline or morpholine were readily reduced by PCS to the corresponding products **7** and **20**. This method demonstrated good functional group tolerance as halogens and nitro-substituted substrates susceptible to reductions allowed for the synthesis of their corresponding aminoalkylphenols (**8**–**14**, **21**–**25**) with morpholine, indoline, and tetrahydroquinoline. Reductions involving ethylaniline as substrate generally gave lower yields, but an optimized protocol employing 1.8 equiv of PCS afforded moderate yields of **22** and **23** (63 and 58%, respectively). The nitro- and methyl-substituted substrate gave a 63% yield of **14**, while that of the nitro and chloro derivative **13** gave a much lower yield of 27%. With the 4-methoxy-substituted 2′-hydroxyacetophenone, **11** was obtained in 60% yield. The alkylnaphtholmethyl amine **15** was also obtained in 50% yield with the standard reaction conditions. Further expansion of the substrate scope to

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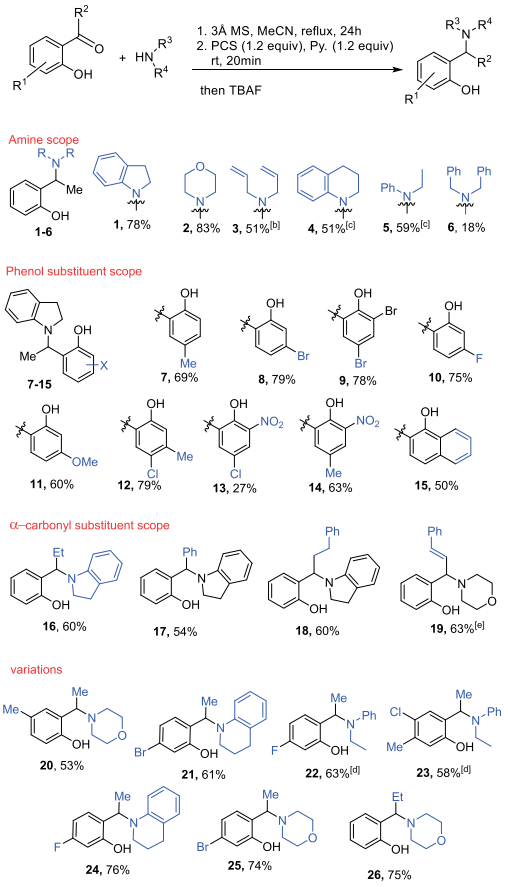
Scheme 2. PCS/Pyridine Reductive Amination Scope[a]



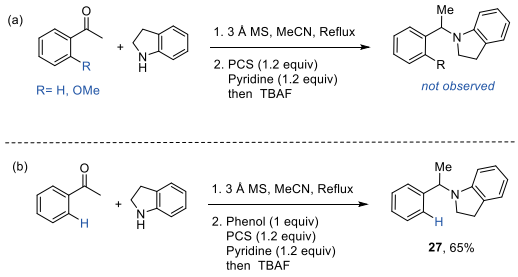
[a]All reactions performed on a 0.54 mmol scale of the hydroxy ketones. Isolated yields.; [b]30 h reflux. [c]Overnight reflux. [d]1.8 equiv of PCS. [e]10 h reflux.

different alkyl- and phenyl-substituted 2′-hydroxyphenones with indoline or morpholine allowed the formation of tertiary amines **16**–**18** and **26** in moderate yields (54–75%), while **19** from a morpholine-derived eniminium was obtained in 63%.

Under the optimized conditions, commercially available diphenylchlorosilane gave **1** in 66% yield after 2 h at rt, after iminium formation. The importance of the phenolic hydroxy group was verified by the absence of product on reduction of an acetophenone- or *o*-methoxyacetophenone-derived iminiums (Scheme 3a). Considering the phenolic OH's role in the reduction process, we also investigated the use of phenol additive for a more practical application of PCS as a reductant. Compound **27** was obtained in 65% yield suggesting a possible intermolecular hydride delivery process.

The reductive amination mechanism was studied via DFT[42] calculations using 2′-(hydroxy)acetophenone and dimethylamine as substrates (Figure 1). The starting point for the calculations is the trialkoxyhydrosilyliminium obtained from HCl loss from the initial hydrosilane.

Scheme 3. Importance of Phenolic Hydroxyl



The reduction proceeds through four steps. In the first step, from **A** to **B**, there is coordination of pyridine to the Si atom in the trialkoxyhydrosilyl iminium. The free energy barrier associated with this step is 2 kcal/mol, with respect to the pair of reactants (**A**), and the emergent Si–N bond in $\mathbf{TS_{AB}}$ is 3.30 Å, which gradually shortens to 2.07 Å, in **B**. The intermediate **B** is only 1 kcal/mol less stable than the separated reagents, and a rotation around the $Si–O_{phenol}$ bond produces **B′**, another conformer of similar stability. In the next step, there is hydride attack into the iminium C atom, from **B′** to **C**, through transition state $\mathbf{TS_{B'C}}$. This step has the highest energy barrier of the entire path, with $\mathbf{TS_{B'C}}$ being 16 kcal/mol less stable than intermediate **B′**.

Subsequently, **C′**, a conformer of **C**, suffers *N*-coordination to the Si atom, resulting in **D**. This occurs through transition state $\mathbf{TS_{C'D}}$ in a barrier less process. In the transition state $\mathbf{TS_{C'D}}$ the new Si–N bond is incipient with a distance of 3.54 Å, still 1.45 Å longer than its value in intermediate **D**. A prompt Si–N bond formation following the hydride attack indicates that those can be viewed as concerted.

Once the intermediate **D** is formed, the last step is liberation of pyridine to give species **E**. This step proceeds through the transition state $\mathbf{TS_{DE}}$ with an associated energy barrier of process of 12 kcal/mol. The distance of $Si–N_{pyridine}$ is elongated from 1.89 Å in **D** to 2.68 Å in the corresponding transition state, $\mathbf{TS_{DE}}$, indicating a well-advanced $Si–N_{pyridine}$ bond breaking. The overall reaction is thermodynamically favored with respect to the separated reactants with $\Delta G = -10$ kcal/mol.

