1 Introduction

1.1 Occurrence of Chiral Saturated Heterocycles

Chiral substituted tetrahydrofuran and dihydrobenzofuran scaffolds are present in numerous biologically active compounds.[1] Prominent examples of such tetrahydrofurans include capecitabine (**1**), an oral chemotherapy agent marketed by Roche under the trade name Xeloda®, which is used in the treatment of colorectal and breast cancer (*Figure 1.1*).[2] Another example is represented by the naturally occurring diastereomeric pair of calyxolanes A and B (**2a**, **2b**) that were isolated from the Caribbean marine sponge *Calyx podatypa*.[3]

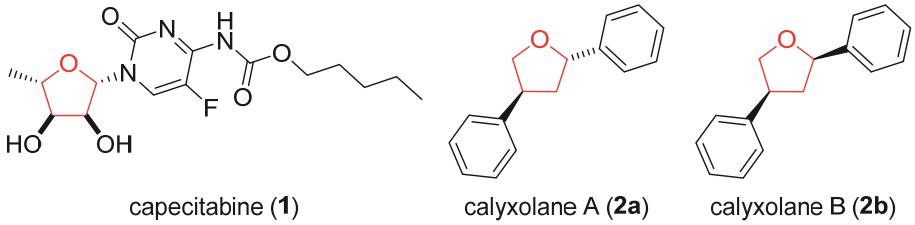


Figure 1.1 Structures of natural and man-made chiral tetrahydrofurans.

Chiral substituted 2,3-dihydrobenzofurans can also be found in natural products such as conocarpan (**3**) and thespesone (**4**) (*Figure 1.2*). Isolated from the wood of *Conocarpus erectus*, conocarpan (**3**) exhibits insecticidal, antifungal and antitrypanosomal activities.[4] Thespesone (**4**), first isolated in 1983 from the heartwood of the tree *Thespesia populnea*, is a *para*-naphtoquinone connected to the dihydrofuran moiety.[5] The first total synthesis of thespesone (**4**) and its non-natural enantiomer was reported by SCHOBERT *et al.*, along with its cytotoxic activity against a small panel of human cancer cell lines.[6]

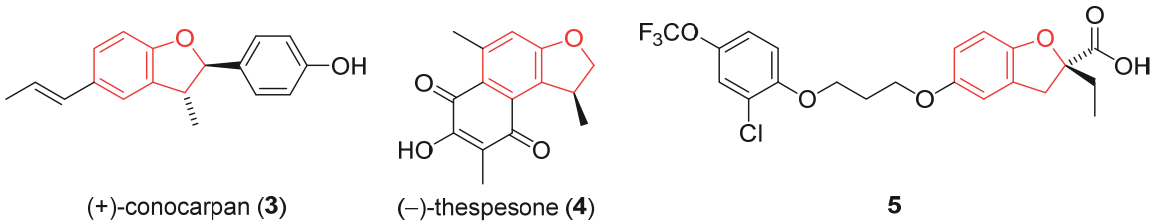


Figure 1.2 Structures of biologically active benzodihydrofurans.

2,3-Dihydrobenzofuran-2-carboxylic acid **5** and its derivatives are potent hypolipidemic agents and subtype-selective PPARα agonists, and therefore were selected as candidates for further preclinical evaluations.[7]

The widespread occurrence of tetrahydrothiophene core structures in natural as well as non-natural products makes them important compounds for the pharmaceutical industry.[8] The essential coenzyme biotin (**6**), a water-soluble vitamin which is responsible for important transformations in the human body, contains such a motif (*Figure 1.3*).[9] The 4'-thioadenosine derivative **7** for example, is a highly potent and selective A_3 adenosine receptor antagonist, whereas sulopenem (**8**), exhibits anti-bacterial properties. Substituted tetrahydrothiophene 1,1-dioxides are also interesting targets for pharmaceutical research as shown by two examples in *Figure 1.3*. Mono-substituted tetrahydrothiophene 1,1-dioxide **9** is a Hepatitis C virus protease inhibitor, whilst the disubstituted analog **10** possesses high HIV-1 protease inhibition activity.[10]