DFT calculations were also performed for the DMPU-promoted mechanism, for comparison purposes (see the SI for details). Lower yields are obtained when DMPU is used as catalyst (Table 2) despite its function as an excellent Lewis base catalyst in the reduction of salicylaldehydes.[41] The reaction mechanism calculated for DMPU parallels the one obtained for pyridine with four consecutive steps. The major difference between the two reactions is the stability of the base–Si adducts in the pyridine and DMPU systems (intermediates **D** and **I**, respectively). The stability of **I**, 24 kcal/mol more stable than the separated reagents, makes DMPU loss the highest barrier step in the path ($\mathbf{TS_{IJ}}$: 26 kcal/mol).

Overall, the pyridine mechanism corresponds to a more facile reaction, the highest barrier being the hydride attack on $C_{C=N}$ ($\mathbf{TS_{B'C}}$, 17 kcal/mol relative to the separated reagents). These results indicate how strongly DMPU, an oxygen base, binds to the Si atom and consequently hampers the liberation of the base catalyst and release of the final product. Therefore, the more stable DMPU–Si adduct accounts for the observed

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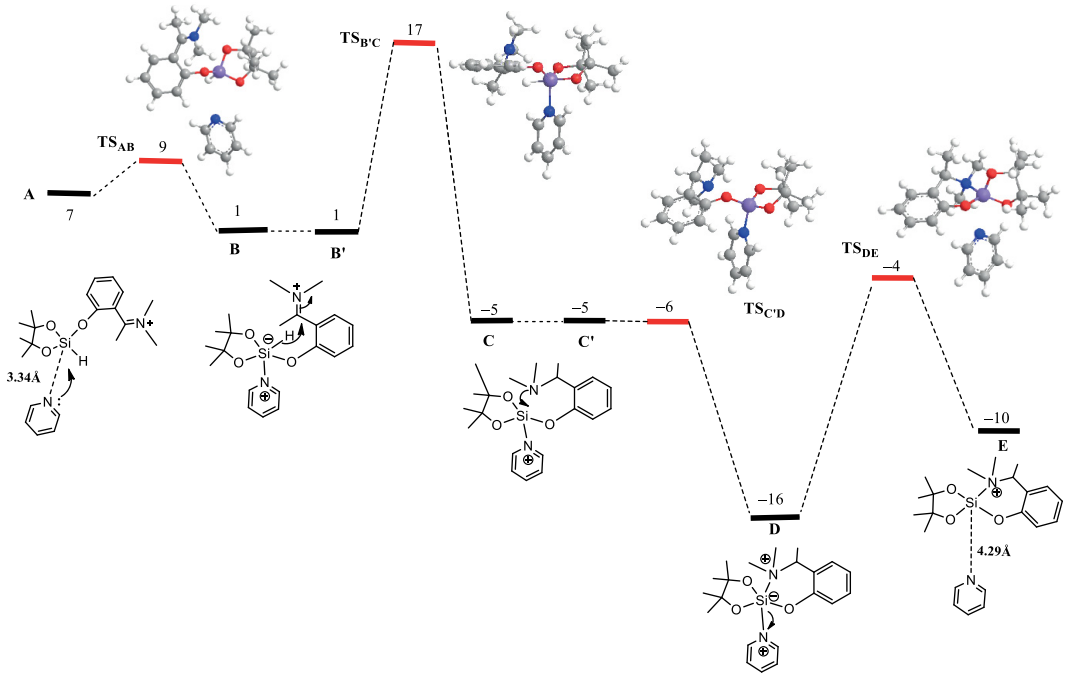

Figure 1. Free energy profile for the pyridine-catalyzed reductive amination. The free energy values (kcal/mol) are relative to the separated reagents: trialkoxyhydrosilyliminium plus pyridine.

lower yields compared to those of the pyridine system. The reductive amination mechanism without a Lewis base was also studied with DFT calculations (see the SI). The mechanism is concerted with simultaneous hydride transfer and N coordination to Si through a transition state with a significant energy barrier of 41 kcal/mol. The reaction is nevertheless exergonic with free energy balance of −15 kcal/mol. Comparison of the barriers calculated for the mechanism with and without Lewis base reveals the active role of that reactant as a promoter.

In summary, we have demonstrated the use of pinacol-derived chlorohydrosilane as an efficient reductant in a Lewis base promoted reductive amination. This protocol, based on the in situ formation of a trialkoxyhydrosilane with concomitant intramolecular hydride delivery, allowed the synthesis of an array of aminoalkylphenols in moderate to high yields while employing equimolar amounts of reactants. The scope of the method could be expanded by using phenol as an additive. The role and nature of the Lewis base were revealed by DFT calculations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00121.

Detailed experimental procedures, additional optimization data, computational data, characterization of compounds, and NMR spectra for all new procedures (PDF)

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Notes

The authors declare no competing financial interest.

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PUBLICATION IV

Synthesis of 6, 12-disubstituted methanodibenzo[*b,f*][1,5]dioxocins: Pyrrolidine catalysed self-condensation of 2'-hydroxyacetophenones.

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Synthesis of 6,12-Disubstituted Methanodibenzo[*b,f*][1,5]dioxocins: Pyrrolidine Catalyzed Self-Condensation of 2′-Hydroxyacetophenones

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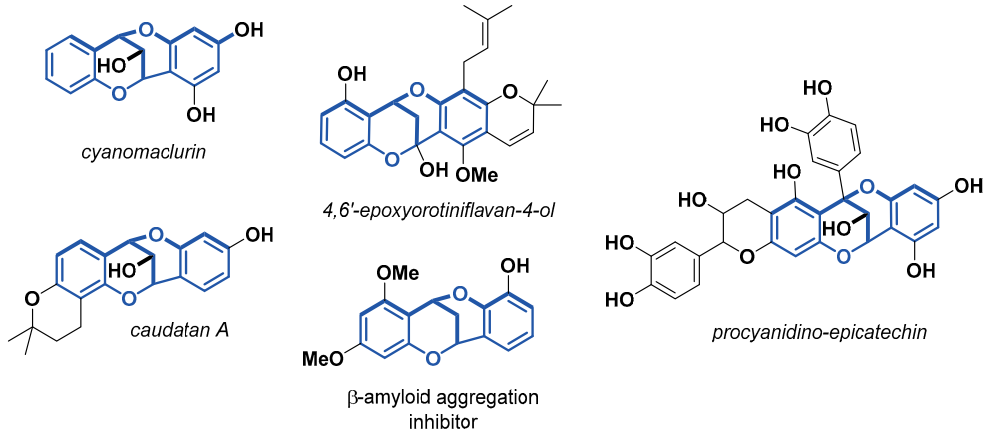
Abstract: The preparation of unprecedented 6,12-disubstituted methanodibenzo[*b,f*][1,5]dioxocins from pyrrolidine catalyzed self-condensation of 2′-hydroxyacetophenones is herein described. This method provides easy access to this highly bridged complex core, resulting in construction of two C–O and two C–C bonds, a methylene bridge and two quaternary centers in a single step. The intricate methanodibenzo[*b,f*][1,5]dioxocin compounds were obtained in up to moderate yields after optimization of the reaction conditions concerning solvent, reaction times and the use of additives. Several halide substituted methanodibenzo[*b,f*][1,5]dioxocins could be prepared from correspondent 2′-hydroxyacetophenones.

Keywords: enamine; 1,5-dioxocin; self-condensation; 2′-hydroxyacetophenone

1. Introduction

Heterocyclic compounds possess fascinating complex structural architecture and are key structural motifs in an array of biologically active natural products and pharmaceutically active compounds [1], which drives the development of improved and new synthetic methodologies [2–9]. In recent years, cascade reactions [10–16] and bio-inspired technologies [17–23] have been employed to access structural complexity in compounds of biological importance.

Methanodibenzo[*b,f*][1,5]dioxocin is a highly strained bridged polycyclic skeleton present in numerous biologically active natural products and pharmaceuticals (Scheme 1). Some of these natural products exhibit inhibition against β-amyloid aggregation, antibacterial activity, potent anti-methicillin-resistant staphylococcus aureus (MRSA) activity, etc. [24–35]. After Nair et al. [29] reported that cyanomaclurin, a compound isolated from the heartwood of *Artocarpus integrifolia* (jackwood) [36], possessed a methanodibenzo[*b,f*][1,5]dioxocin core, considerable attention was paid to its construction. Hennis and co-workers obtained the neutral 6H,12H-6,12-methanodibenzo[*b,f*][1,5]dioxocin and its derivatives after a condensation reaction of either *o*-vinylphenol or *o*-coumaric acid and salicylaldehyde under acidic conditions [37,38].

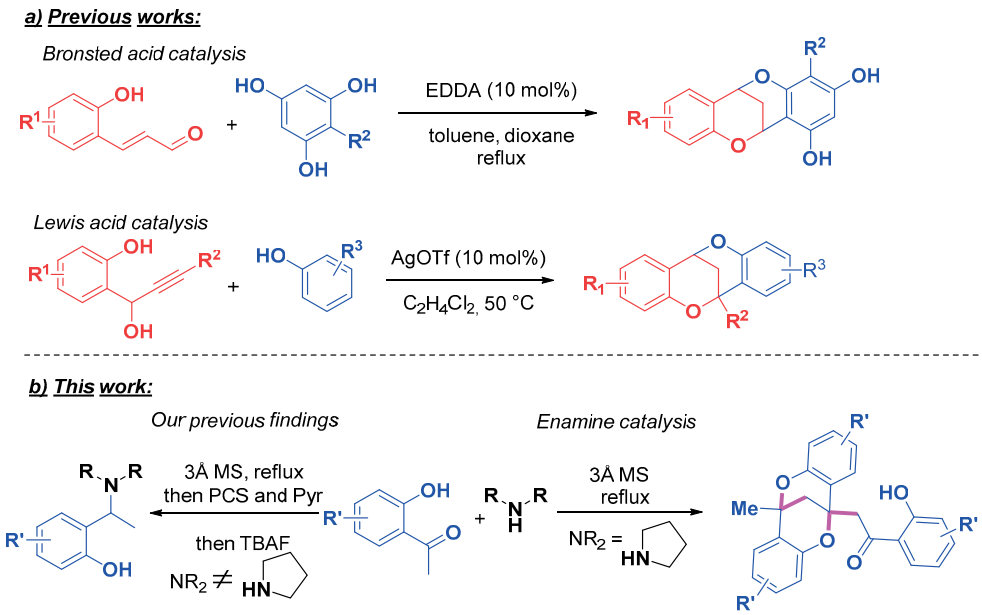


Scheme 1. Selected reported biologically relevant methanodibenzo[*b*,*f*][1,5]dioxocins.

The catalytic preparation of the methanodibenzo[*b*,*f*][1,5]dioxocin core has been recently explored (Scheme 2a). A bioinspired cascade sequence of ethylenediaminediacetic acid (EDDA)-catalyzed olefin isomerization/hemiacetalization/dehydration/[3+3]-type cycloaddition driven by an in situ generated chromenylium intermediate has been reported by Liu et al. in the synthesis of methanodibenzo[*b*,*f*][1,5]dioxocin flavonoids from phloroglucinol and 2-hydroxycinnamalaldehyde [39]. Du and co-workers explored *o*-quinone methide and electron rich phenols as reactants in a silver triflate catalyzed tandem process for the construction of such a core. The formation of alkynyl *o*-quinone methide catalyzed by silver triflate triggers the following intermolecular cascade: 1,4-conjugate addition/6-endo cyclization/1,3-aryl shift/intramolecular 1,4-conjugate addition, providing the 2-substituted methanodibenzo[*b*,*f*][1,5]dioxocin [40]. Notwithstanding these recent developments, more synthetic strategies to access this intricate polycyclic ring system are worth pursuing as accessing [1,5]-dioxocins with different substituents in the bridgehead carbons is still an open issue. Likely due to the limited synthetic methodologies available, the methanodibenzo[*b*,*f*][1,5]dioxocin motif has received little attention as a structural scaffold in drug design.

In our previous endeavor towards the development of a reductive amination protocol for the synthesis of tertiary alkylphenolmethyl amines [41] using a recently developed pinacol-derived chlorohydrosilane (PCS) [42], we were intrigued by the absence of the desired reductive amination product under our hydrosilylation conditions with 2′-hydroxyacetophenone and pyrrolidine (Scheme 2b). Despite the successful use of such a protocol for the synthesis of several tertiary alkylphenolmethyl amines, careful inspection of a reaction mixture containing pyrrolidine and the ketone showed the formation of a 2′-hydroxyacetophenone self-condensation product.