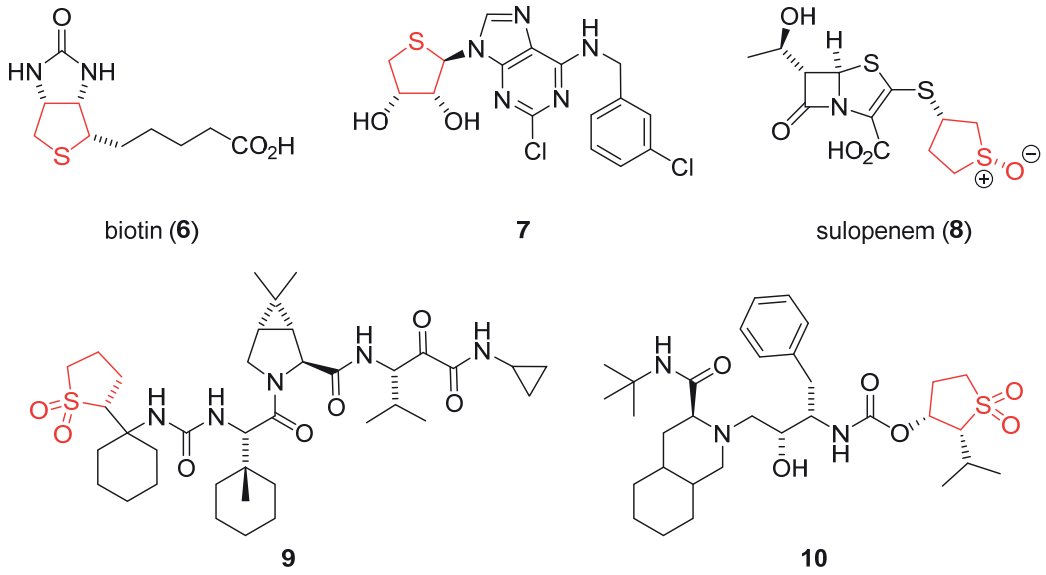
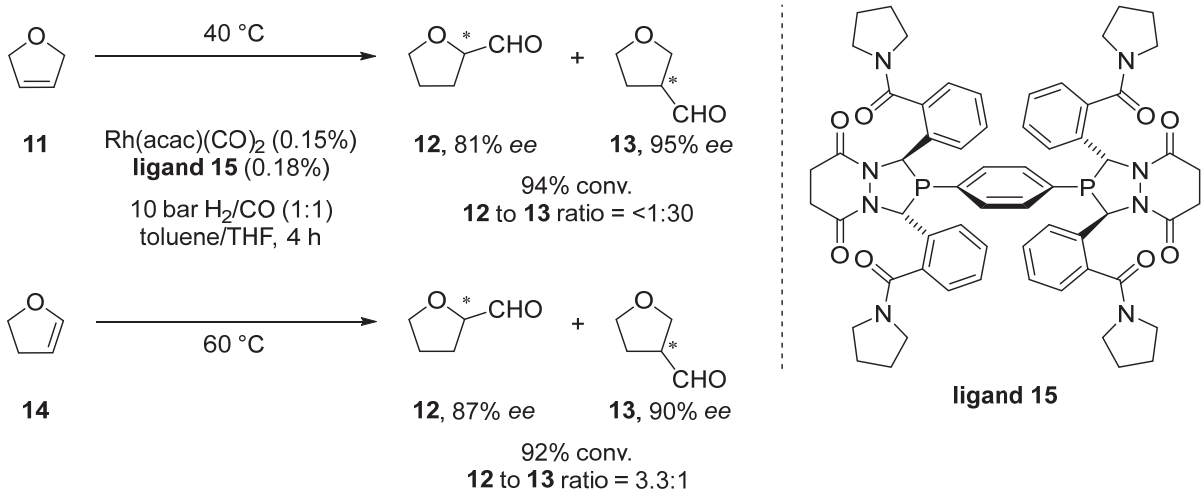


Figure 1.3 Structures of chiral tetrahydrothiophenes and oxidized analogs.