Aware of the limitations of the available methods for the preparation of methanodibenzo[*b*,*f*][1,5]dioxocin, and intrigued by the singular reactivity of pyrrolidine in promoting the self-condensation reaction, we set out to investigate and optimize the reaction conditions to efficiently construct such a polycyclic core from the self-condensation of three 2′-hydroxyacetophenone molecules. Importantly, previously reported attempts to dimerize β-hydroxy ketones using acidic/dehydrating conditions proved unsuccessful, although 6H,12H-6,12-epoxydibenzo[*b*,*f*][1,5]dioxocins could be obtained from the dimerization of salicylaldehydes [43,44].



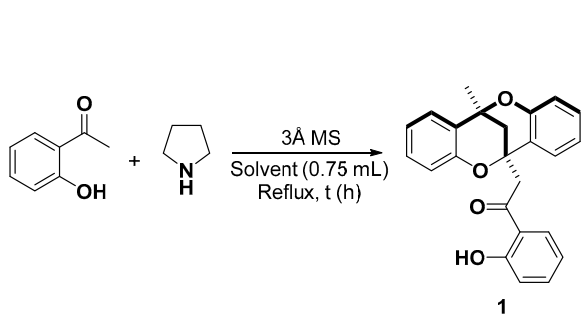
Scheme 2. Previously reported catalytic methods for the synthesis of methanodibenzo[*b,f*][1,5]dioxocins (**a**) and our enamine catalyzed approach (**b**).

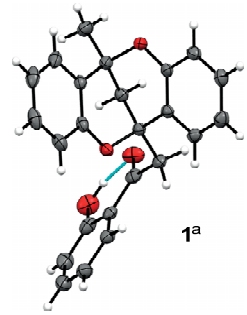
2. Results and Discussion

We began our synthetic efforts to optimize the reaction conditions after obtaining methanodibenzo[*b,f*][1,5]dioxocin **1** at a 9% yield in a failed attempt to aminate 2′-hydroxyacetophenone with pyrrolidine under hydrosilylation conditions, followed by crystallization and unambiguous characterization of the product through single crystal X-ray diffraction analysis (Table 1). The crystal structure of **1** showed an intramolecular hydrogen bond and similar geometric features of the methanodibenzo[*b,f*][1,5]dioxocin core to 7,9-dimethoxy-6H,12H-6,12-methanodibenzo[*b,f*][1,5]dioxocin-4-ol [26], except for the interplanar angle between benzene rings. The interplanar angle was almost ten degrees higher value in **1**, which was rather close to orthogonality (~88°) and corresponded to the value found from (*E*)-2-(4-((12-methyl-6H,12H-6,12-methanodibenzo[*b,f*][1,5]dioxocin-6-yl)methylene)-4H-chromen-2-yl)phenol [45].

Using 2-hydroxyacetophenone as substrate, we investigated the reaction conditions in the hydrosilylation protocol and their effect on the formation of compound **1** (Table 1). The initial use of stoichiometric amounts of 2′-hydroxyacetophenone and pyrrolidine in refluxing acetonitrile gave compound **1** with a 24% yield (Table 1, entry 1). The importance of pyrrolidine and molecular sieves (MS) was verified after not detecting the desired product when running the reaction in the absence of any of these components (entries 2 and 3). Replacing pyrrolidine with anhydrous *p*-toluenesulfonic acid, or use of pyrrolidine as a solvent led to similar outcomes (entries 4 and 5). Decreasing the amount of pyrrolidine to 0.3 equiv. had a positive effect on the formation of **1**, with a yield of 42% (entry 6). Harsher reaction conditions, namely using a sealed tube at 80 °C in the absence of solvent and increased reaction times, allowed formation of product with up to 59% yield (entry 7). Decreasing the amount of the pyrrolidine catalyst did not improve the yield of the desired product (Table 1, entries 8–10). Other reaction conditions tested, including use of additives such as acetic acid or $Cu(OAc)_2$, replacing molecular sieves beads with powder and using different amounts of sieves, invariably led to lower yields.

Table 1. Initial optimization of reaction conditions.



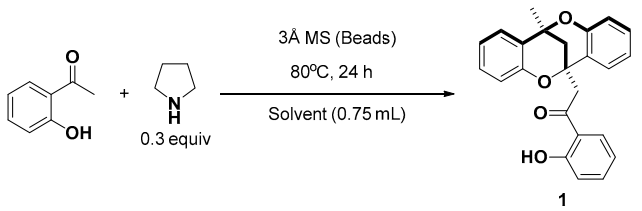


Entry [b]	Pyrrolidine (equiv.)	Solvent	Conditions	Time (h)	Yield (%) [c]
1	1	CH_3CN	Reflux [d]	18	24
2	1	CH_3CN	Reflux [d], no MS	18	n.d. [e]
3	none	CH_3CN	Reflux [d]	18	n.d. [e]
4	none	CH_3CN	dry *p*-TSA (0.2 equiv) [d]	48	n.d. [e]
5	-	Pyrrolidine [g]	Reflux	21	n.d. [e]
6	0.3	CH_3CN	Reflux	24	42
7	0.3	none	Sealed tube	24	41 (59) [f]
8	0.15	none	Sealed tube	24	29
9	0.15	CH_3CN	Sealed tube	24	36
10	0.05	CH_3CN	Sealed tube	24	25

[a] Thermal ellipsoid diagram of the molecular structure of 1-(2-hydroxyphenyl)-2-(12-methyl-6*H*,12*H*-6,12-methanodibenzo[*b*,*f*][1,5]dioxocin-6-yl)ethan-1-one (**1**). [b] Unless otherwise noted, 2′-hydroxyacetophenone (6.22 mmol) in refluxing CH_3CN (0.75 mL), 3 Å molecular sieve (MS, 362 mg) [c] Isolated yield. [d] 1 mL of solvent used. [e] not detected [f] after 72 h. [g] Pyrrolidine used as solvent (2 mL).

At this point, the best conditions identified were the use of 30 mol% pyrrolidine to catalyze the transformation and a solvent-free protocol. While the model compound tested is liquid at room temperature, many 2′-hydroxyacetophenones are solid, which could likely pose reproducibility, heat and mass transfer issues in a solvent free process. Furthermore, after considerable product formation, it is solidified in the mixture, trapping the molecular sieves and hampering efficient stirring of the reaction mixture. Due to this, we decided to search for solvents suitable for the reaction, which would solubilize the starting materials and prevent decomposition of the product. With the aim of getting both the starting material and product soluble in the reaction media, more polar solvents were initially tested in both vessel types, sealed tube and round bottom flask, under argon (Table 2). Interestingly, ethanol, the only protic solvent tested, failed to provide any of the product, and dichloroethane did not provide more than a 15% yield of **1** after 24 h. Other polar solvents, such as acetonitrile and methyl *tert*-butylether, could provide the product in yields of up to 43%, but slightly better yields could be obtained for hexane, while toluene and dioxane were comparable. From the reaction optimizations so far, it appeared that hexane as a solvent favored the yield of compound **1** compared to the others screened in both closed and reflux reaction conditions. A more dilute reaction media in hexane did not affect the yield of **1** considerably (Table 2, entry 7). Thus, we identified the use of 0.3 equiv. of pyrrolidine as a catalyst in refluxing hexane to be the optimal reaction conditions for the synthesis of **1** based on the optimization reactions carried out and also our quest to avoid reactions under neat conditions.

Table 2. Solvent screening.

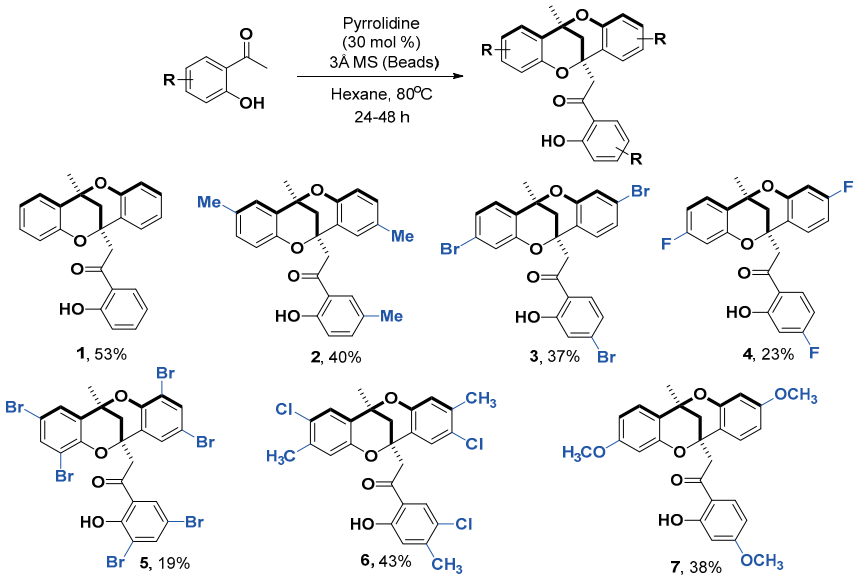


Entry	Solvent	Isolated Yield (%)	
		Sealed Tube	Open Vessel
1	CH_3CN	29	42
2	EtOH	n.d. [a]	-
3	DMSO	28	-
4	MTBE	32	43
5	1,4-Dioxane	-	30
6	DCE	trace	15
7	Hexane	44 [b] (39) [c]	53 (50) [d]
8	Toluene	31 [e]	27
9	Heptane	-	45

[a] not detected, 2 mL of EtOH used. [b] same yield obtained after 48 h. [c] Using 1.5 mL of hexane. [d] Using 5 mL of hexane and 48 h. [e] Powder 3 Å MS and 1.5 mL of toluene were used.

With the established optimal reaction conditions in hand, we proceeded to expand the substrate scope to other substituted 2′-hydroxyacetophenones (Scheme 3). Notwithstanding the modest yields, we were pleased to observe the formation of methanodibenzo[*b*,*f*][1,5]dioxocin derivatives **2**–**7** without the need to use any metals or strongly acidic conditions. The protocol was demonstrated to be suitable for obtaining alkyl-substituted methanodibenzo[*b*,*f*][1,5]dioxocin **2**, the halide substituted derivatives **3**–**6** or the electron rich methoxy derivative **7**. When attempting to verify the suitability of this method for strongly electron-withdrawing groups, nitro substituted 2′-hydroxyacetophenones were tested, resulting only in the isolation of traces of the reduced aniline and unreacted starting material. Also, all attempts to obtain the methanodibenzo[*b*,*f*][1,5]dioxocin analogue of other 2′-hydroxyketones, such as 2′-hydroxypropiophenone or 2′-hydroxy-3-phenylpropiophenone proved futile, therefore limiting this protocol to pyrrolidine catalyzed self-condensation of 2′-hydroxyacetophenones.

Although the details of the mechanisms involved require full clarification, the absence of similar dioxocin products when employing other cyclic secondary amines, such as indoline, morpholine and tetrahydroquinoline, using our hydrosilylation protocol, suggests that an enamine is likely to be involved. Pyrrolidine derived enamines are known to be more reactive that other cyclic amines [46,47], and the protocol for reductive amination from 2′-hydroxyacetophenone and this amine starts with iminium formation at room temperature under neat conditions [48]. Moreover, the same amine was previously reported to promote the formation of 4-chromanones from 2′-hydroxyacetophenones and aliphatic aldehydes and ketones [49].



Scheme 3. Synthesis of substituted methanodibenzo[*b*,*f*][1,5]dioxocin derivatives.

3. Materials and Methods

3.1. General Considerations

All syntheses were carried out in oven-dried glassware under an inert atmosphere. All solvents used were left standing over 3 Å molecular sieves and used without further drying. All other reagents were purchased from Sigma-Aldrich or TCI and used without further purification. Reactions were monitored through thin-layer chromatography (TLC) with commercial silica gel plates (Merck silica gel, 60 F254). Visualization of the developed plates was performed under UV lights at 254 nm and by staining with cerium ammonium molybdate and vanillin. Flash column chromatography was performed on silica gel 60 (40–63 µm) as stationary phase. NMR spectra were recorded with JEOL ECZR 500 instruments using $CDCl_3$ as solvent. Chemical shifts (δ) were reported in ppm and referenced to the $CDCl_3$ residual peak (δ 7.26) or tetramethylsilane (TMS) peak (δ 0.00) for ^{1}H NMR and to $CDCl_3$ (δ 77.16) for ^{13}C NMR. The following abbreviations were used to describe peak splitting patterns: s = singlet, d = doublet, t = triplet and m = multiplet. Coupling constants, *J*, were reported in hertz (Hz). High-resolution mass spectrometry spectra were recorded on a Waters ESI-TOF MS spectrometer.