The medicinal importance of chiral saturated heterocyclic compounds calls for straightforward and high yielding stereoselective methods for their synthesis. Many different approaches are known to produce such scaffolds;[8, 11] some stereoselective variants to synthesize substituted tetrahydrofurans, 2,3-dihydrobenzofurans and tetrahydrothiophene 1,1-dioxides are shown in the following section.

1.2 Asymmetric Synthesis of Saturated Heterocycles

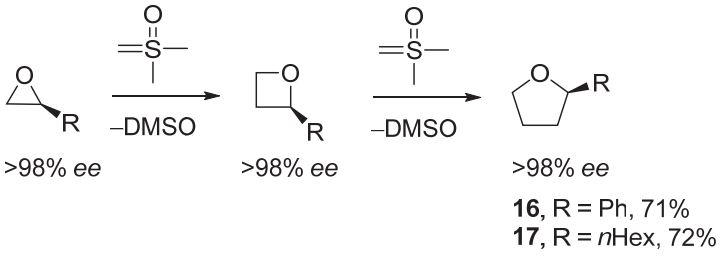
The hydroformylation reaction, discovered by ROELEN in 1938, emerged as an important industrial process for the synthesis of aldehydes from olefins.[12] An asymmetric version of this reaction involving a homogeneous catalyst was recently applied to the synthesis of 2- and 3-substituted tetrahydrofuran carbaldehydes **12** and **13** (*Scheme 1.1*).[13]



Scheme 1.1 Synthesis of 2- and 3-substituted carbaldehydes.

The chiral C_2-symmetric bis-diazaphospholane ligand **15** promotes the asymmetric hydroformylation of 2,5-dihydrofuran (**11**) to give selectively the β-regioisomer **13** and 2,3-dihydrofuran (**14**) as the by-product (4%), while the same reaction with 2,3-dihydrofuran (**14**) yields α-carbaldehyde **12**. Both reactions proceed with high conversion and enantioselectivity. However, the limited substrate scope of this method reduces its applicability.

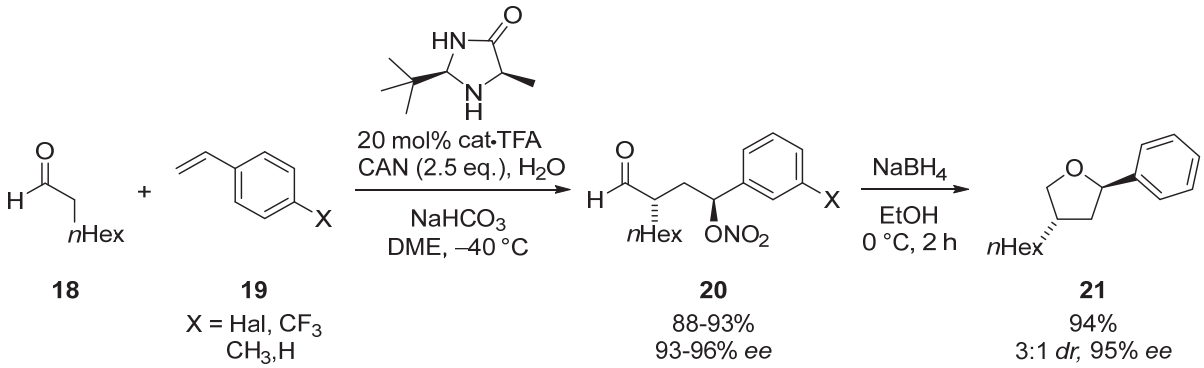
A more broadly applicable transformation is shown in *Scheme 1.2*. The consecutive ring-expansion reaction of epoxides with dimethylsulfonium methylide, gives access to both 2-aryl and 2-alkyl substituted tetrahydrofurans depending on the substitution of the epoxide.[14]



Scheme 1.2 Synthesis of 2-substituted tetrahydrofurans.

Starting with optically pure epoxides, which are readily synthesized by SHARPLESS[15] or SHI[16] epoxidation, the nucleophilic ring expansion proceeds with retention of stereochemistry providing 2-substituted tetrahydrofurans in good yield and unaltered enantiomeric excess.