3.2. General Procedure for the Synthesis of Substituted Methanodibenzo[b,f][1,5]Dioxocin Derivatives **1–7**

In a 10 mL round bottom flask equipped with a condenser, the corresponding 2′-hydroxyacetophenone (6.22 mmol) was heated in hexane (5 mL) for 5–10 min to dissolve completely, after which pyrrolidine (2.08 mmol, 0.33 equiv) and molecular sieves (3 Å beads, 362 mg) were added while stirring under argon. The resulting mixture was refluxed at 80 °C for 24–48 h and then allowed to cool to room temperature. After cooling to room temperatute (r. t.), ethyl acetate was added to the reaction mixture, followed by saturated NH_4Cl (15 mL). The aqueous layer was extracted with ethyl acetate (3 × 20 mL) and the combined organic layers were dried over $MgSO_4$, filtered out and the solvent was removed under reduced pressure. The residue was then purified by flash column chromatography on silica (Hexane:EtOAc 98:2) to give the desired product. 1H and 13C spectra of all compounds, **1–7** is available in the supplementary material.

1-(2-hydroxyphenyl)-2-(12-methyl-6H,12H-6,12-methanodibenzo[b,f][1,5]dioxocin-6-yl)ethan-1-one (**1**). Following the general procedure, 2′-hydroxyacetophenone (845 mg, 6.22 mmol) and pyrrolidine (170 μL, 2.08 mmol) in hexane (1.5 mL) refluxed for 24 h. The purified product was obtained as a pale yellow crystalline solid at a 53% yield (406 mg, 1.09 mmol). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 12.12 (s, 1H, OH), 8.08 (d, *J* = 7.4 Hz, 1H. ArH), 7.44–7.55 (m, 2H, ArH), 7.40 (d, *J* = 7.4 Hz, 1H, ArH), 7.06–7.16 (m, 2H, ArH), 6.93–7.01 (m, 2H, ArH), 6.78–6.92 (m, 3H, ArH), 6.71 (d, *J* = 8.0 Hz, 1H, ArH), 4.16 (d, *J* = 16.0 Hz, 1H, CH_2), 3.79 (d, *J* = 16.0 Hz, 1H, CH_2), 2.68 (d, *J* = 13.7 Hz, 1H, CH_2), 2.26 (d, *J* = 13.7 Hz, 1H, CH_2), 1.87 ppm (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 202.6, 162.6, 154.0, 152.8, 136.6, 130.7, 129.9, 129.7, 126.5, 125.5, 124.2, 122.7, 120.8, 120.6, 119.9, 118.8, 118.4, 117.4, 116.9, 72.1, 70.3, 45.1, 38.7, 25.2. HRMS (ESI) *m*/*z*: Calculated for $C_{24}H_{21}O_4$ $[M + H]^+$ 373.1440. Found 373.1411.

1-(2-hydroxy-5-methylphenyl)-2-(2,8,12-trimethyl-6H,12H-6,12-methanodibenzo[b,f][1,5]dioxocin-6-yl)ethan-1-one (**2**). Following the general procedure, 2′-hydroxy-5′-methylacetophenone (934 mg, 6.22 mmol) and pyrrolidine (170 μL, 2.08 mmol) in hexane (5 mL) refluxed for 48 h. The purified product was obtained as a pale yellow crystalline solid at a 40% yield (341 mg, 0.82 mmol). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 11.94 (s, 1H, OH), 7.86 (d, *J* = 1.7 Hz, 1H, ArH), 7.31 (dd, *J* = 8.6, 2.3 Hz, 1H, ArH), 7.26 (d, *J* = 1.7 Hz, 1H, ArH), 7.15 (d, *J* = 2.3 Hz, 1H, ArH), 6.89–6.95 (m, 2H, ArH), 6.87 (d, *J* = 8.6 Hz, 1H, ArH), 6.69 (d, *J* = 8.0 Hz, 1H, ArH), 6.60 (d, *J* = 8.0 Hz, 1H, ArH), 4.09 (d, *J* = 16.0 Hz, 1H, CH_2), 3.80 (d, *J* = 16.0 Hz, 1H, CH_2), 2.64 (d, *J* = 13.7 Hz, 1H, CH_2), 2.38 (s, 3H, CH_3), 2.22 (s, 3H, CH_3), 2.19 (s, 3H, CH_3), 2.15 (d, *J* = 13.7 Hz, 1H, CH_2), 1.83 ppm (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 202.8, 160.8, 152.1, 150.9, 137.9, 131.0, 130.8, 130.7, 130.2, 129.9, 128.1, 127.0, 125.9, 124.2, 122.7, 119.9, 118.4, 117.3, 116.8, 72.2, 70.5, 45.6, 39.1, 25.6, 20.9, 20.8, 20.7. HRMS (ESI) *m*/*z*: Calculated for $C_{27}H_{27}O_4$ $[M + H]^+$ 415.1909. Found 415.1850.

1-(4-bromo-2-hydroxyphenyl)-2-(3,9-dibromo-12-methyl-6H,12H-6,12-methanodibenzo[b,f][1,5]dioxocin-6-yl)ethan-1-one (**3**). Following the general procedure, 4′-bromo-2′-hydroxyacetophenone (192 mg, 0.90 mmol) and pyrrolidine (24 μL, 0.3 mmol) in hexane (1 mL) refluxed for 48 h. The purified product was obtained as a white crystalline solid at a 37% yield (68 mg, 0.11 mmol). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 12.09 (s, 1H, OH), 7.86 (d, *J* = 8.6 Hz, 1H, ArH), 7.32 (d, *J* = 8.6 Hz, 1H, ArH), 7.17–7.22 (m, 2H, ArH), 7.13 (dd, *J* = 8.6, 1.7 Hz, 1H, ArH), 7.03 (dd, *J* = 8.3, 2.0 Hz, 1H, ArH), 6.96–7.00 (m, 2H, ArH), 6.86 (d, *J* = 1.7 Hz, 1H, ArH), 4.06 (d, *J* = 16.0 Hz, 1H, CH_2), 3.69 (d, *J* = 16.0 Hz, 1H, CH_2), 2.64 (d, *J* = 13.7 Hz, 1H, CH_2), 2.20 (d, *J* = 14.3 Hz, 1H, CH_2), 1.82 ppm (s, 3H, CH_3). ^{13}C NMR (CDCl3, 126 MHz): δ = 201.7, 163.3, 155.1, 153.7, 131.7, 131.6, 128.2, 127.0, 124.7, 124.4, 123.7, 123.4, 123.3, 122.8, 122.0, 121.6, 121.0, 120.3, 118.9, 72.6, 70.9, 45.1, 38.5, 25.2. HRMS (ESI) *m*/*z*: Calculated for $C_{24}H_{16}Br_3O_4$ $[M - H]^-$ 606.8580, 608.8561. Found 606.8564, 608.8533.