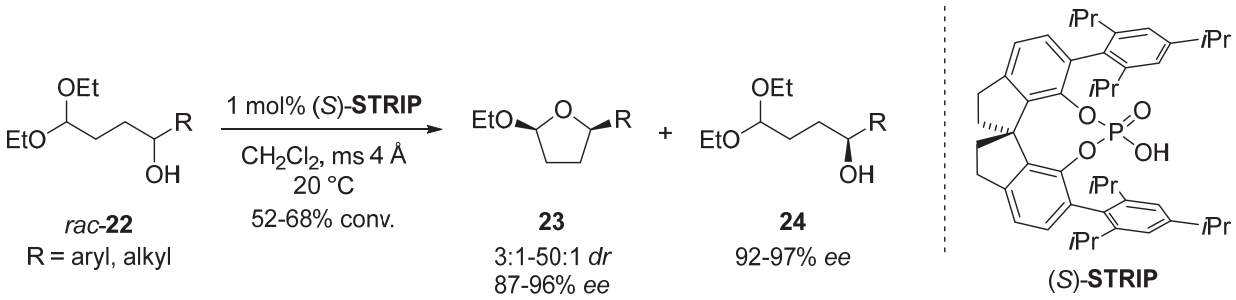
The preparation of 2,4-disubstituted tetrahydrofurans from enantioenriched intermediates can be accomplished by a reduction-cyclization sequence in one step, as shown in the application of enatiopure γ-nitro-aldehydes **20** described by MACMILLAN in the context of the organocatalyzed carbo-oxidation of styrene derivatives (*Scheme 1.3*).[17]



Scheme 1.3 Carbo-oxidation of styrene and subsequent ring formation.

Various substituents are tolerated on both the aldehyde **18** and the styrene **19**. However, the ring closure was performed with only one nitro-aldehyde **20**, affording the product **21** in quantitative yield with moderate diastereo- and high enantioselectivity. The synthesis of other derivatives with different substituents on the heterocycle should be possible by this route.

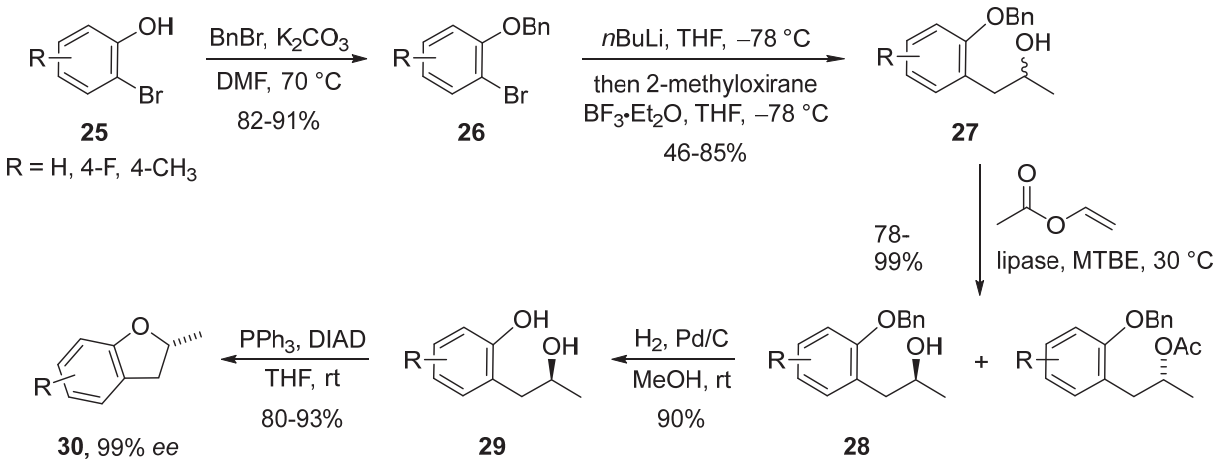
Starting from racemic compounds, as in the kinetic resolution of homoaldols *via* catalytic asymmetric transacetalization, enantioenriched 2,5-disubstituted tetrahydrofurans **23** can be obtained (*Scheme 1.4*).[18]



Scheme 1.4 Synthesis of 2,5-disubstituted tetrahydrofurans **23** *via* acetalization.

This transformation tolerates not only a broad substrate range, but also delivers the products **23** with high enantiomeric excess and moderate to excellent diastereoselectivity. The only limitation is the maximum theoretical yield of 50% and the predefined ether substituent at the 2-position.

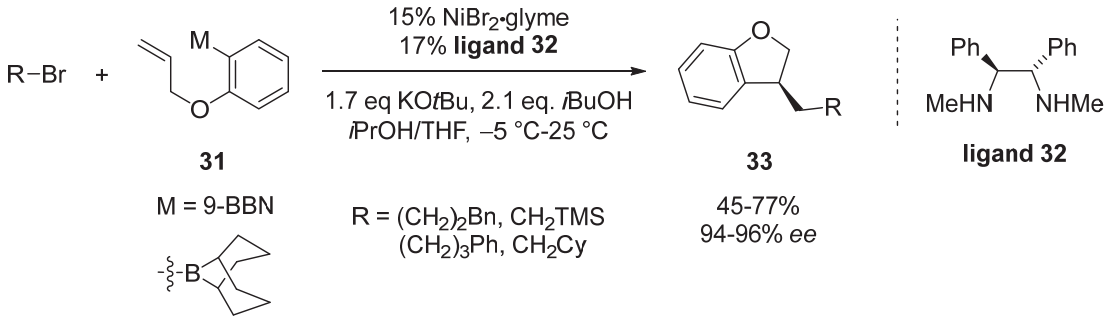
A chemoenzymatic strategy was applied to the asymmetric synthesis of 2,3-dihydrobenzofurans (*Scheme 1.5*).[19] Protection of commercially available phenols **25** followed by reaction with *n*BuLi and 2-methyloxirane resulted in racemic alcohols **27**. The alcohols were enzymatically resolved to deliver suitable enantiopure precursors **28**, which in turn cyclized after deprotection to the desired 2,3-dihydrobenzofurans **30**.



Scheme 1.5 Synthesis of 2,3-dihydrobenzofurans **30** in five steps.

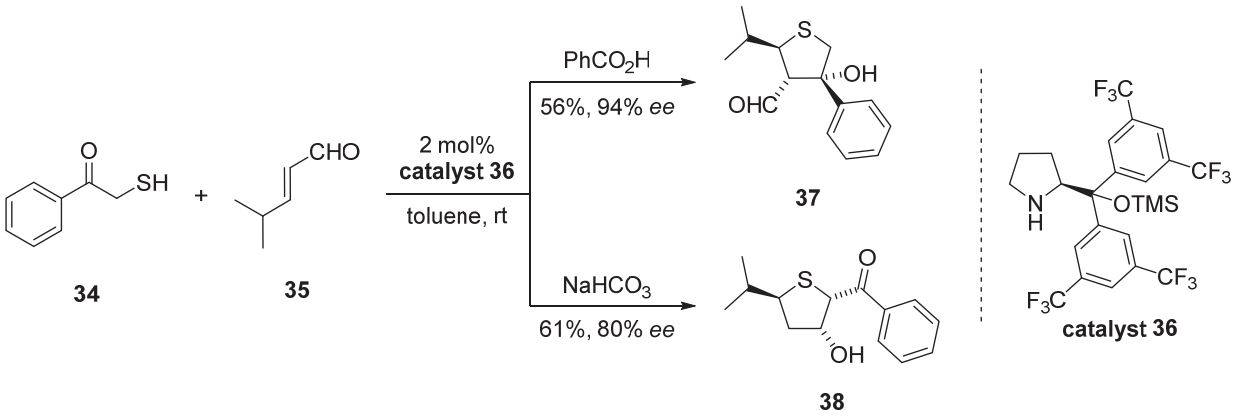
Product **30** was obtained in enantiomerically pure fashion, but with the limitation of a maximum yield of 50% and the drawback of a lengthy synthesis.

Asymmetric cyclization cross-coupling sequence with alkyl electrophiles was pursued by FU *et al.* to selectively obtain 2,3-dihydrobenzofurans substituted at the C3 (*Scheme 1.6*).[20] Transmetallation of the organometallic reagent **31** containing a proximal olefin, followed by cyclization and subsequent cross-coupling with an alkylbromide, leads to two newly formed carbon-carbon bonds and a stereogenic center. Remarkably, almost no direct cross-coupled or endo cyclized by-products were formed (<5%).