2-(3,9-difluoro-12-methyl-6H,12H-6,12-methanodibenzo[b,f][1,5]dioxocin-6-yl)-1-(4-fluoro-2-hydroxyphenyl) ethan-1-one (**4**). Following the general procedure, 4′-fluoro-2′-hydroxyacetophenone (959 mg, 6.22 mmol) and pyrrolidine (170 μL, 2.08 mmol) in hexane (3 mL) refluxed for 48 h. The purified product was obtained as a yellow crystalline solid at a 23% yield (199 mg, 0.47 mmol). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 12.39 (d, *J* = 1.7 Hz, 1H, OH), 8.06 (dd, *J* = 9.2, 6.3 Hz, 1H, ArH), 7.44 (dd, *J* = 8.6, 6.3 Hz, 1H, ArH), 7.30–7.39 (m, 1H, ArH), 6.56–6.74 (m, 4H, ArH), 6.51 (dd, *J* = 9.7, 2.9 Hz, 1H, ArH), 6.41 (dd, *J* = 10.0, 2.6 Hz, 1H, ArH), 4.09 (d, *J* = 16.0 Hz, 1H, CH_2), 3.69 (d, *J* = 16.0 Hz, 1H, CH_2), 2.65 (d, *J* = 13.7 Hz, 1H, CH_2), 2.23 (d, *J* = 13.7 Hz, 1H, CH_2), 1.85 ppm (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 201.2, 167.8 (d, $^1J_{C\text{-}F}$ = 258.3 Hz), 165.6 (d, $^3J_{C\text{-}F}$ = 13.9 Hz), 163.6 (d, $^1J_{C\text{-}F}$ = 249.5 Hz), 163.4 (d, $^1J_{C\text{-}F}$ = 246.9 Hz), 155.7 (d, $^3J_{C\text{-}F}$ = 12.6 Hz), 154.3 (d, $^3J_{C\text{-}F}$ = 12.6 Hz), 133.4 (d, $^3J_{C\text{-}F}$ = 12.6 Hz), 128.3 (d, $^3J_{C\text{-}F}$ = 10.1 Hz), 127.2 (d, $^3J_{C\text{-}F}$ = 10.1 Hz), 120.4 (d, $^4J_{C\text{-}F}$ = 3.8 Hz), 118.8 (d, $^4J_{C\text{-}F}$ = 3.8 Hz), 117.3 (d, $^4J_{C\text{-}F}$ = 2.5 Hz), 108.9 (d, $^2J_{C\text{-}F}$ = 21.4 Hz), 108.6 (d, $^2J_{C\text{-}F}$ = 21.4 Hz), 107.6 (d, $^2J_{C\text{-}F}$ = 23.9 Hz) 105.3 (d, $^2J_{C\text{-}F}$ = 23.9 Hz), 104.7 (d, $^2J_{C\text{-}F}$ = 23.9 Hz), 104.1 (d, $^2J_{C\text{-}F}$ = 23.9 Hz), 72.7, 71.0, 45.3, 38.7, 25.4. HRMS (ESI) *m*/*z*: Calculated for $C_{24}H_{16}F_3O_4$ $[M - H]^-$ 425.1001. Found 425.0961.

1-(3,5-dibromo-2-hydroxyphenyl)-2-(2,4,8,10-tetrabromo-12-methyl-6H,12H-6,12-methanodibenzo[b,f][1,5] dioxocin-6-yl)ethan-1-one (**5**). Following the general procedure, 3′,5′-dibromo-2′-hydroxyacetophenone (1.83 g, 6.22 mmol) and pyrrolidine (170 µL, 2.08 mmol) in hexane (5 mL) refluxed for 48 h. The purified product was obtained as a green crystalline solid at a 19% yield (332 mg, 0.39 mmol). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 12.67 (s, 1H, OH), 8.29 (d, *J* = 2.3 Hz, 1H, ArH), 7.92 (d, *J* = 2.9 Hz, 1H, ArH), 7.59 (d, *J* = 2.3 Hz, 1H, ArH), 7.55 (d, *J* = 2.3 Hz, 1H, ArH), 7.51 (dd, *J* = 4.0, 2.3 Hz, 2H, ArH), 4.38 (d, *J* = 14.9 Hz, 1H, CH_2), 3.37 (d, *J* = 15.5 Hz, 1H, CH_2), 2.57 (d, *J* = 14.3 Hz, 1H, CH_2), 2.18 (d, *J* = 14.3 Hz, 1H, CH_2), 1.90 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 201.5, 158.7, 150.3, 149.0, 142.5, 136.9, 136.4, 133.5, 129.0, 127.8, 126.8, 125.1, 121.5, 114.1, 113.5, 113.4, 113.1, 112.6, 111.1, 73.4, 71.9, 45.5, 37.8, 25.3. HRMS (ESI) *m/z*: Calculated for $C_{24}H_{13}Br_6O_4$ $[M - H]^-$ 842.5875, 844.5855, 846.5837, 848.5820. Found 842.6132, 844.5813, 846.5826 and 848.5784.