Scheme 1.6 Synthesis of 2,3-dihydrobenzofurans **33** *via* a cyclization cross-coupling sequence.

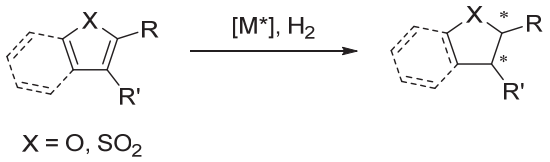
Domino reactions have also been successfully utilized in the asymmetric synthesis of tetrahydrothiophene derivatives, such as the Michael-aldol reaction sequence.[21] Depending on the use of acidic or basic additives in the organocatalytic system, tetrahydrothiophene carbaldehydes **37** or (tetrahydrothiophen-2-yl)phenyl methanones **38** are obtained in moderate to good yield. As an example, reaction of thiol **34** and aldehyde **35** in the presence of L-proline derived catalyst **36** and benzoic acid gives tetrahydrothiophene carbaldehyde **37** as a single isomer (*Scheme 1.7*). In contrast, addition of basic $NaHCO_3$ promotes the domino process to afford a 98:2 mixture of both isomers **37** and **38**; the major product could be isolated in 56% yield and 94% *ee*.



Scheme 1.7 Synthesis of tetrahydrothiophenes **37** and **38** *via* Michael-aldol reaction.

To access the corresponding dioxides one additional step is necessary to oxidize the preformed thioethers.[22]

A direct and very attractive route to enantioenriched reduced heterocycles from aromatic precursors is provided by transition-metal-catalyzed asymmetric hydrogenation (*Scheme 1.8*).



Scheme 1.8 Synthesis of chiral heterocycles *via* asymmetric hydrogenation.

Despite extensive efforts in the field of asymmetric hydrogenation of heteroaromatic compounds over the last two decades, enantioselective hydrogenation of furans, benzofurans and thiophenes is still limited in scope,[23] whereas for substituted thiophene 1,1-dioxides to date no hydrogenation protocol exists.

1.3 Aim of This Work

The main focus of the research presented in this dissertation was to further broaden the substrate scope of the iridium-catalyzed hydrogenation of heterocyclic compounds. The synthesis of various substituted furans and benzofurans is shown in *Chapter 2*, while their asymmetric iridium-catalyzed hydrogenation is the subject of *Chapter 3*. Furthermore, the preparation of disubstituted thiophene 1,1-dioxides and their stereoselective reduction using iridium-catalysts are described in the following two chapters (*Chapter 4*, *Chapter 5*).

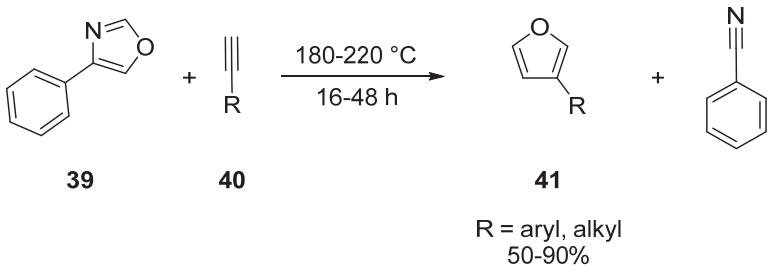
Finally, investigations on the iridium-catalyzed hydrogenation of oxazoles and thiazoles are reported in *Chapter 6*.

2 Synthesis of Furans and Benzofurans as Substrates for Iridium-Catalyzed Asymmetric Hydrogenation

2.1 Introduction

Furan and benzofuran core structures are common subunits in pharmaceuticals, natural products and other biologically important molecules.[24] To access substituted furans and benzofurans two main approaches can be applied. The first strategy is based on the construction of the heterocycle, whereas the second takes advantage of various kinds of ring functionalization methods.

A simple and effective method to synthesize 3-substituted furans, relies on the ring construction in one step *via* a tandem DIELS–ALDER/retro DIELS–ALDER reaction sequence as depicted in *Scheme 2.1*.[25]

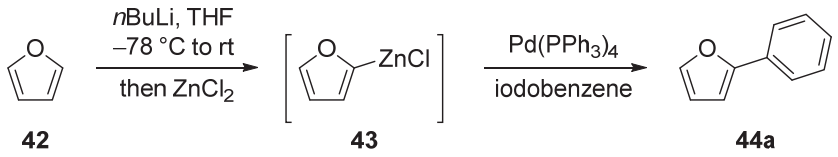


Scheme 2.1 Synthesis of 3-substituted furans *via* tandem DIELS–ALDER/ retro DIELS–ALDER sequence.

4-Phenyloxazole (**39**), as diene and substituted acetylenes **40**, as dienophiles react under thermal conditions to provide both 3-aryl- and 3-alkylfurans **41** in moderate to good yield. Albeit starting materials are broadly accessible and many functional groups are tolerated, high temperature and long reaction times render this sequence unattractive. Another method to access 3-substituted furans in one step, is the nickel-catalyzed KUMADA cross-coupling reaction.[26] This synthetic route has been chosen for the synthesis of some substrates for iridium-catalyzed asymmetric hydrogenation and will be further discussed in *Section 2.2*.

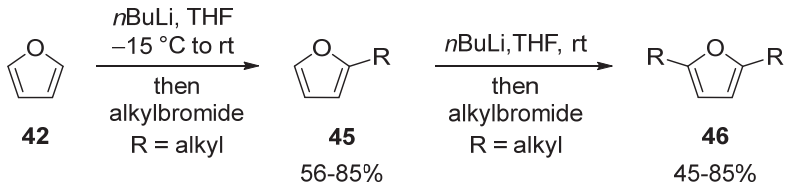
Preparation of 2-substituted furans can be achieved either by electrophilic aromatic substitution or metallation. The latter approach takes advantage of the inductive effect of the oxygen atom, allowing functionalization at the C2/C5 position. The commercially, readily available and relatively cheap furan **42**, a precursor of the widely used solvent tetrahydrofuran (THF) and therefore produced on industrial

scale, is a perfect starting material for the synthesis of 2-substituted furans as shown in *Scheme 2.2*.[27]



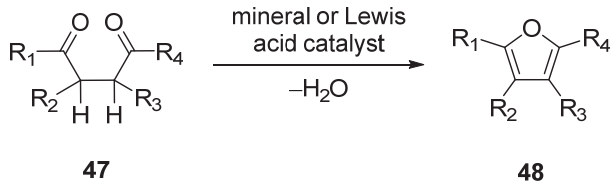
Scheme 2.2 Synthesis of 2-phenylfuran (**44a**) *via* NEGISHI cross-coupling.

Deprotonation of furan (**42**) with one equivalent of *n*BuLi results in 2-lithiofuran, which is transmetallated with zinc chloride to give the heteroaryl zinc compound **43**. Subsequent palladium-catalyzed cross-coupling with aryl iodides or bromides (the latter must be activated by an electron-withdrawing group) affords 2-phenylfuran (**44a**) in good yield. Alternatively, the 2-lithiofuran can be trapped with various electrophiles, providing an entry to 2-alkyl substituted furans in moderate to good yield (*Scheme 2.3)*.[28]



Scheme 2.3 Synthesis of 2-substituted and 2,5-disubstituted furans.

Second lithiation of the 2-substituted product **45** provides 2,5-disubstituted heterocycles with similar chemical yield. Another classical approach to synthesize disubstituted furan rings is represented by the synthesis developed by PAAL and KNORR in 1884.[29] Both groups reported almost simultaneously the cyclizing dehydration of 1,4-diketones **47** upon treatment with strong mineral acids (*Scheme 2.4*).



Scheme 2.4 Synthesis of substituted furans *via* PAAL–KNORR furan synthesis.

This approach results in either 2,5-disubstituted or 3,4-disubstituted furans depending on the substitution pattern of the starting 1,4-dicarbonyl compound **47**. However, it has two major drawbacks. First, the limited availability of 1,4-dicarbonyl compounds and secondly, the restricted functional group tolerance under strongly acidic