1-(5-chloro-2-hydroxy-4-methylphenyl)-2-(2,8-dichloro-3,9,12-trimethyl-6H,12H-6,12-methanodibenzo[b,f][1,5] dioxocin-6-yl)ethan-1-one (**6**). Following the general procedure, 5′-chloro-2′-hydroxy-4′-methylacetophenone (1.15 g, 6.22 mmol) and pyrrolidine (170 µL, 2.08 mmol) in hexane (5 mL) refluxed for 48 h. The purified product was obtained as a brown crystalline solid at a 43% yield (464 mg, 0.90 mmol). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 11.90 (s, 1H, OH), 8.00 (s, 1H, ArH), 7.39 (s, 1H, ArH), 7.24–7.31 (m, 1H, ArH), 6.86 (s, 1H, ArH), 6.67 (s, 1H, ArH), 6.60 (s, 1H, ArH), 4.06 (d, *J* = 16.0 Hz, 1H, CH_2), 3.59 (d, *J* = 16.0 Hz, 1H, CH_2), 2.55 (d, *J* = 13.7 Hz, 1H, CH_2), 2.38 (s, 3H, CH_3), 2.22 ((s, 3H, CH_3), 2.21 ((s, 3H, CH_3), 2.13 (d, *J* = 13.7 Hz, 1H, CH_2), 1.80 ppm (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 201.1, 161.3, 152.6, 151.3, 146.5, 138.5, 138.3, 130.6, 126.8, 126.4, 125.8, 124.5, 123.3, 121.8, 120.7, 119.9, 119.3, 119.0, 72.1, 70.6, 45.4, 38.4, 25.4, 21.0, 20.1, 20.0. HRMS (ESI) *m/z*: Calculated for $C_{27}H_{22}Cl_3O_4$ $[M - H]^-$ 515.0583, 517.0559. Found 515.0589, 517.0613.

2-(3,8-dimethoxy-12-methyl-6H,12H-6,12-methanodibenzo[b,f][1,5]dioxocin-6-yl)-1-(2-hydroxy-4-methoxyphenyl)ethan-1-one (**7**). Following the general procedure, 2′-hydroxy-4′-methoxyacetophenone (1.03 g, 6.22 mmol) and pyrrolidine (170 µL, 2.08 mmol) in hexane (5 mL) refluxed for 48 h. The purified product was obtained as a yellow crystalline solid at a 38% yield (365 mg, 0.79 mmol). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 12.69 (s, 1H, OH), 7.96 (d, *J* = 9.2 Hz, 1H, ArH), 7.36 (d, *J* = 9.2 Hz, 1H, ArH), 7.29 (d, *J* = 9.2 Hz, 1H, ArH), 6.49–6.53 (m, *J* = 2.3 Hz, 1H, ArH),) 6.41–6.47 (m, 2H, ArH), 6.40 (d, *J* = 2.9 Hz, 1H, ArH), 6.30 (d, *J* = 2.9 Hz, 1H, ArH), 6.21 (d, *J* = 2.3 Hz, 1H, ArH), 4.06 (d, *J* = 15.5 Hz, 1H, CH_2), 3.84 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3), 3.57 (d, *J* = 15.5 Hz, 1H, CH_2), 2.58 (d, *J* = 13.7 Hz, 1H, CH_2), 2.20 (d, *J* = 13.2 Hz, 1H, CH_2), 1.82 ppm (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 200.9, 166.4, 165.9, 161.0, 160.9, 155.6, 154.4, 132.8, 127.6, 126.7, 117.0, 115.6, 114.6, 108.5, 108.2, 107.9, 101.4, 101.3, 100.9, 72.7, 71.0, 55.7, 55.3, 55.2, 45.1, 39.2, 25.6. Calculated for $C_{27}H_{25}O_7$ $[M - H]^-$ 461.1600 Found 461.1604.

3.3. Single Crystal X-Ray Diffraction

The crystal data for **1** were collected on an Agilent SuperNova single-source diffractometer equipped with an Eos CCD detector at 120(2) K using mirror-monochromated Mo-Kα (λ = 0.71073 Å) radiation. Data collection (ω scans) and reduction was performed using the program CrysAlisPro [50]. The analytical face-indexing-based absorption correction method was applied. The structure was solved by intrinsic phasing methods [51] and refined by full-matrix least squares on F^2 using SHELXL-2018/1 [52]. Anisotropic displacement parameters were assigned to non-H atoms. All hydrogen atoms (except O–H) were constrained to their idealized positions and refined using riding models with U_{eq}(H) of 1.5U_{eq}(C) for terminal methyl groups and of 1.2U_{eq}(C) for other groups. Hydrogen atoms bonded to O atoms were found from the electron density maps, restrained to their ideal distance (0.84 Å) from the parent atom and refined with U_{eq}(H) of 1.5U_{eq}(O). Deposition Number CCDC-1922829 contains the supplementary crystallographic data for this paper. These data are provided

free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

Crystal data for **1**: $C_{24}H_{20}O_4$ (M = 372.40 g/mol), triclinic, space group P-1 (no. 2), a = 6.8635(3) Å, b = 8.5812(4) Å, c = 16.4282(7) Å, α = 84.240(4)°, β = 82.066(4)°, γ = 72.435(4)°, V = 911.86(7) Å^3, Z = 2, ρ_{calc} = 1.356 g/cm^3, 14,061 reflections measured (3.4° ≤ θ ≤ 29.9°), 4703 unique (R_{int} = 0.0329, R_{sigma} = 0.0351, $I > 2\sigma(I)$ = 3781) which were used in all calculations. The final $R1$ was 0.0467 ($I > 2\sigma(I)$) and w$R2$ was 0.1222 (all data).

4. Conclusions

We have developed a simple, metal-free synthetic route to the highly complex methanodibenzo[*b*,*f*][1,5]dioxocin skeleton from the self-condensation of readily available 2′-hydroxyacetophenones catalyzed by pyrrolidine. Notwithstanding the moderate yields and narrow scope of the transformation, this strategy furnishes, in one-pot, unprecedented 6,12-disubstituted methanodibenzo[*b*,*f*][1,5]dioxocin derivatives with potential usefulness in medicinal chemistry or in the development of bioactive substances.

Supplementary Materials: The following are available online. ^{1}H and ^{13}C spectra of compounds **1**–**7**.

Author Contributions: B.A. and N.R.C. conceived and designed the experiments. B.A., J.R.V. and V.R. performed the experiments. A.V. performed the X-ray crystallographic studies. B.A. prepared the manuscript and N.R.C. revised it. All authors read and approved the final manuscript.

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Sample Availability: Samples of the compounds **1–7** are available from the authors.